



Does C-reactive Protein Have a Predictive Role in the Early Diagnosis of Postoperative Complications After Bariatric Surgery? Systematic Review and Bayesian Meta-analysis

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Published online: 22 June 2019
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Abstract

Background Postoperative leak and intra-abdominal infections are common after bariatric surgery with a significant impact on perioperative outcomes, hospital length of stay, and readmission rates. In the era of enhanced recovery programs, with patients being discharged from the hospital 24–36 h after surgery and potentially before developing any complications, an early indicator of postoperative complications may be decisive. The aim of this study was to evaluate the predictive role of the C-reactive protein (CRP) in the early diagnosis of complications in patients undergoing laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB).

Methods PubMed, Embase, and Web of Science databases were consulted. A systematic review and a fully Bayesian meta-analysis were conducted.

Results Seven studies met the inclusion criteria for a total of 1401 patients. Overall, 57.7% underwent LSG while 42.3% underwent LRYGB. The pooled prevalence of postoperative complications was 9.8% (95% CI = 5–16%). The estimated pooled CRP cut-off value on postoperative day 1 (POD1) was 6.1 mg/dl with a significant diagnostic accuracy and a pooled area under the curve of 0.92 (95% credible interval (CrI) 0.73–0.98). The positive and negative likelihood ratios were 13.6 (95% CrI 8.40–15.9) and 0.16 (95% CrI 0.04–0.31), respectively.

Conclusion A CRP value lower than the derived cut-off of 6.1 mg/dl on POD1, combined with reassuring clinical signs, could be useful to rule out early postoperative leak and complications after LSG and LRYGB. In the context of enhanced recovery after surgery protocols, the integration of a CRP-based diagnostic algorithm as an additional complementary instrument may be valuable to reduce cost and improve outcomes and patient care.

Keywords Laparoscopic sleeve gastrectomy · Laparoscopic Roux-en-Y gastric bypass · Postoperative complications · C-reactive protein · Fast-track surgery

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Introduction

Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) have been shown to be effective for long-term weight loss and comorbid resolution in morbidly obese patients [1–3]. Postoperative leak and intra-abdominal infections represent serious complication with a significant impact on perioperative outcomes, hospital length of stay, and readmission rates [4–6]. In the era of enhanced recovery programs, with patients being discharged from the hospital 24–36 h after surgery and potentially before developing any complications, an early indicator of postoperative complications may be useful to guide further decision-making and safe discharge [7–9]. Early suspicion, diagnosis, and treatment of complications are desirable in this high-risk patient population to improve outcomes and patient care.

White blood cells, neutrophils, and C-reactive protein (CRP) are commonly used as markers of systemic inflammation. CRP is a broadly available and costly investigation that has been identified as a potential predictive marker of subacute complications after bariatric surgery [10, 11]. However, in the era of fast-track surgery, the CRP utility and its predictive role in the diagnosis of early postoperative complications have been appraised in single-center retrospective studies with discordant results [12–17].

The aim of this systematic review and meta-analysis was to assess the utility of CRP as a predictive biomarker of early postoperative leak and complications in patients undergoing LSG and LRYGB for morbid obesity.

Methods

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [18]. A literature search was conducted by two independent authors (AA, ER) until January 31 2019 to identify English-written published series on the predictive value of CRP level for postoperative leak and complications after LSG and LRYGB. PubMed, Embase, and Web of Science databases were consulted matching the terms “morbid obesity” OR “sleeve gastrectomy” OR “Roux-en-Y gastric bypass” AND “C-reactive protein” OR “CRP”. The reference lists of all relevant articles were searched manually to identify further relevant studies.

Abstracts, case reports, case series, and non-English written articles were excluded. Relevant studies not allowing a predictive analysis for anastomotic leak were excluded. Two authors (AA, ER) independently extracted data from eligible studies that were compared only at the end of the review process. Data extracted included study characteristics (first author name, year, journal of publication), number of patients, time frame, demographic and preoperative clinical characteristics, surgical

approach, and postoperative outcomes. The outcome of interest was postoperative leak and intra-abdominal infectious complications, which were counted per event and defined as reported in the included studies. Measures of diagnostic accuracy, including area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were recorded to enable a diagnostic meta-analysis. To obtain a summary graph of postoperative CRP levels, CRP data reported in the text, graphs, or figures of the included studies were used and/or digitalized to obtain the median or mean CRP value on postoperative day (POD). Disagreements between authors were resolved by consensus; if no agreement could be reached, a third senior author (DB) made the decision.

