

C-Reactive Protein Alone or Combined With Cardiac Troponin T for Risk Stratification of Respiratory Intensive Care Unit Patients

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BACKGROUND: Mortality is high among patients admitted to intensive care units (ICUs). Several prognostic markers have been described in such patients, but the literature contains no data comparing C-reactive protein (CRP) and cardiac troponin T (cTn-T), nor of a combination of CRP and cTn-T in the same patient group in the ICU. **METHODS:** This was a retrospective electronic data review of patients who presented to the emergency department for respiratory reasons between December 2007 and December 2009 and in whom CRP and cTn-T levels were measured. Patients with a diagnosis of pulmonary embolism and acute coronary syndrome were excluded. We recorded demographics, chronic diseases, admission diagnosis, Simplified Acute Physiology Score II (SAPS II), ICU stay, and CRP and cTn-T concentrations. **RESULTS:** We included the records of 158 patients. Mean ICU stay was 9.9 days (range 1–65 d), and mean hospital stay was 14.1 days (range 1–72 d). For predicting mortality, receiver operating characteristic analysis gave a CRP cutoff value of ≥ 10 mg/dL, and a cTn-T cutoff value of ≥ 0.01 ng/mL. For CRP the mortality area under the curve was 0.691 (95% CI 0.608–0.775), the sensitivity was 65%, and the specificity was 70%. For cTn-T the mortality area under the curve was 0.733 (95% CI 0.655–0.812), the sensitivity was 78%, and the specificity was 56%. Of the patients who died, 65% had CRP ≥ 10 mg/dL and 78% had cTn-T ≥ 0.01 ng/mL. On multivariable regression analysis, CRP ≥ 10 mg/dL was associated with 6.6-fold higher (95% CI 1.7–21.3) ICU mortality. There was no advantage for models that combined CRP and cTn-T. CRP alone was more valuable in predicting ICU mortality than in combination with troponin or SAPS II. **CONCLUSIONS:** Elevated CRP is an independent early prognostic marker of mortality risk in ICU patients. We suspect that a CRP-based prognosis strategy may be useful. *Key words:* C-reactive protein; troponin; respiratory disease; prognosis; mortality. [Respir Care 2011;56(7):1002–1008. © 2011 Daedalus Enterprises]

Introduction

Cardiac troponins, which include cardiac troponin I (cTn-I) and cardiac troponin T (cTn-T), are highly sensi-

tive and specific biochemical markers of myocardial injury. Elevated cTn-T helps diagnose acute coronary syndrome, whereas serially negative troponins reliably exclude acute coronary syndrome.^{1–3} Elevated cardiac troponins also occur in patients with non-ischemic myocardial injury, who have congestive heart failure, myocarditis, sepsis, or trauma, and in patients with chronic renal insufficiency.⁴ Elevated troponin also correlates with mortality and morbidity in intensive care unit (ICU) patients.^{5–7} The troponin level in these patients is thought to increase secondary to myocardial damage from underlying disease, hypoxia, acidosis, and/or therapies.⁸

C-reactive protein (CRP) is secreted by the liver, and plasma CRP rapidly rises in response to inflammation, so it is an important biomarker of systemic inflammation.⁹ CRP correlates with long-term mortality and morbidity in

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patients with COPD, rheumatoid disease, coronary artery disease, and chronic inflammation.^{10,11} Response to anti-inflammatory treatment can be monitored with CRP.¹² Although the underlying primary disease determines mortality and morbidity in ICU patients, the degree of acute systemic inflammation correlates with ICU and hospital mortality.¹³

Most inflammatory and cardiac biomarkers have been investigated individually, but the use of a single biomarker may not adequately represent the severity of disease process. The use of troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP) in pulmonary embolism, and positive CRP and fibrinogen in cardiovascular diseases predicted overall mortality better than their individual use.^{14,15} Wu et al found that the combination of Tn-I and high Acute Physiology and Chronic Health Evaluation (APACHE II) score was a better risk stratification predictor in ICU patients than was high APACHE II score or elevated Tn-I alone.⁷ Therefore, accumulating evidence appears to support the strategy of using multiple biomarkers and assessment instruments in prognosis.

