

Predictive value of drain pancreatic amylase concentration for postoperative pancreatic fistula on postoperative day 1 after pancreatic resection

An updated meta-analysis

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Abstract

Background: Postoperative pancreatic fistula (POPF) is a potentially fatal complication following pancreaticoduodenectomy. Early prediction and exclusion of POPF may be highly advantageous to enhance patient outcomes, and accelerate recovery. In this meta-analysis, we sought to assess the prediction of drain pancreatic amylase concentration on postoperative day 1 (DPA1) for POPF.

Methods: By searching online databases up to April 2018, all researches mentioned DPA1 for detecting POPF were analyzed. STATA 12.0 was used to analyze pooled predictive parameters.

Results: Seventeen studies were finally analyzed including 4676 patients in total. The pooled sensitivity and specificity of DPA1 were respectively 0.85 (95% CI: 0.71, 0.93), 0.80 (95% CI: 0.74, 0.85) to predict overall POPF, and 0.70 (95% CI: 0.53, 0.82), 0.88 (95% CI: 0.86, 0.90) to predict CR-POPF. If pretest probability was 50%, corresponding post-test (+) were respectively 81%, 86% for overall POPF and CR-POPF when DPA1 was above cutoffs, while the post-test (−) were respectively 16%, 26% when DPA1 was under cutoffs. In subgroup analysis, sensitivities of cutoff >5000 group, 1000 < cutoff <5000 group, and cutoff <1000 group were respectively 0.65 (0.43–0.82), 0.82 (0.71–0.89), 0.87 (0.78–0.92); and specificities were respectively 0.88 (0.83–0.92), 0.83 (0.77–0.88), 0.71 (0.62–0.79). Positive LR was 5.5 (3.4–8.8), 4.8 (3.4–6.7), and 3.0 (2.3–4.0) respectively. Negative LR was 0.40 (0.22–0.72), 0.22 (0.13–0.37), and 0.19 (0.11–0.32) respectively.

Conclusion: DPA1, which has good sensitivity and specificity, is useful for predicting overall POPF and CR-POPF, according to the present studies. Meanwhile, it should be cautious to apply because there is a wide range in cutoffs between different studies.

Abbreviations: DPA1 = drain pancreatic amylase concentration on postoperative day 1, I^2 = inconsistency index, ISGPF = International Study Group on Pancreatic Fistula, LR = likelihood ratio, PD = pancreaticoduodenectomy, POPF = postoperative pancreatic fistula, QUADAS = Quality Assessment of Diagnostic Accuracy Studies.

Keywords: drain pancreatic amylase concentration on postoperative Day 1, meta-analysis, pancreatic resection, postoperative pancreatic fistula, predictive value

1. Introduction

Although perioperative management of patients undergoing pancreatoduodenectomy (PD) has been improved, morbidity still ranges from 20% to 50%.^[1–4]

Postoperative pancreatic fistula (POPF), which develops in a range from 16% to 28% of patients undergoing PD, remains the

major fatal complication.^[5–7] POPF was classified to grades A, B, and C by the International Study Group on Pancreatic Fistula (ISGPF).^[8] Grade A POPF is biochemical fistula, which does not have any adverse consequences. Grade B and C fistulas are generally designated as clinically relevant POPF (CR-POPF), which usually demand percutaneous drainage and hardly, laparotomy.^[8]

So far, it has been proved that early drain removal (postoperative day (POD) <4) decreases incidence of complications, compared with late drain removal (POD >5).^[9] Usually, drains will be removed according to surgeon's discretion after excluding the risk of POPF. The prognosis of POPF can be advantageous to manage drains removal, enhance recovery pathway, and promote hospital discharge.^[9,10]

Recently, many studies show high interests in drain pancreatic amylase concentration on POD 1 (DPA1) for the prediction of POPF. Although DPA1 has been implied with superb specificity and sensitivity for overall POPF and CR-POPF, there is still controversy in inconsistent opinions. The present meta-analysis especially aims to assess the value of DPA1 to predict POPF after PD.

