C-reactive protein concentration as a predictor of in-hospital mortality after ICU discharge: a nested case–control study

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ABSTRACT

Purpose: To assess the ability of potential clinical predictors and inflammatory markers to predict in-hospital mortality after patient discharge from the intensive care unit.

Setting and participants: 1272 patients who survived their index admission to a 22-bed multidisciplinary ICU of a university hospital in 2004.

Design: Nested case–control study with two concurrent control patients for each case of post-ICU discharge in-hospital mortality.

Results: There were 29 unexpected in-hospital deaths after ICU discharge (2.3%). C-reactive protein (CRP) concentrations within 24 hours of ICU discharge were available for 14 of these 29 patients and 22 concurrent control patients. CRP concentration at ICU discharge was associated with subsequent mortality (mean CRP concentrations: cases, 204 mg/L v controls, 63 mg/L; $P = 0.001$). CRP concentration remained significantly associated with post-ICU mortality after adjustment with other potential predictors of mortality (odds ratio [OR] of death for a 10 mg/L increase in CRP concentration, 1.27; 95% CI, 1.09–1.49; $P = 0.005$) and with propensity score (OR, 1.19; 95% CI, 1.05–1.33; $P = 0.004$). The area under the receiver operating characteristic curve for CRP concentrations to predict in-hospital mortality was 0.87 (95% CI, 0.73–0.99; $P = 0.001$). The destination and timing of ICU discharge, SOFA (Sequential Organ Failure Assessment) score, white cell count and fibrinogen concentration at ICU discharge were not significantly associated with in-hospital mortality after ICU discharge.

Conclusions: A high CRP concentration at ICU discharge is an independent predictor of subsequent in-hospital mortality. Prospective cohort studies in ICUs with different casemix, discharge criteria and post-ICU mortality rates are needed to validate and generalise our findings.

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As many as a third of all deaths following critical illness occur during ward care after successful discharge from the intensive care unit.[1] These deaths occur in patients whose physiological status appeared sufficiently stable or improved that they no longer required ICU-specific treatments for organ dysfunction. Post-ICU deaths may arise from incomplete resolution of the primary illness or the development of new complications. Irrespective of the cause of death, it can be argued that death after ICU discharge represents a failure of management of a critical illness, as well as a waste of the substantial resources consumed during the ICU admission.[2] The clinical problem of post-ICU death is increasingly recognised in the critical care literature, with studies identifying age, chronic health status, severity of illness at the time of ICU admission, discharge from the ICU at night, and level of nursing care on the discharge ward as predictive variables.[3-7] Furthermore, the use of post-ICU follow-up teams has been reported to improve post-ICU survival.[8]

We hypothesised that unresolved or latent inflammation and sepsis may be important factors that contribute to death after successful discharge from the ICU. Inflammatory markers such as white cell counts and serum C-reactive protein (CRP) concentrations are used as indicators of infection or inflammation in critically ill patients.[9] Serum fibrinogen concentration is another important inflammatory marker in the development of cardiovascular disease.[10] We conducted a nested case–control study to evaluate the potential ability of inflammatory markers to predict in-hospital mortality after ICU discharge.

Methods

Setting

This retrospective nested case–control study used prospectively collected data from the administrative database of the ICU of Royal Perth Hospital. This is an 800-bed university teaching hospital, and the 22-bed tertiary ICU admits critically ill adult patients in all specialties. An eight-bed high dependency unit adjacent to the ICU is also managed by the ICU team. The ICU team discharges patients to a ward when they no longer require ICU-specific treatments for organ dysfunction, and their condition is deemed stable enough to be managed with low-intensity nursing care (ie, one nurse to four or more patients). Patients who still require continuous monitoring or intermediate-intensity nursing care, including those with a tracheostomy, are discharged to the high dependency unit unless there is a plan to limit therapy.

