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ORIGINAL RESEARCH

Serial C-Reactive Protein Measurements for Prognostication and Antimicrobial Decision-Making in ICU Sepsis Patients: A Retrospective Cohort Study

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Background: C-reactive protein (CRP) is a widely used biomarker for sepsis management; however, its prognostic value remains uncertain. This study evaluated whether serial CRP measurements are associated with mortality in intensive care unit (ICU) patients with sepsis.

Methods: This retrospective cohort study included adult patients admitted to a tertiary-care ICU between 2020 and 2023, who had at least three serial CRP measurements around days 1, 3, and 7 to guide sepsis management as diagnosed by the treating team. We examined the relationship between CRP levels and 90-day mortality.

Results: The study included 171 patients (median age: 67 years; 55% male). Compared to patients with lower CRP levels, those with day-1 CRP ≥75 mg/L (n=87, 50.9%) had similar clinical characteristics, except for a higher prevalence of malignancy. Antibiotic use and clinical outcomes were similar between the groups. Meropenem duration tended to be shorter in patients whose CRP levels decreased from days 1 to 7 than in those whose CRP levels increased (median 7 days vs. 10 days; p=0.06). 42 patients (24.6%) died within 90 days. Compared to survivors, non-survivors had slightly higher CRP levels on day 1 (91 mg/L vs. 70 mg/L, p=0.08) and similar changes in CRP over time. Receiver operating characteristic curve analysis demonstrated that both CRP levels and their temporal changes had poor prediction for 90-day mortality (area under the curve for day-1 CRP, 0.590), with day-1 procalcitonin performing slightly better (area under the curve, 0.658). In the multivariable logistic regression analysis, day-1 CRP was not associated with 90-day mortality.

Conclusion: Serial CRP measurements did not reliably predict mortality in ICU patients with sepsis but may have influenced the antibiotic duration. Routine CRP monitoring in ICU patients with sepsis may have a limited prognostic value.

Plain Language Summary: Sepsis is a serious, potentially life-threatening condition that often requires treatment in the intensive care unit (ICU). One of the blood tests commonly used in these situations is C-reactive protein (CRP) level, which increases in the presence of inflammation or infection. Although CRP is widely measured, it remains uncertain whether repeated CRP results can help to predict which ICU patients with sepsis are more likely to survive. This study examined whether CRP levels measured on days 1, 3, and 7 were associated with death within 90 days.

Our study included 171 adult ICU patients who underwent at least three CRP tests as part of their sepsis management. We compared CRP values and how they changed over time between patients who survived and those who did not. Overall, 24.6% of the patients died within 90 days. Those who died had slightly higher CRP levels on the first day, but the differences were small, and the changes in CRP levels over the week were similar between survivors and non-survivors. CRP levels and trends showed a poor ability to predict which patients would die, indicating that CRP may not be a reliable prognostic tool. Another blood marker, procalcitonin, showed moderately better results. The study also found that CRP levels may have influenced the duration for which physicians continued certain antibiotics such as meropenem.

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In summary, our findings suggest that while CRP may assist physicians in some treatment decisions, serial CRP measurements may not be able to predict survival in ICU patients with sepsis.

Keywords: C-reactive protein, mortality, sepsis, biomarkers, intensive care

Introduction

Inflammatory biomarkers are frequently used in critical care settings to detect systemic inflammation, diagnose infections, evaluate disease severity, assess responses to therapy, and predict outcomes.[1–6] C-reactive protein (CRP) is a biomarker produced by the liver in response to interleukin-6 following inflammation or cellular damage.[1] CRP levels can increase up to 1000 times as compared with normal physiological conditions.[1] CRP can activate the complement pathway by binding to ligands such as lipoproteins, and has an anti-inflammatory effect by inhibiting neutrophils and platelet-activating factors that slow the aggregation process.[1]

CRP is a widely used laboratory marker[7] that has been studied across different patient populations, including those with cancer, heart failure, stroke, venous thromboembolism, general critical illness, and sepsis.[7,8] In the intensive care unit (ICU) setting, many observational studies explored CRP utility in clinical practice using different methodologies. For example, a multicenter prospective observational study of 813 general ICU patients in China found that lower baseline CRP levels were associated with lower ICU mortality, and baseline CRP levels > 62.8 mg/L were independently associated with an almost two-fold increase in ICU mortality on multivariable logistic regression analysis.[9] Similarly, a multicenter retrospective study from Sweden involving 851 patients with sepsis reported that admission CRP levels >100 mg/L were associated with increased ICU and 30-day mortality as well as prolonged stays in the ICU and hospital among survivors.[10] A multicenter prospective cohort study from Portugal evaluated the daily CRP levels in 891 ICU patients with community-acquired pneumonia and found no significant differences in CRP levels between survivors and non-survivors until the third day of antibiotic treatment.[2] CRP levels decreased faster in patients who responded to treatment than in those who did not.[2] Despite these findings, other studies questioned the clinical value of CRP, with a systematic review*)60* studies and 15681 patients) reporting that CRP did not predict 30-day mortality in critically ill patients with sepsis.[11]

Despite the uncertainty and challenges surrounding the application and interpretation of inflammatory biomarkers[3,12] clinicians often place considerable weight on CRP levels when making management decisions, which may lead to inappropriate use.[7] As the relationship between CRP levels and clinical outcomes in ICU patients remains controversial, our study aimed to evaluate whether baseline CRP levels and their serial changes influence clinical management and predict mortality in critically ill patients with sepsis.

