Journal of Pioneering Medical Sciences
Received September 23, 2023 Accept November 14 , 2023 Publish November 16, 2023.
Volume 12, Issue 1, Pages 20-23

DOI https://doi.org/10.61091/jpms20231215

Role of Biomarkers in the Diagnosis of Anastomotic Leakage after Colorectal Surgery: A Systematic Review and Meta-Analysis

Mohammed Yunus[1,*], Amr Zaher[1], Vishnu Teja Obulareddy[2] and Praveen Kumar Gonuguntla Kamma[3]
[1]Department of Pathology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.
[2]Virginia State Dental Association, Richmond, Virginia, USA.
[3]Texas State Dental Association, USA.

Corresponding author: Mohammed Yunus (e-mail: yunusaq@gmail.com).

Abstract **Introduction:** Anastomotic leakage (AL) after colorectal surgery is difficult to diagnose because of its varied presentation and is often identified when the patient becomes critically ill. Biomarkers contribute a significant weightage in identifying AL at earlier stages. Hence, this review assessed the diagnostic role of biomarkers in AL following colorectal surgery. **Methodology:** A literature search was electronically conducted in 3 search engines: Pubmed, Google search, and journal on the web till February 2022. Observational studies of both retrospective and prospective nature were included. Open meta-analyst software was used to assess the prevalence of AL. **Results:** 13 articles fulfilled the eligibility criteria. A pooled prevalence of 8% was noted for AL in colorectal surgeries (95%CI; 6.3:10.1). In the present review, sensitivity ranged from 53.8% to 90% and specificity from 69.6% to 100%. **Conclusion:** Biomarkers proved to be a reliable predictor of AL in patients who have undergone colorectal surgery.

Key Words Colorectal, Diagnostic, Anastomosis, C-reactive protein

1. Introduction

Anastomotic leakage is one of the gravest complications arising after surgeries in the colorectal specialty, associated with higher levels of mortality and morbidity and extended hospitalization [1]–[4]. It can be both a confounding and an independent factor jeopardizing the prognosis. Despite an improved surgical approach and a better understanding of the risk factors for anastomotic leakage, it still remains a serious complication without apparent explanation in some cases with no recognized risk factors [5]. Anastomotic leaks should be detected as soon as feasible to reduce the related morbidity and mortality [6].

In abdominal surgery, surgeons have poor prediction accuracy for anastomotic leakage [7]. Routine imaging is neither dependable nor cost-effective in detecting leaks, and it has the disadvantage of exposing the user to radiation. Therefore, a biomarker would be beneficial if it was cost-effective and sensitive enough to allow the patient to be discharged safely.

A biomarker is a trait that may be objectively assessed as a sign of disease pathogenesis. Literature shows various biomarkers involved in the healing process after colorectal surgery with a potential to detect distinct phases of early ischemia, inflammation, and necrosis [8], [9]. Most of the researchers have concentrated on CRP. C-reactive protein (CRP) has been used to diagnose intra-abdominal surgical infection, as a general marker of a poor postoperative outcome, encompassing surgical and nonsurgical problems [10], [11], and even as a predictive factor for survival following liver metastasis resection. In addition, C-reactive protein has recently been studied as an early predictor of septic problems following esophageal, pancreatic, and rectal resections. An inflammatory measure with a strong negative predictive value could allow safe early hospital discharge in the context of fast-track surgery. Hence the present review was undertaken to assess the diagnostic role of biomarkers amongst patients presenting with anastomotic leakage after colorectal surgery.

2. Materials and Methods

The methodology followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist protocol [12]. The research question was stated per PICO criteria (Population, Intervention, Control, and

Outcome). The review included all prospective and retrospective observational studies that evaluated biomarkers' role in diagnostic accuracy amongst patients treated for colorectal procedures presenting with anastomotic leakage.

