Original Article

Diagnostic value of C-reactive protein and procalcitonin for postoperative pancreatic fistula following pancreatoduodenectomy: a systematic review and meta-analysis

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Background: C-reactive protein (CRP) and procalcitonin (PCT) have recently been used to diagnose and screen for postoperative pancreatic fistula (POPF) following pancreatoduodenectomy (PD), but their reliability is still unclear. Our study aims to assess the efficacy of CRP and PCT in the diagnosis of POPF after PD.

Methods: Electronic databases such as PubMed, Excerpta Medica (EMBASE), the Web of Science (WOS) and the China National Knowledge Infrastructure (CNKI) were used to search for studies and full-text articles that assessed the diagnostic efficacy of CRP and PCT for POPF. Review Manager 5.4 and STATA 14.0 were used to estimate the pooled diagnostic value of CRP and PCT. Sensitivity analyses and Deeks' funnel plot tests were conducted on the selected studies.

Results: Twenty studies that satisfied the established selection criteria were chosen. Both CRP and PCT were shown to be highly effective in diagnosing POPF, each with a high area under the curve (AUC). The AUC of CRP on postoperative day (POD) 4 had a value of 0.86, with a sensitivity and specificity of 0.85 and 0.69, respectively. The AUC of PCT on POD 5 had a value of 0.87, with a sensitivity and specificity of 0.84 and 0.74, respectively.

Discussion: Our research supports the hypothesis that CRP and PCT are valuable diagnostic tools for predicting POPF, especially given the CRP levels on POD 4 and PCT levels on POD 5. Limited by the small number of the studies analyzed herein, we recommend that more randomized controlled trials be performed to verify our conclusions.

Keywords: C-reactive protein (CRP); procalcitonin; postoperative pancreatic fistula (POPF); diagnostic

Submitted Sep 06, 2021. Accepted for publication Oct 29, 2021.
doi: 10.21037/gs-21-658
View this article at: https://dx.doi.org/10.21037/gs-21-658

Introduction

Pancreaticoduodenectomy (PD) is one of the standard surgical methods used to treat ampullary malignant tumors such as carcinoma of the pancreatic head, carcinoma of the lower common bile duct, and carcinoma of the duodenal papilla (1,2). However, postoperative complications still greatly affect patient recovery, presenting an urgent problem for hepatobiliary and pancreatic surgeons. Pancreatic fistula (PF) is a common and potentially severe complication after PD (3,4). Soft pancreas is an independent risk factor for PF after PD. The main pancreatic duct of soft pancreas is often thin, which makes it difficult to operate and the suture is not

firm during PD, thus increasing the risk of PF after PD (2).

Relevant literature shows that the incidence of PF after PD is as high as 30% (5). Furthermore, the occurrence of PF after PD usually leads to other complications (6,7). Both grade B and grade C PF are defined as clinical postoperative pancreatic fistula (POPF) (8). Grade B PF is usually accompanied by abdominal hemorrhage and abdominal infection, while the more severe grade C PF is usually accompanied by organ failure or further complications leading to death. In addition, the occurrence of a POPF will extend the patient's postoperative hospital stay, affect their postoperative healing, and increase the financial and mental burden placed upon them (9,10).

POPF is a serious postoperative complication, and reducing the incidence of POPF is one of the most effective means to reducing further complications after PD (11). Although there have been a large number of studies on the risk factors of POPF after PD, there is still much controversy, and it is difficult to determine all the clinical variables and related risk factors (12,13). Markers for POPF include procalcitonin (PCT), C-reactive protein (CRP), drain amylase, serum lipase, serum amylase, and white blood cells (WBCs) (14-20). The difficulty arises from the sheer number of factors related to POPF, making it impossible to resolve in a single study.

At present, other systematic reviews have studied the diagnostic value of drain amylase and WBC in predicting POPF after PD (21-24), but there are few systematic reviews on the diagnostic value of CRP and PCT in such cases. CRP is a sensitive marker for judging tissue damage and inflammation. PCT is a marker with high specificity to determine bacterial infection. The purpose of this study is to evaluate the diagnostic value of CRP and PCT in predicting POPF after PD by meta-analysis. We present the following article in accordance with the PRISMA-DTA reporting checklist (available at https://dx.doi.org/10.21037/gs-21-658).

