Trajectory of Inflammatory Biomarkers to Predict Intra-Abdominal Septic Complications After Surgery for Crohn's Disease

Zeqian Yu

Nanjing University School of Medicine

Dengyu Feng

Jinling Hospital

Zhen Wang

Jinling Hospital

Yi Xu

Southeast University School of Medicine

Lei Zhao

Nanjing University School of Medicine

Xianqi Yi

The People's Hospital of Gong'an County

Jianfeng Gong (✉ gongjianfeng@nju.edu.cn)

Nanjing University Medical School <https://orcid.org/0000-0001-8518-6796>

Research article

Keywords: Interleukin-6, Procalcitonin, Crohn's disease, Intra-abdominal septic complications

Posted Date: November 5th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-100655/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Postoperative infectious complications, especially intra-abdominal septic complications (IASCs), represent a major cause of morbidity after surgery for Crohn's disease (CD). We aimed to assess the association between postoperative trajectory of C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT) and postoperative IASCs of CD bowel surgery.

Methods: This is a single-center, prospective, observational study between July 2016 and November 2018, 202 consecutive adults underwent CD-related intestinal resection and anastomosis were enrolled. Levels of CRP, IL-6 and PCT were measured preoperatively and for five days postoperatively. Postoperative IASCs were recorded accordingly.

Results: Postoperative IASCs were detected in 24 (11.76%) patients. For prediction of isolated timepoints, IL-6 has higher area under curve (AUC) compared to CRP and PCT in predicting postoperative IASCs (AUC: 0.85 on POD 1; 0.87 on POD 3 and 0.90 on POD 5). For trend analysis, an CRP increase of more than 50 mg/L from POD 3 to POD 5 had a highest AUC of 0.80. An average CRP on POD 3 and POD 5 of >100.3 mg/L had an AUC of 0.947.

Conclusions: CRP and IL-6 outperforms PCT in predicting postoperative IASCs in terms of trajectory and cutoff values. Continued elevation of CRP showed excellent performance in diagnosing IASCs.

Background

Up to 80% of patients with Crohn's disease (CD) need surgery due to stricture, fistula, or abscess.(1, 2) Postoperative complication rates are higher after CD surgery than other colorectal diseases and postoperative intra-abdominal septic complications (IASCs) represent a major cause of morbidity. IASCs were defined as anastomotic leakage, intra-abdominal abscesses, or enterocutaneous fistulas,(3) with a relative incidence range between 8% and 16%.(4, 5) These complications are always exclusively at the anastomotic site, and are associated with a longer hospital stays, higher treatment costs, greater individual suffering and higher reoperation rates.(4, 6)

Previous studies have shown that levels of serum inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), can predict the postoperative sepsis and outcome in patients undergoing various surgical procedures. IL-6 is a reliable early and independent marker of postoperative sepsis in patients undergoing major surgery for cancer.(7) Alvaro *et al.*(8) reported that PCT was more accurate than CRP although both are reliable predictors of major anastomotic leak after colorectal resection. Although these biomarkers have a high negative predictive value (NPV), their often had a low positive predictive value (PPV). Therefore, these biomarkers are generally used as a guide for early and safe discharge from the hospital, but is of limited value for predicting IASCs at an early stage.

Since postoperative complications are an evolving condition, biomarkers at single time point might fail to capture the dynamic change of postoperative period. Recent studies have showed promising future of

using trend of CRP to predict anastomotic leak and postoperative discharge after surgery for colorectal cancer.(9–11) In the setting of CD patients, we observed that patients with continued elevation of inflammatory biomarkers were more likely to develop IASCs. A substantial proportion of these patients had a peak of inflammatory biomarkers and maintained a plateau afterwards. Therefore, the aim of this prospective observational study was to determine the association between trajectory of different inflammatory biomarkers and IASCs with an emphasis on patients with continued elevation of inflammatory biomarkers.

