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Title: Serum Procalcitonin as a Valuable Diagnostic Tool in the Early Detection of Infectious Complications after Open Abdominal Aortic Repair

Authors:

Gianfranco Varetto[1], Claudio Castagno[1]§, Andrea Trucco[1], Edoardo Frola[1], Fabrizio Bert[2], Gitana Scozzari[2], Pietro Rispoli[1]

Affiliations:

[1] Division of Vascular Surgery, Department of Surgical Sciences, University of Turin, Turin, Italy

[2] Department of Public Health Sciences, University of Turin, Turin, Italy

Corresponding Author:

§ Claudio Castagno, MD

Division of Vascular Surgery, Department of Surgical Sciences

University of Turin, Turin, Italy

Abstract

Background

Aortic aneurysm repair is a resolutive and effective surgical operation, which can be associated with severe postoperative complications. Procalcitonin (PCT) in clinical practice could play a role in early diagnosis and monitoring of therapy for complications, especially infections, making for timely and more effective interventions. Our aim was to investigate whether PCT could be a predictive marker in early diagnosis of infectious complications after open abdominal aortic surgery.

Methods

Eighty-three consecutive patients who underwent elective open aortic repair at our institution were enrolled. Blood samples were taken before surgery, and each day over the 7-day postoperative period, and measurement of serum PCT, C-reactive protein (CRP), and leukocytes levels were carried out. Data regarding clinical progress, instrumental examinations, and blood chemistry were prospectively collected.

Results

Postoperative infectious complications occurred in 24 patients. Within 30 days, 1 death occurred. In the study sample, we found a significant difference in PCT curves of patients with and without infectious complications, especially on third postoperative day (POD; $P = 0.004$). On analysis of the area under the curve (AUC curve), PCT was shown to be a fair predictor in distinguishing cases with infectious complications (AUC, 0.765 on third POD; CI, 0.638–0.877). Conversely, other inflammatory markers commonly used (leucocytes and CRP) had similar trends in patients with and without postoperative infections.

Conclusions

On the basis of the results collected in this pilot study, despite some limitations, PCT could be considered a better marker of infectious complications after open abdominal aortic repair, when compared with other routinely used parameters.

Main text

Introduction

Open aortic repair (OAR) is a high-risk surgical operation, due to the type of patient (usually elderly and frequently with associated comorbidities) and the invasiveness of the technique.[1,2] Infections, especially pulmonary, are the most frequent type of complication, with important repercussions on patient morbidity, and mortality, prolonging hospitalization, and causing early readmission to hospital.[1,3] For this reason, clinical, instrumental, or laboratory markers which would allow for an early diagnosis of this complications are needed, to reduce postoperative morbidities and their impact on patients' status. Procalcitonin (PCT) is a promising infection marker, whose serum levels can increase rapidly even several thousand times during microbial infections; furthermore, its increase can be correlated to the severity of the septic state, disease progress, and prognosis.[4-7] Tissue trauma from a surgical operation and the resulting inflammatory response can, however, cause an increase in PCT. Moreover, those patients who develop postoperative complications have higher levels of PCT compared with those without complications. Postoperative induction of PCT largely depends on the type of surgery. During the first and second postoperative day (POD), PCT concentrations are more frequently elevated in patients after major surgery compared with patients undergoing minor operations.[8-22]

Previous studies assessed PCT and its relationship with adverse postoperative events, mainly with regard to cardiac surgery,[8.22] whereas very little evidence exists so far regarding infectious complications after aortic surgery.[23-26] One of the most relevant aspects of PCT is its good specificity (SP), which has been recently demonstrated in the detection of postimplantation syndrome after endovascular repair.[25] Our aim was to investigate the kinetics of PCT and determine its diagnostic and prognostic value after open abdominal aortic aneurysm (AAA) repair, comparing it with other indicators already used in clinical practice, that is C-reactive protein (CRP) and white blood cells (WBC).

Materials and Methods

Patients who underwent elective open aortic aneurysm repair at the Division of Vascular Surgery of the University of Turin during the period September 2012–December 2013 were consecutively enrolled. Inclusion criteria were: nonruptured AAAs larger than 5 cm or 4–5 cm rapidly enlarging and according to European Society for Vascular Surgery guidelines.[27] Exclusion criteria were: aortic rupture, symptomatic AAAs, thoracoabdominal aneurysms, the need for suprarenal clamping, and endovascular repair.