Methods

Literature search strategy

Electronic databases, including PubMed, Excerpta Medica (EMBASE), the Web of Science (WOS), and the China National Knowledge Infrastructure (CNKI) were systematically searched from inception to July 2021 for the following keywords: (I) C-reactive protein (CRP); (II) procalcitonin (PCT); (III) postoperative pancreatic fistula (POPF); and (IV) pancreatoduodenectomy (PD). To broaden the search, numerous combinations of words and strings were applied with the Boolean operators "AND" and "OR". There were no restrictions on the language of publication in document retrieval. To identify additional eligible studies, we reviewed reference lists from eligible trials and relevant reviews and guidelines. Disagreements were resolved through consensus between the two reviewers.

POPF definition

POPF is defined as any measurable excretion volume with an amylase content greater than three times the upper limit of normal serum, and classified as follows (25):

- Grade A: a temporary fistula with no clinical impact; patient can take orally, and clinical condition is good;
- Grade B: patient receives partial or total parenteral or enteral nutrition support, and usually requires continuous drainage for 3 weeks;
- Grade C: clinical management of fistula changes significantly or deviates from the normal clinical pathway, and radiation intervention or reoperation is required.

In our study, grade B and grade C were defined as clinical POPF.

Study selection

In selecting studies for inclusion in this meta-analysis, we applied the following criteria:

(I) Study is about patients with PD;
(II) Study focuses on the value of CRP and/or PCT in the diagnosis of POPF after PD;
(III) Study directly or indirectly provides the following data: true positive (TP), false positive (FP), false negative (FN) and true negative (TN);
(IV) Study is available in full text.

The exclusion criteria agreed upon were as follows:

(I) Study does not meet the inclusion criteria;
(II) Relevant results are not reported or cannot be used;
(III) Only review or abstract is available, or study is a duplicate publication.

Data extraction and quality assessment

The data extracted from the selected studies included: year of publication, country of origin, sample size, patient age, POPF prevalence, reference standard, and tested variables.

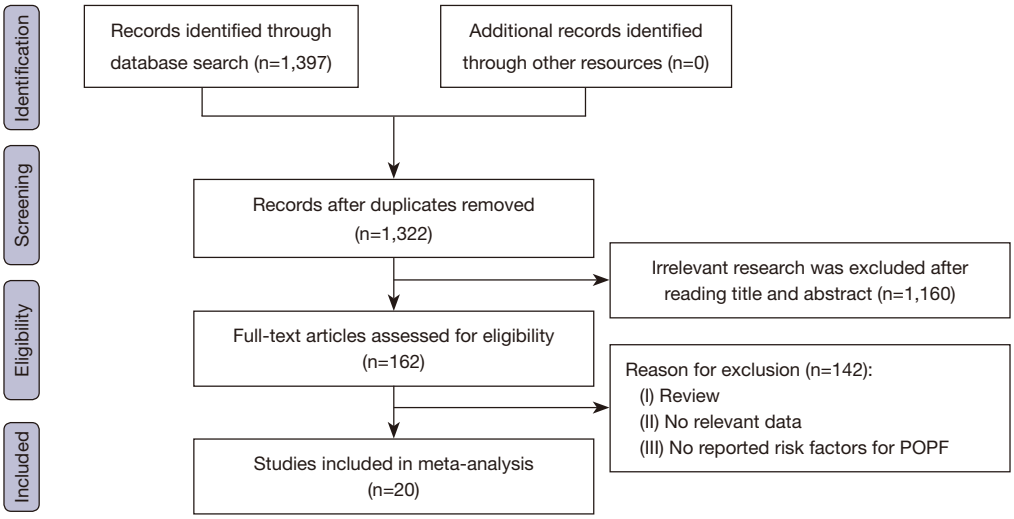

Figure 1 Flow diagram of study selection in the systematic review and meta-analysis.

The validity of the eligible studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool (QUADAS-2) in the RevMan software suite (version 5.4). Data extraction and quality assessment were performed independently by two reviewers, and disagreements were resolved by consensus.

Statistical analysis

The meta-analysis in our study was performed using RevMan 5.4 (The Cochrane Collaboration, Oxford, UK) and STATA 14.0 (STATA Corp., College Station, TX, USA). We evaluated the degree of statistical heterogeneity and inconsistency by using the Chi 2 and I^2 statistics. The random-effect model was applied if heterogeneity was observed, while the fixed-effect model was applied in the absence of between-study heterogeneity. In the meta-analysis of diagnostic test accuracy, the threshold effect is one of the important reasons for the heterogeneity. Therefore, if there is a threshold effect, the best way to merge data is to fit the summary receiver operating characteristic (SROC) curve and calculate the area under the SROC curve (AUC) when performing a Meta-analysis to merge effect values. In this study, we all use SROC curve and AUC to judge the diagnostic value. Sensitivity analysis was conducted by eliminating individual studies one by one, and Deeks' funnel plot was used to identify publication bias when the number of articles included exceeded 10. P>0.05 was considered indicative of no significant publication bias.

