

A PROSPECTIVE OBSERVATIONAL STUDY ON THE ROLE OF C-REACTIVE PROTEIN AS A PREDICTOR OF COLORECTAL ANASTOMOTIC LEAKAGE

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Abstract

Introduction-

Anastomotic leak is a frequent and dreaded complication of colorectal surgery, with incidences ranging from 2-14% recorded. However, early detection may reduce short-term morbidity and death. Advances in surgery have led to the contemporary surgeon seeing colorectal cancer not as an insurmountable hurdle, loaded with morbidity and approaching mortality, but as a task to be tackled, supported by an armament provided by modern oncological surgery and chemo-radiation. As a result, a low-cost, readily accessible marker that can be discovered early in the subclinical stage before overt sepsis emerges would be highly sought.

AIMS & OBJECTIVES

This study aims to assess the role of CRP in early detection of colorectal anastomotic leak

Objectives:

To establish clinically useful post-operative CRP cut-off values to facilitate safe and early discharge after elective colorectal surgery.

RESULTS-

During a span of 18 months, a cohort of 55 patients was enrolled, Afterward, a total of 51 patients were deemed qualified for analysis. Among the cohort of 51 individuals, all of them had a surgical procedure involving the anastomosis of the colon, rectum, and anus. Three individuals did not possess a C-reactive protein (CRP) score on the fourth day. This included leaks from all patients regarding gender distribution, there were 15 female and 36 males who underwent surgery. the three most common procedures were Hartman's reversal, which formed a third of procedures, while low anterior resection, stoma reversal, hartmans reversal, were about 50% of procedure. Logistic regression analysis revealed a p-value of 0.02 for the association between Day 4 CRP levels and the duration of stay. Additionally, a Mann Whitney U test yielded a p-value of 0.01 for the association between Day 4 CRP levels and the presence of non-leak complications. The mean value of day 4. Being 116.57mg/L.

CONCLUSION

We recommend that all patients get a day 4 CRP after undergoing an elective colorectal surgical operation. CRP's relevance in colorectal surgery stems from its capacity to identify anastomotic leaks early, allowing for early management.

INTRODUCTION

Anastomotic leak is a frequent and dreaded complication of colorectal surgery, with incidences ranging from 2-14% recorded. However, early detection may reduce short-term morbidity and death. Advances in surgery have led to the contemporary surgeon seeing colorectal cancer not as an insurmountable hurdle, loaded with morbidity and approaching mortality, but as a task to be tackled, supported by an armament provided by modern oncological surgery and chemo-radiation. Miles' bloody, radical fields of surgery have given way to actual bloodless planes of surgery, and a colon cancer diagnosis is no longer a death sentence. Sadly, despite such fast developments in surgery and the miracles of neo-adjuvant chemo-radiation, the threat of anastomotic leakage continues to hang over even the best-equipped clinics.

An anastomotic leak produces severe morbidity, poses a risk of death, delays treatment, prolongs recovery (1), and entails a large financial burden on the patient, particularly in resource-limited areas such as India. Despite the broad repertory of alternatives available to the contemporary colorectal surgeon, from newer neoadjuvant chemotherapy regimens to advancements in laparoscopic procedures and instruments, anastomotic leak rates have never reached zero in many trials (2).

The typical symptoms of a leak, such as fever, tachycardia, and abdominal indications of peritonitis, or even elevated white cell counts, sometimes appear too late to be clinically relevant (3). The real event may have happened much earlier, although these standard clinical indicators do not become visible until the 7th or 8th day after surgery. In the present age of ERAS (improved recovery after surgery) guidelines, patients may be released as early as the fourth- or fifth-day following surgery, before exhibiting any overt clinical symptoms and may look well. These patients, on the other hand, come a few days later, by which time the patient is already severely septic. Another complicating factor is the difficulty in distinguishing mild indications of early sepsis from the typical post-operative inflammatory stress response

According to Alves et al(4), a delay in diagnosis results in 18% mortality and poor outcomes. By contrast, detecting and treating anastomotic leaks on day 4 or 5 reduces morbidity and improves post-operative outcomes. (5)