Materials and Methods

Patients and Setting

This retrospective cohort study evaluated critically ill patients admitted to the adult Intensive Care Department of King Abdulaziz Medical City in Riyadh, Saudi Arabia. The Intensive Care department has eight different units that admit different types of critically ill patients, with six medical teams performing daily multidisciplinary rounds. Each ICU medical team consisted of one ICU consultant, one staff physician/fellow, and 2–4 residents. Patients were eligible for this study if they were adults (age ≥ 18 years), were admitted to the ICU between January 1, 2020, and December 31, 2023, had an ICU stay of at least 3 days, received antibiotics for sepsis that was clinically suspected or confirmed by the treating ICU team at the first CRP measurement; all patients were subsequently diagnosed to have sepsis and had at least three CRP measurements on different days within 8 days. In our hospital, CRP levels were measured using immunoturbidimetry (Abbott Alinity CI series; Abbott, Illinois, USA). The normal CRP level was up to 5 mg/L.

Data Collection

The collected data included demographic information, medical history (chronic cardiovascular disease, chronic respiratory disease, chronic kidney disease, stroke, cancer, diabetes, and hypertension), admission category (medical, surgical, and trauma), admission Glasgow Coma Scale score, and sepsis-related variables (confirmed vs. suspected at the time of the first CRP measurement, community-acquired vs. hospital-acquired, infection source, culture results, antibiotic therapy, and duration of meropenem therapy). We recorded the following laboratory results: white blood cell count, hemoglobin, creatinine, bilirubin, international normalized ratio, albumin, lactate levels, COVID-19 status, CRP levels on day 1, CRP on day 3–5, CRP on day 6–8, and procalcitonin levels on the same days. We also noted selected management interventions in the ICU including vasopressor use, invasive mechanical ventilation, and renal replacement therapy.

Outcome data in this study included vital status at 30-day and 90-day and hospital mortality, and length of stay (LOS) in the ICU and hospital. Because 30-day mortality was low and hospital LOS was prolonged in most patients, we considered 90-day mortality as the primary outcome.

Statistical Analysis

A modified Sequential Organ Failure Assessment (SOFA) score,[13] which assess the severity of illness, was calculated using available variables (creatinine, bilirubin, Glasgow Coma Scale, vasopressor use, and mechanical ventilation status). The respiratory component was simplified by assigning 3 points for mechanical ventilation and 0 for no mechanical ventilation. The cardiovascular component was scored as 3 for any vasopressor use and 0 for no vasopressor use. The coagulation component was omitted because platelet counts were unavailable. This approach has been used in prior retrospective studies when complete SOFA data were not obtainable.[14]

We calculated the changes in CRP between days 3–5 and day 1 as follows: CRP on day 3 minus CRP on day 1, divided by CRP on day 1. We calculated the changes in CRP between days 6–8 and day 1 as follows: CRP on day 7 minus CRP on day 1, divided by CRP on day 1. Similarly, we calculated the changes in procalcitonin levels. We used two approaches to compare patients. First, to explore the clinical implications of initial CRP levels, we compared patients with higher and lower CRP levels on day 1. This approach aimed to identify factors associated with elevated CRP levels and their corresponding outcomes. Second, we compared patients who died within 90 days with those who survived to assess the relationship between baseline CRP levels, their temporal changes and mortality.

Continuous data are presented as medians with interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Group comparisons were performed using Student's *t*-test or Mann–Whitney *U*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. We performed receiver operator characteristic (ROC) analysis to assess the discriminative ability of CRP levels on days 1, 3, and 7, changes in CRP and procalcitonin levels on days 1, 3, and 7, and changes in procalcitonin to predict 90-day mortality and reported their area under the curve (AUC). We also conducted stepwise multivariable logistic regression analysis, applying backward elimination based on the likelihood ratio test to determine if a CRP level > vs. < 75 mg/L on day 1 was a risk factor for 90-day mortality (binary variable). Clinically significant variables (age, sex, body mass index, chronic comorbidities [diabetes, hypertension, chronic cardiovascular disease, chronic respiratory disease, chronic kidney disease, stroke, and cancer], admission Glasgow Coma Scale score, confirmed vs. suspected sepsis at the time of the first CRP measurement, community-acquired vs. hospital-acquired sepsis, baseline laboratory tests [white blood cell count, hemoglobin, creatinine, bilirubin, international normalized ratio, albumin and lactate levels], modified SOFA score, vasopressor therapy, and mechanical ventilation) were entered into the model as independent variables. In the model, we imputed the missing values for the continuous variables by their respective medians, as most variables were non-normally distributed. The results are presented as odds ratios (OR) with 95% confidence intervals (CI). All statistical analyses were performed using the SPSS version 15. Statistical significance was defined as a two-sided p-value < 0.05.