To our knowledge, no previous studies have investigated the combination of CRP and other biomarkers in the ICU patients. We investigated CRP, Tn-T, and SAPS II in combinations and alone, for predicting mortality in patients admitted to the ICU for respiratory disease.

Methods

This study was approved by our local ethics committee. The data were obtained from our hospital's electronic clinical and laboratory records system.

Patients

We retrospectively analyzed the medical records of 216 consecutive patients admitted to the ICU between December 2007 and December 2009 and whose CRP and troponin levels had been measured. Patients with chest pain and/or suspicion of acute coronary syndrome had been evaluated by a cardiologist. We excluded patients with acute coronary syndrome or pulmonary embolism. Neither CRP nor cTn-T had been used to guide diagnosis, management, or monitoring.

We recorded age, sex, history of hypertension, COPD, coronary artery disease, or renal failure, laboratory data (eg, hemoglobin, leukocyte, platelet count, and arterial blood gases), maximum CRP and cTn-T values at admission; cause of ICU admission, discharge diagnoses, requirement for invasive ventilation or noninvasive ventilation during and after hospitalization; Simplified Acute Physiology Score II (SAPS II) within 24 hours of ICU admission;¹⁶ and, for patients diagnosed with pneumonia, CURB-65 (confusion, urea nitrogen, respiratory rate, blood

pressure, ≥ 65 years of age) score. We included patients who developed acute respiratory distress syndrome according to American-European Consensus Committee criteria.¹⁷

Blood Analysis

Venous and arterial blood samples were collected and analyzed on admission. cTn-T was measured via electrochemiluminescence assay (Elecsys 2010, Roche, Mannheim, Germany). The normal cTn-T value is < 0.01 ng/mL. Serum CRP was measured nephelometrically (Date Behring BN II, Siemens Healthcare Diagnostics, Deerfield, Illinois) The normal CRP value is < 0.5 mg/dL.

Statistical Analysis

Results are given as number and percent, mean \pm SD, or median and range, as appropriate. We compared means with the Student *t* test or the Mann-Whitney test. We used receiver operating curve (ROC) analysis to determine cut-off values for predicting mortality with cTn-T, CRP, and SAPS II. We compared discrete variables with the Fisher exact test (chi-square test). We used univariate regression to analyze mortality risk factors, and multivariate regression with a stepwise descending method for risk factors that had a $P < .10$ in the univariate analysis. We report the multivariable regression results as odds ratio and 95% CI. $P < .05$ was considered statistically significant. Data analysis was with statistics software (SPSS 13.01, SPSS, Chicago, Illinois).

Results

We screened the medical records of 216 patients admitted to our ICU from the emergency department. We excluded 42 patients with pulmonary embolism and 16 patients with incomplete data, and thus analyzed the records of 158 patients (Table 1). The cohort's mean age was 67.1 ± 13.6 years, and 99 (63%) were male. The most common reasons for ICU admission were pneumonia (65 patients), COPD exacerbation (39 patients), and hypercapnic respiratory failure (uncommon type 2 respiratory insufficiency, 18 patients) (Table 2). Comorbid conditions included diabetes mellitus in 29 patients (18%), hypertension in 108 patients (68%), and coronary artery disease in 71 patients (45%). Hepatic dysfunction (aspartate transferase and/or alanine transferase substantially above normal [< 40 mg/dL]) was present in 50 patients (32%). Invasive ventilation was administered to 76 patients (48%), and noninvasive ventilation to 27 patients (17%). Mean ICU stay was 9.9 days (range 1–65 d), and mean total hospital stay was 14.1 days (range 1–72 d).

