THE HIGH ELEVATION OF C-REACTIVE PROTEIN LEVELS AT ADMISSION REPRESENTS AN EARLY MORTALITY PREDICTOR IN PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTIONS

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ABSTRACT

PURPOSE: The aim of this study was to evaluate the highly elevated CRP levels at admission as a mortality predictor in patients with complicated intra-abdominal infections (cIAIs).

METHODS: This retrospective study involved 78 adult patients with diagnosis cIAIs admitted to the Department of Surgical Diseases at a University Hospital Stara Zagora from January 2017 to October 2018. CRP concentrations, white blood cells (WBC) count, qSOFA score and SIRS criteria were determined at admission. We compared their prognostic performance using the area under receiver operating characteristics (AUROC) curves and analyzed the coordinates of the curves.

RESULTS: Of the 78 enrolled patients twenty (25.6%) died during hospitalization. ROC Curve analysis revealed CRP as the best mortality predictor (AUROC = 0.787). The pairwise comparison of ROC curves showed prognostic superiority of CRP compared to WBC (AUROC = 0.787 vs. 0.511, p = 0.0194) and SIRS (AUROC = 0.787 vs. 0.579, p = 0.0315) in outcome prediction. The identified sensitivity and specificity for CRP cut-off value = 210 mg/L were 75.0% and 81.0%, respectively.

CONCLUSION: We found highly elevated CRP levels at admission as a significant prognostic biomarker in patients with cIAIs.

Key words: C-reactive protein, biomarkers, complicated intra-abdominal infections, sepsis, prognosis, outcome, mortality

INTRODUCTION

At the end of the second decade of the 21st century, complicated intra-abdominal infections (cIAIs) remain a serious challenge for general surgeons and critical care medicine physicians, because of their unacceptably high mortality rates. Nowadays cIAIs comprise nearly twenty percent of sepsis in Intensive Care Units (ICUs) and moreover, they hold second place after pneumonia as a cause for infectious morbidity and mortality (1).

In cIAIs, the infectious process spreads beyond the affected intra-abdominal organ and results either in acute local or diffuse peritonitis (2). Usually, cIAIs lead to sepsis that can evolve

into a septic shock, a multiple organ failure and eventually to death, if any delay in treatment occurs. Therefore, early prognosis and timely management are extremely important for the favorable outcome.

Over the years a lot of different biomarkers for early prognostic evaluation were investigated and yet none has shown the required characteristics. The first acute-phase reactant to be characterized as sensitive marker of tissue damage, inflammation and infection was C-reactive protein (CRP) (3). Currently CRP is one of most widely used biomarkers in clinical practice. A lot of researchers explore CRP as a diagnostic biomarker and reported a good accuracy for detection abdominal infection or postoperative complications (4-9). However, the prognostic role of CRP in patients with cIAIs remains unclear. The authors that investigate the predictive performance of CRP

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in cIAIs are not many (10-13) and only few of them have looked at CRP levels at admission as a mortality predictor. (14-16). Despite the routine clinical use of CRP, no study (to the best of our knowledge) analyzed its high elevation at admission as a marker for the detection of fatal outcomes in patients with cIAIs.

Therefore, our aim was to evaluate the highly elevated CRP levels at admission, before an administration of any kind of treatment, as a predictor of death in patients with complicated intra-abdominal infections.

MATERIAL AND METHODS
This was a single center retrospective study conducted in the Department of Surgical Diseases at a University Hospital "Prof. Dr. Stoyan Kirkovich" Stara Zagora. We retrieved data for 78 adult patients admitted to the Department of Surgical Diseases (DSD) from the Emergency Department (ED) and operated on for cIAIs between January 2017 and October 2018. For this time period in DSD were admitted eighty-eight patients with cIAIs. Missing data about CRP levels were found in seven patients, two patients died preoperatively and one was under 18 years old. Finally, seventy-eight patients were included in the retrospective analysis.

