CLINICAL SCIENCE

Evaluation of serial C-reactive protein measurements after surgical treatment of pleural empyema

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OBJECTIVE: Serial C-reactive protein measurements have been used to diagnose and monitor the response to therapy in patients with pneumonia and other infectious diseases. Nonetheless, the role of C-reactive protein measurement after surgical treatment for pleural empyema is not well defined. The aim of this study is to describe the behavior of C-reactive protein levels after the surgical treatment of pleural empyema and to correlate this parameter with the patient's prognosis.

METHODS: We retrospectively analyzed the records of patients with pleural empyema treated by either chest-tube drainage or surgery from January 2006 to December 2008. C-reactive protein levels were recorded preoperatively and 2 and 7 days postoperatively. The clinical outcome was binary: success or failure (mortality or the need for repeated pleural intervention).

RESULTS: The study group comprised fifty-two patients. The median C-reactive protein values were as follows: 146 mg/L (pre-operative), 134 mg/L (post-operative day 2), and 116 mg/L (post-operative day 7). There was a trend toward a decrease in these values during the first week after surgery, but this difference was only statistically significant on day 7 after surgery. Over the first week after surgery, the C-reactive protein values decreased similarly in both groups (successful and failed treatment). No correlation between the preoperative C-reactive protein level and the clinical outcome was found.

CONCLUSIONS: We observed that, in contrast to other medical conditions, C-reactive protein levels fall slowly during the first postoperative week in patients who have undergone surgical treatment for pleural empyema. No correlation between the perioperative C-reactive protein level and the clinical outcome was observed.

KEYWORDS: Pleural Empyema; C-Reactive Protein; Treatment Outcome; Surgery.

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INTRODUCTION

C-reactive protein (CRP) is an acute-phase protein produced primarily in the liver in response to cytokine release; elevated levels of serum CRP are observed with most invasive infections (1). Several studies have investigated the role of serial CRP measurements in the diagnosis of sepsis and infection and in monitoring the response to therapy (2). In patients with community-acquired pneumonia, for instance, CRP has been proven to be a valuable marker of disease severity; in addition, the identification of the CRP response pattern after antibiotic therapy can be useful in the assessment of an individual's clinical course (3-5).

No potential conflict of interest was reported.

Pleural empyema (PE) is a severe infectious condition associated with significant morbidity and mortality, particularly in elderly and immunocompromised populations (6,7). The main goal of surgery for the treatment of PE is to prevent pleural sepsis. The failure of surgical treatment is frequently determined by the presence of fever, leukocytosis, and the presence of residual pleural pus that is confirmed radiologically (8). However, these signs are not specific and can be misleading. Therefore, an accurate laboratory marker capable of identifying persistent infection and the necessity of a second surgery would be clinically useful. Due to the features already reported in other conditions, it was hypothesized that CRP could serve as such a marker; nevertheless, to date, few studies have evaluated the time course and clinical relevance of changes in the CRP levels in patients undergoing surgery for PE (9,10).

The primary endpoint of this study was to evaluate the decrease in CRP levels during the first week after surgical treatment for pleural empyema. The secondary endpoint

was to correlate the preoperative CRP levels and the CRP levels from the first postoperative week with the final outcome of PE surgical treatment.

METHODS

We retrospectively analyzed the medical records of all patients with pleural empyema treated by either chest tube drainage or surgery from January 2006 to December 2008 in a tertiary teaching hospital. Empyema was defined as pleural effusion that met one or more of the following criteria: (1) grossly purulent fluid; (2) positive fluid culture or positive Gram stain for bacteria; and (3) a pH less than 7.20, a lactate dehydrogenase (LDH) level greater than 1,000 IU/L and a glucose level less than 40 mg/dL. In our facility, video-assisted thoracic surgery (VATS) is considered the standard procedure for empyema management; nonetheless, patients with a thick pleural peel (>2 cm) usually undergo open decortication, and those patients in poor clinical condition undergo chest tube drainage as the primary treatment. Patients with chronic empyema that is not suitable for decortication – mostly because the patient is in poor clinical condition — undergo open-window thoracostomy (11) and were not considered for participation in the present study. The ethics committee of our institution approved the study, and informed consent was waived because the study was a retrospective review of patient charts.

