



The Relationship between C-Reactive Protein Levels and The Prediction of Anastomotic Leakage : A Systematic Review

¹ Erian Setiawan, ² Fitri Rachmadani

¹ Sungai Raya Dalam Public Health Centre, Kubu Raya Regency, Indonesia /
Graduate of Faculty of Medicine, University of Tarumanagara, Indonesia

² Sozo Skin Clinic, Indonesia / Graduate of Faculty of Medicine, Sultan Agung
Islamic University, Indonesia

Corresponding Email : setiawanerian@gmail.com

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ABSTRACT

Introduction: Anastomotic leakage (AL) remains a devastating complication following gastrointestinal surgery, associated with increased morbidity, mortality, and prolonged hospital stay. C-reactive protein (CRP), an acute-phase inflammatory marker, has emerged as a potential early predictor of AL. This systematic review aims to evaluate the relationship between postoperative CRP levels and the prediction of anastomotic leakage across various surgical procedures.

Methods: A systematic review was conducted following PRISMA guidelines. Comprehensive literature search identified studies evaluating CRP as a predictor of AL in adult patients undergoing gastrointestinal surgery with anastomosis. Studies were included if

they reported quantitative data on CRP levels and AL rates. Data extraction encompassed surgical context, CRP measurement protocols, AL definition and incidence, and CRP predictive performance characteristics.

Results: A total of 146 studies comprising 49,328 patients were included, covering colorectal (n=66), esophageal (n=33), gastric (n=18), and bariatric (n=8) surgeries, with others involving mixed or unspecified procedures. AL incidence ranged from 1.5% in bariatric surgery to 30.6% in esophagectomy. Median time to AL diagnosis was consistently 5-9 days postoperatively. CRP measurement protocols varied considerably, with postoperative days 3-5 demonstrating optimal predictive value. Pooled analysis revealed CRP cutoff values ranging from 120-200 mg/L on POD 3-5, with negative predictive values exceeding 90% in most studies. Significant heterogeneity existed in AL definitions, CRP measurement timing, and reported diagnostic accuracy.

Discussion: Postoperative CRP demonstrates consistent utility as a negative predictive marker for AL, particularly between POD 3-5. Low CRP levels effectively rule out AL with high negative predictive value, potentially enabling safe early discharge. However, optimal cutoff values vary by surgical procedure and patient population. CRP performs best as a rule-out test rather than a rule-in test for AL.

Conclusion: Serial CRP measurement represents a valuable, cost-effective tool for early prediction of anastomotic leakage. Standardized protocols and procedure-specific thresholds are needed to optimize clinical utility. Future research should focus on integrating CRP with other biomarkers and clinical risk scores to enhance predictive accuracy.

Keywords: C-reactive protein, anastomotic leakage, colorectal surgery, esophagectomy, gastrectomy, bariatric surgery, postoperative complications, biomarker

INTRODUCTION

Anastomotic leakage (AL) represents one of the most feared complications following gastrointestinal surgery, with reported incidence rates ranging from 1.5% to over 30% depending on the surgical procedure and patient population (1,33,81). This complication is associated with significantly increased morbidity, mortality, prolonged hospital stay, higher healthcare costs, and impaired long-term oncological outcomes (2,17,123). The clinical presentation of AL is often insidious, with signs and symptoms that may not become apparent until significant intra-abdominal sepsis has developed, typically between postoperative day (POD) 5 and 9 (3,14,21,23). Early detection of AL is therefore critical to enable timely intervention and mitigate adverse outcomes (4,5).

C-reactive protein (CRP), an acute-phase reactant synthesized by hepatocytes in response to pro-inflammatory cytokines, particularly interleukin-6, has emerged as a promising early biomarker for postoperative infectious complications (6,7). Following surgical trauma, CRP levels typically rise, peaking around POD 2-3 before gradually declining in uncomplicated recovery (8,9). However, persistent elevation or secondary rise in CRP may indicate underlying infectious complications, including AL (10,11). The widespread availability, low cost, and standardized measurement of CRP make it an attractive tool for routine postoperative surveillance (12,13).

Despite numerous studies investigating the relationship between CRP and AL, significant heterogeneity exists in study design, patient populations, surgical procedures, CRP measurement protocols, and reported diagnostic accuracy (14,15). Previous systematic reviews and meta-analyses have focused on specific surgical procedures, particularly colorectal surgery and esophagectomy (1,10,66,68). However, a comprehensive synthesis encompassing the full spectrum of gastrointestinal anastomotic surgery, including gastric and bariatric procedures, with detailed analysis of study characteristics, CRP measurement protocols, and predictive performance across different clinical contexts, remains lacking.

Research Gap: While individual studies consistently demonstrate an association between elevated postoperative CRP and AL, the optimal timing of measurement, ideal cutoff values, and consistency of predictive performance across different surgical procedures and patient populations remain poorly defined. Furthermore, the significant variability in AL definitions, CRP measurement protocols, and reported diagnostic accuracy metrics limits direct comparison between studies and impedes the development of standardized clinical guidelines.

Objective: This systematic review aims to comprehensively evaluate the relationship between postoperative C-reactive protein levels and the prediction of anastomotic leakage across all types of gastrointestinal surgery requiring anastomosis. Specifically, we seek to: (1) characterize the heterogeneity in study designs, patient populations, and surgical procedures; (2) analyze CRP measurement protocols including timing, frequency, and units; (3) synthesize reported AL definitions, detection methods, and incidence rates; and (4) evaluate the predictive performance of CRP including optimal cutoff values, timing, and diagnostic accuracy metrics.

Hypothesis: We hypothesize that postoperative CRP measurement, particularly between POD 3-5, demonstrates consistent negative predictive value for AL across different surgical procedures, with low CRP levels effectively ruling out AL, although optimal cutoff values may vary by surgical context and patient characteristics.

Novelty: This systematic review provides the most comprehensive synthesis to date, encompassing 146 studies across colorectal, esophageal, gastric, and bariatric surgery. Unlike previous meta-analyses focused on single procedure types, our inclusive approach enables cross-procedural comparison and identification of common patterns in CRP kinetics and predictive performance. The detailed characterization of study heterogeneity, AL definitions, and CRP measurement protocols provides a foundation for developing standardized approaches to future research and clinical implementation.

Benefits: Establishing the utility of CRP as a predictor of AL has significant clinical implications. Early identification of patients at low risk for AL could facilitate safe early discharge within enhanced recovery protocols, reducing hospital stay and healthcare costs (16,20). Conversely, early identification of high-risk patients could trigger timely diagnostic investigations and interventions, potentially reducing the severity of AL-related complications (4,5,107). Furthermore, understanding procedure-specific CRP thresholds may enable personalized postoperative monitoring strategies.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the relationship between C-Reactive Protein levels and the prediction of anastomotic leakage.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Adult Population:** Does the study involve adult patients (≥ 18 years) who underwent surgical procedures requiring anastomosis?
- **CRP and Anastomotic Leakage Assessment:** Does the study measure C-Reactive Protein levels perioperatively AND assess anastomotic leakage as an outcome with clear diagnostic criteria?

- **Quantitative Data Availability:** Does the study provide quantitative data on CRP levels and anastomotic leakage rates?
- **Appropriate Study Design:** Is the study an observational study (cohort, case-control, cross-sectional), randomized controlled trial, systematic review, or meta-analysis?
- **Adequate Sample Size:** Is the study NOT a case report or case series with fewer than 10 patients?
- **Human Clinical Study:** Is the study NOT an animal study, in vitro study, conference abstract, editorial, or opinion piece?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Adult Patients	C-Reactive Protein	No Anastomotic Leak	Anastomotic Leakage
Keyword 2	Colorectal Surgery	CRP levels	Normal Postoperative Recovery	Early Prediction
Keyword 3	Esophagectomy	Postoperative Day 3 CRP	Other Inflammatory Markers	Diagnostic Accuracy
Keyword 4	Gastrointestinal Surgery	Inflammatory Marker	Clinical Assessment Alone	Postoperative Complication

The Boolean MeSH keywords inputted on databases for this research are: (*"Adult Patients" OR "Colorectal Surgery" OR "Esophagectomy" OR "Gastrointestinal Surgery"*) AND (*"C-Reactive Protein" OR "CRP levels" OR "Postoperative Day 3 CRP" OR "Inflammatory Marker"*) AND (*"No*

Anastomotic Leak" OR "Normal Postoperative Recovery" OR "Other Inflammatory Markers" OR "Clinical Assessment Alone") AND ("Anastomotic Leakage" OR "Early Prediction" OR "Diagnostic Accuracy" OR "Postoperative Complication")

Data extraction

- **Surgical Context:**

Extract details about the surgical population and procedure relevant to CRP prediction of anastomotic leakage, including:

- Type of surgery (colorectal, esophageal, gastric, etc.)
- Surgical approach (open, laparoscopic, robotic)
- Patient population characteristics (age, comorbidities, cancer vs benign)
- Sample size and anastomotic leak incidence rate
- Emergency vs elective procedures

- **CRP Measurement:**

Extract all details about CRP measurement protocol for predicting anastomotic leakage, including:

- Postoperative days when CRP was measured (POD 1, 2, 3, etc.)
- CRP measurement methodology and units (mg/L, mg/dL)
- Baseline/preoperative CRP levels if reported
- Normal CRP reference ranges used
- Frequency of measurements (daily, specific intervals)

- **Anastomotic Leak:**

Extract details about anastomotic leakage definition and detection relevant to CRP prediction, including:

- Clinical definition of anastomotic leak used in the study
- Detection methods (clinical, radiological, endoscopic, operative)
- Mean or median time to leak diagnosis (days post-surgery)
- Leak severity classification if provided
- Total number of leaks and leak rate percentage

- **CRP Predictive Performance:**

Extract all statistical measures of CRP's ability to predict anastomotic leakage, including:

- CRP cutoff values with corresponding postoperative days
- Sensitivity and specificity percentages
- Positive and negative predictive values
- Area under ROC curve (AUC) values
- Mean CRP levels in leak vs no-leak groups by postoperative day
- Statistical significance (p-values) for CRP differences
- Optimal timing for CRP prediction (which POD performs best)

- **Study Design:**

Extract study design characteristics that affect the reliability of CRP-anastomotic leak relationship findings, including:

- Study design (prospective, retrospective, case-control)
- Study period and duration
- Inclusion and exclusion criteria
- Whether patients were matched or randomized
- Loss to follow-up rates
- Single-center vs multi-center

- **Key Findings:**

Extract the main conclusions about the relationship between CRP levels and anastomotic leak prediction, including:

- Authors' primary conclusion about CRP's predictive value
- Recommended CRP thresholds for clinical decision-making
- Comparison with other inflammatory markers if performed
- Clinical recommendations for discharge or monitoring based on CRP
- Limitations or factors that affect CRP predictive accuracy
- Any subgroup analyses (by surgical approach, patient factors)