As a result, a low-cost, readily accessible marker that can be discovered early in the subclinical stage before overt sepsis emerges would be highly sought. Several biological inflammatory indicators, such as interleukin 6, TNF alpha, and pro-calcitonin, have been suggested to fulfil this function. Unfortunately, many of them are excessively costly, technically difficult to assess, or are not readily accessible. The holy grail of anastomotic leak detection would be a simple, widely accessible, low-cost bedside test that is extremely sensitive and specific and detected early enough to affect therapy. CRP C Reactive Protein, for example, has showed significant promise as a cost-effective and reliable early marker of anastomotic leak. C-reactive protein has been shown in many trials to be a valuable measure of anastomotic healing, with consistently strong negative predictive values (>95%) as early as postoperative day 4 (6-9). Despite consistent evidence to support this, its use is presently constrained by variances in known cut-off values and a scarcity of prospective data.

This research seeks to address the issue of what would be a therapeutically effective cut-off value in early identification of anastomotic leak in our demographic subgroup, with a focus on detection early enough to commence significant intervention to minimise morbidity.

AIMS & OBJECTIVES

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MATERIAL & METHODS

Design centre: We chose our research location since it was a tertiary referral facility with a broad range of patients. We used a prospective observational research design in which patients were recruited sequentially from a prospective surgical theatre posting list. The institutional review board and the ethical committee both reviewed and approved the research design.

We settled on two goals: To create clinically meaningful postoperative CRP cut off values in order to promote safe and early release following elective colorectal surgery, as well as to monitor high-risk patients.

Setting: S.C.B Medical College's hospital wards and labs in Cuttack.

Participants: Patients over the age of 18 who were admitted to S.C.B Medical College for elective colorectal surgery with a main intestinal anastomosis were eligible for this research. All patients were given an information pamphlet that detailed the study, the sort of testing performed on them, and the research's implications. The pamphlet further said that although participation would not directly assist the patient, it would help advance the cause of improved diagnostic techniques. It was also made clear that participation was entirely optional, and that the patient might opt out at any moment.

Inclusion criteria:

All patients who were above the age of 18

All patients who consented to the procedure

Patients undergoing a large intestinal anastomosis This included colectomies: right and left hemi colectomies, sigmoid resections, anterior resections, Hartman's reversals, colostomy closures, ileo rectal anastomoses for procto and pan proctocolectomies - in short, if there was any colonic or rectal or anal anastomosis, it was included in the study.

Exclusion criteria:

1. Emergency surgery
2. Active infection prior to surgery
3. Re-exploration/leak detected before 4th post operative day
4. Acute or chronic liver failure
5. SLE, dermatomyositis, scleroderma
6. Inflammatory bowel disease
7. Leukaemia

Patients who are having emergency operations often have obstruction or sepsis, resulting in a heightened state of acute inflammatory response. Preoperative CRP levels are expected to be significantly increased, which would presumptively hinder the feasibility of obtaining

practically acceptable postoperative measures. All individuals who presented with obstruction or had an emergency colectomy were excluded from the trial. Exclusion criteria included active illnesses, such as wound infection, pneumonia, or urinary tract infections, since their presence would have resulted in elevated pre-operative levels, as previously documented.

Patients who met the eligibility criteria and were found to have a leak before to the fourth day were precluded from participation in this research. Likewise, those requiring a significant interventional operation, such as re-exploration for any reason, including the presence of a leak, were not included in the study. The rationale for this decision was that a significant intervention of this kind would introduce bias into the measurements taken on post-operative day 4.

The exclusion criteria for this study were the presence of acute or chronic hepatic failure, since these conditions are known to result in decreased hepatic production of C-reactive protein (CRP).

Individuals who were diagnosed with systemic lupus erythematosus (SLE), dermatomyositis, and scleroderma prior to surgery had a weak or unusually low inflammatory response. As previously mentioned, these individuals have a diminished C-reactive protein (CRP) response to inflammation due to several factors that have been previously explained, and were thus omitted.

A number of people diagnosed with inflammatory bowel disease need surgical resections; nonetheless, it has been shown that Crohn's disease and ulcerative colitis have divergent responses with respect to C-reactive protein. Crohn's disease is often characterised by high C-reactive protein (CRP) levels that closely correspond to disease activity. In contrast, ulcerative colitis has a diminished response in terms of CRP levels. Although both disease processes may impact CRP levels, they were not included in the current research.