Table 1. Admission diagnosis, discharge SOFA score and C-reactive protein concentration, and cause and timing of all unexpected post-ICU mortality in 2004 ($n = 29$)

Diagnosis on first ICU admission	Cause of death	Discharge SOFA score	C-reactive protein (mg/L)	Time of death after ICU discharge (days)
Acute diverticulitis	Myocardial infarction	0	na	1
Gastrointestinal perforation	Nosocomial pneumonia	9	na	3
Status epilepticus	Nosocomial pneumonia	2	341	7
Intracerebral haemorrhage	Myocardial infarction	6	na	3
Post-cardiac arrest	Ventricular fibrillation	4	na	2
Gastrointestinal perforation	Liver failure/pneumonia	3	203	13
Status epilepticus	Liver failure	4	na	21
Subarachnoid haemorrhage	Cerebral infarction	3	112	4
Gastrointestinal perforation	Nosocomial pneumonia	1	na	6
Postcardiac arrest	Nosocomial pneumonia	6	142	4
Peripheral vascular disease	Sepsis/acute renal failure	5	na	10
Multiple trauma	Pulmonary embolism	2	na	2
Ventricular tachycardia	Ventricular fibrillation	4	277	2
Community-acquired pneumonia	Obstructive cholangitis	3	298	5
Systemic lupus erythematosus	Nosocomial pneumonia	4	258	6
Gastrointestinal obstruction	Acute renal failure/sepsis	5	na	7
Chronic subdural haematoma	Myocardial infarction	2	na	7
Acute subdural haematoma	Myocardial infarction	7	277	37
Drug overdose	Thyrotoxic crisis	1	3	18
Myocardial infarction	Nosocomial pneumonia	4	na	6
Post-bowel resection	Ischaemic bowel disease	3	189	2
Burns	Nosocomial pneumonia	0	na	16
Gastrointestinal obstruction	Nosocomial pneumonia	4	83	5
Neutropenic sepsis	Nosocomial pneumonia	6	233	10
Intra-abdominal sepsis	na	2	na	7
Correction of scoliosis	na	1	na	3
Adrenal carcinoma, sepsis	na	0	350	3
Intracranial haemorrhage	na	6	86	68
Sepsis, acute renal failure	na	7	na	3

SOFA = Sequential Organ Failure Assessment. na = not available. ◆

The study was deemed a clinical audit by the Royal Perth Hospital Ethics Committee, and as such formal human research ethics committee approval was waived.

Subjects

All deaths after ICU discharge during the same hospitalisation were identified and recorded using the ICU database for the 1-year period between 1 January and 31 December 2004. Cases were defined as all patients who died after ICU discharge and who had no limitation on life support in the ICU or the ward. They included two patients who died during their second ICU admission during the same hospitalisation. Information on the causes of in-hospital mortality and whether there was a plan to limit therapy was retrieved from the death registry in the School of Population Health at the University of Western Australia, Perth, and the hospital records, respectively. Five cases were under coroner's investigations, and the exact causes of death were not available.

Two control patients — the patient who was admitted to the ICU immediately before, and the patient who was admitted immediately after, the admission of the "case"— were selected concurrently for each case of hospital mortality after ICU discharge.[11] If the patient who was admitted immediately before or after the case did not survive to ICU discharge or was discharged with limitation placed on subse-

quent use of life support, then the patient admitted before or after the non-survivor was selected as the control instead. Patients who did not survive to ICU discharge were not selected as controls because death after ICU discharge was not possible with these patients.[11,12] No patients were transferred to another hospital or lost to mortality follow-up.

Data collection and analysis

All data were collected prospectively and were subsequently retrieved from the ICU administrative and laboratory databases. The clinical predictors analysed included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II predicted mortality, time of day when the patient was discharged, the destination of ICU discharge (high dependency unit versus ward), and Sequential Organ Failure Assessment score (SOFA) on the day of discharge.[13] For the two patients who died during their second ICU admission during the same hospitalisation, the APACHE II predicted mortality of their first ICU admission was used for all analyses. There were no missing data in the administrative database. The values of the inflammatory markers, including serum CRP concentration, fibrinogen concentration, and white cell count within 24 hours of ICU discharge were retrieved from the laboratory database. Serum CRP concentrations were measured by an immunoenzyme analyser (Hitachi 917, Tokyo, Japan), and serum fibrinogen concentrations were measured by the Clauss technique (Diagnostica STAGO, France).

The association between the potential clinical predictors and inflammatory markers and post-ICU mortality was tested with univariate analyses followed by multivariate analyses. Continuous variables were analysed by *t* tests or, if their distributions were skewed, by Mann–Whitney tests, while categorical variables were analysed by χ^2 tests. Predictors with a $P < 0.25$ in the univariate analyses and interaction terms of these variables were further analysed by multivariate analyses. Variables were removed in a stepwise manner if the *P* value was > 0.25 (Model A).

