

# C – REACTIVE PROTEIN AND PROCALCITONIN IN THE PREDICTION OF POSTOPERATIVE INFECTION WITH USE OF PROCALCITONIN FOR PREDICTION OF SEVERE EVOLUTION OF POSTOPERATIVE SEPSIS

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**Keywords:** APACHE II score, procalcitonin sepsis, C – reactive protein

**Abstract:** C – Reactive Protein (CRP) is an acute phase protein used to diagnose the presence of inflammation. A rise in CRP concentration in serum may be present in trauma, inflammation, infection, or cancer pathology. Many studies have evaluated severe levels of procalcitonin (PCT) as a prediction in the development of sepsis, infected necrosis. **Methods:** Levels of PCT and APACHE II (Acute Physiology and Chronic Health Evolution) were assessed on the day of sepsis diagnosis in 160 septic patients after abdominal and thoracic surgery, and in similar number of cases (n≈160). CRP results, pre and postoperatively were recorded, with considerations of comorbidity and surgical procedure. **Results:** Patients with comorbidity were more likely to have a high CRP. In 68% of patients, during the first 3 days of the postoperative period, CRP was requested. In this study, we observe a CRP peak at postoperative two or three days, and then it fell. In present study, the multivariate analysis shown, that APACHE II score, and PCT level were independent early predictive markers to indicate the severe lethal sepsis. In this study, 70% of the high-risk patients died of sepsis. The predictive power of both parameters (PCT, APACHE II score) in combination was shown to be superior to that of either single parameter. **Conclusions:** In multivariate analysis, both APACHE II score and PCT were identified as independent and early predictive indicators of severe sepsis, and sepsis lethality. The NICE guidelines do not recommend the usual determinations in preoperative of the CRP, and the postoperative levels of CRP have a limited role to screen the infection. The CRP level can be used in diagnosis of infection after the first three postoperative days. The routine use of CRP in preoperatively and in the first 2-3 days postoperatively is not recommended.

**Cuvinte cheie:** APACHE II – scor, procalcitonină, sepsis, proteina C – reactivă

**Rezumat:** Proteina C reactivă (PCR) este o proteină de fază acută, folosită pentru diagnosticarea prevenției unei inflamații. Creșterea concentrației serice al PCR poate fi observată în traumă, inflamație, infecție sau patologie neoplazică. Mai multe studii au evaluat nivelul seric al procalcitoninei (PCT) ca indicator în dezvoltarea sepsisului, necrozei infectate. **Metodă:** nivelul seric al PCR și scorul APACHE II (Acute Physiology and Chronic Health Evolution) a fost determinat în ziua stabilirii sepsisului, la 160 de pacienți după intervenții abdominale și toracice și într-un număr similar (n≈160) analizate rezultatele pre și postoperatorii al nivelului PCR, luând în considerare comorbiditatea și procedeuul chirurgical. **Rezultate:** pacienții prezentând comorbiditate au avut mai frecvent nivel crescut al PCR. În 68% din pacienți, în perioada primelor trei zile postoperatorii a fost cerută determinarea PCR. În acest studiu am observat un vârf al nivelului seric de PCR în ziua a 2-a sau a 3-a postoperabil, după care nivelul seric scade. În studiul de față, analiza multivariată a arătat că scorul APACHE II și nivelul PCR reprezintă markeri predictivi precoce în indicarea sepsisului letal sever. În acest studiu, 70% dintre pacienții cu risc crescut au decedat prin sepsis. Importanța predictivă a ambilor parametri (PCR, scorul APACHE II) în combinație a fost superioară în raport cu cea a fiecărui parametru luat separat. **Concluzii:** în analiza multivariată atât scorul APACHE II, cât și PCT au fost identificați ca indicatori precoce ai sepsisului sever și al sepsisului letal. Ghidul NICE nu recomandă determinarea nivelului seric al PCR preoperator, iar nivelurile postoperatorii ale PCR prezintă un rol limitat în screeningul infecției. Nivelul seric al CRP poate fi utilizat în diagnosticul infecției în perioada după primele trei zile postoperatorii. Folosirea de rutină al CRP-ului în preoperator și în primele 2-3 zile postoperator nu se recomandă.