Patients with leukaemia also exhibited a compromised inflammatory response and were thus excluded from the study.

It is noteworthy that TB was selected for inclusion. The rationale for this was that the correlation between C-reactive protein (CRP) and TB was not as strong as that shown in inflammatory bowel disease (IBD). However, there have been studies that establish a connection between CRP levels and disease activity. The second factor pertained to the nature of Crohn's disease and ulcerative colitis, which exhibit fluctuating patterns and are fundamentally systemic ailments arising from an inherent dysfunction. In contrast, tuberculosis represents an external pathogenic agent akin to other infections, and once effectively treated, it should not adversely affect the production or elimination of C-reactive protein (CRP).

Patients who met the criteria for eligibility were recruited in a sequential manner from the operation registration list, taking into account the viewpoint of the unit. Individuals were enlisted either on their first encounter with the outpatient department or upon their admission to the facility.

The study included all patients who met the criteria and provided their permission. A recruitment target of 80 patients was established, taking into consideration the audit statistics from the preceding year. A cohort of 55 individuals was enrolled during a span of 18 months. Out of the overall sample size of 55 patients, four individuals were eliminated from the research due to different reasons. Specifically, three patients did not possess a post-operative C-reactive protein (CRP) result, while one patient voluntarily withdrew from participation. Consequently, the final number of participants included in the study amounted to 51 individuals.

The primary outcome measure of this study is the calculation of the area under the receiver operating characteristic (ROC) curve, specifically analysing the post-operative day 4 C-reactive protein (CRP) value in connection to the occurrence of anastomotic leak. danger exposure: All patients were subjected to the potential danger of an anastomosis procedure, which might potentially lead to an anastomotic leak.

Effect modifiers refer to factors that might modify the relationship between an exposure and an outcome. In the context of post-operative CRP levels, it has been shown that these levels tend to grow after surgery and reach their highest point on the second day after the procedure. The inclusion of individuals who have a significant surgical intervention prior to the fourth day will impact the CRP value on the fourth day, necessitating their exclusion from the study.

Diagnostic criteria:

Any one of the following:

1. Luminal or feculent contents in the drain or from the wound site
2. Radiological evidence of anastomotic leak: the presence of air or fluid collection in the peri-anastomotic region or intra-abdominal/ pelvic collection or contrast leak from the anastomotic site
3. Evidence of anastomotic dehiscence on re-exploration

The compilation of many specimens All patients who satisfied the inclusion criteria and provided informed permission for participation in the research underwent the collection of two samples. The first sample was obtained before to the surgical procedure, while the second sample was taken on the fourth day after the operation. The standard adhered to for the calculation of post-operative day count was to designate the day of operation as post-operative day zero, and thereafter increment the count for each subsequent day. The specimens were obtained from a peripheral vein using a conventional 5 or 2 cc syringe equipped with a 23-gauge needle via a peripheral puncture. In order to mitigate the potential for sample dilution, patients who were equipped with a central venous catheter had a peripheral venipuncture for sample collection.

The specimens were obtained either by the primary researcher or by a certified phlebotomist employed at the hospital.

The samples were promptly collected in a disposable serum tube. The specimens were promptly conveyed to the microbiology section inside the same institution and afterwards underwent quick processing. The process of sample processing involves a series of steps to prepare a sample for analysis. This often includes steps such as sample collection, The quantification of all C-reactive protein (CRP) data was performed using immuno nephelometry. The lowest limit of the cut-off value was determined to be 3.14 mg/L, while

the maximum limit was set at 203 mg/L. Starting in 2016, larger dilutions were used, resulting in the derivation of values above 203mg/L up to 400mg/L. The data were recorded on the online clinical work station concurrently upon the availability of each respective port.