At our hospital, the level of C-reactive protein is measured by nephelometry. The normal range for this assay is less than 10 mg/L; levels were first routinely measured in patients with pleural empyema in 2006. Nevertheless, some wards in our hospital did not start to routinely use CRP until 2007; therefore, some patients did not undergo CRP measurement during the study period. Patients in whom the serum CRP levels were not quantified were deemed to have incomplete records and were excluded from the analysis. The CRP levels were recorded for all patients preoperatively and on the 2^{nd} and 7^{th} days postoperatively. We chose the 2^{nd} and the 7^{th} postoperative days to analyze the serum CRP levels to minimize the number of missing data because CRP measurements are performed as part of a routine protocol in both the ICU and the clinical ward.

The following data were also collected for each patient: age, sex, comorbidities, etiology of the empyema (pneumonia, tuberculosis, thoracic surgery, trauma), treatment modality (tube thoracostomy, VATS, open decortication), axillary temperature, white blood cell count (WBC), requirement for a second surgical procedure and mortality.

The clinical outcome was binary: success or failure. We considered treatment failure to be mortality during the first 30 days after surgery (or during the same hospitalization period) and/or the requirement for a second surgical intervention (VATS, decortication, open drainage) due to persistent sepsis. During the study period, fever, the white blood cell count, hemodynamic parameters, and radiological results were the factors taken into account when considering whether to perform an additional pleural intervention.

Continuous variables are presented as the median (interquartile range) unless otherwise stated. The Shapiro-Wilkes test was used for the assessment of normality. Comparisons between groups of continuous data were performed using the nonparametric Mann-Whitney U-test and the Wilcoxon signed-rank test. A comparison of CRP values over time was performed using the nonparametric bidirectional Friedman test. To compensate for the multiple testing situation, the *p*-value was adjusted using the Bonferroni test. For comparisons among three groups, a *p*-value below 0.016 was considered statistically significant. We used multiple logistic regression to investigate the association between the outcome of interest and the CRP levels. We included age, sex, and comorbidities (chronic cardiac disease, chronic renal failure, diabetes mellitus, systemic arterial hypertension, chronic pulmonary disease, malignant neoplasm, and immunosuppression) in the baseline model. Age and the CRP level were entered into the model as continuous variables, whereas the other variables were coded as binary variables. We could not find CRP values on some patients' charts; three pre-operative measurements (5.8%) and four measurements taken on postoperative day 7 (7.7%) were missing. We assumed that these data were randomly missing and dealt with them using multiple imputation, in which each missing value was replaced with the group's mean. Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, Ill).

RESULTS

Sixty-nine patients with pleural empyema underwent pleural surgical procedures at our institution during the study period. All of these patients were considered for inclusion, but 17 patients were eventually excluded due to incomplete registration information. Therefore, the study group comprised 52 cases. The demographic and clinical characteristics of the patients are presented in Table 1.

The C-reactive protein values before surgery varied from 3.67 to 434.0 mg/L (median = 146.0 mg/L). Only one patient had a normal preoperative CRP level (3.67 mg/L), but he had already been taking intravenous antibiotics for a week before the surgery; all others had preoperative CRP levels far above the normal limit of 10 mg/L. These values tended to decrease during the first week after surgery, but this difference was only statistically significant on day 7 after surgery, as shown in Figure 1. Subgroup analysis showed that in patients undergoing open decortication, the fall in the CRP level was faster. This decrease was noted as soon as day 2 after surgery (pre-op: 199.7 mg/L; postoperative day 2: 90.6 mg/L; POD 7:

Table 1 - Characteristics of the patient population.