Demographic information, laboratory results, clinical parameters and outcomes were collected from the patients' medical records through a systematic survey. CRP levels and white blood cells (WBC) count were determined from the data at admission to DSD. The qSOFA score was calculated according to values of systolic blood pressure (SBP) ≤ 100 mmHg, respiratory rate (RR) ≥ 22/minute and a Glasgow Coma Scale (GCS) <15 points (1 point for each criterion to yield a score value between 0 and 3). A positive score was identified as ≥ 2 points (17). A presence of systemic inflammatory response syndrome (SIRS) was defined as two or more of the following 4 signs: a heart rate >90/min, tachypnea >20/min, a temperature <36°C or >38°C and a WBC count $<4x10^9$/L or $>12x10^9$/L (18). SIRS and qSOFA were calculated based on patients' clinical data at admission.

Statistical analyses were performed using SPSS Statistics 19.0 (IBM, Chicago, Illinois, USA) and MedCalc 14.8.1 (MedCalc Software, Ostend, Belgium). The sensitivity, specificity and area under receiver operating characteristics (AUROC) curves were computed to evaluate the ability of each inflammatory marker and score to predict the fatal outcome. The comparison of ROC curves was performed using De Long's method. Continuous variables were presented as mean (±SD) for normally distributed data or median (IQR) for non-normally distributed data. Comparisons of group differences for continuous variables were performed by Student t Test or Mann-Whitney U test. Categorical variables were expressed as frequency (%) and compared by Chi-square test or Fisher exact test. Statistically, significant p-value was considered lower than 0.05.

RESULTS
General characteristics
Of the seventy-eight patients, twenty-five (25.6%) had a poor outcome. The patients who died had higher average age than those who survived (73.25±12.18 vs. 54.21±18.29, p < 0.0001). Mortality was significantly higher in patients with chronic renal failure (p = 0.004) and oncological disease (p = 0.017). No significant differences between survivors and non-survivors were found according to gender (p = 0.593), exudate (p = 0.071), source (p = 0.058) and spread of peritonitis (p = 0.065), presence of arterial hypertension (p = 0.219) and diabetes (p = 0.687) (**Table 1**).

Clinical parameters and scores
CRP levels were significantly elevated in patients who died (240.75±99.21 mg/L vs. 127.59±100.73 mg/L, p < 0.0001). There was no significance in outcome prediction according to leucocytosis (p = 0.886). Eight patients (10.3%) had GCS <15 at admission, none of them survived (p < 0.0001). Significant differences between survivors and non-survivors were determined according to SBP ≤ 100 mmHg (p = 0.017) and RR ≥22/minute (p = 0.002). We observed a qSOFA score ≥2 points in eight patients (10.3%), only one (1.7%) of them survived (p < 0.0001). No significance was found for a body temperature >38°C (p = 1.000), a heart rate >90/minute (p = 0.110) and a SIRS (p = 0.300) (**Table 2**).

Table 1. *General characteristics*

Variable	Total population	Survivors(n=58)	Non-Survivors(n=20)	p value
Sex, n(%) *male/female*	43(55.1)/35(44.9)	33(76.7)/25(71.4)	10(23.3)/10(28.6)	0.593
Age, years ±SD	59.09±18.82	54.21±18.29	73.25±12.18	< 0.0001
Source, n(%)				0.058
Appendix	19 (24.4)	18 (31.0)	1 (5.0)	
Stomach/Duodenum	17 (21.8)	12 (20.7)	5 (25.0)	
Hepatobiliary system	16 (20.5)	12 (20.7)	4 (20.0)	
Colon/Rectum	14 (17.9)	7 (12.1)	7 (35.0)	
Small intestine	2 (2.6)	1 (1.7)	1 (5.0)	
Female reproductive system	4 (5.1)	4 (6.9)	0 (0)	
Other	6 (7.7)	4 (6.9)	2 (10.0)	
Peritonitis, n(%)				0.065
Local	29 (37.2)	25 (43.1)	4 (20.0)	
Diffuse	49 (62.8)	33 (56.9)	16 (80.0)	
Exudate, n(%)				0.071
Serous	12 (15.4)	10 (17.2)	2 (10.0)	
Purulent	62 (79.5)	47 (81.0)	15 (75.0)	
Feculent	4 (5.1)	1 (1.7)	3 (15.0)	
Comorbidity, n(%)				
Malignancy	15 (19.2)	7 (12.1)	8 (40.0)	0.017
Hypertension	30 (38.5)	20 (34.5)	10 (50.0)	0.219
Diabetes	9 (11.5)	6 (10.3)	3 (15.0)	0.687
Chronic Renal Failure	6 (7.7)	1 (1.7)	5 (25.0)	0.004

