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Early postoperative inflammatory markers predict major complications after rectal cancer surgery

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Abstract

Background

Postoperative inflammatory response has been associated with complications after colorectal surgery. Early identification of patients at risk of major complications may improve postoperative management. The aim of this study was to evaluate postoperative inflammatory response and the predictive value of C – reactive protein (CRP) and neutrophil – to – lymphocyte ratio (NLR) for major complications after rectal cancer surgery.

Methods

A prospective observational cohort study of 98 patients undergoing rectal cancer surgery between October 2022 and January 2026. Patients underwent laparoscopic surgery (n = 43) or open surgery (n = 55). CRP levels and NLR were measured preoperatively and at 24 and 48 hours postoperatively. ROC curve analysis was performed to evaluate the predictive performance of CRP and NLR. Univariate and multivariate logistic regression analysis was used to identify predictors of major complications, and linear regression analysis was performed to identify factors associated with CRP levels at 48 hours.

Results

A total of 97 patients were included in the study. CRP and NLR levels at 48 hours were significantly higher in patients who developed major complications, while no significant differences were observed at 24 hours. CRP at 48 hours showed good predictive performance for major complications in ROC analysis. In logistic regression analysis, CRP at 48 hours was independently associated with major complications. Linear regression analysis showed that open surgery was associated with higher CRP levels at 48 hours compared with laparoscopic surgery

Conclusions

Postoperative inflammatory response, particularly CRP levels at 48 hours, is associated with major complications after rectal cancer surgery and may be useful for early identification of patients at risk. Monitoring CRP levels in the early postoperative period may help improve postoperative management and early detection of complications

Introduction

The development of surgical approaches to the treatment of rectal cancer that are increasingly less aggressive remains a priority in both clinical practice and cancer research. Colorectal cancer accounts for approximately 10% of all cancer diagnoses worldwide, and rectal cancer constitutes about one-third

of these cases, with an estimated standardised incidence of 17.2 per 100,000 men and 8.6 per 100,000 women, according to data from the Global Cancer Observatory (IARC/WHO). [1]

Therapeutic strategies with curative intent continue to place radical surgical resection based on total mesorectal excision (TME) as the cornerstone of treatment. Open surgery has been the standard approach for decades; however, in recent years, laparoscopic surgery has seen growing adoption as a minimally invasive alternative. [2, 3] Despite its expansion, debate persists as to whether the laparoscopic approach actually reduces surgical trauma and significantly modulates the early systemic inflammatory response compared to open surgery.

A number of meta – analyses have demonstrated that laparoscopic surgery following TME is associated with superior immediate postoperative outcomes in comparison to open surgery, including reduced blood loss, reduced postoperative pain, and decreased hospital stay. Moreover, these studies have confirmed that the oncological outcomes of laparoscopic surgery are comparable to those of open surgery, preserving the radicality of resection and the quality of mesorectal excision. [4, 5] These advantages are attributed to the less invasive nature of the laparoscopic approach, which allows for more careful manipulation of tissues and less disruption of surrounding structures.

Surgical intervention causes controlled trauma that induces alterations in the immunity of patients. [6] Each procedure triggers an inflammatory response proportional to the degree of tissue aggression, followed by a compensatory anti – inflammatory response. Both the inflammatory hyperresponse resulting from tissue destruction and the associated immunosuppression have been linked to adverse clinical outcomes, including organ failure and a high incidence of systemic inflammatory response syndrome (SIRS). [7] This immune imbalance can compromise the curative goal of oncological resections, as postoperative immunosuppression promotes tumour recurrence and metastasis, potentially reducing long – term survival.

It has been demonstrated that the magnitude of the inflammatory response is directly related to the extent of surgical trauma, and thus different surgical approaches could significantly modulate it. [6] In this context, readily obtainable haematological and biochemical parameters, including white blood cell count, C – reactive protein (CRP) and neutrophil – lymphocyte ratio (NLR), serve as valuable instruments for the evaluation of early postoperative inflammation and the comparative impact of diverse surgical techniques on the patient's immune system. [8, 9] Among these markers, CRP at 48 hours postoperatively has the potential to reflect the magnitude of tissue trauma and to predict the onset of major complications, thus allowing the identification of patients who require intensified monitoring in the immediate postoperative period. [9, 10]