## INTRODUCTION

C – reactive protein (CRP) is an acute phase protein with a half-life of 19h.(1,2) A rise in CRP concentrations in serum may be seen with infection, trauma, inflammation, cancer pathology and tissue infarction(3)

The National Institute for Health and Clinical Excellence (NICE) has recently published guidelines on preoperative testing for elective surgery.(4) These guidelines do

not recommend routine CRP testing on patients admitted for elective surgery, but no guidelines on postoperative testing have been published to date.

A rise in CRP may be seen earlier in a disease process, than other non-specific markers, and falls rapidly on resolution of inflammation (3), CRP may therefore be useful as a test to detect an inflammatory response early in its case.

Severe sepsis is still a major cause of postoperative

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morbidity and mortality after abdominal surgery.

A number of studies have investigated clinical and immunologic parameters to determine the risk for the development and the lethal outcome of sepsis.(4-8)

In difficult cases, with major operations, prognostic parameters that may indicate the presence of sepsis in abdominal cavity, should allow for the indication of high risk patients before surgery.

A current major problem is the heterogeneity of sepsis patients from clinical studies. Many studies compared septic complication as peritonitis, pneumonia wound sepsis, therefore the heterogeneity should be reduced by focusing the pathology of a more homogenous group of cases.

In a series on 33 patients with sepsis of different etiologies, Wunder et al. could identify systemic procalcitonin level APACHE II score were found to be correlated with poor outcome.(9)

In this study, we analyse two categories of as patients with abdominal and thoracic surgery.

The aims of this study in the first patients' categories were to analyse and compare the practice of postoperative CRP with the practice of postoperative CRP testing, and review the existing literature such that guidelines could set.

In the second group of the patients PCT was evaluated as predictor of outcome in early postoperative sepsis, with the APACHE II score in major visceral surgery, the sepsis was caused by peritonitis or pleuro-pulmonar infections.

The systemic assessment of patients will allow identification of those as greatest risk and have individualized care to ensure the best possible outcome, a readily identified high risk subgroup accounts for over 80% of postoperative deaths, but less than 15% of in patient procedures.(10-13)

A key component of the high complication rates after surgery is the failure to identify the patients at greatest risk so that appropriate preoperative interventions can be provided (11). For example, in UK less than 30% of high-risk patients are admitted to critical care after surgery.(11,12)

### METHODS

Patients admitted in Ist Surgical Clinic for elective surgery between January 2008 and December 2012 were considered for the study retrospectively CRP results were collected on 160 patients preoperatively, and on the first 5 days postoperatively, and patients who had more than 5 days preoperative admissions were excluded from the study.

Statistical analysis was carried out using the compared t-test, statistically significant differences were identified as  $p < 0,05$ .

For use of procalcitonin for early prediction of postoperative sepsis, the study population considered of 80 consecutive sepsis patients treated in surgical intensive care unit, between January 2008 and December 2012.

Cases as a sequel of major visceral surgery were included as well as patients developing sepsis on initial intestinal perforation, and on initial pleural and pulmonary sepsis.

The clinical profile of patients in this study category (sepsis) is shown in table no. 1.

In accordance with defined criteria, diagnosis of sepsis required confirmation of an infection of 2 or more of the following conditions:(14) temperature greater than 38°C, or less than 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute, and white blood cell count greater than 12.000/ml or less than 4.000/ml or greater than 10% immature forms.

In septic patients, venous blood samples were

collected on the day of sepsis diagnosis.