Results

Characteristics of Patients

The study cohort consisted of 171 patients with a median age of 67 years (IQR, 56–77 years), 55% male, and a median modified SOFA score of 5 (IQR, 2–7) (Table 1). Most patients were admitted to the medical service (64.9%), followed by surgery (23.4%) and hematology/oncology (11.7%). Chronic comorbidities were also common. The median CRP level

Table 1 Characteristics of the Study Cohort Using Two Comparison Groups: Baseline CRP <75 vs. ≥75 mg/L, and 90-Day Outcome (Survivors vs. Non-Survivors)

	All Patients	Comparison 1			Comparison 2		
	N=171	Day-1 CRP <75 mg/L N=84	Day-1 CRP ≥75 mg/L N=87	P-value	Survived at 90 days N=129	Died at 90 days N=42	P-value
Age (years), median (IQR)	67 (56, 77)	65.5 (55.0, 77.0)	68.0 (57.0, 78.0)	0.67*	66 (55, 76.5)	70.5 (60, 80.3)	0.06*
Male sex, n (%) Female sex, n (%)	94 (55.0) 77 (45.0)	46 (54.8) 38 (45.2)	48 (55.2) 39 (44.8)	0.96	70 (54.3) 59 (45.7)	24 (57.1) 18 (42.9)	0.75
Body mass index (kg/m^2), median (IQR)	27.5 (23.8, 32.4)	27.3 (24.2, 31.4)	27.8 (23.3, 33.4)	0.84*	27.5 (23.7, 32.4)	27.3 (23.9, 32.9)	0.86*
Admitting service, n (%)							
Medicine	111 (64.9)	60 (71.4)	51 (58.6)	0.02	84 (65.1)	27 (64.3)	<0.0001
Hematology/Oncology	20 (11.7)	4 (4.8)	16 (18.4)		7 (5.4)	13 (31.0)	
Surgery	40 (23.4)	20 (23.8)	20 (23.0)		38 (29.5)	2 (4.8)	
Comorbidities, n (%)							
Diabetes	119 (69.6)	62 (73.8)	57 (65.5)	0.24	87 (67.4)	32 (76.2)	0.28
Hypertension	130 (76.0)	66 (78.6)	64 (73.6)	0.44	100 (77.5)	30 (71.4)	0.42
Coronary artery disease	47 (27.6)	25 (30.1)	22 (25.3)	0.48	35 (27.3)	12 (28.6)	0.88
Chronic kidney disease	53 (31.0)	26 (31.0)	27 (31.0)	0.99	35 (27.1)	18 (42.9)	0.06
Stroke	37 (21.6)	15 (17.9)	22 (25.3)	0.24	28 (21.7)	9 (21.4)	0.97
Chronic obstructive pulmonary disease	21 (12.3)	11 (13.1)	10 (11.5)	0.75	16 (12.4)	5 (11.9)	0.93
Chronic liver disease	14 (8.2)	8 (9.5)	6 (6.9)	0.53	11 (8.5)	3 (7.1)	1.0
Malignancy	43 (25.1)	12 (14.3)	31 (35.6)	0.001	30 (23.3)	13 (31.0)	0.32
Glasgow Coma Scale†, median (IQR)	14.0 (9.0, 15.0)	14.0 (11.0, 15.0)	14.0 (8.5, 15.0)	0.29*	15.0 (9.0, 15.0)	13.0 (9.5, 15.0)	0.78*
Modified SOFA score‡, median (IQR)	5 (2, 7)	5 (2, 7)	5 (2, 7)	0.44*	4 (2, 6)	6 (2, 8)	0.01
Pertinent laboratory findings, median (IQR)							
White blood cell count x 10^6/L	10.2 (7.1, 13.4)	9.4 (6.0, 13.2)	10.9 (7.9, 14.2)	0.13**	10.2 (7.2, 13.4)	10.7 (6.7, 13.3)	0.68**
Hemoglobin (g/L)	107 (88, 126.5)	110 (92, 129)	100 (86, 117)	0.09*	109 (89, 129)	105 (85, 111)	0.20*
International normalized ratio	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	0.47**	1.1 (1.0, 1.3)	1.2 (1.1, 1.3)	0.01**
Creatinine (μmol/L)	99 (64, 174)	106 (66, 148)	89 (61, 231)	0.62**	98 (63, 151)	114 (72, 227)	0.18**
Lactate (mmol/L)	2.0 (1.3, 3.0)	2.0 (1.1, 2.6)	2.2 (1.4, 3.3)	0.16**	2.0 (1.3, 3.0)	2.0 (1.4, 2.7)	0.85**
Albumin (g/L)	32 (27, 37)	32 (30, 37)	29 (26, 36)	0.003*	32 (28, 37)	30 (25, 34)	0.01*
Total bilirubin (μmol/L)	11.8 (7.1, 18.6)	11.5 (7.0, 18.8)	13.0 (7.3, 17.5)	0.66**	11.5 (6.9, 18.2)	14.7 (7.9, 27.3)	0.13**

Notes: † The score ranges from 3 (worst) to 15 (best) points. ‡ Platelet count unavailable; cardiovascular and respiratory components scored as 3 points for vasopressor use or intubation, otherwise 0. **T*-Test, **Mann–Whitney *U*-test. Number of patients with missing values: albumin n=2, lactate n=20, White blood cell count n=20, International normalized ratio n=50, creatinine n=3, Bilirubin n=10.