Databases of Pubmed, Google scholar, and journals on the web were scrutinized for articles till February 2022. Articles published in the English language only were included. Unpublished literature, reviews, editorials, case reports, dissertations, and articles without open access were excluded. Two independent reviewers searched the database for articles employing the search strategy: "Colorectal Surgery" or "Colorectal resection" and "Anastomotic leak" or "Anastomotic Leakage" and " Biomarkers" or "Inflammatory markers". Each article was evaluated for study ID, Sample, demographic details, clinical symptoms, biomarkers assessed, tools for assessment, outcome, and study design.

Quality Evaluation

Methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) 2 tools.

3. Data Analysis

Open meta analyst software was used for performing meta-analyses for the prevalence of anastomotic leakage in post-surgical colorectal procedures. The heterogeneity of included studies was evaluated using Cochrane Q and the I2. The random-effects or fixed model combined included studies based on the results.

4. Results

The literature search yielded 239 titles from the three databases. No additional articles were identified through a manual search. Duplicates were removed using End note software 8, following which records were further screened by reading abstracts, 14 articles were reviewed in full. After confirming the eligibility, 13 articles were included for analysis. Of the 13 studies, 11 were prospective, and 2 were retrospectives. Data search and studies selection is presented as a Flow diagram (Figure 1).

Data characteristics of the included studies are enumerated in Table 1. The quality of the studies assessed is summarized in Table 2. Overall the studies assessed had good quality. A pooled prevalence of 8% for AL in colorectal surgeries (95%CI; 6.3:10.1) is seen in Figure 2. In the present review, sensitivity ranged from 53.8% to 90% and specificity from 69.6% to 100% (Figure 3 and Figure 4).

5. Discussion

Anastomotic leak following surgeries in the colorectal region is reported with varied prevalence in the literature. Nearly 50% of the cases remain asymptomatic, as witnessed by extra peritoneal localization of leak [26]. The mortality rate is as high as 22%, accounting for 1/3rd of all deaths following surgery [27]. Early detection of this condition reduces morbidity and improves patient outcomes.

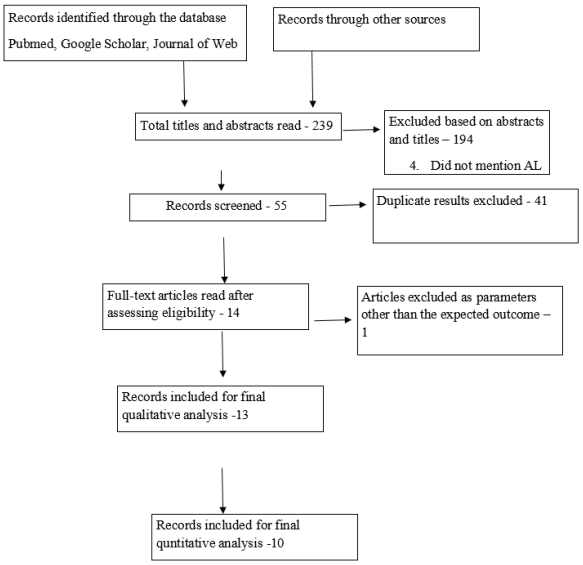

Figure 1: Flow Chart Diagram for Article Inclusion

Diagnostic aids such as angiography and CT have reported 60% and 57% sensitivity rates [26]. The present analysis noted several biomarkers with a varying accuracy range in identifying anastomotic leakage following colorectal procedures 10 and 4 of the studies concluded that CPR and PCT were reliable markers, respectively.

The pathogenesis of AL is poorly understood. According to the 'two-hit' hypothesis of sepsis, a severe insult (surgery) primes the immune system for a later insult, such as AL. This results in a significantly heightened inflammatory response and the release of cytokines. Understanding the composition of the perianastomotic environment and the two-hit concept may be useful in understanding the pathophysiology of AL. Following abdominal surgery, the abdominopelvic cavity is flooded with intraperitoneal biomarkers implicated in the healing process, both pro-inflammatory and anti-inflammatory. The composition of the intra-abdominal milieu takes a predictable path over several weeks in the usual course of healing. However, the inflammatory milieu is altered in the context of AL, and this is assumed to happen before the clinician notices. A systemic inflammatory biomarker or a collection of biomarkers that reflect the perianastomotic intraperitoneal milieu, on the other hand, could be a valuable, minimally invasive objective prediction tool for AL.

