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Systematic Review Of Serum And Tissue Biomarkers For Predicting Anastomotic Leak After Elective Colorectal Cancer Surgery

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ABSTRACT

***Background**: Anastomotic leak (AL) remains one of the most serious complications following elective colorectal cancer (CRC) surgery, contributing to major morbidity, prolonged hospitalization, and adverse oncologic outcomes. Early identification of patients at risk remains challenging because clinical deterioration often occurs after the leak has progressed. Serum biomarkers reflecting postoperative inflammation and infection have been widely investigated as adjunctive tools for early risk stratification; however, the evidence is heterogeneous and lacks standardized, clinically validated thresholds. **Objective**: To systematically evaluate and synthesize the diagnostic accuracy of serum biomarkers for predicting anastomotic leak after elective colorectal cancer resection. **Methods**: A PRISMA-compliant systematic review was conducted. PubMed/MEDLINE, Embase, Scopus, Web of Science, and CENTRAL were searched for studies published between January 2014 and April 2024. Eligible studies were observational cohorts or randomized studies evaluating preoperative or postoperative serum biomarkers for AL prediction in adults undergoing elective CRC surgery. Diagnostic accuracy outcomes included area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and/or extractable contingency data. Methodological quality was assessed using QUADAS-2. Due to heterogeneity in biomarkers, sampling schedules, leak definitions, and cutoffs, a qualitative synthesis was performed. **Results**: Eight observational cohort studies comprising 2,414 patients were included, with 177 AL events (7.3%). C-reactive protein (CRP) was the most frequently evaluated biomarker and demonstrated moderate-to-high discrimination when measured on postoperative days (POD) 3–5 (AUC range: 0.76–0.91), with peak performance commonly observed on POD 4. Procalcitonin showed promising accuracy in two cohorts (AUC approximately 0.83–0.85 on POD 3–4). Evidence for interleukin-6 and presepsin was limited to single-cohort evaluations but suggested potential utility (AUC ~0.80–0.89). QUADAS-2 assessment indicated an overall moderate risk of bias, most commonly related to patient selection, symptom-triggered verification, and derivation of optimal thresholds within study cohorts. **Conclusion**: Serum biomarkers—particularly CRP and procalcitonin measured on POD 3–5—show clinically meaningful potential as adjunctive tools for early postoperative risk stratification of anastomotic leak after elective colorectal cancer surgery. However, substantial heterogeneity and lack of prospectively validated cutoff values limit their standalone diagnostic use. Future multicenter studies should focus on external validation of standardized thresholds and evaluation of biomarker-guided management pathways.*

Keywords
Anastomotic Leak; Colorectal Cancer Surgery; Serum Biomarkers; C-Reactive Protein; Procalcitonin; Diagnostic Accuracy; Systematic Review.

INTRODUCTION

Anastomotic leak (AL) remains one of the most serious complications after elective colorectal cancer (CRC) surgery and continues to be a principal driver of postoperative morbidity, mortality, and resource utilization. Despite advances in perioperative pathways and refinements in operative technique, reported AL incidence remains clinically consequential and variable, reflecting differences in anastomotic level, patient risk profile, and definitions used for diagnosis (1,2). The clinical impact of AL extends beyond immediate sepsis, reoperation, prolonged hospitalization, and stoma formation; it is also associated with impaired recovery, delays or omission of adjuvant therapy, and inferior oncologic outcomes including higher local recurrence and reduced overall survival (3). Given the scale of CRC surgery globally and the severity of this complication, the early and accurate identification of patients at heightened risk for AL remains a critical priority for colorectal surgical practice and postoperative surveillance.

