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ORIGINAL ARTICLE

Drain Fluid Amylase Versus C-Reactive Protein for Predicting Clinically Relevant POPF: a Meta-Analysis

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ABSTRACT

Background: **This study aimed to compare the diagnostic performance of drain fluid amylase (DFA) and serum C-reactive protein (CRP) for predicting clinically relevant postoperative pancreatic fistula (CR-POPF) after pancreatic resection through a classification diagnostic meta-analysis.**
Methods: **Following PRISMA-DTA guidelines, PubMed, Embase, the Cochrane Library, and Web of Science were systematically searched throughout June 2025. Studies reporting 2 x 2 diagnostic accuracy data for DFA or CRP based on ISGPS 2016 POPF definitions were included. Pooled sensitivity and specificity were estimated using a bivariate random-effects model. A biomarker indicator (DFA vs. CRP) was incorporated into meta-regression to assess comparative performance. Heterogeneity (τ^2, I^2) and publication bias (Deeks' test) were evaluated.**
Results: **Twenty-two studies involving 4,203 patients were included (12 DFA, 10 CRP). Pooled sensitivity and specificity were 0.76 (95% CI 0.68 - 0.82) and 0.81 (95% CI 0.73 - 0.86) for DFA and 0.74 (95% CI 0.66 - 0.80) and 0.78 (95% CI 0.69 - 0.84) for CRP. Diagnostic odds ratios were 6.60 and 5.19, respectively. The summary SROC AUC was 0.83 (95% CI 0.80 - 0.86). Meta-regression revealed no significant difference between DFA and CRP (p = 0.606). Heterogeneity was moderate (I^2 = 32.8%), and no publication bias was detected.**
Conclusions: **DFA and CRP demonstrate comparable diagnostic accuracy for predicting CR-POPF. Combined postoperative monitoring may enhance early identification of high-risk patients and improve management strategies.**
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KEYWORDS

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INTRODUCTION

Postoperative pancreatic fistula (POPF) remains one of the most challenging complications after pancreatic resection and contributes substantially to postoperative morbidity and mortality [1,2]. Despite improvements in surgical techniques and perioperative care, the incidence of clinically relevant POPF (CR-POPF) remains between 10 - 30% [1]. POPF can lead to intra-abdominal abscess, hemorrhage, and sepsis, emphasizing the need for early and accurate diagnostic tools.
Drain fluid amylase (DFA) is a direct biochemical indicator of pancreatic leakage and reflects the presence of

activated enzymes in postoperative drainage [3]. Elevated DFA within postoperative days (POD) 1 - 3 has been repeatedly associated with CR-POPF [3,17]. Meanwhile, serum C-reactive protein (CRP), an acute-phase reactant induced by interleukin-6, serves as a systemic inflammatory marker and is widely used to detect postoperative infectious complications [4,19].

Although both biomarkers have been individually evaluated, their comparative diagnostic performance remains unclear due to inconsistent cutoff values, measurement timing, and assay variability across studies [5-8]. Prior meta-analyses focused on single markers and did not directly compare DFA and CRP within a unified framework [7,8].

Therefore, we aimed to perform a classification diagnostic meta-analysis to directly compare the diagnostic performance of DFA and CRP for predicting clinically relevant POPF after pancreatic surgery. By pooling studies according to biomarker type and evaluating differences within a unified bivariate statistical framework, we sought to clarify whether either marker provides superior accuracy and to determine whether heterogeneity in assay methods or cutoff values affects diagnostic performance.

MATERIALS AND METHODS

Search strategy and study selection

This systematic review and meta-analysis adhered to the PRISMA-DTA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies) guidelines [10]. A comprehensive search was conducted in PubMed, Embase, Cochrane Library, and Web of Science databases throughout June 2025, using a combination of the following keywords: "pancreatic fistula," "drain amylase," "C-reactive protein," "CRP," "diagnosis," and "accuracy." The inclusion criteria were the following:

Clinical studies evaluating DFA and/or CRP for predicting POPF after pancreatic resection; sufficient data to construct 2 x 2 contingency tables (true positive, false positive, false negative, true negative); POPF defined according to the 2016 International Study Group on Pancreatic Surgery (ISGPS) criteria (Grades B/C) [1]; human studies published in English.