Although there have been advances in minimally invasive techniques and evidence supporting the postoperative advantages of laparoscopic surgery, there is a significant limitation in the literature regarding the evaluation of the early inflammatory response after TME. Most studies have focused on general clinical parameters or overall complications. However, there is a paucity of systematic analysis of specific markers such as leukocytes, CRP, and NLR in the first 48 hours postoperatively. [5, 11, 12]

This discrepancy hinders our comprehension of the way disparate surgical interventions modulate immediate systemic inflammation and its potential correlation with early clinical outcomes. This study aimed to assess the association between the early postoperative inflammatory response and the occurrence of major complications following TME for rectal cancer. Secondary objectives included analysing the relationship between the surgical approach and the postoperative inflammatory response, and the predictive value of CRP and the NLR at 48 hours for the early detection of major postoperative complications.

Methods

General Information

A prospective observational, analytical, and comparative cohort study was conducted, consecutively including 98 patients undergoing rectal surgery at Brașov County Hospital between October 2022 and January 2026. The study protocol was approved by the local ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki, [13] with informed consent obtained from all patients where applicable. The present study comprised adult patients who underwent scheduled surgery via laparoscopic approach (n = 43) or open surgery (n = 55).

Patients were allocated to the laparoscopic or open surgery groups according with the standard clinical practice of department, taking into account clinical characteristics of the patient, tumour stage, history of abdominal surgery, and the assessment of the surgeon in charge. No randomisation was carried out, as this is a prospective observational study. To minimise the potential impact of confounding factors arising from the lack of randomisation, statistical analyses were performed with adjustments made for clinically relevant variables.

The laparoscopic group underwent laparoscopic TME following standardised protocols, with minimal tissue manipulation and CO_2 insufflation assistance. The open group underwent TME via conventional laparotomy. All procedures were performed by surgeons specialising in colorectal surgery with more than five years' experience in the corresponding technique.

The inclusion criteria included adult patients (> 18 years) with a histological diagnosis of rectal adenocarcinoma, who underwent resection with curative intent using TME, and for whom postoperative clinical and laboratory data were available at 24 and 48 hours. Exclusion criteria included patients undergoing salvage or palliative surgery, those with previous immunosuppression or chronic use of corticosteroids, patients with active infection or inflammatory bowel disease, and those with incomplete postoperative blood count or CRP records.

Demographic and clinical variables were recorded, including age, sex, comorbidities, tumour stage and American Society of Anaesthesiologists (ASA) classification. Perioperative variables included surgical duration, blood loss, and complications.

The early inflammatory response was assessed by counting leukocytes, neutrophils, lymphocytes, CRP, and NLR preoperatively and at 24 and 48 hours postoperatively. In addition, secondary clinical outcomes were analysed, such as the occurrence of major complications (defined according to the Clavien-Dindo classification ≥ III), [14] the need for reoperation, and length of hospital stay.

Surgery Method

Patients in the laparoscopic group underwent TME using a minimally invasive approach, utilising five working ports and controlled – pressure CO_2 pneumoperitoneum at 14 mmHg. Mesorectal dissection was performed following anatomical plane of Heald, [15] with the aim of preserving the autonomic nerves and minimising manipulation of the surrounding tissues. Intestinal resection and vessel management were performed in accordance with standardised protocols, ensuring the integrity of the mesorectum and distal margin.

In the open group, TME was performed via midline laparotomy, following the same anatomical principles of mesorectal dissection and nerve preservation as in the laparoscopic approach, but with direct exposure of the structures and greater tissue manipulation. In both groups, intestinal anastomoses and haemostasis management were performed in accordance with institutional surgical protocols.

Laboratory analysis

All analyses were conducted in the central laboratory of Spitalul Clinic Județean de Urgență Brașov, in accordance with certified internal and external quality control protocols. Peripheral blood samples were obtained by venipuncture, using EDTA tubes for complete blood count and dry tubes with separating gel for biochemical analyses.

The differential white blood cell count was processed using a SYSMEX XN1000-2 automated haematology analyser, employing flow cytometry and a hydrodynamic approach. NLR was calculated as the absolute ratio between neutrophils and lymphocytes. CRP levels were determined using latex particle – enhanced immunoturbidimetry on an integrated Cobas PRO clinical chemistry platform. All quality controls were performed in accordance with the international standards of the hospital's central laboratory.