Measurements of CRP were not available in all subjects, and, to adjust for confounding by selection bias that might have occurred from ordering of CRP in sicker patients, a separate multivariate analysis was used to identify predictors of a CRP test being ordered. The CRP test was most likely to be ordered in emergency admissions and also for patients who were sicker, whose condition was unstable, or who had an infection either initially or near the time of ICU discharge. Therefore, we tested the relationship of the following variables to ordering a CRP test within 24 hours of ICU discharge: whether the admission was an elective or emergency admission, length of ICU stay before ICU dis-

Table 2. Univariate analyses showing the relationships between the potential predictors of in-hospital mortality in case and control patients

Potential predictor	Cases (*n* = 29)	Controls (*n* = 58)	Unadjusted OR (95% CI)	*P*
Mean age in years (SD)*	63.0 (19.6)	53.0 (16.8)	1.39 (1.06–1.83)	0.02
Sex: no. of males/females	14/15	46/12	4.11 (1.56–10.80)	0.006
Discharge to high dependency unit (*n* [%])	6 (21%)	9 (16%)	0.70 (0.22–2.21)	0.55
ICU discharge during the night (*n* [%])†	1 (3%)	2 (3%)	1.00 (0.09–11.51)	1.00
Elective admission (*n* [%])	7 (24%)	27 (47%)	0.37 (0.14–0.99)	0.047
Emergency admission (*n* [%])	22 (76%)	31 (53%)	1.42 (1.01–7.14)	0.047
APACHE II predicted mortality (%): mean (SD)‡	42.3% (22.3%)	16.0% (14.9%)	2.02 (1.48–2.75)	0.001
Median (IQR)	42.2% (24.0%–56.0%)	11.8% (5.8%–20.3%)		
ICU length of stay in days: mean (SD)	4.0 (2.9)	2.3 (4.0)	1.16 (0.97–1.39)	0.10
Median (IQR)	2.9 (1.7–6.7)	1.5 (0.9–2.1)		
Mean discharge SOFA score (SD)	3.6 (2.3)	2.4 (2.4)	1.22 (1.02–1.47)	0.03
Mean white cell count ($\times 10^9$/L) (SD)§	15.5 (18.2)	10.6 (3.3)	1.10 (0.98–1.23)	0.10
Mean fibrinogen concentration (g/L) (SD)¶	4.9 (1.7)	4.8 (1.7)	1.03 (0.78–1.36)	0.84
CRP measured before ICU discharge (*n* [%])	14 (48%)	22 (38%)	1.53 (0.62–1.61)	0.37
CRP concentration (mg/L): mean (SD)**	203.7 (105.6)	62.5 (60.9)	1.20 (1.06–1.35)	0.001
Median (IQR)	218 (106–282)	53 (14–72)		

* Odds ratio represents a 10-year increase in the age of the patient. † During the night defined as between 22:00 and 08:00.
‡ Odds ratio represents a 10% increase in APACHE II predicted mortality.
§ 57 control patients and 28 case patients had white blood cell count measured within 24 hours of ICU discharge.
¶ 51 control patients and 26 case patients had fibrinogen concentration measured within 24 hours of ICU discharge.
** Unadjusted odds ratio represents a 10 mg/L increase in CRP concentration.
CRP = C-reactive protein. OR = odds ratio. IQR = interquartile range (25% to 75%). ◆

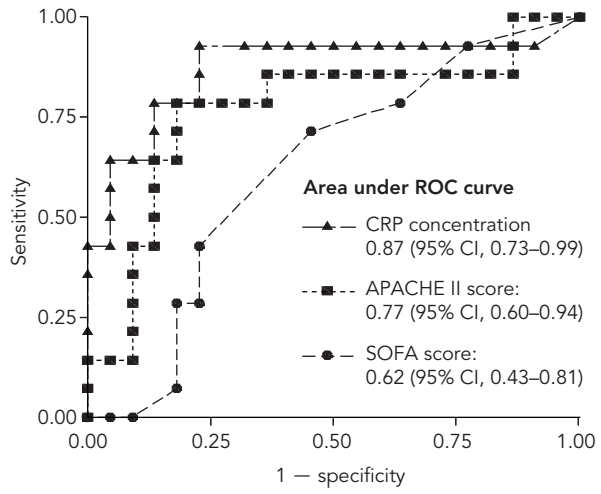
Table 3. Characteristics of case and control patients ($n = 87$) after stratification into three categories of propensity score*