The pathogenesis of AL is multifactorial and reflects the interaction of local tissue factors and systemic host responses. Anastomotic healing requires adequate perfusion and oxygen delivery, intact collagen synthesis and remodeling, controlled inflammation, and freedom from excessive bacterial contamination. Disruption of any of these mechanisms—through ischemia at the anastomotic site, excessive tension, impaired microvascular integrity, malnutrition, anemia, smoking, steroid exposure, or systemic inflammatory dysregulation—can compromise tissue integrity and precipitate dehiscence. In clinical practice, however, AL is often detected only after the onset of overt physiological deterioration, such as fever, tachycardia, abdominal pain, ileus, purulent drain output, or escalating inflammatory markers, at which point significant morbidity may have already developed. Conventional postoperative assessment therefore relies on clinical vigilance supplemented by imaging and operative exploration, but these methods are inherently reactive and may delay diagnosis because early manifestations are non-specific and overlap with the expected postoperative inflammatory response. This diagnostic uncertainty has fueled interest in objective biomarkers capable of identifying occult anastomotic failure earlier in its trajectory, enabling targeted diagnostic escalation or timely intervention.

Among candidate biomarkers, serum inflammatory markers have been studied most extensively because they are widely accessible, inexpensive, and routinely measured after major abdominal surgery. C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to cytokine signaling, has been repeatedly evaluated as a marker of postoperative infectious complications and AL, with evidence suggesting that its discriminatory performance is greatest when assessed serially during postoperative days (POD) 3 to 5 rather than within the first 48 hours after surgery (4,5). This timing corresponds to the period when a leak is likely to progress from subclinical local inflammation to systemic inflammatory activation, making biomarker kinetics biologically plausible and clinically interpretable. Procalcitonin (PCT), which is more closely associated with bacterial infection, has also been investigated as a potentially more specific indicator of evolving septic complications, while interleukin-6 (IL-6) has been proposed as an earlier upstream inflammatory signal given its rapid postoperative rise and association with tissue injury and infection. These biomarkers have attracted attention not only as diagnostic adjuncts but also as potential tools to support safe early discharge protocols, escalation pathways for early imaging, and antibiotic stewardship approaches in enhanced recovery frameworks (5).

Despite this expanding literature, the evidence base remains difficult to translate into standardized clinical practice. Published studies differ substantially with respect to surgical approach, anastomotic level, definitions and grading of AL, timing and frequency of biomarker measurement, and statistical methods used to derive thresholds. Moreover, many studies select optimal cutoffs retrospectively, which can overestimate real-world diagnostic performance and reduce generalizability across settings. Prior syntheses have contributed important insights, particularly on CRP as a rule-out marker for postoperative complications and discharge readiness, but many included heterogeneous colorectal surgical populations, combined cancer and benign indications, or pooled diverse operations that differ in baseline risk and inflammatory trajectories (4,5). In addition, earlier meta-analyses often focused on broad postoperative complication prediction rather than CRC-specific anastomotic failure, and the rapid evolution of perioperative care, minimally invasive approaches, and diagnostic imaging during the last decade underscores the need for an updated, contemporary synthesis grounded in modern practice (2,6). Consequently, clinicians and guideline developers continue to lack definitive CRC-specific evidence regarding which biomarkers provide reliable discrimination, at what postoperative timepoints, and with what reproducible thresholds that can meaningfully inform clinical decision-making.

Against this background, a systematic and methodologically rigorous appraisal of contemporary diagnostic accuracy studies focused specifically on elective CRC surgery is warranted. Such a synthesis is needed to consolidate the predictive performance of commonly used serum biomarkers, evaluate emerging candidates, and critically assess the methodological quality and applicability of the evidence using established tools for diagnostic accuracy research. By restricting inclusion to recent studies in elective CRC resection cohorts and emphasizing clinically meaningful diagnostic accuracy metrics, this review is positioned to clarify which biomarkers have the most consistent evidence for early risk stratification and where the literature remains insufficient or methodologically limited. This systematic review therefore aimed to critically appraise and synthesize the evidence on the diagnostic accuracy of preoperative and early postoperative serum biomarkers—including CRP, PCT, and IL-6—for predicting clinically or radiologically confirmed anastomotic leak following elective colorectal cancer surgery (1-6).

MATERIAL AND METHODS

This review was designed as a PRISMA-compliant systematic review of diagnostic accuracy evidence evaluating serum biomarkers for predicting anastomotic leak after elective colorectal cancer surgery (6). A protocol-driven approach was adopted a priori to ensure methodological rigor, transparency, and reproducibility, with the review question structured around adult patients undergoing elective curative-intent colorectal cancer resection, the measurement of preoperative and/or early postoperative serum biomarkers as index tests, clinically and/or radiologically confirmed anastomotic leak as the target condition, and diagnostic accuracy metrics as primary outcomes.

