Postoperative Interleukin-6 Level and Early Detection of Complications After Elective Major Abdominal Surgery

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Objective: To assess the association of systemic inflammation and outcome after major abdominal surgery.

Background: Major abdominal surgery carries a high postoperative morbidity and mortality rate. Studies suggest that inflammation is associated with unfavorable outcome.

Methods: Levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α and the systemic inflammatory response syndrome (SIRS) were assessed in 137 patients undergoing major abdominal surgery. Blood samples were drawn on days 0, 1, 3, and 7, and SIRS was scored during 48 hours after surgery. Primary outcome was a composite of mortality, pneumonia, sepsis, anastomotic dehiscence, wound infection, noncardiac respiratory failure, atrial fibrillation, congestive heart failure, myocardial infarction, and reoperation within 30 days of surgery.

Results: An IL-6 level more than 432 pg/mL on day 1 was associated with an increased risk of complications (adjusted odds ratio: 3.3; 95% confidence interval [CI]: 1.3–8.5) and a longer median length of hospital stay (7 vs 12 days, $P < 0.001$). As a single test, an IL-6 cut-off level of 432 pg/mL on day 1 yielded a specificity of 70% and a sensitivity of 64% for the prediction of complications (area under the curve: 0.67; 95% CI: 0.56–0.77). Levels of CRP started to discriminate from day 3 onward with a specificity of 87% and a sensitivity of 58% for a cut-off level of 203 mg/L (AUC: 0.73; 95% CI: 0.63–0.83).

Conclusions: A high IL-6 level on day 1 is associated with postoperative complications. Levels of IL-6 help distinguish between patients at low and high risk for complications before changes in levels of CRP.

Keywords: C-reactive protein, interleukin-6, major abdominal surgery, mortality, postoperative complications, systemic inflammatory response syndrome

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Abdominal surgery is one of the most commonly conducted nonday-case procedures.[1] Up to 28% of patients undergoing major abdominal surgery suffer from postoperative complications, including wound infection, sepsis, anastomotic dehiscence, pneumonia, cardiovascular or respiratory events, and mortality.[2–4] Early identification of patients at high risk for developing such complications may aid clinical decision-making and possibly improve outcome.

Several studies suggest that systemic inflammation after surgery has a negative impact on outcome.[5–7] The magnitude of this inflammatory response varies widely between individuals and depends on, for example, the type, duration, and extent of surgery, type of anesthesia, and perioperative blood transfusion.[8–11] Interestingly, polymorphisms in genes encoding for interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are associated with the development of postoperative complications after lung resection.[12,13] Moreover, perioperative use of dexamethasone is associated with improved outcome in patients undergoing cancer resection, suggesting that systemic inflammation is related to adverse outcome.[14] However, most of these studies were conducted in patients undergoing cardiothoracic surgery, included few patients, defined outcome parameters vaguely, or had data collected retrospectively which may have influenced data quality. Whether systemic inflammation after major abdominal surgery is associated with unfavorable outcome still remains to be elucidated.[15–17]

The aim of this study was to investigate the inflammatory response after major abdominal surgery and its association with outcome.

METHODS

Study Population and Design

This prospective single-center cohort study is a substudy of the Myocardial Injury and Complications after major abdominal surgery (MICOLON) study (ClinicalTrials.gov Idenitifier NCT02150486). In short, the MICOLON study investigated the association between highly sensitive cardiac troponin T levels and noncardiac complications after major abdominal surgery in patients at risk for coronary artery disease. Inclusion criteria were elective major (defined as an expected 30-day mortality rate >3%[1]) abdominal surgery, age older than 45, and presence of 1 or more major cardiovascular (CV) risk factors (congestive heart failure, peripheral artery disease including (intermittent claudication or history of vascular surgery), diabetes mellitus, coronary artery disease (history of myocardial infarction, angina pectoris, history of ischemia, or coronary artery disease on cardiac tests), cerebrovascular accident, renal insufficiency (serum creatinine >150 μmol/L), aortic valve stenosis (valve area <1 cm^2), atrial fibrillation, decreased left ventricular function (<55%), or 2 or more minor CV risk factors: age older than 70, hypertension, hypercholesterolemia, low functional capacity (≤4 metabolic equivalents), transient ischemic attack, and chronic obstructive pulmonary disease. A more elaborate description of study methodology has been previously described.[18] The study was approved by the local Medical Ethics Committee (Research and Development Department, St. Antonius Hospital) and informed consent was obtained from all patients. In this substudy, we investigated the systemic inflammatory response and its association with outcome in the first 137 patients included in the MICOLON study. To do so, we determined the occurrence of the systemic inflammatory response syndrome (SIRS) within 48 hours of surgery and evaluated the perioperative leukocyte count and levels of IL-6, TNFα, and C-reactive protein (CRP). Blood samples were collected on the day of surgery after induction of general anesthesia (baseline) and on the first, third, and seventh postoperative day during the routine blood sampling round in the morning. SIRS was considered to be present if at least 2 of the following clinical findings were present:

