Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery

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Background. Patients who undergo major surgery for cancer are at high risk of postoperative sepsis. Early markers of septic complications would be useful for diagnosis and therapeutic management in patients with postoperative sepsis. The aim of this study was to investigate the association between early (first postoperative day) changes in interleukin 6 (IL-6), procalcitonin (PCT) and C-reactive protein (CRP) serum concentrations and the occurrence of subsequent septic complications after major surgery.

Methods. Serial blood samples were collected from 50 consecutive patients for determination of IL-6, PCT and CRP serum levels. Blood samples were obtained on the morning of surgery and on the morning of the first postoperative day.

Results. Sixteen patients developed septic complications during the first five postoperative days (group 1), and 34 patients developed no septic complications (group 2). On day 1, PCT and IL-6 levels were significantly higher in group 1 (P-values of 0.003 and 0.006, respectively) but CRP levels were similar. An IL-6 cut-off point set at 310 pg ml−1 yielded a sensitivity of 90% and a specificity of 58% to differentiate group 1 patients from group 2 patients. When associated with the occurrence of SIRS on day 1 these values reached 100% and 79%, respectively. A PCT cut-off point set at 1.1 ng ml−1 yielded a sensitivity of 81% and a specificity of 72%. When associated with the occurrence of SIRS on day 1, these values reached 100% and 86%, respectively.

Conclusions. PCT and IL-6 appear to be early markers of subsequent postoperative sepsis in patients undergoing major surgery for cancer. These findings could allow identification of postoperative septic complications.

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Major oncological surgery carries a high risk for postoperative sepsis.1 Recent therapeutic advances, both medical and surgical, have improved early postoperative outcome. Despite this progress, certain patients remain at high risk of infection and the attendant morbidity and mortality. During the postoperative period sepsis can be difficult to distinguish from other non-infectious situations, such as postoperative systemic inflammatory response syndrome (SIRS), related to surgical trauma.2 SIRS can be self-limiting or may progress to severe sepsis or septic shock.3 Early diagnosis and treatment of septic patients may greatly improve outcome.4 Considering the difficulties in diagnosis of infection in critically ill patients, an early sensitive and specific marker for SIRS would be of interest. Although cytokines such as interleukin 6 (IL-6) have been shown to relate to the severity of sepsis and patient outcome,5,6 they are not established tools for diagnosis and clinical decision-making. However, we have recently shown that IL-6 is a good independent early marker of postoperative sepsis, severe sepsis or septic shock after major oncological surgery.5 Procalcitonin (PCT) has been shown to increase during severe infection and endotoxaemia.7,8 In a previous study,9 in comparison with PCT, C-reactive protein (CRP) did not differentiate between inflammation and infection. PCT may be a useful tool in the early diagnosis of postoperative sepsis. Early diagnosis could allow early goal-directed
therapy which has been shown to decrease mortality in severe sepsis. The aim of this study was to evaluate PCT, CRP and IL-6, on the first postoperative day, as early markers of subsequent postoperative sepsis after major oncological surgery.