Results

Search process

A total of 1,322 potentially relevant articles from electronic databases were retrieved after the literature search. By preliminary screening of the titles and abstracts, we excluded 1,160 documents, which did not meet the inclusion criteria. After full-text screening, a further 142 articles were excluded. Thus, 20 studies met the criteria for inclusion in the present meta-analysis (26-45). The process of literature retrieval is shown in *Figure 1*.

Characteristics of included studies

The baseline characteristics of the studies included in the meta-analysis are shown in *Table 1*. This study includes ten prospective cohort studies and ten retrospective cohort studies consisting of 4,076 patients. All articles were published from 2013 to 2021. POPF prevalence ranged from 7.5% to 26%. All studies adopted the standard of the International Study Group of Pancreatic Surgery (ISGPS) as the reference standard for POPF.

Results of quality assessment

As shown in *Figure 2*, the QUADAS-2 tool was used to assess the quality of the selected studies, among which two showed a high risk of index test bias, and two others showed a high risk of flow and timing bias. A summary of the risk of bias assessment for each study is shown in *Figure 2B*.

Table 1 Characteristics of included studies

Study	Country	Study design	No. of patients	Gender (M/F)	Age, years	POPF prevalence	Study interval	Reference standard	Tested variables
Fujiwara 2013	Japan	Retrospective	297	181/116	63.4 [13–86]	64 (22%)	January 2001 to December 2011	ISGPF	CRP
Hiyoshi 2013	Japan	Prospective	176	108/68	–	30 (17%)	March 2002 to December 2010	ISGPF	CRP
Kosaka 2013	Japan	Retrospective	100	64/36	–	32 (32%)	January 2009 to October 2012	ISGPF	CRP
Ansorge 2014	Sweden	Prospective	315	141/174	67 [22–87]	48 (15.2%)	January 2008 to June 2012	ISGPF	CRP
Uemura 2014	Japan	Prospective	200	115/85	68 [19–88]	15 (7.5%)	April 2004 to June 2011	ISGPF	CRP
Solaini 2015	UK	Prospective	378	183/195	65 [52–72]	31 (8.2%)	January 2005 to December 2012	ISGPF	CRP
Giardino 2016	Italy	Prospective	84	47/37	64 [56–72]	18 (21.4%)	January 2015 to November 2015	ISGPF	CRP/PCT
Palani Velu 2016	UK	Prospective	230	151/79	–	54 (23.5%)	January 2008 to January 2014	ISGPF	CRP
Bai 2017	China	Prospective	87	53/34	62±10	18 (20.7%)	March 2016 to December 2016	ISGPF	PCT
Partelli 2017	Italy	Prospective	463	261/202	68 [17–85]	64 (14%)	2013 to 2015	ISGPF	CRP
Guilbaud 2018	France	Prospective	110	61/49	65 [24–85]	24 (22%)	January 2013 to November 2016	ISGPF	CRP
Malya 2018	Turkey	Retrospective	117	71/46	60.7±13.3	9 (8.7%)	2012 to 2015	ISGPF	CRP
Li 2019	China	Retrospective	62	41/21	–	12 (19.4%)	April 2016 to April 2017	ISGPF	PCT
Mario 2019	Spain	Prospective	50	29/21	–	13 (26%)	January 2015 to March 2018	ISGPF	CRP
Uchida 2019	Japan	Retrospective	211	126/85	68 [22–85]	38 (18%)	2012 to 2018	ISGPF	CRP
Dongen 2020	Netherlands	Retrospective	202	110/92	68 [59–74[	35 (17.3%)	January 2012 to December 2017	ISGPF	CRP
Mintziras 2020	Germany	Retrospective	188	98/90	67.5 [56.3–75]	30 (16%)	January 2009 to December 2018	ISGPF	CRP/PCT
Zhou 2020	China	Retrospective	67	43/24	–	14 (20.9%)	January 2017 to December 2018	ISGPF	PCT
Farooqui 2021	Denmark	Retrospective	552	281/271	69 [16–90]	48 (8.7%)	January 2015 to December 2019	ISGPF	CRP
Ma 2021	China	Retrospective	186	102/84	61 [52–67]	18 (9.7%)	January 2019 to November 2019	ISGPF	CRP/PCT

POPF, postoperative pancreatic fistula; ISGPS, International Study Group of Pancreatic Surgery; CRP, C-reactive protein; PCT, procalcitonin.