Table 2. *Clinical parameters and scores*

Variable	Total population	Survivors(n=58)	Non-Survivors(n=20)	p value
SBP ≤100mmHg, n(%)	15 (19.2)	7 (12.1)	8 (40.0)	0.017
RR ≥22/min, n(%)	10 (12.8)	3 (5.2)	7 (35.0)	0.002
GCS <15, n(%)	8 (10.3)	0 (0)	8 (40.0)	< 0.0001
Heart rate >90/min, n(%)	24 (30.8)	15 (25.9)	9 (45.0)	0.110
t >38° C, n(%)	13 (16.7)	10 (17.2)	3 (15.0)	1.000
WBC, 10^9/L (IQR)	12.0 (9.2-16.0)	12.0 (9.6-15.4)	11.3 (7.4-16.8)	0.886
CRP, mg/L ±SD	156.60±111.41	127.59±100.73	240.75±99.21	< 0.0001
SIRS, n(%)	24 (30.8)	16 (27.6)	8 (40.0)	0.300
qSOFA≥2, n(%)	8 (10.3)	1 (1.7)	7 (35.0)	< 0.0001

Sensitivity, Specificity and AUROCs
CRP showed the best prognostic the performance (AUROC = 0.787, 95% CI = 0.680 – 0.872). A cut-off value = 210 mg/L permitted prediction of mortality with a sensitivity of 75% and specificity of 81%. The qSOFA score was observed with a little worse predictive performance than CRP (AUROC = 0.746, 95%

CI = 0.635-0.838). The computed sensitivity and specificity for qSOFA score ≥ 2 points were 35.0% and 98.3%, respectively. In contrast, WBC count (AUROC = 0.511, 95% CI = 0.395-0.626), and SIRS (AUROC = 0.579, 95% CI = 0.462 - 0.690) showed poor prognostic value **(Figure 1), (Table 3)**.