Patients and methods
The study was conducted prospectively over a period of 10 months in a cancer hospital. After obtaining the informed consent of patients and approval from our institutional ethics committee, 50 consecutive patients undergoing elective major surgical procedures were studied. The criteria for inclusion were major gastrointestinal or gynaecological tumour resection, with surgery expected to last >5 h. The preoperative exclusion factors were: age <18 yr, emergency surgery, preoperative anti-inflammatory drugs, preoperative infection treatment with corticosteroids or morphine and immunosuppressive illness other than neoplasm. All patients received a standardized premedication of hydroxyzine 100 mg orally the night before and on the morning of surgery. Induction of anaesthesia was with propofol 3 mg kg⁻¹ and fentanyl 3 μg kg⁻¹ with atracurium 0.5 mg kg⁻¹ for tracheal intubation. Anaesthesia was maintained with desflurane 1–1.5 minimal alveolar concentration (MAC) and nitrous oxide 50% in oxygen associated with fentanyl and atracurium as required. Antibiotic prophylaxis consisted of amoxicillin 2 g and clavulanic acid 200 mg, with half that dose repeated every 2 h. All clinical and paraclinical data were collected prospectively for each patient. The Charlson comorbidity index (see Appendix, Table A1) was originally designed to quantify underlying diseases and to classify prognostic comorbidity. Each day the attending physician in the intensive care unit (ICU) evaluated all the study patients for SIRS, sepsis, severe sepsis or septic shock. Sepsis was defined as a SIRS associated with infection according to Bone’s criteria. The signs of SIRS were body temperature <35.6°C or >38.3°C, tachycardia (>90 beats min⁻¹), ventilatory frequency >20 bpm or PAO₂ < 4.27 kPa (unless the patient was mechanically ventilated), a white cell count ≥12×10⁹ litre⁻¹ or ≤4×10⁹ litre⁻¹, or >10% immature neutrophils (bands). Severe sepsis was defined as sepsis with evidence of organ dysfunction and hypoperfusion, acute alteration of mental status, elevated plasma lactate, unexplained metabolic acidosis (arterial pH <7.3), hypoxaemia (PAO₂ <9.33 kPa breathing room air, or an acute drop in PAO₂ of >2 kPa below baseline breathing room air or hypoxaemia requiring mechanical ventilation), prolonged prothrombin time or a decrease in platelet count of >50% or ≤100×10⁹ litre⁻¹, oliguria and hypotension defined as systolic arterial pressure <90 mm Hg or a decrease of >40 mm Hg from baseline. Septic shock was defined as hypotension in addition to sepsis syndrome persisting despite adequate fluid resuscitation and requiring inotropic support. Standard supportive care, surgical procedures (drainage of abscesses, etc.) and broad-spectrum antibiotics were provided to all septic patients. Pneumonia was diagnosed if infiltrates were present on the chest radiograph and, if possible, a positive culture from sputum or bronchial fluid. Abscesses and peritonitis were diagnosed by ultrasoundography or CT scan, together with growth of pathogenic bacteria from aspirated pus. Urinary tract infections were diagnosed by the evidence of leucocyturia and growth of pathogen in urine culture. Septic complications were recorded for 5 days postoperatively. For evaluation, patients were allocated into two groups on the basis of signs of sepsis: Group 1, septic (sepsis or severe sepsis or septic shock); Group 2, non-septic (signs of SIRS or no evidence of sepsis).

Blood sampling
Blood samples were collected in glass tubes before surgery (day 0) and then postoperatively on the morning of day 1. Blood was processed within 2 h. It was centrifuged at 400g for 15 min and then at 10 000g for 15 min. Sera were stored at −80°C. Cytokines and PCT levels were measured after the clinical data were recorded. CRP was determined on the day of sampling. A group of 14 healthy adults were used as controls for the preoperative values.

PCT determination
PCT concentrations were measured in duplicate using 20 μl of serum in an immunoassay with a sandwich technique and a chemiluminescent detection system (LumiTest, Brahms Diagnostica, Berlin, Germany). The intra- and inter-assay coefficients of variation at high and low concentrations were <8% and 7%, respectively. The upper limit of normal was 0.5 ng ml⁻¹.

CRP determination
CRP was determined in 20-μl serum samples immediately after specimen collection and was measured by an immunonephelometric method (Array360-CRP, Beckmann Instruments Inc., Galway, Ireland). The minimum concentration detected was 0.04 mg litre⁻¹. The intra- and inter-assay coefficients of variation at high and low concentrations were <8% and 5%, respectively.

IL-6 determination
Circulating IL-6 was measured by enzyme immunoassay (EIA). The assays were performed in duplicate using kits provided by Immunotech (Marseille, France). The minimum concentration detected was 3 pg ml⁻¹. The intra- and inter-assay coefficients of variation of EIA kits ranged from 5% to 10%.