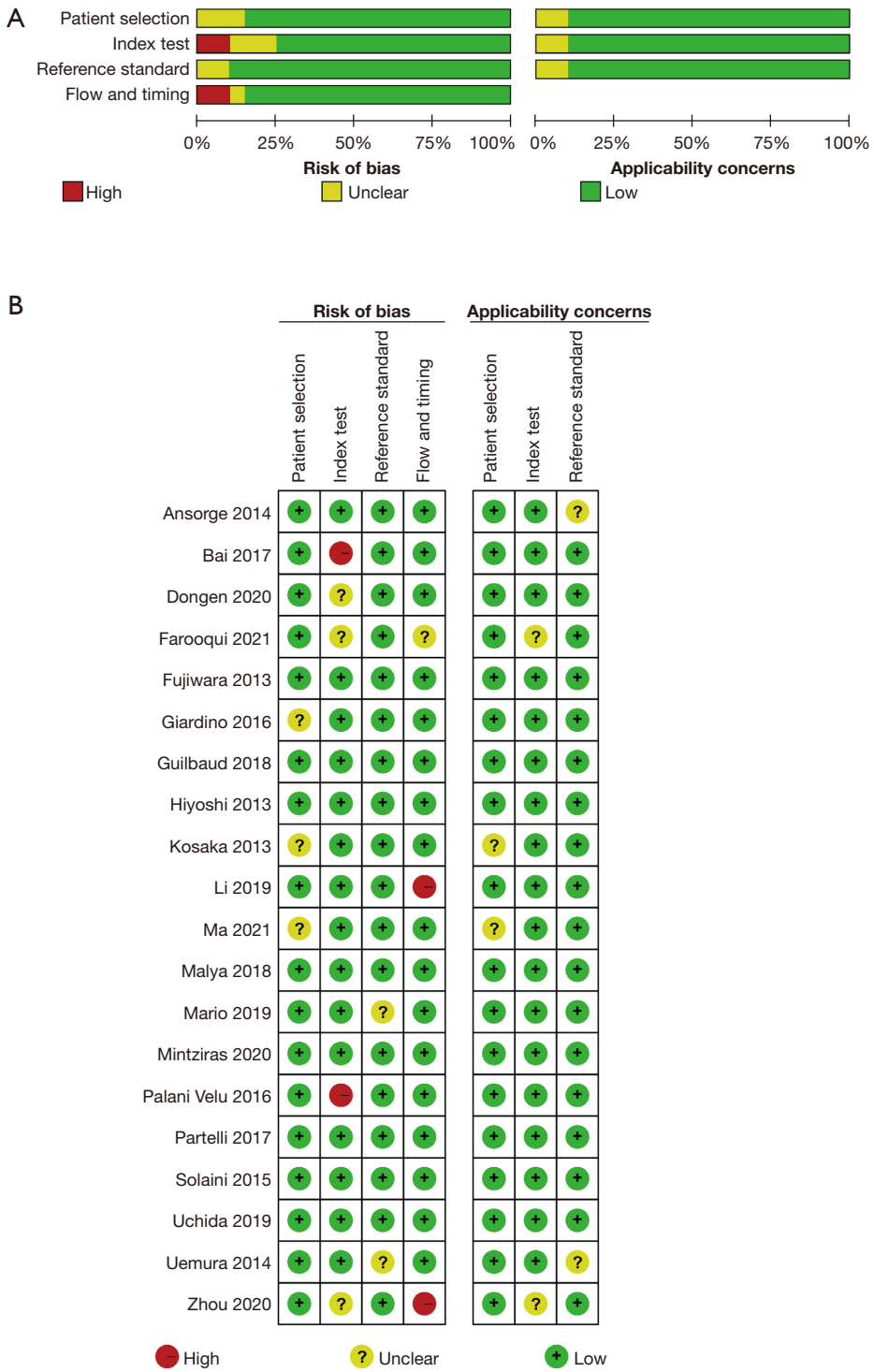

Figure 2 Overall assessment of risk of bias. (A) Proportion of studies with low, high, or unclear risk of bias; (B) risk of bias summary.

Results of diagnostic accuracy

Given the significant changes in PCT and CRP after PD and the likelihood of different diagnostic values on different postoperative days (PODs), we carried out a subgroup analysis according to POD.