Age (years)†	48.0 ± 15.7
Sex (male/female)	36/16
Etiology of empyema	Pneumonia 82.7%
	Thoracic surgery 7.7%
	Tuberculosis 3.8%
	Other* 5.8%
Treatment of empyema	VATS 76.9%
	Open decortication 13.5%
	Tube thoracostomy 9.6%
Comorbidities	
Systemic arterial hypertension	34.6%
Malignant neoplasm	26.9%
Diabetes mellitus	13.5%
Chronic cardiac disease	11.5%
Chronic pulmonary disease	9.6%
Chronic renal failure	7.7%
Immunosuppression	3.8%

†Mean ± std. deviation *Trauma, malignant pleural effusion.

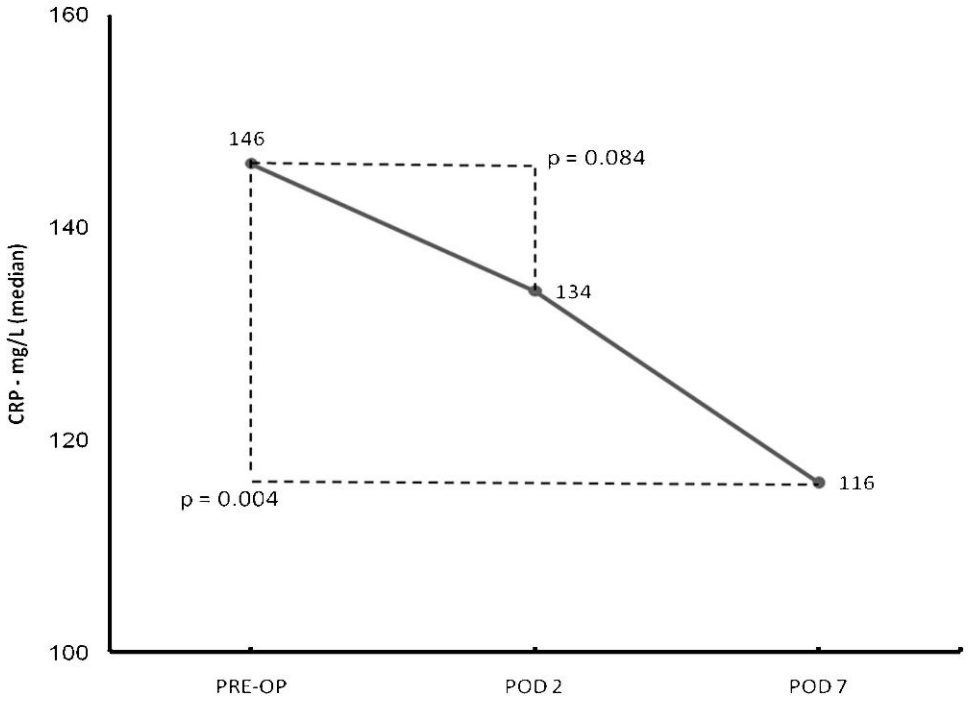

Figure 1 - CRP changes during the first postoperative week.

100.0 mg/L; $p = 0.018$). Moreover, in patients undergoing chest tube drainage and VATS, the fall in CRP was not statistically significant on either POD 2 or POD 7.

Nine patients died (17.3%), and six patients required a second surgery (11.5%). All deaths were caused by septic shock and occurred on average 25 days after surgery. Only two patients died during the first postoperative week, and, interestingly, both displayed a drop in CRP levels – 19% and 50% - relative to the preoperative values. No patient underwent a second pleural intervention during the first postoperative week.

We divided the patients into two groups: successful treatment (69.2%) and failure (30.8%). Over the first week after surgery, the CRP values decreased to a similar extent in both groups ($p = 0.64$; Figure 2). The CRP values and WBC of success and failure groups were not significantly different before surgery or at postoperative days 2 and 7 (Table 2).

We were unable to find any association between the preoperative or first postoperative week CRP levels (POD 2, POD 7) and the clinical outcome (death and/or reoperation). Multivariate logistic regression revealed that only the presence of chronic renal failure ($p = 0.008$) and chronic pulmonary disease ($p = 0.029$) were independently associated with an increased risk of death and/or reoperation in these patients.