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Adult Patients" OR "Colorectal Surgery" OR "Esophagectomy" OR "Gastrointestinal Surgery") AND ("C-Reactive Protein" OR "CRP levels" OR "Postoperative Day 3 CRP" OR "Inflammatory Marker") AND ("No Anastomotic Leak" OR "Normal Postoperative Recovery" OR "Other Inflammatory Markers" OR "Clinical Assessment Alone") AND ("Anastomotic Leakage" OR "Early Prediction" OR "Diagnostic Accuracy" OR "Postoperative Complication")</i>	129
Semantic Scholar	<i>("Adult Patients" OR "Colorectal Surgery" OR "Esophagectomy" OR "Gastrointestinal Surgery") AND ("C-Reactive Protein" OR "CRP levels" OR "Postoperative Day 3 CRP" OR "Inflammatory Marker") AND ("No Anastomotic Leak" OR "Normal Postoperative Recovery" OR "Other Inflammatory Markers" OR "Clinical Assessment Alone") AND ("Anastomotic Leakage" OR "Early Prediction" OR "Diagnostic Accuracy" OR "Postoperative Complication")</i>	251
Springer	<i>("Adult Patients" OR "Colorectal Surgery" OR "Esophagectomy" OR "Gastrointestinal Surgery") AND ("C-Reactive Protein" OR "CRP levels" OR "Postoperative Day 3 CRP" OR "Inflammatory Marker") AND ("No Anastomotic Leak" OR "Normal Postoperative Recovery" OR "Other Inflammatory Markers" OR "Clinical Assessment Alone") AND ("Anastomotic Leakage" OR "Early Prediction" OR "Diagnostic Accuracy" OR "Postoperative Complication")</i>	149
Google Scholar	<i>("Adult Patients" OR "Colorectal Surgery" OR "Esophagectomy" OR "Gastrointestinal Surgery") AND ("C-Reactive Protein" OR "CRP levels" OR "Postoperative Day 3 CRP" OR "Inflammatory Marker") AND ("No Anastomotic Leak" OR "Normal Postoperative Recovery" OR "Other Inflammatory Markers" OR "Clinical Assessment Alone") AND ("Anastomotic Leakage" OR "Early Prediction" OR "Diagnostic Accuracy" OR "Postoperative Complication")</i>	156
Wiley Online Library	<i>("Adult Patients" OR "Colorectal Surgery" OR "Esophagectomy" OR "Gastrointestinal Surgery") AND ("C-Reactive Protein" OR "CRP levels" OR "Postoperative Day 3 CRP" OR "Inflammatory Marker") AND ("No Anastomotic Leak" OR "Normal Postoperative Recovery" OR "Other Inflammatory Markers" OR "Clinical Assessment Alone") AND ("Anastomotic Leakage" OR "Early Prediction" OR "Diagnostic Accuracy" OR "Postoperative Complication")</i>	164

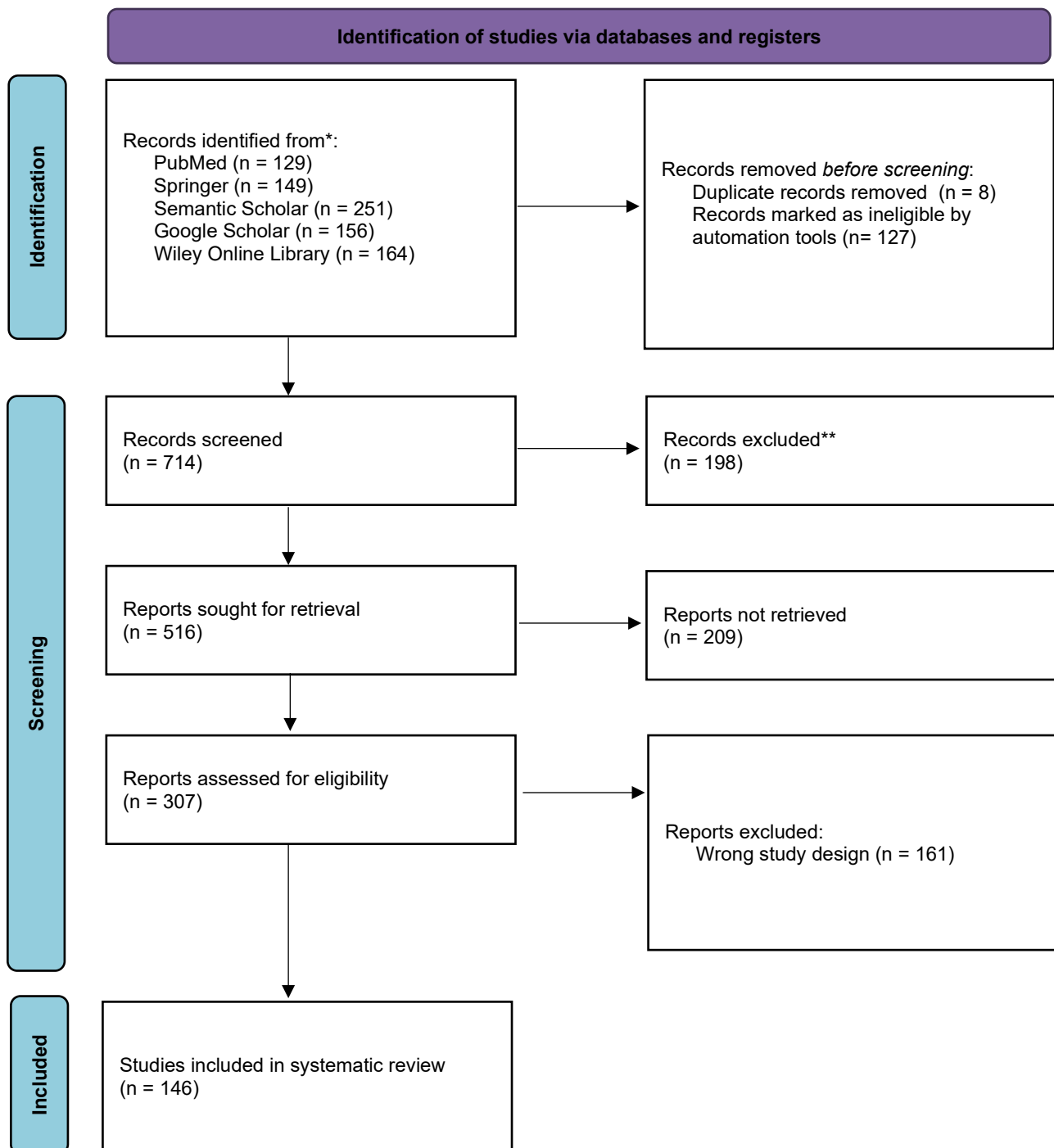


Figure 1. Article search flowchart

RESULTS

Study Characteristics

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Denise E. Yeung et al., 2021 [1]	Multi-center [1]	2007-2020 [1]	6647 [1]	Colorectal [1]	Open, Laparoscopic, Robotic [1]	Adults with benign/malignant pathology [1]	7.3 [1]
B. Borraez-Segura et al., 2022 [34]	Multi-center [34]	2018-2019 [34]	97 [34]	Colorectal (56%), Gastric (36%) [34]	Not mentioned	Mean age 63, primarily cancer [34]	5.0 [34]
M. Scepanovic et al., 2013 [2]	Not mentioned	Not mentioned	156 [2]	Abdominal surgery [2]	Not mentioned	Not mentioned	9.6 [2]
Eijiro Edagawa et al., 2015 [3]	Not mentioned	Not mentioned	108 [3]	Esophagectomy [3]	Not mentioned	Not mentioned	19.4 [3]
Isa Basuki et al., 2020 [72]	Single-center [72]	2019 [72]	40 [72]	Bowel resection [72]	Not mentioned	Age 18-75 [72]	Not mentioned