Diagnostic accuracy of CRP

Table 2 shows the results of the meta-analysis of the diagnostic accuracy of CRP in predicting POPF after PD, presented separately for POD 1–5. The highest sensitivity was found on POD 4 (0.85; 95% CI: 0.78–0.91); the highest specificity occurred on POD 3 (0.74; 95% CI: 0.60–0.84); and the highest diagnostic odds ratio (DOR) was found on POD 4 (13; 95% CI: 4–41). Regarding sensitivity and specificity, the highest AUC was also found on POD 4 (0.86; 95% CI: 0.83–0.89). *Figure 3* shows the AUC on POD 1–5.

Diagnostic accuracy of PCT

Table 3 shows the results of the meta-analysis of the diagnostic accuracy of PCT in predicting POPF after PD, presented separately for POD 1, 3 and 5, as no study chose to display the diagnostic accuracy of PCT on POD 4, and only 1 study provided data for POD 2, making it impossible to conduct a pooled analysis of POD 2 and POD 4. The results show that the highest sensitivity was found on POD 1 (0.84; 95% CI: 0.72–0.91) and POD 5 (0.84; 95% CI: 0.71–0.92); the highest specificity occurred on POD 3 (0.77; 95% CI: 0.61–0.87); and the highest DOR was found on POD 5 (15; 95% CI: 5–44). Regarding sensitivity and specificity, the highest AUC was also found on POD 5 (0.87; 95% CI: 0.84–0.90). *Figure 4* shows the AUC on POD 1, 3 and 5.

Sensitivity analysis

We conducted a sensitivity analysis by excluding the selected studies one by one and observing whether the results obtained changed significantly. No noticeable changes were observed, indicating that these studies are relatively stable.

Publication bias

We evaluated the publication bias of the selected studies using Deeks' funnel plot asymmetry test for the diagnostic value of CRP on POD 3. The P value was 0.70, which indicates that no significant publication bias exists in this meta-analysis (*Figure 5*).

Discussion

POPF is a severe complication of PD, with a high rate of morbidity. The clinically relevant POPF is often accompanied by abdominal cavity infection. Abdominal cavity infection is not only related to POPF, but may also be an important inducing and aggravating factor for the occurrence and development of POPF, but the exact correlation between abdominal cavity infection and POPF is not clear (7).

Current literature shows that many factors determine the risk of developing a PF after PD, including gender, body mass index, diabetes, pancreatic texture, pancreatic duct diameter, intraoperative blood loss, pathological type, anastomosis, neoadjuvant therapy, somatostatin analogues and drainage tube placement (46,47). Based on the above risk factors, several risk prediction scoring systems for POPF have been established, such as the National Cancer Center Hospital (NCCH) POPF prediction scoring system, the Fistula Risk Score (FRS), and the measurement of amylase in postoperative drainage fluid (48,49).

To find a simple and accurate method for assessing POPF, early screening and effective preventive measures for high-risk patients have been the focus of pancreatic surgeons. The detection of blood indexes with high sensitivity and specificity is one of the most reliable predictors of POPF (50). Therefore, clarifying the correlation between early postoperative biochemical sensitive indexes and POPF is of significant clinical value.

Several markers, such as drain amylase, serum lipase, serum amylase and WBC, have been proposed as predictors for POPF (11,17,20,51). Yang *et al.* (52) found that a value of drain fluid amylase on POD 1 over 1,300 U/L indicated a risk factor for PF, with a pooled sensitivity and specificity of 81% and 87%, respectively. Liu *et al.* (53) concluded that the drain/plasma pancreatic amylase value on POD 1 was a useful predictive test for overall POPF and clinical POPF with high sensitivity (92%) and specificity (77%) scores. The present meta-analysis aimed to assess the accuracy of CRP and PCT in the prediction of POPF. To date, there have been few studies to assess the pooled performance of CRP and PCT for POPF after PD.

It was found that both CRP and PCT are effective in helping to diagnose POPF and have a high AUC. They