Table 1. Subjects

	Total (<i>n</i> = 158)	Survivors (<i>n</i> = 80)	Non-Survivors (<i>n</i> = 78)	<i>P</i>
Age (y)	67.1 ± 13.6	66.2 ± 14	67.9 ± 13.3	.39
Male/female, no. (%)	99/59 (63/37)	50/30 (62/38)	49/29 (63/37)	.85
ICU stay (d)	9.9 ± 11.2	9.2 ± 10.8	10.6 ± 11.7	.82
Hospital stay (d)	14.1 ± 12.0	16.9 ± 12	11.4 ± 12.2	< .001
Invasive ventilation, no. (%)	76 (48)	25 (33)	51 (67)	< .001
Noninvasive ventilation, no. (%)	27 (17)	7 (26)	20 (74)	.006
P _{aO₂} (mm Hg)	66 ± 25	72 ± 24	60 ± 25	< .001
P _{aCO₂} (mm Hg)	52 ± 20	49 ± 18	55 ± 22	.07
Troponin T (ng/mL)	0.09 ± 0.30	0.05 ± 0.25	0.14 ± 0.33	< .001
C-reactive protein (mg/dL)	12.8 ± 12.3	8.8 ± 8.3	17.0 ± 14.0	< .001
Hepatic dysfunction, no. (%)*	50 (32)	26 (33)	24 (31)	.80
Leukocyte count (cells × 10 ³)	13.4 ± 6.0	13.6 ± 5.9	13.4 ± 6.2	.86
Hemoglobin (g/dL)	13.4 ± 7.5	13 ± 2.2	13.6 ± 10.5	.08
Platelet count (cells × 10 ³)	247 ± 105	250 ± 113	243 ± 98	.99
Troponin T ≥ 0.01 ng/mL, no. (%)	96 (61)	35 (37)	61 (63)	< .001
C-reactive protein ≥ 10 mg/dL, no. (%)	75 (48)	24 (32)	51 (68)	< .001
SAPS II	36.3 ± 10.5	32.5 ± 8.7	40.1 ± 10.9	< .001

± values are mean ± SD.

* Hepatic dysfunction means elevated aspartate transferase and/or alanine transferase.

ICU = intensive care unit

SAPS = Simplified Acute Physiology Score

Table 2. Admission Diagnoses (*n* = 158)*

	No. (%)
Acute respiratory distress syndrome	8 (5)
Infection	75 (47)
Sepsis	40 (53)
Pneumonia	25 (33)
Other infection	10 (14)
Interstitial lung disease	8 (5)
Cor pulmonale	6 (4)
Hypercapnic respiratory failure	18 (11)
COPD	39 (25)
Obesity-hypoventilation syndrome	5 (3)
Uncommon cause	9 (6)

* Ten patients had more than one diagnosis.

Of the 65 patients admitted to the ICU with a diagnosis of pneumonia, 51 (78%) had a CURB-65 score ≥ 3 (Table 3). Sepsis was present in 40 of the patients with pneumonia. Other system infections were present in 10 patients. There was no significant difference in mortality between the patients with and without sepsis (*P* = .37).

Fig. 1 shows the ROC curves for CRP, cTn-T, and SAPS II. Table 4 shows the sensitivity, specificity, and predictive values of cTn-T, CRP, and SAPS II for mortality.

Median CRP concentration at admission was 9.0 mg/dL (range 0.12–62.4 mg/dL). CRP was normal in 8 patients

Table 3. Distribution of CURB-65 Scores

CURB-5 Score	No. (%)
1	5 (8)
2	9 (14)
3	28 (43)
4	17 (26)
5	6 (9)

CURB-65 = index of confusion, urea nitrogen, respiratory rate, blood pressure, ≥ 65 years of age.

(5%) and elevated in the remaining 150 patients (95%). ROC analysis found a CRP cutoff value of ≥ 10 mg/dL. The CRP area under the curve for mortality was 0.691 (95% CI 0.608–0.775, *P* < .001), and the sensitivity and specificity for mortality were 65% and 70%, respectively.

Median cTn-T concentration at admission was 0.015 ng/mL (range 0.01–2.1 ng/mL). cTn-T was normal in 62 patients (39%) and elevated in the remaining 96 patients (61%). ROC analysis found a cTn-T cutoff value of ≥ 0.01 ng/mL. The cTn-T area under the curve for mortality was 0.733 (95% CI 0.655–0.812, *P* < .001), and the sensitivity and specificity for mortality were 78% and 56%, respectively.