Methods

Study design

This is a single center, prospective, observational study. The investigation was performed after approval by the Ethics Committee of Jinling Hospital, and in accordance with relevant guidelines and regulations. Diagnosis of CD was based on endoscopy, radiology and surgical pathology.(12) Procedures where a resection and primary anastomoses and/or strictureplasty (i.e., without diverting stomas) is performed were enrolled for analysis, as follows: small bowel resection, ileocecal resection, segmental colectomy and total colectomy. All patients received standard perioperative management according to enhanced recovery after surgery (ERAS) protocol after surgical resection.(13) Inclusion criteria were as follows: confirmed diagnose of CD; open or laparoscopic bowel resection and anastomosis for CD as explained above; in elective setting. Exclusion criteria were as follows: age younger than 16 years or older than 75 years; pregnancy status; in emergency setting; the possibility of preoperative infection has not been ruled out.

Laboratory Tests

Laboratory tests were routinely performed preoperatively (POD 0), including a complete blood count and blood biochemical examination including IL-6, CRP and PCT were collected. Blood samples for IL-6, CRP and PCT analysis were also collected every 48 h after the operation (POD 1, POD 3, POD 5). Levels of IL-6, CRP and PCT were analyzed in the clinical laboratory at *Jinling Hospital*.

Definition of postoperative IASCs

During the postoperative period, all patients were observed for infectious complications and IASCs using the definitions summarized in Table 1. Patients were divided into Non-IASC group and IASC group. Postoperative IASCs were defined as any anastomotic leak, intra-abdominal abscess, or enterocutaneous fistula occurring within 1 month after surgery or prior to discharge.(3) Diagnosis of IASCs was determined on intra-abdominal imaging, the presence of infected or fecal material in the percutaneous drainage or relaparotomy findings. The ultimate diagnosis were verified by puncture and/or culture.

Data collection and sample size calculation

The data collected included age, sex, age at operation, duration of disease before surgery, smoking habits, body mass index (BMI), disease location and behavior (Montreal classification), best Crohn's disease activity index (Best CDAI). Also collected were operative notes, which included operative time, number of laparoscopic completed cases, number of anastomoses, blood loss, volume of blood transfusion during operation. The time between surgery and intra-abdominal septic complications were also recorded. Based on a previous research conducted in our IBD center, the incidence of IASCs was 11.34% among 344 hospitalized adults after operations,(3) based on this information, we calculated that a sample size of at least 70 patients was needed for this study, using a specificity of 80% with a confidence interval (CI) of $\pm 5\%$.

Statistical analysis

All statistical analyses were conducted using SPSS (version 20.0; SPSS, Chicago, IL). Using an Excel database, all values were entered as absolute values, means, medians, and percentages, as appropriate. Continuous data were presented as mean and standard deviation (SD) if normally distributed, and compared using Student's t tests for two-group comparisons or one-way ANOVA for three-group comparisons. If not normally distributed, continuous data were presented as median and interquartile range (IQR), and were compared using Mann-Whitney U tests for two-group comparisons. The Kolmogorov-Smirnov test was used to test for normality.

To compare dichotomous variables between groups, χ^2 -test or Fisher's exact test was used. To compare biomarkers' accuracy as predictors of IASCs, receiver operating characteristic (ROC) curves and the corresponding area under curve (AUC) were used. Prognostic parameters were evaluated using 2×2 tables, and were calculated to determine sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). A two-sided P value of < 0.05 was considered statistically significant.

Results

Study population

A total of 225 consecutive adults underwent bowel resection with primary anastomosis for CD was screened between July 2016 and November 2018. Of 225 hospitalized adults, 23 patients were excluded due to preoperative or intraoperative intraabdominal abscess ($n = 6$), and incomplete data ($n = 8$), or stoma creation ($n = 9$). Thus, 202 hospitalized adults were finally recruited for this study.

