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REVIEW ARTICLE

C-reactive Protein and Procalcitonin Levels to Predict Anastomotic Leak After Colorectal Surgery: Systematic Review and Meta-analysis

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Abstract

Background Anastomotic leak (AL) is a feared complication after colorectal surgery. Prompt diagnosis and treatment are crucial. C-reactive protein (CRP) and procalcitonin (PCT) have been proposed as early AL indicators. The aim of this systematic review was to evaluate the CRP and CPT predictive values for early AL diagnosis after colorectal surgery.

Methods Systematic literature search to identify studies evaluating the diagnostic accuracy of postoperative CRP and CPT for AL. A Bayesian meta-analysis was carried out using a random-effects model and pooled predictive parameters to determine postoperative CRP and PCT cut-off values at different postoperative days (POD).

Results Twenty-five studies (11,144 patients) were included. The pooled prevalence of AL was 8% (95 CI 7–9%), and the median time to diagnosis was 6.9 days (range 3–10). The derived POD3, POD4 and POD5 CRP cut-off were 15.9 mg/dl, 11.4 mg/dl and 10.9 mg/dl respectively. The diagnostic accuracy was comparable with a pooled area under the curve (AUC) of 0.80 (95% CIs 0.23–0.85), 0.84 (95% CIs 0.18–0.86) and 0.84 (95% CIs 0.18–0.89) respectively. Negative likelihood ratios (LR−) showed moderate evidence to rule out AL on POD 3 (LR− 0.29), POD4 (LR− 0.24) and POD5 (LR− 0.26). The derived POD3 and POD5 CPT cut-off were 0.75 ng/ml (AUC = 0.84) and 0.9 ng/ml (AUC = 0.92) respectively. The pooled POD5 negative LR (−0.18) showed moderate evidence to rule out AL.

Conclusions In the setting of colorectal surgery, CRP and CPT serum concentrations lower than the derived cut-offs on POD3-POD5, may be useful to rule out AL thus possibly identifying patients at low risk for AL development.

Keywords C-reactive protein · Procalcitonin · Anastomotic leak · Colorectal surgery

Introduction

Anastomotic leak (AL) is a feared complication after colorectal surgery with a reported incidence ranging from 2 to 17% depending on patient comorbidities, operating surgeon expertise, emergency/elective settings and hospital volume.[1–8] AL has been shown to be associated with increased mortality, prolonged hospital stay, substantial healthcare costs and worsening oncological outcomes (i.e. increased local recurrence).[9–11] Even if several risk factors have been identified for postoperative AL, it remains difficult to predict its development. This is because the onset of AL is insidious with a potential early or late presentation.

Prompt diagnosis and treatment are crucial to potentially limit the related consequences.[12,13] Inflammatory biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) have been proposed as decision-making indicators for patient discharge and proposed for early AL diagnosis.[14–16] CRP has been shown to have a significant correlation with postoperative infectious complications while PCT seems more sensitive and reliable for AL.[17–21] Previous meta-analyses evaluated the predictive value of both CRP and PCT for the development of AL after colorectal surgery.[22–25] However, results were conflicting and heterogeneous. Therefore, since

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the publication of recent studies, a new evidence has become available.

Hence, the aim of the present Bayesian meta-analysis was to perform an updated systematic literature review and investigate the association of postoperative serum CRP/PCT concentrations with AL and assess their predictive role in the early diagnosis of AL after colorectal surgery.

Materials and Methods

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[26] Institutional review board approval was not required. MEDLINE, Scopus, Web of Science, Cochrane Central Library, and ClinicalTrials.gov were used.[27] The last date of search was 28 February 2022. A combination of the following MeSH (Medical Subject Headings) terms was used ("C-reactive protein" (tiab), OR "CRP" (tiab)) AND ("procalcitonin" (tiab), OR "PCT" (tiab)) AND ("leak" (tiab), OR "anastom* leak" (tiab), OR "fistula", OR " dehiscence") AND ("colorec*" (tiab), OR "colon" (tiab), OR "bowel", OR "gastrointestinal") AND ("surgery" (tiab), OR "operation" (tiab)) AND ("laparotomy" (tiab), OR "laparosc*" (tiab), OR "rob*"). All titles were initially evaluated and suitable abstracts extracted. The search was completed by consulting the listed references of each article. The study protocol was registered at the PROSPERO (International prospective register of systematic reviews) (Registration Number: CRD42020220698).

Eligibility Criteria

Inclusion criteria were as follows: (a) comparative studies investigating serum CRP (mg/dl) and PCT (ng/ml) data and their predictive values for AL at different postoperative days (POD) in patients undergoing colorectal surgery with resection and anastomosis; (b) comparative studies reporting data for open and minimally invasive (laparoscopic and robotic) approaches for both benign (i.e. inflammatory bowel disease, symptomatic diverticular disease or other indications) and malignant diseases; (c) English written; (d) when two or more papers were published by the same institution or study group or used the same data-set, or articles with the largest sample size; (e) in case of duplicate studies with accumulating numbers of patients, only the most complete reports were included for quantitative analysis. Exclusion criteria were as follows: (a) studies not reporting the predictive value for postoperative serum CRP and PCT; (b) studies not reporting AL outcome separately from other septic complications; (c) not English-written; (d) abstracts, case reports and case series with less than 10 patients.

Data Extraction

The following data were collected: authors, year of publication, country, study design, number of patients, sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, comorbidities, surgical indication, emergent vs. urgent procedure, surgical approach (open vs. minimally invasive), area under the receiver operating characteristics (ROC) curve, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Furthermore, serum CRP (mg/dl) and CPT (ng/ml) values were collected at different PODs. To obtain a summary graph of postoperative CRP and CPT levels, data reported in the text, graphs or figures of the included studies were used and/or digitalized to obtain the median or mean values. The outcome of interest was AL, which was counted per event and defined as reported in the included studies (Supplementary Table 1). In general, AL was defined as radiological, endoscopic or operative evidence of defect in the enteric wall at the site of the anastomosis. If necessary, corresponding authors were contacted to obtain the missing data if not retrievable from the article. All data were computed independently by four investigators (AA, AS, LC, GB) and compared at the end of the reviewing process. A fifth author (DB) reviewed the database and determined discrepancies.

Outcomes

The primary outcome was the assessment of postoperative serum CPR (mg/dl) values at different intervals (from POD1 to POD5) and its predictive value for AL. The secondary outcome was postoperative serum CPT (ng/ml) assessment at POD3 and POD5 and its predictive value for AL.