The mean SAPS II was 36.3 ± 10.5. ROC analysis found a SAPS II cutoff value of 35. The SAPS II area under the curve was 0.707 (95% CI 0.626–0.788, *P* < .001),

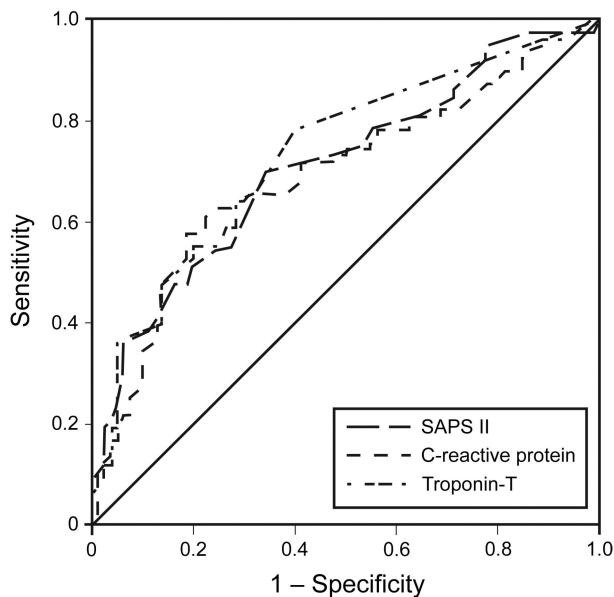


Fig. 1. Receiver operating characteristic curves showing the association between at-admission troponin T, C-reactive protein, and Simplified Acute Physiology Score II (SAPS II) and ICU survival.

and the specificity and sensitivity were 66 and 69, respectively.

Seventy-eight patients (48%) died: 31 (40%) from pneumonia or sepsis, 8 (10%) from uncommon type 2 respiratory failure, 17 (22%) from COPD, 6 (8%) from acute respiratory distress syndrome, 4 (5%) from cor pulmonale, and 12 (15%) from unusual causes. There was no significant age difference between the patients discharged and those who died ($P = .32$). Hospital stay was shorter in the patients who died (7.0 d vs 14.0 d, $P < .001$). ICU stay was longer in the non-survivors than in the survivors (7.0 d vs 6.0 d, $P = .75$), but the difference did not reach statistical significance. Troponin level among patients with cardiac disease such as coronary artery disease or cardiac failure was not significant ($P = .16$). Mortality in patients who received invasive ventilation was 67%. Mortality was 29% in those with a normal troponin level (18 patients) and 63% in those with high troponin (60 patients) ($P < .001$). CRP was ≥ 10 mg/dL in 65% (51 patients) of the subjects who died, and < 10 mg/dL in 32% (27 patients) of those who died ($P < .001$). Hemoglobin, leukocyte, and platelet count were the same in the patients who survived and those who died. Median CRP in the non-survivors was 14.0 mg/dL (range 0.3–62.4 mg/dL) and 5.9 mg/dL (range 0.1–41.2 mg/dL) in those who survived ($P < .001$). The mean SAPS II was 40.1 ± 10.9 in the non-survivors, and 32.5 ± 8.7 in the survivors ($P < .001$). There was no significant correlation between disease type and mortality.

Because the SAPS II scoring system incorporates age, vasopressor use, mechanical ventilation, leukocyte count, and serum creatinine, these variables were not incorporated as separate variables in the univariate analysis. Stepwise univariate logistic regression analysis found that independent predictors of ICU mortality were cTn-T ≥ 0.01 ng/mL ($P < .001$), CRP ≥ 10 mg/dL ($P < .001$), SAPS II > 35 ($P < .001$), and longer hospital stay ($P = .007$). Variables that were not independent predictors of ICU mortality were history of hypertension or coronary artery disease, lower hemoglobin level, male sex, longer ICU stay, or CRP combined with cardiac cTn-T or SAPS II.