**Table no. 1. Data of sepsis patients – Procalcitonine use**

Data		Number
Malignant disease		50
Non-malignant disease		30
Neoadjuvant therapies	No-neoadjuvant therapy	69
	Chemotherapy	4
	Radio-chemotherapy	7
Surgery	Gastrectomy	8
	Colorectal resection	27
	Small intestine	8
Site of septic forms	Pulmonary	9
	Pleural cavity	8
	Esophagus	1
	Colon	4
	Stomach	1

### RESULTS

In 160 preoperative elective surgery patients had their CRP checked preoperatively (figure no. 1).

**Figure no. 1. Perioperative CRP for elective surgery**

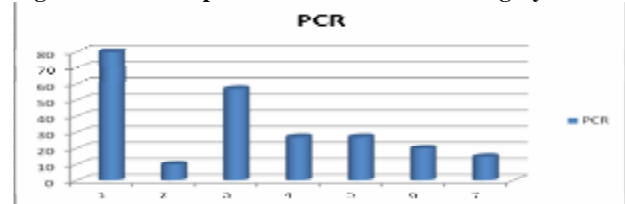


Table no. 2 shows that 55% of patients who had had CRP checked had CRP with normal value ( $< 6$  mg/l), 5% had a CRP  $> 30$  mg%, and the other had mild elevation in CRP (40%).

**Table no. 2. CRP results on 160 preoperative patients**

CRP (mg/l)	Patients (%)
$< 6$	55
$< 10$	75
$< 20$	90
$< 30$	96

In this study the patients had no co-morbidity, CRP were lower than were co-morbidity was recorded ( $p < 0.0001$ ).

Table no. 3 showed that patients with diabetes, cancer, renal disease presents with high CRP ( $\geq 30$ mg/l) are admission

**Table no. 3. Preoperative CRP with or without co-morbidity**

Nr of patients	No Comorbidity	Comorbidity	Cancer	Diabetes	Renal	Cardiac
Nr of patients	30	123	56	40	9	55
CRP $< 6$ mg/l %	68	50	41	42	50	26
CRP $< 10$ ml/l %	92	68	57	63	50	67
CRP $< 20$ mg/l %	100	87	84	80	61	90
CRP $< 30$ mg/l %	100	92	88	85	76	97

In 160 patients CRP were made preoperatively and during the first 3 days postoperatively during the investigation time.

Figure no. 1 showed that postoperatively 70% of patients had CRP checked one or more times in the first 3 days, and that majority had on days less than 20% of patients had their CRP checked after the third postoperative day.

The data of CRP determination shows that CRP was

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received in the first 3 days after surgery, and that this peaked at day 2, and the levels fell over the following 2 days.

In second study patients group with level of procalcitonin (PCT) sepsis developed on postoperative day 8. The majority of patients developed sepsis on postoperative day 1 after surgery for intestinal perforation (14,5%). Overall sepsis mortality was 36%. PCT and APACHE II scores on first day of sepsis could be identified as the only significant independent predictors of lethal outcome of all the parameters analyses.

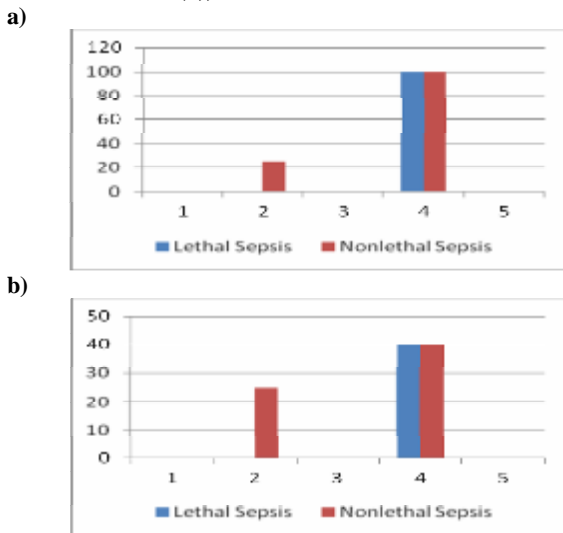
PCT univariate  $p < 0.01$ , PCT multivariate  $p = 0.05$ , APACHE II univariate  $p < 0.001$  and multivariate  $p = 0.001$  (table no. 4).