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temperature less than 36.0°C or greater than 38.0°C, heart rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute or $PaCO_2$ less than 32 mm Hg, leukocyte count less than 4 or greater than 12 (10^9/L).[19] Patients on antibiotic therapy before surgery were excluded. Perioperative antimicrobial prophylaxis was routinely administered in all patients. Patients were operated under general anesthesia or general anesthesia combined with epidural anesthesia. Perioperative anesthetic management was at the discretion of the attending anesthesiologist.

The primary study parameter was a composite of 30-day mortality (death of any cause), pneumonia (purulent sputum, positive sputum or blood culture, and clinical symptoms, eg, cough, fever, or consolidation on chest radiograph), sepsis (SIRS with suspected or proven infection), anastomotic dehiscence (luminal contents through drain or wound site or leak detected on imaging studies), wound infection (purulent drainage from superficial incision or deliberate opening of superficial incision by surgeon and pain, tenderness, swelling, or redness), reoperation, respiratory insufficiency (hypoxia or hypercapnia leading to ICU (re)admission), atrial fibrillation (new-onset atrial fibrillation), congestive heart failure (pleural effusion or pulmonary edema requiring diuretic therapy), and myocardial infarction (elevated cardiac biomarkers in combination with clinical symptoms or electrocardiography changes). The length of hospital stay was recorded. Each individual study parameter was assessed after careful review of medical charts and during patient visits conducted by research personnel blinded to laboratory results. At 30 days after surgery, a follow-up telephonic interview was carried out if patients were discharged from the hospital at that time. Patients were asked whether a medical complication had occurred since their discharge from the hospital. If so, medical details were retrieved from their treating physicians. Information from routine postoperative clinic visits was used if patients could not be reached by telephone. An event committee consisting of 2 independent medical doctors judged every individual study parameter and, if no consensus was reached, a third specialist was consulted.

Biochemical Analyses

After blood samples were drawn and centrifuged, samples were stored in frozen aliquots at –80°C. After inclusion of all patients, samples were shipped to laboratory HaemoScan (Groningen, The Netherlands) for batch analyses. Tumor necrosis factor-α and IL-6 were determined by a solid-phase ELISA, with capture and peroxidase-labeled tracer antibody (Biolegend, San Diego, CA, USA). The oxidase converts phenyldiamine-dihydrochloride to a yellow color, which is proportional to the concentration of TNF-α or IL-6. A microtiter plate reader measured the color at 490 nm. Leukocyte count and levels of CRP were part of routine perioperative laboratory tests and were retrieved from computerized medical charts.

Clinical Characteristics

Each patient visited the outpatient preoperative anesthesia clinic. During this visit, medical history and preoperative medicine use (e.g., steroids, statins, aspirin) were recorded. Information regarding duration of surgery, operative blood loss, packed red blood cell transfusion (during the first 48 hours after surgery), type of anesthesia, and postoperative temperature, heart rate, and respiratory rate were collected from computerized medical records.

Statistical Analysis

For statistical analysis, the IBM SPSS version 22 was used. A 2-tailed $P < 0.05$ was considered statistically significant in all tests. Continuous data are presented as mean and standard deviation (SD) if normally distributed and as median and interquartile range (IQR) if not normally distributed. The Kolmogorov–Smirnov test was used to test for normality. To compare independent continuous variables between groups, a Student t test or Mann-Whitney U test was conducted where appropriate. Categorical variables are given as frequencies and percentages. To compare dichotomous variables between groups, a χ^2-test or Fisher's exact test was used. A receiver operator characteristics (ROC) curve was created to determine the optimal cut-off point for continuous variables. The goodness of fit for the multivariable predictive model was quantified by the c-statistic. The length of hospital stay in patients with and without postoperative complications was presented using a Kaplan-Meier curve together with the log rank test. For multivariate analysis, we used binary logistic regression. All variables that were imbalanced between the 2 groups ($P \leq 0.10$), as depicted in Table 1, were considered potential confounders of the association between inflammatory state and the