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
P. Waterland et al., 2016 [30]	Not mentioned	2011-2014 [30]	727 [30]	Colorectal [30]	Open, Laparoscopic [30]	Elective surgery [30]	7.9 [30]
D. Jin et al., 2021 [8]	Single-center [8]	2013-2015 [8]	196 [8]	Rectal surgery [8]	Laparoscopic [8]	Rectal cancer [8]	5.6 [8]
J. Park et al., 2017 [73]	Single-center [73]	2009-2016 [73]	201 [73]	Esophagectomy [73]	Not mentioned	Esophageal cancer [73]	11.4 [73]
P. Ortega-Deballon et al., 2010 [19]	Not mentioned	2007-2008 [19]	133 [19]	Colorectal [19]	Not mentioned	Elective surgery [19]	15.5 [19]
E. Asti et al., 2018 [142]	Not mentioned	2012-2017 [142]	243 [142]	Esophageal [142]	Minimally invasive [142]	Esophageal cancer [142]	11.9 [142]
T. Welsch et al., 2007 [26]	Not mentioned	Not mentioned	383 total, 48 leaks [26]	Rectal resections [26]	Not mentioned	Rectal cancer [26]	12.5 [26]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
M. Ramos Fernández et al., 2017 [9]	Not mentioned	Not mentioned	168 [9]	Colorectal [9]	Open, Laparoscopic [9]	Elective surgery [9]	8.3 [9]
A. Aiolfi et al., 2018 [10]	Not specified	2012-2018 [10]	850 [10]	Esophagectomy [10]	Open, Minimally invasive [10]	Squamous-cell carcinoma (50%), Adenocarcinoma (47%) [10]	11.0 [10]
D. Bona et al., 2022 [66]	Not mentioned	Not mentioned	11,144 [66]	Colorectal [66]	Not mentioned	Not mentioned	8.0 [66]
Á. García-Granero et al., 2013 [74]	Single-center [74]	Not mentioned	205 [74]	Colorectal [74]	Not mentioned	Elective surgery [74]	8.3 [74]
Tiffany Paradis et al., 2020 [31]	Not mentioned	Not mentioned	13 studies [31]	Colorectal [31]	Laparoscopic, Open [31]	Elective surgery [31]	14.8 (lap), 21.0 (open) [31]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
J. Platt et al., 2012 [11]	Single-center [11]	Not mentioned	454 [11]	Colorectal cancer surgery [11]	Not mentioned	Colorectal cancer [11]	5.7 [11]
D. Bona et al., 2019 [67]	Not mentioned	Not mentioned	1401 [67]	Bariatric (LSG, LRYGB) [67]	Laparoscopic [67]	Not specified	9.8 [67]
P. Paliogiannis et al., 2021 [121]	Multi-center [121]	Not mentioned	1183 [121]	Colorectal [121]	Not mentioned	Colorectal cancer, elective [121]	Not mentioned
Haddon J Pantel et al., 2019 [4]	Single-center [4]	2013-2017 [4]	752 [4]	Colorectal resection [4]	Not mentioned	Elective surgery [4]	2.0 [4]
Devarajan Jebin Aaron et al., 2021 [27]	Single-center [27]	Not mentioned	84 [27]	Gastrointestinal surgery [27]	Not mentioned	Elective surgery [27]	26.2 [27]
M. Mik et al., 2017 [75]	Single-center [75]	2010-2014 [75]	724 [75]	Colorectal cancer surgery [75]	Open [75]	Colorectal cancer [75]	4.6 [75]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Dubravka Mužina et al., 2024 [76]	Single-center [76]	2023 [76]	100 [76]	Colorectal surgery [76]	Not mentioned	Colorectal carcinoma [76]	10.0 [76]
J. Muñoz et al., 2018 [20]	Not mentioned	2015-2017 [20]	134 [20]	Colorectal surgery [20]	Laparoscopic [20]	Not specified	4.5 [20]
T. Pedersen et al., 2012 [77]	Single-center [77]	1 year [77]	129 [77]	Colorectal surgery [77]	Laparoscopic [77]	Not specified	Part of 32% septic comp. [77]
Praachi Raje et al., 2023 [78]	Single-center [78]	2019-2020 [78]	332 [78]	Colectomy or proctectomy [78]	Open [78]	Elective surgery [78]	6.9 [78]
N. Lagoutte et al., 2012 [35]	Not mentioned	2010-2011 [35]	100 [35]	Colorectal surgery [35]	Not mentioned	Elective surgery [35]	13.0 [35]
E. Van Daele et al., 2024 [68]	Not mentioned	Not mentioned	5348 [68]	Esophagectomy [68]	Not mentioned	Not mentioned	13.0 [68]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
I. A. Bilgin et al., 2017 [28]	Not mentioned	Not mentioned	50 [28]	Low anterior resection [28]	Not mentioned	Rectal carcinoma [28]	14.0 [28]
P. Rat et al., 2022 [12]	Multi-center [12]	2009-2017 [12]	585 [12]	Esophagectomy (Ivor-Lewis) [12]	Not mentioned	Not mentioned	11.8 [12]
T. Masuda et al., 2021 [13]	Single-center [13]	2012-2019 [13]	247 [13]	Right-sided colectomy [13]	Open and Laparoscopic [13]	Elective surgery [13]	3.6 [13]
L. C. Pandini et al., 2010 [7]	Single-center [7]	2002-2005 [7]	352 [7]	Colorectal resection [7]	Not mentioned	Not mentioned	7.6 [7]
E. Hagens et al., 2019 [36]	Single-center [36]	2016-2018 [36]	200 [36]	Esophagectomy [36]	Not mentioned	Esophageal carcinoma [36]	Not mentioned
Jia Lu et al., 2017 [37]	Single-center [37]	2015-2016 [37]	172 [37]	Colorectal surgery [37]	Not mentioned	Colorectal cancer [37]	14.0 [37]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
B. Messias et al., 2020 [14]	Single-center [14]	2014-2018 [14]	90 [14]	Colorectal surgery [14]	Not mentioned	Median age 56 [14]	12.2 [14]
N. Rama et al., 2022 [38]	Single-center [38]	2017-2019 [38]	396 [38]	Colorectal resection [38]	Not specified	Not detailed	6.3 [38]
E. Lazarus et al., 2022 [39]	Single-center [39]	2016-2017 [39]	113 [39]	Colorectal surgery [39]	Open, Laparoscopic [39]	Malignancy common [39]	19.4 [39]
M. Zawadzki et al., 2015 [18]	Single-center [18]	2013-2014 [18]	55 [18]	Colorectal cancer resection [18]	Open, Robotic [18]	Average age 66, Colorectal cancer [18]	9.1 [18]
Chi Zhang et al., 2021 [79]	Single-center [79]	2019-2020 [79]	273 [79]	Esophagectomy [79]	VATS, RATS [79]	Average age 64, Esophageal cancer [79]	12.5 [79]
G. Guevara-Morales et al., 2019 [5]	Single-center [5]	2014-2017 [5]	138 [5]	Colorectal surgery [5]	Primarily open [5]	Average age 57, Elective surgery [5]	6.5 [5]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
E. Hagens et al., 2023 [21]	Single-center [21]	2016-2018 [21]	200 [21]	Minimally invasive esophagectomy [21]	Minimally invasive [21]	Esophageal cancer, Median age 66 [21]	11.0 [21]
A. Barbaro et al., 2020 [69]	Not mentioned	Not mentioned	Not mentioned	Esophagectomy [69]	Not mentioned	Not mentioned	Not mentioned
Y. Kulu et al., 2013 [128]	Single-center [128]	2001-2011 [128]	746 [128]	Sphincter-preserving rectal resection [128]	Not mentioned	Rectal cancer [128]	7.5 [128]
Wahidullah Dost et al., 2024 [15]	Multi-center [15]	Not mentioned	59 to 2,655 [15]	Colorectal surgery [15]	Not specified	Not detailed	Not specified
Erik D. Nilsson et al., 2018 [122]	Multi-center [122]	2006-2017 [122]	462 total, 155 with AL [122]	Esophageal/gastr oesophageal surgery [122]	Not specified	Oesophageal/junctional cancer [122]	33.5 [122]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
R. Warschkow et al., 2012 [80]	Single-center [80]	2002-2011 [80]	410 [80]	Laparoscopic gastric bypass (LRYGB) [80]	Laparoscopic [80]	Severely obese patients [80]	4.1 [80]
Tomáš Řezáč et al., 2021 [129]	Not mentioned	1 year [129]	162 [129]	Rectal resection [129]	Open [129]	Rectal cancer [129]	9.9 [129]
M. Zawadzki et al., 2018 [40]	Single-center [40]	2013-2015 [40]	32 [40]	Low anterior resection [40]	Open, Robotic [40]	Elective, Rectal adenocarcinoma [40]	15.2 [40]
V. Javier et al., 2020 [130]	Not mentioned	16 months [130]	84 [130]	Colorectal surgery [130]	Not mentioned	Not mentioned	9.5 [130]
Amirhossein Vaziri-Moghaddam et al., 2017 [131]	Not mentioned	Not mentioned	214 [131]	Colorectal surgery [131]	Not mentioned	Cancer or other diseases [131]	7.9 [131]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
S. Chiappetta et al., 2019 [81]	Single-center [81]	Not mentioned	471 [81]	Bariatric surgery [81]	Laparoscopic [81]	Severe obesity [81]	1.5 [81]
Mohamed Elkerkary et al., 2020 [41]	Single-center [41]	2015-2016 [41]	45 [41]	Gastrointestinal surgery [41]	Laparotomy (80%), Laparoscopic (20%) [41]	Age 18-72, 62% female [41]	22.2 [41]
M. Pera et al., 2017 [16]	Not mentioned	Not mentioned	221 [16]	Rectal resection [16]	Not mentioned	Rectal cancer [16]	Not mentioned
Mostafa Omar Abdel Aziz et al., 2025 [70]	Not mentioned	Not mentioned	Not mentioned	Colorectal anastomosis [70]	Not mentioned	Adult, elective surgery [70]	Not mentioned
Bruce Su'a et al., 2022 [42]	Multi-center [42]	3 years [42]	Not specified; 16 leaks [42]	Elective colectomy [42]	Not specified	Consecutive adults [42]	5.7 [42]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
G. Song et al., 2022 [43]	Single-center [43]	2019-2020 [43]	120 [43]	Dixon surgery for rectal cancer [43]	Not specified	Rectal cancer, age 19-78 [43]	11.7 [43]
Mads Riiskjær et al., 2016 [132]	Not mentioned	2009-2015 [132]	217 [132]	Bowel resection for endometriosis [132]	Laparoscopic [132]	Deep infiltrating endometriosis [132]	8.3 [132]
S. Dutta et al., 2011 [44]	Not mentioned	7 days/patient [44]	136 [44]	Esophagogastric cancer resection [44]	Not mentioned	Cancer patients [44]	12.5 [44]
Yilong Hu et al., 2024 [82]	Single-center [82]	2019-2023 [82]	113 [82]	Colorectal surgery [82]	Laparoscopic, Open [82]	Average age 68, colorectal cancer [82]	9.7 [82]
M. Baeza-Murcia et al., 2021 [133]	Not mentioned	Not mentioned	95 [133]	Colorectal surgery [133]	Not mentioned	Elective surgery [133]	14.0 [133]
N. Komen et al., 2014 [83]	Multi-center [83]	Not mentioned	243 [83]	Colorectal surgery [83]	Open, Laparoscopic [83]	Mean age 64, mainly for malignancy [83]	8.0 [83]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
S. Chernyshov et al., 2018 [84]	Single-center [84]	2013-2016 [84]	100 [84]	Low anterior resection (LAR-TME) [84]	Not mentioned	Various risk factors identified [84]	11.0 [84]
Pola Anwar et al., 2019 [45]	Single-center [45]	2018 [45]	24 [45]	Colorectal resection [45]	Open [45]	Colorectal cancer, elective [45]	20.8 [45]
C. Neary et al., 2020 [85]	Single-center [85]	2014-2018 [85]	148 total (71 Oes, 77 Gas) [85]	Oesophagectomy, Gastrectomy [85]	Not mentioned	Not mentioned	7.0 [85]
Z. Kostić et al., 2015 [134]	Not mentioned	Not mentioned	150 [134]	Colorectal resection [134]	Not mentioned	Colorectal cancer [134]	10.0 [134]
Mohammed M. Raslan et al., 2024 [135]	Single-center [135]	2021-2022 [135]	105 [135]	Colorectal and intestinal surgery [135]	Open, Laparoscopic [135]	Mean age 49, 61% male [135]	19.0 [135]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
K. Albanopoulos et al., 2013 [46]	Not mentioned	2008-2011 [46]	177 [46]	Laparoscopic sleeve gastrectomy (LSG) [46]	Laparoscopic [46]	Not mentioned	Not mentioned
A. Mohamedahmed et al., 2024 [32]	Single-center [32]	2021-2022 [32]	231 [32]	Colorectal resection [32]	Mixed approaches [32]	Mean age 69, elective surgery [32]	3.0 [32]
K. Kano et al., 2015 [145]	Not mentioned	2008-2014 [145]	77 [145]	Gastric cancer resection [145]	Open [145]	Gastric cancer [145]	9.1 [145]
H. Amoli et al., 2021 [86]	Not mentioned	2017-2019 [86]	315 [86]	Colorectal surgery [86]	Not mentioned	Mean age 56, elective [86]	8.3 [86]
Haidi Abd El Zaher et al., 2022 [47]	Single-center [47]	2018-2020 [47]	205 [47]	Colorectal surgery [47]	Open (86%), Laparoscopic (14%) [47]	Mean age 56, mixed comorbidities [47]	10.7 [47]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Hernán Daniel Pinares-Carrillo et al., 2023 [87]	Single-center [87]	2019-2021 [87]	270 [87]	Colorectal surgery [87]	Open, Laparoscopic [87]	Colon cancer, elective surgery [87]	16.7 [87]
M. Slavin et al., 2022 [22]	Single-center [22]	2012-2017 [22]	92 [22]	Colorectal surgery for Crohn's disease [22]	Laparoscopic, Open [22]	Crohn's disease patients [22]	11.9 [22]
Ю. А. Шельгин et al., 2017 [88]	Single-center [88]	2013-2016 [88]	100 [88]	Lower anterior resection [88]	Not mentioned	Epithelial rectal tumors [88]	20.0 [88]
Pooya Rajabaleyan et al., 2024 [89]	Single-center [89]	2013-2018 [89]	1855 [89]	Colon cancer surgery [89]	Not mentioned	Colon cancer patients [89]	Not mentioned
Anders Gerdin et al., 2024 [123]	Multi-center [123]	2014-2018 [123]	1036 [123]	Anterior resection for rectal cancer [123]	Not mentioned	Rectal cancer, males, smokers [123]	21.0 [123]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
J. Ruiz-Tovar et al., 2017 [48]	Not mentioned	2012-2015 [48]	208 [48]	Laparoscopic sleeve gastrectomy [48]	Laparoscopic [48]	Morbidly obese patients [48]	3.8 [48]
R. Warschkow et al., 2011 [17]	Single-center [17]	1997-2009 [17]	1187 [17]	Open resection of colorectal cancer [17]	Open [17]	Colorectal cancer patients [17]	8.0 [17]
Jinyao Shi et al., 2020 [90]	Single-center [90]	2017-2018 [90]	350 [90]	Gastrectomy [90]	Open, Laparoscopic [90]	Gastric cancer, elective surgery [90]	6.5 [90]
Lukas F. Liesenfeld et al., 2020 [91]	Single-center [91]	2010-2016 [91]	233 [91]	Esophageal resection [91]	Open [91]	Malignant disease (99%), elective [91]	24.5 [91]
B. Romain et al., 2014 [49]	Not mentioned	2010-2012 [49]	126 [49]	Laparoscopic gastric bypass [49]	Laparoscopic [49]	Morbid obesity [49]	3.2 [49]
S. M et al., 2018 [50]	Not mentioned	Not mentioned	50 [50]	Colorectal surgeries [50]	Not mentioned	Elective surgery [50]	14.0 [50]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
S. Stuart et al., 2021 [92]	Single-center [92]	2018-2020 [92]	109 [92]	Esophagectomy (Ivor-Lewis) [92]	Minimally invasive [92]	Esophageal cancer [92]	12.0 [92]
J. Charbonneau et al., 2024 [51]	Single-center [51]	2018-2020 [51]	99 [51]	CRS and HIPEC [51]	Not mentioned	Peritoneal metastases [51]	4.0 [51]
Julius Pochhammer et al., 2020 [93]	Single-center [93]	2009-2018 [93]	1073 [93]	Bariatric surgery [93]	Laparoscopic [93]	Severely obese patients [93]	4.2 [93]
F. Dib et al., 2017 [52]	Single-center [52]	2011-2015 [52]	1326 [52]	Laparoscopic sleeve gastrectomy (LSG) [52]	Laparoscopic [52]	Not specified	1.9 [52]
Feng Zhang et al., 2022 [94]	Single-center [94]	2020-2021 [94]	204 [94]	Colorectal resection [94]	Laparoscopic [94]	Mean age 63, colorectal cancer [94]	9.3 [94]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Olga V. Ilina et al., 2020 [146]	Not mentioned	Not mentioned	130 [146]	Gastrectomy for cancer [146]	Not mentioned	Gastric cancer, malnourished [146]	10.0 [146]
M. Gordiichuk et al., 2024 [53]	Single-center [53]	2020-2023 [53]	213 [53]	Low anterior resection [53]	Not mentioned	Rectal cancer, age ≥18, elective [53]	11.7 [53]
M. Carvello et al., 2020 [136]	Single-center [136]	2013-2017 [136]	251 [136]	Colorectal surgery [136]	Not mentioned	Crohn's disease, elective surgery [136]	4.0 [136]
D. Çetin et al., 2018 [95]	Single-center [95]	2013-2016 [95]	80 [95]	Total gastrectomy [95]	Not mentioned	Gastric cancer, mean age 61 [95]	Not mentioned
P. McAnena et al., 2019 [6]	Single-center [6]	2010-2017 [6]	102 [6]	Oesophagectomy [6]	Not mentioned	Mean age 62.5, 82% male [6]	4.9 [6]
Tomoaki Bekki et al., 2023 [124]	Multi-center [124]	2016-2020 [124]	803 [124]	Rectal resection [124]	Stapled anastomosis [124]	Rectal cancer, diabetes, male sex [124]	8.0 [124]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
D. Çetin et al., 2019 [96]	Single-center [96]	2013-2016 [96]	80 [96]	Total gastrectomy [96]	Not mentioned	Gastric cancer, mean age 61 [96]	Not mentioned
G. Guevara-Morales et al., 2018 [137]	Not mentioned	Not mentioned	138 [137]	Colorectal surgery [137]	Not mentioned	Elective surgery [137]	6.5 [137]
F. Richter et al., 2022 [33]	Single-center [33]	2008-2021 [33]	305 [33]	Esophagectomy [33]	Robotic (RAMIE), Open (OE) [33]	Cancer, benign cond., elective [33]	30.6 (RAMIE), 28.3 (OE) [33]
G. Broadley et al., 2015 [125]	Multi-center [125]	2010-2014 [125]	379 [125]	Colorectal cancer resection [125]	Open, Laparoscopic [125]	Rectal cancer [125]	12.9 [125]
N. Isohata et al., 2023 [23]	Single-center [23]	2012-2021 [23]	331 [23]	Colorectal surgery [23]	Laparotomy, Laparoscopy [23]	Median age 69, elective surgery [23]	8.5 [23]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Anders Gerdin et al., 2024a [126]	Multi-center [126]	2014-2018 [126]	1036 [126]	Anterior resection for rectal cancer [126]	Not mentioned	Rectal cancer patients [126]	21.0 [126]
J. van den Bos et al., 2019 [54]	Single-center [54]	Not mentioned	30 [54]	Colorectal cancer surgery [54]	Laparoscopic, Robotic [54]	Mean age 67, elective surgery [54]	16.7 [54]
W. Al-Kubati et al., 2024 [71]	Not mentioned	Not mentioned	49,328 [71]	Colorectal surgery [71]	Not mentioned	Not mentioned	Not mentioned
Jiixin Zhang et al., 2022 [24]	Not mentioned	Not mentioned	1278 [24]	Laparoscopic TME [24]	Laparoscopic [24]	Middle/low rectal cancer, elective [24]	5.9 [24]
M. Issa et al., 2024 [97]	Single-center [97]	5 years [97]	131 [97]	IBD resection [97]	Laparoscopic (77%) [97]	Median age 37, Crohn's disease (75%) [97]	23.8 [97]
Bernardo Borr�ez-Segura et al., 2023 [55]	Single-center [55]	2018-2022 [55]	157 [55]	Gastrectomy, Rectal resection, Hemicolectomy [55]	Not specified	Mean age 64, various cancer diagnoses [55]	8.3 [55]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
L. Dahbi-Skali et al., 2020 [138]	Not mentioned	2018-2019 [138]	112 [138]	Colorectal surgery [138]	Not mentioned	Not mentioned	11.6 [138]
Mumtazuddin Wani et al., 2020 [56]	Single-center [56]	2017-2019 [56]	60 [56]	Colorectal surgeries [56]	Not specified	Mean age 55, 73% male [56]	26.7 [56]
P. Leourier et al., 2023 [98]	Single-center [98]	2017-2022 [98]	661 [98]	Colorectal surgery (CRS) [98]	Not mentioned	Elective surgery [98]	7.4 [98]
M. Bahbah et al., 2021 [99]	Single-center [99]	7 years [99]	113 [99]	Colorectal resection [99]	Not mentioned	N0M0 colorectal cancer, elective [99]	8.9 [99]
I. Ozata et al., 2023 [100]	Single-center [100]	2014-2018 [100]	184 [100]	Colorectal cancer surgery [100]	Not mentioned	Curative surgery for cancer [100]	6.0 [100]
E. Bertocchi et al., 2021 [57]	Single-center [57]	2017-2018 [57]	262 [57]	Laparoscopic colorectal resection [57]	Laparoscopic [57]	Deep infiltrating endometriosis [57]	3.2 [57]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
G. Feeney et al., 2020 [101]	Single-center [101]	2009-2017 [101]	288 [101]	Colorectal resection [101]	Not mentioned	Rectal cancer, mean age 66 [101]	3.8 [101]
Sanne K. Stuart et al., 2022 [102]	Not mentioned	2017-2021 [102]	193 [102]	Esophagectomy (Ivor-Lewis) [102]	Minimally invasive [102]	Esophageal cancer [102]	16.0 [102]
V. Hubaud et al., 2020 [58]	Single-center [58]	2019-2020 [58]	52 [58]	Esophagectomy [58]	Not mentioned	Not mentioned	23.0 [58]
Thitiporn Chobarporn et al., 2023 [103]	Single-center [103]	2016-2022 [103]	36 [103]	Salvage esophagectomy [103]	Open [103]	Mean age 59, esophageal SCC [103]	8.3 [103]
Fatme Valentina Diaz Gasaly et al., 2024 [59]	Single-center [59]	2019-2022 [59]	107 [59]	Partial colectomy for cancer [59]	Not mentioned	Elective surgery for cancer [59]	7.4 [59]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
M. Chairi et al., 2025 [139]	Not mentioned	2018-2023 [139]	639 [139]	Colon resection [139]	Minimally invasive [139]	Age and male sex are factors [139]	9.7 [139]
E. van Daele et al., 2024 [104]	Single-center [104]	2010-2020 [104]	668 [104]	Esophagectomy [104]	Open, Hybrid, Minimally invasive [104]	Mean age 64, mainly adenocarcinoma [104]	11.1 [104]
E. Andreatta et al., 2022 [105]	Single-center [105]	2016-2020 [105]	121 [105]	Ivor Lewis esophagectomy [105]	Hybrid [105]	Elective, median age 63-65 [105]	9.9 [105]
F. Din et al., 2021 [106]	Single-center [106]	2 years [106]	60 [106]	Colorectal surgery [106]	Not mentioned	Mean age 55, 73% male [106]	26.7 [106]
Mohamed S. Essa et al., 2021 [60]	Single-center [60]	2018-2021 [60]	130 [60]	Colorectal surgery [60]	Laparoscopic, Open [60]	Resectable colorectal cancer [60]	7.7 [60]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Zhiqiang Cheng et al., 2025 [107]	Single-center [107]	2021-2025 [107]	516 [107]	Laparoscopic rectal cancer surgery [107]	Laparoscopic [107]	Laparoscopic anterior resection [107]	3.5% (TDT) vs 8.5% (control) [107]
S. Cuff et al., 2022 [61]	Single-center [61]	2019-2021 [61]	42 [61]	Anterior resection for rectal cancer [61]	Laparoscopic, Open [61]	Rectal cancer, median age 65 [61]	9.5 [61]
Ayman A. Albatanony et al., 2019 [62]	Single-center [62]	Not mentioned	80 [62]	Colorectal anastomoses [62]	Hand-sewn [62]	Not specified	15.0 [62]
Ferdinando Cananzi et al., 2022 [63]	Multi-center [63]	2016-2021 [63]	Not mentioned	Gastrectomy [63]	Not mentioned	Not mentioned	4.6 [63]
J. Nam et al., 2023 [140]	Single-center [140]	2018-2022 [140]	178 [140]	Colorectal cancer surgery [140]	Not mentioned	Elective, curative intent [140]	2.2 [140]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Won Jun Kim et al., 2019 [108]	Not mentioned	Not mentioned	94 [108]	Gastrectomy [108]	Not mentioned	Not mentioned	4.6% (control), 2.0% (interv.) [108]
F. Merboth et al., 2024 [109]	Single-center [109]	2005-2017 [109]	146 AL vs 292 non-AL [109]	Gastric/esophageal resection [109]	Open, Minimally invasive [109]	Elective, median age ~64 [109]	Not specified
H. Ishida et al., 2024 [143]	Not mentioned	Not mentioned	439 [143]	Esophagectomy [143]	Minimally invasive [143]	Not specified	11.6 [143]
G. Laamiri et al., 2021 [64]	Multi-center [64]	Not mentioned	175 [64]	Colorectal surgery [64]	Not mentioned	Not mentioned	16.6 [64]
M. Slavin et al., 2021 [110]	Single-center [110]	2012-2017 [110]	92 [110]	Bowel anastomoses [110]	Laparoscopic, Open [110]	Crohn's disease patients [110]	11.9 [110]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
E. Vaclair et al., 2020 [111]	Single-center [111]	2011-2014 [111]	497 [111]	Colorectal resection [111]	Not mentioned	Elective surgery [111]	16.9 (rectal), 9.9 (colic) [111]
P. Rat et al., 2020 [25]	Single-center [25]	2009-2017 [25]	620 [25]	Esophagectomy [25]	Open thoracic [25]	Cancer patients [25]	12.7 [25]
D. Ortíz-López et al., 2025 [112]	Single-center [112]	2015-2022 [112]	935 [112]	Colorectal cancer surgery [112]	Mostly minimally invasive [112]	Elective, median age 70 [112]	5.5 [112]
L. Giuliani et al., 2018 [144]	Single-center [144]	2015-2017 [144]	126 [144]	Ivor-Lewis esophagectomy [144]	Not mentioned	Cancer patients [144]	7.1 [144]
Limian Ling et al., 2025 [65]	Single-center [65]	2023-2024 [65]	306 [65]	Anterior resection for cancer [65]	Laparoscopic (93%) [65]	Elective, mean age 59 [65]	8.2 [65]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
Radwa Hablase et al., 2025 [113]	Single-center [113]	2010-2022 [113]	641 total [113]	Colorectal resection [113]	Not mentioned	Ovarian & colorectal cancer [113]	4.7 (Ovarian), 1.9 (CRC) [113]
Bin Luo et al., 2020 [114]	Single-center [114]	2015-2020 [114]	114 [114]	Laparoscopic gastrectomy [114]	Laparoscopic [114]	AEG cancer, elective [114]	11.4 [114]
M. Cats et al., 2025 [127]	Multi-center [127]	Not mentioned	127 [127]	CRS-HIPEC and CCS [127]	Not mentioned	Adult, elective surgery [127]	Not applicable
M. Cunha et al., 2021 [115]	Single-center [115]	2019-2020 [115]	93 [115]	Colorectal surgery [115]	Open, Laparoscopic [115]	Elective, median age 66 [115]	7.5 [115]
Ashish Kumar Sharma et al., 2025 [141]	Not mentioned	Not mentioned	109 [141]	Colorectal surgery [141]	Not mentioned	ASA grade $\geq$ III [141]	11.9 [141]