Statistical analysis
Statistical analysis was performed using SPSS software (version 12.0, SPSS Inc., Chicago, IL). Data for the clinical characteristics of patients are expressed as median
(25th–75th percentile). The clinical characteristics of the patients were compared using the \( \chi^2 \)-test or the Mann–Whitney \( U \)-test according to the variable type and the data distribution. The Mann–Whitney \( U \)-test was performed for two independent groups. The Wilcoxon signed-rank test was performed for intragroup changes. \( P<0.05 \) was considered to be significant.

The accuracy of PCT, IL-6 and CRP in the diagnosis of postoperative septic complications was assessed by comparing the area under the receiver operating characteristics curve (AUC-ROC) of each test using the methodology described by Hanley and McNeil.\(^\text{12}\)

**Results**

**Patient characteristics and septic complications**

Fifty consecutive patients were included in the study. Sixteen patients developed a septic complication during the first 5 postoperative days (Group 1, septic patients). In this group, four patients developed septic shock, four developed severe sepsis, and eight developed sepsis without any organ dysfunction. Thirty-four patients had no septic complications (Group 2, non septic patients): 16 of these had an uneventful outcome, two had a haemorrhagic complication, and 16 developed at least two criteria of SIRS without any infection. There was no significant difference between the two groups, except for preoperative Charlson comorbidity index and Acute Physiology and Chronic Health Evaluation II (APACHE II) score\(^\text{13}\) at ICU admission, which were higher in septic patients (Table 1).

**Table 1** Perioperative clinical characteristics of the two groups of patients. Data are expressed as median (25th–75th percentile). Charlson comorbidity index\(^\text{10}\) quantifies underlying disease. NS, not significant

<table>
<thead>
<tr>
<th></th>
<th>Non-septic patients (n=34)</th>
<th>Septic patients (n=16)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 (52–65)</td>
<td>51 (43–62)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>12/22</td>
<td>8/8</td>
<td>NS</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>3 (2–8)</td>
<td>8 (5–8)</td>
<td>0.038</td>
</tr>
<tr>
<td>Apache II score on day 1</td>
<td>8 (6–9)</td>
<td>10.5 (8–12)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

**PCT, IL-6 and CRP levels**

On day 0, IL-6 levels were significantly higher in patients than in healthy controls (5.8 [3–23] pg ml\(^{-1}\) vs 3 [3–3] pg ml\(^{-1}\), \( P<0.0001 \)), PCT levels were similar (0.18 [0.12–0.33] ng ml\(^{-1}\) vs 0.13 [0.10–0.27] ng ml\(^{-1}\), \( P=0.13 \)) and CRP levels were similar (5 [5–38] mg ml\(^{-1}\) vs 5 [5–5] mg ml\(^{-1}\), \( P=0.55 \)). PCT, IL-6 and CRP levels were similar in the two groups on day 0, but on day 1 these levels were significantly increased in both groups (Figs 1, 2 and 3).

On day 0, PCT levels were similar in the two groups (0.21 [0.11–0.35] ng ml\(^{-1}\) in septic patients vs 0.17 [0.11–0.25] ng ml\(^{-1}\) in non-septic patients), but on day 1 they were significantly higher in septic patients (2.1 [1.17–4.20] ng ml\(^{-1}\) vs 0.56 [0.29–1.28] ng ml\(^{-1}\), \( P=0.003 \)) (Fig. 1).

A similar pattern was seen with IL-6. On day 0 levels were similar in the two groups (5.8 [3.0–35.9] pg ml\(^{-1}\) in septic patients vs 5.8 [3.0–16.9] pg ml\(^{-1}\) in non-septic patients), and on day 1 levels were significantly higher in septic patients (741.4 [355.5–1300.3] pg ml\(^{-1}\) vs 275.5 [136.2–495.5] pg ml\(^{-1}\), \( P=0.006 \)) (Fig. 2).