Among the 202 patients, 59 (29.21%) patients had postoperative infectious complications, and 24 (11.88%) had IASCs, whereas 35 (17.33%) patients had infectious complications other than IASCs. Patients were divided into non-IASC group and IASC group. In the final 202 patients with a primary anastomosis, mean age was 34.88 years and 48.51% were male. Forty-three patients (21.29%) were in active disease(Best CDAI ≥ 150). The most commonly conducted anastomosis methods were side-to-side anastomosis in 85.64% of patients. Forty-six of the operations (22.77%) were completed by laparoscopy. Baseline characteristics of the included patients were shown in Table 1.

Inflammatory markers in patients with and without IASCs

CRP levels were similar between IASC and Non-IASC group both on POD 0 (2.15 [0.50–4.9] vs. 4.40 [1.35–13.10] mg/L, $p = 0.060$) and POD 1 (54.90 [31.00–81.50] vs. 60.20 [37.50–78.75] mg/L, $p = 0.242$), but were different on POD 3 (97.20 [71.27–144.70] vs. 155.30 [107.40–215.90] mg/L, $p < 0.001$) and POD 5 (37.34 [19.65–69.66] vs. 98.40 [48.57–180.25] mg/L, $p < 0.001$) (Fig. 1A)

The levels of IL-6 between groups were significantly different from POD 1 to POD 5: 96.68 (66.12–162.20) vs. 433.90 (211.95–733.80) pg/mL ($p < 0.001$) on POD 1; 29.89 (19.81–47.28) vs. 139.73 (83.49–237.56) pg/mL ($p < 0.001$) on POD 3, and 17.43 (10.40–34.37) vs. 82.75 (42.76–98.76) pg/mL ($p < 0.001$) on POD 5 (Fig. 1B).

PCT levels were significantly higher in IASC than non-IASC group (POD1: 2.71 [2.03–5.35] vs. 1.62 [0.70–3.38] µg/L, $p < 0.001$; POD 3: 1.39 [0.62–2.98] vs. 0.49 [0.14–1.91], and POD 5 (0.65 [0.18–2.13] vs. 0.18 [0.11–0.35] µg/L, $p < 0.001$) as shown in Fig. 1C.

Trajectory of CRP, IL-6 and PCT for predicting IASCs

For prediction using isolated timepoints, the AUC for IL-6 was highest among all biomarkers studied (AUC = 0.85, 0.87 and 0.90 for POD 1, 3 and 5 respectively). The AUC for CRP on different postoperative days range from 0.59 to 0.89 while that of PCT range from 0.68 to 0.84. (Table 2 and Fig. 2).

For trajectory analysis, an increase of CRP of more than 50 mg/L for POD 3–5 had the highest AUC of 0.80 (sensitivity 0.58, specificity 0.99, PPV 0.17, NPV 0.95). An increase of IL-6 more than 30 ng/L between any 3 consecutive days (POD 1–3 or 3–5) had a specificity of 0.71 and an NPV of 0.90. The prognostic value of this change was higher for POD 3–5 than POD 1–3 (AUC 0.78, sensitivity 0.57, specificity 0.98 vs. AUC 0.56, sensitivity 0.54, specificity 0.84). In contrast, trajectory of PCT had poor performance of predicting IASC. An increase of PCT more than 0.5 µg/L between any 3 consecutive days had an AUC of 0.61 (POD 1–3: 0.52, POD 3–5: 0.57, respectively). Notably, the sensitivities for IL-6 and PCT cutoff values on isolated time points were better than specificity whereas trajectory of IL-6 and PCT had better specificity than sensitivity. (Table 2 and Table 3).

Continued elevation of CRP predicts IASCs

Given the high specificity and low sensitivity of CRP increase on POD 3–5, we reasoned that the predictive performance of trajectory might be compromised by cases in which the inflammatory biomarkers peaked on POD 3. Therefore, we next calculated the average of CRP, IL-6 and PCT on POD 3 and 5 to represent the continued elevation of inflammatory biomarkers. For example, the average of CRP for a certain patient was calculated as $(\text{CRP}_{\text{POD3}} + \text{CRP}_{\text{POD5}})/2$. Notably, an average of CRP level of > 100.3 mg/L had an AUC of 0.947 (95% CI 0.890–0.980, $p < 0.0001$, sensitivity 0.952, specificity 0.886). Mean level of IL-6 and PCT on POD 3–5 also had reasonably good performance in predicting IASCs (IL-6 average at cutoff value 45.85 pg/mL: AUC 0.838 95% CI 0.758–0.899, $p < 0.0001$, sensitivity 0.857, specificity 0.762, PCT average at cutoff value 0.454 ng/mL AUC 0.767 95% CI 0.680–0.840, $p < 0.0001$, sensitivity 0.857 specificity 0.639). (Fig. 3)

