Albumin and CRP, Which is the Best Biomarker for Postoperative Complications on Colorectal Surgery? Prospective Cohort Study

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Albumin and CRP, which is the best biomarker for postoperative complications on Colorectal Surgery? Prospective cohort study

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Abstract

Aim Our purpose was to investigate the potential role of albumin variation in comparison to C-reactive protein (CRP) variation as a predictive marker for postoperative complications in colorectal surgery.

Methods An prospective cohort study was conducted. Adult patients who underwent elective colorectal surgery between January 2019 and December 2020 were eligible. Serum levels of albumin and CRP were measured preoperatively and on the first 4 postoperative days. Univariate analysis were performed to assess the association of albumin (Alb) and CRP with postoperative complications. Serum albumin variation (ΔAlb) and CRP variation (ΔCRP) were calculated. Receiver operating characteristic curve analysis and the Youden test were used to determine acuity and predictive cut-off values.

Results Ninety-three patients were included. A CRP cut-off of 83.4 mg/dL on postoperative day (POD) 4 was the best predictor of postoperative global complications ($p<0.001$; AUC 0.83, 70% sensitivity, 91% specificity). Major complications were best correlated with ΔAlb on POD 2, 3 and 4 ($p<0.001$), with a ΔAlb cut-off of 27.4% on POD 2 showing the strongest association with this outcome (AUC 0.834, 83% sensitivity, 90% specificity). Regarding anastomotic leak, CRP on POD 3 showed better predictive values ($p=0.037$; AUC 0.792) with a cut-off value of 88.7 mg/dL (100% sensitivity, 52% specificity).

Discussion Herein, the authors demonstrate there is a role for albumin variation, as an earlier and sensitive marker, to predict major postoperative complications in colorectal surgery. This analysis may be further applied to aid in the early identification of significant causes of re-operation and long-term morbimortality.

Keywords:
CRP; Albumin; Complications; Postoperative complications; Colorectal Surgery;

BACKGROUND

Despite significant progress in surgical techniques and perioperative care, postoperative complications are still a concern for both, surgeons and patients. These account for a prolonged hospital stay, associated costs and non-negligible morbidity and mortality rates (30% and 2-5%, respectively).(1, 2) Therefore, the early detection and timely approach of these complications are of crucial importance to improve surgical outcomes. As so, during the last years, the search for a reliable biomarker that could early predict the occurrence of postoperative complications has been encouraged.

The cellular response to surgical aggression is driven by immune system activation and the release of pro-inflammatory cytokines.(3) These are responsible for the variation of acute-phase proteins, such as C-reactive protein (CRP), albumin, interleukin-6, procalcitonin, ferritin, transferrin and fibrinogen.(3) The rise of these proteins and cytokines is associated with the magnitude of systemic inflammatory response after surgical stress.(4)

The prognostic role of preoperative hypoalbuminemia in patients submitted to colorectal surgery is established, being malnutrition of paramount importance.(5) Still, few studies have evaluated the correlation between albumin variation and the prediction of postoperative complications.

Our study aims to assess the potential role of albumin variation in comparison with CRP variation as a predictive marker of postoperative complications in colorectal surgery.

METHODS

This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Selection

The authors performed an prospective design cohort study from 2019 to 2020. Inclusion criteria were as follows: patients aged over 18 years old who underwent elective colorectal surgery between January of 2019 and December of 2020 in *Centro Hospitalar Universitário do Algarve – Unidade de Portimão*. Additionally, exclusion criteria were multi-visceral resection, palliative or emergency surgery, metastatic disease and perioperative intravenous administration of albumin. Also, patients with known liver function alteration or without available laboratory albumin values during the studied timepoints were excluded.

Biological markers

Serum albumin (normal range 3.2-4.5 g/dL) and CRP levels (normal range 0.0-5.0 mg/dL) were measured preoperatively (morning before surgery) and on the first 4 postoperative days (POD 1, 2, 3, 4). Serum levels of total proteins (normal range 6.3-8.3 g/dL) were measured to ensure a reliable albumin concentration. Blood samples were collected in a fasting state in the early morning, always at the same time of day.

Data Extraction and Quality Assessment

In the selected patient sample, sociodemographic, clinical and biochemical data were collected by two independent authors.
The anonymisation and security of the data were assured. Only the investigator (M.C) and sub-investigator (P.M.) had access to patients' information. The records were destroyed at the end of the study. The Algarve University Hospital Review Board and ethics committee approved this prospective study. The intervention in this study only regarded the inclusion of albumin values in the blood samples that were already collected pre and postoperatively in the surgical department's regular practice. As so, waiver of consent was approved.