Statistical Analysis

Statistical processing was performed using R software (v. 4.5.2). The distribution of continuous variables was assessed using normality tests. According to the results, continuous variables were expressed as median and interquartile range (IQR) or as mean ± standard deviation (SD), depending on the distribution, while categorical variables were presented in frequencies and percentages.

Differences between groups (laparoscopic vs. open approach) were analysed using the Wilcoxon – Mann – Whitney test for non – parametric continuous variables and exact test of Fisher for categorical

variables. Postoperative inflammatory biomarkers, including CRP and NLR, were evaluated in relation to the occurrence of major complications.

The postoperative inflammatory response was assessed by measuring CRP levels and the NLR in the early postoperative period. Because CRP values showed a skewed distribution, logarithmic transformation was applied before linear regression analysis. To evaluate the association between the surgical approach and CRP levels at 48 hours, linear regression models were constructed and adjusted for clinically relevant variables, including neoadjuvant therapy, type of surgery and operating time.

To evaluate the diagnostic performance of CRP and NLR at 48 hours in predicting major complications, receiver operating characteristic (ROC) curves were constructed and the areas under the curve (AUC) were calculated. Optimal cut – off values were determined using the Youden index.

Logistic regression models were constructed to identify predictors of major complications. Due to the limited number of events, the number of variables included in the multivariate models was restricted to prevent overfitting.

A p – value < 0.05 was considered statistically significant.

Results

The study cohort included a total of 98 patients, of whom 43 underwent laparoscopic surgery and 55 underwent open surgery. As shown in Table 1, both groups were adequately balanced in terms of their demographic and baseline clinical characteristics. No statistically significant differences were observed between the groups in variables such as age, sex, body mass index (BMI) or ASA classification ($p > 0.05$). However, a significantly higher proportion of patients in the laparoscopic group received neoadjuvant chemoradiotherapy compared with the open surgery group ($p = 0.020$).

Table 1
Clinical characteristics of patients.

Characteristic	Laparoscopic N = 43[1]	Open N = 55[1]	p-value[2]
Age (years)	65 (11)	66 (12)	0.943
Sex			0.459
Female	18 (42%)	19 (35%)	
Male	25 (58%)	36 (65%)	
BMI (kg/m²)	25.72 (3.15)	25.55 (3.17)	0.753
ASA Physical Status			0.532
2	24 (56%)	29 (53%)	
3	18 (42%)	26 (47%)	
4	1 (2.3%)	0 (0%)	
Neoadjuvant Therapy (TNT)			0.020
Chemo-radiotherapy	37 (86%)	35 (64%)	
Chemotherapy only	6 (14%)	19 (35%)	
Radiotherapy only	0 (0%)	1 (1.8%)	

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Abbreviations: BMI, Body Mass Index; ASA, American Society of Anaesthesiologists; TNT, Total Neoadjuvant Therapy; SD, Standard Deviation.

As shown in Table 2, with regard to neoadjuvant treatment, most patients who underwent open surgery received chemotherapy prior to surgery, while chemoradiotherapy was more common in the laparoscopic group. In terms of perioperative outcomes, surgical time was significantly shorter in the open surgery group compared to the laparoscopic group (221 vs. 250 min; $p < 0.001$). Likewise, the open approach was associated with a longer hospital stay. Although the incidence of major complications was higher in the open surgery group compared to the laparoscopic group, this difference did not reach statistical significance in this cohort of patients.

Table 2
Perioperative and postoperative outcomes.

Characteristic	Laparoscopic N = 43[1]	Open N = 55[1]	p-value[2]
Surgical Procedure			0.029
Abdominoperineal Resection	10 (23%)	25 (45%)	
Anterior Rectal Resection	31 (72%)	25 (45%)	
Hartmann's Procedure	2 (4.7%)	5 (9.1%)	
Operative Time (min)	250 (18)	221 (33)	< 0.001
Length of Stay (days)	6.9 (4.0)	11.4 (7.4)	< 0.001
Major Complications (CD > = 3)	3 (7.0%)	10 (18%)	0.105

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Postoperative inflammatory response was evaluated using CRP levels and NLR. As shown in Fig. 1, CRP levels were higher in the open surgery group at both time points evaluated. This difference was particularly evident at 48 hours, where the open group had significantly higher CRP concentrations (median: 132.00 mg/L; IQR: 86.81–206.39) compared to the laparoscopic group (median: 90.50 mg/L; IQR: 61.00–126.20; $p < 0.001$). Conversely, a greater dispersion of CRP values was observed in the open group at 48 hours, with some patients reaching values close to 300 mg/L. In contrast, NLR levels did not show significant differences between the surgical groups at either 24 hours ($p = 0.6$) or 48 hours ($p = 0.4$).