Abbreviations: BMI, Body mass index; CRP, c-reactive protein; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

on day 1 was 76 mg/L (IQR 20, 148). 84 patients (49.1%) had the first CRP < 75 mg/L and 87 (50.9%) ≥ 75 mg/L. Compared to patients with lower CRP levels, those with CRP levels ≥ 75 mg/L had similar demographics and clinical characteristics, except for a higher prevalence of malignancy (35.6% vs. 14.3%, p=0.001) and lower albumin levels. Forty-two patients (24.6%) died within 90 days and tended to be older (median age 70.5 vs. 66 years, p=0.06), with more admissions under hematology/oncology (31% vs. 5.4%, p<0.0001) and higher median SOFA score (6 vs.s 4, p=0.01) (Table 1).

Sepsis Characteristics and Diagnostic Workup, Including CRP Levels

Table 2 presents data related to sepsis. Among the 171 patients, sepsis was suspected in 64.3% and confirmed in 35.7% of patients when the first CRP level was measured. The most common source of infection was respiratory infection (36.2%).

Table 2 Sepsis Workup Results and Key Management in the Intensive Care Unit for the Study Cohort. We Used Two Comparison Groups: Baseline CRP <75 vs. ≥75 mg/L, and 90-Day Outcome (Survivors vs. Non-Survivors)

	All Patients	Comparison 1			Comparison 2		
	N=171	Day-1 CRP <75 mg/L N=84	Day-1 CRP ≥75 mg/L N=87	P-value	Survived at 90 days N=129	Died at 90 days N=42	P-value
Sepsis when the first CRP was measured, n (%)							
Suspected	110 (64.3)	60 (71.4)	50 (57.5)	0.06	89 (69.0)	21 (50.0)	0.03
Confirmed	61 (35.7)	24 (28.6)	37 (42.5)		40 (31.0)	21 (50.0)	
Source of infection*, n (%)							
Blood stream	15 (8.8)	5 (6.0)	10 (11.5)	0.20	7 (5.4)	8 (19.0)	0.01
Respiratory	62 (36.2)	29 (34.5)	33 (37.9)	0.64	49 (38.0)	13 (31.0)	0.41
Urine	21 (12.3)	12 (14.3)	9 (10.3)	0.43	16 (12.4)	5 (11.2)	0.93
Abdominal	2 (1.2)	1 (1.2)	1 (1.1)	0.98	1 (0.8)	1 (1.2)	0.43
Soft tissue	4 (2.3)	1 (1.2)	3 (3.4)	0.33	2 (1.6)	2 (4.8)	0.25
Indeterminate	73 (42.7)	40 (47.6)	33 (37.9)	0.20	58 (45.0)	15 (35.7)	0.29
Community-acquired, n (%)	74 (43.3)	39 (46.4)	35 (40.2)	0.41	56 (43.4)	18 (42.9)	0.95
Hospital-acquired, n (%)	95 (55.6)	45 (53.6)	50 (57.5)	0.61	71 (55.0)	24 (57.1)	0.81
Results of sepsis workup, n (%)							
Positive blood culture	52/162 (32.1)	23 (29.1)	29 (34.9)	0.43	34/121 (28.1)	18/41 (43.9)	0.06
MDRO from any culture source	30 (17.5)	12 (14.3)	18 (20.7)	0.27	19 (14.7)	11 (26.2)	0.09
Influenza	3/81 (3.7)	2 (4.9)	1 (2.5)	1.0	2/62 (3.2)	1/19 (5.3)	0.68
COVID-19	26/125 (20.8)	12 (20.3)	14 (21.2)	0.90	19/98 (19.4)	7/27 (25.9)	0.46
Intravenous antimicrobial use, n (%)							
Ceftriaxone	23 (13.5)	10 (11.9)	13 (14.9)	0.56	18 (14.0)	5 (11.9)	0.74
Meropenem/imipenem	87 (50.9)	39 (46.4)	48 (55.2)	0.25	57 (44.2)	30 (71.4)	0.002
Piperacillin/tazobactam	83 (48.5)	43 (51.2)	40 (46.0)	0.50	64 (49.6)	19 (45.2)	0.62
Vancomycin/linezolid	65 (38.0)	31 (36.9)	34 (39.1)	0.77	44 (34.1)	21 (50.0)	0.07
Antifungal agents	22 (12.9)	9 (10.7)	13 (14.9)	0.41	12 (9.3)	10 (23.8)	0.02
Biomarker levels, median (IQR)							
CRP day 1 (mg/L)	76 (20, 148)	20 (9, 47)	148 (105, 226)	<0.001**	70 (16.5, 146. 5)	91 (35, 156)	0.08**
CRP day 2 (mg/L)	78 (29, 146.5)	40 (13, 89)	114 (69, 231)	<0.001**	78 (23, 140.5)	83 (43, 219)	0.18**

(*Continued*)

Table 2 (Continued).