Most of the studies employed a prospective study design in the present review, which led to enhanced harmonisation and higher power to detect an outcome. Another merit is the inclusion of articles irrespective of location. However, certain drawbacks were that the studies did not adhere to any standard operational definition of AL and biomarkers noted in 1 to 5 postoperative days.

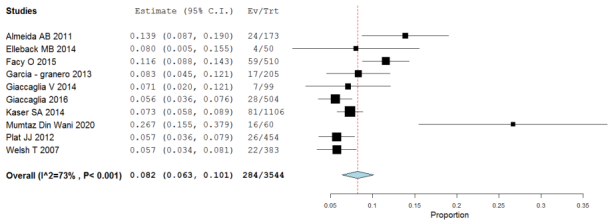

Figure 2: Forest Plot for the Prevalence of AL

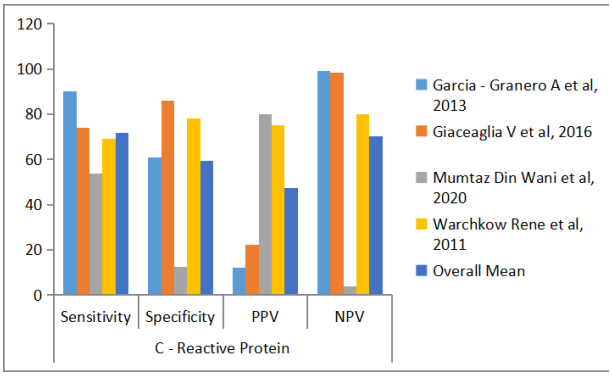

Figure 3: Sensitivity Prediction for CRP

6. Conclusion

Biomarkers were considered good predictors for detecting AL in patients with colorectal surgeries. Multicentric, high-quality prospective studies are recommended to further validate the findings.

Conflict of Interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

References

[1] Alves, A., Panis, Y., Trancart, D., Regimbeau, J. M., Pocard, M., & Valleur, P. (2002). Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World Journal of Surgery, 26, 499-502.

[2] Buchs, N. C., Gervaz, P., Secic, M., Bucher, P., Mugnier-Konrad, B., & Morel, P. (2008). Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. International Journal of Colorectal Disease, 23, 265-270.

[3] Makela, J. T., Kiviniemi, H., & Laitinen, S. (2003). Risk factors for anastomotic leakage after left-sided colorectal resection with rectal anastomosis. Diseases of the colon & rectum, 46, 653-660.

[4] Veyrie, N., Ata, T., Muscari, F., Couchard, A. C., Msika, S., Hay, J. M., ... & French Associations for Surgical Research. (2007). Anastomotic leakage after elective right versus left colectomy for cancer: prevalence and independent risk factors. Journal of the American College of Surgeons, 205(6), 785-793.

[5] Matthiessen, P., Henriksson, M., Hallbook, O., Grunditz, E., Noren, B., & Arbman, G. (2008). Increase of serum C-reactive protein is an early indicator of subsequent symptomatic anastomotic leakage after anterior resection. Colorectal Disease, 10(1), 75-80.

[6] Doeksen, A., Tanis, P. J., & Vrouenraets, B. C. (2007). Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection. World Journal of Gastroenterology: WJG, 13(27), 3721.

[7] Karliczek, A., Harlaar, N. J., Zeebregts, C. J., Wiggers, T., Baas, P. C., & Van Dam, G. M. (2009). Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. International Journal of Colorectal Disease, 24, 569-576.

[8] Chuang, D., Paddison, J. S., Booth, R. J., & Hill, A. G. (2006). Differential production of cytokines following colorectal surgery. ANZ Journal of Surgery, 76(9), 821-824.