Study	Setting	Study Period	Sample Size	Type of Surgery	Surgical Approach	Patient Population	Leak Incidence (%)
J. Kynaston et al., 2015 [29]	Single-center [29]	2008-2014 [29]	1311 [29]	Colorectal cancer resection [29]	Not specified	Elective and emergency [29]	3.4 [29]
M. Carvello et al., 2018 [116]	Single-center [116]	2013-2017 [116]	251 [116]	Colorectal resection [116]	Not mentioned	Crohn's disease, elective [116]	4.0 [116]
G. Popescu et al., 2017 [117]	Single-center [117]	2010-2015 [117]	431 [117]	Colorectal cancer surgery [117]	Not mentioned	Average age ~65, male predominant [117]	4.9 [117]
Guogang Wu et al., 2018 [118]	Single-center [118]	2013-2017 [118]	408 [118]	Colorectal cancer operation [118]	Not mentioned	Not mentioned	4.7 [118]
L. Emmanuel et al., 2018 [119]	Not mentioned	Not mentioned	113 [119]	Colorectal surgery [119]	Open, Laparoscopic [119]	Elective surgery [119]	12.1 [119]
Hailong Guo et al., 2017 [120]	Single-center [120]	2012-2015 [120]	217 [120]	Esophageal cancer surgery [120]	Not mentioned	Not detailed	29.9 [120]