DISCUSSION

This study showed that, in a population of patients with PE surgically treated in a tertiary hospital, the CRP levels fall slowly during the first week after surgery and are significantly reduced on POD 7. We also noticed that the CRP levels and the WBC, measured before surgery and on POD 2 and POD 7, were not associated with outcome (mortality and/or reoperation).

C-reactive protein is an acute-phase protein synthesized by the liver in response to tissue damage. Interleukin-6 (IL-6) is thought to be the primary trigger of CRP release, although tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), and other cytokines are thought to be involved. The secretion of CRP begins within 4-6 hours of the stimulus, doubling every 8 hours and peaking at 36-50 hours. After the disappearance or removal of the stimulus, the CRP level falls rapidly, as it has a half-life of 19 hours. However, the CRP level can remain elevated, even for very long periods, if the underlying cause of the elevation persists (1). The evaluation of a single CRP measurement is useful in the diagnosis of sepsis and as a prognostic marker. Nevertheless, following its evolution over the duration of a hospital stay can be more helpful in diagnosis and in the monitoring of the response to therapy.

Some studies have shown that in patients with community-acquired pneumonia, a decrease of 50% or more in the CRP level at day 4 (after starting antibiotics) is usually observed in patients in whom treatment has been successful. Therefore, the CRP level after the start of antibiotic administration seems to be a good marker of prognosis (3,4). In our study, CRP was not so useful during the first week after the surgical treatment of PE: a significant decrease (40%) in the CRP level was only observed at day 7 after surgery. Similar results were obtained by Carboni et al. (9), who analyzed 22 patients undergoing surgery for pleural empyema. The CRP values decreased slowly: on day 7, only 12 patients had CRP values of 100 mg/L or below. Furthermore, CRP measurement could not discriminate between patients with and without sepsis during the postoperative period. The authors suggested that procalcitonin is a more appropriate laboratory parameter than CRP when monitoring the postoperative course of these patients.

The slow decline of the CRP level observed in our study after surgical treatment of PE might be explained by two technical features of this type of therapy. First, the surgery itself can lead to substantial elevation of the CRP