CRP levels were similar in the two groups on day 0 (5.0 [5.0–33.0] mg ml\(^{-1}\) in septic patients vs

![Fig 1](image-url) Box plot (with interquartile range) of PCT levels on day 0 and day 1 in non-septic patients (n=34) and septic patients (n=16). *\( P<0.001 \) compared with day 0; *\( P=0.003 \) compared with non-septic patients.
5.0 [5.0–36.7] mg ml\(^{-1}\) in non-septic patients) and day 1 (82.0 [66.2–106.5] mg ml\(^{-1}\) in non-septic patients vs 103.0 [69.0–162.7] mg ml\(^{-1}\) in septic patients) (Fig. 3).

Sensitivity, specificity, positive and negative predictive values, and ROC curves

The accuracy of the inflammatory markers in distinguishing septic from non-septic patients is shown in Table 2 and Figure 4. At a cut-off point set at 310 pg ml\(^{-1}\), IL-6 yielded a sensitivity of 90% and a specificity of 58%. On day 1, with higher values of IL-6 (>310 pg ml\(^{-1}\)) and signs of SIRS, these values reached 100% and 79%, respectively (Table 3).

At a cut-off point set at 1.1 ng ml\(^{-1}\), PCT yielded a sensitivity of 81% and a specificity of 72%. In association with the occurrence of SIRS on day 1 these values reached 100% and 86%, respectively (Table 3).
IL-6 yielded the highest discriminative value with an AUC of 0.82 (95% confidence interval [CI] 0.66–0.98) followed by PCT (AUC = 0.75, CI 0.6–0.90) and CRP (AUC = 0.67, CI 0.5–0.83) (Table 2).

Discussion

Patients undergoing major surgical resection for cancer are at high risk for postoperative septic complications. Early identification of patients who subsequently develop postoperative sepsis would enable the selection of patients who may benefit from early intensive management. This study confirms the importance of septic complications in this situation\(^1\) and emphasizes the value of adding clinical information (i.e. the presence or absence of signs of SIRS) to the biochemical information. Postoperatively, PCT levels in septic patients were increased, suggesting that surgical trauma induced immediate postoperative increase in PCT levels.\(^1\) However, on day 1 patients in group 1 had PCT levels significantly higher than patients in group 2. As septic events always occurred after day 2 in our study, PCT was an early marker of postoperative infections following major oncological surgery. The cut-off ROC curve value of PCT levels to diagnose postoperative sepsis (1.1 ng ml\(^{-1}\)) showed good sensitivity (81%) and specificity (72%). In association with the occurrence of SIRS on day 1, these values reached 100% and 86%, respectively. The serum IL-6 response to surgical trauma has been characterized extensively. Elective surgery induces an increase in

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**Table 2** Sensitivity, specificity, positive and negative predictive values, and areas under the curve (AUC) for C-reactive protein (CRP), procalcitonin (PCT) and IL-6 on day 1 in diagnosing septic complications during the first 5 postoperative days

<table>
<thead>
<tr>
<th></th>
<th>CRP (cut-off 93 mg ml(^{-1}))</th>
<th>PCT (cut-off 1.1 ng ml(^{-1}))</th>
<th>IL-6 (cut-off 310 pg ml(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>63</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>72</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>53</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>79</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>AUC (% [95% CI])</td>
<td>(49.3–83.5)</td>
<td>(60.2–89.6)</td>
<td>(66.1–98.2)</td>
</tr>
</tbody>
</table>

**Table 3** Sensitivity, specificity, positive and negative predictive values for C-reactive protein (CRP), procalcitonin (PCT) and IL-6 when associated with occurrence of SIRS on day 1 in diagnosing septic complications during the first 5 postoperative days

<table>
<thead>
<tr>
<th></th>
<th>CRP (cut-off 93 mg ml(^{-1}))</th>
<th>PCT (cut-off 1.1 ng ml(^{-1}))</th>
<th>IL-6 (cut-off 310 pg ml(^{-1}))</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity (%)</td>
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<tr>
<td>Specificity (%)</td>
<td>80</td>
<td>86</td>
<td>79</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>67</td>
<td>81</td>
<td>75</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

