CHEST

Original Research

CRITICAL CARE MEDICINE

Plasma C-Reactive Protein Levels Are Associated With Improved Outcome in ARDS

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Background: **C-reactive protein (CRP) has been studied as a marker of systemic inflammation and outcome in a number of diseases, but little is known about its characteristics in ARDS. We sought to examine plasma levels of CRP in patients with ARDS and their relationship to outcome and measures of illness severity.**

Methods: **We measured CRP levels in 177 patients within 48 h of disease onset and tested the association of protein level with 60-day mortality, 28-day daily organ dysfunction scores, and number of ventilator-free days.**

Results: **We found that CRP levels were significantly lower in nonsurvivors when compared with survivors ($p = 0.02$). Mortality rate decreased with increasing CRP decile ($p = 0.02$). An increasing CRP level was associated with a significantly higher probability of survival at 60 days ($p = 0.005$). This difference persisted after adjustment for age and severity of illness in a multivariable model ($p = 0.009$). Multivariable models were also used to show that patients in the group with higher CRP levels had significantly lower organ dysfunction scores ($p = 0.001$) and more ventilator-free days ($p = 0.02$).**

Conclusions: **Increasing plasma levels of CRP within 48 h of ARDS onset are associated with improved survival, lower organ failure scores, and fewer days of mechanical ventilation. These data appear to be contrary to the established view that CRP is solely a marker of systemic inflammation.** ***(CHEST 2009; 136:471–480)***

Abbreviations: ALI = acute lung injury; APACHE = acute physiology and chronic health evaluation; CAD = coronary artery disease; CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; IQR = interquartile range; MODS = multiple organ dysfunction score

C-reactive protein (CRP) is a 21-kd protein that is synthesized primarily in the liver and found in blood plasma. Originally extracted from the blood of patients with pneumonia, CRP was the first of the acute-phase reactant proteins to be discovered.[1] Plasma CRP levels undergo a rapid and robust rise in response to inflammatory stimuli. Because of this phenomenon, plasma levels of CRP have long been considered to be an important biomarker for detecting the presence of systemic inflammation.[2] Measurement of CRP level has been shown to have prognostic and/or diagnostic value in a large number of disease states, including sepsis, pneumonia, appendicitis, coronary artery disease (CAD), stroke,

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diabetes, and rheumatic disease, among others.[3–7] In most cases, higher CRP levels have been associated with adverse outcomes.

ARDS is an inflammatory process in the lung that occurs in response to pulmonary or extrapulmonary injury.[8] In recent years, a number of studies[9–11] have focused on defining the role of plasma mediators or markers of inflammation and their association with phenotype and outcome in this disease. However, despite the body of literature connecting CRP with prognosis in other diseases, little is known about the characteristics of CRP levels in patients with ARDS and acute lung injury (ALI). In addition, *in vitro* and animal-model studies[12–17] have suggested that CRP may play a pathogenic role by inhibiting neutrophil chemotaxis or modulating vascular permeability in ways that could potentially be protective in patients with these diseases.

Therefore, to further evaluate the clinical implications of these relationships, we sought to study the characteristics of plasma CRP levels in patients with early ARDS. We conducted a prospectively enrolled observational study in the ICUs of a large academic medical center.

Materials and Methods

Study Design and Enrollment

The study was performed in the context of an ongoing study of the molecular epidemiology of ARDS. Adult patients admitted to ICUs at Massachusetts General Hospital from September 1999 to May 2005 were considered for enrollment in a prospective cohort of patients at-risk for ARDS if they had any ARDS risk factor, with no exclusion criteria. Risk factors and exclusion criteria are as previously defined.[18] Informed written consent was obtained from patients or surrogates. Patients who developed ARDS according to American–European Consensus Committee criteria[19] were included. The study was approved by the Human Subjects Committee of our institution.