Table 2 Diagnostic accuracy of CRP levels from POD 1–5

Study	POPF prevalence	Cut-off values (mg/L)	Sensitivity	Specificity	AUC	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled DOR (95% CI)	Pooled AUC (95% CI)
POD 1									
Guilbaud 2018	24 (22%)	100	0.84	0.61	0.72	0.78 (0.66–0.86)	0.43 (0.27–0.60)	3 [2–4]	0.69 (0.65–0.73)
Malya 2018	9 (8.7%)	55	0.7	0.27	0.407				
Ma 2021	18 (9.7%)	65	0.625	0.684	0.625				
Giardino 2016	18 (21.4%)	92	0.87	0.57	0.72				
Palani Velu 2016	54 (23.5%)	98	0.796	0.347	0.573				
Fujiwara 2013	64 (22%)	94	0.643	0.596	0.644				
Farooqui 2021	48 (8.7%)	64	0.959	0.117	0.582				
POD 2									
Mario 2019	13 (26%)	250	0.69	0.87	0.79	0.75 (0.55–0.88)	0.65 (0.47–0.80)	6 [3–13]	0.76 (0.72–0.80)
Ma 2021	18 (9.7%)	217	0.875	0.715	0.794				
Palani Velu 2016	54 (23.5%)	230	0.611	0.619	0.682				
Farooqui 2021	48 (8.7%)	114	0.931	0.408	0.668				
POD 3									
Dongen 2020	35 (17.3%)	200	0.72	0.62	0.79	0.74 (0.63–0.83)	0.74 (0.60–0.84)	8 [4–17]	0.80 (0.77–0.84)
Ansorge 2014	48 (15.2%)	200	0.78	0.83	0.854				
Partelli 2017	64 (14%)	185	0.94	0.62	0.796				
Solaini 2015	31 (8.2%)	272	0.50	0.77	0.644				
Malya 2018	9 (8.7%)	225	0.70	0.71	0.668				
Hiyoshi 2013	30 (17%)	200	0.846	0.982	0.843				
Mintziras 2020	30 (16%)	203	0.63	0.84	0.81				
Ma 2021	18 (9.7%)	201	0.647	0.643	0.629				
Palani Velu 2016	54 (23.5%)	204	0.63	0.624	0.692				
Farooqui 2021	48 (8.7%)	122	0.906	0.404	0.762				
POD 4									
Kosaka 2013	32 (32%)	93	0.86	0.89	0.90	0.85 (0.78–0.91)	0.69 (0.41–0.88)	13 [4–41]	0.86 (0.83–0.89)
Uemura 2014	15 (7.5%)	156	0.867	0.87	0.866				
Palani Velu 2016	54 (23.5%)	134	0.834	0.538	0.708				
Farooqui 2021	48 (8.7%)	62	0.912	0.319	0.781				
POD 5									
Dongen 2020	35 (17.3%)	150	0.71	0.75	0.78	0.80 (0.68–0.89)	0.69 (0.59–0.78)	9 [5–16]	0.81 (0.78–0.85)
Malya 2018	9 (8.7%)	190	0.9	0.822	0.851				
Uchida 2019	38 (18%)	50	0.941	0.585	0.802				
Ma 2021	18 (9.7%)	95	0.813	0.603	0.702				

POPF, postoperative pancreatic fistula; AUC, area under the curve; DOR, diagnostic odds ratios.