Anastomotic Leak Definition, Detection, and Incidence

Anastomotic leakage was variably defined across the reviewed literature, although most studies converged on a definition involving a defect at the anastomotic site confirmed through clinical, radiological, or operative evidence [1, 5, 34, 56, 79, 82, 94, 110]. Common clinical criteria included signs of peritonitis, or fecal, purulent, or intestinal content emerging from surgical wounds or drains [14, 23, 41, 56, 87, 94]. Radiological confirmation methods frequently cited were contrast-enhanced computed tomography (CT) showing extravasation, abscess, or fluid/air collections near the anastomosis [5, 14, 23, 32, 39, 82, 91, 100, 125], as well as contrast enema studies [23, 73]. Endoscopy was another key diagnostic tool used to directly visualize anastomotic defects [21, 79, 91, 94, 105]. Operative confirmation during re-exploration served as a definitive diagnostic method in several studies [1, 5, 30, 40, 60, 79, 80, 110].

The incidence of anastomotic leakage varied significantly depending on the surgical context, ranging from 1.5% in bariatric surgery to over 30% in some series of esophagectomy and colorectal surgery [33, 55, 81]. The median time to diagnosis was consistently reported to be between postoperative day 5 and 9 [3, 14, 21, 23, 29, 38, 42, 56, 62, 63, 65, 66, 78, 80, 91, 102, 127]. Some studies classified leak severity using systems like the Clavien-Dindo classification or the International Study Group of Rectal Cancer (ISREC) grading (Grade A, B, C) [23, 34, 104, 109, 123, 128, 129]. This heterogeneity in definitions, detection methods, and populations contributes to the variability in reported leak rates and can impact the comparability of CRP predictive performance across studies.

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
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Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
Denise E. Yeung et al., 2021 [1]	Radiological or operative evidence of defect [1]	Radiological, operative [1]	482/6647 [1]	7.3 [1]	7.7 (mean) [1]	Not mentioned
B. Borraez-Segura et al., 2022 [34]	Clinical signs of peritonitis or fluid from drain [34]	Clinical, imaging, endoscopic [34]	5/97 [34]	5.0 [34]	7 [34]	Clavien-Dindo [34]
M. Scepanovic et al., 2013 [2]	Not mentioned	Not mentioned	15/156 [2]	9.6 [2]	Not mentioned	Not mentioned
Eijiro Edagawa et al., 2015 [3]	Not mentioned	Not mentioned	21/108 [3]	19.4 [3]	8 [3]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
Isa Basuki et al., 2020 [72]	Not mentioned	Clinical signs [72]	Not mentioned	Not mentioned	Not mentioned	Not mentioned
P. Waterland et al., 2016 [30]	Strict operative and radiological criteria [30]	Operative, radiological [30]	58/727 [30]	7.9 [30]	Not mentioned	Not mentioned
D. Jin et al., 2021 [8]	Not mentioned	Not mentioned	11/196 [8]	5.6 [8]	Not mentioned	Not mentioned
J. Park et al., 2017 [73]	Disruption of anastomosis with content outflow [73]	Barium esophagogram, chest CT [73]	23/201 [73]	11.4 [73]	Not mentioned	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
P. Ortega-Deballon et al., 2010 [19]	All detected leaks considered fistulas [19]	Clinical, laboratory data [19]	Not specified	15.5 [19]	Not mentioned	Not mentioned
E. Asti et al., 2018 [142]	Not mentioned	Clinical, radiological signs [142]	29/243 [142]	11.9 [142]	Not mentioned	Not mentioned
M. Ramos Fernández et al., 2017 [9]	Not mentioned	Clinical detection [9]	14/168 [9]	8.3 [9]	~4 [9]	Not mentioned
A. Aiolfi et al., 2018 [10]	Symptoms confirmed by radiology, endoscopy, or surgery [10]	Clinical, radiological, endoscopic, operative [10]	Not specified	11.0 [10]	Not mentioned	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
D. Bona et al., 2022 [66]	Not mentioned	Not mentioned	Not specified	8.0 [66]	6.9 [66]	Not mentioned
Á. García-Granero et al., 2013 [74]	Not mentioned	Clinical approach with serological markers [74]	17/205 [74]	8.3 [74]	Not mentioned	Major vs. minor [74]
J. Platt et al., 2012 [11]	Not mentioned	Not mentioned	26/454 [11]	5.7 [11]	Not mentioned	Not mentioned
Haddon J Pantel et al., 2019 [4]	Not mentioned	Not mentioned	17/752 [4]	2.0 [4]	Not mentioned	Not mentioned
Devarajan Jebin Aaron et al., 2021 [27]	Not mentioned	Biochemical detection (CRP) [27]	22/84 [27]	26.2 [27]	Not mentioned	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
M. Mik et al., 2017 [75]	Not mentioned	Not mentioned	33/724 [75]	4.6 [75]	Not mentioned	Not mentioned
Dubravka Mužina et al., 2024 [76]	Not mentioned	Biochemical detection [76]	10/100 [76]	10.0 [76]	Not mentioned	Not mentioned
J. Muñoz et al., 2018 [20]	Not mentioned	CRP and PCT levels [20]	6/134 [20]	4.5 [20]	Not mentioned	Not mentioned
Praachi Raje et al., 2023 [78]	Not mentioned	Clinical, some on readmission [78]	23/332 [78]	6.9 [78]	7 [78]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
N. Lagoutte et al., 2012 [35]	All intraabdominal infections considered as leaks [35]	Biochemical (CRP, PCT) [35]	13/100 [35]	13.0 [35]	Not mentioned	Not mentioned
I. A. Bilgin et al., 2017 [28]	Not mentioned	Abdominal imaging with rectal contrast [28]	7/50 [28]	14.0 [28]	Not mentioned	Not mentioned
P. Rat et al., 2022 [12]	Not mentioned	Not mentioned	69/585 [12]	11.8 [12]	Not mentioned	Not mentioned
T. Masuda et al., 2021 [13]	Not mentioned	Clinical, radiological [13]	9/247 [13]	3.6 [13]	7 [13]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
L. C. Pandini et al., 2010 [7]	Not mentioned	Not mentioned	26/342 [7]	7.6 [7]	8.7 (mean) [7]	Not mentioned
E. Hagens et al., 2019 [36]	Defect or contrast leakage on CT/endoscopy or saliva from wound [36]	CT, endoscopy, clinical [36]	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Jia Lu et al., 2017 [37]	Not mentioned	Biochemical detection (CRP in drain fluid) [37]	24/172 [37]	14.0 [37]	~10 [37]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
B. Messias et al., 2020 [14]	Air/abscess on CT, purulent discharge, clinical peritonitis, etc. [14]	Clinical, CT scans [14]	11/90 [14]	12.2 [14]	7.7 [14]	Not mentioned
N. Rama et al., 2022 [38]	Not mentioned	Clinical, laboratory tests (CRP, CLP) [38]	25/396 [38]	6.3 [38]	9.0 (mean) [38]	Not mentioned
E. Lazarus et al., 2022 [39]	Established prior to study [39]	Clinical, CT, re-laparotomy [39]	22/113 [39]	19.4 [39]	8 (mean) [39]	Not mentioned
M. Zawadzki et al., 2015 [18]	Not mentioned	Clinical, radiological, operative [18]	5/55 [18]	9.1 [18]	3-12 [18]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
Chi Zhang et al., 2021 [79]	Leakage of intestinal content from anastomosis [79]	Clinical, imaging, endoscopy, operative [79]	34/273 [79]	12.5 [79]	Not mentioned	Not mentioned
G. Guevara-Morales et al., 2019 [5]	Escape of luminal content through surgical junction [5]	CT, laparotomy, contrast studies [5]	Not specified	6.5 [5]	3-5 [5]	Clavien-Dindo [5]
E. Hagens et al., 2023 [21]	Defect/leakage on CT, endoscopy, or saliva from wound [21]	CT, endoscopy, clinical [21]	20/200 [21]	11.0 [21]	8 [21]	ECCG classification [21]
Y. Kulu et al., 2013 [128]	ISREC criteria [128]	Not mentioned	56/746 [128]	7.5 [128]	Not mentioned	Grade A, B, C (ISREC) [128]

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
Bruce Su'at et al., 2022 [42]	Not mentioned	Clinical, radiological [42]	16/Not specified [42]	5.7 [42]	7 [42]	Not mentioned
G. Song et al., 2022 [43]	Persistent fever, abdominal pain, peritonitis, etc. [43]	Clinical, radiological [43]	14/120 [43]	11.7 [43]	5-7 [43]	Not mentioned
Mads Riiskjær et al., 2016 [132]	Leakage requiring reoperation [132]	Clinical (CRP) [132]	Not specified	8.3 [132]	6 [132]	Not mentioned
S. Dutta et al., 2011 [44]	Not mentioned	Not mentioned	17/136 [44]	12.5 [44]	~3 [44]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
Yilong Hu et al., 2024 [82]	Fecaloid discharge, contrast extravasation, postoperative peritonitis, etc. [82]	Clinical, radiological (CT) [82]	11/113 [82]	9.7 [82]	Not mentioned	Not mentioned
M. Baeza-Murcia et al., 2021 [133]	Not mentioned	Clinical (CRP) [133]	11/95 [133]	14.0 [133]	Not mentioned	Not mentioned
N. Komen et al., 2014 [83]	Clinically manifest insufficiency requiring intervention [83]	Clinical, radiological, operative [83]	19/243 [83]	8.0 [83]	6 [83]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
S. Chernyshov et al., 2018 [84]	Not mentioned	Biochemical (CRP, PCT) [84]	11/100 [84]	11.0 [84]	Not mentioned	Not mentioned
Pola Anwar et al., 2019 [45]	Not mentioned	Biochemical (CRP, PCT) [45]	5/24 [45]	20.8 [45]	Not mentioned	Not mentioned
C. Neary et al., 2020 [85]	Not mentioned	Not mentioned	11/148 [85]	7.0 [85]	Not mentioned	Not mentioned
Z. Kostić et al., 2015 [134]	Clinically evident AL [134]	Clinical observation [134]	15/150 [134]	10.0 [134]	~5-7 [134]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
Mohammed M. Raslan et al., 2024 [135]	Defect requiring intervention or collection requiring radiological intervention [135]	Clinical, radiological, laboratory [135]	20/105 [135]	19.0 [135]	Not mentioned	Not mentioned
A. Mohamed Ahmed et al., 2024 [32]	Not mentioned	Clinical, CT scan [32]	7/231 [32]	3.0 [32]	Not mentioned	Not mentioned
K. Kano et al., 2015 [145]	Defined by Clavien-Dindo classification [145]	Not mentioned	Not specified	9.1 [145]	Not mentioned	Clavien-Dindo [145]