TABLE 1. Baseline Characteristics According to the Occurrence of a Postoperative Complication

Variable	Complication (n = 39)	No Complication (n = 96)	P
Male, n (%)	27 (69.2)	53 (55.2)	0.133
Age, yr	69 ± 10	67 ± 11	0.425
BMI, kg/m^2	27.1 ± 5.2	28.9 ± 8.3	0.218
Comorbidity			
Diabetes, n (%)	13 (33.3)	31 (32.3)	0.907
Current smoking, n (%)	4 (10.3)	19 (19.8)	0.182
COPD, n (%)	8 (20.5)	29 (30.2)	0.252
Hypertension, n (%)	32 (82.1)	74 (77.1)	0.524
Coronary artery disease, n (%)	9 (23.1)	20 (20.8)	0.774
Atrial fibrillation, n (%)	10 (25.6)	5 (5.2)	0.001
Previous stroke, n (%)	12 (30.8)	13 (13.5)	0.020
Surgery for malignancy, n (%)	28 (71.8)	62 (64.6)	0.420
ASA physical status ≥III, n (%)	12 (30.8)	28 (29.2)	0.853
POSSUM	6.0 (1.9–13.0)	4.5 (1.9–10.6)	0.189
Medication use			
Aspirin, n (%)	11 (28.2)	33 (34.4)	0.488
Statin, n (%)	20 (51.3)	46 (47.9)	0.723
RAAS inhibitors, n (%)	24 (61.5)	31 (32.3)	0.002
Other antihypertensive drugs, n (%)	30 (76.9)	69 (61.5)	0.086
Steroids, n (%)	2 (5.1)	5 (5.2)	1.000
Type of surgery			
Colorectal, n (%)	19 (48.7)	48 (50.0)	0.893
Gastroesophageal, n (%)	14 (35.9)	15 (15.6)	0.009
Pancreatic, n (%)	5 (12.8)	9 (9.4)	0.545
Gastric bypass, n (%)	1 (2.6)	13 (13.5)	0.067
Hepatic, n (%)	1 (2.6)	8 (8.3)	0.446
Other, n (%)	2 (5.1)	4 (4.2)	1.000
Type of anesthesia			
TIVA, n (%)	29 (74.4)	53 (55.2)	0.039
Epidural anesthesia, n (%)	30 (76.9)	58 (60.4)	0.068
Duration of surgery (min)	154 (120–240)	120 (75–180)	0.028
Blood loss (mL)	200 (58–400)	100 (20–300)	0.037
RBC transfusion, n (%)	12 (30.8)	11 (11.5)	0.007

Data are presented as mean (SD), median with interquartile range, or absolute numbers. Stroke is the composite of patients with a history of transient ischemic attack or cerebrovascular accident.

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Association of Anesthesiologists physical status classification system; POSSUM, Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; RAAS, renin-angiotensin-aldosterone system inhibitors; TIVA, total intravenous anesthesia; RBC, red blood cell transfusion.

TABLE 2. Clinical Outcomes According to IL-6 Levels on day 1

	High* IL-6 (n = 52)	Low† IL-6 (n = 80)	P
Sepsis, n (%)	11 (21.2)	4 (5.0)	0.004
Reoperation, n (%)	9 (17.3)	4 (5.0)	0.020
Anastomotic dehiscence, n (%)	9 (17.3)	2 (2.5)	0.007
Atrial fibrillation, n (%)	7 (13.5)	5 (6.3)	0.216
Respiratory insufficiency, n (%)	7 (13.5)	1 (1.3)	0.006
Pneumonia, n (%)	5 (9.6)	3 (3.8)	0.263
Wound infection, n (%)	6 (11.5)	3 (3.8)	0.154
Congestive heart failure, n (%)	4 (7.7)	3 (3.8)	0.433
Myocardial infarction, n (%)	0	0	
Mortality, n (%)	3 (5.8)	0 (0.0)	0.059
Any event, n (%)	23 (44.2)	13 (16.3)	<0.001

In 3 patients, levels of IL-6 on day 1 were not available. Patients could suffer from more than 1 complication.
*High IL-6 > 432 pg/mL.
†Low IL-6: ≤ 432 pg/mL.

occurrence of postoperative complications. In addition, variables known for their immunomodulatory effects, such as anti-inflammatory drug use, packed red blood cell transfusion, malignancy, and diabetes mellitus were also considered. A variable was retained in the final model as a confounder if it changed the odds ratio (OR) of the inflammatory marker of interest and the outcome by more than 10%.

