C-Reactive Protein Levels Correlate With Mortality and Organ Failure in Critically Ill Patients*

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Study objectives: C-reactive protein (CRP) is an acute-phase protein, the blood levels of which increase rapidly in response to infection, trauma, ischemia, burns, and other inflammatory conditions. Although used frequently in the ICU as a sepsis marker, the relation of CRP levels to organ damage is not well known. This study assessed the association between early serum CRP concentrations and the development of organ failure and mortality in ICU patients.

Design: A prospective cohort study.

Setting: A 31-bed ICU in a university hospital.

Patients: All 313 patients admitted to the ICU during the 4-month study period.

Interventions: None.

Measurements and results: Patients with high CRP levels at ICU admission had more severe organ dysfunction (higher sequential organ failure assessment scores, days of renal extracorporeal support therapy), longer ICU stays, and higher mortality rates than patients with normal ICU admission CRP levels. CRP concentrations were correlated with the presence and number of organ failures. ICU admission serum CRP levels > 10 mg/dL were associated with a significantly higher incidence of respiratory (65% vs 28.8%, p < 0.05), renal (16.6% vs 3.6%, p < 0.05), and coagulation (6.4% vs 0.9%, p < 0.05) failures, and with higher mortality rates (36% vs 21%, p < 0.05) than CRP levels < 1 mg/dL. In patients with CRP concentrations > 10 mg/dL on ICU admission, a decrease in CRP level after 48 h was associated with a mortality rate of 15.4%, while an increased CRP level was associated with a mortality rate of 60.9% (relative risk, 0.25; 95% confidence interval, 0.07 to 0.91; p < 0.05).

Conclusions: In a heterogeneous ICU population, elevated concentrations of serum CRP on ICU admission are correlated with an increased risk of organ failure and death. Moreover, persistently high CRP concentrations are associated with a poor outcome. Serial measurements may be helpful to identify those patients who require more aggressive interventions to prevent complications. (CHEST 2003; 123:2043–2049)

Key words: ICU; outcome; sepsis marker; sequential organ failure assessment

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; CRP = C-reactive protein; IL = interleukin; NS = not significant; RR = relative risk; SOFA = sequential organ failure assessment

Multiple organ dysfunction is a major cause of death in ICU patients. A number of inflammatory cells and mediators involved in the inflammatory response have been assessed for their role as potential markers of the presence and severity of the inflammatory response and organ failure. Serum levels of C-reactive protein (CRP), an acute-phase protein synthesized by the liver following stimulus by various cytokines including tumor necrosis factor-α and interleukin (IL)-6, markedly increase within hours after infection or inflammation. Numerous studies have demonstrated increased CRP levels in patients with sepsis, but their relation to multiple organ dysfunction and failure has not been well evaluated. Some studies have suggested that CRP may be an indicator of organ dysfunction.
failure.18–22 Pinilla et al18 demonstrated a strong correlation between the ratio of CRP to prealbumin and the severity of organ dysfunction in critically ill patients. Waydhas et al19 reported that, in poly-trauma patients, high CRP levels after a second insult, *ie*, a surgical procedure, were related to the development of organ failure. Other investigators have reported CRP levels to be associated with multiple organ dysfunction in patients with acute pancreatitis.20–22 We studied the relationship between early CRP measurements and the severity of organ dysfunction and mortality in a heterogeneous group of ICU patients.

**Materials and Methods**

During a 4-month period (from April to July 1999), we prospectively studied 313 consecutive patients admitted to the ICU for > 48 h. Six patients were excluded for a missing ICU admission CRP level. The remaining 307 patients were classified arbitrarily into three groups according to their ICU admission CRP level: group 1, CRP of < 1 mg/dL (n = 110); group 2, CRP of 1 to 10 mg/dL (n = 119); and group 3, CRP of > 10 mg/dL (n = 78).