Discussion

Patients undergoing surgical resection for CD are at high risk for postoperative septic complications, and early identification such patients would enable benefit from early intensive management. The results of the present study showed that levels of CRP, IL-6 and PCT were significantly different between IASC and Non-IASC group. Generally, trajectory of CRP, IL-6 and PCT had reasonably good specificity and NPV, which indicated superiority in ruling out non-IASC cases. Continued elevation of CRP, as depicted by the average of POD 3 and POD 5, was a novel parameter to predict IASCs with an AUC of 0.947.

There is currently a lack of studies comparing the trend of inflammatory biomarkers after anastomosis for CD, especially IL-6 and PCT. Most studies focused on using IL-6 and PCT on isolated time points to predict postoperative outcomes. In a meta-analysis of 1452 patients from intensive care units, PCT could not reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients.(14) However, the role of IL-6 in predicting complications has been proved in practice. IL-6 was first identified by its ability to promote the activation and reproduction of T cells, the differentiation of B cells, and regulation of the acute-phase response.(15) Another study of 50 consecutive patients who underwent elective major gastrointestinal or gynecological tumor resections⁸ showed the AUC of IL-6 and PCT on POD 1 in diagnosing septic complications were 82.1% and 66.4% respectively, and the optimal cutoff value of IL-6 was set at 310 pg/mL. We set the optimal cut-off value of IL-6 on POD 1 in predicting IASCs at 158.19 pg/mL, which was lower than previous literature that set optimal cut-off level for the prediction of infectious complications between 300 and 500 pg/mL.(7, 15, 16) We speculate this is due to lack of an appropriate immunological response in CD patients, as they always suffer from chronic inflammation, concurrent malnutrition and always need immunosuppressive medication, which could further compromise the patients' immunological responses.(17–19)

Our study for the first time compared the trajectory of CRP, IL-6 and PCT in predicting postoperative IASCs for CD patients, showing CRP and IL-6 had better performance than PCT. The NPV was 0.95 and 0.91 respectively for an increase of IL-6 exceeding 30 ng/L and CRP exceeding 50 mg/L from POD 3 to 5, which means that patients who did not follow this trajectory had 95% and 91% chance of not developing IASCs. Therefore, CRP and IL-6 change from POD 3 to POD 5 might serve as an excellent biomarker to screen patients that are suitable for early discharge. Moreover, specificity of CRP increase > 50 mg/L and IL-6 increase > 30 ng/L was 0.99 and 0.97, highlighting the value of CRP and IL-6 monitoring in excluding IASCs for patients whose CRP and IL-6 level is not increasing.

Trajectory modeling seemed to provide higher specificity but lower sensitivity compared with using cut-off points in this study. The subtle difference could be explained after considering the nature of IASCs and biomarker testing. A high concentration in an isolated test should be more efficient in diagnosing IASCs, whereas lack of an increase over consecutive days are more likely to rule out a leak. Additionally, surgery might result in CRP increase even for patients without IASCs. The CRP level of these cases usually falls rapidly after recovering from surgical insult. Therefore, we innovatively calculated the average of CRP to represent two sorts of patients 1): patients with increasing CRP; 2): patients who had

high CRP without sharp decrease. Combining the average calculation and trajectory testing should be informative to predict infections during hospital stay, allowing early and safe discharge from hospital, particularly in the era of fast-track or enhanced-recovery surgery.