RESULTS

Patient Characteristics and Outcome

One hundred thirty-seven patients were included. Two patients had a more than 4000-fold increased baseline IL-6 level compared to the average baseline IL-6 level and were excluded from analysis. The final study population consisted of 135 patients. Mean age was 68 years and 59% of all patients were male. Forty patients (30%) had an ASA physical status of 3 or more. The most commonly conducted abdominal procedures were colorectal surgery, gastroesophageal surgery, and pancreatic surgery in 50%, 22%, and 10% of patients respectively. Two-thirds of the procedures (67%) were undertaken to treat malignant tumors. Medications that suppress inflammation, such as statins, aspirin, and steroids, were used by 49%, 34%, and 5% of all patients, respectively. Other baseline characteristics are shown in Table 1.

Thirty-nine patients (29%) suffered from at least 1 postoperative complication (Table 2). The median time between surgery and a complication was 5 days (IQR 3–8). Intraoperative characteristics such as an increased duration of surgery and blood loss were associated with adverse outcome. Preoperative statin ($P = 0.723$), aspirin ($P = 0.488$), or steroid use ($P = 1.000$) was not related to the occurrence of a complication.

Inflammatory Markers in Patients With and Without Complications

Preoperative levels of IL-6, TNFα, CRP, and leukocyte count were similar in patients with and without a postoperative complication (Fig. 1). Postoperatively, the inflammatory marker levels between patients with and without complications were most pronounced for IL-6: 596 (219–989) pg/mL versus 303 (127–501) pg/mL ($P < 0.01$) on day 1; 128 (61–342) pg/mL versus 69 (30–115) pg/mL, ($P < 0.01$) on day 3; and 76 (20–175) pg/mL versus 27 (11–48) pg/mL ($P = 0.02$) on day 7 (Fig. 1a). C-reactive protein level was similar in both groups on day 1 (90 [62–119] mg/L versus 78 [53–109] mg/L, $P = 0.131$), but differed on day 3 (223 [145–316] mg/L versus 131 [87–189] mg/L, $P < 0.001$) to day 7 (131 [65–178] mg/L versus. 63 [33–84] mg/L, $P < 0.001$) (Fig. 1b). Tumor necrosis factor-α level was different only on day 7 between patients with and without a postoperative complication (0.5 [0–1.8] pg/mL versus 0 [0–0.4] pg/mL, $P < 0.01$) (Fig. 1c). Postoperative leukocyte count was similar in both groups on all sample days (Fig. 1d).

Predictive Value of Inflammatory Markers

Using an ROC curve, the ideal cut-off point for IL-6 on day 1 for the prediction of a postoperative complication was set at 432 pg/mL. This yielded a specificity of 70%, sensitivity of 64%, positive predictive value of 44%, negative predictive value of 84%, and area under the curve of 67% (95% CI: 56–77%). Patients with an IL-6 level of >432 pg/mL (“high” group) on day 1 had an increased length of hospital stay compared to patients with an IL-6 level of 432 pg/mL or less (“low” group) (12 days [IQR 7–22] versus 7 days (IQR 4–9), $P < 0.001$) (Fig. 2). In multivariate regression analysis, a high IL-6 level on day 1 was independently associated with a postoperative complication (AOR: 3.3, 95% CI: 1.3–8.5; $P < 0.02$) (Table 3). The c-statistic of the model including a high IL-6 level on day 1, atrial fibrillation, gastroesophageal surgery, and the preoperative use of renin–angiotensin–aldosterone system (RAAS) inhibitors was 0.83 (95% CI: 75%–91%; $P < 0.001$) (Fig. 3).