Table 1—*Characteristics of the Study Population*

Characteristics	Survivors (n = 107)	Nonsurvivors (n = 70)	p Value
Demographic data			
Age, yr*	56.0 (29.0)	71.5 (21.0)	< 0.0001
Female gender†	51 (48)	28 (40)	0.35
White†	99 (93)	66 (94)	0.64
Health status data†			
Acute hepatic failure		4 (5.7)	0.01
Cirrhosis	2 (1.9)	8 (11.4)	0.007
Corticosteroid therapy	14 (13)	16 (23)	0.10
Diabetes history	25 (23)	15 (21)	0.74
Smoking history	59 (66)	40 (65)	0.89
Metastatic solid-organ malignancy	3 (2.8)	2 (2.8)	0.99
Etiology of ARDS (some patients had multiple etiologies)†			
Pneumonia	79 (75)	53 (76)	0.86
Septic shock	58 (55)	46 (66)	0.18
Sepsis (without shock)	34 (32)	19 (27)	0.49
Trauma	6 (6)	1 (1)	0.16
Aspiration	8 (8)	8 (11)	0.38
Multiple transfusions	8 (8)	6 (9)	0.81
Baseline physiologic variables*			
Aggregate APACHE III score	73.0 (28.0)	90.0 (30.0)	< 0.0001
Lowest WBC count (1,000/μL)	12.1 (9.2)	11.6 (10.0)	0.61
Highest WBC count (1,000/μL)	16.1 (9.8)	16.4 (13.0)	0.70
Lowest mean arterial pressure, mm Hg	58.0 (9.0)	56.0 (9.0)	0.04
Serum BUN, mg/dL	23.0 (23.0)	34.0 (30.0)	0.03
Serum creatinine, mg/dL	1.2 (1.0)	1.5 (1.4)	0.59
24-h urine output, mL	1,687.5 (1478.0)	1,214.0 (1230.0)	0.008
Serum total bilirubin, mg/dL	0.7 (0.7)	0.90 (2.0)	0.01
RBC units transfused	1.5 (3.0)	2 (4.0)	0.16
Platelet count	178.0 (147.0)	193.5 (187.0)	0.35
APACHE III oxygenation score‡	11.0 (5.0)	12.5 (5.0)	0.75
APACHE III acid-base abnormality score§	3.0 (4.0)	4.0 (7.0)	0.04

*Values are presented as median (IQR).

†Values are given as No. (%).

‡APACHE III oxygenation score reflects either PaO_2 or alveolar-arterial oxygen pressure difference depending on patient status; higher scores reflect lower PaO_2 or higher alveolar-arterial oxygen pressure difference.

§APACHE III acid-base derangement score is computed from pH and $PaCO_2$; higher scores reflect greater derangement from normal values.

Data Collection

Demographic data were collected at baseline, as well as data used for acute physiology and chronic health evaluation (APACHE) III score calculation according to the methods of the APACHE investigators.[20] Patients were screened on each ICU day for ARDS. Data were recorded until ICU discharge or for 28 days if the patient remained in the ICU. Patients were followed for the primary endpoint of 60-day mortality. Secondary endpoints were daily multiple organ dysfunction score (MODS), calculated as defined by Brussels criteria,[21] and number of days free of mechanical ventilation.

Sample Collection and Testing

Blood samples were taken in ethylenediaminetetraacetic acid-treated plasma from within 48 h of fulfillment of all ARDS criteria and stored at a temperature of −80°C until testing. CRP levels were tested by using a high-sensitivity immunoassay (Hitachi 917 analyzer; Roche Diagnostics; Indianapolis, IN) according to manufacturer protocols.

Statistical Analysis

Statistical analyses were performed by using a statistical software package (SAS, version 9.1.3; SAS Institute; Cary, NC). p Values of < 0.05 were considered statistically significant for all analyses. Univariate analyses were performed by using χ^2 tests, two-sample *t* tests, or Wilcoxon rank-sum tests as appropriate. CRP levels were log-transformed to achieve normality. Patients were divided into 10 groups by increasing CRP level, and the association of increasing CRP level with mortality was evaluated by using the Cochrane–Armitage χ^2 test of trend.

Cox proportional hazards modeling was used to compare the association of log-transformed CRP level with survival, adjusted for other variables of interest. We planned *a priori* to adjust this analysis for age and severity of illness (as measured by APACHE III score). The age component was subtracted from APACHE III scores to avoid co-linearity between these variables. Other variables of clinical relevance, potential confounders, or those with significant differences between groups on univariate analysis were considered for inclusion in the model by using a backward stepwise selection algorithm with $p \leq 0.2$ as the cutoff for inclusion. Factors considered included all baseline demographic, chronic health, etiologic, and physiologic variables with significant differences between survivors and nonsurvivors as listed in Table 1. The diagnoses of pneumonia and of trauma were evaluated in the model to address concerns of confounding; both variables dropped out because they did not meet the threshold for inclusion. Receipt of corticosteroid therapy was forced into the model. One additional variable, presence of acute hepatic failure, met criteria for inclusion in the model. All covariates in

Table 2—*Differences in Baseline Characteristics Between Tested and Nontested Patients*