Quality Assessment

Three investigators (AA, AS, LC) independently evaluated the methodological quality of the papers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[28,29] This assessed the risk of bias and concerns about applicability by evaluating four key domains: patient selection, index test, reference standard and flow of patients through the study and timing of tests.

Statistical Analysis

Bivariate meta-analysis was conducted using a fully Bayesian approach via integrated nested Laplace approximations (INLA). Compared to traditional meta-analyses, the Bayesian approach takes into account all sources of variation and

reflects these variations in pooled results.[30,31] Furthermore, the Bayesian approach can provide more accurate estimates for small samples.[32] Chu and Cole's bivariate generalized linear mixed effect with exact binomial likelihood model was used to summarize the results of several diagnostic studies by modelling sensitivity and specificity jointly (binomial-normal model).[33] We assume that both sensitivity and specificity were modelled with the same logit link function. Normal prior with zero mean and 100 variance is used for the fixed effects. Variance components of random effect were modelled using penalized complexity priors choosing the parameters believing that the sensitivities or specificities lie in the interval [0.5, 0.95] with probability 0.95, according to Wakefield.[34] The binomial-normal model was also used to calculate the hierarchical summary receiver operating characteristic (HSROC) model according to Rutter et al.[35] Uniform distribution on [−1,1] was the choice for a vague prior of the random effects correlation parameter. Bayesian sensitivity analysis was performed changing the variance component priors. Pooled estimates of likelihood ratios (LR) and diagnostic odds ratio (DOR) were estimated according to Zwinderman and Bossuyt.[36] The geometric mean of the reported CRP and CPT cut-off values at each POD was used to derive the pooled CRP and CPT cut-off values.[19] The pooled prevalence of anastomotic leak was calculated according to Bona et al.[37] Credible intervals (CIs) at 95% were computed. All analyses and figures were carried out using R software package version 3.4.3.[38]

Results

Systematic Review

Twenty-five studies met the inclusion criteria (Figure 1). The results of quality assessment using the QUADAS-2 tool are shown in Figure 2. The applicability of included studies was good. Overall, 11,144 patients were included (range 32–2501). All reports were observational; fifteen were of prospective while ten were of retrospective design. Demographic, clinical and operative variables of the patient sample are shown in Table 1. The age of the patient population ranged from 18 to 93 years, and half were males (55.9%). The preoperative ASA score was reported in ten studies[39–48] and BMI in five studies.[20,41,45,49,50] Elective surgery was performed in 93.3% of patients. Colorectal resections were performed via open (49.1%) and minimally invasive (laparoscopic or robotic) approaches in 50.9%. The type of anastomosis was specified in seven studies[15,21,40,41,51–53] with stapled anastomosis being fashioned in the majority of patients (76.2%). Ileocolic, colocolic and rectal anastomoses were performed in 35.1%, 31.8% and 33.1% respectively. Surgery for cancer was performed in 75.6% of patients with almost

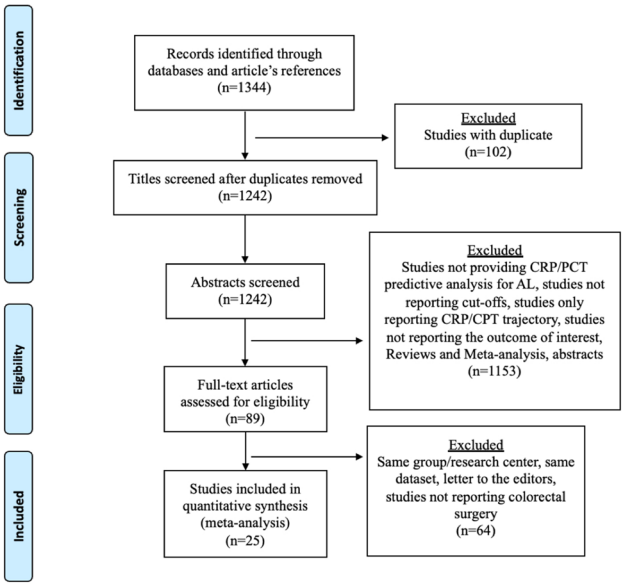

Fig. 1 The Preferred Reporting Items for Systematic Reviews and meta-analyses checklist (PRISMA) diagram

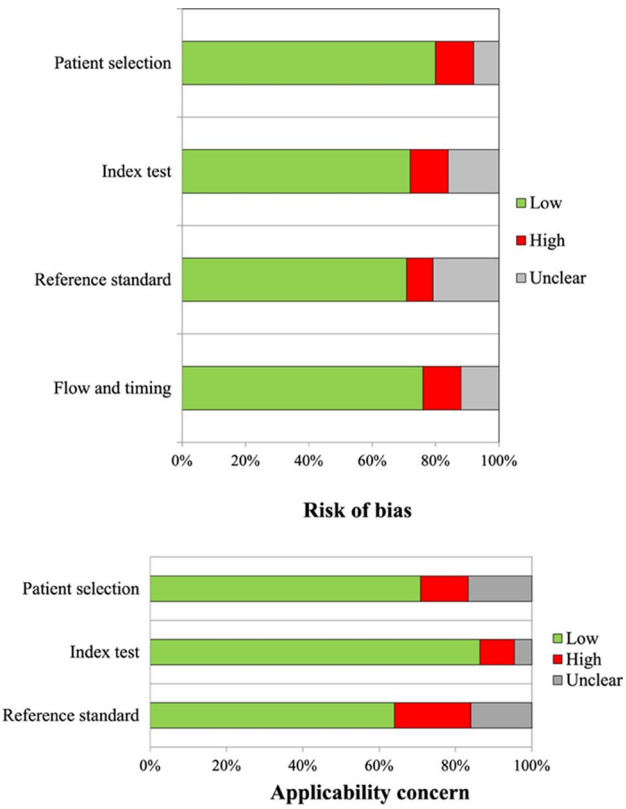

Fig. 2 Quality assessment using the quality of assessment of diagnostic accuracy studies 2 tool (QUADAS-2). Proportion of studies with low (green), high (red), or unclear risk of bias (grey). Data are presented as %

Table 1 Baseline characteristics of the included studies. Data are reported as numbers, mean (± standard deviation), or median (range)