2. Methods

The PRISMA statement and appropriate methods for meta-analysis were followed.^[11,12] The ethical statement is not necessary for this meta-analysis.

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2.1. Study selection

MEDLINE (PubMed), Cochrane Database, Embase, and other databases were retrieved to find out corresponding papers published until April 2018. The following items were searched: “pancreatectomy,” “pancreaticoduodenectomy,” “whipple,” “pancreatic resection,” “pancreatic fistula,” “drain amylase,” “intraperitoneal drainage amylase,” “early drain removal,” “sensitivity and specificity.” Two researchers independently reviewed the articles. When disagreements appeared, a final consensus was reached after arguing with each other.

2.2. Inclusion and exclusion criteria

Studies were selected by inclusion criteria as follows: prediction of DPA1 for POPF after PD; POPF recorded and defined as grade A, B, and C according to ISGPF; articles published in English language in peer-reviewed journals. Editorials, case reports, expert opinions, letters, abstracts, and studies without sufficient data to assess predictive value of DPA1 were excluded.

2.3. Quality assessment

The QUADAS criteria was accorded to evaluate qualities of involved studies.^[13]

2.4. Data collection and statistical analysis

Data including sensitivity, specificity, and cutoff values of DPA1 for the prediction of POPF or CR-POPF were documented.

STATA 12.0 was used for statistical analysis. The following figures were calculated: sensitivity, specificity, positive likelihood ratio (LR), negative LR (with corresponding 95% confidence interval), pretest probabilities, corresponding post-test probabilities, Cochran Q test, inconsistency index (I^2), and area under the receiver operating characteristic curve (AUROC). Deeks funnel plot asymmetry test was performed to assess publication bias.

Two investigators (Y Liu and Y Li) independently extracted the data, and disagreements were settled by discussion with each other.

3. Results

3.1. Description of studies

Finally, 17 articles with a total of 4676 patients in 8 countries were involved.^[5,14–29] The procedure of selection is illustrated in Fig. 1. The information of the involved 17 studies is displayed in Table 1. There are 11 prospective and 6 retrospective studies. Diagnostic index of studies assessing prediction of DPA1 for overall POPF and CR-POPF is integrated in Table 2. Twelve studies supplied cutoffs for overall POPF, extending from 100 to 5000 U/L, while 6 for CR-POPF ranging from 1000 to 5000 U/L. And there were no significantly threshold effects of DPA1 for overall POPF and CR-POPF.