**Table no. 4. Clinical parameters, PCT, APACHE II score, with sepsis related death – uni and multivariate model**

	P value	
	Univariate	Multivariate
Age	208	No significant (NS)
Cancer	270	NS
PCT	$< 0.001$	0.005
APACHE II	$< 0.0001$	0.001
Type of surgery	120	0.001
Site of sepsis	0.2	NS

Patients with lethal sepsis exhibited significantly higher PCT levels compared to sepsis survivors ( $p < 0.001$ ), APACHE II scores were higher in lethal sepsis ( $p < 0.0001$ ) (figure no. 2 a,b).

**Figure no. 2. PCT and APACHE scores at sepsis (PCT (a); Score APACHE (b))**



Using the prognosis score, lethal sepsis could be detected with a sensitivity of 70%, while sepsis survivors were identified with a specificity of 77% (table no. 5).

**Table no. 5. Specificity and sensitivity for prognosis – PCT levels, APACHE II scores**

	Lethal sepsis	Non lethal sepsis	Total
Low risk	28,5%	75%	59%
High risk	71%	27,3%	40%

### DISCUSSIONS

This study has demonstrated that preoperatively, most patients with no comorbidity had a normal with or only slightly elevated CRP, and CRP results were more likely to be abnormal in presence of co-morbidity. Current NICE guidelines do not

recommend routine CRP testing preoperative in elective surgery.(4) In colorectal and oesophageal carcinoma preoperative CRP concentration is a prognostic indicator (15,16,17) in part, to the secretion of CRP by the tumour.(18) Some studies shown that patients with oesophagogastrrectomy and raised preoperative CRP are more likely to develop complications.(3)

Early diagnosis of a postoperative sepsis and sepsis severity, thus prognosis are essential for emergency and adequate treatment.

Several studies from literature have been reported the evaluation of the sepsis (7,8), the APACHE II score have been used frequently for risk estimation in Intensive Care Unit.(19)

The nonspecific nature of CRP measurements suggests results should be interpreted with caution when used to evaluate prognosis and the likelihood of postoperative complications, a rise in CRP has been demonstrated that occur as a result of surgical trauma and peaks at 48h postoperatively.(20,21)

Some studies have shown a link between the peak postoperative CRP response and degree of surgical trauma (22) both we did not found this correlation. The CRP response in individual patients is highly variable, may be incomplete or even absent.(23,24)

In this study CRP was measured postoperatively, the results showed that CRP was raised in the postoperative period peaked at days 2-3 and than fell. This confirms that a raised CRP is to be expected after surgery in majority of elective surgical procedures, and agrees with previous studies.

For risk evaluation in sepsis we have combined the APACHE II score and serum PCT in a single prognosis model, after identifying them both as independent predictors of sepsis mortality and was shown that the predictive power of both parameters in combination was superior to that of either single parameter, and sepsis related death could be predicted with high specificity and sensitivity. We did not see any correlation between CRP level and occurrence of infection in the first 3 days, and after publications have concluded that CRP is not a good indicator of the presence of early postoperative infection.(26,27)

A rising CRP after the second or third postoperative day in major surgical procedures may indicate the presence of infection.(28,29)

Lindberg et colab (27) indicate the cause of two or more markers in detecting infection after the third postoperative day.(30)

### CONCLUSIONS

Preoperatively routine determination of CRP in the first 2-3 days after surgery is not recommended, and in high-risk patients can be used for screening in the 3-rd and 5-th postoperative days. The APACHE II score, and the PCT are identified as independent predictive indicators of lethal evolution of the sepsis, and might help to improve prognosis of postoperative peritonitis.

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