Author	Study design	No. of patients	Age (years)	Sex M/F	BMI (kg/m^2)	Surgery for cancer (no.)	Surgical approach (OPEN/MI)	Elective surgery (no.)	Tumour stage (0/I/II/III/IV)	Anastomosis technique (H/S)	Type anastomosis (ileocolic-colo-colic-rectal)
Korner et al (2009) [39]	Ret	231	71 (18–93)	106/125	nr	146	nr	176	nr	nr	97/87/47
Ortega-Deballon et al. (2010) [51]	Pros	133	65 ± 16	85/48	nr	82	117/16	100	nr	62/52	0/57/78
Warschkow et al. (2011) [49]	Ret	530	66.9 ± 12	nr	25.6 ± 4.4	nr	nr	nr	nr	nr	nr
Platt et al. (2012) [16]	Ret	454	nr	251/203	nr	454	454/0	395	0/62/196/196/0	nr	nr
Almeida et al. (2012) [55]	Ret	173	Leak 69 No leak 65	89/85	nr	129	142/31	164	nr	nr	68/68/35
Lagoutte et al. (2012) [15]	Pros	100	63 (20–87)	58/42	nr	52	65/35	100	nr	43/57	nr
Garcia-Granero et al. (2013) [40]	Pros	205	63.3 ± 15	112/93	nr	150	162/43	205	nr	85/120	58/62/68
Waterland et al. (2016) (OPEN) [56]	Ret	259	69 (18–24)	449/310	nr	nr	259/0	259	nr	nr	75/97/87
Waterland et al. (2016) (MI) [56]	Ret	468			nr	nr	0/468	468	nr	nr	217/57/194
Giaccaglia et al. (2016) [57]	Pros	504	67.6	294/210	nr	nr	126/378	504	nr	nr	178/149/177
Facy et al. (2016) [20]	Pros	501	65.4 ± 14	287/214	26.1 ± 4.9	348	353/149	nr	nr	nr	318/132
Fernandez et al. (2017) (OPEN) [41]	Pros	88	62	46/42	nr	51	88/0	80	nr	26/62	26/36/26
Fernandez et al. (2017) (MI) [41]	Pros	80	65 ± 13	41/39	26.4 ± 3.8	73	0/80	85	nr	13/67	27/09/44
Reynolds et al. (2017) [42]	Pros	211	64.3 ± 1	150/61	nr	211	164/47	211	2/16/36/146/11	nr	0/0/211
Mik et al. (2017) [43]	Pros	724	62.4 ± 12	377/347	nr	724	724/0	724	0/128/256/263/77	nr	188/231/305
Zawadzki et al. (2018) [44]	Pros	32	nr	20, 12	nr	32	18/14*	32	1/4/13/14/0	nr	0/0/32
Munoz et al. (2018) [45]	Pros	134	66.5 (11.2)	73/61	27.4 (4.5)	134	0/134	134	nr	nr	nr
Pantel et al. (2019) [46]	Ret	752	62	346/406	nr	227	197/555	752	nr	nr	259/245/124
Pantoja-Pachajoa et al. (2020) [47]	Ret	116	62 (19–90)	60/56	nr	86	65/51	101	nr	nr	30/63/19

Table 1 (continued)

Author	Study design	No. of patients	Age (years)	Sex M/F	BMI (kg/m^2)	Surgery for cancer (no.)	Surgical approach (OPEN/MI)	Elective surgery (no.)	Tumour stage (0/I/II/III/IV)	Anastomosis technique (H/S)	Type anastomosis (ileocolic-colo-colic-rectal)
Stephensen et al. (2020) [50]	Pros	833	64	380/453	28 ± 6	584	nr	833	nr	nr	353/102/378
Messias et al. (2020) [52]	Ret	90	56.0 (36–68)	50/40	nr	25	nr	64	nr	20/70	39/9/42
iCral study group (2020) [58]	Pros	1546	nr	nr	nr	1064	255/1291	nr	nr	nr	nr
Jin et al. (2021) [54]	Ret	196	nr	126/70	nr	196	0/196	196	0/14/60/122/0	nr	0/0/196
Hernandez et al. (2021) [21]	Pros	2501	67.7 ± 22	1504/997	nr	2065	1237/1264	2333	nr	416/2085	1052/975/474
Baeza-Murcia et al. (2021) [48]	Pros	95	62.9 ± 15	64/31	nr	75	55/40	95	nr	nr	40/30/25
Zaher et al. (2022) [53]	Pros	205	56.4 ± 13	115/90	nr	205	177/28	nr	nr	126/79	61/89/55

OPEN open approach, *MI* minimally invasive approach, *Ret* retrospective design, *Pros* prospective design, *BMI* body mass index, *H* hand-sewn anastomosis, *S* stapled anastomosis, *nr* not reported

*Robotic

one-fourth of procedures being performed for benign diseases (i.e. diverticulitis, inflammatory bowel disease, etc.). Tumour stage was reported in five studies,[16,42–44,54] and the use of neoadjuvant chemoradiotherapy was specified in two studies.[15,42]

The included studies reported measuring CRP and CPT in the postoperative period according to different institutional protocols. The median time to AL diagnosis was 6.9 days (range 3–10). Patients were stratified according to the presence of anastomotic leak (AL group) vs. no AL (no AL group). Overall, 12 studies reported CRP levels on POD1, 13 studies on POD2, 17 studies on POD3, 13 studies on POD4 and 11 studies on POD5. The CRP serum concentration peak was observed on POD3. The pooled postoperative CRP serum levels in the two groups are shown in Figure 3. There was a statistically significant difference comparing the mean CRP concentration between the two groups on POD3 (20.5 vs. 11.5; $p = 0.021$), POD4 (17.8 vs. 9.6; $p = 0.017$) and POD5 (16.3 vs. 7.4; $p = 0.024$). Similarly, eight studies reported serum CPT concentrations on POD3 and 4 studies on POD5. The median PCT concentrations were significantly higher for AL vs. no AL on POD3 (3.7 vs. 0.59; $p = 0.001$) and POD5 (4.25 vs. 0.36; $p < 0.001$).

Bayesian Meta-Analysis

In addition to a systematic review, we performed a study-level fully Bayesian meta-analysis. Considering the random effect bivariate model, the estimated pooled POD3 CRP cut-off, resulting from 17 studies (6807 patients), is 15.9 mg/dl. The estimated pooled AUC is 0.80 (95% CIs 0.23–0.85) (Figure 4A, B, C). The calculated correlation between sensitivity and specificity was 0.09 suggesting no threshold effect. The estimated pooled POD4 CRP cut-off, resulting from 14 studies (7366 patients), is 11.4 mg/dl (Figure 5A, B, C). The estimated pooled AUC is 0.84 (95% CIs 0.18–0.86). The calculated correlation between sensitivity and specificity was −0.13 suggesting no threshold effect. The estimated pooled POD5 CRP cut-off, resulting from 12 studies (3943 patients), is 10.9 mg/dl. The estimated pooled AUC is 0.84 (95% CIs 0.18–0.89) (Figure 6A, B, C). The calculated correlation between sensitivity and specificity was −0.11 suggesting no threshold effect.