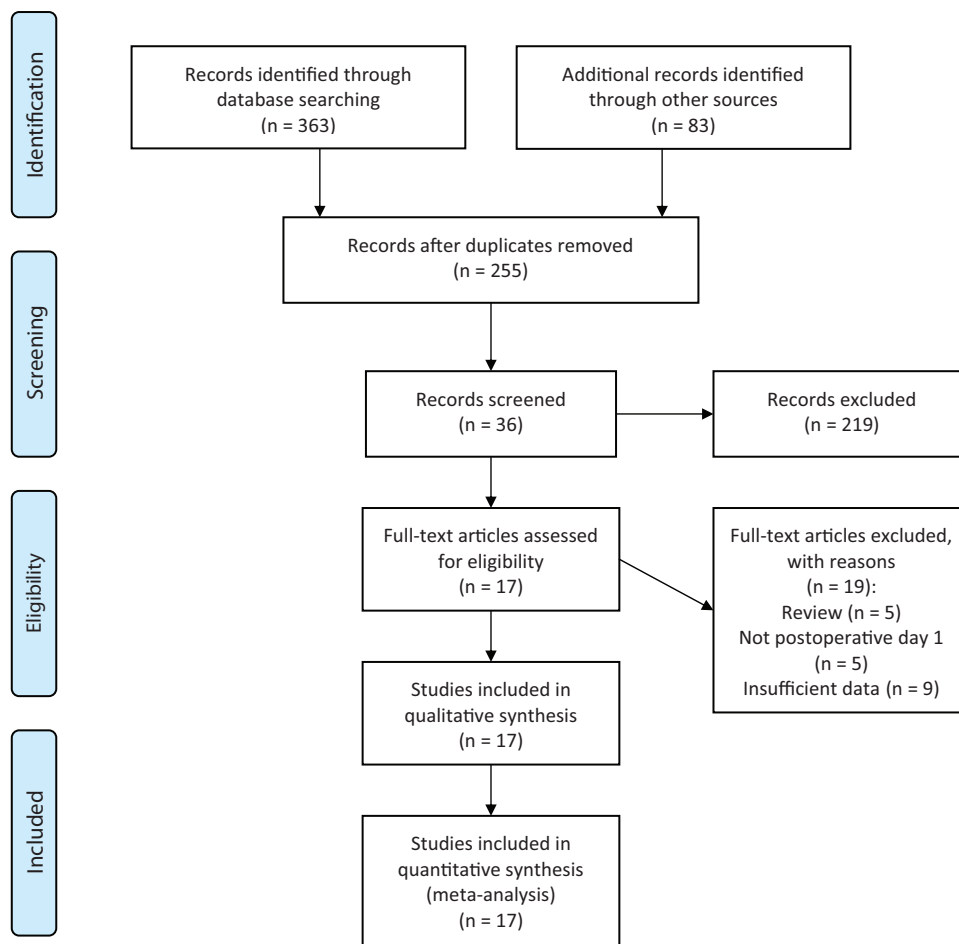


Figure 1. Flowchart showing literature search and selection.

Table 1**Characteristics of the selected studies.**

Author	Country	Years	N	Gender (M/F)	Settings	Pathology	T	Stent	Pancreatic soft texture
Ansorge ^[5]	Sweden	2008–2012	315	174/141	Prospective	44 benign; 271 malignant	PD	Nonstented	NR
Zelga ^[14]	UK	2002–2012	405	218/187	Prospective	263 malignant; 142 other	PD	Internal	NR
Yamane ^[15]	Japan	2006–2016	99	69/30	Retrospective	59 malignant; 40 other	PD	NR	43
Nissen ^[16]	America	2007–2010	76	40/36	Prospective	33 PDAC; 43 other	PD	NR	27
Takeishi ^[17]	Japan	2005–2013	120	61/59	Retrospective	46 cancer; 74 other	PD	NR	55
Dugalic ^[18]	Serbia	2005–2012	382	231/151	Prospective	74 benign; 308 malignant	PD	NR	84
Casadei ^[19]	Italy	2015–2017	84	43/41	Prospective	44 malignant; 40 other	PD	NR	50
Israel ^[20]	America	2010–2012	63	30/33	Prospective	45 PDAC; 18 Unclear	54 PD; 9 Other	NR	32
El Nakeeb ^[21]	Egypt	2001–2012	471	278/193	Retrospective	59 benign; 412 malignant	PD	NR	307
Jin ^[22]	China	2012–2014	61	37/24	Prospective	40 biliary; 21 other	PD	External	23
Molinari ^[23]	Italy	2005–2006	137	71/66	Prospective	88 benign; 49 malignant	101 PD; 36 Other	NR	71
Partelli ^[24]	Italy	2011–2012	231	121/110	Retrospective	115 benign; 116 malignant	PD	NR	NR
Maggino ^[25]	America	2012–2017	338	144/194	Retrospective	133 malignant; 205 other	PD	NR	252
Fong ^[26]	America	2009–2012	369	186/183	Prospective	129 benign; 240 malignant	PD	90.4% external	175
Bertens ^[27]	America	2013–2015	216	104/112	Prospective	115 malignant; 101 other	PD	Internal	90
Sutcliffe ^[28]	English	2009–2010	70	39/31	Prospective	14 benign; 56 malignant	PD	NR	NR
Kawai ^[29]	JAPAN	2005–2009	1239	749/490	Retrospective	210 benign; 972 malignant	PD	NR	648

M/F = male/female, N = number of patients, NR = not reported, PD = pancreaticoduodenectomy, PDAC = pancreatic ductal adenocarcinoma, T = type of operation.