[9] Pasternak, B., Matthiessen, P., Jansson, K., Andersson, M., & Aspenberg, P. (2010). Elevated intraperitoneal matrix metalloproteinases-8 and-9 in patients who develop anastomotic leakage after rectal cancer surgery: a pilot study. Colorectal Disease, 12(7Online), e93-e98.

[10] Karamarkovic, A., Radenkovic, D., Milic, N., Bumbasirevic, V., & Stefanovic, B. (2005). Protein C as an early marker of severe septic complications in diffuse secondary peritonitis. World Journal of Surgery, 29, 759-765.

[11] Eriksson, S., Olander, B., Pira, U., & Granstrom, L. (1997). White blood cell count, leucocyte elastase activity, and serum concentrations of interleukin-6 and C-reactive protein after open appendicectomy. The European Journal of Surgery= Acta Chirurgica, 163(2), 123-127.

[12] Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine, 151(4), 264-269.

[13] Almeida, A.B., Faria, G., Moreira, H., Pinto-de-Sousa, J., Correia-da-Silva, P. and Maia, J.C., 2012. Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery. International Journal of Surgery, 10(2), pp.87-91.

[14] EllebÃ¦k, M.B., Baatrup, G., Gjedsted, J., Fristrup, C. and Qvist, N., 2014. Cytokine response in peripheral blood indicates different pathophysiological mechanisms behind anastomotic leakage after low anterior resection: a pilot study. Techniques in Coloproctology, 18, pp.1067-1074.

[15] Facy, O., Paquette, B., Orry, D., Binquet, C., Masson, D., Bouvier, A., Fournel, I., Charles, P.E., Rat, P. and Ortega-Deballon, P., 2016. Diagnostic accuracy of inflammatory markers as early predictors of infection after elective colorectal surgery. Annals of Surgery, 263(5), pp.961-966.

[16] Garcia-Granero, A., Frasson, M., Flor-Lorente, B., Blanco, F., Puga, R., CarratalÃ¡, A. and Garcia-Granero, E., 2013. Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: a prospective observational study. Diseases of the colon & rectum, 56(4), pp.475-483.

[17] Giaccaglia, V., Salvi, P.F., Cunsolo, G.V., Sparagna, A., Antonelli, M.S., Nigri, G., Balducci, G. and Ziparo, V., 2014. Procalcitonin, as an early biomarker of colorectal anastomotic leak, facilitates enhanced recovery after surgery. Journal of Critical Care, 29(4), pp.528-532.

[18] Giaccaglia, V., Salvi, P.F., Antonelli, M.S., Nigri, G., Pirozzi, F., Casagranda, B., Giacca, M., Corcione, F., de Manzini, N., Balducci, G. and Ramacciato, G., 2016. Procalcitonin reveals early dehiscence in colorectal surgery. Annals of Surgery, 263(5), pp.967-972.

[19] KÃ¤ser, S.A., Nitsche, U., Maak, M., Michalski, C.W., SpÃ¤th, C., MÃ¼ller, T.C., Maurer, C.A., Janssen, K.P., Kleeff, J., Friess, H. and Bader, F.G., 2014. Could hyponatremia be a marker of anastomotic leakage after colorectal surgery? A single center analysis of 1,106 patients over 5 years. Langenbeck's Archives of Surgery, 399, pp.783-788.

