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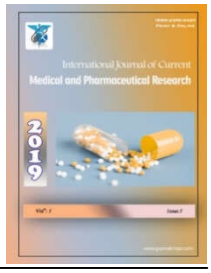

Research Article

MORTALITY PROGNOSTICATING PERFORMANCE COMPARISONS OF C-REACTIVE PROTEIN AND ITS RATIO TO ALBUMIN DURING FIRST WEEK OF ADMISSION IN SEPTIC CRITICALLY ILL PATIENTS

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ABSTRACT

Background: C-reactive protein (CRP) and albumin level (ALB) are acute phase reactants and are used in many studies as mortality prognosticators.
Objective: The aim of this study is to evaluate the prediction performance differences betweenCRP at admission (CRP_1)and its ratio to ALB($CRP:ALB_1$), CRP 1 week after admission (CRP2) and its ratio to ALB ($CRP:ALB_2$),and percentage changes of CRP to ALB ratio during first week of ICU admission (% Δ CRP:ALB ratio) for prediction of early ICU mortality (≤14 days of admission), late ICU admission (>14 days of admission), and overall 28-ICU mortality in critically ill patients with septic shock who were taking norepinephrine.
Methods: This single-center retrospective study conducted in the department of adult Intensive Care Unit (ICU) by examining the medical records between April 2017 to Sep 2018. Allpatient's variables were analyzed using independent samples T-test, χ 2 test, or Mann-Whitney U test.
Result: The mean overall age was 58.37±9.96 years, and 112 subjects (68.71%) were male. The early, late, and overall 28-day ICU mortality rate were 16 patients (9.82%), 48 patients (29.45%), and 64 patients (39.26%), respectively.The CRP_2, $CRP:ALB_2$, and %ΔCRP:ALB were significantly higher in nonsurvivors than survivors. %ΔCRP: ALB shows the highest performance for prediction of late (66.00%) and overall 28-day mortality (81.40%) in compared with other tested prognosticators.
Conclusion: %ΔCRP:ALB is an effective, realistic, dynamic, reliable, and discriminative prognosticator with high performance, specificity, positive predictive value, and accuracy when compared with other relative tested prognosticators for prediction of late and 28-day but not early ICU mortality.

INTRODUCTION

Globally, sepsis is defined as systemic inflammatory response syndrome (SIRS) with evidence of infection which poses substantial clinical, financial, logistical challenges, and chronic inflammatory and nutritional negative impacts.[1-3]This physiological response to systemic inflammation onset positive-phase reactants synthesis like CRP in preference of negative-phase reactants like ALB.CRP is a useful positive acute-phase reactant marker that can predict morbidity and mortality among critically ill patients and may be used to predict the prognosis of septic patients.[4-9] The prognostic roles of CRP and ALB can be explained by their direct and indirect relationships regarding ALB synthesis rate, ALB catabolic rate, ALB transcapillary escaping rate (TER), and mal-nutrition status in which the clinical usefulness of CRP: Ratio are proved in many retrospective and prospective studies.[10-22] Based on these interrelated correlations and the dynamic instability status of the critically ill patients, we proposed that the prognosticator efficacy of CRP: ALB ratio may be increased if we assessed the changes of CRP:ALB over the first week of ICU admission because this mortality predictors is a reliable, affordable, and clinically applicable that may help prognosticate the survival of these patients and would subsequently force the care of septic critically ill patients and assist in the course of effective treatment. Our objective was to test the hypothesis that % Δ CRP:ALB ratio have a higher mortality prognostic performance than the other objective analogue independent prognostic indicators of CRP_1, CRP_2, $CRP:ALB_1$, and $CRP:ALB_2$in prediction the primary outcome of overall 28-day mortality, and the secondary outcomes of early mortality (≤ 14 days), late mortality (>14 days), and overall hospital and ICU length of stay (LOS) in septic critically ill patients who are taking norepinephrine as a vasopressor taking into consideration the dynamic pattern of these cohort patients. This study also aimed to determine the optimal cut-off point of the five tested prognosticators and to examine these five mortality predictors as a novel prognostic factors.