Table 2**Diagnostic data evaluating DPA1 for overall POPF (0 vs A+B+C) and CR-POPF (0+A vs B+C).**

Author	0 vs A+B+C			0+A vs B+C		
	Cutoff	Sensitivity (%)	Specificity (%)	Cutoff	Sensitivity (%)	Specificity (%)
Ansorge ^[5]				1322	80	86
Zelga ^[14]	1400	76	70			
Yamane ^[15]				5000	71.4	80.8
Nissen ^[16]	5000	100	93.2			
Takeishi ^[17]	1300	79	81			
Dugalic ^[18]	1200	93.1	87.5	1200	92.3	87.5
Casadei ^[19]				5000	44.1	92
Israel ^[20]	100	96	69			
El Nakeeb ^[21]				1000	71.9	86.5
Jin ^[22]	5000	50	71.1			
Molinari ^[23]	5000	92.6	83.6			
Partelli ^[24]	5000	71	90			
Maggino ^[25]	2000	74.3	62.1			
Fong ^[26]	600	95.7	70.3			
Bertens ^[27]	600	94	60			
Sutcliffe ^[28]	350	100	79			
Kawai ^[29]				4000	62.2	89

3.2. Overall diagnostic indices

Sensitivity and specificity of DPA1 for overall POPF and CR-POPF are displayed in Table 3. For predicting overall POPF, sensitivity and specificity of DPA1 were respectively 0.85 (0.71–0.93) and 0.80 (0.74–0.85), while positive and negative LR were respectively 4.30 (3.24–5.70) and 0.19 (0.10–0.37). AUROC, which was 0.87 (0.84–0.90), is illustrated in Fig. 2A. Cochran Q test showed there was significant heterogeneity of DPA1 ($I^2=97.28\%$, $P<.001$), which implied nonthreshold effects.

For predicting CR-POPF, sensitivity and specificity of DPA1 were respectively 0.70 (0.53–0.82) and 0.88 (0.86–0.90). Positive LR, negative LR, and AUROC were respectively 5.90 (4.90–7.10), 0.34 (0.21–0.55), and 0.89 (0.86–0.92) as in Fig. 2B.

3.3. Fagan plot analysis

In Fig. 3, the Fagan plot in DPA1 for overall POPF^[14,16–18,20,22–28] implied that when the pretest probabilities were respectively 25%, 50%, 75% the positive post-test probabilities (post-test (+)) were 0.59, 0.81, 0.93 and the negative post-test probabilities (post-test (–)) were 0.06, 0.16, 0.36. For CR-POPF^[5,15,18,19,21,29] when the pretest probabilities were respectively 25%, 50%, 75% the post-tests (+) were 0.66, 0.86, 0.95, and the post-tests (–) were 0.10, 0.26, 0.51.

3.4. Meta-regression and subgroup analysis

For the wide range of cutoffs between studies when predicting overall POPF in DPA1, meta-regression analysis was applied to

Table 3**Meta-analysis of predictive data for overall POPF and CR-POPF.**

0 vs A+B+C	Studies	Pooled sensitivity	Pooled specificity	Positive LR	Negative LR	AUROC	Cochran Q Test	I ²	Pretest probability	Post-test (+)	Post-test (-)
DPA1	12	0.85 (0.71–0.93)	0.80 (0.74–0.85)	4.30 (3.24–5.70)	0.19 (0.10–0.37)	0.87 (0.84–0.90)	73.60 (<i>P</i> <.001)	97.28	0.25	0.59	0.06
									0.50	0.81	0.16
									0.75	0.93	0.36
0+A vs B+C	Studies	Pooled sensitivity	Pooled specificity	Positive LR	Negative LR	AUROC	Cochran Q Test	I ²	Pre-test probability	Post-test (+)	Post-test (-)
DPA1	6	0.70 (0.53–0.82)	0.88 (0.86–0.90)	5.90 (4.90–7.10)	0.34 (0.21–0.55)	0.89 (0.86–0.92)	24.16 (<i>P</i> <.001)	92.25	0.25	0.66	0.10
									0.50	0.86	0.26
									0.75	0.95	0.51

AUROC=area under receiver operating characteristic, LR=likelihood ratio.