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**Fig 4** (A) ROC curves for CRP (dashed line) on day 1 for diagnosis of postoperative septic complications. (B) ROC curves for IL-6 (dotted line) on day 1 for diagnosis of postoperative septic complications. (C) ROC curves for PCT (solid line) on day 1 for diagnosis of postoperative septic complications.
circulating IL-6 within 1–3 h, which may remain elevated for 48–72 h in uncomplicated cases. The magnitude of elevation is related directly to tissue injury and postoperative septic morbidity. We have recently shown that IL-6 is an early indicator of postoperative sepsis after major cancer surgery and during the early postoperative period. In the present study the pattern of change of IL-6 was similar to that of PCT. The cut-off ROC curve value of serum IL-6 to diagnose postoperative sepsis (310 pg ml\(^{-1}\)) showed a very good sensitivity (90%) and a poor specificity (58%). When associated with the occurrence of SIRS at day 1 these values reached 100% and 79%, respectively. However, IL-6 is not yet available for routine diagnosis.

Concentrations of CRP have been used to follow septic patients, but were unable to predict the outcome of disease or severity. CRP has also failed to allow immediate diagnosis and prognosis because of the time taken to produce a reaction and the duration of increased serum concentration. These facts may explain its lower sensitivity in the early postoperative period.

Major surgical trauma may induce a non-septic SIRS which can be difficult to distinguish from early postoperative septic complications. PCT could be helpful in the early diagnosis of postoperative infection after major surgery. PCT is known to be an early marker of severe sepsis, but it is correlated with the severity of SIRS after severe trauma and so may be distorted by major surgery. PCT was identified as a better discriminator than CRP in characterizing the degree of inflammation related to infection. PCT was more specific for sepsis-induced inflammation than CRP, but no better than CRP at identifying infection uncomplicated by sepsis or organ failure. Our results suggest that PCT measurements may be useful for early diagnosis of septic postoperative complications. A PCT level >1.1 ng ml\(^{-1}\) associated with SIRS on day 1 could allow diagnosis of postoperative septic complications with a high probability (positive predictive value of 81%). This is in agreement with Reith and colleagues who studied the prognostic capacity of elevated PCT levels in 70 patients undergoing elective colorectal surgery and aortic surgery. An increase of PCT levels >1.0 ng ml\(^{-1}\) the day after surgery was closely related to postoperative complications such as pneumonia or anastomotic leak. These results are also similar to those of Harbarth and colleagues who differentiated non-septic SIRS from a sepsis, with the same PCT cut-off value, in newly admitted ICU patients.

Our data are of importance because the epidemiology of SIRS, sepsis, severe sepsis and septic shock shows that 35% of patients who were clinically septic were prescribed antibiotics empirically without a site with positive culture. Early identification of patients with insidious septic illness allows early therapeutic intervention which may favourably influence outcome. Future studies in larger groups of patients should specifically address this issue.

In conclusion, patients who undergo major cancer surgery are at high risk of postoperative sepsis. During the early postoperative period, PCT and IL-6 are early markers of postoperative sepsis when associated with SIRS on day 1. These findings may aid early therapeutic intervention in high-risk surgical patients.

### Appendix

#### Table A1: Charlson comorbidity index. Assigned weights for each condition that a patient has. The total equals the score. For example, chronic pulmonary disease (1)=lymphoma (2)=total score of 3

<table>
<thead>
<tr>
<th>Assigned weights for diseases</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes</td>
</tr>
<tr>
<td>2</td>
<td>Hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumour, leukaemia, lymphoma</td>
</tr>
<tr>
<td>3</td>
<td>Moderate or severe liver disease</td>
</tr>
<tr>
<td>6</td>
<td>Metastatic solid tumour, AIDS</td>
</tr>
</tbody>
</table>

#### References

12 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143: 29–36