Three investigators independently evaluated the methodological quality of the papers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [19]. 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

We performed a fully Bayesian study-level meta-analysis. Compared with the frequentist meta-analysis, the Bayesian approach takes into account all sources of variations, reflects these variations in the pooled result, and provides accurate estimates for small samples. Furthermore, the Bayesian posterior analysis yields the exact coverages independent of sample size [20]. The pooled estimates of sensitivity and specificity, summary receiver operating characteristic curve (SROC), and optimal cut-off were estimated implementing different random intercept and different random slope Bayesian models [21], assuming normal distribution for CRP. Model selection was performed by the deviance information criterion (DIC). Pooled estimates of likelihood ratios (LR) were estimated according to Zwinderman and Bossuyt [22]. For model parameters, we use diffuse normal prior with mean equal to zero and Wishart prior distribution for variance components; as sensitivity analysis, we change the standard deviations of normal priors. The inference was performed using mean or median and relative 95% credible intervals (CrI), based on draws from marginal posterior distribution in Monte Carlo Markov chain (MCMC), simulating 40,000 iterations after a burn in a period of 10,000 iterations. We consider the estimated parameter statistically significant when its 95% CrI encompasses a null hypothesis value. The accuracy of the inference was assessed by convergence of the MCMC algorithm, checked using graphical inspection of running means, MCMC error, and diagnostic statistics included into the CODA package [23]. The pooled CRP dosages in different postoperative days were estimated using a Bayesian normal likelihood model with

inverse gamma non-informative prior for variability and compared between non-complicated (NC) and complicated (C) patients. All statistical analyses were carried out using STAN and R Cran 3.4.3 [24, 25].

Results

Systematic Review

After excluding duplicate results, the search retrieved 119 articles. Of these studies, 112 were excluded because they were off the topic, did not contain a predictive analysis for postoperative complications, and lacked postoperative CRP data. Seven studies met the inclusion criteria for a total of 1401 patients (range 61–523) (Fig. 1). All reports were observational, cohort studies. Demographic, clinical, and operative variables of the patient sample are shown in Table 1. Patients' age ranged from 18 to 61 years, the BMI ranged from 36.5 to 62.5 kg/m², and 70.6% were females. The American Society of Anesthesiologists (ASA) score was reported in three studies, and preoperative patients'

comorbidities were reported in three studies. All operations were performed laparoscopically; six studies (1126 patients) specifically reported the type of operation with 650 patients that underwent LSG (57.7%) and 476 that underwent LRYGB (42.3%). In one study, the results were reported as aggregated with no distinction between LSG and LRYGB. Primary surgery was performed in the majority of the patients while 3.8% underwent revisional surgery. The reported postoperative complications were urinary tract infection (2.4%), postoperative leak (1.9%), incisional surgical site infection (1.75%), intra-abdominal abscess (1.7%), pulmonary complications (1.3%), and other surgery-related complications (0.8%).

The included studies reported measuring CRP in the postoperative period according to different institutional protocols. Six studies reported CRP levels on POD1 and three on POD2. Patients were stratified according to the presence of complications (C group) or no complications (NC group). The median pooled postoperative CRP on POD1 was significantly lower in the NC group (4.3 mg/dl, range 2.9–7.5) compared with the C group (14.9 mg/dl, range 7.8–20.8) ($p = 0.013$) (Fig. 2). Similarly, on