Table 3. *Sensitivity, Specificity and AUROCs*

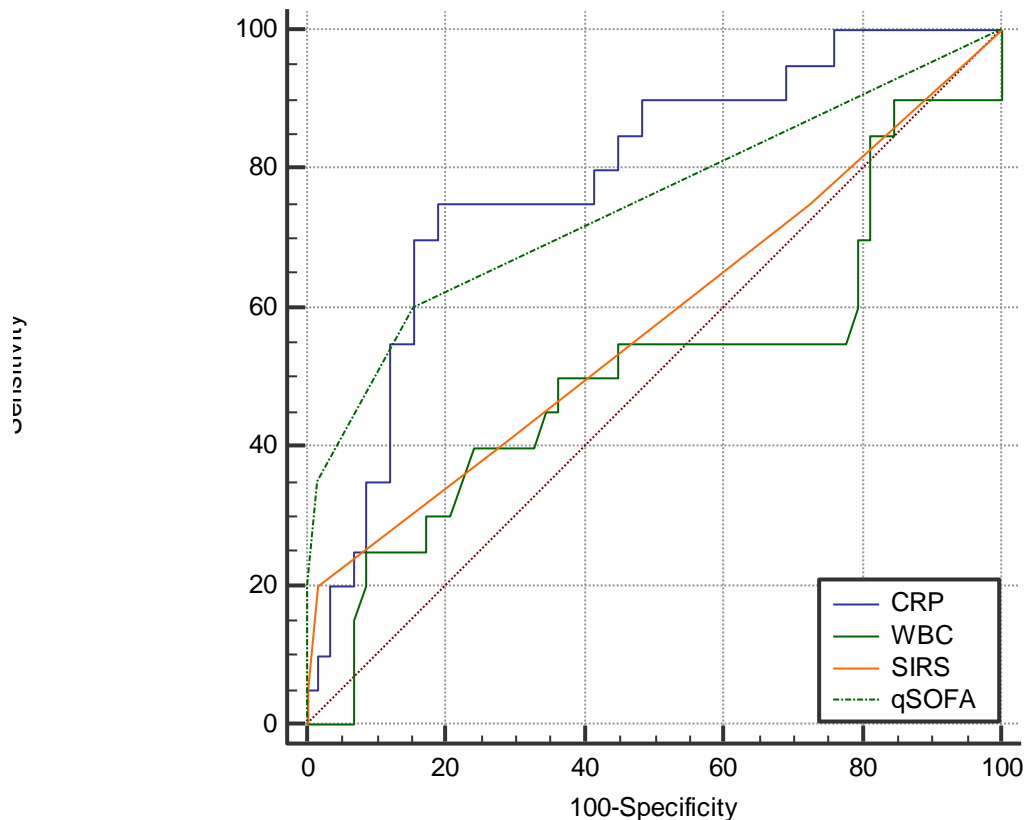| Variable	Cut-off value	Sensitivity,%	Specificity,%	AUROC
CRP	210 mg/L	75.0	81.0	0.787(0.680-0.872)
WBC	12.01x10^9/L	55.0	50.0	0.511(0.395-0.626)
qSOFA	≥ 2 points	35.0	98.3	0.746 (0.635-0.838)
SIRS	≥ 2 points	40.0	72.4	0.579 (0.462-0.690)

Figure 1. Comparison of ROC Curves

Using a pairwise comparison of ROC Curves we observed prognostic superiority of CRP than WBC (difference between areas = 0.276, 95% CI = 0.0446-0.508, p = 0.0194) and SIRS (difference between areas = 0.208, 95% CI = 0.0184-0.398, p = 0.0315), and comparability to qSOFA (difference between areas = 0.0409, 95% CI = -0.121-0.203, p = 0.6195) (**Table 4**).

Table 4. *Pairwise comparison of ROC curves*

	CRP ~ WBC	**CRP ~ SIRS**	**CRP ~ qSOFA**
Difference between areas	0.276	0.208	0.0409
Standart Error[c]	0.118	0.0968	0.0825
95% CI	0.0446-0.508	0.0184-0.398	-0.121-0.203
Significance	p = 0.0194	p = 0.0315	p = 0.6195

DISCUSSION

Complicated intra-abdominal infections involve a wide spectrum of patient populations, which makes the suggestion of a general treatment strategy a difficult task and demonstrates the necessity of an individual approach to each patient (19). Early prognostic assessment of cIAIs provides an opportunity to differentiate the patients at a higher risk of death and a chance to change the inadequate management plan in an early stage, so the adverse outcome to be improved. These findings show the need for specific methods, which would help for the early prognosis and could determine the aggressiveness of conservative and surgical treatment.

Prediction of mortality using routinely and available biomarkers represents a quick and cheap way to provide adequate information about the risk of a fatal outcome in every hospital all around the world. Nowadays CRP is one of the most commonly used markers in everyday practice. CRP is for sure not ideal biomarker, but it could be very helpful in terms of identifying patients at a higher risk of

adverse outcome, who need ICU admission, close monitoring and re-evaluation of the aggressiveness of management. The validity of CRP in estimating the prediction of mortality in patients with cIAIs is still not well known. In this regard there are contradictory data in the literature.