Outcome measures
Two researchers independently used Clavien-Dindo classification (C-D) to assess and classify postoperative complications within 30 days after surgery. Grades I and II were considered minor and grades III to V major complications. Any disagreement between the two researchers was resolved through discussion together with a third researcher, if necessary.

Albumin variation (ΔAlb) and CRP variation (ΔCRP) were calculated. The relative variations were defined as (preoperative value - POD value)/preoperative value x 100% and (POD value - preoperative or POD value)/POD value x 100%.

Anastomotic leakage was diagnosed and classified according to the validated International Study Group of Rectal Cancer (ISREC) classification.(6, 7)

Statistical analysis
All data was analysed using SPSS® version 27. Continuous data were presented as mean ± standard deviation (SD) or median ± interquartile range (IQR), whereas we used absolute values and percentages for categorical data. The Student t-test and Mann Whitney U test were used to analyse continuous variables, depending on the sample's parametric or non-parametric distribution, respectively. One-way ANOVA and Kruskal-Wallis tests were used to compare different groups, depending on the sample's parametric or non-parametric distribution, respectively.
Receiver operating characteristic (ROC) curve and area under the curve (AUC) were determined to assess acuity and predictive values. Youden test was used to determine the best cut-off for outcome prediction.
By convention, we used a 95% confidence interval (95% CI) for all predictive values and *P* values <0.05 were considered statistically significant.

RESULTS

Ninety-three patients were included, of which 61 (65.6%) were male. The median age was 66 years old (57.5-78.0). As shown in Figure 1, 20 patients (21.5%) presented with sigmoid, 19 (20.4%) with rectal and 10 (10.8%) with ascending colon cancer. Among the most performed surgeries, 30 (33.2%) were right hemicolectomies, followed by sigmoidectomy and anterior resection of the rectum (Figure 1). Concerning the

operative approach, 52 (55.9%) were open surgeries, and 41 (44.1%) were laparoscopic. The median length of hospital stay was 7 (5.0-13.0) days.

Postoperative complications

Forty-six patients (49.5%) had postoperative complications according to the Clavien-Dindo classification (Figure 2). Of this group, 34 (36.6%) had minor, and 12 (12.9%) had major complications (C-D III-IV). Furthermore, 11 patients (11.8%) had surgical site infections and 7 (7.5%) experienced anastomotic leak (AL). There were no postoperative mortality cases in our cohort.

Biomarkers perioperative profile

Figure 3 shows albumin and CRP absolute variation from the preoperative day and until the 4th postoperative day.

When we look at the global peri-operative profile of Albumin, we can see that its value decreases from the preoperative to the post operative period, and afterwards it stabilizes during the 4 post operative days (figure 3a). Comparing patients with and without complications, figure 3b shows that the absolute value of Albumin increases and decreases, respectively. However, CRP absolute values increases until the 2nd post operative day, but subsequently decreases both for patients with and without complications (figure 3d).

Predictive value of albumin and CRP for postoperative complications

We evaluated the association between albumin and CRP absolute values, absolute variation and relative variation with postoperative complications – global occurrence, major, minor and anastomotic leakage (Table 1).

Both ΔAlb, CRP and ΔCRP were associated with the occurrence of postoperative complications. Again, major complications were both correlated with ΔAlb, CRP and ΔCRP. However, minor complications were only associated with CRP measurements on POD 2 to 4 and ΔCRP. Moreover, AL was only associated with CRP measurements on POD 3 and 4.

Accuracy of ΔAlb, CRP and ΔCRP for the prediction of postoperative complications

The best predictors for major and minor postoperative complications and anastomotic leakage were determined using ROC curves and AUC (Figure 4).

A CRP cut-off of 83.4 mg/dL on POD 4 was the best predictor of postoperative complications ($P<0.001$; AUC 0.83, 70% sensitivity, 91% specificity).

Regarding major postoperative complications, this outcome was strongly correlated with ΔAlb on POD 2, 3 and 4 ($p<0.001$), with a ΔAlb cut-off of 27.4% on POD 2 showing the strongest association with this outcome (AUC 0.834, 83% sensitivity, 90% specificity). Concerning minor complications, CRP was the only one that showed a predictive role (AUC 0.731; 95% CI 61.8-84.5%).

