Clinical Usefulness Of C-Reactive Protein Versus Shock Index In Predicting Mortality In Septic Critically Ill Patients Who Are Taking Nor-epinephrine

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ABSTRACT

Objective: C-reactive protein (CRP) and shock index (SI) have been previously shown to identify high risk septic shock patients.Our objective was to compare the ability of SI and CRP to predict the primary outcome of overall 28-day mortality, and the secondary outcomes of early mortality (≤ 14 days), late mortality (>14 days) in septic critically ill patients who are taking norepinephrine as a vasopressor.

Methods: We performed a retrospective analysis of patientsadmitted to our adult ICU between April 2017 and Sep 2018 who were meet the inclusion criteria. Independent T-test, Mann Whitney U test, and χ^2 test were used to express all patient variables.A receiver operating characteristic (ROC) curve followed by sensitivity analysis was generated to determine the predictive performances, and the optimal cut-off values for CRP and SI. The binary logistic regression model was used to generate CRP and SI predictive equations and correlation plots for early, late, and overall 28-day ICU mortality.

Results: A total of 163 critically ill patients were finally included in this study. 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 were9.82%, 29.45%, and 39.82%, respectively. SI and CRP were significantly higher in non-survivors (1.29±0.17 bpm/mmHg and 43.09±19.28 mg/dl, $p<0.05$) than in survivors (1.12±0.03 bpm/mmHg, and 28.38±14.38 mg/dl).

Conclusion: SI is an effective, no-cost bedside modality, which is a realistic, reliable, and discriminative prognosticator with high sensitivity, specificity, performance, and accuracy when compared with CRP.

Key words: C-reactive protein, Shock index, Critically ill patients, Norepinephrine.

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Introduction

Sepsis is a complex syndrome caused by the body's systemic response to an infection with a

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major cause of high treatment cost, single or multiple organ dysfunction, morbidity, and mortality [1]. The importance of having reliable, cost effective, and easily attainable clinical prognostic indicators that would help to predictand differentiate the mortality risk of these critically ill patientsis invaluable within an Intensive Care Unit (ICU). C-reactive protein (CRP) is a useful positive acute-phase reactant marker that can predict morbidity and mortality among critically ill patients. However,the results of CRP and other severity indices of sepsis may not be immediately available upon request [2], potentially delaying effective dynamic risk stratification and goal directed management in these unstable studied cohort. Also, Shock index (SI), defined as heart rate (HR) over systolic blood pressure (SBP)is a readily and affordable attained comprehensive parameter that combines two physiological variables (HR and SBP) into a single ratio that has previously been shown to stratify and served as an early warning indicator of high risk haemorrhagic shock from various aetiologies when compared to other conventional vital signs [3-8].From previous studies, SI has never been compared with CRP for its value in predicting early mortality (≤ 14 days), late mortality (> 14 days), and overall 28-day mortality among septic critically ill patients who are taking nor-epinephrine. Our objective was to compare the mortality risk stratifying ability of SI and CRP regarding the primary outcome of overall 28-day mortality, and the secondary outcomes of early and late mortality and ICU length of stay.

Methods

Study design and setting

This was a single-centreobservational retrospective study conducted in the department of adult ICU of King Hussein Medical Centre (KHMC) at Royal Medical Services (RMS) in Jordan. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included a cohort of critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medicalor surgical problems. Flow chart of critically ill patient’s selection and data collection process is fully illustrated in (Figure1).