MATERALS AND METHODS

This retrospective study was conducted in the department of adult Intensive Care Unit (ICU) of King Hussein Medical

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Center (KHMC), Royal Medical Services, Jordan. This study was approved by our institutional review board, and a requirement for consent was waived owing to its retrospective design. Patients were included if the study patients were admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problem between April 2017 to Sep 2018. Flow chart of critically ill patient's selection and data collection process is fully illustrated in **Figure 1**.All patient continuous variables were expressed as mean± standard deviation by using the independent samples T-test while categorical and ordinal variables were expressed as numbers with percentages by using the χ^2 test or as median (interquartile range) by using the Mann-Whitney U test, respectively. Analysis values were compared for the two tested groups (survivors vs. non-survivors) and the non-survival group was further analysed after being divided into 2 subgroups, early (≤14 days) and late (>14 days) mortality. A receiver operating characteristic (ROC) curve followed by sensitivity analysis was used to determine the area under the ROC curves (AUROCs), predictive performances, and the optimal cut-off values for the five tested prognosticators. Youden's indices, sensitivities, specificities, positive and negative predictive values, and accuracy indices were also calculated. Statistical analyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

RESULT

The mean overall age was 58.37±9.96 years, and 112 subjects (68.71%) were male. The early, late, and overall 28-day ICU mortality rate were 16 patients (9.82%), 48 patients (29.45%), and 64 patients (39.26%), respectively. Pre-ICU, ICU, and overall hospital stay days were significantly higher in non-survivors than survivors (7.42±4.57 days, 17.30±4.14 days, and 24.72±1.98 days vs 2.23±1.06 days, 9.23±1.06 days, and 11.46±2.12 days, respectively). There were insignificant differences between the survivors and nonsurvivors regarding average child-Pugh score, average Glasgow coma scale (GSC), and average norepinephrine infusion rate. Despite CRP_1 was insignificantly higher in nonsurvivors than survivors (8.29±3.77 mg/dl vs 7.69±2.54 mg/dl), the $CRP:ALB_1$ was significantly higher (3.21±1.79 vs 2.84±1.21) due to significantly higher ALB_1in survivors in compared with nonsurvivors (2.79±0.20 g/dl vs was2.74±0.29 g/dl). The CRP_2, $CRP:ALB_2$, and %ΔCRP:ALB were significantly higher in nonsurvivors than survivors (49.80±16.05 mg/dl, 33.00±19.77, and 1111.16%±824.86% vs 22.96±8.18 mg/dl, 8.29±4.70, and 202.88%±119.13%, respectively) while ALB_2 was significantly higher in survivors than nonsurvivors (2.98±0.41 g/dl vs 1.79±0.52 g/dl). Regarding nutritional indices, only protein density (PD) and percentage of protein calorie from total calorie (%PC_TC) were significantly higher in survivors than nonsurvivors (3.72±0.74 g/100 Cal and 10.84%±2.74% vs 3.50±0.36 g/100 Cal and 9.45%±0.99%, respectively) while total calorie (TC) was insignificantly higher in survivors than nonsurvivors (1357.56±270.23 Cal/day vs 1280.54±243.32 Cal/day).Demographics, anthropometrics, assessment scores, nutritional variables, stay days, and follow-up tested mortality predictors comparison data of the study's critically ill patients are fully summarised in Table 1. Table 2 shows the optimal cut-off point, sensitivity (TPR), specificity (TNR), Youden's index (YI), positive and negative predictive values (PPV and NPV), negative likelihood ratio (NLR), and accuracy index (AI) of the five tested prognosticators among the three stratified mortalities. The best cut-off values for CRP_1, $CRP:ALB_1$, CRP_2, $CRP:ALB_2$, and %Δ CRP:ALB in our study among mechanically ventilated critically ill patients were (12.55 mg/dl, 18.91 mg/dl, 5.29:1, 7.87:1, 61.25%, respectively) for overall 28-day ICU mortality, (13.70 mg/dl, 27.18 mg/dl, 5.91:1, 12.06:1, and 86.52%, respectively) for early ICU mortality, and (10.63 mg/dl, 17.71 mg/dl, 4.29:1, 6.85:1, and 48.89%, respectively) for late mortality.The AUROCs of the five tested prognosticators in this study were significantly greater for %ΔCRP: ALBthan CRP_2, $CRP:ALB_2$, CRP_1, and $CRP:ALB_1$ (0.971, 0.941, 0.925, 0.701, and 0.701, respectively). The ROC curve analyses of the five tested prognosticators for early, late, and overall 28-day ICU mortality are fully shown in **Fig 2-4.**