Linear regression analysis was performed to identify factors associated with CRP levels at 48 hours (Table 3). Open surgery was significantly associated with higher CRP levels at 48 hours (B = 0.46, 95% CI 0.10–0.81, $p = 0.012$). Neoadjuvant therapy, surgical procedure, and operative time were not significantly associated with CRP levels.

Table 3
Linear Regression analysis for factors associated with CRP levels at 48 hours

Characteristic	Beta	95% CI	p-value
Surgery Modality			
Laparoscopic	—	—	
Open	0.45	0.10, 0.81	**0.012**
TNT groups			
None	—	—	
Chemotherapy only	-0.22	-1.2, 0.73	0.7
Radiotherapy only	-1.4	-3.1, 0.33	0.11
Chemo-radiotherapy	-0.52	-1.4, 0.39	0.3
Surgical Procedure EN			
Abdominoperineal Resection	—	—	
Anterior Rectal Resection	-0.10	-0.45, 0.26	0.6
Hartmann's Procedure	0.34	-0.38, 1.1	0.4
Operative Time	0.00	0.00, 0.01	0.6
Abbreviation: CI = Confidence Interval			

Postoperative inflammatory biomarkers according to the occurrence of major complications are shown in Table 4. CRP levels at 48 hours were significantly higher in patients who developed major complications compared with patients without complications. Similarly, NLR at 48 hours was significantly higher in patients with major complications. No significant difference were observed for CRP or NLR at 24 hours.

Table 4
Postoperative inflammatory biomarkers according to complications

Characteristic	No N = 85[1]	Yes N = 13[1]	p-value[2]
CRP_24h	73 (44, 102)	76 (66, 137)	0.3
CRP_48h	108 (67, 145)	223 (156, 286)	0.001
NLR_24h	12 (6, 18)	15 (10, 24)	0.3
NLR_48h	8 (5, 11)	18 (11, 31)	0.002
[1]Median (Q1, Q3)			
[2]Wilcoxon rank sum test			

ROC curve analysis at 48 hours demonstrated good predictive performance for both inflammatory markers (Fig. 2). The optimal cut-off for CRP was 203.2 mg/L, yielding an area under the curve (AUC) of 0.79, with a sensitivity of 72.7% and a specificity of 90.7%. For NLR, the optimal threshold was 10.5, with an AUC of 0.80, a sensitivity of 81.8%, and a specificity of 73.3%.

Logistic regression analysis was performed to identify predictors of major postoperative complications. In univariate logistic regression analysis, higher CRP and NLR levels at 48 hours were significantly associated with major complications (Table 5). Open surgery showed a higher risk of major complications compared with laparoscopic surgery, although the difference did not reach statistical significance (p = 0.066).

Table 5
Univariate logistic regression analysis for prediction of major complications.

Variable	OR	95% CI	p-value
CRP at 48 hours	1.01	1.00, 1.03	**0.005**
NLR at 48 hours	1.08	1.01, 1.17	**0.025**
Surgical Approach			0.066
Laparoscopic	—	—	
Open	5.89	0.90, 117	
Abbreviations: CI = Confidence Interval, OR = Odds Ratio			

In multivariate logistic regression analysis including CRP at 48 hours and surgical approach, only CRP at 48 hours remained independently associated with major complications. (Table 6).

Table 6
Multivariate logistic regression for major complications

Characteristic	OR	95% CI	p-value
CRP 48h	1.01	1.00, 1.02	**0.002**
Surgery Modality			0.6
Laparoscopic	—	—	
Open	1.49	0.35, 7.64	
Abbreviations: CI = Confidence Interval, OR = Odds Ratio			

Overall, postoperative inflammatory response, particularly CRP levels at 48 hours, was strongly associated with the occurrence of major postoperative complications and showed good predictive performance for early identification of patients at risk.

Discussion

This study evaluated the early postoperative inflammatory response and its association with major complications after rectal cancer surgery. The main findings of this study were that CRP and NLR levels at 48 hours were significantly associated with major postoperative complications, and CRP at 48 hours was an independent predictor of major complications. Additionally, open surgery was associated with higher postoperative inflammatory response compared with laparoscopic surgery.