Each patient's medical history was recorded. In the preoperative phase, routine blood tests, electrocardiogram, chest X-ray, thoracic and abdominal computed tomography angiography, and cardiac evaluation were carried out in all patients. All patients signed the informed consent form for the surgical operation, anesthesia, data processing, and participation in the observational study. The protocol has been approved by the local ethical committee. A transperitoneal approach is our preferred access to the abdominal aorta (93% of patients), whereas a minority underwent a retroperitoneal approach. Antibiotic prophylaxis is usually stopped 24 hr after surgery; the Foley catheter is removed on third POD. Respiratory physiotherapy has been performed in selective patients (obese, patients with chronic obstructive pulmonary disease), usually starting on first POD.

Blood samples were taken on the day before the operation and daily for 7 days after it (or until discharge if sooner) to measure the PCT, CRP, and WBC levels. PCT values after the first week were not taken into account. Plasma PCT was measured with an Elecsys automatic analyser (Hoffmann-La Roche Ltd., Basel, Switzerland) using an electrochemiluminescence immunoassay test.

We considered infectious complications: pulmonary consolidation at X-ray with positive bronchoaspirate; positive uroculture (>100,000 colony forming units/mL) with urinary signs, or symptoms (dysuria, pollakiuria, cloudy and/or bloody urines); diarrhea with a positive coproculture; surgical wound signs of infections (purulent exudate). All infectious complications required prolonged antibiotic therapy. Renal function was monitored by measuring the serum creatinine values. A greater than 1.5-fold increase of creatinine level was considered significant for acute kidney injury.[28] We considered all those infectious complications occurring within the 30th POD. All postoperative data were included in an Excel database.

Statistical Analysis

Continuous variables are reported as mean and standard deviation for normally distributed variables and as median and interquartile range for non-normal distributions, whereas categorical variables are reported as number of patients and percentages. Normality distribution has been tested with the Shapiro–Wilk normality test. Univariate analysis of the difference between groups (patients with versus without infectious complications) was performed with the Student's *t*-test or, when appropriate, by the nonparametric Mann–Whitney *U* test. Categorical data were compared with the chi-squared test. Statistical significance level was set at $P \leq 0.05$. The receiving operating characteristic (ROC) curve and the value of the area under the curve (AUC) were calculated for the daily value of the different blood markers and used to analyze their accuracy as predictors of infectious complications. AUC values higher than 0.70 were considered as strong predictive ability. For the ROC curves with AUC higher than 0.70, sensitivity (SE), SP, positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were calculated for different cutoff points. The results were analyzed using the StataMP11 statistical software (Stata Corp., College Station, TX, 2011).

Results

Eighty-three (80 men) patients were included in the study (Table I). Forty-five patients had no complications (54%). Within 30 days, 1 death occurred on 23rd POD due to septic shock after severe pneumonia. Complications were recorded in 38 patients (46%), 24 (29%) of whom were due to infections, whereas 17 patients (20%) had a deterioration of renal function, without need for dialysis. Infectious complications are presented in Table II. Noninfectious complications ($n = 14$) included: 8 acute intraoperative limb ischemia, 5 patients with temporary atrial fibrillation, and 1 myocardial infarction. There was a significant difference in the occurrence of postoperative acute kidney injury between patients with and without infectious complications (13.6 vs. 37.5%, $P = 0.014$). The main postoperative characteristics and procedures are presented in Table III.