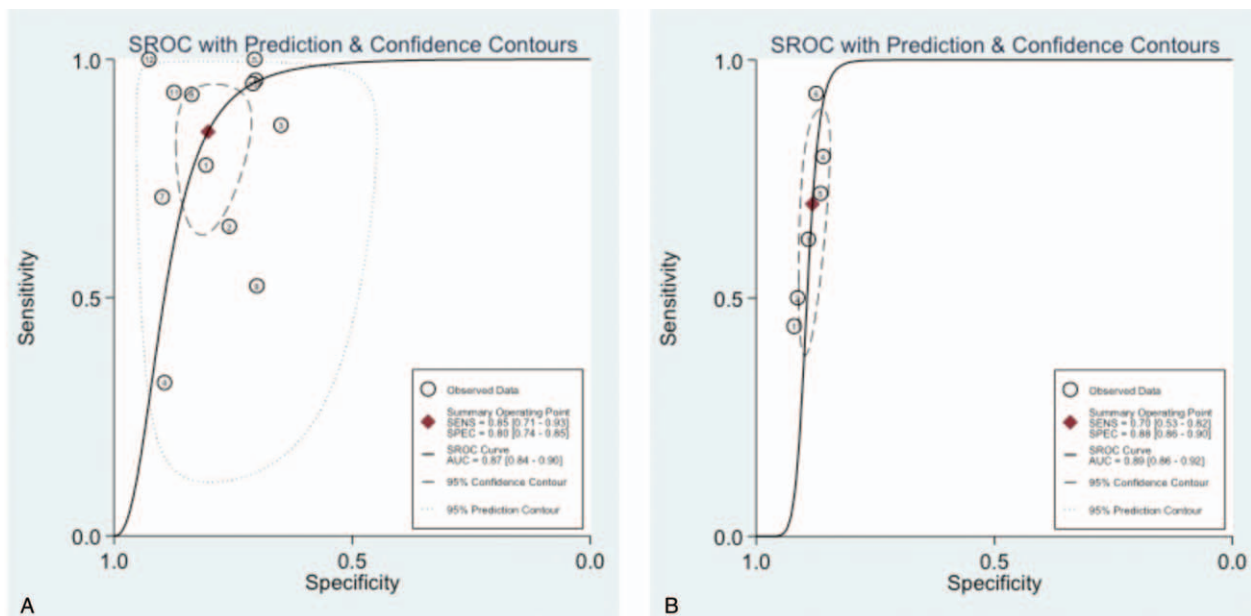


Figure 2. ROC curve analysis of DPA1 for the prediction of POPF (A) overall POPF: AUROC=0.87, 95% CI (0.84, 0.90). B, CR-POPF: AUROC=0.89, 95% CI (0.86, 0.92). AUROC=area under receiver operating characteristic, ROC= receiver operating characteristic, CR=clinically relevant, DPA1 = drain pancreatic amylase concentration on postoperative day 1, POPF = postoperative pancreatic fistula.

find the heterogeneity sources. The “country,” “study setting,” “stent,” “type of operation,” and “pancreatic soft texture” were involved. According to the results, the main sources of heterogeneity were country, type of operation, and pancreatic soft texture.

Huge differences of various cutoffs existed in the involved studies, and then subgroup analysis was performed. Results are demonstrated in supplementary Table 1, <http://links.lww.com/MD/C504>. The summary sensitivities of cutoff ≤ 1000 group, $1000 < \text{cutoff} < 5000$ group, and cutoff ≥ 5000 group were respectively 0.87 (0.78–0.92), 0.82 (0.71–0.89), and 0.65 (0.43–0.82); the summary specificities were respectively 0.71 (0.62–0.79), 0.83 (0.77–0.88), and 0.88 (0.83–0.92). Positive LR were respectively 3.0 (2.3–4.0), 4.8 (3.4–6.7), and 5.5 (3.4–8.8). Negative LR were respectively 0.19 (0.11–0.32), 0.22 (0.13–0.37), and 0.40 (0.22–0.72). AUROC were respectively 0.86