Serum CRP levels were measured using an immunochemistry analyzer (IM Modular; Hitachi; Tokyo, Japan). The APACHE (acute physiologic and chronic health evaluation) II score23 was calculated on ICU admission. Organ function was evaluated daily according to the sequential organ failure assessment (SOFA) score.24 For each of the six organ systems included in the SOFA score (respiratory, cardiovascular, neurologic, renal, hematologic, and hepatic), organ failure was defined as a score of ≥ 3. Infection was diagnosed according to usual clinical, laboratory, and microbiological parameters.25

Results are expressed as mean ± SD. Continuous variables were compared with analysis of variance for repeated measurements. Proportions were compared using the Z test. Relative risk (RR) and 95% confidence intervals (CIs) were calculated. The incidence of death was estimated by the Kaplan-Meier method, and significance was calculated with the log-rank test. A P value < 0.05 was considered statistically significant.

**Results**

Demographic and outcome data are presented in Table 1. Patients with high CRP levels had significantly higher SOFA scores, days of renal extracorporeal support therapy, infection, mortality rates, and ICU stays than patients with normal CRP levels. The incidence of infection was directly related to the CRP level on ICU admission (Table 1). In the whole group, patients with infection had significantly higher CRP levels on ICU admission (9.5 ± 10.8 mg/dL vs 4.5 ± 6.9 mg/dL, P < 0.05) and at 48 h (12.8 ± 9.1 mg/dL vs 10.0 ± 8.3 mg/dL, P < 0.05) than noninfected patients.

The 223 patients (73%) who had at least one organ failure during their ICU stay had significantly higher ICU admission CRP levels than the 84 patients (27%) with no organ failure (8.4 ± 10.3 mg/dL vs 3.2 ± 4.8 mg/dL, P < 0.05). The number of organs failing during the ICU stay increased with increasing CRP concentrations, both at ICU admission and at 48 h (Fig 1). The incidence of coagulation failure was directly proportional to ICU admission CRP levels (Table 2). Coagulation failure was uncommon in patients with ICU admission CRP concentrations < 1 mg/dL (0.9%); it was twice as common for ICU admission CRP levels in the range of 1 to 10 mg/dL (2.5%), and seven times higher ICU for admission CRP values > 10 mg/dL (6.4%). At 48 h, CRP levels > 10 mg/dL were associated with a significantly higher incidence of respiratory and cardiovascular dysfunction than CRP levels < 1 mg/dL (Table 2).

The overall mortality rate was 24%. Nonsurvivors had significantly higher CRP levels than survivors at ICU admission (10.0 ± 11.0 mg/dL vs 6.0 ± 8.5 mg/dL, P < 0.05) and at day 2 (15.8 ± 9.2 mg/dL vs 10.1 ± 8.2 mg/dL, P < 0.05) [Fig 2]. Patients with CRP concentrations between 1 mg/dL and 10 mg/dL on ICU admission, in whom the serum CRP concentration was unchanged or decreased after 48 h (n = 21), had similar APACHE II scores (14.9 ± 6.0 vs 15.3 ± 7.4, not significant [NS]) but lower SOFA ICU admission (4.0 ± 3.1 vs 6.1 ± 3.1, P < 0.05) and SOFA maximum (6.5 ± 4.9 vs 8.6 ± 4.1, P < 0.05) scores, and a nonsignificant lower mortality rate (8.7% vs 19.6%; RR, 2.25; 95% CI, 0.56 to 8.99; NS), than those whose CRP levels increased on day 2 (n = 98). Patients with CRP concentrations > 10 mg/dL on ICU admission in whom the serum concentration decreased after 48 h (< 10 mg/dL) had no differences in APACHE II score (14.0 ± 5.4 vs 15.6 ± 7.7, NS), SOFA ICU