The estimated pooled POD3 CPT cut-off, resulting from 9 studies (5791 patients), is 0.75 ng/ml. The estimated pooled AUC is 0.84 (95% CIs 0.18–0.89). The calculated correlation between sensitivity and specificity was −0.59 suggesting the presence of threshold effect. The estimated pooled POD5 CPT cut-off, resulting from 4 studies (1009 patients), is 0.90 ng/ml. The estimated pooled AUC is 0.92 (95% CIs 0.89–0.97). The calculated correlation between sensitivity and specificity was −0.45 suggesting the presence of

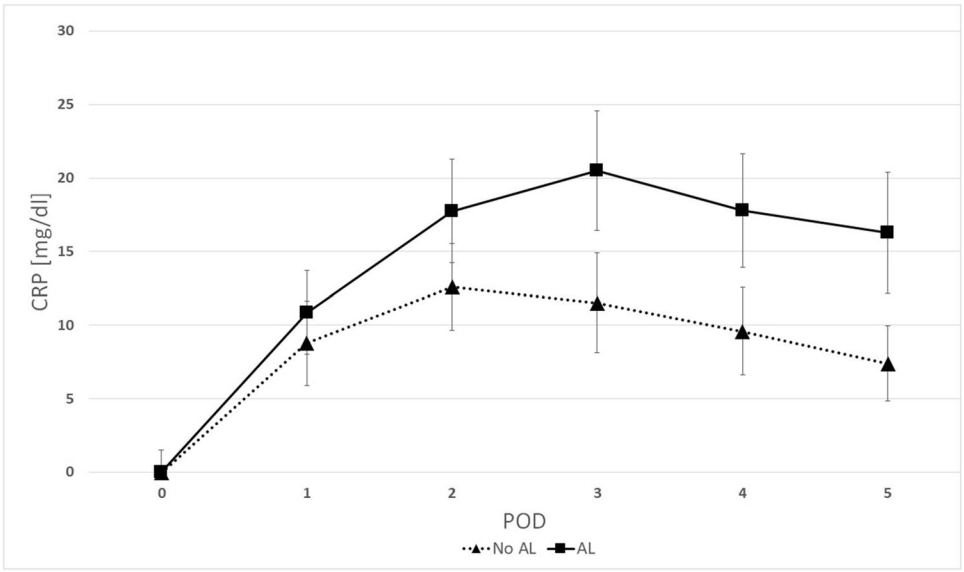

Fig. 3 C-reactive protein (CRP) levels in the postoperative period in the two patient groups at different postoperative day (POD). Values are reported as mean (± standard deviation). AL anastomotic leak. No AL

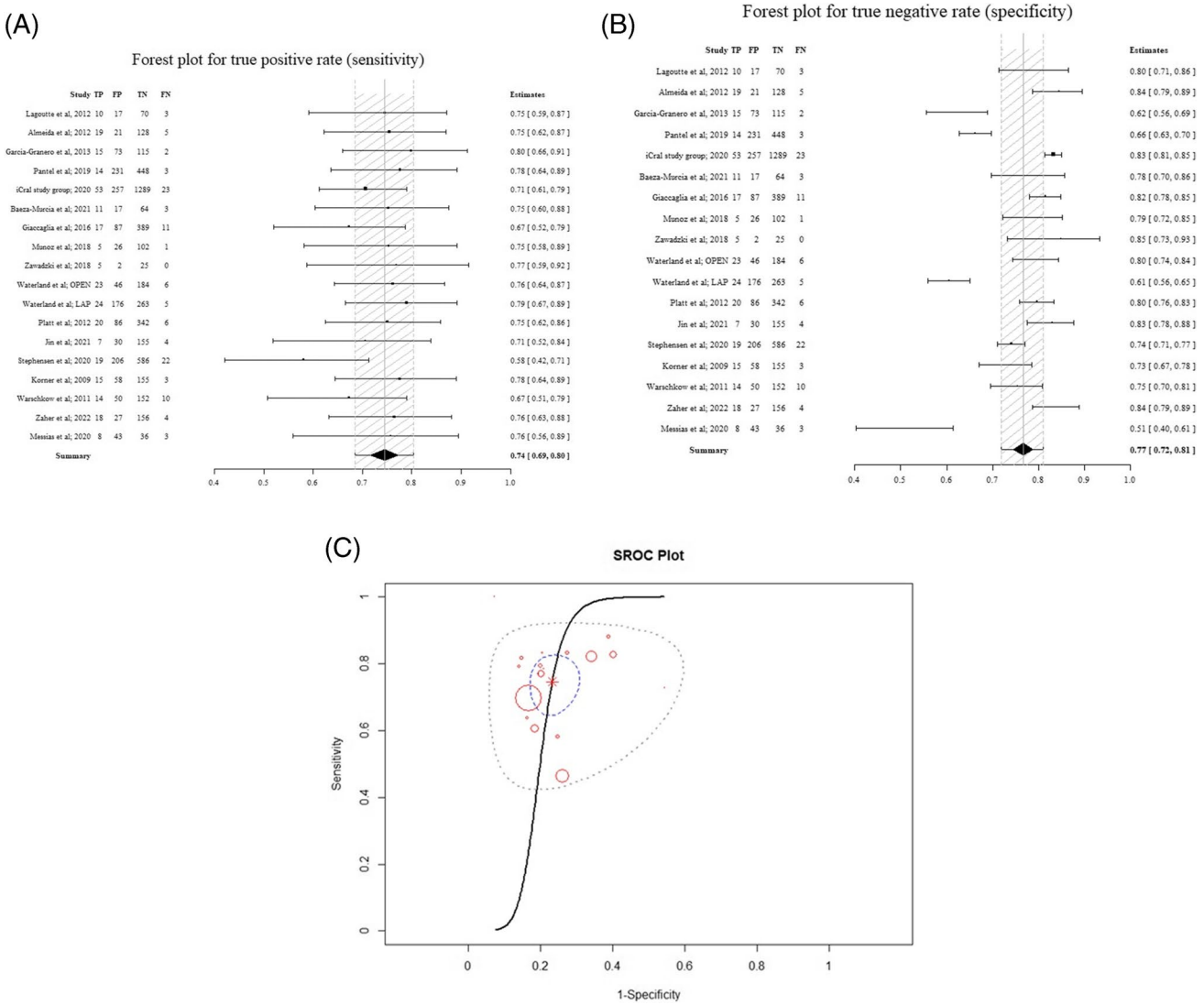

Fig. 4 Forest plot. Estimated pooled sensibility (**A**), specificity (**B**) and summary ROC curve (**C**) for CRP on POD3