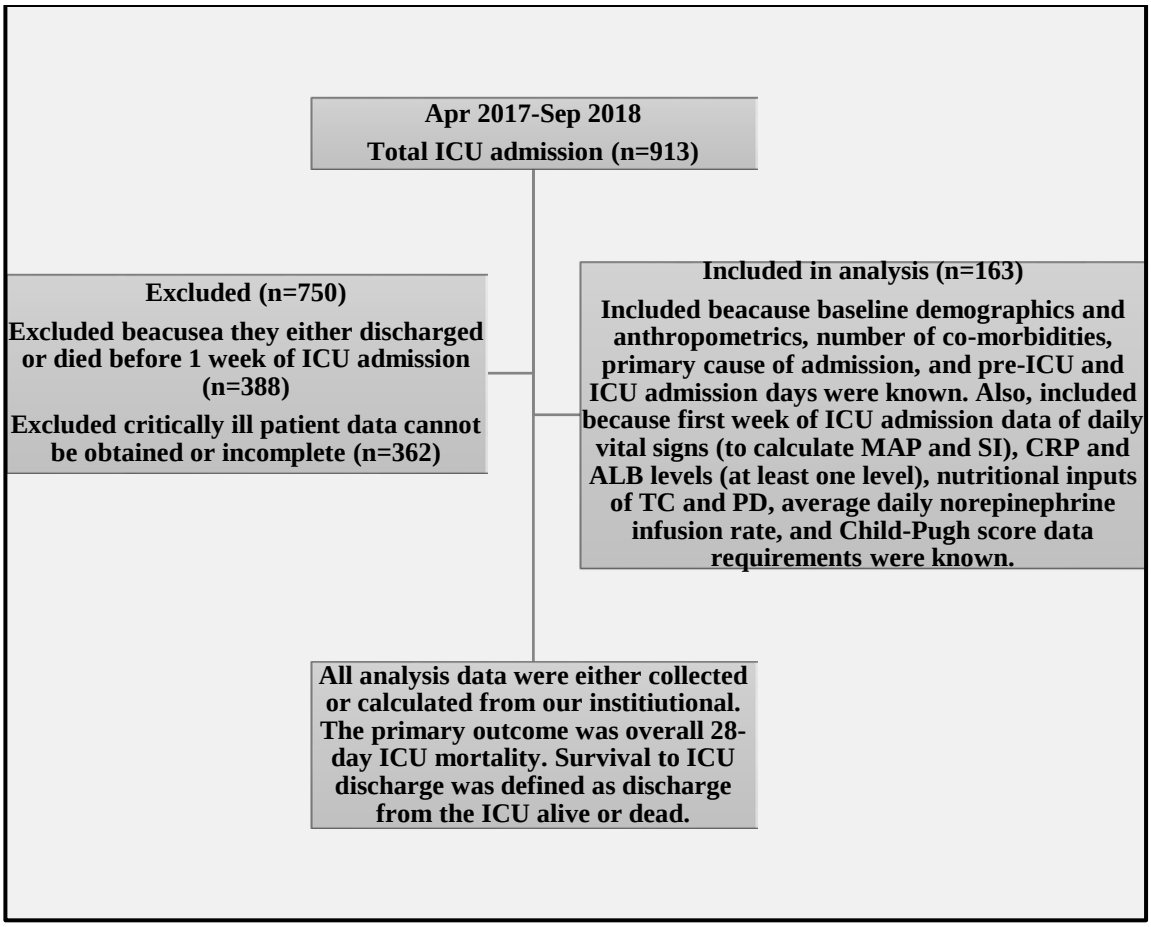

Fig 1. Flow chart of critically ill patient's selection and data collection process.

Apr: April. CRP: C-reactive protein.PD: Protein density.
Sep: September. MAP: Mean arterial pressure.ALB: Albumin.
ICU: Intensive Care Unit. SI: Shock index.TC: Total calorie.

Statistical analysis

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. Univariate analysis was conducted first followed by multivariate logistic regression for the most possible affected patient's variables associated with ICU mortality. A receiver

operating characteristic (ROC) curve followed by sensitivity analysis wasused to determine the area under the ROC curves (AUROCs), predictive performances, and the optimal cut-off values for CRP and SI. Youden indices, sensitivities, specificities, positive and negative predictive values, and accuracy indices were also calculated. The binary logistic regression model was used to generate CRP and SI predictive equations and correlation plots for early, late, and overall 28-day ICU mortality. Statisticalanalyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

Results

Characteristics of the subjects

The mean overall age was 58.37±9.96 years, and 112 subjects (68.71%) were male. The overall 28-day ICU mortality rate was 39.26% (64 patients); in16 patients (9.82%), this was early mortality and in 48 patients (29.45%) it was late mortality. Demographics, admission co-morbidities and class, anthropometrics, and follow-up comparison data of the study's critically ill patients are fully summarised in (Table I) and (Table II) , respectively.