Lastly, CRP on POD 3 showed better predictive values for AL ($p=0.037$; AUC 0.792) with a cut-off value of 88.7 mg/dL (100% sensitivity, 52% specificity).

DISCUSSION AND CONCLUSIONS

The search for an early and reliable predictor of postoperative complications has been a challenge during the past years. CRP has been proposed as a biomarker of complications after colorectal surgery.(8, 9) However, some studies point out its slow variation profile as a major limitation, which may not guarantee a timely therapeutic approach.(8, 10, 11) Recently, ΔAlb has been associated with the prediction of these postoperative complications, although this hypothesis still required external validation.(12, 13) Albumin is an available, low-priced and widely used biomarker in clinical practice. This could further allow its far-reaching application if a significant improvement in predicting surgical complications was indeed confirmed. The present study highlights the role of albumin and CRP as potential predictors of complications after elective colorectal surgery. This study adds to the literature as it shows major postoperative complications may be predicted earlier than previously reported by albumin.

Perioperative values of albumin and CRP were obtained and their kinetic profile after surgery was studied. As a negative acute-phase reactant protein, an initial swift decrease in albumin was observed, reaching a *plateau* on POD 1 and 4 (Figure 3a). These results are similar to the ones described by Hübner *et al*. and Labgaa *et al*.(12, 13) Although mean ΔAlb values were higher in patients with postoperative complications, this variation was stable between POD 1 and 4 (Figure 3b). These findings may indicate that the calculation of ΔAlb (preoperative - postoperative) should be preferred compared to PODs absolute values.

On the other hand, an increase in CRP was observed with a maximum peak on POD 2, and a gradual decrease on POD 3 and 4 (Figure 3c). Facy *et al.* and Platt *et al.* showed a similar kinetic in their studies.(10, 14) Despite the superior mean postoperative CRP values in patients with complications, its variation profiles were identical to those obtained from patients without complications (Figure 3d). This suggests that for CRP, absolute values are preferred to variation analysis.(10, 15)

In our study, CRP on POD 4 was the best predictor of postoperative complications. Similarly, other studies consistently reported CRP as one of the best predictive markers. However, the cut-off value with the best performance in the present study was inferior to the ones obtained elsewhere.(8, 15, 16) This might be explained by the fact that our study had a higher rate of laparoscopically performed surgeries, which may be associated with a lesser inflammatory response when compared to open surgery.(17)

Regarding major complications, notably, ΔAlb on POD 2 showed the best predictive value among all markers and time points (Figure 4b). Wang et al. obtained similar results by showing that ΔAlb on POD 2 was an independent risk factor for major postoperative complications after laparoscopic colorectal surgery.(18)

Regarding the prediction of minor complications, CRP on POD 4 showed the best predictive value (Figure 4c). To our knowledge, there are no other studies that independently evaluate the association of these markers with minor complications.

Regarding AL, CRP on POD 3 showed the best predictive value (Figure 4d). Several authors pointed CRP on POD 3 as the marker of choice, offering the best predictive value for anastomotic dehiscence.(19-21) Again, our cut-off value was inferior to the ones shown in other studies.(19-21)

Our study has several limitations. It is a single-centre study, and the sample size is relatively small precluding generalization of the result. Secondly, the authors did not consider other confounding factors such as malnutrition that could impact albumin values. Still, using variation calculation and the patient as its own control diminishes this selection bias. Lastly, the use of biomarkers does not exclude critical thinking and patient observation, having only an adjuvant role in ascertaining complication risk.
We believe our study has strengths that should be highlighted. It is a prospective study, adequate for the external validation of albumin as an adequate biomarker for postoperative complication prediction in real-life clinical practice. Several measures were taken to improve the study reliability and validity: 1) blood collections were performed at the same time period for the 4 consecutive days, minimizing biomarkers known daily variation interference; 2) patients with altered liver function (cirrhosis, metastatic disease) were excluded from the analysis as these conditions could alter albumin levels; 3) multi-visceral resection was an exclusion criteria in order diminish the heterogeneity of the sample .