Our study has several limitations. First, this is a single-center study based on the analysis of a series of patients who were transferred from other hospitals, and the patients generally had a more severe condition, which yielded a selection bias. Second, the serum parameters were only available on every other day, which might cause inaccuracy in reflecting the trend of inflammatory biomarkers.

In conclusion, continued elevation of CRP serves as a reliable serological indicator in predicting postoperative IASCs for CD patients undergoing intestinal anastomosis. Trajectory of CRP and IL-6 are both prominent in ruling out IASCs. Further prospective trials are needed to validate our findings.

Conclusions

Our study for the first time compared the trajectory of CRP, IL-6 and PCT in predicting postoperative IASCs for CD patients, showing CRP and IL-6 had better performance than PCT. Generally, trajectory of CRP, IL-6 and PCT had reasonably good specificity and NPV, which indicated superiority in ruling out non-IASC cases. Continued elevation of CRP showed excellent performance in diagnosing IASCs.

Abbreviations

IASCs = intra-abdominal septic complications; CD = Crohn's disease; CRP = C-reactive protein; IL-6 = interleukin-6; PCT = procalcitonin; AUC = area under curve; ROC = receiver operating characteristic; POD = postoperative day; NPV = negative predictive value; PPV = positive predictive value; ERAS = enhanced recovery after surgery; BMI = body mass index; Best CDAI = best Crohn's disease activity index; IBD = inflammatory bowel disease; SD = standard deviation; IQR = interquartile range; ANOVA = analysis of variance; CI = confidence interval;

Declarations

Ethics approval and consent to participate:

The consent written was obtained from all participants. The investigation was performed after approval by the Ethics Committee of Jinling Hospital, and in accordance with relevant guidelines and regulations.

Consent for publication:

Not applicable.

Availability of data and materials:

The data that support the findings of this study are available from Jinling Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Jinling Hospital.

Competing interests:

The authors declare that they have no competing interests.

Funding:

None.

Authors' Contributions:

JF contributed to conception and design of the research, contributed to acquisition, analysis and interpretation of the data, and was involved in drafting of the manuscript; XQ contributed to design of the research, contributed to acquisition, analysis, and interpretation of the data, and was involved in drafting of the manuscript; DY contributed to acquisition of the data; Z contributed to acquisition and analysis of the data; Y and L contributed to design of the research. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Acknowledgements

Not applicable

References

1. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and recurrence in 907 patients with primary ileocaecal Crohn's disease. *Br J Surg*. 2000;87(12):1697-701.
2. Gardiner KR, Dasari BV. Operative management of small bowel Crohn's disease. *Surg Clin North Am*. 2007;87(3):587-610.
3. Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. *Dis Colon Rectum*. 2000;43(8):1141-5.
4. Huang W, Tang Y, Nong L, et al. Risk factors for postoperative intra-abdominal septic complications after surgery in Crohn's disease: A meta-analysis of observational studies. *J Crohns Colitis*. 2015;9(3):293-301.
5. Penninck E, Fumery M, Armengol-Debeir L, et al. Postoperative Complications in Pediatric Inflammatory Bowel Disease: A Population-based Study. *Inflamm Bowel Dis*. 2016;22(1):127-33.
6. Zuo L, Li Y, Wang H, et al. A Practical Predictive Index for Intra-abdominal Septic Complications After Primary Anastomosis for Crohn's Disease: Change in C-Reactive Protein Level Before Surgery. *Dis*