	Low propensity (0–0.33)		Medium propensity (0.34–0.66)		High propensity (0.67–1.0)	
Variables	Cases ($n = 7$)	Controls ($n = 27$)	Cases ($n = 12$)	Controls ($n = 28$)	Cases ($n = 10$)	Controls ($n = 3$)
Propensity score: mean (SD)	0.17 (0.03)	0.20 (0.04)	0.49 (0.06)	0.51 (0.07)	0.83 (0.17)	0.78 (0.07)
Sex: no. of males/females	5/2	21/6	5/7	22/6	4/6	3/0
Mean age in years (SD)	59.6 (25.9)	56.7 (15.4)	61.9 (17.8)	50.0 (18.4)	66.7 (18.5)	47.3 (5.5)
Elective admission (*n* [%])	7 (100%)	27 (100%)	0	0	0	0
Emergency admission (*n* [%])	0	0	12 (100%)	28 (100%)	10 (100%)	3 (100%)
Mean ICU length of stay in days (SD)	1.9 (0.9)	1.3 (0.6)	2.3 (1.1)	1.9 (0.9)	7.4 (2.2)	14.6 (14.2)
CRP tested (*n*)	2	4	4	16	8	2

* The propensity score represented the probability of the CRP test being ordered. It was generated from ICU length of stay and whether the ICU admission was an emergency or an elective admission. CRP = C-reactive protein. ◆

charge, APACHE II predicted mortality, SOFA score on the day of ICU discharge, white cell count on the day of ICU discharge, discharge during the night, discharge to the high dependency unit or ward, and the age of the patient. Only emergency admission (odds ratio [OR], 4.0; 95% CI, 1.31–12.0; $P = 0.02$) and days in ICU before discharge (OR, 1.3; 95% CI, 0.9–1.7; $P = 0.06$) were found to be associated with ordering of a CRP test (Hosmer–Lemeshow χ^2 statistic, 6.96; $P = 0.43$, indicating the model had a good fit). A propensity score was then generated by logistic regression analysis for each case and control patient from the duration of ICU stay and whether the admission was an emergency admission.[14] These scores represented the probability of a CRP test being ordered based on these two variables[15] and ranged between 0 and 1. The cases and controls were compared in three categories of propensity score (0–0.33, 0.34–0.66 and 0.67–1.0) to confirm that their characteristics were more balanced after stratification by propensity score.[16] Propensity scores can balance baseline covariates between exposure groups and produce estimates that are less biased, more robust, and more precise than a multivariate logistic regression model when the outcome is rare relative to the number of confounders.[14,15] The prognostic significance of CRP was then further analysed by repeating the multivariate analysis with the propensity scores as a continuous covariate in addition to the significant variables in Model A.

Figure 1. Receiver operating characteristic (ROC) curves showing the ability of CRP concentrations, APACHE II predicted mortality and discharge SOFA scores to predict in-hospital mortality after ICU discharge



The results after adjustment with the propensity scores (Model B) were compared with the results obtained by the traditional multivariate logistic regression model (Model A). We used statistical adjustment with propensity scores and multivariate analysis rather than matching, as the latter does not allow the association between the matching variables and the outcome to be assessed.[11] A P value < 0.05 was regarded as statistically significant, and all statistical tests were performed with SPSS for Windows version 11.01 (SPSS Inc, Chicago, Ill, USA, 2001).

Results

There were 1405 ICU admissions in 2004, with 1272 of these patients (90.5%) discharged alive from the ICU. The mean APACHE II predicted hospital mortality of the entire cohort ($n = 1272$) was 22.1% (median, 10.7%; interquartile range [IQR], 5.0%–23.8%), and the actual hospital mortality, including patients who died in the ICU, was 13.0%. Twenty patients were discharged from the ICU with a plan

Table 4. Multivariate analysis showing predictors associated with in-hospital mortality after ICU discharge

Model, no. of patients	Variable	Odds ratio (95% CI)	*P*
Model A			
35	APACHE II predicted mortality*	1.59 (0.79–3.21)	0.19
35	White cell count ($\times 10^9$/L)	1.23 (0.91–1.67)	0.17
35	CRP (mg/L)†	1.27 (1.09–1.49)	0.005
29	Emergency admission	0.05 (0.01–1.73)	0.10
12	Female sex	21.3 (1.07–421)	0.047
Model B‡			
36	CRP (mg/L)†	1.19 (1.05–1.33)	0.004
36	Propensity score*	1.11 (0.68–1.80)	0.67
12	Female sex	6.13 (0.77–48.70)	0.09