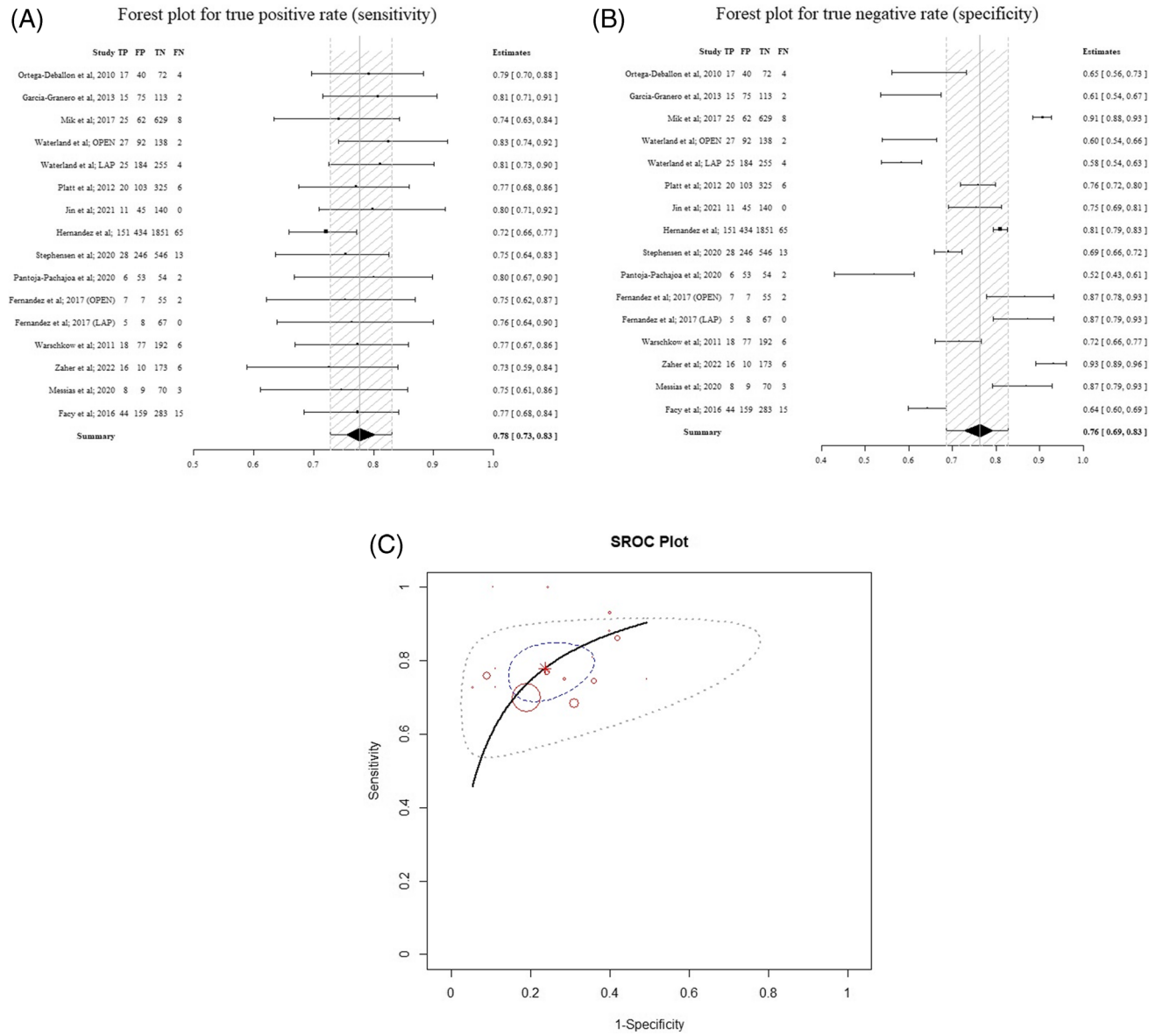

Fig. 5 Forest plot. Estimated pooled sensibility (**A**), specificity (**B**) and summary ROC curve (**C**) for CRP on POD4

threshold effect. Pooled sensitivity, specificity, positive LR, negative LR and DOR are reported in Table 2.

The estimated pooled prevalence of anastomotic leak resulting from 25 studies (11,144 patients) is 8% (95% CI = 7–9%) (Figure 7). The Fagans' nomograms for CRP on POD3, POD4 and POD5 are shown in Figure 8A, B, C.

Discussion

This meta-analysis shows that postoperative CRP serum concentrations on POD3, POD4 and POD5 and the PCT serum concentration on POD5 may be useful tests to rule out AL. These markers should be considered as negative tests while values below the cut-off may theoretically help in the identification of patients who are unlikely to develop AL.

The incidence of AL after colorectal surgery has been reported ranging from 2 to 17% depending on surgeon experience, hospital volumes, surgical indications and technical approaches.[1–5] AL remains a disastrous consequence with increased resources utilization, costs, hospital length of stay, morbidity and related mortality.[6–11] In the era of fast-track recovery, early detection and treatment of AL are even more critical to optimizing perioperative care, minimizing surgical complications and expediting recovery thus possibly reducing the rate of surgical revision. In the present study, the estimated pooled prevalence of postoperative AL was 8% (95% CIs 7–9%).