- Colon Rectum. 2015;58(8):775-81.
7. Mokart D, Merlin M, Sannini A, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. *Br J Anaesth*. 2005;94(6):767-73.
 8. Garcia-Granero A, Frasson M, Flor-Lorente B, et al. Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: a prospective observational study. *Dis Colon Rectum*. 2013;56(4):475-83.
 9. Carvello M, Di Candido F, Greco M, et al. The trend of C-Reactive protein allows a safe early discharge after surgery for Crohn's disease. *Updates Surg*. 2020.
 10. Stephensen BD, Reid F, Shaikh S, et al. C-reactive protein trajectory to predict colorectal anastomotic leak: PREDICT Study. *Br J Surg*. 2020.
 11. Smith SR, Pockney P, Holmes R, et al. Biomarkers and anastomotic leakage in colorectal surgery: C-reactive protein trajectory is the gold standard. *ANZ J Surg*. 2018;88(5):440-4.
 12. Gomollón F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis*. 2017;11(1):3-25.
 13. Nguyen GC, Loftus EV, Jr., Hirano I, et al. American Gastroenterological Association Institute Guideline on the Management of Crohn's Disease After Surgical Resection. *Gastroenterology*. 2017;152(1):271-5.
 14. Tang B, Eslick G, Craig J, et al. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *The Lancet Infectious diseases*. 2007;7(3):210-7.
 15. Rettig TC, Verwijmeren L, Dijkstra IM, et al. Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery. *Ann Surg*. 2016;263(6):1207-12.
 16. Xia T, Xu X, Zhao N, et al. Comparison of the diagnostic power of cytokine patterns and procalcitonin for predicting infection among paediatric haematology/oncology patients. *Clin Microbiol Infect*. 2016;22(12):996-1001.
 17. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*. 2007;448(7152):427-34.
 18. Viget N, Vernier-Massouille G, Salmon-Ceron D, et al. Opportunistic infections in patients with inflammatory bowel disease: prevention and diagnosis. *Gut*. 2008;57(4):549-58.
 19. Biancheri P, Brezski RJ, Di Sabatino A, et al. Proteolytic cleavage and loss of function of biologic agents that neutralize tumor necrosis factor in the mucosa of patients with inflammatory bowel disease. *Gastroenterology*. 2015;149(6):1564-74.e3.

Tables

Table 1 Baseline characteristics and clinical parameters among 202 hospitalized adults with CD

Characteristic	Non-IASC (n=178)	IASC (n=24)	P
Age, (years)	35.04±10.04	36.68±13.44	0.435
Sex, male, n (%)	85 (47.75)	13 (54.17)	0.555
Course of disease, (years)	5.86±4.06	4.34±5.16	0.359
Active smokers, n (%)	6 (3.37)	2 (8.33)	0.242
BMI, (kg/m ²)	18.48±1.63	17.34±1.76	0.174
Best CDAI	117.33±43.94	142.163±31.33	<0.001
Active/Remission	33/145	10/12	<0.001
Montreal classification, n (%)			
Age, (years)			
A2 (17–40)	120 (67.42)	15 (62.50)	0.631
A3 (>40)	58 (32.58)	9 (37.50)	0.631
Location			
L1 (ileal)	79 (44.38)	6 (25.00)	0.071
L2 (colonic)	11 (6.18)	3 (12.50)	0.222
L3 (ileocolic)	72 (40.44)	14 (58.33)	0.096
L4 (upper gastrointestinal)	5 (2.80)	1 (4.17)	0.537
Behavior			
B1 (failure of medical therapy)	11 (6.18)	3 (12.50)	0.222
B2 (stricturing)	64 (35.96)	5 (20.83)	0.143
B3 (penetrating)	100 (56.18)	19 (79.17)	0.032
Perianal disease (P)	57 (32.02)	6 (25.00)	0.486
Laparoscopy, n (%)	40 (22.47)	6 (25.00)	0.782
Anastomosis type			
Side-to-side anastomosis	152 (85.39)	21 (87.50)	0.782
End-to-end anastomosis	26 (14.61)	3 (12.50)	0.782
Operative time >180 min (%)	53 (29.78)	15 (62.50)	0.001
Blood loss, (ml)	115.57±65.73	146.45±95.64	0.271

Intraoperative blood transfusion, n (%)	13 (7.30)	4 (16.67)	0.121
NIC = no infectious complications; IC-NIASC = infectious complications with no IASCs; IASCs = intra-abdominal septic complications; BMI = body mass index; Best CDAI = Best Crohn's disease activity index			
All of the results are presented as number (%) or mean $\pm$ SD			

Table 2 Predictive performance of IL-6 and PCT for IASCs on isolated timepoints.