A comprehensive literature search was conducted across PubMed/MEDLINE, Embase (via Ovid), Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials to identify relevant studies published from January 2014 to April 2024. The search strategy combined controlled vocabulary (MeSH and Emtree terms where applicable) and free-text keywords covering three core domains: colorectal cancer surgery, anastomotic leak, and biomarkers. Search strings used Boolean operators and appropriate truncation, and included terms such as “colorectal neoplasms,” “colorectal surgery,” “colectomy,” “proctectomy,” “anastomotic leak,” “anastomotic leakage,” “biomarker,” “C-reactive protein,” “procalcitonin,” “interleukin-6,” and related synonyms. Database-specific syntax was adapted to optimize sensitivity. To identify additional eligible studies, reference lists of included articles and relevant review papers were manually screened. All retrieved records were exported to EndNote version 20 (Clarivate Analytics) for duplicate removal and then imported into the Rayyan web application to facilitate blinded screening by multiple reviewers (7).

Eligibility criteria were defined before screening and applied consistently. Studies were eligible if they were original observational studies (prospective or retrospective cohort studies, including diagnostic cohort designs) or randomized trials that evaluated the diagnostic accuracy of one or more serum biomarkers for predicting anastomotic leak in adult patients (≥18 years) undergoing elective colorectal cancer resection with primary anastomosis. Eligible index tests included any serum biomarker measured preoperatively or postoperatively, provided the study reported diagnostic accuracy outcomes such as sensitivity, specificity, area under the receiver operating characteristic curve (AUC), predictive values, likelihood ratios, or sufficient data to reconstruct contingency tables. The reference standard was clinically and/or radiologically confirmed anastomotic leak as defined by each study, including confirmation by computed tomography, contrast studies, endoscopy, reoperation, or a combination of accepted clinical and imaging criteria. Studies were excluded if they were not published in English, were conference abstracts,

editorials, letters, narrative reviews, systematic reviews, meta-analyses, case reports, or animal/in vitro studies, or if they focused exclusively on non-malignant colorectal disease. Studies enrolling mixed colorectal surgery populations were excluded when colorectal cancer-specific data could not be extracted separately.

Study selection was performed independently by two reviewers in two stages. First, titles and abstracts were screened for potential eligibility. Second, full-text articles of potentially relevant records were retrieved and assessed in detail against the inclusion and exclusion criteria. Any disagreements were resolved through consensus discussion, and when required, adjudication was sought from a third senior reviewer. The study selection process was documented using a PRISMA flow diagram, including reasons for exclusion at the full-text stage (6).

Data extraction was conducted independently by two reviewers using a standardized, pilot-tested extraction form developed in Microsoft Excel. Extracted variables included bibliographic details (first author, year, country), study design, clinical setting, sample size, number and proportion of anastomotic leak events, patient characteristics (age, sex), tumor and operation characteristics (colonic vs rectal surgery, approach, type of resection where reported), definition and confirmation method for anastomotic leak, biomarker(s) evaluated, timing of biomarker sampling, assay method where available, cutoff values, and diagnostic accuracy metrics. Where available, 2×2 diagnostic contingency data (true positives, false positives, true negatives, false negatives) were extracted directly; if not reported, values were derived from reported sensitivity/specificity and event counts when mathematically feasible. When key diagnostic performance details were missing or unclear, corresponding authors were contacted by email to request clarification or additional data.