	All Patients	Comparison 1			Comparison 2		
	N=171	Day-1 CRP <75 mg/L N=84	Day-1 CRP ≥75 mg/L N=87	P-value	Survived at 90 days N=129	Died at 90 days N=42	P-value
CRP day 3 (mg/L)	73 (29.5, 127)	46 (18, 95)	95 (45, 167)	<0.001**	63 (24, 117.5)	103 (45, 153)	0.02**
CRP day 1: albumin ratio	2.2 (0.6, 5.4)	0.6 (0.2, 1.4)	5.3 (3.7, 7.1)	<0.001**	1.9 (0.5, 5.3)	3.3 (1.1, 5.9)	0.03**
Change in CRP 3_1 (fraction)	0.00 (−0.39, 0.90)	0.54 (−0.23, 1.79)	−0.26 (−0.50, 0.18)	<0.001**	0.0 (−0.4, 1.0)	−0.37 (0.03, 0.48)	0.56**
Change in CRP 7_1 (fraction)	−0.08 (−0.53, 1.00)	0.88 (−0.30, 4.25)	−0.32 (−0.72, 0.01)	<0.001**	−0.08 (−0.55, 1.19)	0.04 (−0.37, 0.48)	0.82**
Procalcitonin day 1 (ng/mL)	0.31 (0.08, 0.79)	0.09 (0.05, 0.31)	0.57 (0.27, 1.82)	<0.001**	0.20 (0.06, 0.66)	0.51 (0.24, 1.11)	0.02**
Procalcitonin day 3 (ng/mL)	0.43 (0.11, 1.44)	0.25 (0.07, 0.81)	0.62 (0.17, 2.32)	0.001**	0.30 (0.09, 1.30)	0.58 (0.31, 2.49)	0.01**
Procalcitonin day 7 (ng/mL)	0.31 (0.10, 1.15)	0.17 (0.05, 0.53)	0.70 (0.20, 3.17)	<0.001**	0.23 (0.07, 0.88)	0.75 (0.30, 4.73)	<0.0001**
Change in procalcitonin 3_1 (fraction)	0.14 (−0.38, 1.97)	0.31 (−0.14, 2.52)	−0.05 (−0.57, 1.40)	0.08**	0.02 (−0.47, 1.83)	0.29 (−0.19, 2.34)	0.14**
Change in procalcitonin 7_1 (fraction)	0.20 (−0.37, 1.52)	0.16 (−0.25, 1.83)	0.25 (−0.66, 1.27)	0.35**	0.04 (−0.48, 1.20)	0.66 (−0.13, 4.77)	0.02**
Management in the intensive care unit, n (%)							
Vasopressor use	31 (18.1)	15 (17.9)	16 (18.4)	0.93	16 (12.4)	15 (35.7)	0.001
Kidney replacement therapy	36 (21.1)	16 (19.0)	20 (23.0)	0.53	20 (15.5)	16 (38.1)	0.002
Mechanical ventilation	89 (52.0)	43 (51.2)	46 (52.9)	0.83	6 4 (49.6)	25 (59.5)	0.26
Tracheostomy	21 (12.3)	8 (9.5)	13 (14.9)	0.28	15 (11.6)	6 (14.3)	0.65

Notes: *some patients had more than one source. **Mann–Whitney *U*-test. Number of patients with missing values: procalcitonin day 1 n=35, procalcitonin day 3 n=48, procalcitonin day 7 n=46.
Abbreviations: CRP, C-reactive protein; IQR, interquartile range; MDRO, multidrug resistant organism.

Multidrug-resistant organisms from different sources were identified in 17.5% of the patients. COVID-19 and influenza were detected in 20.8% and 3.7% of the patients, respectively. The CRP levels on days 1, 3, and 7 were 76 mg/L, 78 mg/L, and 73 mg/L, respectively. The CRP/albumin ratio on day 1 was 2.2. The proportional changes in CRP from day 1 to day 3 and from day 1 to day 7 were 0.00 and −0.08, respectively. Procalcitonin levels on days 1, 3, and 7 were 0.31, 0.43, and 0.31 ng/mL, respectively. The proportional changes in procalcitonin were 0.14 and 0.20, respectively.

Compared to survivors, non-survivors had a significantly higher rate of confirmed sepsis (50.0% vs. 31.0%, p=0.03), bloodstream infections (19.0% vs. 5.4%, p=0.01), and multidrug-resistant organisms (26.2% vs. 14.7%, p=0.09). Figure 1A shows the serial CRP measurements. The CRP level on day 1 was slightly higher in the non-survivors (p=0.08). CRP/albumin on day 1 and CRP on day 7 were significantly higher in the non-survivors (p=0.020 and p=0.03, respectively). However, the proportional changes in the CRP levels over time were similar. Procalcitonin levels on days 1, 3, and 7 were significantly higher in non-survivors, especially on day 7 (p<0.0001), with a proportional change from day 1 to day 7 (p=0.02) (Figure 1B).

Sepsis Management

Meropenem/imipenem (50.9%) and piperacillin/tazobactam (48.5%) were the most commonly administered antibiotics used. Among these patients, 18.1% required vasopressors, 21.1% underwent renal replacement therapy, and 52.0% required mechanical ventilation. The median number of administered antibiotics was one in the low CRP group (IQR: 1, 2) and two in the high CRP group (IQR: 1, 3; p=0.46). Although meropenem duration was similar between the high and low CRP groups, it tended to be shorter in patients who had a decrease in CRP levels from days 1 to 7 (median 7 days [IQR: 5–10]) than in those whose CRP levels increased (median 10 days [IQR: 7–14]; p=0.06). ICU interventions did not differ significantly between the two CRP groups. Surprisingly, no association was observed between meropenem duration and PCT changes over time.