Characteristics	Tested (n = 177)	Nontested (n = 245)	p Value
Demographic data			
Age, yr*	62.5 (29.0)	62.0 (27.0)	0.42
Female gender†	77 (44)	93 (38)	0.20
White†	162 (93)	223 (91)	0.44
Health status data†			
Acute hepatic failure	4 (2)	7 (3)	0.71
Cirrhosis	10 (6)	13 (5)	0.86
Corticosteroid therapy	29 (16)	20 (8)	0.007
Diabetes history	39 (22)	42 (18)	0.20
Smoking history	99 (66)	125 (68)	0.76
Metastatic solid-organ malignancy	5 (3)	7 (3)	0.99
Etiology of ARDS (some patients had multiple etiologies)†			
Pneumonia	130 (75)	150 (61)	0.004
Septic shock	103 (59)	142 (58)	0.80
Sepsis (without shock)	53 (30)	60 (24)	0.17
Trauma	7 (4)	25 (10)	0.02
Aspiration	16 (9)	23 (9)	0.95
Multiple transfusions	14 (8)	24 (10)	0.54
Baseline physiologic variables*			
Aggregate APACHE III score	79.5 (30.0)	76.0 (32.0)	0.10
Lowest WBC count (1,000/μL)	12.1 (8.9)	8.1 (8.8)	0.27
Highest WBC count (1,000/μL)	16.3 (11.6)	15.8 (10.2)	0.50
Lowest mean arterial pressure, mm Hg	57.0 (9.0)	57.0 (13.0)	0.52
Serum BUN, mg/dL	25.0 (25.0)	23.0 (25.5)	0.33
Serum creatinine, mg/dL	1.3 (1.0)	1.3 (1.5)	0.21
24-h urine output, mL	1,535 (1,474)	1,512 (1,495)	0.84
Serum total bilirubin, mg/dL	0.8 (1.0)	0.8 (1.1)	0.46
RBC units transfused	1.5 (3.0)	1.0 (3.0)	0.86
Platelet count	186 (164)	184 (166)	0.75
APACHE III oxygenation score‡	11.0 (5.0)	11.0 (9.0)	0.07
APACHE III acid-base abnormality score§	3.0 (4.0)	3.0 (5.0)	0.38

*Values are presented as median (IQR).

†Values are given as No. (%).

‡APACHE III oxygenation score reflects either PaO_2 or alveolar-arterial oxygen pressure difference depending on patient status; higher scores reflect lower PaO_2 or higher alveolar-arterial oxygen pressure difference.

§APACHE III acid-base derangement score is computed from pH and $PaCO_2$; higher scores reflect greater derangement from normal values.

the final model were tested to ensure that they did not violate the proportional hazards assumption.

The Youden method[22] was used to select an "optimal" CRP level for predicting mortality. Patients were segregated into two groups according to this cutpoint (226 mg/L) for stratified analyses. Kaplan–Meier curves were constructed by using these strata and compared using log-rank testing. Daily MODSs, compared between CRP strata, were modeled by using a linear mixed-effects model (PROC MIXED in SAS 9.1.3)[23] with age and admission APACHE III score included as fixed effects and daily MODSs as repeated measures. An unstructured covariance matrix was assumed. The number of ventilator-free days was studied against CRP level by using a generalized linear model including age and admission APACHE III score as covariates.

Results

Study Population and CRP Levels

During the study period, 1,427 patients with eligible risk factors and no exclusion criteria were enrolled in the cohort and followed for development of ARDS. A total of 418 patients developed ARDS. Largely because of delays in obtaining surrogate consent, or because the first 48 h of ARDS occurred at an outside institution, not all patients could be enrolled within 48 h of ARDS onset. A total of 177 enrolled patients had blood drawn and were included in this study. Median length of time between admission and development of ARDS was 1 day with an interquartile range (IQR) of 2 days.

Excluded patients were compared with tested patients across the spectrum of demographic, chronic health, etiologic, and physiologic variables listed in Table 2, as well as across individual APACHE III components. Mortality was similar between studied and excluded patients (40% vs 40%, respectively; $p = 0.99$). There were no significant differences between studied patients and nonparticipants in terms of demographic or physiologic characteristics (full results are presented in Table 1). Study patients were significantly more likely to have pneumonia than nonparticipants (75% vs 61%, respectively; $p = 0.004$), less likely to have trauma (4% vs 10%, respectively; $p = 0.02$), and more likely to have received corticosteroids (16% vs 8%, respectively; $p = 0.01$). Inclusion criteria for the cohort had changed early in the study to allow patients who had received corticosteroid therapy.[18]

Baseline characteristics of the study population, shown in Table 1, are sorted by primary outcome of survival at 60 days after onset of ARDS. Survivors were significantly younger than nonsurvivors and had significantly lower severity of illness as measured by APACHE III score but otherwise did not differ in terms of the characteristics studied. The overall mortality rate was 40%. Median CRP concentration in the study population was 155 mg/L (IQR, 160 mg/L).