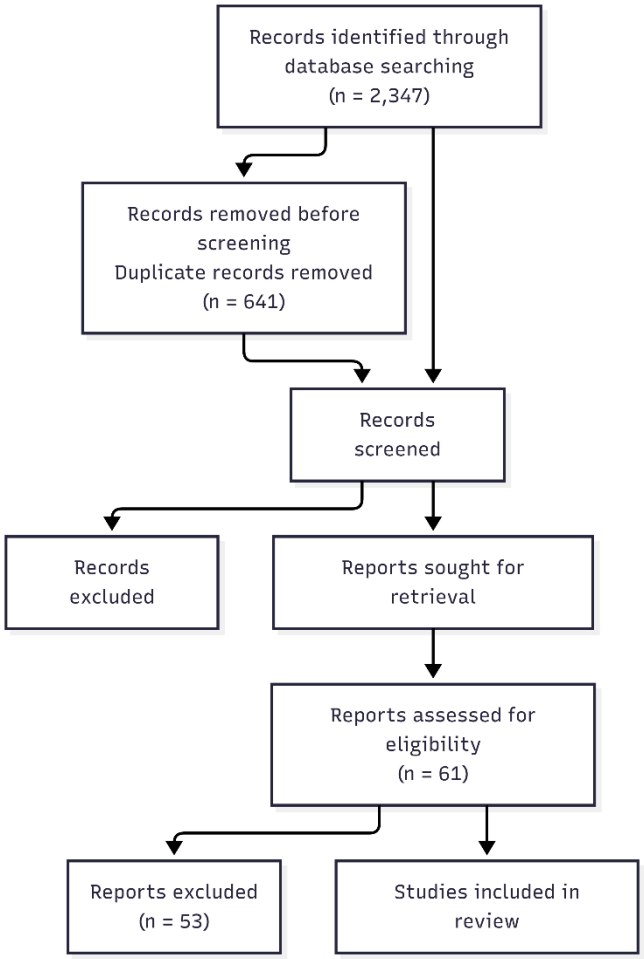

Figure 1 PRISMA Flowchart

Methodological quality and risk of bias were assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, consistent with Cochrane recommendations for diagnostic accuracy reviews (8). Each included study was evaluated across four domains—patient selection, index test, reference standard, and flow and timing—for risk of bias, and for concerns regarding applicability in the first three domains. Two reviewers assessed QUADAS-2 judgments independently, with discrepancies resolved by consensus. Risk-of-bias assessments were used to inform the interpretation of findings and to contextualize the strength of evidence across biomarkers and timepoints rather than to exclude studies post hoc.

Given anticipated heterogeneity in biomarker selection, sampling schedules, leak definitions, thresholds, and analytical methods, synthesis was planned primarily as a qualitative, structured narrative summary. Findings were grouped by biomarker and postoperative timepoint, with diagnostic performance summarized using AUC, sensitivity, specificity, and reported thresholds where available. A quantitative synthesis using hierarchical/bivariate random-effects modeling for pooled sensitivity and specificity was considered where at least three studies evaluated the same biomarker at a comparable postoperative timepoint using sufficiently similar definitions and where contingency data were available; however, where heterogeneity precluded pooling, results were presented descriptively with emphasis on clinical interpretability and sources of between-study variation (9). Where patterns across studies suggested clinically meaningful time-dependent performance (for example, higher discrimination on POD 3–5 compared with POD 1–2), these were highlighted and interpreted in relation to postoperative inflammatory physiology and the typical

clinical course of anastomotic leak. All analyses and evidence synthesis decisions were aligned with established guidance for diagnostic test accuracy reviews (6,8,9).

RESULTS

The systematic search across electronic databases yielded a total of 2,347 records. Following the removal of 641 duplicates, 1,706 unique records underwent title and abstract screening. Of these, 1,645 were excluded as they clearly did not meet the inclusion criteria, primarily because they were not original research on biomarkers for anastomotic leak, focused on benign disease, or were review articles. The full texts of the remaining 61 articles were retrieved and assessed in detail. A further 53 studies were excluded at this stage for reasons detailed in the PRISMA flow diagram (Figure 1), with the most common reasons being lack of elective colorectal cancer–specific data (n=18), insufficient diagnostic accuracy data for extraction (n=15), and study population overlapping with a larger, more recent publication (n=8). Consequently, eight studies met all predefined eligibility criteria and were included in the final qualitative synthesis (10–17). A quantitative meta-analysis was not performed due to significant clinical and methodological heterogeneity across studies in biomarker selection, sampling schedules, definitions and ascertainment of anastomotic leak, and reported cutoff values.