An interesting finding of this study was the higher proportion of patients receiving neoadjuvant chemoradiotherapy in the laparoscopic group. Neoadjuvant treatment is often associated with increased technical difficulty and a potentially greater inflammatory response. [16] However, despite this imbalance, patients undergoing laparoscopic surgery demonstrated lower postoperative inflammatory biomarker levels and a lower rate of major complications. This finding may further support the potential advantages of the minimally invasive approach in reducing surgical stress and postoperative inflammatory response.

Postoperative CRP has been widely studied as an early marker of postoperative complications in colorectal surgery. Several studies have demonstrated that elevated CRP levels on postoperative day 2 or 3 are associated with an increased risk of anastomotic leak and other major complications. [17, 18] Our results are consistent with previous studies, showing that CRP at 48 hours was significantly higher in patients who developed major complications and showed good predictive performance in ROC analysis. The high specificity observed for CRP and the high sensitivity of NLR indicate that these markers not only reflect the degree of surgical trauma but may also contribute to the early detection of serious complications. These findings are consistent with those of Řezáč et al., who identified CRP as a robust predictor of complications after rectal resection. However, while their study was limited to open surgery with an optimal diagnosis on day 4 (175.4 mg/L), [19] our model allows for earlier detection at 48 hours.

NLR has also been proposed as a marker of systemic inflammatory response and postoperative complications. In our study, NLR at 48 hours was significantly higher in patients who developed major complications, although CRP showed a stronger association and better predictive performance compared with NLR.

Taken together, these findings suggest that CRP and NLR may play complementary roles in postoperative monitoring. While the high sensitivity of NLR in our cohort (81.8% at a threshold of 10.5) may facilitate early identification of patients at risk, the high specificity of CRP (90.7% at a cut – off value of 203.2 mg/L) may help confirm clinical suspicion and support further diagnostic evaluation. These observations support the potential clinical value of inflammatory biomarkers in the early postoperative assessment of patients undergoing rectal cancer surgery.

Our results are consistent with previous studies that have demonstrated a lower postoperative inflammatory response following laparoscopic surgery compared to open surgery in the treatment of colorectal cancer. [20, 21] Specifically, the significantly lower CRP levels observed in our laparoscopic cohort at 24 and 48 hours reflect the results of recent meta – analyses, which demonstrate that minimally invasive techniques are associated with a lower surgical inflammatory response. [22, 23] Greater tissue manipulation and wider surgical exposure favour a more intense activation of the postoperative inflammatory response, with the release of pro – inflammatory cytokines such as interleukin – 6, which stimulates hepatic synthesis of CRP protein in the early postoperative period. [24] This attenuated response to surgical stress probably explains the significantly shorter hospital stay observed in our laparoscopic patients, as a lower inflammatory burden facilitates faster functional recovery.

Interestingly, although open surgery was associated with higher inflammatory response, surgical approach was not an independent predictor of major complications in multivariate analysis, whereas CRP remained independently associated with complications. This suggests that the postoperative inflammatory response rather than the surgical approach itself may be more directly associated with the development of major complications.

From a clinical perspective, early identification of patients at risk of major complications is extremely important in rectal cancer surgery. CRP measurement at 48 hours is simple, inexpensive, and widely available, and may help identify patients who require closer monitoring, additional imaging, or early intervention. Incorporating CRP monitoring into postoperative protocols may improve early detection of complications and potentially improve patient outcomes.

One of the limitations to be taken into account when interpreting the results is related to the sample size; although it allowed significant associations to be identified, the absolute number of major complications was relatively low. Due to the limited number of events, the number of variables included in the multivariate logistic regression model had to be restricted to avoid model overfitting. Therefore, although CRP at 48 hours remained independently associated with major complications in the adjusted model, it

was not possible to include all potential confounding variables, and the results should be interpreted with caution. Larger prospective studies are needed to validate these findings.

The most notable confounder was the significantly higher proportion of neoadjuvant chemoradiotherapy in the laparoscopic group ($p = 0.020$). However, since neoadjuvant therapy typically increases surgical complexity and exacerbates inflammation, the fact that the laparoscopic cohort still demonstrated significantly lower CRP levels reinforces the potential of the minimally invasive approach to attenuate surgical trauma. Finally, the study was conducted at a single centre, which may limit the generalisation of the results to other institutions or surgical settings. However, the marked homogeneity of the sample and the robustness of the p – values obtained reinforce the internal validity of this work as a basis for future prospective and multicentre research.