In contrast, when comparing survivors with non-survivors, antibiotic and ICU management patterns differed significantly. Non-survivors were more likely to receive broad-spectrum antibiotics such as meropenem/imipenem

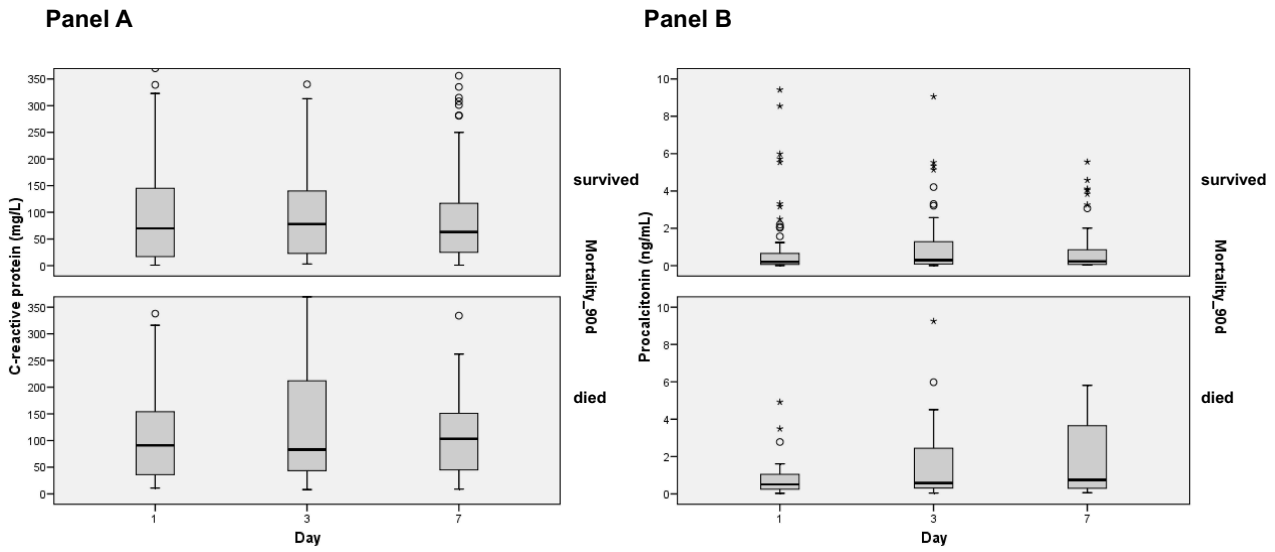

Figure 1 Box plots for C-reactive protein (**A**) and procalcitonin (**B**) levels on days 1, 3 and 7 in patients who died and did not die at 90 days after hospital admission. Circles indicate mild outliers. Stars indicate extreme outliers.

(71.4% vs. 44.2%, p=0.002; similar meropenem duration) and antifungal therapy (23.8% vs. 9.3%, p=0.02). They also received more intensive support including vasopressors (35.7% vs. 12.4%, p=0.001) and renal replacement therapy (38.1% vs. 15.5%, p=0.002) (Table 2).

Outcomes

In the study cohort, 30-day mortality rate were 11.7%, 90-day mortality 24.6%, and hospital mortality reached 29.8%, respectively (Table 3). Patients with lower and higher baseline CRP levels had similar outcomes, with 30-day mortality rates of 8.37% and 14.9%, respectively (p=0.18) and hospital mortality rates of 25.0% and 34.5%, respectively (p=0.18). The 90-day mortality rate in the high CRP group was 29.9% compared with 19.0% in the lower CRP group (p=0.10). ROC curve analysis revealed that CRP on day1 had poor discrimination between 90-day survivors and non-survivors (AUC 0.590, 95% CI 0.498–0.681) (Figure 2A and Table 4). Changes in CRP levels from day 1 to days 3 and 7 also did not predict mortality (AUC 0.470, 95% CI 0.377–0.562 and AUC 0.512, 95% CI 0.423–0.601, respectively). Procalcitonin levels were more accurate in predicting 90-day mortality (Figure 2B and Table 4). On multivariable

Table 3 Other Outcomes of the Study Cohort. We Used Two Comparison Groups: Baseline CRP <75 vs. ≥75 mg/L, and 90-Day Outcome (Survivors vs. Non-Survivors)

	All Patients	Comparison 1			Comparison 2		
	N=171	Day-1 CRP <75 mg/L N=84	Day-1 CRP ≥75 mg/L N=87	P-value	Survived at 90 days N=129	Died at 90 days N=42	P-value
30-day mortality, n (%)	20 (11.7)	7 (8.3)	13 (14.9)	0.18	0 (0.0)	20 (47.6)	<0.0001
Hospital mortality, n (%)	51 (29.8)	21 (25.0)	30 (34.5)	0.18	9 (7.0)	42 (100.0)	<0.0001
Mechanical ventilation duration (days), median (IQR)	5.0 (2.0, 14.0)	5.0 (2.0, 14.0)	3.5 (1.3, 14.8)	0.19*	5.0 (2.0, 14.3)	4.0 (1.5, 19.0)	0.86*
Stay in intensive care unit (days), median (IQR)	10.0 (5.0, 25.0)	8.5 (5.0, 25.0)	12.0 (5.0, 26.0)	0.29*	9.0 (4.5, 25.0)	15.5 (7.0, 27.5)	0.08*
Stay in hospital (days), median (IQR)	28.0 (18.0, 64.0)	25.5 (17.0, 51.3)	31.0 (18.0, 69.0)	0.17*	28.0 (17.0, 81.0)	36.0 (23.0, 47.5)	0.68*

Note: *Mann–Whitney *U*-test.
Abbreviations: CRP, C-reactive protein; IQR, interquartile range.