Table I: Demographics and anthropometrics comparison of study's critically ill patients.

Variables		Total (n=163)	Survivors (n=99)	Non-survivors (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		0.92 NS
				62.31±11.12	56.69±9.38	
Gender	Male	112 (68.71%)	67 (67.68%)	45 (70.31%)		0.79 NS
				11 (68.75%)	34 (70.83%)	
	Female	51 (31.29%)	32 (32.32%)	19 (29.69%)		
				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		0.00 S
				13.31±5.89	5.46±1.10	
ICU Stay day(s)		12.40±4.79	9.23±1.06	17.30±4.14		0.00 S
				10.56±1.97	19.54±1.10	
Hospital Stay day(s)		16.67±6.81	11.46±2.12	24.72±1.98		0.00 S
				23.87±3.93	25.00±0.00	
Number of comorbidities	0, 1	74 (45.39%)	52 (52.53%)	22 (34.38%)		0.03 NS
				3 (18.75%)	19 (39.58%)	
	2 , 3, 4+	89 (54.60%))	47 (47.47%)	42 (65.63%)		
				13 (81.25%)	29 (60.42%)	

Admission class	**Medical**	105 (64.42%)	50 (50.51%)	55 (85.94%)		0.00 S
				14 (87.5%)	41 (85.42%)	
	Surgical	58 (35.58%)	49 (49.49%)	9 (14.06%)		
				2 (12.5%)	7 (14.58%)	
BW_1(Kg)		74.17±10.24	74.63±10.06	73.45±10.56		0.61 NS
				69.44±9.34	74.79±10.69	
BMI_1 (Kg/m²)		25.92±4.00	26.19±3.85	25.50±4.22		0.31 NS
				24.11±4.28	25.97±4.14	
28-day ICU Survival				99 (60.74%)		
28-day ICU Mortality	**Overall Mortality**			64 (39.26%)		
	Early Mortality (≤14 days)			16 (9.82%)		
	Late Mortality (>14 days)			48 (29.45%)		

Values are presented as mean±standard deviation or number (%).
Yrs: Years.
Kg: Kilogram.
m: Meter.
BW_1: Actual body weight at admission.
BMI_1: Body mass index at admission.
ICU: Intensive care unit.
S: Significant (P-Value <0.05).
NS: Non-significant (P-Value >0.05).
n: Number of study's critically ill patients.

Table II: Follow-up data comparison of study's critically ill patients.

Variables	**Total (n=163)**	**Survivors (n=99)**	**Non-survivors (n=64)**		**P-Value**
			Early Mortality (≤14 days) (n=16)	**Late Mortality (>14 days) (n=48)**	
Norepinephrine Rate (mcg/min)	9.53±1.79	9.27±1.68	9.94±1.89		0.72 NS
			9.94±2.49	9.94±1.67	
GCS (3-15)	12 (12-13)	12 (12-13)	12 (12-13)		0.34 NS
			12 (12-13)	12 (12-13)	
Child-Pugh Score(5-15)	6 (6-8)	6 (6-8)	6 (6-7)		0.09 NS
			6 (6-7)	6 (6-7)	
ALB $_1$ (g/dl)	2.75±0.32	2.63±0.20	2.94±0.39		0.00 S
			3.28±0.46	2.82±0.28	
Human Albumin Dose (g/day)	16.99±5.11	18.89±3.16	14.06±6.09		0.00 S
			9.38±6.80	15.63±5.01	
ALB (g/dl)	2.61±0.13	2.64±0.12	2.57±0.13		0.44 NS
			2.55±0.11	2.57±0.14	
CRP (mg/dl)	34.16±17.9	28.38±14.38	43.09±19.28		0.01