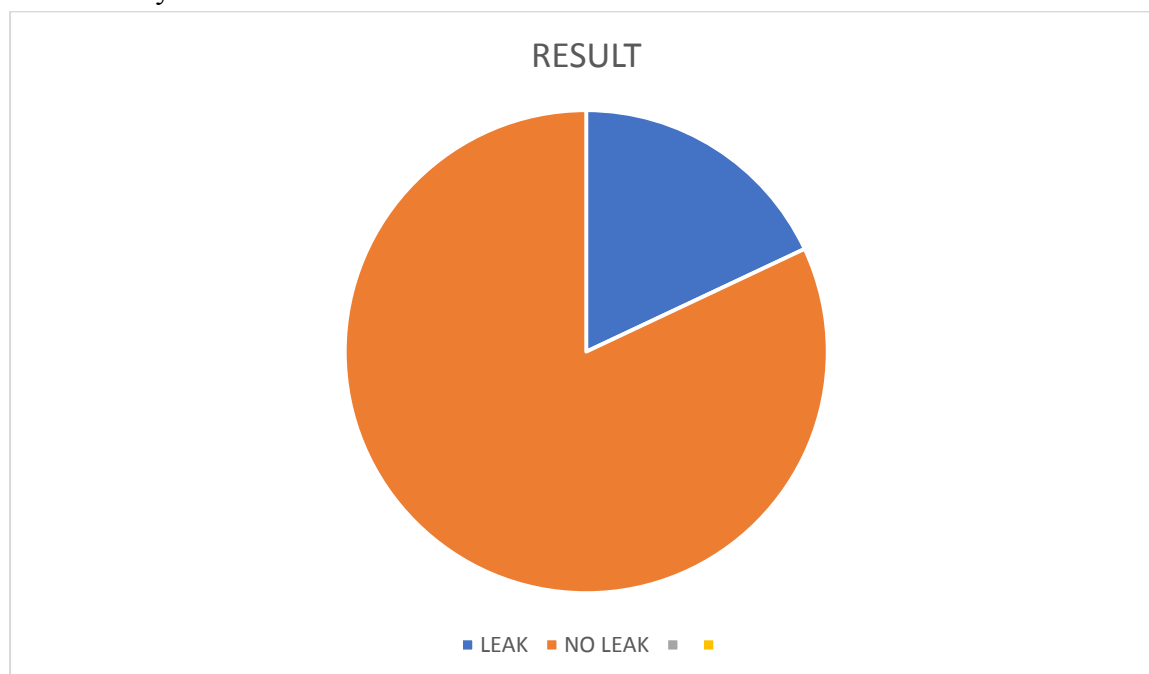
OBSERVATION

During a span of 18 months, a cohort of 55 patients was enrolled, including individuals who provided informed permission and fulfilled the predetermined qualifying criteria.

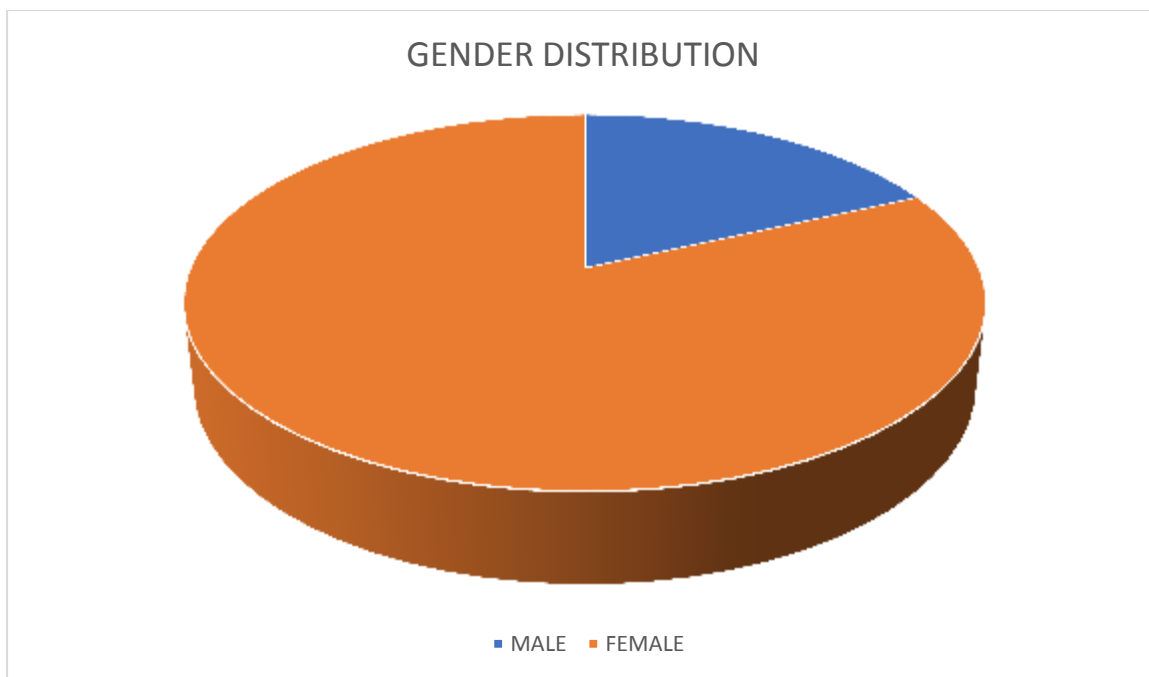
As previously stated, four patients were eliminated from the study following the application of the exclusion criteria. Afterward, a total of 51 patients were deemed qualified for analysis. Among the cohort of 51 individuals, all of them had a surgical procedure involving the anastomosis of the colon, rectum, and anus. Three individuals did not possess a C-reactive protein (CRP) score on the fourth day. This discrepancy might perhaps be attributed to a laboratory mistake during the separate processing of the samples or a failure in collecting the samples on day 4. One patient originally provided permission but then declined to undergo the day 4 assessment, resulting in their exclusion from the study.