To investigate whether the combination CRP with cTn-T or SAPS II has any advantage over the aforementioned strategy for predicting ICU mortality, we analyzed 6 patient groups:

- CRP ≥ 10 mg/dL alone
- cTn-T ≥ 0.01 ng/mL alone
- SAPS II > 35 alone
- CRP ≥ 10 mg/dL combined with cTn-T ≥ 0.01 ng/mL
- CRP ≥ 10 mg/dL combined with SAPS II > 35
- SAPS II > 35 combined with cTn-T ≥ 0.01

None of those variables/combinations had an advantage in predicting mortality in multivariate analysis, whereas multivariable regression analysis found that CRP ≥ 10 mg/dL was associated with 6.6-fold higher ICU mortality (95% CI 1.7–21.3, $P = .005$) (Table 5).

Discussion

To our knowledge, CRP, troponin, and SAPS II, combined or alone, have not previously been investigated for predicting mortality in a group of ICU patients with respiratory disease. Our results indicate that CRP concentration alone is more useful than any combination of CRP, troponin, or SAPS II for predicting mortality in medical ICU patients.

Serum CRP is an acute-phase protein synthesized by the liver following stimulation by various cytokines, including tumor necrosis factor and interleukin-6. CRP rises substantially within hours of infection or inflammation,¹⁸ so critically ill patients often have elevated CRP at ICU admission. In our study, 48% of the patients had CRP ≥ 10 mg/dL, which was associated with a 6.6-fold higher risk of death from any cause. Lobo et al reported that CRP > 10 mg/dL was associated with a 1.7-fold higher risk of ICU mortality than CRP < 1 mg/dL, and that CRP rose further in respiratory diseases than in renal, cardiovascular, or neurological diseases.¹⁹ Prieto et al found that CRP > 10 mg/dL (in 33% of their patients) was associated with a 2.3-fold higher

Table 4. Sensitivity, Specificity, and Predictive Values of Cardiac Troponin T, C-Reactive Protein, and SAPS II for Mortality*

	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
Cardiac troponin T \geq 0.01 ng/mL	78 (67–86)	56 (45–67)	73 (60–83)	64 (53–73)
C-reactive protein \geq 10 mg/dL	65 (54–76)	70 (59–79)	67 (56–77)	68 (56–78)
SAPS II > 35	69 (57–78)	66 (54–76)	69 (57–79)	67 (55–77)

* All values are percent and 95% CI.

SAPS = Simplified Acute Physiology Score

Table 5. Multivariable Regression Analysis for Overall Mortality

	Odds Ratio	95% CI	P
C-reactive protein \geq 10 mg/dL	6.6	1.7–21.3	.005
SAPS II > 35	3.4	0.9–13.2	.07
Cardiac troponin T \geq 0.01 ng/dL	2.3	0.6–9.8	.24
C-reactive protein \geq 10 mg/dL and cardiac troponin T \geq 0.01 ng/dL	1.1	0.2–5.4	.92
C-reactive protein \geq 10 mg/dL and SAPS II > 35	0.6	0.1–2.9	.52
Cardiac troponin T \geq 0.01 ng/dL and SAPS II > 35	1.3	0.3–5.4	.70

SAPS = Simplified Acute Physiology Score

ICU mortality.²⁰ Therefore, a CRP > 10 mg/dL is of critical importance on ICU admission.

Serum cTn-T was elevated in 61% of our patients. Myocardial injury is common in ICU patients, and troponin is elevated in 12–85% of ICU patients without acute coronary syndrome.²¹ Troponin level is reportedly higher in patients with sepsis and hypotension: 85% and 74%, respectively.^{5,22} In our study the highest troponin levels were in the patients with cor pulmonale and COPD: 67% and 66%, respectively. In another study, elevated cardiac troponin was found in 70% of patients with COPD exacerbation.²³ As expected, high troponin level in patients with COPD and cor pulmonale is correlated with myocardial damage caused by elevated pressure in the right ventricle secondary to hypoxia. In the present study, elevated cTn-T was associated with 4.6-fold higher overall mortality on univariate analysis. A meta-analysis found that elevated troponin was associated with a 2.5-fold higher risk of ICU mortality.²¹