* Odds ratio represents a 10% increase in predicted mortality or propensity score.
† Odds ratio represents a 10 mg/L increase in CRP concentration.
‡ Adjustment with the propensity score as a continuous covariate. The propensity score represents the probability of CRP test being ordered and was generated from the length of ICU stay and whether the ICU admission was an emergency admission.
The Hosmer–Lemeshow χ^2 statistics for the goodness of fit of Model A was 8.48 ($P = 0.29$) and for Model B was 3.68 ($P = 0.82$).
Interaction terms formed between SOFA score and CRP concentrations and between APACHE II predicted mortality and CRP concentrations were not significant and were not retained in the models.
CRP = C-reactive protein. ◆

to limit life support and ICU readmission. There were 18 unplanned ICU readmissions during the same hospitalisation in 2004, and two patients died during their second ICU admission. Twenty-seven patients (2.1%) died unexpectedly in the ward after ICU discharge. Therefore, there were a total of 29 in-hospital deaths after discharge from the index ICU admission in patients with no plan to limit subsequent use of life support. The causes of death were available in 24 patients (83%). Five cases were under investigation by the coroner's office, and the cause of death was not available. Septic (45%), cardiovascular (21%), and thromboembolic (10%) complications were the commonest causes of death, and most of these deaths occurred within 2 weeks of ICU discharge (mean, 9.7 days; median, 6.0 days; IQR, 3–10 days) (Table 1).

Older age, female sex, emergency admission, and higher APACHE II predicted mortality, discharge SOFA score and CRP concentration were associated with in-hospital mortality after ICU discharge in the univariate analyses (Table 2). White cell counts and fibrinogen concentrations within the 24 hours before ICU discharge were available in 96% of cases and controls, but CRP concentrations were available in only 14 cases (48%) and 22 controls (38%), a difference

Table 5. Probability of post-ICU death, using the odds ratio of CRP from Model B and post-ICU death rate of the whole cohort as baseline incidence

Risk factor	Probability of post-ICU death (%)
Baseline incidence of post-ICU death of whole cohort (assuming baseline CRP = 50 mg/L)	2.3%
CRP concentration within 24 h of ICU discharge	
100 mg/L	5.3%
200 mg/L	24.2%
300 mg/L	64.5%

CRP = C-reactive protein. ◆

of 10.3% (95% CI, –10.9% to 31.0%). CRP testing was not associated with post-ICU mortality in the univariate analysis (Table 2). The area under the receiver operating characteristic (ROC) curve for CRP concentrations to predict in-hospital mortality after ICU discharge was 0.87 (95% CI, 0.73–0.99; $P = 0.001$) (Figure 1).

The distributions of emergency admissions and ICU length of stay were more balanced after stratifying the cases and controls into three categories of propensity score (Table 3). In the multivariate logistic regression analyses, only female sex and CRP concentration were significantly associated with in-hospital mortality after ICU discharge (Model A in Table 4). After further adjustment for potential confounding by selection bias using the propensity scores, CRP concentration but not female sex remained significantly associated with post-ICU mortality (Model B in Table 4). The Hosmer–Lemeshow χ^2 statistics for the goodness of fit of Model A and Model B were 8.48 ($P = 0.29$) and 3.68 ($P = 0.82$), respectively. The estimated probability of post-ICU mortality based on CRP concentration within 24 hours of ICU discharge is described in Table 5.

Discussion

The in-hospital mortality rate (2.3%) after ICU discharge of our cohort was lower than that reported in other studies.[1-6] A contributing factor was the exclusion of 20 patients (1.4%) who had limitation of life support when discharged from the ICU or subsequently in the ward. The use of strict ICU discharge criteria and a high dependency unit may also have contributed to the low post-ICU mortality in our patients. Our univariate analyses showed that age, female sex, emergency admission, discharge SOFA score, and severity of acute illness and chronic health status as summarised by APACHE II predicted mortality were significantly associated with in-hospital mortality after apparently successful ICU treatment.