Exclusion criteria encompassed non-original studies (e.g., case reports, letters to the editor), animal experiments, studies with fewer than 10 patients, and those lacking the necessary data for calculating sensitivity and specificity. Two reviewers independently screened titles and abstracts, followed by a full-text review of potentially eligible articles. Any discrepancies were resolved through discussion or by consultation with a third reviewer.

Data extraction and quality assessment

From each included study, the following data were extracted: first author, publication year, country of origin, type of surgical procedure (e.g., pancreaticoduodenectomy, distal pancreatectomy, or mixed), sample size, biomarker cutoff value, assay type, postoperative day of measurement, and diagnostic outcomes (TP, FP, FN, TN).

The methodological quality of each study was assessed using the QUADAS-2 tool [11], which evaluates four key domains: 1) patient selection, 2) index test, 3) reference standard, and 4) flow and timing. Each domain was rated as having a "low," "high," or "unclear" risk of bias. Two reviewers independently performed the quality assessment, and any disagreements were resolved by consensus.

Statistical analysis

All statistical analyses were performed using R software (version 4.3.2) with the mada, metafor, and meta packages. Diagnostic accuracy measures were synthesized using the Reitsma bivariate random-effects method [12]. The diagnostic odds ratio (DOR) was calculated for each study as (TP x TN)/(FP x FN). Heterogeneity was quantified using τ^2 and I^2 following established recommendations [13]. Meta-regression was conducted to explore potential sources of heterogeneity, including assay type (e.g., ELISA vs. automatic biochemical analyzer), cutoff value (using common clinical thresholds: $< 5{,}000$ vs. $\geq 5{,}000$ IU/L for DFA, and < 150 vs. ≥ 150 mg/L for CRP), and study sample size (< 100 vs. ≥ 100 patients). Publication bias was evaluated using Deeks' funnel plot asymmetry test [14], with a p-value < 0.05 indicating significant bias. This approach accounts for the inherent correlation between sensitivity and specificity across studies.

All pooled estimates are reported with their 95% confidence intervals (CI).

RESULTS

Study selection

The initial search identified 1,149 records. After removing duplicates and screening titles and abstracts, 22 studies met the inclusion criteria and were included in the final quantitative synthesis. Among these, 12 studies assessed DFA, 10 assessed CRP, and 3 studies reported data for both markers independently. The study selection process is detailed in the PRISMA flowchart (Figure 1).

Study characteristics

The 22 included studies, published between 2012 and 2024, involved a total of 4,203 patients who underwent pancreatic surgery. The cutoff values for DFA ranged from 1,000 to 5,000 IU/L, with 3,000 IU/L being the most frequently used. For CRP, cutoff values ranged from 100 to 200 mg/L, with a median of 150 mg/L. Most studies measured DFA on postoperative days (POD) 1 - 3 and CRP on POD 3 - 5. The key characteristics and diagnostic performance parameters of the in-

Table 1. Study characteristics and individual diagnostic performance parameters.

Marker	k	DOR	AUC	Tau^2	Deeks p
DFA	12	6.60	0.720	1.016	0.498
CRP	10	5.19	0.695	0.774	0.391

DOR: diagnostic odds ratio, AUC: area under the curve.

Table 2. Key p-value from meta-regression (CRP vs. DFA).