Using an ROC curve, the ideal cut-off point for CRP on day 3 for the prediction of a complication was set at 203 mg/L. This yielded a specificity of 87%, sensitivity of 58%, positive predictive value of 65%, negative predictive value 82%, and area under the curve of 73% (95% CI: 63%–83%). Patients with a CRP level of >203 mg/L on day 3 were at increased risk of a postoperative complication (OR: 8.8, 95% CI: 3.6–21.5; $P < 0.001$). When levels of CRP on day 3 were added to the multivariate model, including a high IL-6 level on day 1, atrial fibrillation, gastroesophageal surgery, and the preoperative use of RAAS inhibitors, the c-statistic increased to 0.87 (95% CI: 0.80–0.93; $P < 0.001$) (Fig. 3). The combination of IL-6 level on day 1 and CRP level on day 3 yielded a specificity of 93%, sensitivity of 39%, positive predictive value of 67%, and negative predictive value of 80%.

Seventy-four patients (55%) developed SIRS during the first 48 hours after surgery. Patients with SIRS had higher levels of IL-6 (418 [219–775] pg/mL versus 260 [83–456] pg/mL, $P < 0.01$) and CRP (90 [61–120] mg/L versus 72 [51–101] mg/L, $P < 0.02$) on days 1 and 3 (95 [52–214] pg/mL versus 53 [17–117] pg/mL, $P < 0.01$, and 182 [115–226] mg/L versus 123 [78–176] mg/L, $P < 0.01$ respectively) compared to patients without SIRS. The development of SIRS was associated with an increased risk of a postoperative complication (OR 3.3, 95% CI: 1.4–7.5; $P < 0.01$), but this relation was lost in multivariate analysis. The specificity, sensitivity, positive predictive value, and negative predictive value of SIRS for the prediction of postoperative complications were 53%, 74%, 39%, and 84% respectively. The addition of SIRS criteria to levels of IL-6 did not improve the prediction of postoperative complications.

DISCUSSION

Our results show that patients with a high IL-6 level on the first postoperative day had a 3-fold increased risk of a postoperative complication and an increased length of hospital stay. Levels of IL-6 distinguished between patients at low and high risk for postoperative complications in an earlier stage than levels of CRP. As a single test, both high IL-6 levels on day 1 and high CRP levels on day 3 showed low diagnostic accuracy for predicting complications. The diagnostic value of IL-6 levels on day 1 in predicting postoperative complications improved when combined with CRP levels on day 3.