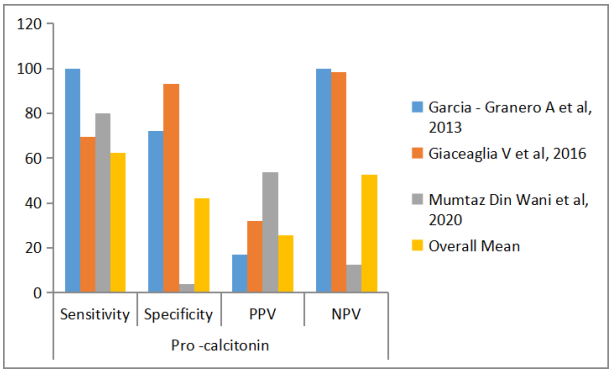

Figure 4: Sensitivity Prediction for PCT

Study ID	Sample	Demographics	Clinical symptoms	Biomarkers assessed	Assessment tool	Results	Study Design
[13]	173 patients between January 2008 to October 2009	Mean age of 69.5 years; Males: Females ratio is 54.2% versus 45.5%	Peritonitis and free feaceal fluid flowing from the drain site or within the abdomen	Serum CRP		24 (13.8%) reported AL. Authors concluded that values >140mg/L of CRP on the 3rd day postoperatively enhance specificity and sensitivity	Prospective
[14]	50 patients were operated on for anterior resection of rectosigmoid cancer	Mean age - 61.5 years (56 - 81);		IL -1, IL - 4, IL - 6, IL - 8, IL - 10	Bio-Plex suspension array System	4 developed ALs. All the biomarkers were increased in the patients with an anastomotic leak on the 5th POD	Prospective
[15]	501 patients were treated between November 2011 to April 2014	Mean age of 66.7 + 14.9 years; M: F=33:26	Fever before the fourth POD	CRP and PCT	CRP assessed by Immunonephelometry; PCT by Brahms PCT Krypton	C - Reactive protein was found to be better reliable than procalcitonin for colorectal complications	Prospective Observational
[16]	205 patients were operated on between November 2008 to March 2010	The mean age was 63.3 + 15.5 years; 112 males versus 93 females	Drainage from wound margin and signs of inflammation	CRP and PCT	PCT measured by electrochemiluminescence Immunoassay; C-reactive protein serum levels assessed by latex-immunoturbidimetric method	8.3% (17 cases) developed AL. Though PCT and CRP were reliable as markers to detect anastomotic leakage, PCT was more accurate.	Prospective
[17]	99 patients intervened between September 2011 and September 2012	The mean age is 68 years	Peritonitis at drain site, presence of air or fluid in the infected region	PCT and CRP	Dimension vista analysis	7 (7.1%) reported Anastomotic leakage	Prospective
[18]	504 patients operated for laparotomic or laparoscopic colorectal surgery from September 2013 to October 2014	Mean age was 58.3 years, with 58.3% being males	Wound margins presenting with purulent drainage	PCT and CRP	Not mentioned	5.6% (28) patients were recorded with anastomotic leakage	Multicentric
[19]	1106 patients treated between July 2007 to July 2012	Mean age of 62.3 years(28 - 87 years); 67% males	Abscess in proximity to the anastomosis	Hyponatremia (HN)and Leukocytosis (LC)	Serum analysis	81 (73%) had Anastomotic leakage; HN was more specific in detecting AL than LC	Prospective
[20]	246 patients operated for colorectal resection between January to December 2004	The median age was 71 years (18 - 93); 125 (54%) were females	Elevated temperature levels >380c; inflammatory biochemical markers	CRP	Hematological	CRP measurements posed as a greater reliable aid in intra- abdominal inflammation assessment	Prospective
[21]	60 patients in Government Medical College, Srinagar	25 - 70 year aged patients who have undergone colorectal surgeries	>380c in 36.7%, absence of bowel action in 23.3%, diarrhea in 73.3%, and renal failure in 16.7%	CRP, Serum procalcitonin level, iL - 6, iL - 10, TNF-a	Not mentioned	Anastomotic leak was found in 26.7% of patients. A significant relationship was observed between peritoneal fluid biomarkers and clinical symptoms severity	Prospective
[22]	133 patients were electively operated on between November 2007 to October 2008	Mean age: 65 + 16 years; M: F ratio was 85:48	Fever, abnormal bowel movements, and abdominal signs	CRP	Immunonephelometry as say	The prevalence rate of 15.5%. CRP values can be used as an indicator for safe discharge	Prospective
[23]	454 patients were treated between January 1997 to February 2007 for curative resection	M: F ratio was 62:42	Confirmed radiographically or by relaparotomy.	CRP	Turbidimetric assay	26 cases had AL; CRP levels measured 3rd POD was a reliable predictor for infective consequences	Retrospective
[24]	1238 cases of colorectal adenocarcinoma treated between January 1997 and August 2009	Mean age of 68.2±12.1 years		CRP, WBC measurement	Automated analytic analyzer for CRP	The highest diagnostic accuracy was noted on the 4th POD for CRP	Retrospective
[25]	383 patients treated for rectal resections between October 2001 to November 2005	66 years (Range is 47-81)	Abscess or wound infection at the surgical site	CRP	Turbidometry	22 (5.7) CRP greater than 140 mg/dl on the 3rd or 4th POD can be predictive of inflammatory complications of colorectal	Retrospective