The provided information pertains to descriptive data.

Data Incompleteness: The research removed patients with missing data, namely three individuals who did not have a day 4 CRP level. Among the 51 anastomoses observed, 9 leaks were identified based on the previously specified diagnostic criteria for leaks. The average age of the participants was 55.5 years, with a range spanning from 23 to 84 years. The average length of stay for all patients was found to be 14 days, with a standard deviation of 7.392 days.

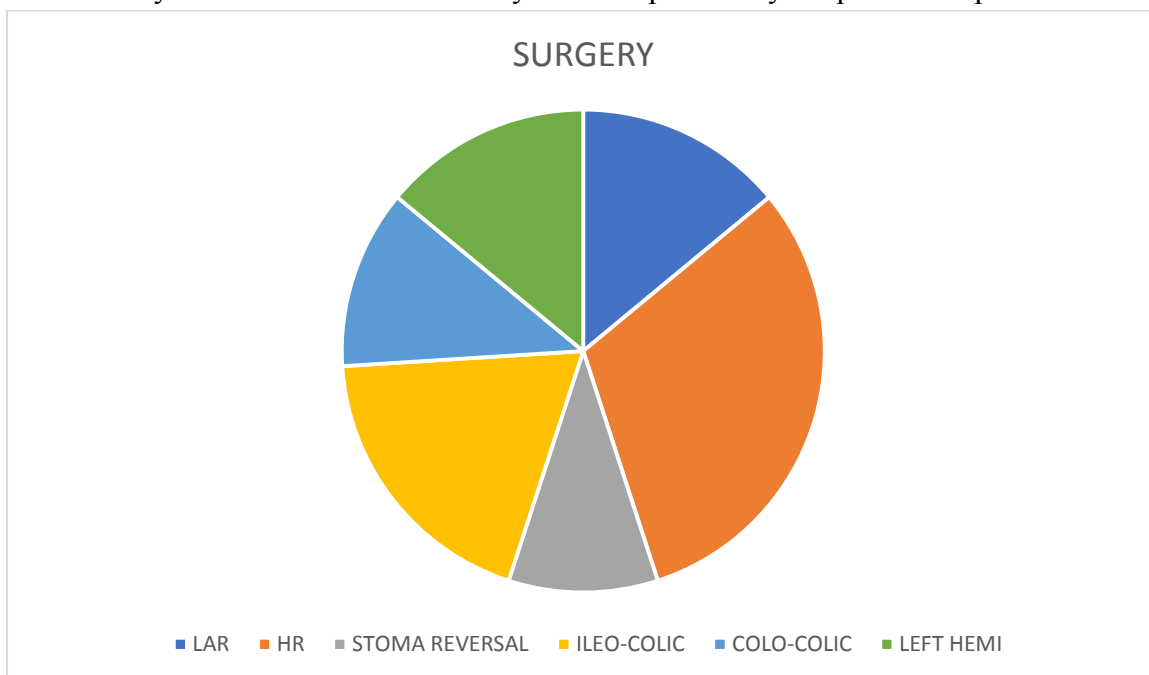


This included leaks from all patients regarding gender distribution, there were 15 female and 36 males who underwent surgery.