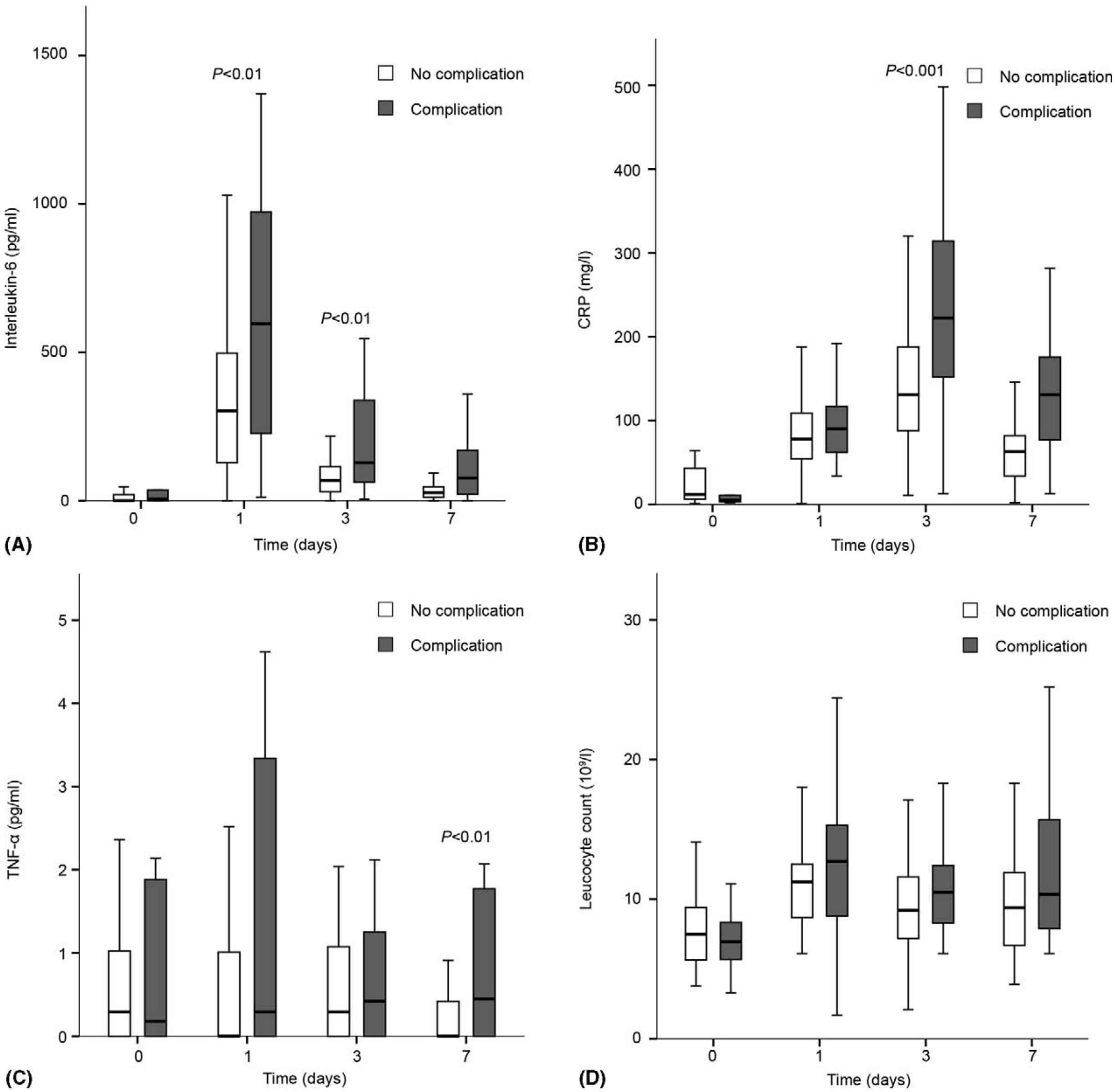

FIGURE 1. Inflammatory markers before surgery and on days 1, 3, and 7 dependent on the occurrence of a postoperative complication.

Few studies investigated the diagnostic value of IL-6 in predicting complications after major abdominal surgery. Szczepanik et al. prospectively studied 99 patients undergoing subtotal or total gastrectomy for malignancy.[4] Twenty-eight (28%) patients developed a postoperative complication within 30 days of surgery. Patients were divided into 2 groups: high (>279 ng/L) versus low ($\leq$279 pg/L) IL-6 level on the first postoperative day. A high IL-6 level was independently associated with an increased risk of a postoperative complication (hazard ratio: 3.6, 95% CI: 1.2–11.0), which is similar to our results (AOR: 3.3, 95% CI: 1.3–8.5). In another study, 50 patients undergoing major gastrointestinal and gynecologic tumor resection were studied.[17] Levels of IL-6, CRP, and procalcitonin were evaluated on the first postoperative day as early markers for postoperative sepsis. Patients who developed sepsis within 5 days of surgery had higher levels of IL-6 on the first postoperative day compared to patients without sepsis (741 pg/mL versus. 276 pg/mL, $P < 0.01$). The accuracy of IL-6 in predicting postoperative sepsis was highest with the cut-off point set at 310 pg/mL. However, a multivariate analysis of levels of IL-6 and sepsis was not reported.

There is no specific IL-6 cut-off level reported in the literature to distinguish patients at increased risk for postoperative complications. Sczepanik et al. used the 90th percentile (279 pg/mL), whereas the optimal cut-off level in the study of Mokart et al. was 310 pg/mL, as assessed using an ROC curve.[4,17] In our patient group, the accuracy of IL-6 on day 1 was highest with a cut-off level of 432 pg/mL, suggesting that the optimal cut-off level for the prediction of complications in major abdominal surgery is somewhere between 300 and 400 pg/mL.