Table 1: Study Characteristics of Included Articles

Reference	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
[13]	+	?	+	+	–	–	+
[14]	–	–	?	–	–	–	–
[15]	–	–	-	?	–	–	–
[16]	–	–	+	+	–	–	–
[17]	–	–	+	+	–	–	–
[18]	–	–	+	+	–	–	–
[19]	+	–	+	+	+	–	–
[20]	–	–	+	+	–	–	–
[21]	–	–	–	–	–	–	–
[22]	–	–	–	–	+	–	–
[23]	?	–	+	+	+	–	–
[24]	–	–	+	+	–	–	–
[25]	+	–	+	+	+	–	–

Table 2: QUADAS-2-Risk of Bias Assessment

[20] KÃ¸rner, H., Nielsen, H.J., SÃ¸reide, J.A., NedrebÃ¸, B.S., SÃ¸reide, K. and Knapp, J.C., 2009. Diagnostic accuracy of C-reactive protein for intraabdominal infections after colorectal resections. Journal of Gastrointestinal Surgery, 13, pp.1599-1606.

[21] Wani, M. D., Din, F. M. U., Bhat, A. R., Kumar, I. A., Raina, A. H., and Gul, Z. (2020). Role of biomarkers in predicting anastomotic leakage following colorectal surgeries. International Journal of Research in Medical Sciences, 8(7), 2562â€“2567. https://doi.org/10.18203/2320-6012.ijrms20202896

[22] Ortega-Deballon, P., Radais, F., Facy, O., dâ€™Athis, P., Masson, D., Charles, P.E., Cheynel, N., Favre, J.P. and Rat, P., 2010. C-reactive protein is an early predictor of septic complications after elective colorectal surgery. World Journal of Surgery, 34, pp.808-814.

[23] Platt, J.J., Ramanathan, M.L., Crosbie, R.A., Anderson, J.H., McKee, R.F., Horgan, P.G. and McMillan, D.C., 2012. C-reactive protein as a predictor of postoperative infective complications after curative resection in patients with colorectal cancer. Annals of Surgical Oncology, 19, pp.4168-4177.

[24] Warschkow, R., Tarantino, I., Torzewski, M., NÃ¤f, F., Lange, J. and Steffen, T., 2011. Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: a retrospective study of 1,187 patients. International Journal of Colorectal Disease, 26, pp.1405-1413.

[25] Warschkow, R., Tarantino, I., Torzewski, M., NÃ¤f, F., Lange, J. and Steffen, T., 2011. Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: a retrospective study of 1,187 patients. International Journal of Colorectal Disease, 26, pp.1405-1413.

[26] Nesbakken, A., Nygaard, K., Lunde, O. C., Blucher, J., Gjertsen, ∅., & Dullerud, R. (2005). Anastomotic leak following mesorectal excision for rectal cancer: true incidence and diagnostic challenges. Colorectal Disease, 7(6), 576-581.

[27] Alberts, J. C. J., Parvaiz, A., & Moran, B. J. (2003). Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Disease, 5(5), 478-482.