	3		50.55±21.88	40.61±17.89	S
SBP (mmHg)	99.19±5.70	102.29±2.19	94.39±6.14		0.00
			86.44±7.04	97.04±2.44	S
DBP (mmHg)	49.19±5.70	52.29±2.19	44.39±6.14		0.00
			36.44±7.04	47.04±2.44	S
MAP (mmHg)	65.87±5.72	68.95±2.27	61.11±6.18		0.00
			53.13±7.00	63.77±2.56	S
HR (bpm)	117.16±4.67	114.76±1.19	120.88±5.55		0.00
			128.06±7.15	118.48±1.20	S
SI (bpm/mmHg)	1.19±0.14	1.12±0.03	1.29±0.17		0.00
			1.49±0.23	1.22±0.04	S
TC (Cal/day)	1327.32±261.96	1357.56±270.23	1280.54±243.32		0.58
			1181.86±269.47	1313.43±227.52	NS
PD (g/100Cal/day)	3.64±0.63	3.72±0.74	3.50±0.36		0.00
			3.46±0.42	3.52±0.35	S

Values are presented as mean ± standard deviation, median (range), or number (%).
n: Number of study's critically ill patients.
bpm: beat per minute.
mcg: microgram.
min: minute.
1: At admission.

S: Significant (P-Value <0.05).
NS: Non-significant (P-Value >0.05).
MAP: Mean arterial pressure.
HR: Heart rate.
SBP: Systolic blood pressure.
DBP: Diastolic blood pressure.

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

Mortality was significantly higher in medical than surgical critically ill patients. Baseline pre-ICU admission days and number of co-morbidities were also significantly higher in non-survivors than survivors. There were insignificant differences between the two groups regarding average child-Pugh score, average Glasgow coma scale (GSC), and average norepinephrine infusion rate. Despite baseline albumin levels (ALB_1)being significantly higher in non-survivors (2.94±0.39 g/dl)than survivors (2.63±0.20 g/dl), survivors had significantly higher average administered human albumin dosesand average protein density (PD) inputs (18.89±3.16 g/day and 3.72±0.74 g/100 Cal, respectively)than non-survivors (14.06±6.09 g/day and3.50±0.36 g/100 Cal). SI, HR, and CRP were significantly higher in non-survivors (1.29±0.17 bpm/mmHg, 120.88±5.55 bpm, and 43.09±19.28 mg/dl, respectively) than in survivors (1.12±0.03 bpm/mmHg, 114.76±1.19 bpm, and 28.38±14.38 mg/dl). In contrast, all haemodynamic parameters of SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) had significantly higher values in survivors (102.29±2.19 mmHg, 52.29±2.19 mmHg, and 68.95±2.27 mmHg, respectively) than in non-survivors (94.39±6.14 mmHg, 44.39±6.14 mmHg, and 61.11±6.18 mmHg, respectively). SI and CRP were significantly higher in early non-survivors (1.49±0.23 bpm/mmHg and 50.55±21.88 mg/dl, respectively) than in late non-survivors (1.22±0.04 bpm/mmHg and 40.61±17.89 mg/dl, respectively).

Logistic regression analysis

In the univariate analyses, child-Pugh score, CRP, SBP, DBP, MAP, and SI showed statistically significant associations with early (OR, 0.07, 0.47,0.45, 0.45, 0.45, and $5.0*10^{28}$, respectively), late (OR, 0.31,0.87,0.91, 0.91, 0.92, and 11.25, respectively), and overall 28-day ICU mortality (OR, 0.17, 0.78, 0.42, 0.42, 0.45, and $1.6*10^{38}$, respectively),while total calorie (TC) inputs and HR showed only statistically significant associations with early mortality (OR, 0.99) and late mortality (OR, 1.08), respectively. Average albumin levels (ALB) during the first week of ICU admission showed astatistically significant association with both early (OR, 248.65) and overall 28-day ICU mortality (OR, 47.06). After adjusting for these variables, only SI still showed a statistically significant association with early, late, and overall 28-day ICU mortality,while CRP still showed statistically significant association with only overall 28-day ICU mortality. The odd ratios (ORs) of early, late, and all-cause 28-day ICU mortality events are shown in (Table III).