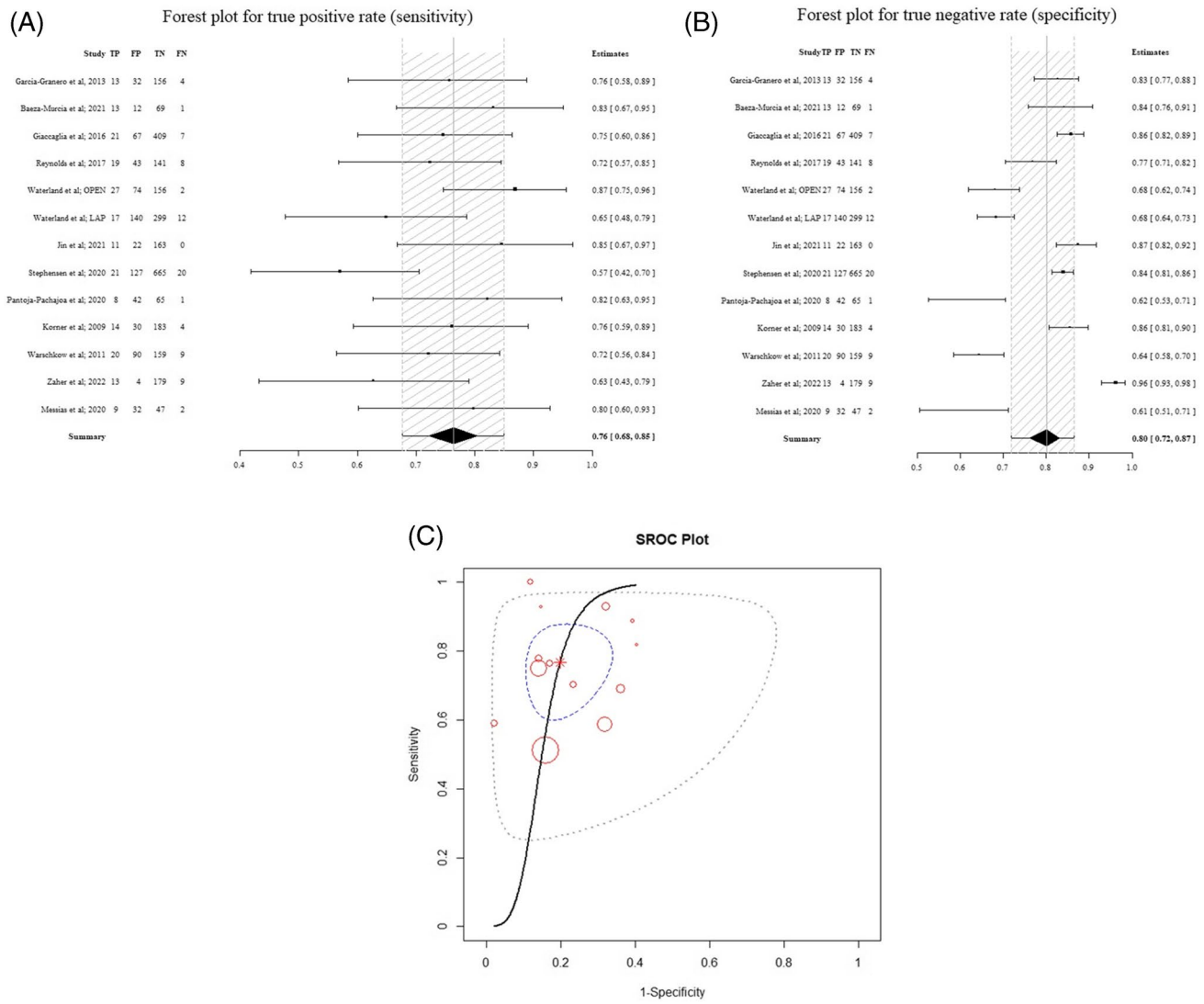

Fig. 6 Forest plot. Estimated pooled sensibility (**A**), specificity (**B**) and summary ROC curve (**C**) for CRP on POD5

Various risk factors have been reported to be associated with AL; however, its prediction remains challenging in individual patients.[4–6] Different strategies for early AL detection have been proposed using serum inflammatory biomarkers. Specifically, postoperative CRP and CPT serum concentrations at different POD have been proposed with contrasting results. CRP is a serum acute-phase reactant synthesized almost exclusively in the liver and is released in response to stimulation by proinflammatory cytokines such as interleukin 6 and tumour necrosis factor α.[59] CRP is a reliable, but non-specific, marker of acute inflammation and has been investigated as an early indicator of infectious complications following abdominal surgery. In contrast, PCT is a peptide precursor of the hormone calcitonin produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine.[60] PCT is classified as a sensitive and reliable acute-phase reactant while its serum concentration rises in response to pro-inflammatory stimulus, especially of bacterial origin.[61] It has been suggested that the identification of clinically relevant CRP serum concentrations and cut-off may be helpful to fast-track pathways by providing an early alert for leakage.[62,63] In our study, we noticed significantly higher serum CRP concentrations in patients with AL compared to patients with no AL with a peak value on POD3 (Figure 3). The derived pooled CRP cut-off values on POD3, POD4 and POD5 were 15.9 mg/dl, 11.4 mg/dl and 10.9 mg/dl respectively. The diagnostic accuracy of these values is comparable and supported by the pooled AUC ROC curves of 0.80 (POD3), 0.84 (POD4) and 0.84 (POD5) respectively. The accuracy of the cut-off was also assessed with the analysis of LRs. Compared to predictive values that are useful to measure the accuracy

Table 2 Bayesian meta-analysis of predictive data for anastomotic leak

	No. of studies (no. of patients)	Derived cut-off (mg/dl)	Pooled AUC (95% CIs)	Pooled sensitivity (95% CIs)	Pooled specificity (95% CIs)	Pooled LR+ (95% CIs)	Pooled LR− (95% CIs)	Pooled DOR (95% CIs)
CRP POD1	4 (1596)	9.9 (6.0–12.5)	0.70 (0.46–0.85)	0.80 (0.60–0.92)	0.53 (0.34–0.70)	1.66 (1.20–2.59)	0.39 (0.13–0.75)	4.38 (1.73–12.49)
CRP POD2	5 (3142)	12.6 (6.2–17.8)	0.75 (0.44–0.86)	0.77 (0.66–0.87)	0.66 (0.57–0.74)	2.23 (1.66–3.18)	0.35 (0.18–0.55)	6.32 (3.11–15.97)
CRP POD3	17 (6807)	15.9 (10.3–22)	0.80 (0.23–0.85)	0.74 (0.69–0.80)	0.77 (0.72–0.81)	3.21 (2.57–4.06)	0.29 (0.21–0.39)	9.67 (6.39–15.21)
CRP POD4	14 (7366)	11.4 (6.4–18)	0.84 (0.18–0.86)	0.78 (0.73–0.83)	0.76 (0.69–0.83)	3.29 (2.42–4.69)	0.24 (0.19–0.36)	11.31 (7.16–19.23)
CRP POD5	12 (3943)	10.9 (5.4–21)	0.84 (0.18–0.89)	0.76 (0.68–0.85)	0.80 (0.72–0.87)	3.81 (2.62–5.86)	0.26 (0.18–0.42)	13.07 (6.83–27.11)
CPT POD3	9 (5791)	0.75 (0.12–2.7)*	0.81 (0.38–0.92)	0.74 (0.64–0.84)	0.77 (0.63–0.88)	3.27 (1.96–6.26)	0.34 (0.20–0.46)	9.95 (4.72–24.25)
CPT POD5	4 (1009)	0.90 (0.19–4.93)*	0.92 (0.89–0.97)	0.85 (0.65–0.97)	0.87 (0.65–0.96)	6.28 (2.18–22.53)	0.18 (0.03–0.45)	38.7 (7.7–47.24)