Discharge during the night and discharge to a ward rather than the high dependency unit were not significant predictors of in-hospital mortality in the univariate analysis. In addition, we could not confirm age or discharge SOFA score as significant predictors of in-hospital mortality in the multivariate analyses. This could be due to differences between patient cohorts and the very low post-ICU mortality rate in this study arising from strict ICU discharge criteria and the use of the high dependency unit. Patient sex has not been reported as a significant factor in post-ICU mortality, and, after adjustment with the propensity score in Model B, our results also showed that it was not significant. Therefore, the significance of sex in Model A is likely to be spurious, resulting from the small sample size. However, we did observe a consistent association between an elevated CRP concentration within the 24 hours before ICU discharge and subsequent in-hospital mortality in the multivariate analyses.

The reason for this association between persistently elevated CRP concentration and mortality after ICU discharge is uncertain. Circulating CRP is an acute phase reactant exclusively produced by hepatocytes, predominantly under transcriptional control by cytokine interleukin-6 (IL-6) during bacterial infections and inflammation.[17] CRP concentrations have been shown to correlate with plasma concentrations of IL-6 and organ dysfunction in critically ill patients.[18-20] In a heterogeneous group of critically ill patients, concentrations of CRP fell as organ dysfunction resolved in survivors, but remained elevated in those who did not survive.[18] It is possible that an elevated CRP concentration at the time of ICU discharge represents a marker of emerging subclinical nosocomial infection or unresolved inflammation in critically ill patients. However, there is also growing evidence that CRP is actively involved in endothelial dysfunction and thrombosis.[21-23] CRP has been shown to bind to endothelial cells, leading to an increase in interleukin-8, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 and a decrease in endothelial nitric oxide and prostacyclin production.[23] In fact, infusion of recombinant human CRP to healthy volunteers has been shown to activate coagulation and inflammation cascades.[24] High CRP concentrations have also been shown to be an independent risk factor for hospital readmission and mortality in patients with heart failure, for development of atrial fibrillation, and for thromboembolic events and progression of renal disease in the elderly.[25-28]

The relatively short half-life of 19 hours makes CRP a potentially useful indicator for following the inflammatory response.[18] Liver failure impairs CRP production, but no other pathologies and very few drugs reduce CRP concentrations unless they also affect the underlying pathology providing the acute phase stimulus.[17] Despite the potential advantages of CRP, its use as a marker of resolution of critical illness and a predictor of outcome after ICU discharge has not been thoroughly investigated. We recently found that CRP concentration at ICU discharge is associated with a higher risk of unplanned ICU readmission during the same hospitalisation.[29] As far as we know, this study is the first to provide preliminary data concerning the predictive ability of CRP concentrations on mortality after ICU discharge. CRP measurement is widely available and easier to interpret than complicated prognostic scores.[30,31] If our preliminary results are confirmed by future studies, then measurement of CRP concentrations will be useful for risk stratification and decision-making about ICU discharge, and may potentially reduce inappropriate early ICU discharge.

This preliminary study has some limitations. First, observational studies are prone to bias. CRP concentrations were available in only 14 (48%) and 22 (38%) of the case and control patients, respectively (difference, 10.3%; 95% CI, –10.9% to 31.0%). Missing data can lead to selection bias and may have created a false positive result. The CRP concentrations, but not female sex, remained a consistently significant predictor associated with in-hospital mortality after ICU discharge after adjustment for potential selection bias using the propensity scores. Furthermore, propensity score was not a significant variable (Model B in Table 4), and the inferred selection bias in ordering CRP was not a significant factor in the relationship between CRP and post-ICU mortality. Second, because the number of unexpected post-ICU deaths was small in this study, the results were imprecise, with wide confidence intervals.

Finally, many inflammatory markers have been reported to be associated with the outcomes of critically ill patients. For example, procalcitonin concentrations have been shown to be more specific than CRP concentrations in predicting sepsis, and a persistently elevated procalcitonin concentration is associated with a worse outcome in patients with ventilator-associated pneumonia.[32,33] Recently, serial levels of a newly identified inflammatory marker, soluble triggering receptor expressed on myeloid cells (sTREM)-1, have been shown to be more sensitive than CRP and procalcitonin concentrations in predicting ICU mortality.[34] We have no data on procalcitonin and sTREM-1 concentrations in our patients, and the performance of these inflammatory markers relative to CRP concentrations in predicting resolution of critical illness and outcome after ICU discharge remains uncertain and deserves further investigation.

Conclusions

A high CRP concentration at ICU discharge is an independent predictor of subsequent in-hospital mortality. This was a small preliminary study to test a speculative hypothesis.

Prospective cohort studies in ICUs with different casemix, discharge criteria, and post-ICU mortality rates are needed to validate and generalise our findings.

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