In conclusion, there is mounting evidence on the role of albumin in predicting major postoperative complications after colorectal surgery. Herein, the authors demonstrate there is a role for albumin variation, as an earlier and sensitive marker, to predict major postoperative complications in colorectal surgery. However, larger multicenter studies are warranted. Moreover, studies aiming to assess the different cut-off values performances in different surgical approaches and techniques may expand knowledge on how these proteins behave as early predictors for postoperative complications.

List of Abbreviations:

Albumin - **Alb**
Anastomotic Leak - **AL**
Area under the Curve - **AUC**
Clavien-Dindo classification - **C-D**
C-reactive protein - **CRP**
C-reactive protein variation - **ΔCRP**
Mean ± standard deviation - **SD**
Median ± interquartile range - **IQR**
Postoperative day - **POD**
Receiver operating characteristic - **ROC**
Serum albumin variation - **ΔAlb**
95% confidence interval - **95% CI**

DECLARATIONS

Ethics approval and consent to participate: The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. All efforts were made to ensure confidentiality of the data. The ethics commission approval from Centro Hospitalar Universitario do Algarve was assured with the reference 106/19. This manuscript follows the standards for reporting observational studies outlined in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.
All the patients who agreed to participate signed an dated the study informed consent.

Consent of Publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests*:* The *authors have* no conflicting and competing interests to declare.

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Authors Contribution: MC as principal investigator, performed the protocol, was responsible for the implementation of the study and was a major contributor in writing the manuscript. PM analyzed and interpreted the patient data and contributed to the writing manuscript. BM and IM were responsible for collecting data and major contributors in the writing manuscript. JR, EA and PCB performed major methodologic and clinical guidance and collaborate on the writing manuscript.
All authors read and approved the final manuscript.

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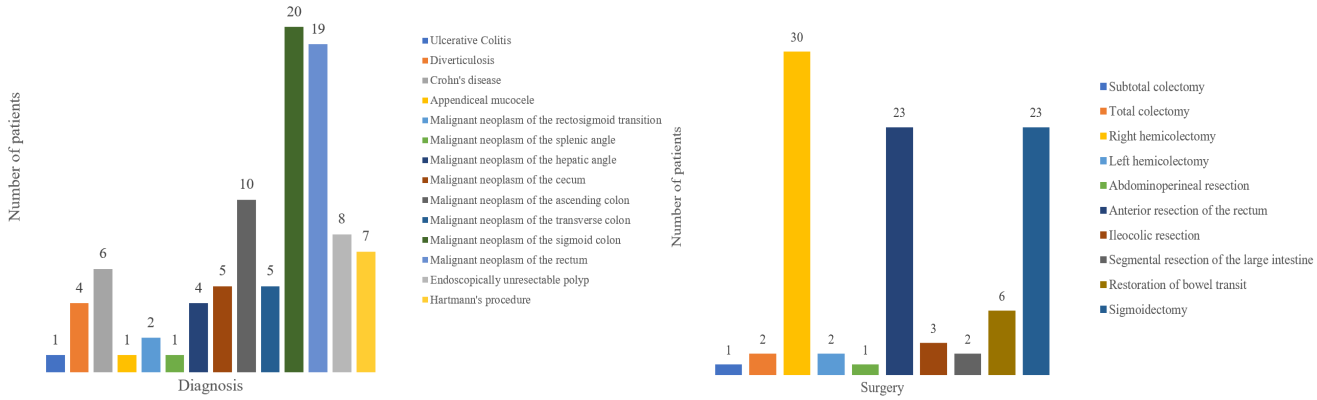


(a) (b)

Figure 1. (a) Patients characteristics according to diagnosis. (b) Patients characteristics according to surgery type.

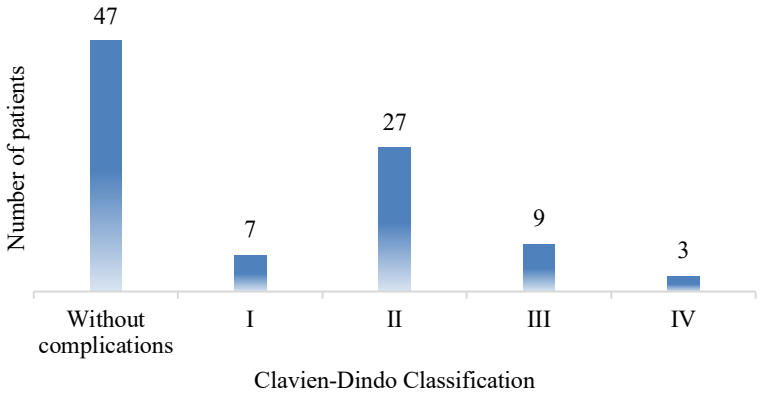


Figure 2. Postoperative complications according to the Clavien-Dindo classification.