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

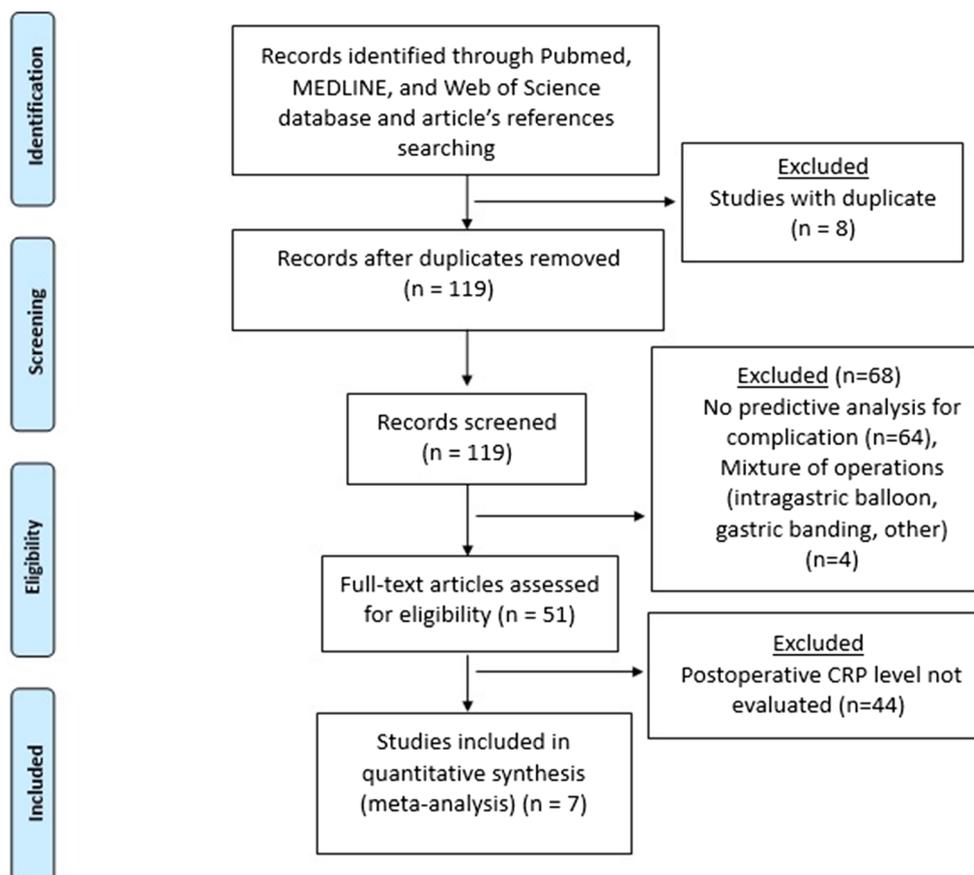


Table 1 Demographic and clinical characteristics of the patient population. *Ret* retrospective, *BMI* body mass index (kg/m²), *ASA* American Society of Anesthesiologists, *DM* diabetes, *SAHS* obstructive sleep apnea-hypopnea syndrome, *HYT* hypertension, *DYS* dyslipidemia, *LRYGB* laparoscopic Roux-en-Y gastric bypass, *LSG* laparoscopic sleeve gastrectomy, *nr* not reported. Numbers are presented as numbers, mean ± standard deviation, or median (range)

Author	Years	Study design	No. of patients	Age (years)	M/F	BMI (kg/m ²)	ASA score	DM	SAHS	HYT	DYS	Surgical approach
Warschkow et al., 2012 [12]	2002–2011	Ret	61	44 (36–52)	nr	46 (42–50)	nr	nr	nr	nr	nr	LRYGB
Albanopoulos et al., 2013 [13]	2008–2011	Ret	177	38 (18–61)	75/102	48.9 (38.2–69.5)	nr	nr	nr	nr	nr	LSG
Pike et al., 2015 [14]	2010–2013	Ret	112	44 (18–73)	35/77	49.4 (36.5–75)	nr	nr	nr	nr	nr	LRYGB
Muñoz et al., 2016 [15]	2012–2015	Ret	115	44.8 ± 10.2	29/86	44 ± 4.82	nr	35	57	47	35	LSG
Williams et al., 2017 [16]	2010–2015	Ret	138	44 (20–68)	34/104	50.6 (38.3–62.5)	2 (2–3)	nr	nr	nr	nr	LRYGB
Kröll et al., 2018 [17]	2010–2017	Ret	523	40 ± 20	165/358	43 ± 8.7	> 2: 393	112	201	244	235	LSG (358), LRYGB (165)
Villard et al., 2018 [9]	2013–2017	Ret	275	45.6 ± 12.2	56/219	46.4 ± 8.9	> 2: 250	169	98	144	84	LSG, LRYGB