Patients with pneumonia had significantly lower CRP levels than those without (median, 137.5 mg/L [IQR, 162.0] vs median, 181.5 mg/L [IQR, 121.0], $p = 0.01$), but there was not a significant difference in mortality between them (40% with pneumonia vs 38% without, $p = 0.86$). Patients with trauma had no significant difference in CRP level ($p = 0.73$) or in mortality (14% vs 41%, respectively; $p = 0.16$), although the number of trauma patients in the study was small.

ARDS Outcomes and CRP Levels

When segregated by the primary outcome of survival at 60 days, CRP levels were significantly higher in ARDS survivors vs nonsurvivors (median, 176.5 mg/L [IQR, 173.0] vs median, 133.5 mg/L [IQR, 161.0], $p = 0.02$) [Fig 1]. Dividing patients by increasing CRP level demonstrated that mortality

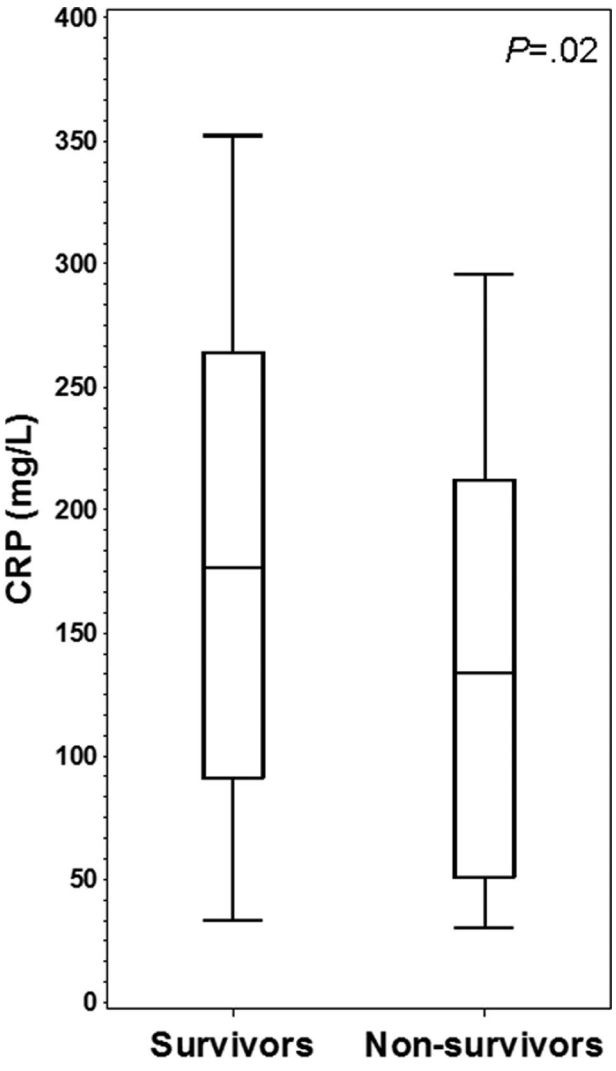

Figure 1. Plasma CRP levels compared between ARDS survivors and nonsurvivors (p value stated for Wilcoxon rank-sum test; vertical bars represent 5 to 95% range).