DISCUSSION

The present study included septic mechanically ventilated critically ill patients who were taking norepinephrine as a vasopressor at an overall average rate of 9.53±1.79 mcg/min. To the best of our knowledge, this is the first study that compare five prognosticators of CRP and their ratios and changes over first week of ICU admission to prognosticate early, late, and overall ICU mortality. In the context of ever-shrinking resources, early stratification with affordable, valid, reliable, and discriminative predictive tools are critically needed in this unstable, high acuity, and high uncertainty status of the septic critically ill to avoid any potential delay or under-triaging while appropriately assigning a higher priority to sicker patients.[23-28]The greater significant ALB_2 in survivors in compared with nonsurvivors (2.98±0.41 g/dl vs 1.79±0.52 g/dl) may be attributed to multifactorial reasons included; significant lower CRP_2 (22.96±8.18 mg/dl vs 49.80±16.05 mg/dl), significantly higher PD and %PC_TC (3.72±0.74 g/100 Cal and 10.84%±2.74% vs 3.50±0.36 g/100 Cal and 9.45%±0.99%, respectively), and significantly higher human albumin dose (18.89±3.159 g/day vs 14.06±6.09 g/day).After careful analysis of the data, %ΔCRP: ALBshows higher performance, specificity, positive predictive value, and accuracy (81.40%, 97.00%, 94.79%, and 92.05%, respectively) for 28-day ICU mortality than CRP_2, $CRP:ALB_2$, CRP_1, and $CRP:ALB_1$.Also, %ΔCRP: ALBstill shows the highest performancein compared withCRP_2, $CRP:ALB_2$, CRP_1, and $CRP:ALB_1$(66.00% vs 62.20%, 55.70%,60.90%, and 30.80%) for late mortality. In case of early mortality, CRP_2 has the highest performance in compared with %ΔCRP:ALB, $CRP:ALB_2$, CRP_1, and $CRP:ALB_1$ (98.00% vs 87.70%, 93.20%, 67.30%, and 67.30%, respectively), possibly due to H.ALB administration that underestimate the performance of CRP:ALB as early mortality prognosticators.In summary, %ΔCRP:ALB is an effective, realistic, dynamic, reliable, and discriminative prognosticator with high performance, specificity, positive predictive value, and accuracy when compared with other relative prognosticators like; CRP_2, $CRP:ALB_2$, CRP_1, and $CRP:ALB_1$for prediction of late and 28-day ICU mortality while in case of early ICU mortality, CRP change and ratio have a lower performance than CRP alone due to underestimation effects of H.ALB in septic mechanically ventilated critically ill patients whoare taking norepinephrine. This study is limited by its retrospective design, confounder effect of H.ALB, and using single-centre data, including only septic mechanically ventilated ICU patients. Nonetheless, our centre is an experienced and high-volume unit, so our data may be useful in other centres. A

larger, multisite, and prospective study is needed to control for multiple confounders and to clarify the mortality performance of the five tested prognosticators for mortality risk early stratification of hospitalized patients including critically ill cohorts.

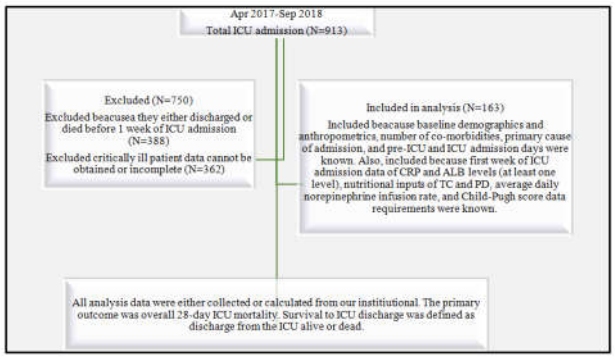

Fig 1 Flow chart of critically ill patient's selection and data collection process.
Apr: April.CRP: C-reactive protein.PD: Protein density.
Sep: September.ALB: Albumin.TC: Total calorie.
ICU: Intensive Care Unit. N: Number of studied critically ill patients.