POD2, the median pooled postoperative CRP was significantly lower in the NC group (8.6 mg/dl vs. 23.7 mg/dl, $p = 0.001$). CRP cut-off values were reported in 5 studies on POD1 and 3 studies on POD2. The analytical laboratory system for CRP measuring was reported in two studies. The results of quality assessment using the QUADAS-2 tool are shown in Fig. 3. Overall, the applicability of the included studies was good.

Meta-analysis

In addition to a systematic review, we performed a fully Bayesian meta-analysis. Considering the random effects model, the optimal POD1 CRP cut-off, resulting from 5 studies and 1202 patients, is 6.1 mg/dl. The pooled sensibility is 0.82 (95% CrI 0.71–0.91) (Fig. 4a) and the specificity is 0.92 (95% CrI 0.71–0.99) (Fig. 4b). The SROC is 0.92 (95% CrI 0.73–0.98) for sensitivity given specificity and 0.92 (95% CrI 0.90–0.93) for specificity given sensitivity. The pooled positive LR is 13.6 (95% CrI 8.40–15.9) and the pooled negative LR is 0.16 (95% CrI 0.04–0.31).

Considering the random effects model, the optimal POD2 CRP cut-off, resulting from 3 studies and 311 patients, is 15.4 mg/dl. The pooled sensibility is 0.84 (95% CrI 0.42–0.97) and the specificity is 0.78 (95% CrI 0.57–0.89). The SROC is 0.87 (95% CrI 0.21–0.99) for sensitivity given specificity and 0.87 (95% CrI 0.45–0.99) for specificity given sensitivity. The pooled LR+ is 3.8 (95% CrI 0.98–8.8) and the pooled LR– is 0.2 (95% CrI 0.03–1.2). The sensitivity analysis confirmed the robustness of our results, regarding the choice of prior distribution.

The estimated pooled prevalence of postoperative complication resulting from 7 studies, which include a total of 1401 patients, is 9.8% (95% CI = 5–16%). The related heterogeneity was high ($I^2 = 91%$; 95% CI 84–95.1%; $p < 0.001$). The Fagan nomogram for POD1 showed that in a morbidly obese patient, with a pretest probability of 9.8% and a negative test on POD1 (CRP < 6.1 mg/dl), the probability of having or developing a postoperative leak or complication is 1.7% (Fig. 5).

Discussion

This systematic review and meta-analysis show that serum CRP concentration may be a useful marker to rule out early postoperative leak and complications after LSG and LRYGB. On POD1, a CRP lower than the derived 6.1 mg/dl cut-off value, in the absence of clinical and radiological suspicious signs, seems associated with a minimal risk (< 2%) of developing a leak or an intra-abdominal infectious complication. Furthermore, a

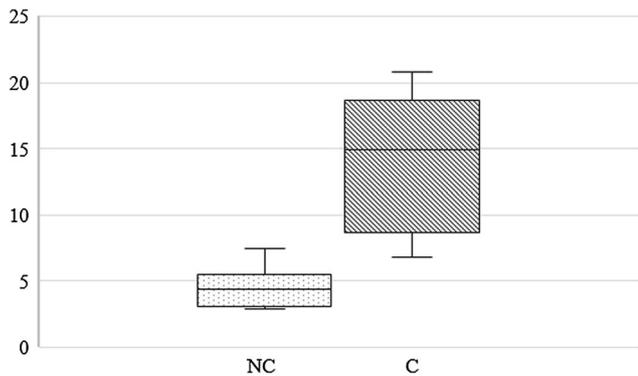


Fig. 2 Pooled postoperative CRP levels (mg/dl) for non-complicated (NC) and complicated (C) patients on POD1. The pooled postoperative CRP was significantly lower in the NC group compared with the C group ($p = 0.013$). The box plot shows the median, lower quartile, upper quartile, and range

CRP value higher than the cut-off seems of value for the identification of high-risk patients that may require prolonged hospitalizations and radiological studies.