Test	p-value
Marker effect (CRP vs. DFA)	0.606

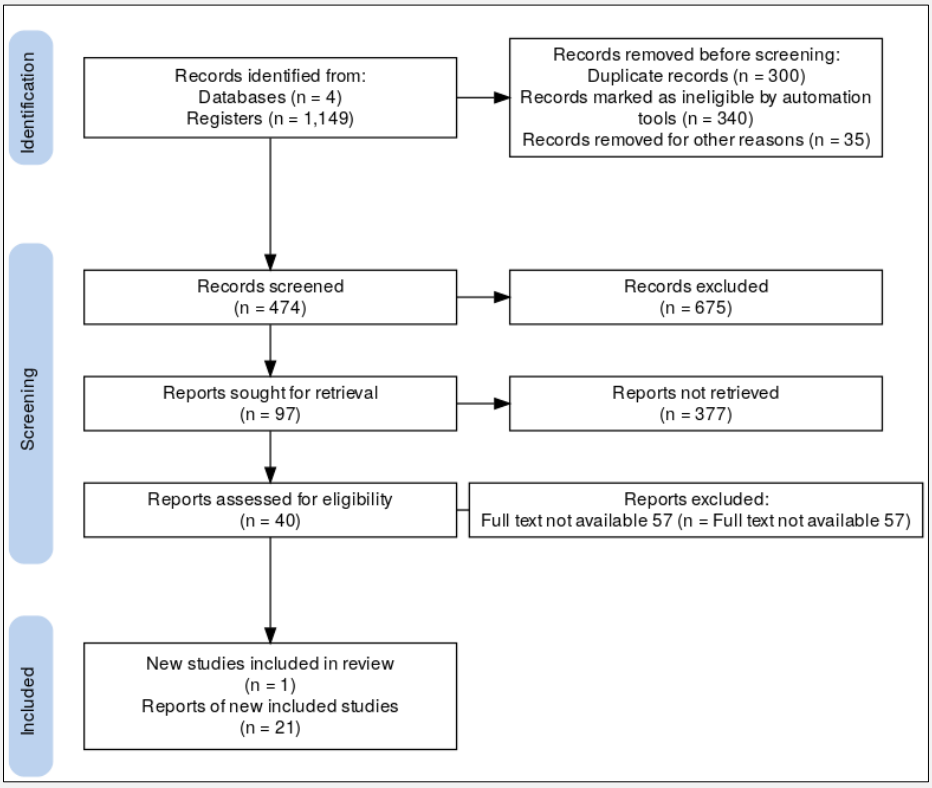


Figure 1. PRISMA 2025 flow diagram of study selection.

cluded studies are summarized in Table 1. Key p-values from comparative analyses are provided in Table 2. Table 1 reports model-based AUC estimates for individual markers, whereas the summary AUC (0.83) reflects the global SROC curve derived from the full classification model.