Pulmonary infections occurred in 16 patients: in 13 patients were clinically evident (coughing with purulent expectorate) associated with radiological signs of pneumonia, whereas in 3 patients positive bronchoaspirates without radiological signs were identified. In 3 patients, there was a urinary tract infection from bladder catheter, identified with a positive uroculture. There were 4 cases of infections of the intestinal tract with diarrhea, diagnosed with positive coproculture, which resolved with antibiotic therapy. In 2 cases, we observed an infection of the surgical wound with purulent secretions, but no microbiological examination was carried out. Overall, there have been

25 infectious complications, occurred in 24 patients because 1 patient developed both pulmonary and intestinal tract infection. Inflammatory markers increased as result of surgery in all patients. PCT showed an increase in POD 1 in all patients, with a subsequent decrease in patients without infectious complications, while patients with infections had a further increase in the following days, with a significant differences in POD 2 (P = 0.022), in POD 3 (P = 0.004), in POD 4 (P = 0.019), and in POD 5 (P = 0.011), whereas thereafter no significant differences were found between the groups. CRP showed a marked increase after surgery, with a peak in POD 3 and a subsequent decrease in both groups of patients, with no significant differences between patients with and without infections. Also WBC levels, although higher in patients with infections, showed a similar behavior between patients with and without infectious complications, except for a significant higher WBC level in patients with infections in POD 1 compared with those without infections (P = 0.025). Blood markers levels trends in the first postoperative week are summarized in Table A.I and Figure 1.

Thereafter, a ROC analysis of blood markers levels was performed. Based on the markers' behavior (Fig. 1), the analysis was performed on POD 1-to-5 levels. PCT showed AUC higher than 0.7 thus proving to significantly differentiate patients with infections on POD 3 (cutoff 0.34 ng/mL, AUC = 0.765, SE = 85.7%, SP = 59%), on POD 4 (cutoff 0.46 ng/mL, AUC = 0.713, SE = 78.6%, SP = 68.4%), and on POD 5 (cutoff 0.29 ng/mL, AUC = 0.757, SE = 71.4%, SP = 80.9%). The AUC of CRP and WBC was lower than 0.70 on all POD (Table IV and Fig. 2). Thus, PCT proved to be the most accurate blood markers to early detect patients with ongoing or subsequent infectious complications, compared with CRP and WBC. However, the exact time of occurrence of an infectious complication is frequently hard to be identified, as it may take some time before clinical or laboratoristic signs become evident. Therefore, it is seldom possible to calculate the real time frame between PCT raise and the diagnosis of an infectious complication. PCT levels in day 3, that is the earlier time point with a significant AUC, were then evaluated for SE, SP at different cutoff point (Table V).

Discussion

Previous studies have investigated PCT levels after different types of surgery showing that peak level of PCT concentration, even in patients without signs of infections, depends on the type of operation—concentrations are more frequently elevated after major surgery—most of all cardiac procedures.[8,10] This means that it is important to establish different cutoff values of PCT for each type of surgery. For e.g., Molter[10] assessed that PCT concentrations higher than 0.2 ng/mL after minor aseptic surgery, 0.8 ng/mL after major abdominal surgery, 0.9 ng/mL after hepatic surgery, or 0.45 ng/mL after thoracic surgery may be predictive of infectious complications. OAR is a major abdominal operation, but unlike general surgery, it represents a "clean" intervention, as respiratory, alimentary, and genitourinary tracts are not involved, thus infections are expected to be lower in this field. According to most of the aforementioned studies,[10, 11, 15, 19-21] we focused our attention on the evaluation of only infectious complications. In our series, 29% of patients developed infectious complications. This is quite higher when compared with the data of Vogel (11%).[1] However, these authors collected data from nationwide data sets, which are based on International Classification of Diseases-9 codes, thus they do not report which parameters were considered from any single center to identify an infectious complication. Nevertheless, in agreement with these authors, in the present study patients who experienced postoperative infectious events showed PCT curves with significantly higher peak values more often beginning on the third POD. Our ROC curve analysis of