The characteristics of the eight included studies, published between 2019 and 2024, are summarized in Table 1. The studies were conducted across diverse geographical regions, including Europe, Asia, and South America. Sample sizes varied considerably, ranging from 102 to 587 patients, yielding a cumulative cohort of 2,414 patients. Among these, 177 patients (7.3%) developed an anastomotic leak, with incidence rates within individual studies ranging from 5.1% to 12.5%. All included studies were observational in design, comprising six prospective cohort studies (10,12,13,15–17) and two retrospective cohort studies (11,14). The investigated biomarkers primarily reflected inflammatory and sepsis-associated pathways. The most frequently evaluated biomarker was C-reactive protein (CRP), assessed in five studies at various postoperative days (POD) (10,11,13,14,17). Other biomarkers included procalcitonin (PCT) (12,15), interleukin-6 (IL-6) (16), and presepsin (13), with one study evaluating a combined panel of CRP, PCT, and white blood cell count (WBC) (17). Biomarker assessment was predominantly performed in the early postoperative period, with POD 3–5 consistently identified as the most informative window for discrimination.

Table 1: Characteristics of Included Studies
(retain your table as-is, but ensure the citations match your reference list; CRP is correctly cited as 10,11,13,14,17 — not 18).

Table 1. Characteristics of Included Studies (Revised, Publication-Ready)

Author (Year), Country	Design	Sample Size (n)	AL Cases n (%)	Biomarker(s)	Key Sampling Timepoint(s)	Primary Discrimination Metric
Gärtner et al. (2024), Germany (10)	Prospective cohort	587	30 (5.1)	CRP	POD 3, 4, 5	AUC 0.88 (POD 4)
Silva et al. (2023), Brazil (11)	Retrospective cohort	215	27 (12.5)	CRP	POD 3, 5	AUC 0.79 (POD 5)
Kärjä et al. (2022), Finland (12)	Prospective cohort	102	12 (11.8)	PCT (± IL-6)	Preop, POD 1–3	AUC 0.85 (POD 3)
Benedetti et al. (2022), Italy (13)	Prospective cohort	310	25 (8.1)	CRP, Presepsin	POD 3	CRP AUC 0.82; Presepsin AUC 0.80
Lee et al. (2021), South Korea (14)	Retrospective cohort	489	36 (7.4)	CRP	POD 3, 4	AUC 0.76 (POD 4)
Soria et al. (2021), Spain (15)	Prospective cohort	178	15 (8.4)	PCT	POD 1–4	AUC 0.83 (POD 4)
Tan et al. (2020), Singapore (16)	Prospective cohort	265	18 (6.8)	IL-6	POD 1–3	AUC 0.89 (POD 3)
Xu et al. (2019), China (17)	Prospective cohort	268	14 (5.2)	CRP, PCT, WBC	POD 1–5	CRP AUC 0.91 (POD 4)

Abbreviations: AL = anastomotic leak; CRP = C-reactive protein; PCT = procalcitonin; IL-6 = interleukin-6; WBC = white blood cell count; POD = postoperative day; AUC = area under the receiver operating characteristic curve.

The assessment of methodological quality using the QUADAS-2 tool indicated a mixed but generally moderate risk of bias across studies, with the most frequent concerns arising from patient selection and the prespecification of index test thresholds. In the patient selection domain, the two retrospective studies were judged to be at higher risk of bias due to potential spectrum effects and non-consecutive inclusion, and several prospective cohorts were also judged as having unclear or elevated risk where exclusions were not fully justified or where the enrolled population was not clearly representative of routine elective colorectal cancer practice (11,12,14,17). Concerns regarding applicability were raised in three studies where patient selection criteria, surgical subgroup restrictions, or clinical setting limited generalizability to broader elective colorectal cancer populations (12,14,17). For the index test domain, most studies were judged as low risk because biomarker measurement was undertaken using standard laboratory methods; however, a common limitation was the lack of pre-specified, prospectively validated biomarker cutoff values, as several studies derived “optimal” thresholds within the same cohort used for evaluation, potentially inflating diagnostic performance. The reference standard domain was generally assessed as low risk, as AL was diagnosed using clinical and radiological criteria consistent with accepted practice, although explicit standardization of AL definitions and grading was variably reported. In the flow and timing domain, both retrospective studies were considered at higher risk because not all patients may have undergone uniform reference standard assessment (e.g., imaging triggered by symptoms), introducing differential verification and timing bias (11,14).