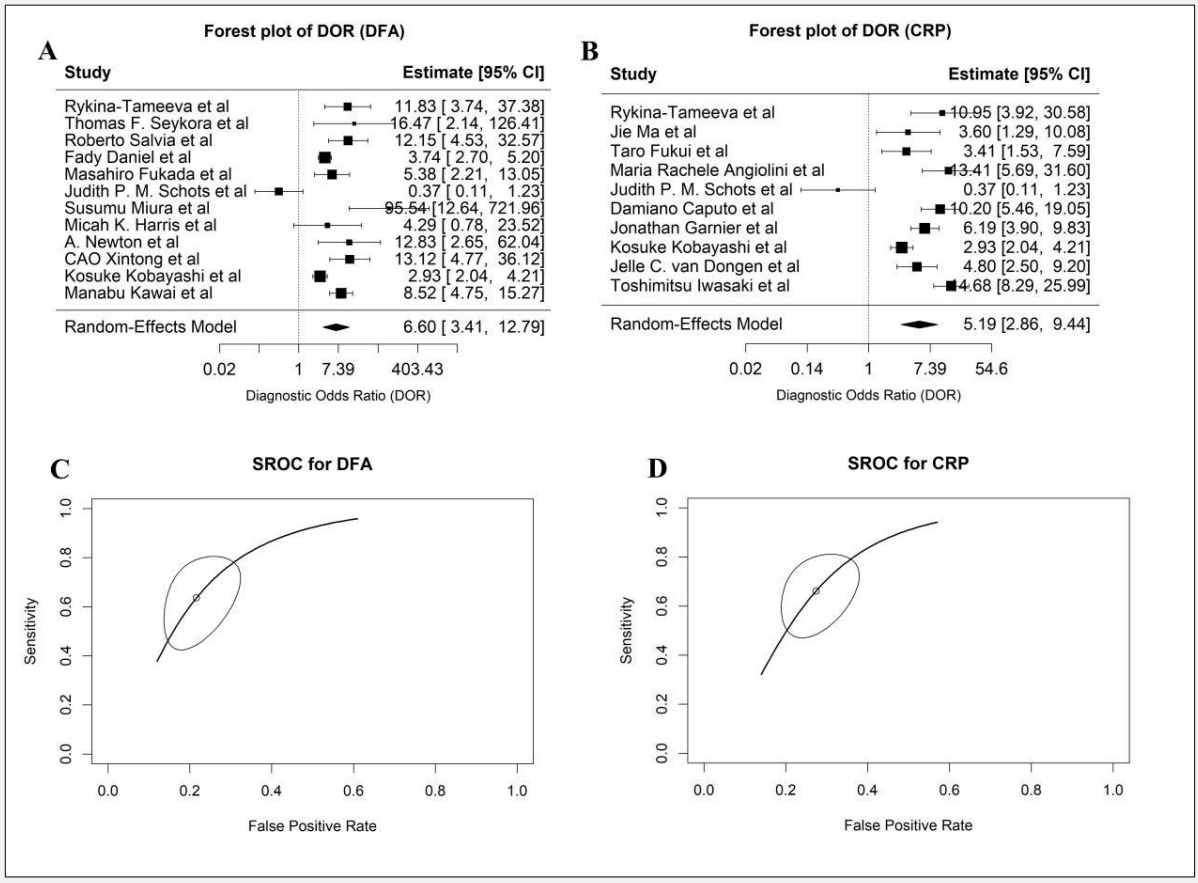


Figure 2A - D. Forest plots and SROC curves of pooled sensitivity and specificity for DFA (A, C) and CRP (B, D).

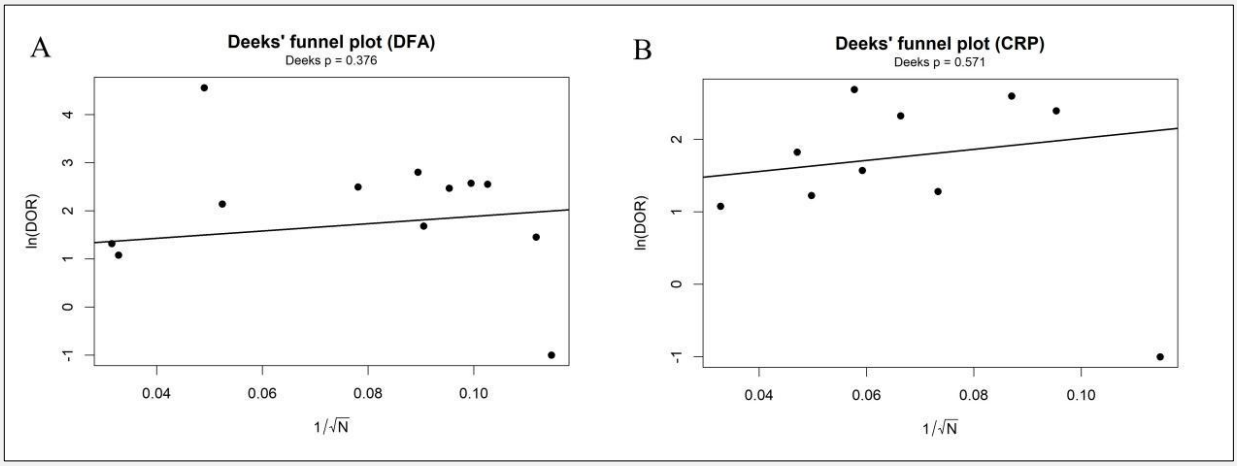


Figure 3. Deeks' funnel plot for assessing publication bias for DFA (A) and CRP (B).