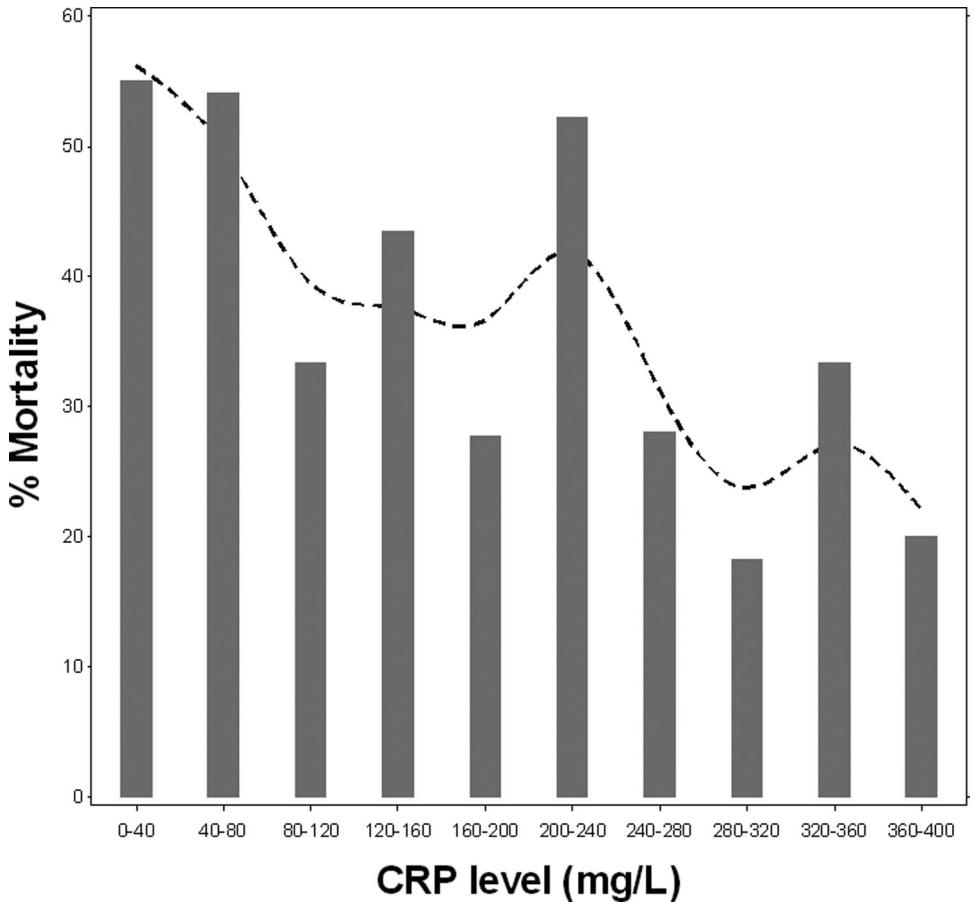

FIGURE 2. Plot of % mortality by log-CRP decile. Superimposed dashed trend line represents a fitted spline interpolated using a cubic function.

decreased with increasing category; this association was statistically significant ($p = 0.02$) and is represented graphically in Figure 2.

Kaplan–Meier curves demonstrating probability of survival of > 60 days in each stratum are shown in Figure 3. When compared using the log-rank test, patients with higher CRP levels had significantly better survival time ($p = 0.005$).

In an unadjusted Cox proportional hazards model, an increasing log-transformed CRP level was associated with a decreased hazard of 60-day mortality (hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.65 to 0.98; $p = 0.03$). The results of the full Cox model are shown in Table 3, demonstrating that this association persisted after adjusting for covariates. This association was also modeled with CRP levels stratified according to the cutpoint of 226 mg/L rather than as a continuous variable; a CRP level above the cutpoint was found to be associated with a decreased hazard of 60-day mortality (adjusted HR, 0.50; 95% CI, 0.26 to 0.98; $p = 0.04$). To demonstrate that the effect was robust with regard to statistical technique, the primary analysis was repeated in a logistic regression model constructed similarly. This also showed a significant relationship between increasing log-transformed CRP level and mortality (odds ratio, 0.65; 95% CI, 0.42 to 1.00; $p = 0.05$). Area under the receiver operating characteristic curve was also similar for each model (c-statistic = 0.84; 95% CI, 0.73 to 0.94 [for logistic regression]; c-statistic = 0.79; 95% CI, 0.66 to 0.88 for proportional hazards modeling).

Corticosteroid Therapy and CRP Levels

Given the body of evidence showing that corticosteroid therapy can affect CRP levels, such as in postoperative patients,[24] this factor was evaluated for confounding as well. Corticosteroid therapy was associated with significantly lower CRP levels (median, 96.0 mg/L [IQR, 103.0] in those who received steroids vs 180.0 mg/L [IQR, 169.0] in those who did not, $p = 0.006$) and higher mortality (60% vs 38%, respectively; $p = 0.003$). However, when this association was adjusted for severity of illness and the presence of septic shock, it lost significance (adjusted