The synthesis of diagnostic accuracy outcomes suggested that serum biomarkers demonstrated their strongest discriminatory performance in the POD 3–5 interval. CRP consistently emerged as the most robust and frequently studied biomarker when measured on POD 3–5, with reported AUC values ranging from 0.76 to 0.91 across included cohorts (10,13,14,17). The study by Gärtner et al. reported that a CRP level >172 mg/L on POD 4 yielded a sensitivity of 83% and specificity of 86% for subsequent anastomotic leak, highlighting clinically relevant discrimination at this timepoint (10). Procalcitonin also showed promising performance in two studies, with reported AUCs of 0.85 on POD 3 and 0.83 on POD 4, supporting its potential utility in distinguishing developing septic complications from the expected postoperative inflammatory response (12,15).

The study evaluating IL-6 reported a high AUC of 0.89 on POD 3, suggesting that upstream cytokine signaling may provide an earlier predictive signal, although evidence remains limited to a single cohort (16). Presepsin demonstrated discriminatory performance comparable to CRP in one pilot study (AUC 0.80 on POD 3), indicating potential value as an emerging marker, but with insufficient evidence for definitive conclusions (13). Across studies, biomarkers generally performed less well on POD 1–2 than on POD 3–5, underscoring the importance of timing and postoperative inflammatory kinetics in clinical interpretation. Finally, the study by Xu et al. suggested that the combined measurement of CRP, PCT, and WBC did not clearly outperform CRP alone in terms of overall discrimination, indicating that multimarker approaches may not provide clinically meaningful incremental value without standardized algorithms and external validation (17).

DISCUSSION

This systematic review synthesised contemporary evidence from eight observational studies involving 2,414 patients to evaluate the diagnostic accuracy of serum biomarkers for predicting anastomotic leak after elective colorectal cancer surgery. The principal finding is that serum inflammatory and sepsis-associated biomarkers demonstrate the most clinically meaningful discriminatory performance when measured in the early postoperative period, particularly between postoperative days (POD) 3 and 5. Among the biomarkers assessed, C-reactive protein (CRP) was the most frequently evaluated and displayed consistently moderate-to-high discriminatory accuracy, with reported AUC values ranging from 0.76 to 0.91, typically peaking around POD 4 (10,11,13,14,17). Procalcitonin (PCT) also demonstrated promising performance in two cohorts, with AUC values around 0.83–0.85 on POD 3–4, supporting its potential role as a complementary marker of evolving infectious complications (12,15). Evidence for interleukin-6 (IL-6) and presepsin remains preliminary, but findings from single-cohort evaluations suggest these markers may provide useful early postoperative signals warranting further validation (13,16).

The observed time-dependent performance across biomarkers is biologically plausible and clinically relevant. Early postoperative elevations in systemic inflammatory markers are expected following major colorectal surgery and may not reliably differentiate physiological inflammation from pathological processes within the first 48 hours. In contrast, persistently elevated or rising biomarkers on POD 3–5 likely reflect failure of normal resolution of inflammation or progression toward sepsis, aligning with the typical clinical trajectory of anastomotic disruption and intra-abdominal contamination (1,4). This temporal pattern reinforces the clinical value of integrating serial biomarker measurements into a structured postoperative monitoring strategy, where abnormal trajectories could prompt earlier diagnostic escalation, including cross-sectional imaging, targeted antibiotic initiation, or closer observation in high-risk patients.