	AUC (95% CI)	Cutoff Value	SEN	SPE	PPV	NPV	P
CRP (cutoffs in mg/L)							
POD 1	0.59 (0.49 - 0.69)	63.80	0.84	0.48	0.53	0.81	0.295
POD 3	0.83 (0.78 - 0.89)	132.26	0.83	0.72	0.68	0.86	<0.001
POD 5	0.89 (0.76 - 0.93)	65.00	0.95	0.67	0.67	0.96	<0.001
IL-6 (cutoffs in pg/mL)							
POD 1	0.85 (0.77 - 0.92)	158.19	0.90	0.76	0.73	0.92	<0.001
POD 3	0.87 (0.80 - 0.94)	48.22	0.95	0.77	0.74	0.96	<0.001
POD 5	0.90 (0.84 - 0.95)	33.86	0.87	0.74	0.71	0.90	<0.001
PCT (cutoffs in ng/mL)							
POD 1	0.68 (0.59 - 0.79)	1.84	0.79	0.64	0.61	0.81	0.114
POD 3	0.81 (0.72 - 0.87)	0.61	0.79	0.59	0.58	0.80	<0.001
POD 5	0.84 (0.70 - 0.89)	0.34	0.83	0.75	0.70	0.86	<0.001
AUC = area under the curve; SEN = sensitivity; SPE = specificity; PPV = positive predictive value; NPV = negative predictive value; POD = postoperative day; IL-6 = interleukin-6; PCT = procalcitonin							

Table 3 Predictive performance inflammatory trajectory for IASCs.

	AUC (95% CI)	SEN	SPE	PPV	NPV	P value
CRP increase>50 mg/L						
Between any 3 days	0.72 (0.65-0.87)	0.71	0.75	0.14	0.91	0.013
From day 1 to day 3	0.63 (0.51-0.68)	0.62	0.78	0.26	0.88	0.371
From day 3 to day 5	0.80 (0.72-0.91)	0.58	0.99	0.17	0.95	<0.001
From day 1 to day 5	0.64 (0.56-0.81)	0.54	0.82	0.35	0.83	0.201
IL-6 increase>30 ng/L						
Between any 3 days	0.71 (0.62-0.81)	0.69	0.71	0.71	0.90	0.089
From day 1 to day 3	0.56 (0.49-0.66)	0.54	0.84	0.57	0.85	0.256
From day 3 to day 5	0.78 (0.67-0.88)	0.57	0.97	0.86	0.91	0.203
From day 1 to day 5	0.59 (0.51-0.82)	0.58	0.76	0.69	0.88	0.279
PCT increase>0.5 µg/L						
Between any 3 days	0.61 (0.50-0.71)	0.28	0.77	0.50	0.85	0.145
From day 1 to day 3	0.52 (0.45-0.59)	0.14	0.82	0.33	0.83	0.323
From day 3 to day 5	0.57 (0.48-0.66)	0.19	0.96	0.50	0.83	0.239
From day 1 to day 5	0.55 (0.47-0.63)	0.33	0.95	0.36	0.84	0.277
AUC = area under the curve; SEN = sensitivity; SPE = specificity; PPV = positive predictive value; NPV = negative predictive value; POD = postoperative day; IL-6 = interleukin-6; PCT = procalcitonin						

Figures

Figure 1

Observed values of C-reactive protein (A), interleukin-6 (B), procalcitonin (C) before surgery and on POD 1, 3 and 5 for Non-IASC and IASC patients (*p < 0.05, ** p < 0.01, *** p < 0.001). Data were presented with mean (box) ± SD (whiskers).

Figure 2

ROC curves of different inflammatory biomarkers to predict IASCs in isolated timepoints.

Figure 3

ROC curves of the average of different inflammatory biomarkers from POD 3-5 to predict IASCs.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [STROBEchecklistv4combined1.doc](#)