Pooled diagnostic accuracy

For DFA, the pooled sensitivity was 0.76 (95% CI: 0.68 - 0.82) and the pooled specificity was 0.81 (95% CI: 0.73 - 0.86). For CRP, the pooled sensitivity was 0.74 (95% CI: 0.66 - 0.80) and the pooled specificity was 0.78 (95% CI: 0.69 - 0.84). The pooled diagnostic odds ratios were 6.6 (95% CI: 3.41 - 12.79) for DFA and 5.19 (95% CI: 2.86 - 9.44) for CRP (Figure 2A - B). The overall summary AUC was 0.83 (95% CI: 0.80 - 0.86), indicating excellent diagnostic differentiation. Heterogeneity across studies was moderate (I^2 = 32.8%). The estimated correlation between logit sensitivity and logit (1 - specificity) was -0.17, suggesting a mild negative dependence (Figure 2C - D).

Meta-regression and subgroup analysis

Meta-regression revealed no statistically significant difference in diagnostic performance between DFA and CRP ($p = 0.606$). Subgroup analyses based on cutoff values, assay methods, and sample sizes did not identify any significant modifiers of diagnostic accuracy (all $p > 0.10$). However, studies with smaller sample sizes (< 100 patients) tended to exhibit wider confidence intervals and greater heterogeneity (Table 2).

Publication bias

Deeks' funnel plot asymmetry test yielded p-values of 0.376 for DFA and 0.571 for CRP, indicating no significant publication bias (Figure 3A - B).

DISCUSSION

This diagnostic meta-analysis demonstrates that both drain fluid amylase (DFA) and C-reactive protein (CRP) exhibit strong and comparable diagnostic performance for predicting postoperative pancreatic fistula (POPF) following pancreatic resection. The pooled AUC of 0.83, coupled with diagnostic odds ratios in the range of 5 - 7 for both biomarkers, indicating moderate-to-high differentiation ability underscores their excellent overall differentiation ability [15]. The observed sensitivity (approximately 0.75) and specificity (approximately 0.80) for both markers indicate robust accuracy suitable for postoperative risk stratification. This classification diagnostic meta-analysis demonstrated that DFA and CRP exhibit similar diagnostic performance for predicting CR-POPF, consistent with earlier findings for individual biomarkers [7,8,16]. Notably, the observed heterogeneity across studies was moderate (I^2 = 32.8%), suggesting a relative consistency in diagnostic trends despite variations in assay methods and cutoff values.

The biological rationale for their comparable performance lies in the dual nature of POPF: DFA reflects local enzymatic leakage [3,17]. Elevated DFA levels on postoperative days 1 - 3 have been consistently associated with the development of clinically relevant fistulae (ISGPS Grade B/C) [18]. In contrast, CRP reflects systemic inflammation triggered by pancreatic leakage complications [4,19]. Our results indicate that both markers possess similar diagnostic accuracy, suggesting that systemic inflammation parallels local enzymatic leakage in clinically significant cases. This biological complementarity may explain why combining DFA and CRP could improve early detection sensitivity without compromising specificity [20].

Previous meta-analyses focusing solely on DFA reported pooled AUCs between 0.82 and 0.87 [7,21], which aligns closely with our estimate of 0.83. Similarly, studies evaluating CRP reported comparable accuracy ranges (AUC ≈ 0.80) [8,22]. However, most prior works analyzed each marker independently, without adjusting for inter-marker variance or study-level covariates. Our mixed-model approach, which pools all available evidence under a common variance-covariance structure, minimizes bias arising from cross-study heterogeneity and enables a direct statistical comparison [9,12]. Moreover, the non-significant result in our meta-regression ($p = 0.606$) statistically confirms that DFA and CRP perform equivalently in predicting clinically relevant POPF.