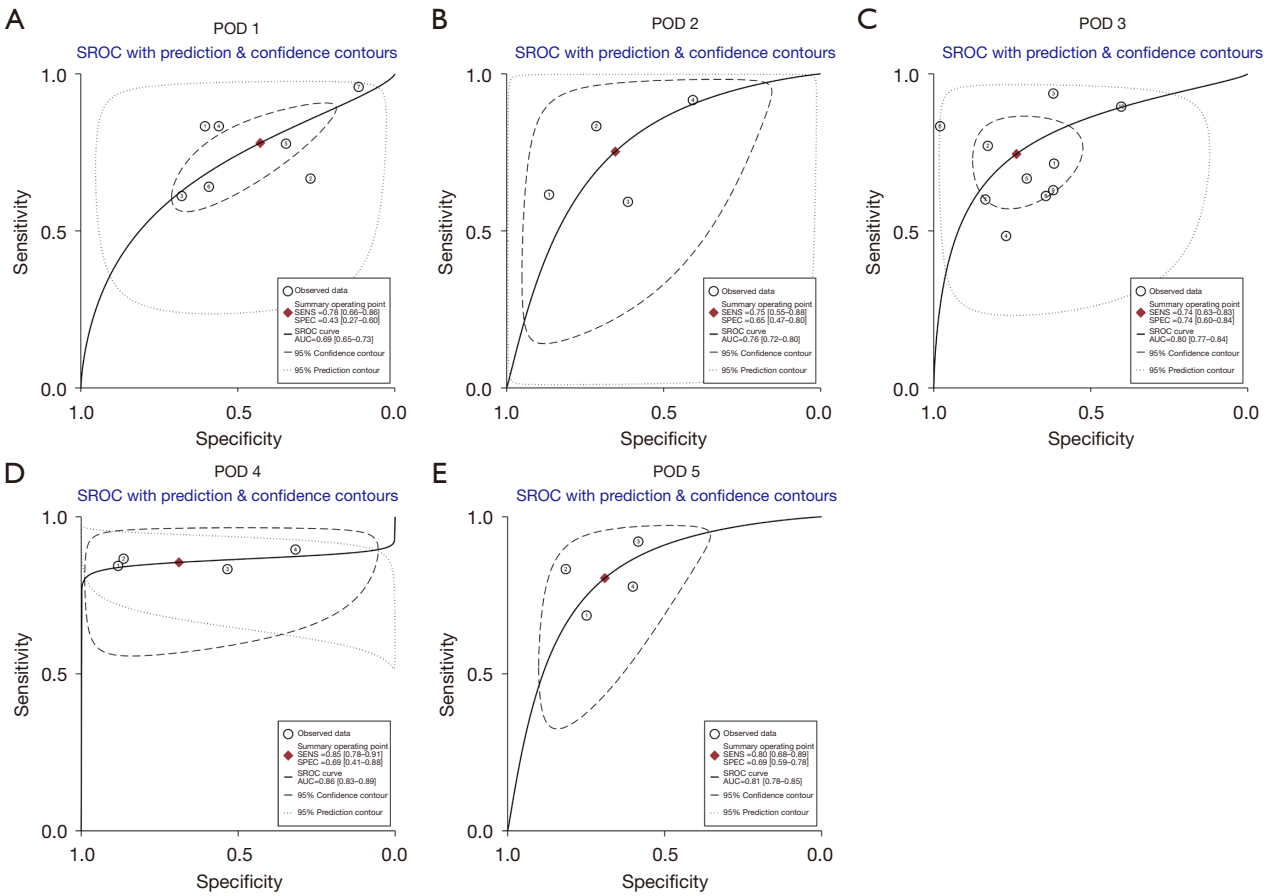

Figure 3 ROC curve plots for the diagnostic accuracy of CRP levels on POD 1–5 for POPF. ROC, receiver operating characteristic; CRP, C-reactive protein; POD, postoperative day; POPF, postoperative pancreatic fistula.

could therefore be used as a routine means for diagnosing POPF. Regarding the AUC value: an AUC of 0.5–0.7 suggests low diagnostic accuracy; AUC of 0.7–0.9 suggests medium diagnostic accuracy; and AUC >0.9 suggests high diagnostic accuracy. Our study showed that the AUC of CRP on POD 3–5 was greater than 0.80, especially the AUC of CRP on POD 4, which had a value of 0.86, with a sensitivity and specificity of 0.85 and 0.69, respectively, illustrating the positive diagnostic value of CRP for POPF. The AUC of PCT on POD 5 also showed high diagnostic accuracy for POPF with a value of 0.87, and a sensitivity and specificity of 0.84 and 0.74, respectively.

Several limitations should be noted. The ISGPF published two slightly different versions of POPF in 2005 and 2016 (54,55). Most of the studies included in this meta-analysis adopted the 2005 version, although some adopted the 2016 version, which may impact the results. Secondly, there were differences in the cutoff values of CRP and PCT in each study, which will have a certain impact on the final sensitivity and specificity and consequently affect the results of the AUC. Thirdly, the number of studies on the diagnosis of POPF by PCT was small, and more studies are needed to confirm its accuracy.

In conclusion, CRP and PCT have a high diagnostic value in predicting POPF, especially the CRP levels on POD 4 and PCT levels on POD 5. Given the study's limitations, more randomized controlled trials should be implemented to provide further unbiased evidence.

Table 3 Diagnostic accuracy of PCT levels from POD 1–5

Study	POPF prevalence	Cut-off values (μg/L)	Sensitivity	Specificity	AUC	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled DOR (95% CI)	Pooled AUC
POD 1									
Zhou 2020	14 (20.8%)	0.67	0.737	0.761	0.77	0.84 (0.72–0.91)	0.70 (0.54–0.82)	12 [5–28]	0.86 (0.82–0.88)
Ma 2021	18 (9.7%)	0.65	0.813	0.759	0.788				
Giardino 2016	18 (21.4%)	0.4	0.93	0.43	0.70				
Li 2019	12 (19.4%)	0.38	1	0.80	0.92				
POD 2									
Ma 2021	18 (9.7%)	3.3	0.813	0.937	0.931				
POD 3									
Zhou 2020	14 (20.8%)	0.56	0.895	0.642	0.83	0.74 (0.59–0.85)	0.77 (0.61–0.87)	9 [4–24]	0.81 (0.78–0.84)
Mintziras 2020	30 (16%)	0.85	0.52	0.83	0.77				
Ma 2021	18 (9.7%)	2.1	0.882	0.929	0.951				
Bai 2017	18 (20.7%)	0.259	0.778	0.537	0.689				
Li 2019	12 (19.4%)	0.44	0.833	0.74	0.89				
POD 4									
None									
POD 5									
Zhou 2020	14 (20.8%)	0.46	0.684	0.761	0.72	0.84 (0.71–0.92)	0.74 (0.57–0.86)	15 [5–44]	0.87 (0.84–0.90)
Ma 2021	18 (9.7%)	0.91	0.938	0.879	0.930				
Bai 2017	18 (20.7%)	0.126	0.889	0.475	0.723				
Li 2019	12 (19.4%)	0.98	0.917	0.76	0.84				