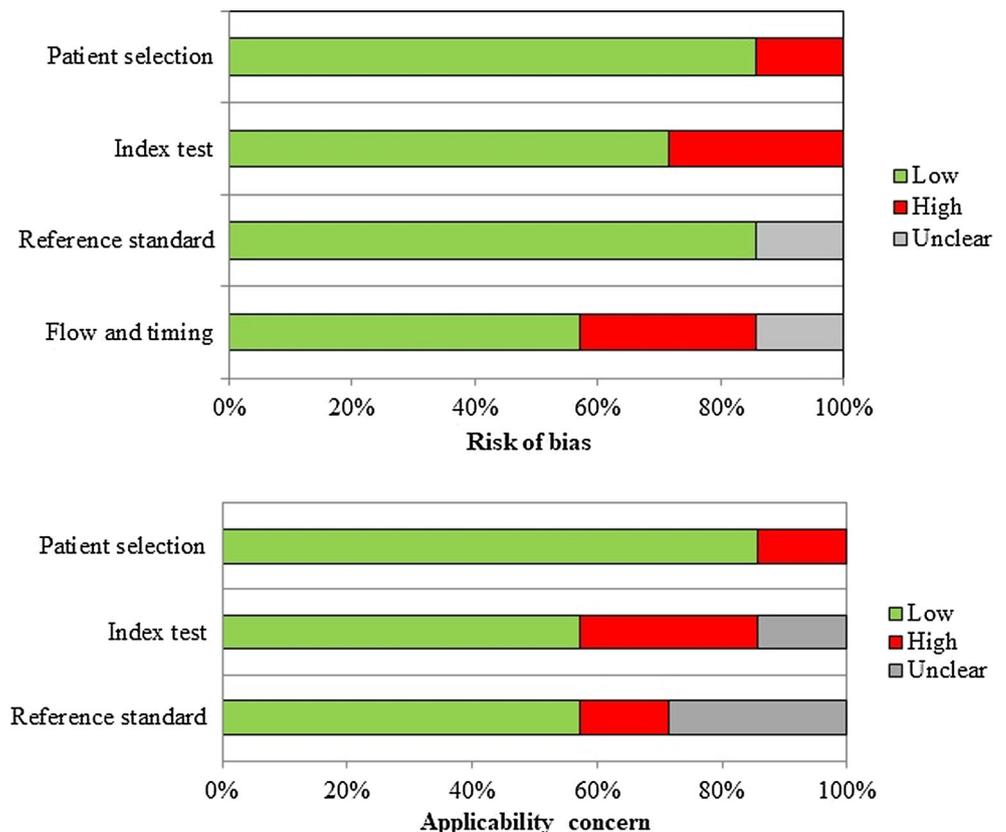
The application of the enhanced recovery after surgery (ERAS) protocol has been shown to be feasible and safe in bariatric surgery with an early hospital discharge (within the first 24–48 h) [7, 26, 27]. The rationale is to reduce the perioperative stress response and facilitate early return to bodily function with early restoration of oral nutrition thus leading to a quicker recovery [28]. However, especially in obese patients

with non-specific or subtle symptoms, postoperative complication such as leak or intra-abdominal infections can appear after the patient has been discharged [29]. For these reasons, the identification of laboratory markers that may alert the surgeon on the development of an early complication that may not have been clinically evident is of crucial importance particularly in the setting of ERAS programs.

CRP testing has gained progressive clinical acceptance because of its broad availability, low cost, and good reliability [17]. The rationale is in the CRP pharmacokinetics as an acute-phase reactant. Synthesized by the liver within 6 h after surgery, postoperative serum CRP levels reach a peak value after about 48 h with a concentration that reflects the intensity of the acute inflammatory stimulus [30]. Notably, the beginning of the CRP increase takes place before the onset of the clinical symptoms of a postoperative septic complication, such as fever, tachycardia, and pain acting as an early marker of postoperative complications [15].