(0.83–0.89), 0.89 (0.86–0.91), and 0.89 (0.86–0.91). The results of Fagan plot analysis show that, in cutoff ≥ 5000 group, when the pretest probabilities were respectively 25%, 50%, 75%, post-test (+) were 0.65, 0.85, 0.94, and post-test (–) were 0.12, 0.28, 0.54; in $1000 < \text{cutoff} < 5000$ group, post-test (+) were 0.61, 0.83, 0.93, and post-test (–) were 0.07, 0.18, 0.40; and in cutoff ≤ 1000 group, post-test (+) were 0.50, 0.75, 0.90, and post-test (–) were 0.06, 0.16, 0.36.

Meta regression was applied to estimate overall sensitivity and specificity, using the various cutoffs among studies as an independent predictor in Fig. 4.

3.5. Publication bias

Deeks funnel plot asymmetry test indicates there is no publication bias among the studies in Fig. 5.

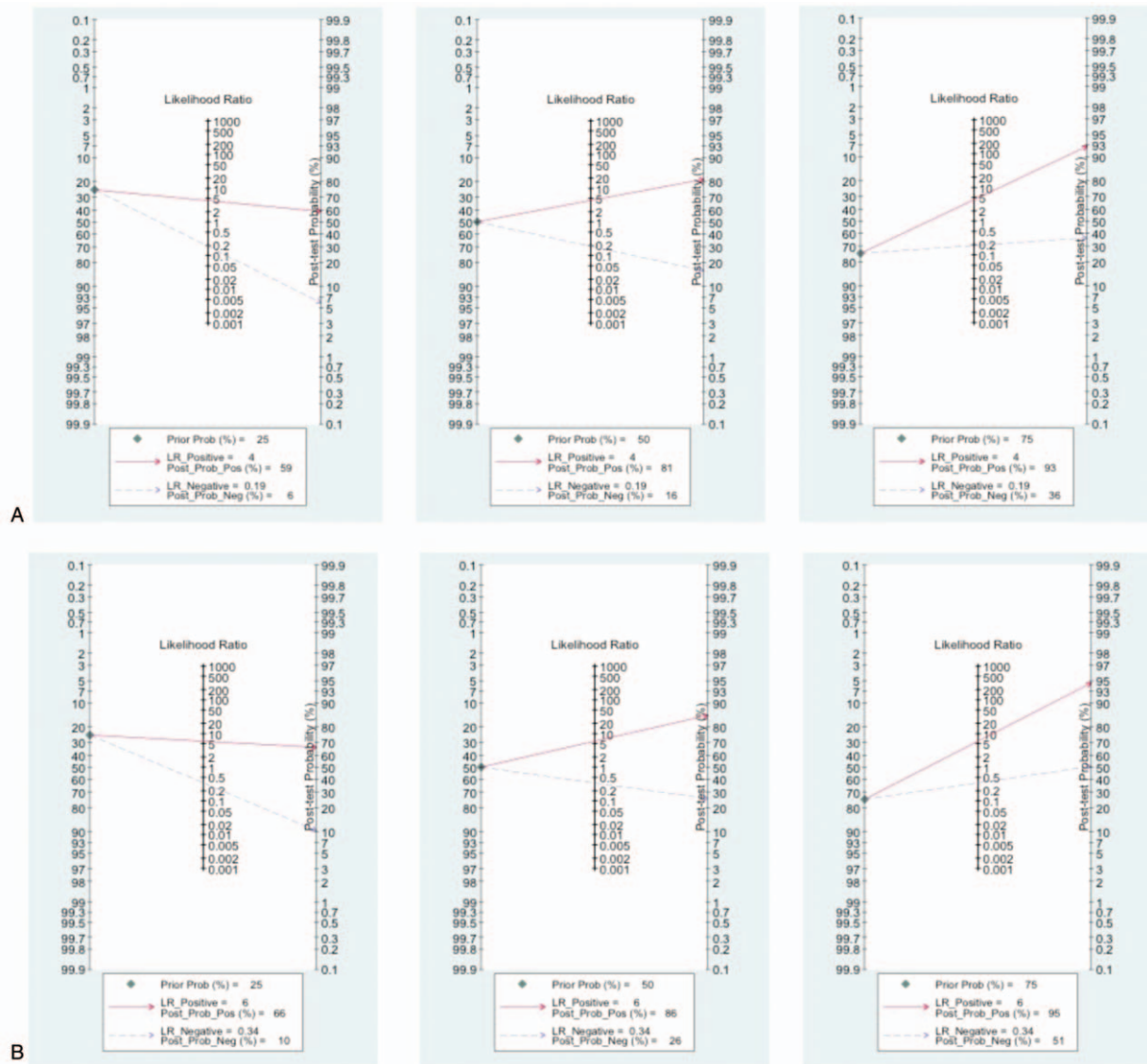


Figure 3. Fagan plot for the assessment of clinical application (A) DPA1 for overall POPF. B, DPA1 for CR-POPF. CR= clinically relevant, DPA1 = drain pancreatic amylase concentration on postoperative day 1, POPF = postoperative pancreatic fistula.

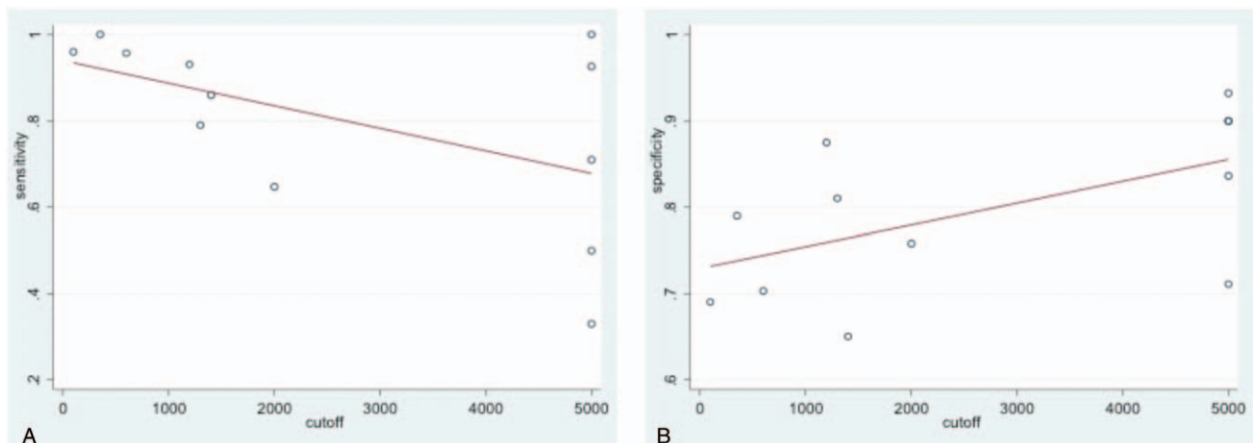


Figure 4. Meta regression of DPA1 for overall POPF (A) sensitivity. B, Specificity. DPA1 = drain pancreatic amylase concentration on postoperative day 1, POPF = postoperative pancreatic fistula.