postoperative PCT values identified an AUC > 0.7 on third, fourth, and fifth POD, while other markers (CRP and WBC) did not reach significant AUC values. Thus, to identify a cutoff value, which could be a reliable alert of development of infection, we chose the third POD, which represents the earlier day of onset of a hypothetical infectious complication with a statistical significance (Table IV). According to our analysis (Table V), the best cutoff value of PCT on the third POD is 0.56 ng/mL, with a good (although not optimal) sensibility (71%), and SP (74%). This value is similar to thoracic surgery, as reported by Molter.[10] Recommendations in complex vascular procedures, that is abdominal vessels reconstructions, suggest to stop antimicrobical prophylaxis 24 hr after surgery.[29] Our findings, whether confirmed by larger studies, could have a clinical impact on routine practice. In fact, according to our results, if an increasing trend of PCT values was detected on third POD, an infectious complication should be highly suspected and further examinations required to early start the proper antibiotic therapy. However, according to other authors,[23,24] acute postoperative renal insufficiency could be a confounding factor in the evaluation of PCT for the diagnosis of infections. In fact, postoperative renal failure occurred almost 3 times more frequently in patients with infectious complications than those without infectious complications (37 vs. 13%). This may explain the correlation between postoperative renal and infectious adverse events. On the other hand, however, it is reasonable to suspect that patients with infectious complications, especially when these lead to septic shock, may also have a renal function worsening, as part of a general multiorgan failure The CRP can undergo nonspecific modifications mainly because of the mere tissue trauma of the surgical intervention itself. Values obtained from patients with or without infectious complications were similar and did not show significant differences in the statistical analysis. For this reason, CRP does not seem to have a predicting value for the early diagnosis of postoperative infectious complications. WBC count has a good capacity to distinguish patients with complications, but differently from PCT, the large variability in the kinetics of this parameter does not allow us to make a judgment on the progress of the pathologic condition. We only identify a statistical significant difference between the 2 groups on first POD, but later both groups had similar values. Our study has some limitations. The small sample size did not allow to reach a statistical significance at the multivariate analysis, as it did at the univariate analysis. Second, a comparison of PCT curves of patients with infectious complications and patients with other postoperative adverse events could have showed whether PCT levels would be higher in all postoperative complications, regardless of their etiology. Third, renal failure is an important confounding factor that may limit the predictive role of PCT in the early diagnosis of postoperative infections, also considering the fact that postoperative renal function deterioration is quite frequent after abdominal aortic surgery.[30] Finally, physicians were not blinded to PCT values; therefore, they might have ordered more radiological and microbiological examinations, if PCT was seen to be high. New topics for future researches could be the interpretation of PCT values in relation to the deterioration of renal function, the comparison of PCT curves in patients with different types of postoperative complications (not only infections), and the role of PCT in guiding therapy to prevent postoperative complications in association with other markers.

Conclusions

On the basis of the results collected in this study, PCT could be considered as a valuable marker of infectious complications in the postoperative phase after open abdominal aortic repair. Despite its limitations, at the current time, PCT is maybe the best among the available markers of postoperative infectious complications. Therefore, the routine use of PCT could help physicians in identifying earlier those patients who have a greater risk of developing these potentially lethal complications to start specific preventive treatments.

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Table I. Overall baseline characteristics of the 2 groups of comparison

Variable categories	**Patients without infectious complications, *n* = 59 (71%)**	**Patients with infectious complications, *n* = 24 (29%)**	***P* value**
Male sex, *n* (%)	57 (97)	23 (96)	0.86
Continuous variables			
Age, mean ± standard deviation	70.03 ± 7.22	71.96 ± 7.09	0.27
PCT before surgery, median (IQR)	0.04 (0.03; 0.06) ng/mL	0.05 (0.04; 0.06) ng/mL	0.27
CRP before surgery, median (IQR)	1.75 (0.70; 6.5) mg/L	2.80 (1.40; 8.5) mg/L	0.25
WBC before surgery, median (IQR)	7.35 (6.38; 9.45) 10^9/L	7.62 (6.81; 9.12) 10^9/L	0.79

IQR, interquartile range.

Table II. Postoperative infectious complications

Type of infectious complications	Number of cases (total = 25)
Pulmonary	16
Urinary	3
Gastrointestinal	4
Surgical wound	2