Our multivariate analysis found that CRP \geq 10 mg/dL, considered alone, was associated with a 6.6-fold higher ICU mortality. Interestingly, combining CRP with cTn-T or SAPS II made no contribution to predicting mortality. Although the combination of CRP and Tn-T was a mortality predictor in univariate analysis, it was not significant in the multivariate analysis. cTn-T and CRP are released via different pathways, have different half-lives, and CRP

induced by a stimulus rises faster than cTn-T. Therefore, a normal admission troponin level could cause a false negative assessment of ICU mortality risk. Combination biomarkers strategies for risk prediction is an emerging field, particularly for pulmonary embolism and cardiovascular diseases, but this may not be true for ICU patients because of their complexity and heterogeneity.

The prognostic role of CRP in cardiovascular diseases in particular has been well described. High CRP is an independent risk factor for hospital readmission and mortality in patients with cardiac failure, development of atrial fibrillation, and thromboembolism.²⁴ CRP can be used in deciding on early or late ICU discharge and in monitoring response to treatment. A rising CRP in an ICU patient may also indicate nosocomial infection. In a large hospital-based study of the relationship of CRP and mortality, Mar-sik et al suggested CRP as a factor in triage.²⁵ CRP can also be a criterion in selecting the treatment for underlying disease, and prospective studies are needed. Moreover, CRP can be used very quickly, is economical, and the results can easily be interpreted and compared to cTn-T and other complex biomarkers. The SAPS and APACHE scores commonly used in ICU prognosis are complex, involve several variables, and are difficult to interpret.

In contrast to the literature, mortality was quite high in our study. In several studies, mortality in diseases stemming from the respiratory system was compared to that from other systems. Our study included only respiratory patients, and the need for invasive ventilation was quite high, at 48%. In a study with 108 patients, Wu et al administered invasive ventilation to 53% of the patients, and total mortality was 39%.⁷ In a study by Minkin et al, 62% of patients required mechanical ventilation, and total mortality was 39%.²⁶ In another study, total mortality was 20%, and 34% in pulmonary diseases.¹³ King et al had a total mortality of 19%, and 33% in pulmonary diseases.⁸ In addition, in our study, patients with severe pneumonia made up 40% of the non-survivors, and 78% of the pneumonia patients had a CURB-65 score \geq 3. Mortality was 48% in patients admitted to the ICU with a diagnosis of pneumonia. The literature has reported mortality of 15–57% in patients with a CURB-65 score \geq 3.²⁷ A multi-

center study with 1,426 respiratory disease patients admitted to the respiratory ICU had a mortality of 44%.²⁸ The main reason for the high mortality in our ICU patients may have been those patients, because ours is a tertiary-care hospital, where patients are admitted for severe illness. The low number of beds in our ICU might also have increased the mortality, because less seriously ill patients were not admitted to the ICU.

Limitations

This was a retrospective study, though the fact that all patient data, epicrisis, and daily progress were available is important to the study's reliability. Further prospective randomized clinical trials are needed to evaluate the use of biomarkers for determining who should be admitted to the ICU from the emergency department.

Second, we did not ascertain the post-discharge long-term outcomes of the survivors. Previous studies found a correlation between elevated CRP and troponin and post-ICU-discharge mortality.^{13,24,29} Grander et al determined that every unit of CRP increase raised post-discharge mortality 1.46-fold.¹³ Ho et al found a post-ICU mortality of 4% in patients with a CRP of 9 mg/dL, and 22% in patients with a CRP of 30 mg/dL.²⁴

Third, troponin levels were not subsequently measured in patients with initial normal troponin and included in the study. This is potentially important, because troponin can rise 6–12 hours after hospital admission.³⁰

Conclusions

As in previous studies, this study showed that elevated CRP at prognostic scanning of medical ICU patients was an independent mortality risk factor. In addition, CRP is an easily applicable, simple biomarker and can be used for risk stratification of ICU patients.

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