Regarding the distribution of disease type, the majority of resection and anastomosis occurred for Hartman’s reversal for sigmoid volvulus: 2nd was ileo-colic anastomosis combined from benign and infective aetiology

There was a total of 19 malignancies operated upon, 6 diseases of infective aetiology. These were usually cases who had been mainly diverted previously for perianal sepsis.



Thus, the three most common procedures were Hartman’s reversal, which formed a third of procedures, while low anterior resection, stoma reversal, hartmans reversal, were about 50% of procedure.

Complications unrelated to leakage were seen in 29% of the patient population. Most of the infections seen were classified as superficial wound infections.

Superficial wound infections constituted 9.8% of the total sequelae, whereas pneumonias accounted for 11% and urinary tract infections represented 5.8%. Other serious issues accounted for most non-leak complications. The entities include abdomens, intra-abdominal collections, and a pelvic collection. The pelvic collections that were identified were not considered as an anastomotic leak due to the criteria established at the start of the research, which did not classify a collection without clear radiological evidence as indicative of a leak. A significant number of patients had a regression during the early phase of their stay. A mere 22% of patients had the outcome of being released and then readmitted in a moribund state, specifically accounting for 2 out of 9 patients who exhibited this phenomenon. Of the leaks that were manifest controlled conservatively

The bi-variate studies conducted to examine the relationship between the incidence of leaks and various factors such as sex, kind of illness, type of surgical operation, degree of anastomosis, stapled vs hand sewed, and curative versus palliative, did not provide statistically significant results, as determined by Chi square tests.

In contrast, the results indicate that there is a significant association between Day 4 CRP levels and both the length of stay and the presence of non-leak problems. Logistic regression analysis revealed a p-value of 0.02 for the association between Day 4 CRP levels and the duration of stay. Additionally, a Mann Whitney U test yielded a p-value of 0.01 for the association between Day 4 CRP levels and the presence of non-leak complications.

The mean value of day 4. Being 116.57mg/L.

Plotting of optimal CRP cut off values:

The cut off value for CRP was calculated by plotting a ROC curve, with sensitivity and 1-specificity on the different axes. The optimal value with maximum sensitivity and specificity was calculated.

The data was analysed by SPSS software, SPSS, IBM.

The area under the curve was 0.964 corresponding to the diagnostic accuracy of 96.4% for CRP in detecting patents with an anastomotic leak. The CRP cutoff value of 154 mg/L yielded the maximum sensitivity and specificity (88.9% and 88.1% respectively)

This cut off value is derived from all patients,

DISCUSSION

The main benefit of CRP is that it enables the treating physician to diagnose anastomotic leakage sooner than existing approaches. Thus, an increased Day4CRP value indicates anastomotic leaking early.

Patients with clinical symptoms, aberrant values such leukocytopenia or leukocytosis, or peritonitis are suspected of an anastomotic occurrence. However, none of these can identify an anastomotic leak early. The biggest risk of an anastomotic incident is delayed presentation and misdiagnosis, which may have grave consequences.

An early discovery might result in

- a. Earlier cross-sectional imaging
- b. Antibiotics, albumin, and tpn are started earlier
- c. Speedier surgery post-decision
- d. Preventing sepsis improves overall.

CRP analysis and testing do not prevent leaks, but they lessen the significant morbidity and death of delayed anastomotic leak identification.

Garcia et al., Almeida et al. (9) and others have proven that typical leak detection techniques including tachycardia, tachypnoea, gastrointestinal symptoms, and fever fail. Since CRP is a sensitive non-specific marker of inflammation, it rises early in stable patients before acute sepsis. It helps the treating doctor manage sepsis early and avoids late discovery morbidity and consequences.

Anastomotic leaks benefit from early diagnosis, hence CRP plays a role. Procalcitonin levels can detect earlier than CRP, however the test is more expensive, making it unsuitable for resource-poor situations. CRP is well known for detecting cellular inflammation and anastomotic leak early.

A post-operative day 4 CRP value has 3 further benefits.