The utility of CRP measurements to rule out postoperative leak and complications has been previously demonstrated in meta-analyses after elective colorectal and esophageal surgery [31, 32]. In accordance with the low sensitivity of the serum CRP concentration, these studies showed a principal role for diagnostic exclusion (rule out). The applicability of this concept in the field of bariatric surgery has been proposed in few observational studies with contrasting results [10–17]. The predictive

Fig. 3 The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Proportion of studies with low, high, or unclear risk of bias (%)



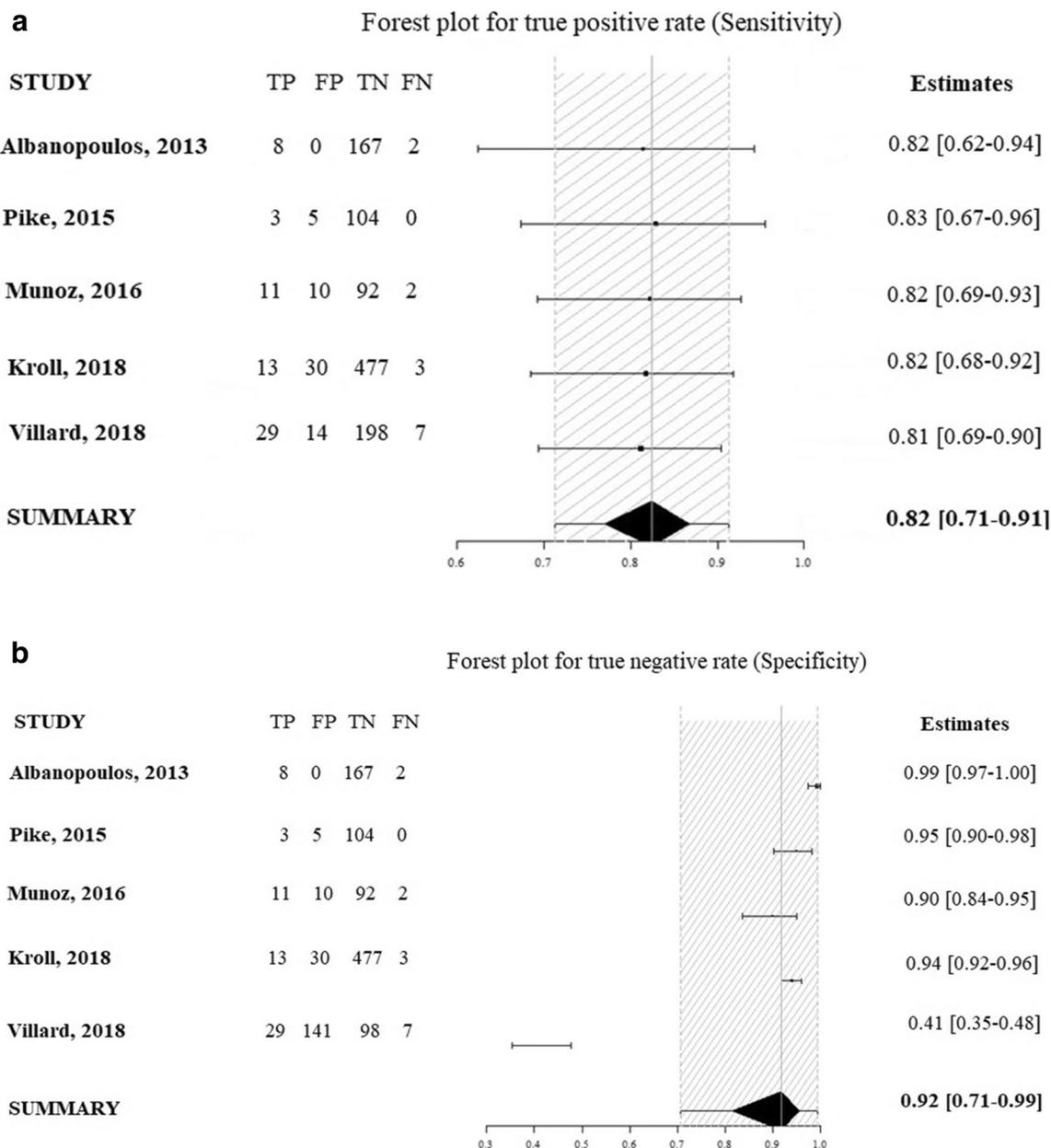
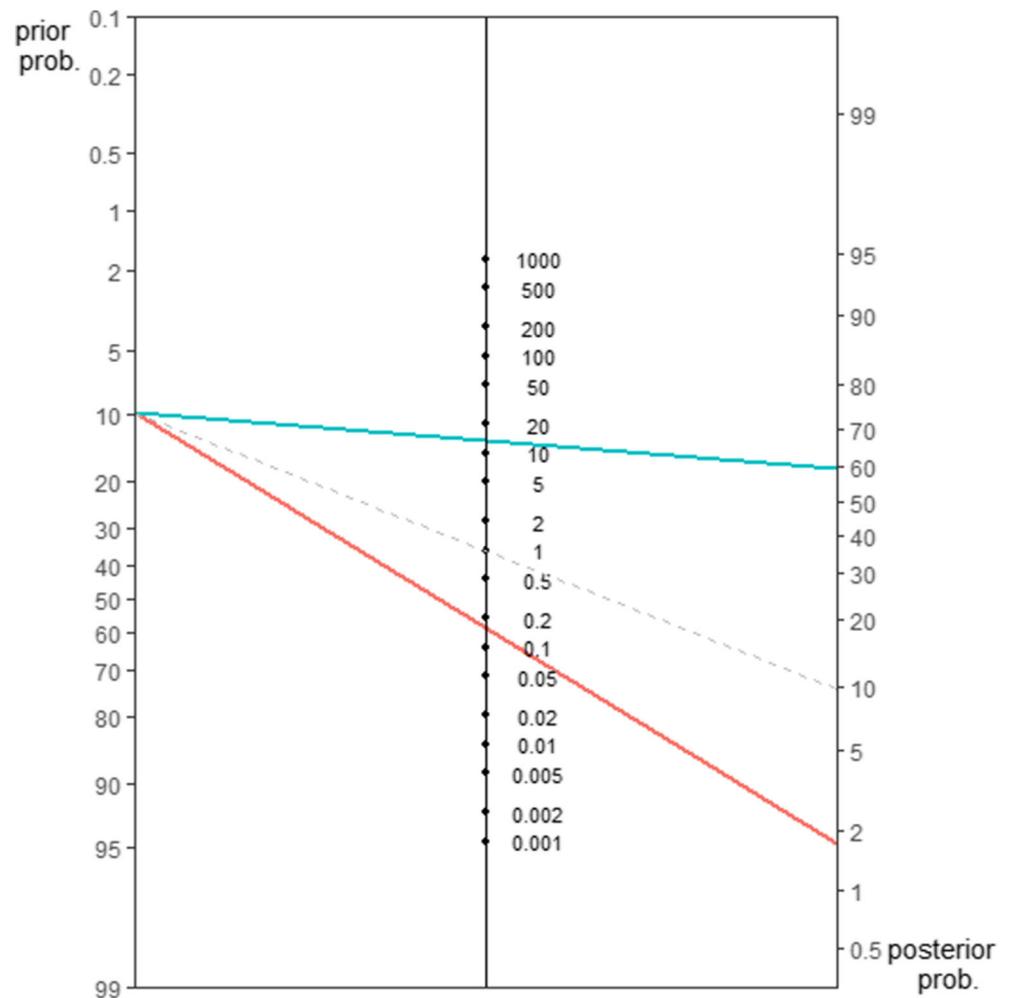