We found only one study (14) that considered the high elevation of CRP concentrations at admission as a mortality predictor in patients with cIAIs. Unfortunately, the authors did not analyze these findings. Significant differences between survivors and non-survivors were observed according to CRP levels >200 mg/L ($p < 0.0001$). This cut-off value could predict the fatal outcome with a sensitivity of 25% and specificity of 86.7%.

In our study the highly elevated CRP levels at admission showed significant association with the fatal outcome. We have identified a much higher sensitivity of 75% and similar specificity of 81% for CRP threshold = 210 mg/L.

Pandey et al. (16) investigated preoperative CRP levels in 86 surgical patients with an acute abdomen. At a cut-off value >150 mg/L the observed sensitivity and specificity were 90% and 42.1%, respectively. The mortality rate was higher among patients with preoperative CRP levels >150 mg/L as compared to those patients with preoperative CRP levels ≤150 mg/L ($p = 0.049$).

Mulari et Leppäniemi (15) observed that the highest CRP examined during the first three days after the operation differs significantly according to outcome (192, 0–361 mg/L vs. 216, 27–378 mg/L, $p = 0.015$), however, its levels at admission did not reach statistical significance between patients who died and those who survived.

In our study, CRP concentrations at admission were significantly elevated in non-survivors compared to survivors (240.75±99.21 mg/L vs. 127.59±100.73 mg/L, $p < 0.0001$).

No prognostic significance for CRP levels examined preoperatively was found by several authors - Yamamoto et al. (13) in patients with colorectal perforation (survivors 124 ± 110 mg/L vs. non-survivors 68 ± 68 mg/L, $p = 0.171$), Akcay et al. (11) in patients with perforation of peptic ulcer (survivors 150±79 mg/L vs. non-survivors 234±143 mg/L, p

>0.05), small bowel (survivors 175±105 mg/L vs. non-survivors 130±54 mg/L, p >0.05) and colon (survivors 199±176 mg/L vs. non-survivors 288±315 mg/L, p >0.05), and Pehlivanli et al. (20) in patients with secondary peritonitis (survivors 190.85 mg/L vs. non-survivors 187.78, $p = 0.79$).

Two studies examined CRP levels postoperatively in surgical patients with cIAIs as a predictor of mortality. Neither Suarez de-la-Rica et al. (12) (survivors 192 mg/L vs non-survivors 268 mg/L, $p = 0.07$), nor Pupelis et al. (10) (survivors 150 mg/L vs. non-survivors 226 mg/L, $p = 0.058$) found significant prognostic value of CRP measured after surgery.

In patients with sepsis CRP also shows conflicting results. Stalder et al. (21) reported very poor prognostic performance (AUROC = 0.556), whereat survivors had higher CRP levels at admission than non-survivors (262 mg/L vs. 225 mg/L, $p = 0.383$). Unlike them, Koozi et al. (22) observed higher CRP levels in non-survivors (141 mg/L vs. 95 mg/L, $p = 0.023$) as well as Ryoo et al. (23) in septic shock patients (non-survivors 147 mg/L vs. survivors 119 mg/L, $p = 0.003$).

Our study is the first one (to the best of our knowledge) that analyzes ROC Curves of CRP, WBC, SIRS and qSOFA using a pairwise comparison analysis. Thus, we found the superiority of CRP than WBC and SIRS and comparability to qSOFA score in outcome prediction.

As limitations of our study, we can highlight the single-center experience, the retrospective design, and the small sample size.

CONCLUSION
In patients with complicated intra-abdominal infections, the high elevation of C-reactive protein levels examined on admission represents an early and important predictor of death. At admission, non-survivors have significantly higher CRP levels than survivors, whereat a threshold = 210 mg/L is associated with an increased risk of an unfavorable outcome.

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