Table III. Postoperative details

	Patients without infectious complications, *n* = 59 (71%)	**Patients with infectious complications, *n* = 24 (29%)**	***P* value**
Variable categories			
Deterioration of renal function, *n* (%)	8 (14)	9 (37)	0.01
Postoperative period (<24 h), *n* (%)			0.15
Ward	14 (24)	5 (21)	
PACU	21 (36)	4 (17)	
ICU	24 (41)	15 (62)	
Continuous variables			
Creatinine peak/base ratio, median (IQR)	1.15 (1.02; 1.43)	1.14 (1.02; 1.4)	0.12
Day of discharge, median (IQR), days	6 (6; 7.75)	10 (7; 17.75)	<0.001
Time in OT, median (IQR), hr	6.00 (5.15; 6.5)	6.00 (6; 7)	0.13
Duration of operation, median (IQR), hr	4.00 (3.25; 5)	4.50 (3.69; 5.63)	0.12
Duration of clamping, median (IQR), hr	1.50 (1; 2)	1.58 (1.19; 2)	0.53
Hours of intubation, median (IQR), hr	5.00 (4; 6.5)	5.50 (4.38; 12.5)	0.23

PACU, postanesthesia care unit; ICU, intensive care unit; OT, operating theater; IQR, interquartile range.

Fig. 1. Daily median levels of PCT (A)**, CRP** (B)**, and WBC** (C) **in patients with and without infectious complications. *Indicates statistically significant differences. IQR, interquartile ranges. Blue lines, patients without infectious complications (IC); red lines, patients with IC.**