Major abdominal surgery is a frequently conducted procedureand is associated with a high complication rate. It is plausible that

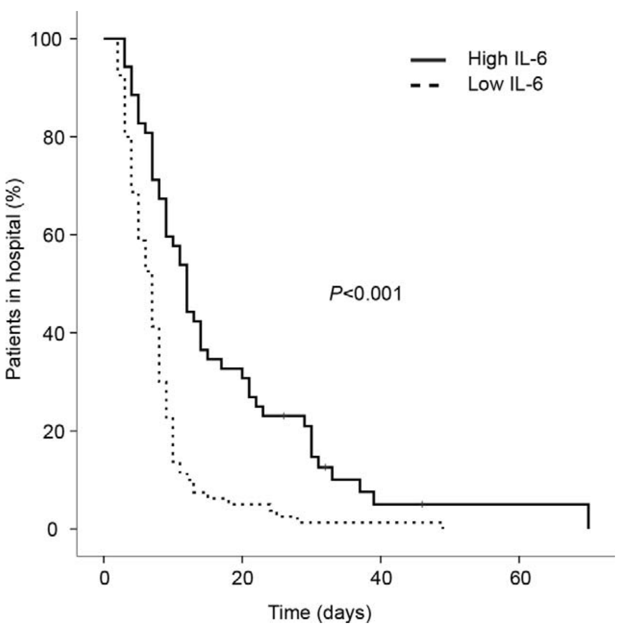

FIGURE 2. Median length of hospital stay dependent on high (>432 pg/mL) or low (≤432 pg/mL) IL-6 level.

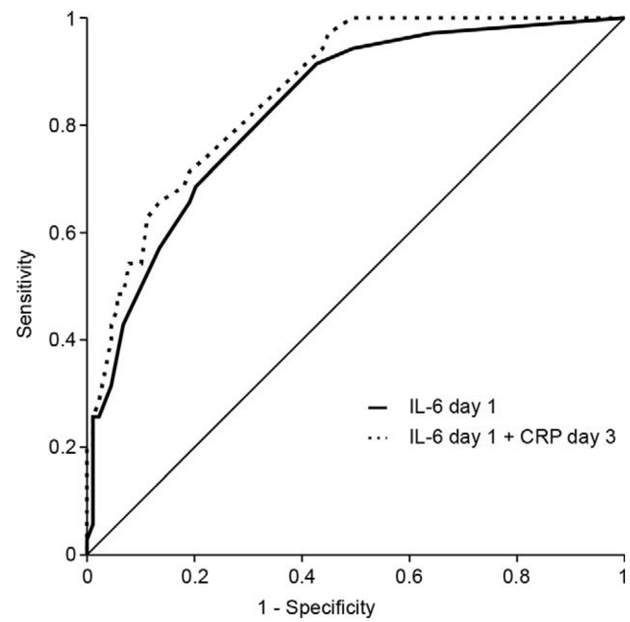

FIGURE 3. Receiver operating characteristic (ROC) curve to determine the goodness of fit for the multivariable predictive model. Interleukin-6 on day 1 represents the model that includes a high (>432 pg/mL) IL-6 level on day 1, atrial fibrillation, gastroesophageal surgery, and the preoperative use of RAAS inhibitors. Interleukin-6 on day 1 and CRP on day 3 represents the same model, with the addition of a high (>203 mg/L) CRP level on day 3.

early recognition of postoperative complications optimizes the chance of better outcome. One way to enhance early detection of complications is using inflammatory markers as predictors of outcome.[20] Usually, levels of CRP are used to monitor the condition of a patient over time after surgery. For example, high levels may support the decision to perform a reoperation when anastomotic dehiscence is suspected. However, inflammatory biomarkers, such as a CRP, are only useful as predictors for such complications when their diagnostic accuracy is sufficient to identify patients at increased risk of complications well in advance of clinical symptoms. In a recent meta-analysis, levels of CRP for the prediction of postoperative complications were assessed.[21] In this study, 1832 patients undergoing colorectal surgery were included and levels of CRP were evaluated during the first 5 postoperative days. The diagnostic performance of CRP to predict postoperative infectious complications was worst on day 1 (area under the curve 0.64) and highest on day 4 (area under the curve 0.81). The time between surgery and complications was not provided. In our study population, levels of CRP on day 1 were similar in patients with and without a complication, and the median time from surgery to a complication was 5 days (IQR 3–8). This means that a substantial number of patients are diagnosed with a postoperative complication before CRP is even able to identify patients at increased risk of complications. Our results show that levels of IL-6 on the first postoperative day could be helpful to distinguish between patients with and without complications. We recognize that high levels of IL-6 showed poor accuracy for predicting postoperative complications. Interestingly, the accuracy of IL-6 was in accordance with the accuracy of CRP—an inflammatory marker that is commonly used for the detection of postoperative complications. The diagnostic value of IL-6 level on day 1 in our study population was also similar to the accuracy