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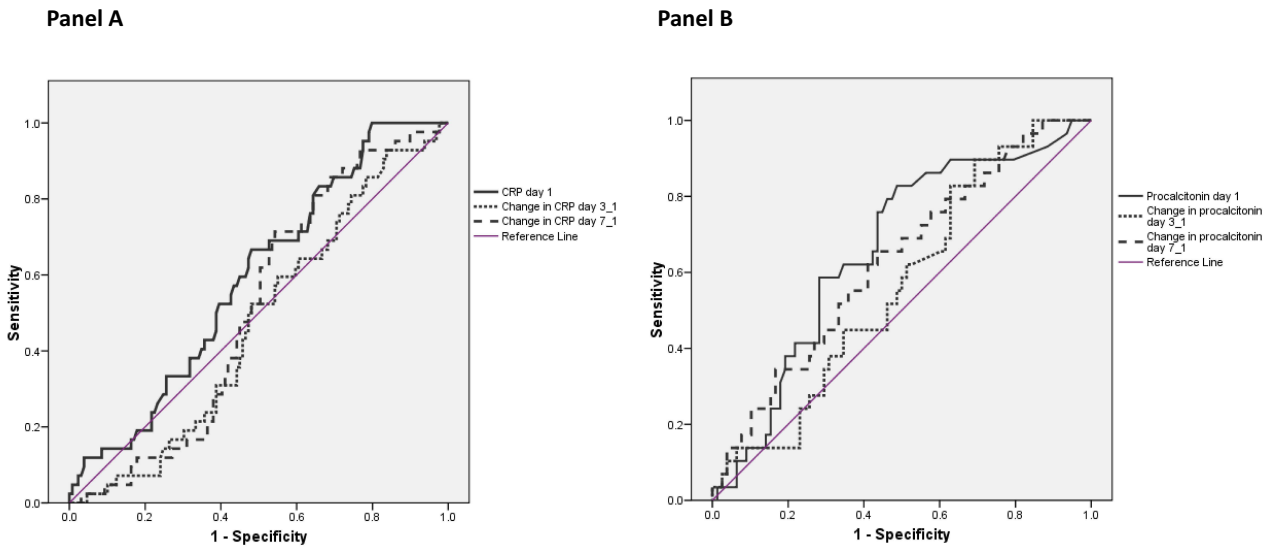

Figure 2 Receiver operating characteristic (ROC) curve analysis evaluating the ability of C-reactive protein (CRP) levels and their changes over time (**A**) and procalcitonin levels and their changes over time (**B**) to predict 90-day mortality.

logistic regression analysis, the CRP level on day 1 was not associated with 90-day mortality. The significant risk factors were age (OR per one-year increment, 1.044, 95% CI 1.010–1.079, p=0.01), hypertension (OR 0.138, 95% CI 0.041–0.462, p=0.001), chronic kidney disease (OR 2.720, 95% CI 1.039–7.121, p=0.04), and modified SOFA score (OR per unit increment 1.208, 95% CI 1.066–1.369, p=0.003).

There were no differences in other outcomes, including duration of mechanical ventilation and length of stay in the ICU and hospital, between the lower and higher CRP groups and 90-day survivors and non-survivors, except for a slightly longer LOS in the ICU for non-survivors (15.5 vs. 9.0 days, p=0.08) (Table 3).

Table 4 Receiver Operating Characteristic Curve Analysis for Ability of C-Reactive Protein (CRP) and Procalcitonin Levels, and Their Temporal Changes, to Predict 90-Day Mortality

Variable	Area Under the Curve	95% Confidence Interval	P-value
CRP on day 1	0.590	0.498, 0.681	0.081
CRP on day 3	0.569	0.471, 0.667	0.178
CRP on day 7	0.622	0.525, 0.719	0.018
Change in CRP between day 3 and day 1	0.470	0.377, 0.562	0.377
Change in CRP between day 7 and day 1	0.512	0.423, 0.601	0.818
Procalcitonin on day 1	0.658	0.547, 0.770	0.012
Procalcitonin on day 3	0.654	0.547, 0.760	0.010
Procalcitonin on day 7	0.714	0.617, 0.811	<0.001
Change in procalcitonin between day 3 and day 1	0.565	0.450, 0.680	0.303
Change in procalcitonin between day 7 and day 1	0.627	0.511, 0.742	0.045

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Discussion

Several inflammatory markers are used during critical illness for diagnostic, risk stratification, management, and prognostic purposes and may be used as part of individualized medicine.[4,5] These biomarkers include white blood cell count, differential cell ratios, erythrocyte sedimentation rate, and acute phase proteins such as CRP and procalcitonin.[4,5] CRP is a fast, easy-to-use, and cost-effective measurement. It has become a routinely used test in the management of hospitalized patients.[7,8] In sepsis, one of the main clinical applications of CRP in sepsis is to guide antibiotic therapy. A meta-analysis of three randomized controlled trials, including 727 hospitalized patients with sepsis, found that CRP-guided management reduced the antibiotic duration by almost 2 days without a significant increase in mortality.[6] A similar finding was observed in a trial involving patients with community-acquired pneumonia.[15] However, a recent multicenter trial in 2760 ICU adults patients with suspected sepsis found that while a procalcitonin-guided protocol shortened antibiotic duration, a CRP-guided protocol did not provide benefits compared with standard care.[16] We found a trend for a shorter meropenem duration in patients who had CRP levels decreased from days 1 to 7, suggesting that clinicians may have incorporated serial CRP measurements into antibiotic decision-making.