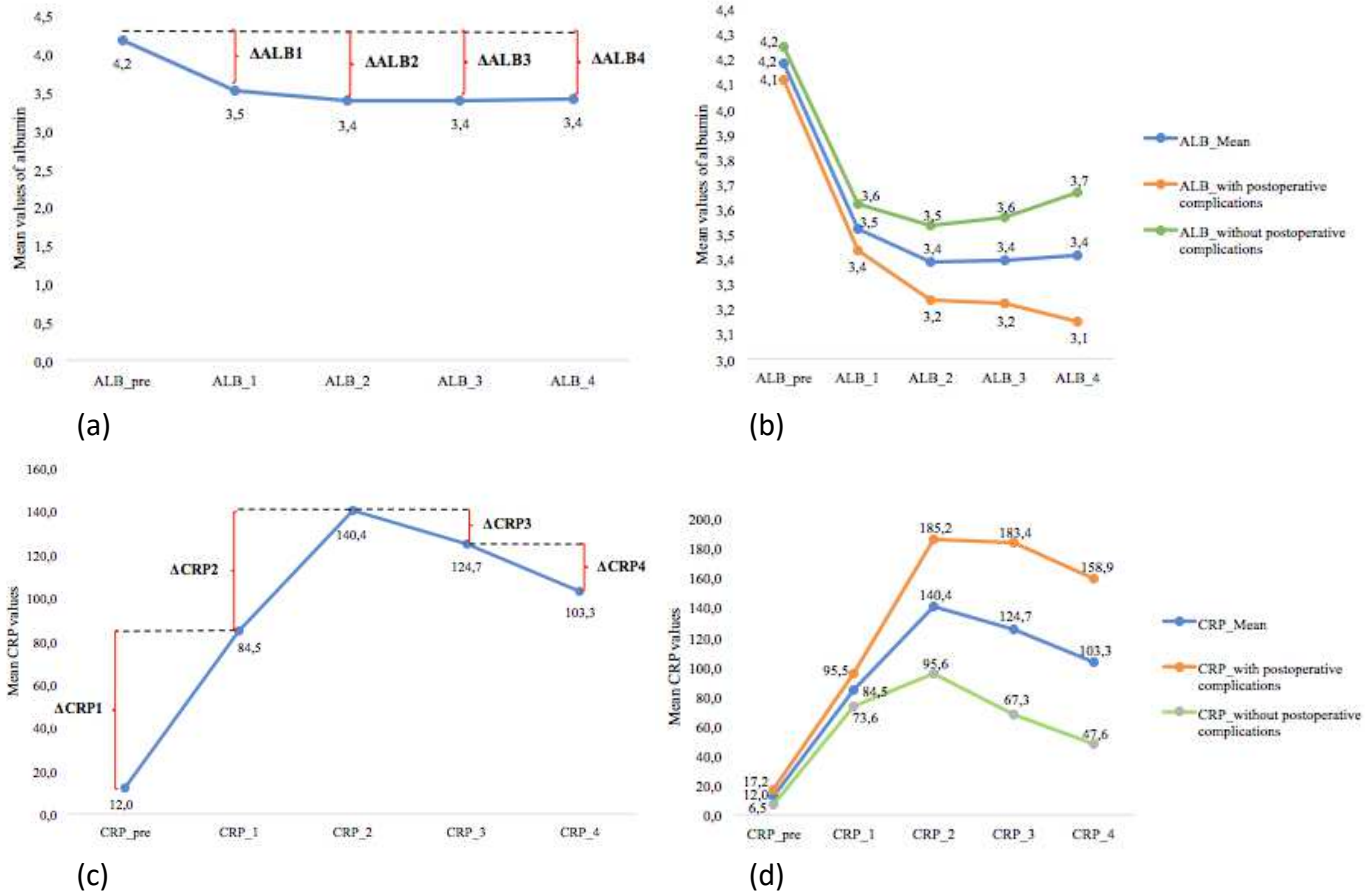
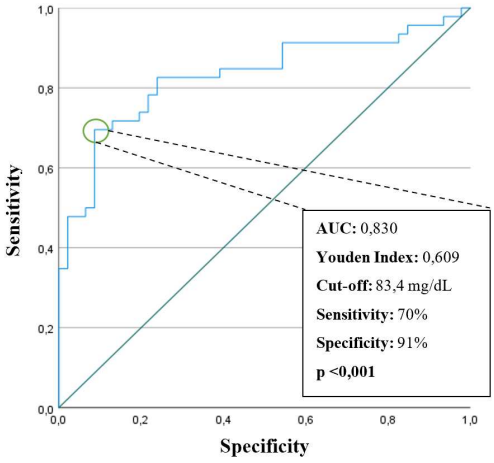