TABLE 3. Uni- and Multivariate Logistic Regression Analysis for Predictors of a Postoperative Complication

Univariate Analysis				Multivariate Analysis			
	OR	(95% CI)	*P*		OR	(95% CI)	*P*
"High" IL-6 level* on day 1	4.1	(1.8–9.2)	0.001	"High" IL-6 level on day 1	3.3	(1.3–8.5)	0.016
Atrial fibrillation	6.3	(2.0–19.9)	0.002	Atrial fibrillation	10.6	(2.4–47.7)	0.002
RAAS inhibitor	3.4	(1.6–7.3)	0.002	RAAS inhibitor	9.0	(3.0–27.2)	0.000
Gastroesophageal surgery	3.0	(1.3–7.1)	0.011	Gastroesophageal surgery	4.9	(1.6–14.9)	0.005
SIRS	3.3	(1.4–7.5)	0.005				
Previous stroke	2.8	(1.2–7.0)	0.023				
RBC transfusion	3.4	(1.4–8.7)	0.009				
TIVA	2.4	(1.0–5.4)	0.042				
Duration of surgery (min)	1.0	(1.0–1.0)	0.099				
Blood loss (mL)	1.0	(1.0–1.0)	0.182				

*High IL-6 > 432 pg/mL.

RAAS indicates renin-angiotensin-aldosterone system inhibitors; RBC, red blood cell transfusion, SIRS, systemic inflammatory response syndrome; TIVA, total intravenous anesthesia.

of CRP level in the meta-analysis previously mentioned.[21] Furthermore, the accuracy of CT scanning for anastomotic dehiscence after colorectal surgery matched the accuracy of IL-6 level on day 1 in the present study.[22]

Patients who developed SIRS had higher levels of IL-6 and CRP on days 1 and 3, confirming that the combination of relatively unspecific clinical symptoms such as tachycardia, high respiratory rate, and fever are an expression of inflammation.[5,23] However, in multivariate analysis, the association of SIRS and outcome was lost, indicating that IL-6 is a more specific marker for inflammation. Moreover, SIRS did not contribute to the prediction of postoperative complications in contrast to results previously mentioned.[17] This might be explained by the difference in endpoints studied.

Why the outcome is influenced by postoperative systemic inflammation is not straightforward. In short, tissue damage induces the proliferation of immunocompetent cells, such as monocytes, macrophages, dendritic cells, lymphocytes, and neutrophils.[24] This, in turn, triggers the production of cytokines and chemokines. As a result, the endothelium produces nitric oxide (NO) to maintain normal homeostasis. However, altered concentrations of NO inhibit the function of mitochondria, which may lead to adenosine triphosphate (ATP) depletion. Excessive depletion of ATP results in cell necrosis and, ultimately, induces organ failure.[25]

Our study has several limitations. First, we used a composite endpoint including infectious and noninfectious complications. At the start of the study, we considered studying individual outcomes (e.g., anastomotic dehiscence), but because these outcomes are rare, statistical power is often insufficient. Moreover, the effect of postoperative inflammation is not confined to infectious complications alone, but to many different types of complications.[26] Second, we only investigated inflammatory biomarkers before surgery and on days 1, 3, and 7. Levels of CRP peak after 48 hours and a CRP level on day 2 could have resulted in a higher accuracy of predicting complications, although this is not seen in previous studies.[21] In addition, it may be that levels of IL-6 on day 2 have better discriminative power than IL-6 levels on day 1 for the prediction of postoperative complications. Third, time between surgery and the collection of blood samples on day 1 was somewhat variable between patients due to variations in surgical starting times. Considering the vivid dynamics of levels of IL-6 during the early phase of inflammation, this may have introduced variation in IL-6 levels outside the development of postoperative complications. On the other hand, measuring IL-6 levels in the morning on the first postoperative day is more suitable in clinical practice than individualizing the exact sampling moment for every patient. Besides this, other studies that investigated inflammatory markers after surgery had a similar study approach, which allowed us to compare our results with previous work. And fourth, this is a single-center observational study in a relative small cohort of patients.

In conclusion, a high IL-6 level on the first postoperative day after major abdominal surgery is independently associated with the occurrence of postoperative complications. The diagnostic accuracy of IL-6 on day 1 for predicting postoperative complications is similar to the accuracy of CRP on day 3. Interleukin-6 levels can have added value in early clinical decision-making.

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