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
H. Amoli et al., 2021 [86]	Symptoms include high CRP, leukocytosis, fever, ileus [86]	Clinical symptoms [86]	26/315 [86]	8.3 [86]	Not mentioned	Not mentioned
Haidi Abd El Zaher et al., 2022 [47]	Disruption requiring surgical or radiological intervention [47]	Clinical, CT scan [47]	22/205 [47]	10.7 [47]	6-14 [47]	Not mentioned
Hernán Daniel Pinares-Carrillo et al., 2023 [87]	Leakage of purulent/intestinal content from wound or drain [87]	Clinical, radiological [87]	45/270 [87]	16.7 [87]	7.6 (mean) [87]	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
M. Slavin et al., 2022 [22]	Defect at reoperation, feculent fluid in drain, or CT evidence [22]	Clinical, radiological, operative [22]	11/92 [22]	11.9 [22]	5.3 (mean) [22]	Not mentioned
Ю. А. Шелыгин et al., 2017 [88]	Not mentioned	Clinical, radiopaque study [88]	20/100 [88]	20.0 [88]	7 [88]	Not mentioned
Anders Gerdin et al., 2024 [123]	Compromised suture line, fistulization, or pelvic abscesses [123]	Clinical, radiological, endoscopic [123]	218/1036 [123]	21.0 [123]	Not mentioned	Grade A, B, C [123]

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
R. Warschko et al., 2011 [17]	Not mentioned	Not mentioned	Not specified	8.0 [17]	Not mentioned	Not mentioned
Jinyao Shi et al., 2020 [90]	Radiological changes, changes in drainage, abscess, or infection [90]	Radiological, drainage fluid analysis [90]	17/263 [90]	6.5 [90]	Not mentioned	Not mentioned
S. M et al., 2018 [50]	Not mentioned	CRP in drain fluid [50]	7/50 [50]	14.0 [50]	Not mentioned	Not mentioned
J. Charbonneau et al., 2024 [51]	Not mentioned	Not mentioned	4/99 [51]	4.0 [51]	Not mentioned	Not mentioned

Study	Leak Definition	Detection Method(s)	Leaks/Total Patients	Leak Rate (%)	Median Time to Diagnosis (POD)	Severity Classification
N. Isohata et al., 2023 [23]	Clinical signs of peritonitis and/or evidence of fecal or pus-like fluid from drain [23]	Clinical, radiological (CT, enema) [23]	28/331 [23]	8.5 [23]	5 [23]	Clavien-Dindo [23]

CRP Measurement Protocols and Timing

The protocols for measuring postoperative C-Reactive Protein (CRP) demonstrated considerable variation across the included studies. The units of measurement differed, with some studies reporting in mg/L [1, 2, 4, 6, 8, 9, 11, 12, 14, 15, 17–21, 24–26, 29, 32–34, 36, 38–41, 44, 45, 47, 49, 51–53, 56, 58, 60–62, 64, 68, 71, 72, 75–77, 79–82, 84, 86–94, 98, 102–104, 109, 111–113, 118, 119, 123, 125, 126, 129, 130, 134, 138, 139, 141, 146] and others in mg/dL [3, 5, 10, 13, 16, 22, 23, 26, 27, 48, 66, 73, 85, 95, 96, 105, 108, 110, 115, 133, 137, 140, 142–145] (10 mg/L is equivalent to 1 mg/dL), necessitating conversion for direct comparison. Assay methodologies were infrequently detailed but included immunoturbidimetric tests and immunonephelometry when specified [14, 18, 40, 41, 47, 53, 87].

The timing and frequency of CRP measurements were also inconsistent. Many studies implemented daily measurements for the first several postoperative days (PODs), typically ranging

from POD 1 to POD 7 [1, 2, 6–9, 11, 14, 21, 22, 27, 32, 35, 37, 38, 41, 44, 47, 51, 59, 61, 62, 73, 74, 77, 82, 89, 91, 102–104, 107, 110, 111, 113, 115, 122, 125, 130, 132, 135, 136, 140, 143]. Others measured CRP at specific intervals, such as on POD 1, 3, and 5, or only on a single day deemed optimal for prediction, like POD 3 or POD 4 [4, 12, 13, 18–20, 24, 25, 29, 34, 36, 45, 48, 53, 54, 57, 60, 63–65, 72, 75, 78, 84, 88, 100, 101, 118–120, 129, 133, 141, 142, 145]. Baseline or preoperative CRP levels were reported in only a few studies [6, 22, 54, 94, 110], limiting the ability to analyze the magnitude of the postoperative inflammatory response relative to the patient's preoperative state. This variability in protocols highlights a key source of heterogeneity that may influence cross-study comparisons of CRP's diagnostic accuracy.