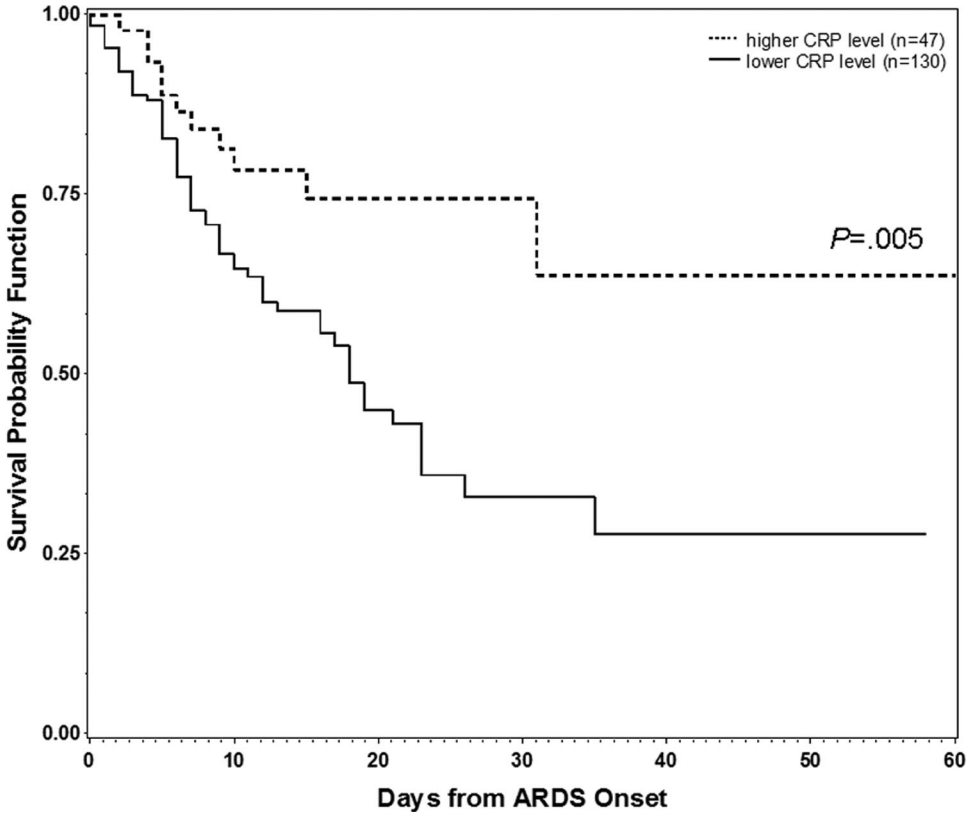

FIGURE 3. Kaplan-Meier survival probability by CRP strata above and below the cutpoint of 226 mg/L (p value stated for log-rank test).

HR, 1.84; 95% CI, 0.95 to 3.56; p = 0.07). Furthermore, when patients who had received corticosteroids (n = 30) were excluded from the primary analysis, the association between CRP and survival remained robust (adjusted HR, 0.58; 95% CI, 0.41 to 0.82; p = 0.002).

Acute Hepatic Failure and CRP Levels

Although only 4 patients in the present study had acute hepatic failure, they had significantly lower CRP levels than other patients (median, 45.5 mg/L [IQR, 54.0] vs median: 158.5 mg/L [IQR, 165.0], p = 0.02), and their mortality was significantly higher (100% vs 40%, respectively; p = 0.01). CRP was significantly associated with ARDS mortality even after adjusting for hepatic failure (Table 3), and after excluding patients with hepatic failure, the association of increasing CRP with improved survival was maintained (adjusted HR, 0.70; 95% CI, 0.53 to 0.93; p = 0.01).

Table 3—*Cox Proportional Hazards Model for Association of CRP Level With Hazard of 60-Day Mortality*

Variable	HRadj	95% CI	p Value
CRP level (log-transformed, per unit)	0.67	0.52–0.87	0.003
Age (per yr)	1.05	1.03–1.07	< 0.0001
APACHE III (per point)	1.01	0.99–1.02	0.17
Corticosteroid therapy	1.06	0.56–1.98	0.86
Acute hepatic failure	3.99	1.20–13.20	0.02

HRadj = adjusted hazard ratio.

Secondary Outcomes

Patients with higher CRP levels had less organ dysfunction over time than those with lower levels (Fig 4). This difference was significant in the mixed-effects model (p = 0.001). A generalized linear model showed that the number of ventilator-free days was significantly associated with increasing CRP level (p = 0.02).

DISCUSSION

We found that among patients with early ARDS, plasma CRP levels were significantly higher among patients who survived ≥ 60 days. In keeping with that finding, there was an inverse association between increasing CRP level and 60-day mortality, organ failure, and requirement for mechanical ventilation.