Figure 3. (a) Mean values of serum albumin on the preoperative day (ALB-pre) and POD 1-4 (ALB1-4). (b) Mean values of serum albumin on the preoperative day (ALB-pre) and POD1-4 (ALB1-4) in patients with and without postoperative complications. (c) Mean values of CRP on the preoperative day (CRP-pre) and in POD1-4 (CRP1-4). (d) Mean values of CRP on the preoperative day (CRP-pre) and POD1-4 (CRP1-4) in patients with and without postoperative complications.



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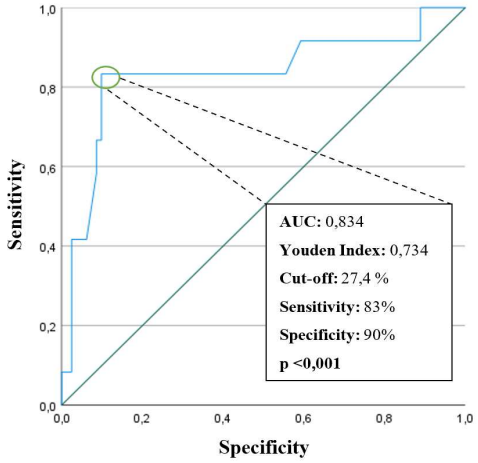

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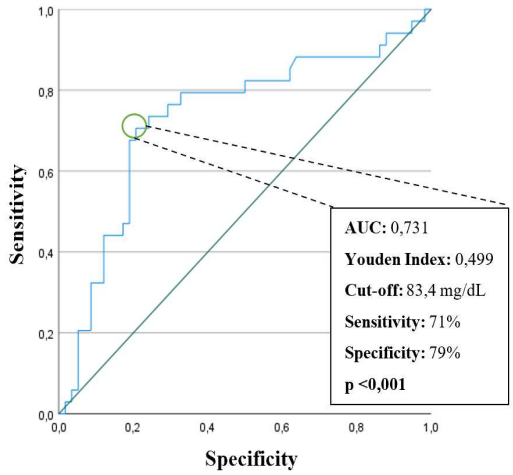

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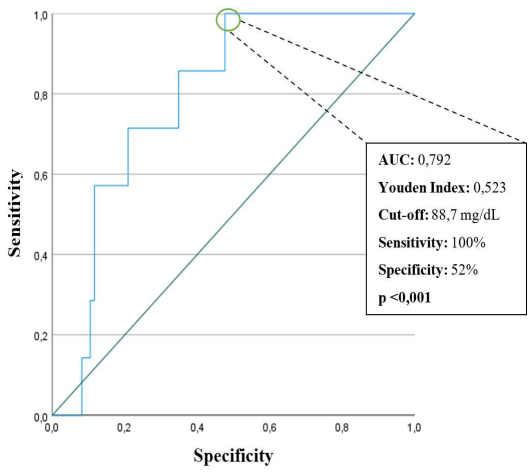

(d)

Figure 4. (a) ROC curve analysis of the CRP on POD 4 as the best predictor for postoperative complications. (b) ROC curve analysis of the ΔALB on POD 2 as the best predictor for major postoperative complications. (c) ROC curve analysis of the CRP on POD 4 as the best predictor for minor postoperative complications. (d) ROC curve analysis of the CRP on POD 3 as the best predictor for anastomotic dehiscence.

Table 1. Univariate analysis of biochemical parameters associated with postoperative complications.