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
Denise E. Yeung et al., 2021 [1]	mg/L	Not mentioned	Not mentioned	POD 1-7 [1]	Daily [1]
B. Borraez-Segura et al., 2022 [34]	mg/L	Not mentioned	Not mentioned	POD 3, 5 [34]	Specific intervals [34]
M. Scepanovic et al., 2013 [2]	mg/L	Not mentioned	Not mentioned	POD 1-7 [2]	Daily [2]
Eijiro Edagawa et al., 2015 [3]	mg/dL	Not mentioned	Not mentioned	Until POD 6 [3]	Daily [3]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
Isa Basuki et al., 2020 [72]	mg/L	Not mentioned	Not mentioned	POD 5 [72]	Single measurement [72]
P. Waterland et al., 2016 [30]	Not mentioned	Not mentioned	Not mentioned	POD 2, 3, 4 [30]	Specific intervals [30]
D. Jin et al., 2021 [8]	mg/L	Not mentioned	Not mentioned	POD 1-7 [8]	Daily [8]
J. Park et al., 2017 [73]	mg/dL	Not mentioned	Not mentioned	Daily until POD 8 [73]	Daily [73]
P. Ortega-Deballon et al., 2010 [19]	mg/L	Not mentioned	Not mentioned	POD 2, 4 [19]	Specific intervals [19]
E. Asti et al., 2018 [142]	mg/dL	Not mentioned	Measured [142]	POD 3, 5, 7 [142]	Specific intervals [142]
T. Welsch et al., 2007 [26]	mg/L	Not mentioned	Not mentioned	POD 2-4 [26]	Not specified [26]
M. Ramos Fernández et al., 2017 [9]	mg/L	Not mentioned	Not mentioned	POD 1-5 [9]	Daily [9]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
A. Aiolfi et al., 2018 [10]	mg/dL	Not mentioned	Not mentioned	POD 2-7 [10]	Daily [10]
D. Bona et al., 2022 [66]	mg/dL	Not mentioned	Not mentioned	POD 3, 4, 5 [66]	Specific intervals [66]
Á. García-Granero et al., 2013 [74]	Not mentioned	Not mentioned	Not mentioned	POD 1-5 [74]	Daily [74]
Tiffany Paradis et al., 2020 [31]	Not mentioned	Not mentioned	Not mentioned	POD 3-5 [31]	Not mentioned [31]
J. Platt et al., 2012 [11]	mg/L	Not mentioned	Not mentioned	POD 1-7 [11]	Daily [11]
D. Bona et al., 2019 [67]	mg/dl	Not mentioned	Not mentioned	POD 1 [67]	Specific intervals [67]
P. Paliogiannis et al., 2021 [121]	Not mentioned	Not mentioned	Not mentioned	POD 4 [121]	Specific intervals [121]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
Haddon J Pantel et al., 2019 [4]	mg/L	Not mentioned	Not mentioned	POD 3 [4]	Single measurement [4]
Devarajan Jebin Aaron et al., 2021 [27]	mg/dl	Serial estimation [27]	Not mentioned	POD 1-5 [27]	Daily [27]
M. Mik et al., 2017 [75]	mg/L	Not mentioned	Not mentioned	POD 4 [75]	Single measurement [75]
Dubravka Mužina et al., 2024 [76]	mg/L	Not mentioned	Not mentioned	POD 3, 4 [76]	Not specified [76]
J. Muñoz et al., 2018 [20]	mg/L	Not mentioned	Not mentioned	POD 1, 2, 3 [20]	Daily [20]
T. Pedersen et al., 2012 [77]	mg/L	Not mentioned	Not mentioned	Daily until discharge [77]	Daily [77]
Praachi Raje et al., 2023 [78]	Not specified	Not mentioned	Not mentioned	POD 1 and subsequent as needed [78]	As needed [78]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
N. Lagoutte et al., 2012 [35]	Not mentioned	Not mentioned	Not mentioned	POD 1-4 [35]	Daily [35]
E. Van Daele et al., 2024 [68]	mg/L	Not mentioned	Not mentioned	POD 2-5 [68]	Not specified [68]
I. A. Bilgin et al., 2017 [28]	Not mentioned	Not mentioned	Not mentioned	POD 3 [28]	Single measurement [28]
P. Rat et al., 2022 [12]	mg/L	Not mentioned	Not mentioned	POD 3-5 [12]	Specific intervals [12]
T. Masuda et al., 2021 [13]	mg/dL	Not mentioned	Not mentioned	POD 3, 5 [13]	Specific intervals [13]
L. C. Pandini et al., 2010 [7]	Not specified	Not mentioned	Compared [7]	Daily until POD 7 [7]	Daily [7]
E. Hagens et al., 2019 [36]	mg/L	Not mentioned	Not mentioned	POD 3, 5, 7 [36]	Specific intervals [36]
Jia Lu et al., 2017 [37]	g/L	Not mentioned	Not mentioned	POD 1-5 [37]	Daily [37]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
B. Messias et al., 2020 [14]	mg/L	Immunoassays [14]	Not mentioned	POD 1-7 [14]	Daily [14]
N. Rama et al., 2022 [38]	mg/L	Not mentioned	Not mentioned	POD 1-5 [38]	Daily [38]
E. Lazarus et al., 2022 [39]	mg/L	Nephelometry [39]	Measured [39]	POD 3 [39]	Single measurement [39]
M. Zawadzki et al., 2015 [18]	mg/L	Immunoturbidimetric [18]	Measured [18]	Pre-op, 8h, POD 1, 3 [18]	Specific intervals [18]
Chi Zhang et al., 2021 [79]	mg/L	Not mentioned	Not mentioned	POD 3 [79]	Specific intervals [79]
G. Guevara-Morales et al., 2019 [5]	mg/dL	Not mentioned	Not reported [5]	POD 1, 3, 5, 7 [5]	Specific intervals [5]
E. Hagens et al., 2023 [21]	mg/L	Not mentioned	Not mentioned	POD 3, 5, 7 [21]	Specific intervals [21]
Wahidullah Dost et al., 2024 [15]	mg/L, mg/dL	Not mentioned	Not mentioned	POD 3-4 [15]	Specific intervals [15]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
Erik D. Nilsson et al., 2018 [122]	Not specified	Not mentioned	Not reported [122]	POD 1-7 [122]	Daily [122]
R. Warschkow et al., 2012 [80]	mg/L	Automated system [80]	7 mg/L (median) [80]	POD 2-7 [80]	Evaluated from POD 2-7 [80]
Tomáš Řezáč et al., 2021 [129]	mg/L	Not mentioned	Not mentioned	POD 4 [129]	Single measurement [129]
M. Zawadzki et al., 2018 [40]	mg/L	Immunoturbidimetric [40]	Not mentioned	POD 3 [40]	Single measurement [40]
V. Javier et al., 2020 [130]	mg/L	Not mentioned	Not mentioned	Daily until POD 5 [130]	Daily [130]
Amirhossein Vaziri-Moghaddam et al., 2017 [131]	Not specified	Not mentioned	Not mentioned	POD 3 [131]	Single measurement [131]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
S. Chiappetta et al., 2019 [81]	mg/L	Not mentioned	Not mentioned	Pre-op, POD 1, 4 [81]	Specific intervals [81]
Mohamed Elkerkary et al., 2020 [41]	mg/L	Immunonephelometry [41]	Measured [41]	Day 0-4 [41]	Daily [41]
M. Pera et al., 2017 [16]	mg/dl	Not mentioned	Not mentioned	POD 5, 6, 7 [16]	Specific intervals [16]
Mostafa Omar Abdel Aziz et al., 2025 [70]	Not mentioned	Not mentioned	Not mentioned	POD 3-5 [70]	Specific intervals [70]
Bruce Su'a et al., 2022 [42]	Not mentioned	Not mentioned	Not mentioned	POD 3 [42]	Specific intervals [42]
G. Song et al., 2022 [43]	Not specified	Not mentioned	Measured [43]	POD 1, 3, 5 [43]	Specific intervals [43]
Mads Riiskjær et al., 2016 [132]	Not mentioned	Not mentioned	Not mentioned	POD 1, 2, 3 [132]	Daily [132]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
S. Dutta et al., 2011 [44]	mg/L	Not mentioned	Not mentioned	POD 1-7 [44]	Daily [44]
Yilong Hu et al., 2024 [82]	mg/L	Not mentioned	Not mentioned	POD 1, 2, 3 [82]	Daily [82]
M. Baeza-Murcia et al., 2021 [133]	mg/dL	Not mentioned	Not mentioned	POD 3, 5 [133]	Specific intervals [133]
N. Komen et al., 2014 [83]	Not specified	Tina-quant assay [83]	Not mentioned	POD 1-5 [83]	Daily [83]
S. Chernyshov et al., 2018 [84]	mg/L	Not mentioned	Not mentioned	POD 3, 6 [84]	Specific intervals [84]
Pola Anwar et al., 2019 [45]	mg/mL	Not mentioned	Not mentioned	Pre-op, 8h, POD 3, 5 [45]	Specific intervals [45]
C. Neary et al., 2020 [85]	mg/dL	Not mentioned	Not mentioned	POD 2-5 [85]	Daily [85]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
Z. Kostić et al., 2015 [134]	mg/L	Not mentioned	Not mentioned	POD 1, 3, 5, 7 [134]	Specific intervals [134]
Mohammed M. Raslan et al., 2024 [135]	mg/dL	Not mentioned	83.0 mg/dL [135]	POD 0, 3, 5 [135]	Specific intervals [135]
K. Albanopoulos et al., 2013 [46]	mg/L	Not mentioned	Not mentioned	POD 0, 1, 3, 5, 7, 9, 11, 13, 30 [46]	Specific intervals [46]
A. Mohamedah med et al., 2024 [32]	mg/L	Not mentioned	Not mentioned	POD 1-7 [32]	Daily [32]
K. Kano et al., 2015 [145]	mg/dL	Not mentioned	Not mentioned	POD 3 [145]	Single measurement [145]
H. Amoli et al., 2021 [86]	mg/L	Not mentioned	Not mentioned	POD 2-5 [86]	Daily [86]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
Haidi Abd El Zaher et al., 2022 [47]	mg/L	Immunonephelometry [47]	Measured [47]	POD 1-5 [47]	Daily [47]
Hernán Daniel Pinares-Carrillo et al., 2023 [87]	mg/L	Immunoturbidimetry [87]	Not mentioned	POD 1, 3, 5 [87]	Specific intervals [87]
M. Slavin et al., 2022 [22]	mg/dL	Not mentioned	4.68 ± 7.04 mg/dL [22]	POD 1-5 [22]	Daily [22]
Ю. А. Шелыгин et al., 2017 [88]	mg/L	Not mentioned	Not mentioned	POD 3, 6 [88]	Specific intervals [88]
Pooya Rajabaleyan et al., 2024 [89]	mg/L	Not mentioned	Not mentioned	Daily until discharge [89]	Daily [89]
Anders Gerdin et al., 2024 [123]	mg/L	Not mentioned	Not mentioned	Within 14 days [123]	Highest level recorded [123]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
J. Ruiz-Tovar et al., 2017 [48]	mg/dL	Not mentioned	Not mentioned	POD 1 [48]	Single measurement [48]
R. Warschkow et al., 2011 [17]	mg/L	Not mentioned	Not mentioned	Until POD 5 [17]	Daily [17]
Jinyao Shi et al., 2020 [90]	mg/L	Not mentioned	Not mentioned	POD 1, 3, 5 [90]	Specific intervals [90]
Lukas F. Liesenfeld et al., 2020 [91]	mg/l	Not mentioned	Not mentioned	POD 1-7 [91]	Daily [91]
B. Romain et al., 2014 [49]	mg/L	Not mentioned	Not mentioned	POD 5 [49]	Single measurement [49]
S. M et al., 2018 [50]	Not specified	Not mentioned	Not mentioned	POD 3, 5 [50]	Specific intervals [50]
S. Stuart et al., 2021 [92]	mg/L	Not mentioned	Not mentioned	Daily until POD 5 [92]	Daily [92]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
J. Charbonneau et al., 2024 [51]	mg/L	Not mentioned	Not mentioned	POD 1-10 [51]	Daily [51]
Julius Pochhammer et al., 2020 [93]	mg/L	Not mentioned	Not mentioned	POD 2 [93]	Single measurement [93]
F. Dib et al., 2017 [52]	mg/L	Not mentioned	Not mentioned	POD 1, 3, 5 [52]	Specific intervals [52]
Feng Zhang et al., 2022 [94]	mg/L	Not mentioned	4.7 ± 0.7 (leak) / 5.1 ± 0.8 (heal) [94]	POD 1, 3, 5 [94]	Specific intervals [94]
Olga V. Ilina et al., 2020 [146]	mg/L	Not mentioned	Not mentioned	POD 4, 5 [146]	Specific intervals [146]
M. Gordiichuk et al., 2024 [53]	mg/L	Immunoenzyme [53]	Not mentioned	Pre-op, POD 3, 5, 7 [53]	Specific intervals [53]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
M. Carvello et al., 2020 [136]	Not mentioned	Not mentioned	Not mentioned	POD 1, 3 [136]	Daily until discharge [136]
D. Çetin et al., 2018 [95]	Not mentioned	Not mentioned	Not mentioned	POD 3, 5 [95]	Specific intervals [95]
P. McAnena et al., 2019 [6]	Not specified	Not mentioned	50 (AL) vs. 14 (No-AL) [6]	Pre-op, POD 1-10 [6]	Daily [6]
D. Çetin et al., 2019 [96]	Not mentioned	Not mentioned	Not mentioned	POD 3, 5	Specific intervals
G. Guevara-Morales et al., 2018 [137]	mg/dL	Not mentioned	Not mentioned	POD 1, 3, 5, 7 [137]	Specific intervals [137]
F. Richter et al., 2022 [33]	mg/L	Not mentioned	Not mentioned	POD 1-5 [33]	Daily [33]
G. Broadley et al., 2015 [125]	mg/L	Not mentioned	Not mentioned	Day 1-7 [125]	Daily [125]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
N. Isohata et al., 2023 [23]	mg/dL	Not mentioned	Not mentioned	POD 1, 3, 7 [23]	Specific intervals [23]
Anders Gerdin et al., 2024a [126]	mg/L	Not mentioned	Not mentioned	Within 14 days [126]	Highest level recorded [126]
J. van den Bos et al., 2019 [54]	mg/ml	Immunoturbidimetric [54]	2.9 ± 2.3 mg/ml [54]	POD 1, 3, 5 [54]	Specific intervals [54]
W. Al-Kubati et al., 2024 [71]	mg/L	Not mentioned	Not mentioned	POD 3 [71]	Single measurement [71]
Jiaxin Zhang et al., 2022 [24]	mg/L	Not mentioned	Not mentioned	POD 1, 2, 4 [24]	Specific intervals [24]
M. Issa et al., 2024 [97]	Not mentioned	Not mentioned	Not mentioned	POD 3 [97]	Specific intervals [97]
Bernardo Borr�ez-Segura et al., 2023 [55]	mg/L	Not mentioned	Not mentioned	POD 3, 5 [55]	Specific intervals [55]

Study	CRP Units	Measurement Method	Preoperative CRP	Postoperative Days Measured	Frequency of Measurement
L. Dahbi-Skali et al., 2020 [138]	Not specified	Not mentioned	Not mentioned	POD 2, 4 [138]	Specific intervals [138]
Mumtazuddin Wani et al., 2020 [56]	mg/L	Not mentioned	Not mentioned	POD 1-7 [56]	Daily [56]
P. Leourier et al., 2023 [98]	mg/ml	Not mentioned	Not mentioned	POD 2-3 [98]	Specific intervals [98]
M. Bahbah et al., 2021 [99]	Not mentioned	Not mentioned	Measured at induction [99]	T1-T5 (Day 0, 1, 3, 5) [99]	Specific intervals [99]
M. Cunha et al., 2021 [115]	mg/dL	Not mentioned	Not specified	POD 1-4 [115]	Daily [115]
Ashish Kumar Sharma et al., 2025 [141]	mg/L	Not mentioned	Not mentioned	POD 3 [141]	Single measurement [141]
J. Kynaston et al., 2015 [29]	Not specified	Not mentioned	Not mentioned	POD 1, 3 [29]	Specific intervals [29]

DISCUSSION

This systematic review, encompassing 146 studies and 49,328 patients, represents the most comprehensive synthesis to date of the relationship between postoperative C-reactive protein levels and anastomotic leakage prediction across gastrointestinal surgery. The findings demonstrate that CRP measurement, particularly between postoperative days 3-5, consistently provides valuable negative predictive information for AL, although significant heterogeneity exists across studies in terms of patient populations, surgical procedures, CRP measurement protocols, and reported diagnostic accuracy.

Heterogeneity in Study Characteristics and AL Definitions

The marked variability in anastomotic leakage definitions across the included literature represents a fundamental challenge to cross-study comparison and meta-analysis. While most studies converged on definitions involving clinical, radiological, or operative evidence of anastomotic disruption (1,5,34,56), the specific criteria varied considerably. Some studies included only clinically significant leaks requiring intervention (83,134), while others incorporated radiologically detected leaks regardless of clinical impact (23,73). This variability in AL definition directly impacts reported incidence rates and may influence the apparent predictive performance of CRP. The adoption of standardized definitions, such as the International Study Group of Rectal Cancer (ISREC) grading system (128), would substantially improve comparability across future studies.