Fig. 4 a–b Forest plot for POD1: estimated pooled sensibility and specificity (a, b)

role of CRP has been largely opposed by many because its baseline concentration in obese patients is higher than normal for the so called “inflammatory noise” related to the metabolic effect of the centrally deposited adipose tissue and insulin resistance [33, 34]. In addition, many patients who do not develop anastomotic leak or complications may reveal a severe systemic inflammatory response with increased CRP levels related to the severity of surgical trauma, blood loss, and duration of operation [35, 36]. However, the derived POD1 cut-off value is higher than the expected “inflammatory noise” limit, and the narrower gap interval may give further significance to the negative predictive value of the pooled cut-off. Therefore, CRP is not a positive predictive biomarker of complications but rather a potential

instrument to exclude the event in case of negative test. In a morbidly obese patient with a pretest probability of 10% and a negative test on POD1 (CRP < 6.1 mg/dl) in the absence of suspicious clinical signs, the probability of developing an early leak or intra-abdominal infectious complication is less than 2%. The diagnostic accuracy of the cut-off is supported by the valuable pooled sensibility (0.82), specificity (0.92), and AUC ROC curve (0.92). In addition, the pooled LR– indicate moderate evidence to rule out leakage with a CrI lower limit of 0.04. In clinical practice, negative LR is relevant to exclude (rule out) the disease/complication providing an individual risk assessment [37, 38]. This further suggests that, in the absence of clinical and/or radiological suspicion signs, POD1 CRP serum concentration

Fig. 5 The Fagan nomograms for POD1



may provide a complementary and additional indication to rule out early postoperative leak and complications and may be helpful for a safe early discharge of the patient. By contrast, in the presence of clinical suspicious signs and serum CRP values higher than the cut-off, a delayed hospital discharge and radiological investigations should be recommended. Despite the fact that the estimated POD2 CRP cut-off had not such robust evidence and was determined in a limited patient population ($n = 311$), this can be of further guidance with a moderate diagnostic accuracy (AUC 0.87) and LR⁻ (0.2).

Owing to differences in the patient population, study design, and methodology, this meta-analysis is limited by the heterogeneity of the included studies and population in terms of BMI, ethnicity, and indication for surgery. In addition, the various surgical approaches and techniques and definitions of outcomes and complications may represent additional confounders that should be considered. There is no uniform consensus on the classification of postoperative leaks or septic complications after bariatric surgery, and classifications differ within studies regarding the time of onset, clinical presentation, location, and radiographic appearance. Finally, all studies were

of fair quality with a retrospective design. However, postoperative CRP measurements were performed in all patients, thus reducing the possibility of diagnostic accuracy overestimation. Finally, it should be considered that longitudinal studies with repeated measurements taken over time are more reliable in establishing causality [39]. To the best of our knowledge, this is the first meta-analysis that evaluated the prognostic value of CRP to rule out early leak and postoperative complications after LSG and LRYGB. Compared with previous single-center studies, the present meta-analysis provides a more precise estimation of CRP cut-off values because of the considerable amount of data and statistical power. Although meta-analysis is not a widely approved method for summarizing predictive data, the cut-off values suggested in the present study could be used to interpret postoperative CRP measurements and may be integrated in ERAS protocols. The results of the present study should not be considered conclusive, and further high-quality studies are needed to validate these results in conjunction with the evaluation of the predictive role of other inflammatory biomarkers such as procalcitonin (PCT) and fibrinogen.

Conclusions

In previous studies, increased postoperative levels of CRP have been shown to be associated with anastomotic leak and infectious complications after LSG and LRYGB. A CRP value lower than the derived cut-off of 6.1 mg/dl on POD1, combined with reassuring clinical signs, could be useful to rule out early postoperative leak or surgery-related complications. In the context of ERAS protocols, the integration of a CRP-based diagnostic algorithm as an additional complementary tool may be useful to reduce cost and improve outcomes and patient care.

Author Contribution AA, ER, and MC did the literature search. DB and AA formed the study design. Data collection was done by AA, VP, MC, ER, and DB. AA and GB analyzed the data. AA, GB, and DB interpreted the data. DB and AA wrote the manuscript. DB, GM, and AA critically reviewed the manuscript.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Not applicable.

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