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**Table 1—Demographic Data and Outcome in Relation to CRP Levels at ICU Admission**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (CRP &lt; 1 mg/dL)</th>
<th>Group 2 (CRP 1–10 mg/dL)</th>
<th>Group 3 (CRP &gt; 10 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No. (%)</td>
<td>110 (36)</td>
<td>119 (39)</td>
<td>78 (25)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>56 ± 16</td>
<td>59 ± 18</td>
<td>58 ± 16</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>6.5 ± 6.1</td>
<td>8.4 ± 8.7</td>
<td>9.1 ± 6.8</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>13.9 ± 6.3</td>
<td>15.2 ± 7.1</td>
<td>15.2 ± 7.3</td>
</tr>
<tr>
<td>SOFA ICU admission</td>
<td>4.9 ± 3.0</td>
<td>5.7 ± 3.2</td>
<td>6.6 ± 3.6</td>
</tr>
<tr>
<td>SOFA day 2</td>
<td>5.4 ± 3.6</td>
<td>6.8 ± 7.4</td>
<td>7.6 ± 4.9</td>
</tr>
<tr>
<td>SOFA maximum</td>
<td>6.6 ± 3.5</td>
<td>8.2 ± 4.3</td>
<td>8.8 ± 4.6</td>
</tr>
<tr>
<td>Ventilator days, No.</td>
<td>2.5 ± 6.3</td>
<td>2.8 ± 5.3</td>
<td>3.8 ± 6.6</td>
</tr>
<tr>
<td>REST days, No.</td>
<td>0.3 ± 0.8</td>
<td>1.0 ± 2.3</td>
<td>1.4 ± 2.3</td>
</tr>
<tr>
<td>Infected patients, No. (%)</td>
<td>34 (31)</td>
<td>66 (56)</td>
<td>57 (73)</td>
</tr>
<tr>
<td>Deaths, No. (%)</td>
<td>23 (21)</td>
<td>21 (18)</td>
<td>28 (36)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.

†p < 0.05 vs group 1.

‡p < 0.05 vs group 2.

REST = renal extracorporeal support therapy.
admission (5.7 ± 3.7 vs 7.2 ± 3.5, NS) score, or maximum SOFA (7.6 ± 5.2 vs 9.7 ± 4.4, NS) scores, but had a lower mortality rate (15.4% [2 of 13 patients] vs 60.9% [39 of 64 patients]) compared with those whose CRP levels increased on day 2 (>10 mg/dL) [RR, 0.25; 95% CI, 0.07 to 0.91; p < 0.05]. Nevertheless, and as anticipated, the predictive value of CRP for mortality was not as good as the APACHE II or SOFA scores (Fig 3).

**DISCUSSION**

CRP is a marker of inflammation that has been used to monitor the course of infection and inflammatory diseases. Recently, CRP has been seen not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response. In this context, we evaluated the correlation of CRP levels with organ failure and mortality early after ICU admission in a heterogeneous group of ICU patients. We found that increased CRP concentrations were associated with organ failure, prolonged ICU stay, and high infection and mortality rates. CRP concentrations >10 mg/dL on ICU admission were associated with a particularly high mortality. Increasing or persistently high levels, suggesting ongoing inflammatory activity, indicated a poor prognosis, while declining values, suggesting a

**Table 2—Incidence of Organ Failures (SOFA Score 3 or 4) on ICU Admission (Day 0) and the Second ICU Day (Day 2), According to CRP Level***

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (CRP &lt; 1 mg/dL)</th>
<th>Group 2 (CRP 1–10 mg/dL)</th>
<th>Group 3 (CRP &gt; 10 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>0 (28.8)</td>
<td>50 (42)</td>
<td>78 (142)</td>
</tr>
<tr>
<td>Renal</td>
<td>0 (3.6)</td>
<td>12 (10)</td>
<td>13 (16.6)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>2 (7.1)</td>
<td>7 (5.1)</td>
<td>22 (15.4)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0 (1.0)</td>
<td>3 (2.5)†</td>
<td>5 (6.4)†</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (3.5)</td>
<td>10 (2.7)</td>
<td>12 (8.4)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>0 (22.5)</td>
<td>29 (24.3)</td>
<td>15 (19.2)</td>
</tr>
<tr>
<td></td>
<td>2 (14.2)</td>
<td>23 (16.9)</td>
<td>34 (23.9)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.
†p < 0.05 vs group 1.
‡p < 0.05 vs group 2.
diminishing inflammatory reaction, were associated with a more favorable prognosis. Hence, trends in CRP concentrations during the first 48 h of ICU admission can be important in helping to decide whether or not further, more invasive, diagnostic procedures are needed and whether therapeutic interventions should be maintained or modified.