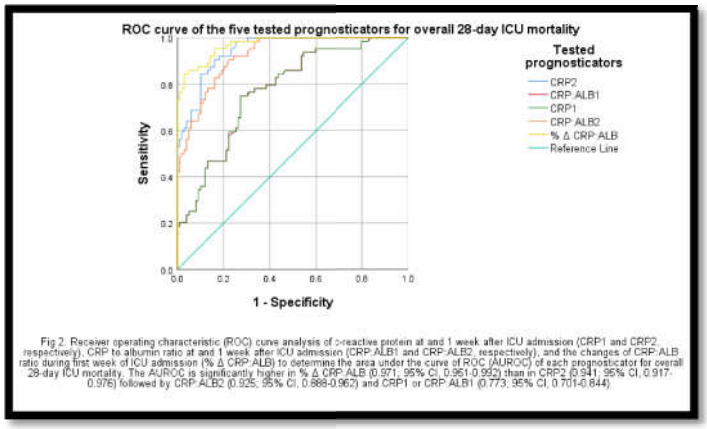

Fig 2. Receiver operating characteristic (ROC) curve analysis of c-reactive protein at and 1 week after ICU admission (CRP1 and CRP2 respectively), CRP to albumin ratio at and 1 week after ICU admission (CRP:ALB1 and CRP:ALB2, respectively), and the changes of CRP:ALB ratio during first week of ICU admission (% Δ CRP:ALB) to determine the area under the curve of ROC (AUROC) of each prognosticator for overall 28-day ICU mortality. The AUROC is significantly higher in % Δ CRP:ALB (0.971; 95% CI, 0.951-0.992) than in CRP2 (0.941; 95% CI, 0.917-0.976) followed by CRP:ALB2 (0.925; 95% CI, 0.888-0.962) and CRP1 or CRP:ALB1 (0.773; 95% CI, 0.701-0.844)

Table 1 Baseline and follow-up data of the comparative studied critically ill patient

Variables	Total(N=163)	Survivors(N=99)	Nonsurvivors (N=64)		P-Value
			Early Mortality(≤14 days) (N=16)	Late Mortality (>14 days) (N=48)	
Age (Yrs)	58.37±9.96	58.55±9.948	58.09±10.053	56.69±9.38	0.917 NS
Gender: Male	112 (68.71%)	67 (67.68%)	11 (68.75%)	34 (70.83%)	0.796 NS
Gender: Female	51 (31.29%)	32 (32.32%)	5 (31.25%)	14 (29.17%)	
Day(s) Pre-ICU admission (day(s))	4.27±3.91	2.23±1.06	7.42±4.57	5.46±1.10	0.000 S
ICU Stay day(s)	12.40±4.79	9.23±1.06	17.30±4.14	19.54±1.10	0.000 S
Hospital Stay day(s)	16.67±6.81	11.46±2.12	24.72±1.98	25.00±0.00	0.003 S
BW_1 (Kg)	74.17±10.24	74.63±10.06	73.45±10.56	74.79±10.69	0.609 NS
BMI_1 (Kg/m²)	25.92±4.00	26.19±3.85	25.50±4.22	25.97±4.14	0.311 NS
Child-Pugh $Score_{avg}$ (5-15)	6 (6-8)	6 (6-8)	6 (6-7)	6 (6-7)	0.088 NS
GCS $_{avg}$ (3-15)	12 (12-13)	12 (12-13)	12 (12-13)	12 (12-13)	0.341 NS
Human Albumin Dose $_{avg}$ (g/day)	16.99±5.11	18.89±3.159	14.06±6.09	15.63±5.01	0.02 (S)
ALB_1 (g/dl)	2.77±0.25	2.79±0.20	2.74±0.29	2.69±0.29	0.049 (S)
CRP_1 (mg/dl)	7.94±3.12	7.69±2.54	8.29±3.77	8.95±3.77	0.053 (NS)
$CRP:ALB_1$ (X:1)	2.99±1.49	2.84±1.21	3.21±1.79	3.53±1.89	0.032 (S)
ALB_2 (g/dl)	2.48±0.74	2.98±0.41	1.79±0.52	1.98±0.49	0.000 (S)
CRP_2 (mg/dl)	34.16±17.94	22.96±8.18	49.80±16.05	43.01±11.97	0.000 (S)
$CRP:ALB_2$ (X:1)	18.60±17.99	8.29±4.70	33.00±19.77	25.12±14.37	0.000 (S)
%ΔCRP:ALB	581.80%±701.04%	202.88%±119.13%	1111.16%±824.86%	624.76%±156.77%	0.000 (S)
TC $_{avg}$ (Cal/kg/day)	19.33±3.41	19.79±3.56	18.62±3.06	18.97±2.81	0.208 NS
TC $_{avg}$ (Cal/day)	1327.32±261.96	1357.56±270.23	1280.54±243.32	1313.43±227.52	0.581 NS
PD_{avg} (g/100Cal/day)	3.64±0.63	3.72±0.74	3.50±0.36	3.52±0.35	0.002 S
% PC_TC_{avg} (%)	10.29%±2.32%	10.84%±2.74%	9.45%±0.99%	9.60%±0.98%	0.000S
Norepinephrine Rate $_{avg}$ (mcg/min)	9.53±1.79	9.27±1.68	9.94±1.89	9.94±1.67	0.724 NS
28-day ICU Mortality: 28-day ICU Survival			9.94±2.49		
28-day ICU Mortality: Overall Mortality			99 (60.74%)		
28-day ICU Mortality: Early Mortality (≤14 days)			64 (39.26%)		0.000 S
28-day ICU Mortality: Late Mortality (>14 days)			16 (9.82%)		
			48 (29.45%)		