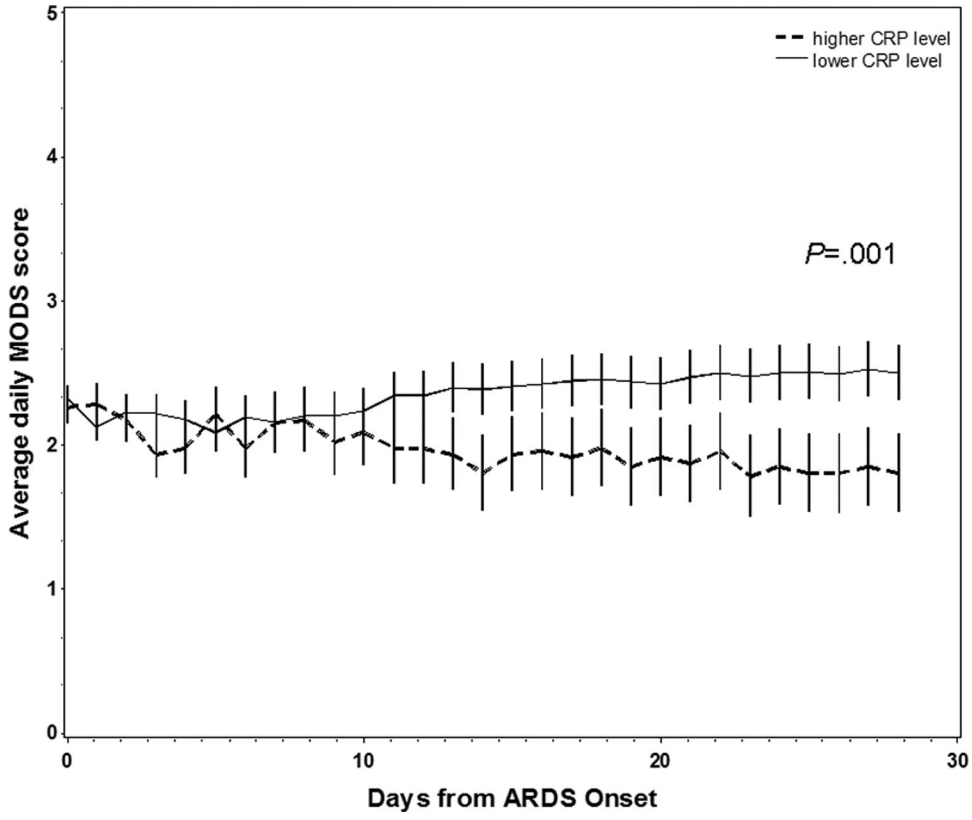

FIGURE 4. MODS by CRP strata above and below the cutpoint of 226 mg/L (p value stated for mixed-effects model); vertical bars represent SEMs.

The strengths of this study include its use of a well-characterized, prospectively enrolled cohort. In the absence of a true "gold standard," the use of the standard American–European Consensus Committee definition for ARDS helps limit misclassification bias. Although restricting the measurement of plasma CRP to a single time point early in the course of ARDS reduced the sample size, it also helped reduce bias introduced by treatment decisions or complications of the disease.

These findings seem to contradict long-held views regarding the role of CRP as an inflammatory marker predictive of risk. Indeed, CRP has recently attracted particular attention for its powerful prognostic role in CAD.[25] However, while some studies[26] have demonstrated a strong link between elevated CRP levels and adverse outcomes in CAD, other studies[27] have produced conflicting results and controversy persists in this area. Studies in some patients with acute illness, such as sepsis,[28] or other critical illness[29] have shown associations between higher CRP levels and adverse outcomes, but there are few if any studies, to our knowledge, evaluating CRP levels in patients with ARDS or ALI. In studies of patients with sepsis and septic shock, which contain a significant proportion of patients with ARDS, CRP levels have largely not been found to be associated with altered outcomes.[30–32] Historically, many of the original studies of the utility of CRP as a biomarker were conducted in neonates with sepsis. One of the earliest studies of this type[33] suggested that CRP elevation played a protective role in these patients. Other studies[34,35] have suggested that failure of CRP to decrease over time is predictive of a worse outcome. Interestingly, our findings suggested that the greatest difference in mortality occurred between patients in the two highest and two lowest deciles of CRP level. This outcome may suggest an alternative interpretation wherein CRP levels are associated with prognosis mainly or entirely at these extreme ranges.