Evaluating changes in variables over time may be very helpful to assess the effects of interventions, as has been shown for organ dysfunction scoring systems. Lopes Ferreira et al reported that an increase in SOFA score during the first 48 h in the ICU predicts a mortality rate of at least 50%, while a decreasing SOFA score is associated with a decrease in mortality rates from 50 to 27%. In patients with sepsis, Presterl et al demonstrated a correlation between the plasma levels of CRP, IL-6 and tumor necrosis factor-sR, and the APACHE III and mortality probability model II scores. Both scoring systems, as well as CRP levels, were significantly higher in the nonsurvivors compared with the survivors. Nonsurvivors had significantly higher CRP levels from day 3 onwards. Our findings on the relation between the peak concentrations of CRP and the number of organs failing indicate that both these parameters are useful indicators of severity and prognosis.

CRP is predominantly produced and secreted by hepatocytes, although other cells including alveolar macrophages may also synthesize CRP. CRP is thought to represent a measure of cytokine-induced protein synthesis. Due to the fast rise in CRP concentrations, critically ill patients will often already have raised CRP levels on ICU admission. The relatively short half-life of approximately 19 h makes it a useful monitor for follow-up of inflammatory response, infection, and antibiotic treatment. In addition, laboratory tests for CRP are easily available and less costly than cytokine tests.

Previous reports have reported CRP levels to be a prognostic index in different entities, including ischemic stroke, acute pancreatitis, IgA nephropathy, terminal renal failure, and cardiovascular diseases. Bonig et al reported that CRP levels > 10 mg/dL were predictive of poor outcome after hematopoietic stem cell transplantation in children. Chronic inflammation plays a role in the pathogenesis of cardiovascular diseases and elevated serum levels of CRP are associated with an increased risk of myocardial infarction and sudden cardiac death in apparently healthy subjects. Zimmermann et al reported that high CRP levels in hemodialysis patients were closely related to high levels of vascular atherogenic risk factors and cardiovascular deaths. Serum concentrations of CRP and IL-6 have been shown to be inversely related to renal function in the predialytic phase of renal failure. In the present study, high CRP levels at ICU admission were associated with more days of receiving extracorporeal support.

CRP may be more than an indicator of inflammation and has been shown to be involved in multiple immunoregulatory functions, acting on the complement cascade, opsonizing bacteria for phagocytosis, and stimulating phagocytic cells. Expression of human CRP by CRP transgenic mice is protective against lethal infection by Streptococcus pneumoniae, an effect likely mediated by the ability of CRP to bind to this Gram-positive pathogen. In addition, in vivo, complement and CRP amplify the protective capacity of each other, particularly during the early course of infection.

Although CRP is largely proinflammatory, it may...
have immunosuppressive effects in some tissue compartments; for example, polymorphonuclear blood monocytes cells release IL-1β and IL-1 receptor antagonist in response to CRP or lipopolysaccharide. However, when combined with lipopolysaccharide, CRP can inhibit IL-1 and IL-1 receptor antagonist release in lung macrophages. Elevation in serum CRP may be a mechanism to control acute inflammation by down-regulating some neutrophil functions. Serum from high-risk and ARDS patients has significantly less neutrophil chemotactic activity than serum from normal subjects. In isolated rabbit lungs, Abernathy et al reported that CRP could prevent increases in pulmonary artery pressure and permeability induced by stimulated polymorphonuclear cells, and, in animal models of alveolitis, CRP inhibits neutrophil influx, protects lung tissue from vascular injury induced by activated polymorphonuclear cells.

Figure 3. Receiver operating characteristics curves showing that CRP levels have a lower predictive value than APACHE II and SOFA scores on ICU admission (top, A) and after 48 h (bottom, B).
clear cells, and prevents increases in vascular permeability.46 CRP also may be an important modulator of platelet activation.51–53

The present study is the first to detail the relation between CRP concentrations and the severity and pattern of multiple organ dysfunction in ICU patients. We can conclude that CRP levels are a good early marker of morbidity and mortality in these patients. In addition, CRP concentrations may be a valuable addition to APACHE II scores to predict the risk of death, as the APACHE scores for all three groups were similar on ICU admission, yet there were more deaths in the group with higher CRP levels than in the other two groups. Serial measurements of CRP concentrations in critically ill patients may help to identify patients who may require more aggressive diagnostic and therapeutic interventions to avoid complications. CRP concentrations may also be helpful in clinical trials, to identify high-risk patients who would benefit from new therapeutic interventions.

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