CRP C-reactive protein, *PCT* procalcitonin, *POD* postoperative day, *AUC* area under the curve, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio, *DOR* diagnostic odds ratio, *95%* Cis 95% credible intervals

*Nanograms per millilitre

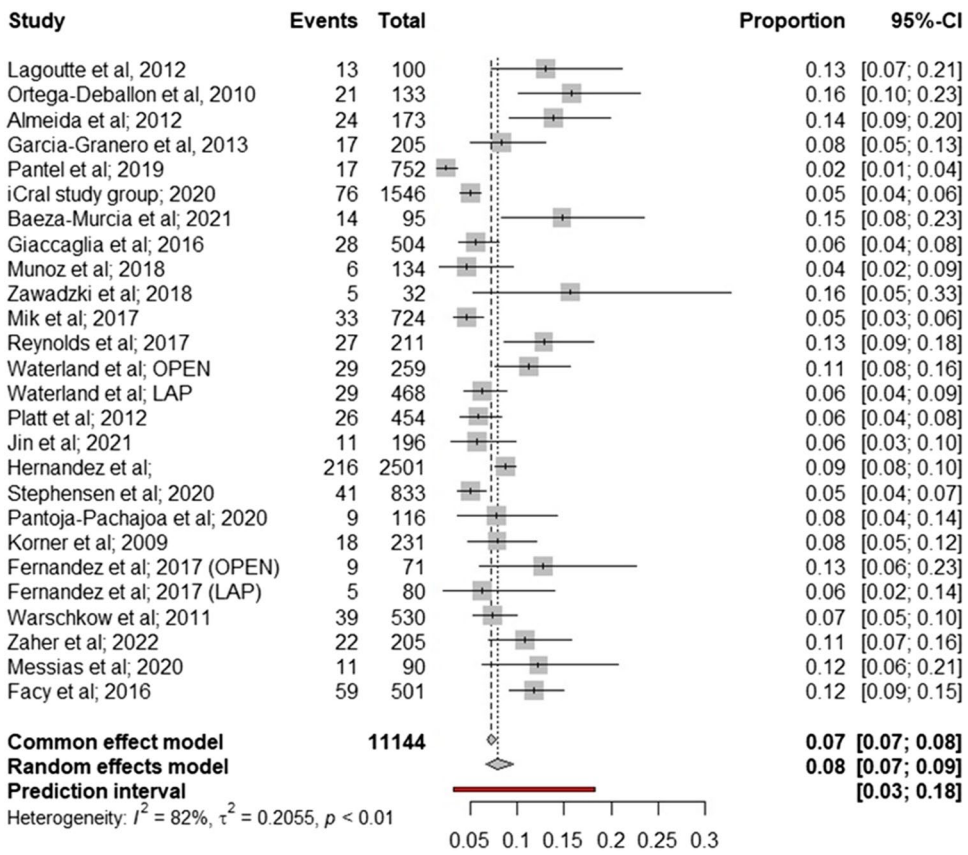

Fig. 7 Forest plot. Pooled post-operative anastomotic leak

of a predictive test, LRs are more precise in estimating the diagnostic probability of a single test, thus providing a more precise individual risk assessment. For these reasons, positive LRs are used in clinical practice to confirm (rule in) while negative LRs are used to exclude (rule out) a specific outcome or complication.[64,65] In the present article, reflecting the poor CRP specificity, positive LRs were associated with weak evidence for AL diagnosis on POD 3 (LR+ 3.21), POD4 (LR+ 3.29) and POD 5 (LR+ 3.81). On the other hand, negative LRs showed moderate evidence to exclude (rule out) leakage on POD 3 (LR− 0.29), POD4 (LR− 0.24) and POD5 (LR− 0.26). This means that for a patient with a pre-test probability of 8%, a serum CRP concentration below the identified cut-off values on POD3 (CRP <15.9 mg/dl), POD4 (11.4 mg/dl) and POD5 (10.9 mg/dl), the post-test probability of AL is about 2.3% (Figure 8A, B, C). Notably, the lower limit of CIs of negative LR for CRP on POD3, POD4 and POD5 were 0.21, 0.19 and 0.18, respectively. This suggests that, in the absence of clinical and/or radiological suspicion, CRP may provide reasonable evidence to exclude (rule out) leakage and identify patients at low risk of AL development. By including a larger patient sample, our results broaden and further corroborate findings of previous meta-analyses. Specifically, Singh et al. in their 2013 meta-analysis included seven studies (2483 patients).[19] The authors identified different CRP cut-offs on POD3 (172 mg/l), POD4 (124 mg/l) and POD5 (144 mg/l) with comparable diagnostic accuracy and remarkable associated negative LR. The authors concluded that CRP is a useful negative predictive test to rule out AL following colorectal surgery. Similarly, Yeung et al. in their 2021 analysis included 23 articles (6647 patients).[22] The authors found a significantly higher serum CRP concentration in patients with AL compared to patients without AL and identified specific CRP cut-offs for POD3 (148 mg/l), POD4 (123 mg/l) and POD5 (115 mg/l) useful to predict AL after colorectal surgery. However, with the noteworthy diagnostic accuracy tested with AUC, the authors failed to assess and report pooled LRs. Compared to predictive values, these are more accurate for an individual risk assessment.