In conclusion, postoperative inflammatory response, particularly CRP levels at 48 hours, was strongly associated with major postoperative complications after rectal cancer surgery. CRP at 48 hours was an independent predictor of major complications and showed good predictive performance. Monitoring CRP levels in the early postoperative period may help identify patients at risk of complications and improve postoperative management.

Declarations

Ethics approval and consent to participate:

The study protocol was approved by the local Ethics Committee of Spitalul Clinic Județean de Urgență Brașov and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Funding:

The authors declare that no external funding was received for this study.

Author Contribution

AML and MM conceptualized and designed the study. AML, MH, AH collected and organized the clinical data. CM and AML performed the statistical analysis. AML and MH drafted the manuscript. MM and CM critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

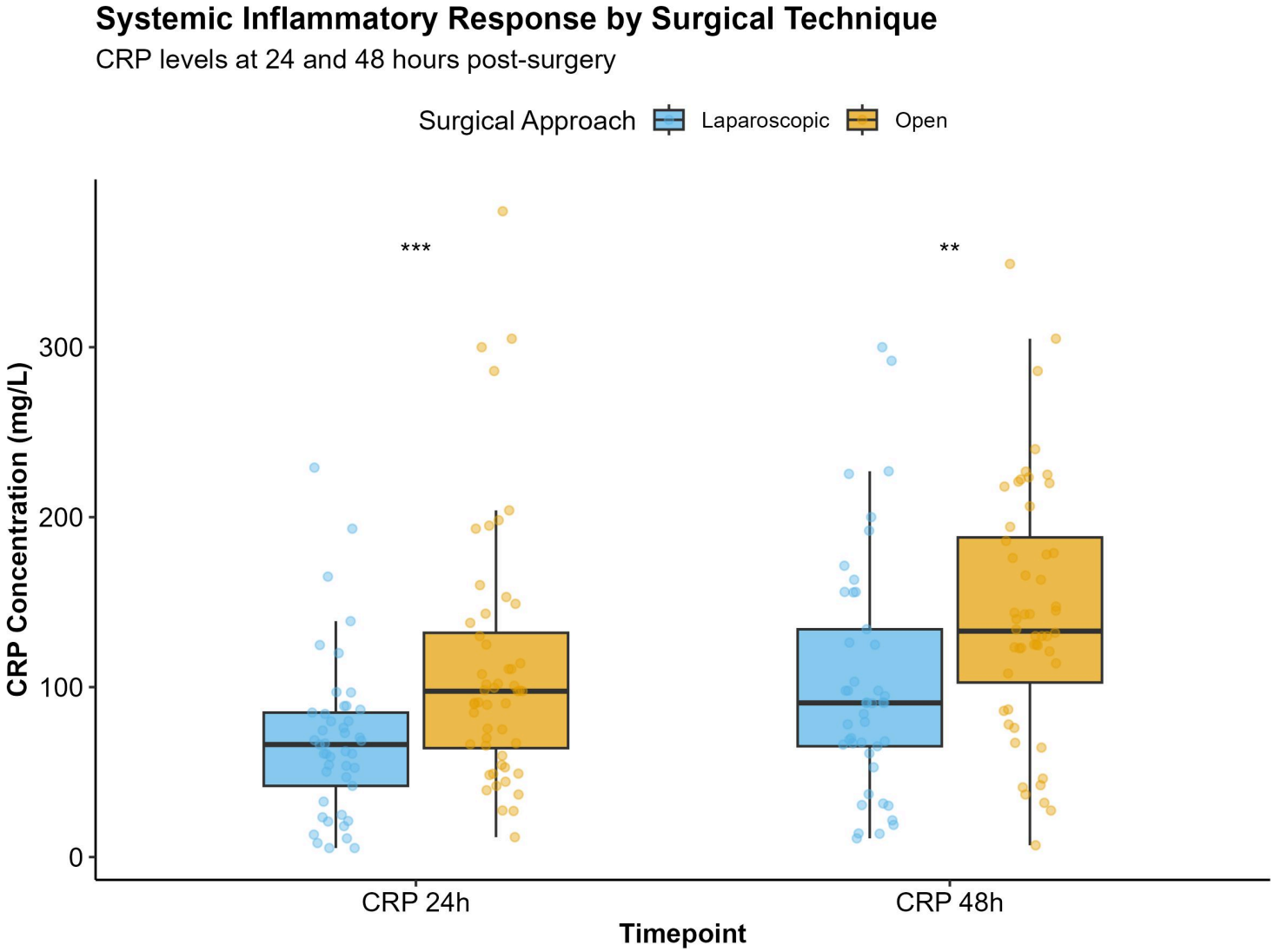


Figure 1

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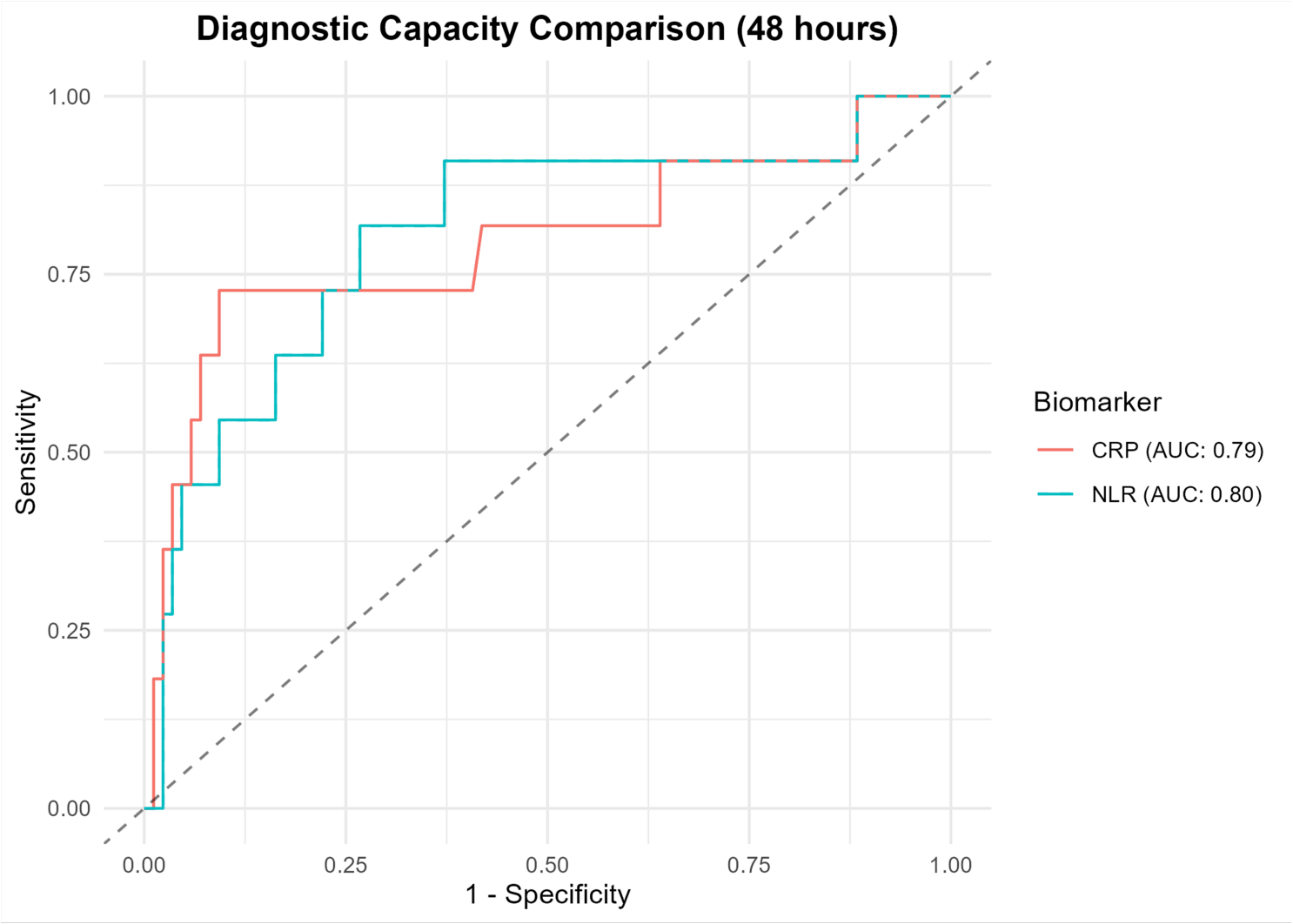


Figure 2

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