Although clinical data regarding CRP and lung injury are lacking, a protective role is biologically plausible. Neutrophils are known to accumulate in the lungs of patients with ARDS and are thought to play a pivotal role in lung injury.[36] To cause injury, neutrophils must be recruited to the lung, primarily through the effect of chemoattractant molecules,[37] and then activated to release a variety of injurious substances.[38] Then, delayed apoptosis prolongs the lifespan of neutrophils in the lung and perpetuates injury leading to ALI/ARDS.[39] CRP does appear to

play an important role in neutrophil chemotaxis, but its role may be more complex than serving to act solely as a chemoattractant; more than 20 years ago, Buchta and colleagues[40] showed that CRP stimulated chemotaxis at lower concentrations but inhibits it, along with other characteristic neutrophil functions, at higher concentrations. These data appear to establish a basis for our findings that CRP may play a protective role at high concentrations without contradicting other studies suggesting an association between CRP and worse outcomes. Patients in many of these studies[41] typically have CRP levels much lower than those observed in our critically ill population.

Mechanistically, CRP may inhibit neutrophil function in numerous ways. One suggested mode is via CRP-mediated inhibition of p38 mitogen-associated–protein kinase activity, reducing neutrophil signal transduction proteins involved in response to chemotactic stimuli.[42] Another report[43] suggests a potential interaction with phosphatidylinositol-3 kinase activity, whereas another[44] suggests a role for CRP in inhibiting the neutrophil respiratory burst. In addition, human CRP has been found to inhibit *in vitro* neutrophil chemotaxis in human serum.[17] By contrast, there are few studies indicating that CRP is involved in causing or potentiating lung injury, although it has been mechanistically linked to alterations in function of the endothelium and of surfactant.[13,45]

In animal models, Heuertz and colleagues[15] showed that artificially stimulated elevation of serum CRP inhibited neutrophil chemotaxis and ameliorated the resultant alveolitis in experimentally induced lung injury in rabbits. The same group demonstrated decreased neutrophil influx and alveolar protein leakage in response to lung injury in transgenic mice induced to overexpress rabbit CRP,[16] and later demonstrated similar findings in mice using exogenously administered CRP.[14] Abernathy and colleagues[12] showed that CRP abrogated increased vascular permeability in rabbit lungs subjected to neutrophil stimulation.

Therefore, in both basic models and in animal models, plausible data exist suggesting that elevation of CRP levels may lead to protection from lung injury. These more experimental data appear to support our clinical findings suggestive of a paradoxically protective role of CRP in patients with ARDS. In all of these studies, elevation of *in vivo* CRP levels through various means resulted in protection from lung injury.

We acknowledge that there are certain limitations to this study. The design of this study also limits the ability to generalize our results to other populations of patients, including immunocompromised patients, those without risk factors for ARDS, or patients with risk factors other than those included. We were only able to study CRP levels at one time point, making it impossible to assess the behavior of CRP levels over time, while other studies have suggested that failure of CRP levels to decrease is an important indicator of mortality. Furthermore, we do not have measures of the intensity of the inflammatory process in the lung and thus cannot assess the relationship of circulating CRP and pulmonary inflammation. Nonetheless, the relationship between CRP levels and measured outcomes appears robust across analyses.

The inability to enroll all eligible patients in our cohort within the 48-h window for blood sampling raises the possibility of selection bias. Unfortunately, this issue arises commonly in clinical research, particularly in an acute illness such as ARDS where virtually all informed consents must be obtained from surrogates, patients may present at all hours, and the time period for enrollment is narrowly defined.[46] We have attempted to deal with this by conducting a detailed nonparticipant analysis and adjusting for identified factors by using multivariable modeling to make these results more generalizable. Nonetheless, this possibility exists, and the findings should be replicated in other patient populations before conclusions can be drawn.

In summary, although CRP has widely been considered to be a marker of systemic inflammation, our findings show that higher levels of CRP are associated with decreased mortality, organ failure, and need for mechanical ventilation among patients with ARDS. Based on prior *in vitro* and animal studies, these results are biologically plausible and suggest a possible protective role for CRP, although this obviously must be confirmed in other patient populations and in mechanistic studies. These findings could have broad implications; from the standpoint of the clinician, CRP assays are widely available in practice and might be used as a moderate indicator of prognosis. From the standpoint of the investigator, CRP may present a target for further investigation into its role in pathogenesis. If confirmed, some of the conventional wisdom regarding the role of CRP in human disease may require reappraisal.

Acknowledgments

Author contributions: All authors participated in planning the study. Drs. Thompson, Gong, Christiani, and Bajwa participated in assembling the study population. Drs. Bajwa and Januzzi participated in biomarker testing, and Drs. Bajwa and Khan performed the statistical analyses. All authors participated in manuscript preparation and review.

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