Postoperative serum CPT concentrations were significantly higher on POD3 (3.7 vs. 0.59; $p = 0.001$) and POD5 (4.25 vs. 0.36; $p < 0.001$) in patients with AL compared to patients with no AL. Pooled CPT cut-off values were 0.75 mg/dl and 0.9 ng/ml respectively. The related AUC ROC curves were 0.81 and 0.92. Interestingly, negative LR (−0.18) showed moderate evidence to rule out leakage on POD 5. Again, this means that for a patient with a pre-test probability of 8%, a serum CPT concentration below the identified cut-off value of 0.9 ng/ml (POD5), the post-test probability of AL is almost 2%. This result is similar to what previously reported by Su'a et al. and Cousin et al.,

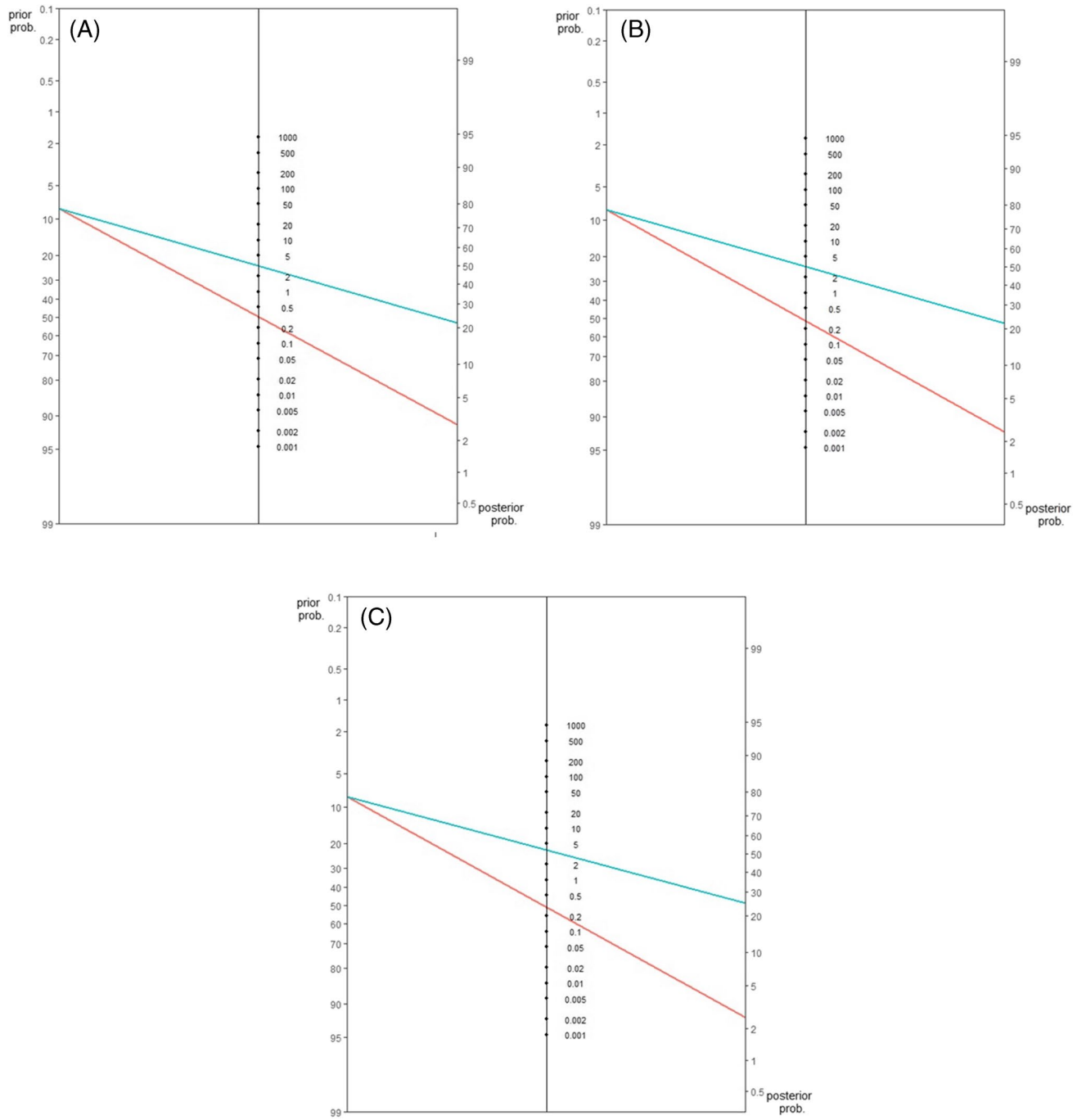

Fig. 8 Fagans' nomograms for CPR on POD3 (**A**), POD4 (**B**) and POD5 (**C**)

who defined a high diagnostic PCT accuracy for AL on POD5.[25,66]

The main result of the present study is the association among high postoperative serum CRP/CPT concentrations and AL. The identification of postoperative cut-offs at various POD may be useful to exclude (rule out) AL or to identify patients at low risk for AL development. Therefore, in the context of a fast-track recovery protocol, CRP and CPT may be possibly useful for early diet advancement and safe discharge.[29] However, owing to differences in patient population, study design and methodology, our results are limited by the heterogeneity of the included studies. The different surgical approaches (open vs. minimally invasive), emergency or elective settings, benign or malignant pathology, different definitions of anastomotic leak, level of anastomosis (ileocolic vs. colocolic vs. rectal), type of anastomosis

(hand-sewn or stapled), severity of AL with different degrees of peritoneal contamination and effect of neoadjuvant treatment may contribute to inter-study heterogeneity. Furthermore, few of the included studies were of retrospective design while postoperative CRP and CPT measurements were not performed sequentially on each POD. Although meta-analysis is not a widely approved method for summarizing predictive data, this study may provide a useful guide for the interpretation of CRP and CPT measurements following colorectal surgery. These cut-offs are not a *panacea* and their isolated use and dichotomous interpretations are not advisable, while a parallel consideration of trends in conjunction with clinical and radiological signs seems prudent.[50] Therefore, cut-offs should be considered as complementary tools and additional arrows and in any surgeons' quiver.

Conclusions

CRP and CPT values lower than the derived cut-offs on POD3-POD5 may be useful tools to rule out leak after colorectal surgery thus identifying patients at low risk for AL development. In the context of enhanced recovery after surgery protocols, the integration of a CRP and CPT-based diagnostic algorithm as complementary instruments to clinical assessment may be valuable to reduce global cost, improve outcomes and patient care.

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Author Contribution AA, AS, LC and MS did the literature search. AA and DB formed the study design. Data collection was done by AA, MS and FL. AA, GB, GC and DB analysed the data. AA, PD and DB interpreted the data. AA, GB, and DB wrote the manuscript. All authors critically reviewed the manuscript.

Declarations

Conflict of Interest The authors declare no competing interests.

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