1. An objective leak probability metric without bias
2. Increases cross-sectional imaging's 'CRP first' positive predictive value.
3. As a discharge-facilitating negative predictive value index.

Undoubtedly, excellent clinical practise and insight are unmatched. Clinical evaluation rule: Pain, temperature, tachycardia, and abdominal symptoms are not necessary.

A day 4 CRP level may confirm clinically suspected anastomotic events or aid decision-making in cases of ambiguous clinical indications that do not indicate discharge.

We wanted to find the best cut-off ratio for safe discharge. We calculated open procedure cutoffs at 154 mg/L on day 4 of admission. This threshold of 151mg/L has 88.9% sensitivity and 88.1% specificity. This matched previous researchers' threshold levels (7,9,22). Our cut-off values were higher than Almeida(22) 140mg/L, Garcia et al (9) 135mg/L, and Ortega et al (7) 125mg/L. Plotting the cut-off values against their sensitivities and specificities, we found that 143 mg/L had 100% sensitivity and 78% specificity. Specificity was 97% with a 44% reduction in sensitivity when cutoff values were increased to 178 mg/L. The optimal cut-off value was 151 mg/L (100%, 85%) to 177 mg/L (77%, 97%).

When discharging a patient, readmission concerns must be weighed against needless stay expenditures. A test to assist professionals evaluate it is helpful. When combined with clinical data, CRP helps identify at-risk individuals.

A CRP cutoff value of >200mg/L would detect only leakers and have excellent specificity, but it would also increase false negatives. Our false negative necessitates a readmission with a greater mortality and morbidity rate.

Clinical judgement favours high sensitivity over a few false positives. The sensitivity levels between 154 and 158 mg/L remained 88% in our data. Above 86%, 147 mg/L showed 86% sensitivity and 84% specificity.

Thus, the 154mg/L threshold was maintained for admission.

We believe that monitoring CRP's main value is its ability to discover leaks early enough to enable significant actions to improve outcomes.

AUTOMOTIVE LEAK DETECTION

CRP is most beneficial for leak identification early. CRP helps physicians notice these occurrences sooner in colorectal surgery.

The key to save a patient from spending days in the ICU moribund with a high mortality and morbidity risk is to speed up detection processing so treatment may begin before the patient is so severely septic that heroic efforts are ineffective.

CRP is a marker for subclinical leaks, not a leak predictor.

We believe CRP's main purpose in colorectal surgery is leak detection to prevent morbidity.

EARLY DISCHARGE TOOL

This cut off is useful when diagnosing whether to discharge or monitor.

WBC counts and clinical indicators have failed to identify anastomotic events in the first five days after surgery (7).

A toxic patient with a peritonitic abdomen, fever, and tachycardia is almost certain to have an anastomotic episode.

However, a patient who has emptied his bowels, is afebrile, but has stomach pain that has not entirely settled, maybe because to slightly higher ileostomy outputs, may be hiding a leak that will reveal itself after 5 or 6 days.

ERAS PROTOCOLS CRP

In this age of fast track and accelerated recovery regimens, practitioners are occasionally asked to justify maintaining a patient with just subjective illness symptoms when their clinical experience suggests an anastomotic occurrence. Objective CRP readings at day 4 will aid clinical decision-making. Patients with a day 4 result above 154mg/L should be monitored and maybe imaged.

CRP FIRST APPROACH

Another concern is whether a rigorous cut off would boost cross-sectional imaging to find the leak's origin. While increased CRP may indicate CT scans, it is also beneficial as a pre-test predictor for CT scanning, the "CRP first approach." (10) An increased CRP may only guide CT scan use and boost pre-test positive.

CONCLUSION

We recommend that all patients get a day 4 CRP after undergoing an elective colorectal surgical operation. CRP's relevance in colorectal surgery stems from its capacity to identify anastomotic leaks early, allowing for early management. The morbidity and mortality associated with delayed discovery would be reduced as a result. Based on our findings, we believe that otherwise healthy individuals with a CRP value of less than 154mg/L on day 4 may be safely released. Because we did not include laparoscopic operations in this research, the cut off value for laparoscopic procedures may vary from that of open procedures. An increased CRP level on day 4 should encourage the physician to investigate possible causes of sepsis, most notably an anastomotic leak, and to explore imaging with a CT scan.

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