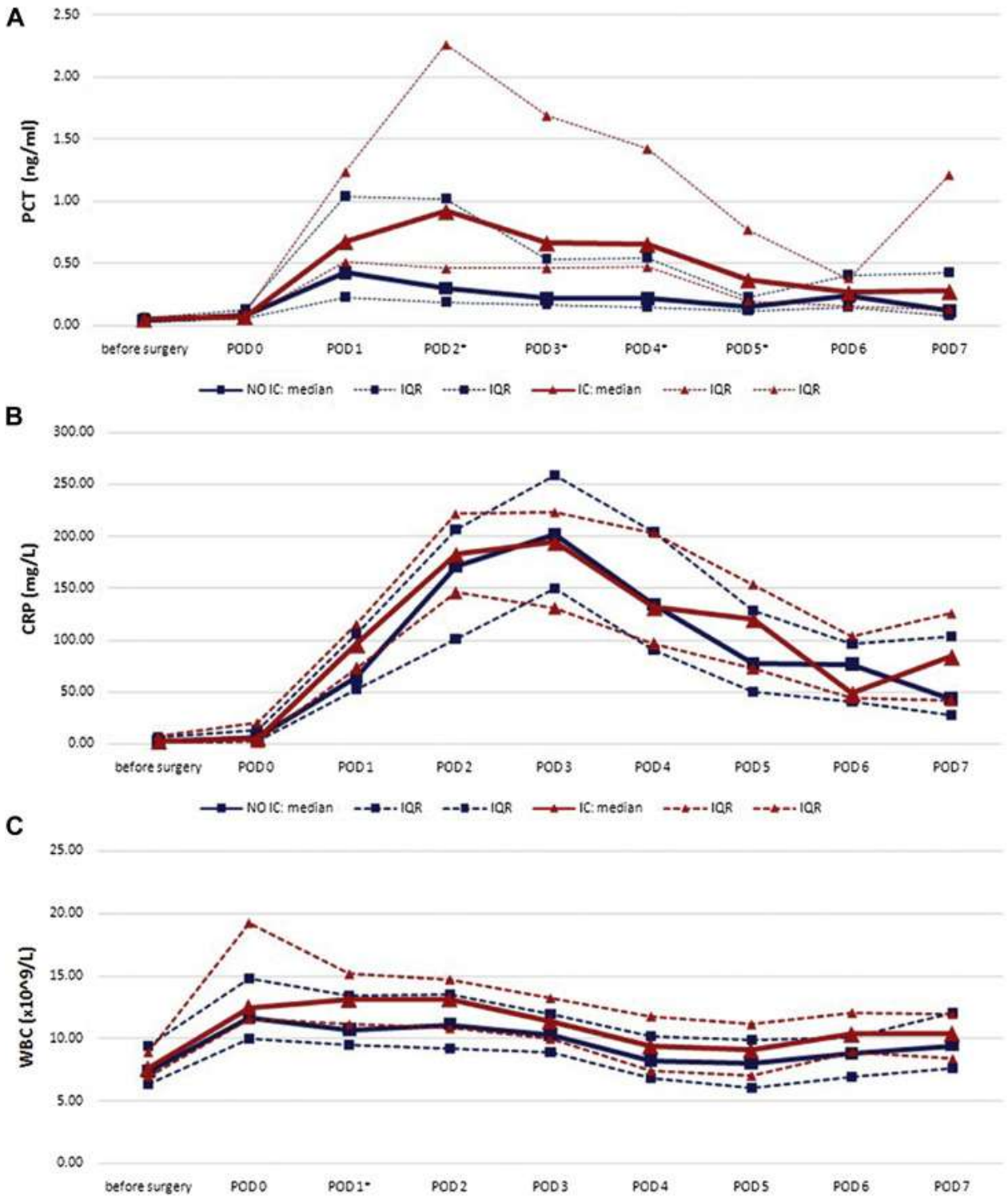

Table IV. Comparison of the accuracy of blood markers to detect infectious complications on POD 1-to-5

	AUC (95% CI)
PCT POD1	0.617 (0.436–0.798)
PCT POD2	0.690 (0.544–0.836)
PCT POD3	**0.765 (0.622–0.907)**
PCT POD4	**0.713 (0.544–0.883)**
PCT POD5	**0.757 (0.571–0.943)**
CRP POD1	0.607 (0.443–0.771)
CRP POD2	0.615 (0.460–0.770)
CRP POD3	0.474 (0.287–0.660)
CRP POD4	0.527 (0.340–0.714)
CRP POD5	0.641 (0.448–0.833)
WBC POD1	0.659 (0.526–0.791)
WBC POD2	0.617 (0.470–0.764)
WBC POD3	0.602 (0.453–0.752)
WBC POD4	0.599 (0.441–0.757)
WBC POD5	0.622 (0.471–0.773)

Bold indicates strong predictive values of PCT.

Fig. 2. ROC curves comparison among PCT, CRP, and WBC levels on POD 3 (A)**, 4** (B)**, and 5** (C)**.**

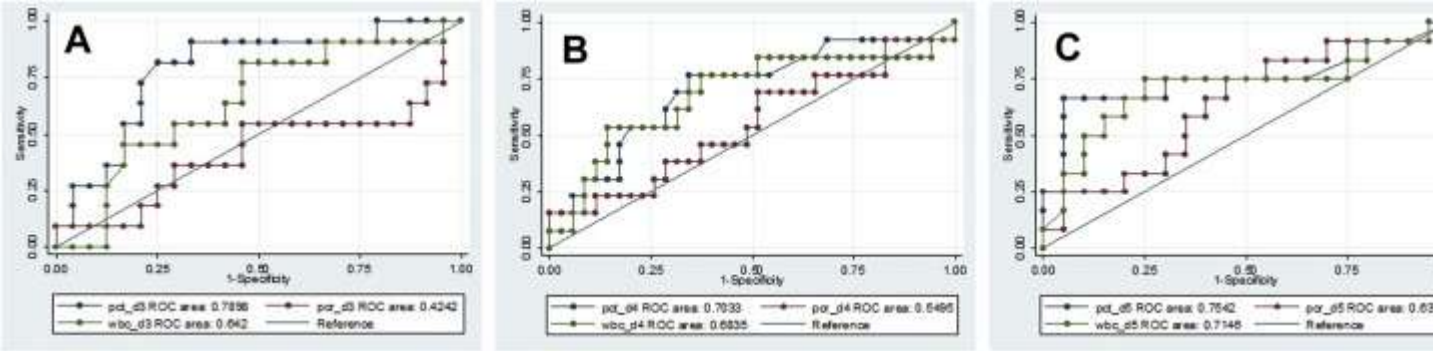

Table V. Comparison of the accuracy of different PCT cutoff points on POD 3

Cutoff, ng/mL	SE (%)	SP (%)	LR+	LR−
0.20	93	46	1.72	0.15
0.29	86	54	1.86	0.27
0.34	86	59	2.09	0.24
0.41	79	62	2.04	0.35
0.48	71	72	2.53	0.40
0.56	71	74	2.79	0.38
0.60	57	77	2.48	0.56
0.70	50	82	2.79	0.61
0.98	43	85	2.79	0.68

LR+, positive likelihood ratio; LR−, negative likelihood ratio.