Values are presented as mean ± SD, median (range), or number (%).
N: Number of study's critically ill patients.
ICU: Intensive care unit.
1: Baseline at ICU admission.
2: 1 week after ICU admission.

Δ: Changes.
Avg: Average.
BMI: Body mass index.
BW: Body weight.
g: Gram.

S: Significant (P-Value <0.05).
NS: Non-significant (P-Value >0.05).
mcg: microgram.
Cal: Kcal.

TC: Total calories.
PD: Protein density.
CRP: C-reactive protein.
GCS: Glasgow coma scale.
ALB: Albumin level.

Table 2 Sensitivity, specificity, positive and negative predictive values, youden's and accuracy indices of the five tested prognosticators for overall 28-day ICU mortality, early and late ICU mortality.

Prognostic Indicator		Cutoff Values	TPR	FPR	YI	TNR	PPV	NPV	NLR	AI
Overall 28-day mortality	CRP_1	12.55	75.00%	27.30%	47.70%	72.70%	63.98%	81.81%	34.39%	73.60%
	CRP_2	18.91	90.60%	16.20%	74.40%	83.80%	78.33%	93.24%	11.22%	86.47%
	$CRP:ALB_1$	5.29	75.00%	27.30%	47.70%	72.70%	63.98%	81.81%	34.39%	73.60%
	$CRP:ALB_2$	7.87	90.60%	22.20%	68.40%	77.80%	72.51%	92.76%	12.08%	82.83%
	%Δ CRP:ALB	61.25%	84.40%	3.00%	81.40%	97.00%	94.79%	90.58%	16.08%	92.05%
Early mortality (≤14 days)	CRP_1	13.70	100.00%	32.70%	67.30%	67.30%	66.41%	100.00%	0.00%	80.14%
	CRP_2	27.18	100.00%	2.00%	98.00%	98.00%	97.00%	100.00%	0.00%	98.79%
	$CRP:ALB_1$	5.91	100.00%	32.70%	67.30%	67.30%	66.41%	100.00%	0.00%	80.14%
	$CRP:ALB_2$	12.06	100.00%	6.80%	93.20%	93.20%	90.48%	100.00%	0.00%	95.87%
	%Δ CRP:ALB	86.52%	93.80%	6.10%	87.70%	93.90%	90.86%	95.91%	6.60%	93.86%
Late mortality (>14 days)	CRP_1	10.63	91.70%	60.90%	30.80%	39.10%	49.33%	87.93%	21.23%	59.75%
	CRP_2	17.71	97.90%	35.70%	62.20%	64.30%	63.94%	97.93%	3.27%	77.49%
	$CRP:ALB_1$	4.29	91.70%	60.90%	30.80%	39.10%	49.33%	87.93%	21.23%	59.75%
	$CRP:ALB_2$	6.85	100.00%	44.30%	55.70%	55.70%	59.34%	100.00%	0.00%	73.09%
	%Δ CRP:ALB	48.89%	93.80%	27.80%	66.00%	72.20%	68.57%	94.74%	8.59%	80.68%