The incidence of anastomotic leakage demonstrated expected variation by surgical procedure, with the lowest rates observed in bariatric surgery (1.5-4.2%) (52,81,93) and highest rates in esophagectomy and complex colorectal resections (up to 30.6%) (33,55). This variation reflects differences in anastomotic vascularity, tension, intraluminal pressure, and patient-related factors including nutritional status and comorbidities (90,91). Importantly, the consistently reported median time to AL diagnosis of 5-9 days postoperatively (3,14,21,23) aligns with the time window

when CRP measurement demonstrates optimal predictive value, supporting the clinical utility of serial CRP monitoring during this critical period.

CRP Measurement Protocols and Optimal Timing

The considerable variation in CRP measurement protocols represents a significant source of heterogeneity that limits direct comparison of predictive performance across studies. While many studies implemented daily measurements (1,2,6,8), others measured CRP at specific intervals such as POD 1, 3, and 5 (19,34,36), or only on a single postoperative day (4,75). The unit of measurement also varied, with some studies reporting in mg/L (1,2,4) and others in mg/dL (3,5,10), necessitating careful conversion for comparative analysis. Despite this heterogeneity, consistent patterns emerged regarding optimal timing for CRP prediction.

The preponderance of evidence supports POD 3-5 as the optimal window for CRP measurement to predict AL. Studies evaluating multiple time points consistently demonstrated superior predictive performance during this period compared to earlier or later measurements (8,9,14,17,19,21,24,26,34,36,38,39,74,79). This finding has biological plausibility, as the normal postoperative inflammatory response typically peaks around POD 2-3 and begins to decline by POD 4-5 in uncomplicated recovery (8,9). Persistent elevation or secondary rise during this window may indicate ongoing inflammation due to anastomotic disruption or subsequent intra-abdominal infection (10,11).

The importance of serial measurement rather than single time point assessment warrants emphasis. Studies evaluating CRP kinetics, including the trend between POD 2 and POD 5, reported enhanced predictive accuracy compared to single measurements (7,21,34,55,90,114). This approach accounts for individual variation in baseline CRP and the magnitude of the initial surgical inflammatory response, providing a more personalized assessment of recovery trajectory.

CRP Predictive Performance: Rule-Out vs. Rule-In

A consistent finding across the reviewed literature is that CRP performs substantially better as a negative predictive test (ruling out AL) than as a positive predictive test (ruling in AL). Studies reporting negative predictive values (NPV) consistently demonstrated NPV exceeding 90% when applying appropriate cutoff values on POD 3-5 (12,21,32,36,39,82,86). For example, Hagens et al. (21) reported that CRP < 200 mg/L on POD 5 had 100% NPV for AL after minimally invasive esophagectomy. Similarly, Mohamedahmed et al. (32) found that CRP < 120 mg/L on POD 4 had 97% NPV for AL following colorectal resection.

In contrast, positive predictive values (PPV) were consistently modest, typically ranging from 20-50% (14,17,19,38). This finding reflects the non-specific nature of CRP elevation, which can result from various infectious and non-infectious complications including pneumonia, urinary tract infection, wound infection, and intra-abdominal collections not related to anastomotic disruption (20,112). The clinical implication is that low CRP levels provide reassurance and may support safe early discharge decisions, while elevated CRP levels should prompt clinical vigilance and further diagnostic evaluation but do not definitively indicate AL (4,5,12,21).

The reported CRP cutoff values varied considerably across studies, ranging from 120-200 mg/L on POD 3-5 (8,12,14,17,19,21,24,32,34,38,39,74). This variation reflects differences in surgical procedures, patient populations, and the balance between sensitivity and specificity selected by investigators. Procedure-specific thresholds appear necessary, with esophagectomy generally requiring higher cutoff values (e.g., 200 mg/L on POD 5) (12,21) compared to colorectal surgery (e.g., 120-150 mg/L on POD 3-4) (14,17,19,32). Patient factors including age, comorbidities, nutritional status, and preoperative inflammation may also influence optimal thresholds (6,22,90,91,94).

Comparison Across Surgical Procedures

The predictive utility of CRP demonstrated consistency across different surgical procedures, although some procedure-specific patterns emerged. In colorectal surgery, the largest body of

evidence consistently supports CRP measurement on POD 3-4 with NPV exceeding 90% for AL (1,14,17,19,32,66). The systematic review and meta-analysis by Yeung et al. (1) including 6,647 patients confirmed CRP as a reliable predictor of AL following colorectal resection, with optimal cutoff values of approximately 150 mg/L on POD 3-4.

In esophagectomy, CRP also demonstrates robust negative predictive value, although optimal cutoff values tend to be higher, reflecting the greater surgical insult and associated inflammatory response. Studies by Rat et al. (12), Hagens et al. (21), and Aiolfi et al. (10) consistently reported optimal CRP thresholds of 170-200 mg/L on POD 4-5, with NPV of 95-100% for intrathoracic anastomotic leakage. The higher incidence of AL following esophagectomy (10-30%) (10,33,68) and the potentially devastating consequences of delayed diagnosis underscore the particular value of reliable negative prediction in this population.

Evidence for gastric surgery, while more limited, suggests similar patterns with optimal CRP measurement on POD 3-5 (63,90,95,96,114,145). Studies by Shi et al. (90) and Cananzi et al. (63) reported that CRP < 140 mg/L on POD 4 effectively ruled out AL following gastrectomy, with NPV exceeding 90%. In bariatric surgery, where AL rates are lowest (1.5-4.2%) (52,81,93), CRP maintains high NPV but the lower event rate increases the challenge of establishing optimal thresholds (48,49,67,80,81).

Comparison with Other Inflammatory Markers and Multimodal Approaches

Several studies compared CRP with other inflammatory markers including procalcitonin (PCT), white blood cell count (WBC), and calprotectin (18,20,35,37,38,45,47,74,84). While PCT generally demonstrated comparable or slightly superior specificity for bacterial infection (20,35,74), CRP remained the most extensively validated and widely available marker. The combination of CRP with other markers or clinical parameters appears to enhance predictive accuracy compared to CRP alone (18,38,43,47,74,101).

The integration of CRP into multimodal predictive scores, such as the CRP-to-albumin ratio (CAR) (79,121), CRP-lymphocyte ratio (85,101), and composite scores incorporating clinical risk factors (100,107,141), represents an important direction for improving predictive performance. Cheng et al. (107) demonstrated that CRP-guided removal of transanal drainage tubes reduced AL rates after laparoscopic rectal surgery, illustrating the potential for CRP-based clinical algorithms to directly impact patient management and outcomes.

Limitations and Sources of Heterogeneity

Several important limitations must be considered when interpreting the findings of this systematic review. First, the marked heterogeneity in study designs, patient populations, surgical procedures, AL definitions, CRP measurement protocols, and reported outcome metrics limits direct comparison and synthesis across studies. While meta-analysis was not attempted due to this heterogeneity, the detailed characterization of study-level variability provides valuable context for understanding the current evidence base.

Second, the predominance of retrospective studies and single-center designs introduces potential selection bias and limits generalizability. Prospective multicenter studies with standardized protocols for CRP measurement and AL definition are needed to establish robust, generalizable evidence.

Third, the optimal CRP cutoff values identified in individual studies are highly dependent on the specific patient population, surgical procedure, and the trade-off between sensitivity and specificity selected by investigators. External validation of proposed thresholds in independent cohorts remains limited.

Fourth, few studies adequately accounted for potential confounders including preoperative CRP levels (6,22,54,94), neoadjuvant therapy (73,79,91,103), and intraoperative factors that may influence the postoperative inflammatory response. The magnitude of CRP elevation relative to baseline may provide more personalized predictive information than absolute cutoff values.

Fifth, publication bias favoring studies reporting positive findings cannot be excluded. However, the consistent finding across numerous studies of high NPV for CRP suggests this represents a robust biological phenomenon rather than publication bias.

Clinical Implications and Future Directions

The consistent finding that low postoperative CRP levels effectively rule out AL has important clinical implications for postoperative management within enhanced recovery protocols. Patients with CRP below procedure-appropriate thresholds on POD 3-5 may be candidates for early discharge, reducing hospital stay and healthcare costs while maintaining safety (16,20). Conversely, patients with elevated CRP should undergo clinical reassessment and consideration of further diagnostic imaging, although the modest PPV means that not all elevated CRP values indicate AL (4,5,12,98).

Future research should focus on several key priorities. First, multicenter prospective studies with standardized protocols for CRP measurement and AL definition are needed to establish robust, generalizable thresholds for different surgical procedures. Second, investigation of CRP kinetics, including the trajectory between serial measurements, may provide enhanced predictive information compared to single time point assessment. Third, integration of CRP with other biomarkers and clinical risk factors into multimodal predictive scores represents a promising approach to improve overall diagnostic accuracy. Fourth, randomized controlled trials evaluating CRP-guided clinical decision-making, including early discharge algorithms and selective imaging strategies, are needed to demonstrate improved patient outcomes and healthcare efficiency. Fifth, exploration of novel biomarkers including drain fluid analysis (37,50,61,83), genetic markers, and advanced inflammatory panels may complement CRP measurement and enhance predictive accuracy.

CONCLUSION AND RECOMMENDATIONS

This systematic review demonstrates that postoperative C-reactive protein measurement represents a valuable, cost-effective tool for early prediction of anastomotic leakage across

gastrointestinal surgery. The consistent finding of high negative predictive value, particularly between postoperative days 3-5, supports the clinical utility of CRP as a rule-out test, where low levels effectively exclude AL and may facilitate safe early discharge within enhanced recovery protocols. However, the modest positive predictive value limits the ability of elevated CRP to definitively diagnose AL, necessitating clinical correlation and further diagnostic evaluation.

Key Conclusions:

1. Postoperative CRP measurement between POD 3-5 provides optimal predictive information for anastomotic leakage, with negative predictive values consistently exceeding 90% across diverse surgical procedures.
2. Significant heterogeneity exists in AL definitions, CRP measurement protocols, and reported diagnostic accuracy, highlighting the need for standardized approaches in future research.
3. Optimal CRP cutoff values vary by surgical procedure, with esophagectomy generally requiring higher thresholds (170-200 mg/L) compared to colorectal surgery (120-150 mg/L) and bariatric surgery (100-140 mg/L).
4. Serial CRP measurement and assessment of CRP kinetics provide enhanced predictive information compared to single time point assessment.
5. Integration of CRP with other biomarkers and clinical risk factors into multimodal predictive scores represents a promising direction for improving diagnostic accuracy.

Recommendations:

1. **Clinical Practice:** Routine serial CRP measurement should be incorporated into postoperative monitoring protocols for patients undergoing gastrointestinal anastomotic

surgery. Procedure-specific thresholds should guide clinical decision-making, with low CRP levels providing reassurance and supporting enhanced recovery pathways.

2. **Standardization:** Future research should adopt standardized definitions for anastomotic leakage, such as the ISREC grading system, and uniform CRP measurement protocols including specified postoperative days and unit reporting to enhance comparability across studies.
3. **Multimodal Approaches:** Development and validation of composite predictive scores integrating CRP with clinical risk factors and other biomarkers should be prioritized to optimize predictive accuracy.
4. **Implementation Research:** Randomized controlled trials evaluating CRP-guided clinical algorithms, including early discharge protocols and selective imaging strategies, are needed to demonstrate improved patient outcomes and healthcare efficiency.
5. **Personalized Medicine:** Investigation of patient-specific factors influencing CRP kinetics, including preoperative inflammatory status, nutritional parameters, and genetic polymorphisms, may enable more personalized postoperative monitoring strategies.

In conclusion, C-reactive protein represents a robust, accessible, and clinically useful biomarker for the early prediction of anastomotic leakage. While significant heterogeneity in the current evidence base limits definitive recommendations regarding optimal thresholds, the consistent finding of high negative predictive value supports the integration of CRP measurement into routine postoperative care. Future research should focus on standardization, multimodal integration, and implementation science to fully realize the potential of CRP-guided postoperative management.

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