The between-study heterogeneity was moderate (I^2 = 32.8%), primarily attributable to variability in cutoff values and the postoperative timing of measurement. Studies employing higher DFA thresholds (> 5,000 IU/L) or later CRP measurements (POD ≥ 5) tended to yield slightly higher specificities at the cost of lower sensitivities, indicating potential for optimization through dynamic monitoring at multiple time points [23]. The absence of significant small-study effects in Deeks' tests further supports the robustness of our pooled estimates. Sensitivity analyses excluding studies rated as having a higher risk of bias according to QUADAS-2 did not materially alter the pooled AUC or DOR values.

Our findings have meaningful implications for postoperative management. DFA can be readily obtained from surgical drains, providing an early warning signal within 24 - 48 hours after surgery [3]. CRP, routinely measured in most clinical centers, offers a convenient complementary indicator of systemic inflammatory stress [4]. Combined biochemical monitoring of both markers may therefore enable more accurate and earlier identification of patients at high risk for clinically relevant POPF, facilitating tailored management strategies such as prolonged drainage or intensified imaging surveillance [20,24]. In practical terms, a DFA cutoff of 3,000 IU/L and a CRP cutoff of 150 mg/L on POD 3 appear to offer an optimal balance between sensitivity and specificity for clinical decision-making [17,19].

Looking ahead, the integration of DFA and CRP into machine learning-based predictive algorithms holds promise for further refining postoperative risk assessment [25]. Emerging studies that combine biochemical, radiologic, and intraoperative features suggest that artificial intelligence (AI) models, particularly those utilizing gradient boosting or deep learning, can identify

complex, nonlinear patterns predictive of POPF earlier than conventional cutoff-based approaches [25,17]. The robust, pooled evidence generated by this meta-analysis provides a solid foundation for the training and validation of such models. Prospective multicenter trials that integrate these biomarkers with imaging data and patient-specific factors are warranted to construct explainable AI frameworks for real-time POPF prediction. Such integration may ultimately reduce postoperative morbidity through earlier and more precise risk stratification. Taken together, these findings highlight the complementary diagnostic roles of DFA and CRP and support their combined use in clinical algorithms.

Several limitations of this study must be acknowledged. First, the majority of included studies were retrospective and single-centered, which may introduce selection bias. Second, variations in the definition of POPF prior to the widespread adoption of the ISGPS 2016 criteria could affect diagnostic consistency across earlier studies [1]. Third, heterogeneity in assay methods and sampling timing limited the precision of our subgroup analyses. Finally, the relatively smaller number of studies evaluating CRP alone reduced the statistical power for detecting subtle differences between the two biomarkers. Despite these limitations, the stability of our pooled estimates and the absence of significant publication bias support the reliability of our conclusions.

CONCLUSION

Both drain fluid amylase and C-reactive protein are reliable and complementary biomarkers for predicting postoperative pancreatic fistula after pancreatic resection. Their pooled diagnostic performance (AUC = 0.83, DOR > 20), coupled with moderate heterogeneity, confirms their clinical utility. Routine dual-marker monitoring could enhance early risk stratification, thereby enabling individualized postoperative management. Future integration of these biomarkers into AI-assisted predictive systems may represent the next step toward precision perioperative care in pancreatic surgery.

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Declaration of Generative AI in Scientific Writing:
The author declares that no Generative Artificial Intelligence tools were used to generate scientific content or to analyze or interpret data. Any assistance provided by AI tools was limited to language polishing and did not influence the scientific conclusions of this study.

Declaration of Interest:
The author declares no conflict of interest.

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