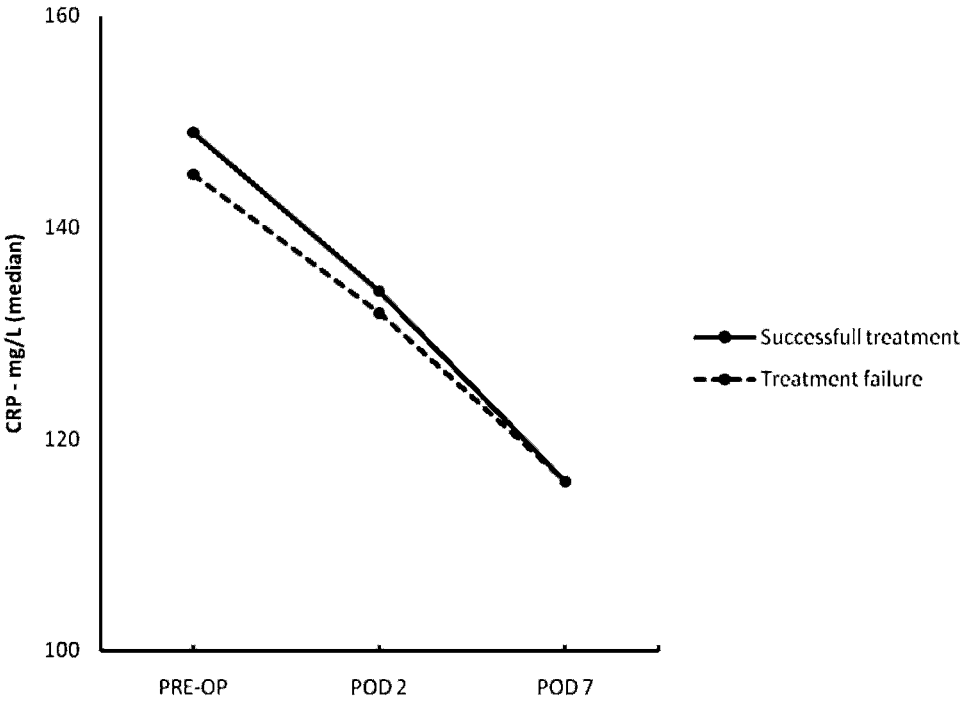

Figure 2 - The CRP pattern of change according to outcome.

concentration (1), which could counter-balance the decrease in the CRP level induced by the control of sepsis and therefore contribute to the slow postoperative fall in CRP levels. In the study by Icard et al. (10), which evaluated the utility of CRP measurements for empyema diagnosis after pneumonectomy, even in patients without postoperative complications, there was a rapid postoperative rise in the CRP levels until a peak or plateau was reached within 3 to 6 days, followed by a progressive decline to a value of less than 75 mg/L on day 9 and less than 50 mg/L on day 12. Second, the surgery for pleural empyema frequently does not remove all of the infected tissue. This surgery allows for the debridement and removal of adhesions, which allows for adequate drainage of the pleural space, but complete resolution of the infection may take several days. Moreover, full lung expansion – one of the goals of therapy – is not frequent after video thoracoscopy or chest tube drainage in patients with malignant pleural effusion (12); we would expect a similar trend after PE treatment. One fact that reinforces the hypothesis of slow intrapleural sepsis control is the observation that CRP levels fall faster after open decortications; an open technique would allow for more effective cleaning of the pleural cavity, and, therefore, a faster decrease in the CRP level.

The main limitation of our study is the retrospective design based on chart review, which resulted in many losses due to incomplete registries. The small sample size is also a limitation in terms of obtaining significant results. Given the limited number of missing data (<10%) and the fact that these data were missing at random, the imputation method (in which each missing value is replaced with the mean of the group) may lead to an overestimation of the association of interest. Another significant limitation is the fact that some patients had already had some sort of medical treatment prior to the surgical treatment, many of them elsewhere. This prior treatment may have interfered with the preoperative CRP levels measured in the present study.

Our data suggest that neither the preoperative nor the first postoperative week CRP serum levels in patients who underwent an invasive treatment for pleural empyema correlate with the final outcome (reoperation or death). Finally, we observed that, in contrast to the case for other medical conditions, CRP levels fall slowly during the first postoperative week in patients who undergo surgical treatment for PE. We should expect a slow decline during the first several days after surgery, and a significant 40% difference – relative to the preoperative values – will be reached on approximately the seventh day.

Table 2 - CRP and WBC values in patients in which treatment was successful or failed.

	Successful treatment group (n = 36)	Treatment failure group (n = 16)	*p*-value
CRP before surgery	149.0 (111.2-187.7)	145.0 (92.1-230.4)	0.835
CRP on POD 2	134.0 (86.9-172.0)	131.9 (96.4-163.7)	0.781
CRP on POD 7	116.0 (82.0-154.0)	116.0 (73.2-171.5)	0.843
WBC before surgery	11.87(7.53-16.52)	12.02 (8.84-16.08)	0.905
WBC on POD 2	11.98 (10.01-16.81)	13.73 (6.51-17.30)	0.736
WBC on POD 7	9.65 (6.89-11.68)	9.66 (7.23-14.30)	0.912

CRP: C-reactive protein (mg/L); WBC: white blood cell count (x 1,000/mm^3); POD: postoperative day.
Values are expressed as the median (interquartile range: 25-75).

AUTHOR CONTRIBUTIONS

Medeiros IL, Terra RM contributed to the study design, data collection and manuscript writing. Choi EM contributed to data collection and manuscript writing. Pego-Fernandes PM contributed to study design, data analysis and manuscript revision. Jatene FB contributed to study design and manuscript revision.

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