POPF, postoperative pancreatic fistula; AUC, area under the curve; DOR, diagnostic odds ratios; POD, postoperative day.

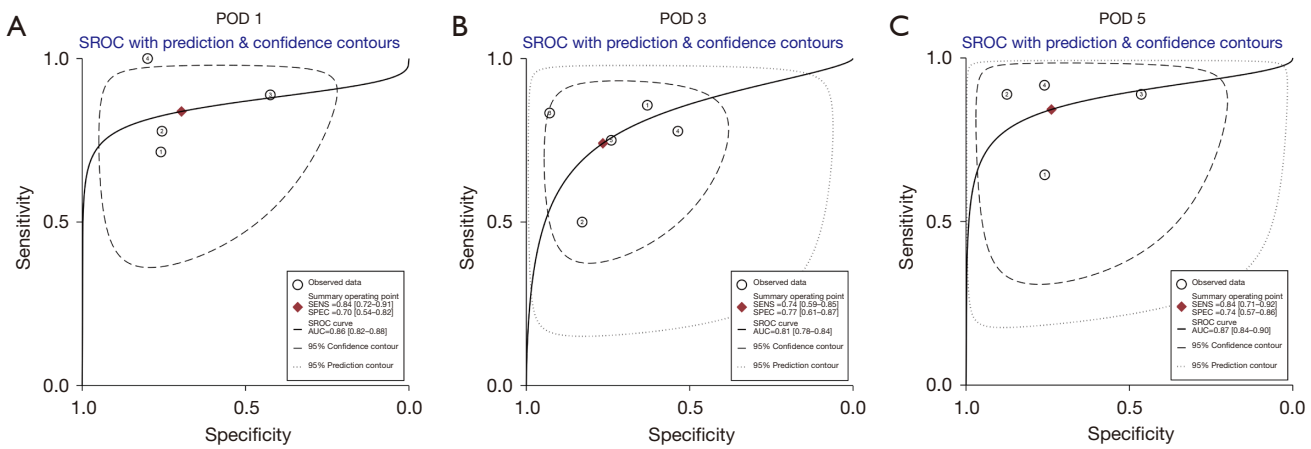

Figure 4 ROC curve plots for the diagnostic accuracy of PCT levels on POD 1, 3, 5 for POPF. ROC, receiver operating characteristic; PCT, procalcitonin; POD, postoperative day; POPF, postoperative pancreatic fistula; SROC, summary receiver operating characteristic.

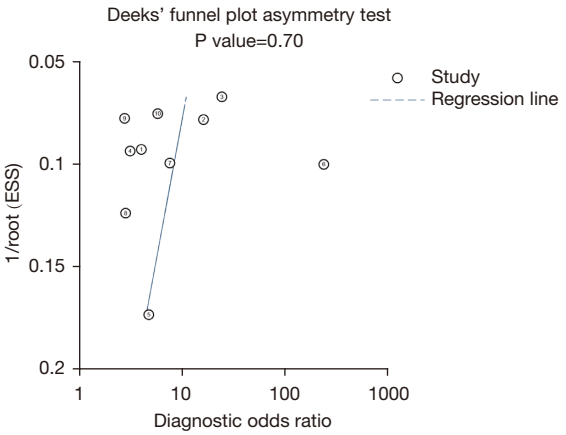

Figure 5 Deeks' funnel plot asymmetry test for the evaluation of publication bias.

Acknowledgments

Funding: This work was supported by research grants from the science and technology plan project for research and development in Chengde (No. 201804A039).

Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://dx.doi.org/10.21037/gs-21-658

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/gs-21-658). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: L. Roberts)

Cite this article as: Chen G, Yi H, Zhang J. Diagnostic value of C-reactive protein and procalcitonin for postoperative pancreatic fistula following pancreatoduodenectomy: a systematic review and meta-analysis. Gland Surg 2021;10(12):3252-3263. doi: 10.21037/gs-21-658