CRP_1: C-reactive protein at ICU admission.
CRP2: C-reactive protein after 1 week of ICU admission.
$CRP:ALB_1$: C-reactive protein to albumin level ratio at ICU admission.
$CRP:ALB_2$: C-reactive protein to albumin level ratio 1 week of ICU admission.
%ΔCRP:ALB: Percentage changes of CRP:ALB during 1 week of admission.
TPR: True positive rate (sensitivity)
FPR: False positive rate.
TNR: True negative rate (Specificity).
PPV: Positive predictive value.
NPV: Negative predictive value.
NLR: Negative likelihood ratio.
AI: Accuracy index.
YI: Youden's index.

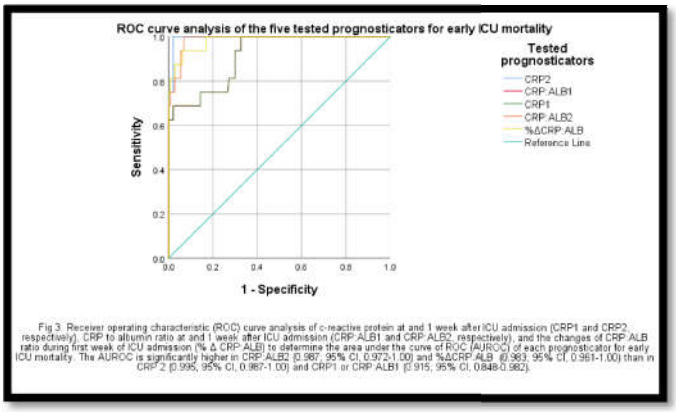

Fig 3. Receiver operating characteristic (ROC) curve analysis of c-reactive protein at and 1 week after ICU admission (CRP1 and CRP2 respectively), CRP to albumin ratio at and 1 week after ICU admission (CRP:ALB1 and CRP:ALB2, respectively), and the changes of CRP:ALB ratio during first week of ICU admission (% Δ CRP:ALB) to determine the area under the curve of ROC (AUROC) of each prognosticator for early ICU mortality. The AUROC is significantly higher in CRP:ALB2 (0.987, 95% CI, 0.972-1.00) and %ΔCRP:ALB (0.983, 95% CI, 0.961-1.00) than in CRP2 (0.995, 95% CI, 0.987-1.00) and CRP1 or CRP:ALB1 (0.915, 95% CI, 0.848-0.982).

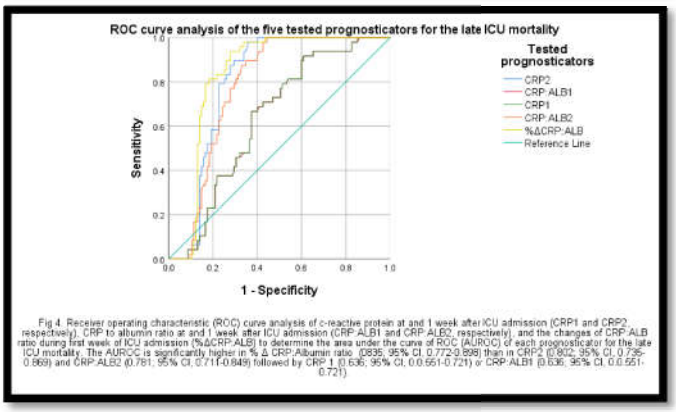

Fig 4. Receiver operating characteristic (ROC) curve analysis of c-reactive protein at and 1 week after ICU admission (CRP1 and CRP2 respectively), CRP to albumin ratio at and 1 week after ICU admission (CRP:ALB1 and CRP:ALB2, respectively), and the changes of CRP:ALB ratio during first week of ICU admission (%ΔCRP:ALB) to determine the area under the curve of ROC (AUROC) of each prognosticator for the late ICU mortality. The AUROC is significantly higher in % Δ CRP:Albumin ratio (.0835, 95% CI, 0.772-0.898) than in CRP2 (0.802, 95% CI, 0.735-0.869) and CRP:ALB2 (0.781, 95% CI, 0.711-0.849) followed by CRP 1 (0.636, 95% CI, 0.0.551-0.721) or CRP:ALB1 (0.636, 95% CI, 0.0.551-0.721)

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