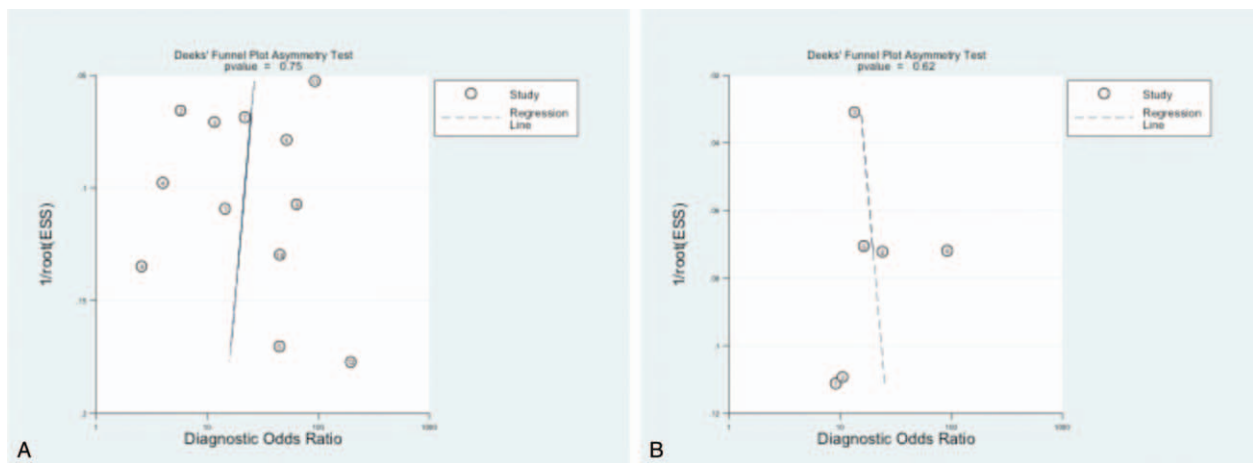


Figure 5. Assessment of publication bias (A) overall POPF. B, CR-POPF. CR = clinically relevant, POPF = postoperative pancreatic fistula.

4. Discussion

POPF is still a potentially fatal complication, which may increase financial utilization after pancreatic resection. There already arise controversies about intraperitoneal drains following PD. In a recent study,^[29] it indicated that early drains removal (POD 4) had significant benefits on decreasing incidence of POPF. Furthermore, in a prospective study with 84 patients who were performed PD, it revealed that it is safe to pull out drains on POD 3 following PD with a lower incidence of POPF in patients with $DPA1 \leq 5000$ U/L.^[19]

Early prediction of POPF can significantly benefit the patient following PD; however, few studies have assessed the predictive accuracy of DPA for developing of POPF.

Several markers, such as DPA, CRP, WBC, have been proposed as predictors for POPF.^[5–7,28,30,31] It was implied by Molinari et al^[23] that $DPA1 > 5000$ U/L had a respectively sensitivity and specificity of 93% and 84% for the prediction of POPF following PD. Besides, Ansorge et al^[5] recommended serum CRP association with DPA to predict CR-POPF. With the comprehensive consideration, this meta-analysis aimed to assess the accuracy of DPA1 for the prediction of POPF. Up to now, there are few studies to assess the pooled performance of DPA1 for overall and clinically relevant POPF.

In this meta-analysis, DPA1 displayed an outstanding capability in identifying POPF with a high positive LR, which could be acted as a rule-in means for the diagnosis of POPF. Meanwhile, it also showed an acceptable sensitivity and specificity. When the pretest probability was set at 50%, DPA1 indicated an accurate diagnosis of overall POPF in 81% patients and misdiagnosis only in 16% patients by Fagan plot analysis, besides, it also showed accuracy for CR-POPF in 86% positive patients and misdiagnosis in 26% patients. With comprehensive consideration of the pooled results, DPA1 is an appropriate marker for the prediction of POPF. Certainly, more randomized controlled trials should be implemented to provide evidence.

In the present study, it supplies beneficial information to help researchers and clinicians to predict POPF by DPA1. However, there are several limitations in this meta-analysis. First, few studies are assessed as high quality to offer unbiased data. Second, studies involved in this meta-analysis had a vast range in cut-off values. Besides, few studies provided specific amylase

range or cutoff at each grade of POPF. Therefore, it is necessary to further explore the values of DPA1 and other markers for predicting the grade of POPF in randomized studies.

It is concluded that DPA1 is a valuable marker to predict POPF, and more randomized controlled trials should be implemented to provide unbiased evidences.

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Author contributions

Y Liu proposed the study. Y Liu and Y Li performed research, collected the data, and wrote the first draft. Y Li and LW analyzed the data. C-JP revised the manuscript. All authors contributed to the design and to further drafts.

Data curation: Yao Liu, Yang Li, Ling Wang.

Software: Ling Wang.

Writing – original draft: Yao Liu, Yang Li.

Writing – review & editing: Ci-Jun Peng.

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