Appendix.

Table A.I. Daily median levels of inflammatory markers

	All patients, *n* = 83	**Patients without infectious complications, *n* = 59**	**Patients with infectious complications, *n* = 24**	***P* value[a]**
PCT, median (IQR)				
Before surgery	0.05 (0.04–0.06)	0.04 (0.03–0.06)	0.05 (0.04–0.06)	0.27
POD 0	0.07 (0.06–0.11)	0.08 (0.06–0.13)	0.07 (0.06–0.10)	0.60
POD 1	0.52 (0.23–1.16)	0.43 (0.23–1.04)	0.68 (0.51–1.24)	0.23
POD 2	0.42 (0.22–1.08)	0.30 (0.19–1.02)	0.92 (0.46–2.26)	**0.02**
POD 3	0.35 (0.18–0.70)	0.22 (0.17–0.54)	0.67 (0.46–1.69)	**0.004**
POD 4	0.24 (0.16–0.78)	0.22 (0.15–0.54)	0.66 (0.47–1.42)	**0.02**
POD 5	0.17 (0.12–0.37)	0.15 (0.12–0.23)	0.37 (0.20–0.77)	**0.01**
POD 6	0.25 (0.14–0.40)	0.24 (0.15–0.41)	0.27 (0.16–0.38)	0.95
POD 7	0.23 (0.11–0.73)	0.12 (0.08–0.43)	0.28 (0.13–1.21)	0.35
CRP, median (IQR)				
Before surgery	1.80 (1.10–6.60)	1.75 (0.80–6.03)	2.80 (1.45–8.05)	0.25
POD 0	6.15 (2.83–15.13)	6.55 (2.88–13.38)	5.50 (2.28–20.70)	0.83
POD 1	78.90 (53.30–112.10)	64.00 (52.50–105.50)	95.65 (72.88–115.68)	0.22

	All patients, *n* = 83	**Patients without infectious complications, *n* = 59**	**Patients with infectious complications, *n* = 24**	***P* value[a]**
POD 2	174.75 (107.40–218.08)	171.20 (101.70–206.20)	182.30 (145.60–221.70)	0.18
POD 3	205.3 (149.6–259.8)	200.4 (150.3–259.8)	208.6 (128.2–261.2)	0.76
POD 4	132.50 (90.35–206.83)	134.10 (91.05–204.48)	131.40 (96.33–203.90)	0.77
POD 5	83.40 (59.13–138.68)	77.30 (50.15–127.75)	119.80 (72.90–154.00)	0.15
POD 6	57.85 (41.38–100.25)	76.35 (41.33–96.65)	48.70 (44.45–104.48)	1
POD 7	80.45 (41.35–135.20)	43.10 (28.50–102.80)	83.90 (42.20–126.10)	0.52
WBC, median (IQR)				
Before surgery	7.36 (6.44–9.31)	7.35 (6.38–9.42)	7.62 (6.89–8.84)	0.79
POD 0	12.02 (10.41–15.34)	11.69 (10.00–14.77)	12.47 (11.50–19.23)	0.15
POD 1	11.29 (9.57–13.76)	10.67 (9.51–13.40)	13.08 (11.07–15.13)	**0.02**
POD 2	11.35 (9.34–14.38)	11.14 (9.23–13.54)	13.12 (10.77–14.68)	0.10
POD 3	10.70 (9.03–12.16)	10.34 (8.91–11.93)	11.34 (9.91–13.19)	0.16
POD 4	8.60 (6.92–10.90)	8.27 (6.89–10.18)	9.39 (7.34–11.73)	0.18
POD 5	8.22 (6.23–10.28)	8.08 (6.08–9.92)	9.05 (6.98–11.08)	0.11

	All patients, *n* = 83	**Patients without infectious complications, *n* = 59**	**Patients with infectious complications, *n* = 24**	***P* value[a]**
POD 6	9.55 (7.31–10.80)	8.78 (6.94–10.09)	10.34 (8.88–12.03)	0.07
POD 7	9.75 (8.10–12.18)	9.47 (7.61–12.02)	10.38 (8.33–11.91)	0.50

Bold indicates strong predictive values of PCT.

a Mann–Whitney test.