Our findings showed that baseline CRP level was not independently associated with 90-day mortality in ICU patients with sepsis. Multiple observational studies have demonstrated that CRP has prognostic value;[9,10] however, this was not observed in other studies. Our findings align with those of a systematic review in which the baseline CRP level in critically ill patients was not associated with mortality at 28–30 days (OR 1.01, 95% CI 0.87–1.17), even after adjusting for covariates such as age and severity score.[11] Other biomarkers, including baseline procalcitonin and interleukein-6, did not perform better.[11] Heterogeneity across studies, including differences in patient characteristics and study methodologies, likely contributes to the variability in the reported findings. For example, one study found that CRP levels were higher in gram-negative infections than in gram-positive infections[17] suggesting that the prognostic performance of a biomarker may be affected by patient characteristics, which may vary across studies.

We also found that CRP changes over time (days 3 and 7) did not have a better predictive accuracy for mortality than baseline CRP. In contrast, Povoa et al found that CRP levels decreased faster in patients with community-acquired pneumonia who responded to treatment than in non-responders.[2] Another study found that changes in CRP were significantly associated with mortality in patients with sepsis but with poor discriminatory ability (AUC 0.629).[18] In a large ICU cohort of 1464 patients with sepsis, four CRP trajectories were identified: persistently low, intermediate, gradually increasing, and persistently high.[19] The multiple logistic regression analysis showed that patients with persistently high and unexpectedly low CRP levels had a higher risk of in-hospital mortality than those with intermediate CRP levels.[19] Our findings further challenge the assumption that CRP kinetics is a reliable prognostic marker in critically ill patients with sepsis.

In the present study, procalcitonin outperformed CRP in the prediction of mortality. In contrast to CRP, procalcitonin levels were significantly higher in non-survivors at all time points and showed better discrimination of the 90-day mortality. This supports growing evidence that procalcitonin may be a more robust biomarker for risk stratification in sepsis. A systematic review of 44 studies performed between 1997 and 2024 with 10755 patients, procalcitonin exhibited a higher pooled AUC of 0.74 (95% CI 0.62–0.84) than CRP, which had an AUC of 0.67 (95% CI 0.56–0.77).[20] The 2026 international guidelines for sepsis management discourage procalcitonin for antibiotic initiation but suggests its use, with clinical judgment, to guide discontinuation.[21]

The strengths of this study include real-world data from a high-volume tertiary ICU in Saudi Arabia, serial CRP measurements, and evaluation of the clinical significance of CRP levels using different statistical methods. However, this study has several limitations. First, the retrospective observational design is prone to confounding, and the single-center data and inclusion of patients with at least 3 different CRP measurements within 8 days may have excluded the sickest patients and early deaths, introducing selection bias and limiting generalizability of our findings. Second, the sample size (171 patients with 42 death events within 90 days) was relatively small, which may have underpowered our ability to detect significant associations. The small number of early deaths further reduced power to study the association between CRP levels and short-term outcomes. Third, we were not able to verify whether Sepsis-3 criteria or other sepsis definitions were applied by the ICU team for sepsis diagnosis. Fourth, we could not calculate the full SOFA score

because of unavailable data. While modified SOFA scores are used in retrospective analysis, they may affect the accuracy of illness-severity assessment and subsequent inferential analysis. Fifth, factors such as infection source control, antibiotic appropriateness, and the timing of interventions were not evaluated and may have influenced the outcomes and the observed associations. Lastly, many patients had missing procalcitonin level data, preventing robust comparison with CRP.

Conclusions

In this study, serial CRP measurements appeared to influence antimicrobial decision-making, but did not reliably differentiate survivors from non-survivors, challenging the assumption that CRP kinetics serve as robust indicators of outcome in critically ill patients. This suggests that the prognostic utility of CRP in sepsis is limited and supports a more cautious and context-specific use of CRP in prognostication. Our study highlights the critical need for rigorous, prospective, multicenter studies to clearly define the role of inflammatory biomarkers in sepsis management.

AI Declarations

All authors declare that AI tools were not utilized in the writing of the manuscript, creation of images, or collection and analysis of the data.

Data Sharing Statement

Data supporting the findings of this study are available upon request from the corresponding author. The data were not publicly available due to privacy or ethical restrictions.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of the Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia (study number: NRR24/038/8; IRB approval no: 0000036924). As the study was retrospective, with no direct contact with the patients, the requirement for informed consent was waived. This study was conducted in accordance with the guidelines of the Declaration of Helsinki (2000) and *Good* Clinical Practice E6 (R2).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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