	Postoperative complications (*n* =93)						With minor complications (*n*=34)			With major complications (*n*=12)		With anastomotic dehiscence (*n*=7)	
	No	Yes	*n*			*p value*	Mean ±SD	*n*	*p value*	Mean ±SD	*p value*	Mean ±SD	*p value*
			No	Yes	Total								
Preoperative Albumin [a]	4,2 ±0,3	4,1 ±0,4	46	46	92	0,236	4,1 ±0,4	34	0,075	4,3 ±0,3	0,428	4,1 ±0,4	0,285
ALB1[a]	3,6 ±0,3	3,4 ±0,4	45	46	91	**0,010**	3,5 ±0,4	34	0,239	3,4 ±0,3	**0,034**	3,3 ±0,2	0,115
ALB2 [a]	3,5 ±0,3	3,2 ±0,4	46	46	92	**0,001**	3,3 ±0,5	34	0,298	3,1 ±0,2	**<0,001**	3,1 ±0,2	**0,044**
ALB3 [a]	3,6 ±0,4	3,2 ±0,5	47	46	93	**<0,001**	3,3 ±0,5	34	0,098	3,0 ±0,4	**<0,001**	3,1 ±0,4	0,095
ALB4 [a]	3,7 ±0,4	3,1 ±0,5	46	44	90	**<0,001**	3,2 ±0,5	32	**0,008**	3,0 ±0,4	**<0,001**	3,1 ±0,3	0,230
ΔALB1 [b]	15,1 ±7,0	16,4 ±8,7	45	46	91	0,431	14,7 ±8,5	34	0,326	21,3 ±7,7	**0,009**	17,3 ±11,9	0,844
ΔALB2 [b]	16,9 ±6,7	21,2 ±11,1	47	46	93	**0,026**	18,6 ±10,8	34	0,755	28,5 ±8,6	**<0,001**	24,1 ±10,8	0,263
ΔALB3 [b]	16,1 ±8,1	21,5 ±11,8	47	46	93	**0,011**	18,7 ±10,3	34	0,937	29,7 ±12,4	**<0,001**	24,4 ±11,1	0,321
ΔALB4 [b]	13,5 ±8,3	23,0 ±11,6	46	45	91	**<0,001**	20,2 ±10,5	33	0,201	30,8 ±11,3	**<0,001**	23,0 ±9,0	0,505
Preoperative CRP [a]	6,5 ±17,4	17,2 ±46,1	43	45	88	**0,026**	21,5 ±53,3	33	0,101	5,4 ±5,0	0,355	10,6 ±5,6	0,704
CRP1 [c]	73,6 ±44,9	95,5 ±57,0	46	46	92	**0,032**	93,2 ±55,0	34	0,138	102,0 ±64,5	0,289	86,5 ±30,9	0,773
CRP2 [c]	95,6 ±54,6	185,2 ±113,2	46	46	92	**<0,001**	175,0 ±99,8	34	**0,002**	214,3 ±145,9	**0,024**	179,7 ±80,5	0,264
CRP3 [c]	67,3 ±38,5	183,4 ±141,5	47	46	93	**<0,001**	168,7 ±125,8	34	**<0,001**	225,0 ±178,6	**0,005**	187,9 ±74,4	**0,037**
CRP4 [c]	47,6 ±30,2	158,9 ±126,8	46	46	92	**<0,001**	145,1 ±109,4	34	**<0,001**	197,9 ±166,0	**0,005**	190,8 ±120,0	**0,032**
ΔCRP1 [b]	4102,5 ±5971,9	4722,0 ±8383,3	43	45	88	0,374	5192,7 ±9524,6	33	0,246	3427,4 ±3836,4	0,734	2737,1 ±2543,1	0,288
ΔCRP2 [b]	47,6 ±63,3	107,6 ±101,2	46	46	92	**0,004**	103,3 ±103,8	34	0,106	119,5 ±96,7	**0,050**	126,6 ±26,6	0,540
ΔCRP3 [b]	-24,6 ±27,3	-4,2 ±42,9	47	46	93	**0,002**	-7,8 ±28,7	34	**0,035**	6,0 ±70,0	0,120	21,5 ±85,4	0,207
ΔCRP4 [b]	-18,4 ±95,4	-7,2 ±56,3	47	46	93	**0,012**	-11,4 ±50,2	34	0,065	4,8 ±72,3	0,271	0,4 ±44,8	0,196

[a] Values are expressed as mean ±SD (g/L);
[b] Values are expressed as mean ±SD (%);
[c] Values are expressed as mean ±SD (mg/dL);
p values were calculated by applying the t-Student, Mann-Whitney U, One-way ANOVA and Kruskal-Wallis tests