When contextualised within prior evidence, the findings support and refine earlier syntheses that identified CRP as a practical postoperative marker for detecting complications and informing discharge decisions after colorectal surgery (4,5). However, most earlier meta-analyses pooled broader colorectal populations, including benign disease, and often focused on postoperative complications in general rather than colorectal cancer–specific anastomotic leak. By restricting the population to elective colorectal cancer resections and concentrating on biomarker diagnostic accuracy for leak prediction, this review provides a focused synthesis that is directly applicable to oncologic colorectal surgery pathways. Notably, the evidence base for PCT appears to be expanding, and its biologic specificity for bacterial infection may provide additional discriminatory value in distinguishing evolving septic complications from sterile postoperative inflammation (12,15). Nevertheless, current evidence remains insufficient to recommend biomarker use as a standalone diagnostic test.

A key barrier to clinical implementation is the heterogeneity in threshold derivation and reporting across studies. Many investigations determined “optimal” cutoffs retrospectively within the study cohort, which risks overestimating diagnostic accuracy and limits external validity. Cutoffs varied widely, and sensitivity and specificity values were inconsistently reported, reducing comparability and limiting the ability to develop standardised clinical algorithms. This limitation is particularly important because clinical utility depends not only on discrimination (AUC) but also on selecting thresholds that optimise rule-out or rule-in performance depending on clinical context. Moreover, verification and ascertainment bias remains a concern, especially in retrospective cohorts where imaging or invasive confirmation may have been symptom-triggered rather than systematically applied to all patients, potentially inflating diagnostic estimates (11,14). The QUADAS-2 assessment therefore supports a cautious interpretation: while the direction and timing of biomarker signal are consistent, the certainty of evidence for generalisable thresholds remains moderate.

The evidence also suggests that multi-marker approaches may not necessarily provide meaningful incremental benefit over CRP alone. In the single included study evaluating combined CRP, PCT, and WBC, the multimarker strategy did not clearly outperform CRP in discrimination, indicating that the added complexity and cost of multiparametric testing may not be justified without standardised prediction models and external validation (17). However, this conclusion should be interpreted carefully, as it is based on limited evidence and does not exclude the potential value of biomarker combinations when integrated with clinical variables and dynamic trends.

From a clinical standpoint, the findings support incorporation of CRP-based monitoring, particularly on POD 3–5, as an adjunct to clinical assessment rather than a replacement. Persistently elevated CRP or abnormal trajectories should heighten clinical suspicion and could be used to trigger earlier diagnostic imaging, closer monitoring, and timely intervention, especially in patients with additional clinical risk factors (2). PCT may be considered a complementary marker in selected settings, particularly where bacterial sepsis differentiation is clinically relevant, although wider adoption requires stronger evidence for reproducible thresholds and cost-effectiveness. Importantly, biomarkers should be interpreted within a multimodal framework that includes clinical examination, vital signs, radiological findings, and knowledge of perioperative course.

Future research should prioritise prospective, multicentre validation studies with standardised leak definitions and uniform reference-standard application. Studies should predefine biomarker thresholds and evaluate reproducibility across settings, while also assessing whether biomarker-guided protocols improve patient-centred outcomes such as reduced leak severity, earlier intervention, lower reoperation rates, and improved oncologic treatment continuity. Interventional trials testing biomarker-triggered imaging or management pathways would provide the strongest evidence for implementation and could move the field from diagnostic prediction toward prevention and harm reduction.

CONCLUSION

In conclusion, this PRISMA-compliant systematic review indicates that serum biomarkers—particularly C-reactive protein and procalcitonin—demonstrate clinically meaningful discriminatory accuracy for predicting anastomotic leak after elective colorectal cancer surgery when measured serially during postoperative days 3 to 5. CRP, the most consistently evaluated biomarker, shows moderate-to-high diagnostic performance across

contemporary cohorts, while PCT offers additional promise as a marker of evolving infectious complications. However, heterogeneity in study design, cutoff derivation, reference-standard verification, and inconsistent reporting of threshold-based accuracy metrics limits the translation of these findings into standardised clinical protocols. Biomarkers should therefore be used as adjunctive tools within multimodal postoperative surveillance rather than as standalone tests. Future prospective studies must focus on external validation of clinically actionable thresholds and on biomarker-guided intervention trials to determine whether structured biomarker pathways improve early detection and postoperative outcomes.

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