Table III: ORs for early, late, and all-cause in-ICU mortality events

Variable		Univariate			Multivariate		
		OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Age (Yrs)	**Overall 28-day mortality**	0.99	0.96-1.03	0.78 (NS)	----	-----	-----
	Early mortality (≤ 14 days)	1.05	0.99-1.10	0.09 (NS)	----	-----	-----
	Late Mortality (> 14 days)	0.98	0.94-1.01	0.17 (NS)	----	-----	-----
Gender (Male)	**Overall 28-day mortality**	1.13	0.57-2.24	0.72 (NS)	----	-----	-----
	Early mortality (≤ 14 days)	1.00	0.33-3.05	0.99 (NS)	----	-----	-----
	Late Mortality (> 14 days)	1.15	0.55-2.40	0.71 (NS)	----	-----	-----
BMI (Kg/m^2)	**Overall 28-day mortality**	0.96	0.84-1.04	0.28 (NS)	----	-----	-----
	Early mortality (≤ 14 days)	0.88	0.76-1.01	0.06 (NS)	----	-----	-----
	Late Mortality (> 14 days)	1.00	0.92-1.09	0.92 (NS)	----	-----	-----
Child-Pugh score (5-15)	**Overall 28-day mortality**	0.17	0.06-0.45	0.00 (S)	----	-----	-----
	Early mortality (≤ 14 days)	0.07	0.01-0.68	0.02 (S)	----	-----	-----
	Late Mortality (> 14 days)	0.31	0.12-0.82	0.02 (S)	----	-----	-----
PD (g/100 Cal/day)	**Overall 28-day mortality**	0.52	0.28-0.97	0.52 (NS)	----	-----	-----
	Early mortality (≤ 14 days)	0.503	0.16-1.63	0.25 (NS)	----	-----	-----
	Late Mortality (> 14 days)	0.59	0.31-1.16	0.13 (NS)	----	-----	-----

TC (Cal/day)	**Overall 28-day mortality**	0.99	0.99-1.00	0.07 (NS)	-----	-----	-----
	Early mortality (≤ 14 days)	0.99	0.99-1.00	0.02 (S)	----	-----	-----
	Late Mortality (> 14 days)	1.00	0.99-1.00	0.66 (NS)	----	-----	-----
ALB (g/dl)	**Overall 28-day mortality**	47.06	10.50-210.91	0.00 (S)	----	-----	-----
	Early mortality (≤ 14 days)	248.65	24.66-2507.44	0.00 (S)	----	-----	-----
	Late Mortality (> 14 days)	2.48	0.89-6.89	0.08 (NS)	----	-----	-----
CRP (mg/dl)	**Overall 28-day mortality**	0.78	0.62-0.83	0.00 (S)	0.10	0.01-0.72	0.02 (S)
	Early mortality (≤ 14 days)	0.47	0.34-0.66	0.00 (S)	----	-----	-----
	Late Mortality (> 14 days)	0.87	0.77-0.98	0.03 (S)	----	-----	-----
SBP (mmHg)	**Overall 28-day mortality**	0.42	0.32-0.55	0.00 (S)	----	-----	-----
	Early mortality (≤ 14 days)	0.45	0.28-0.74	0.00 (S)	----	-----	-----
	Late Mortality (> 14 days)	0.91	0.86-0.97	0.00 (S)	----	-----	-----
DBP (mmHg)	**Overall 28-day mortality**	0.42	0.32-0.55	0.00 (S)	----	-----	-----
	Early mortality (≤ 14 days)	0.45	0.28-0.74	0.00 (S)	----	-----	-----
	Late Mortality (> 14 days)	0.91	0.86-0.97	0.00 (S)	----	-----	-----
MAP (mmHg)	**Overall 28-day mortality**	0.45	0.35-0.58	0.00 (S)	----	-----	-----
	Early mortality (≤ 14 days)	0.45	0.28-0.73	0.00 (S)	----	-----	-----
	Late Mortality (> 14 days)	0.92	0.86-0.97	0.01 (S)	----	-----	-----
HR (bpm)	**Overall 28-day mortality**	$5.3*10^{9}$	0.00-#	0.989(NS)	----	-----	-----
	Early mortality (≤ 14 days)	$3.6*10^{14}$	0.00-#	0.98 (NS)	----	-----	-----
	Late Mortality (> 14 days)	1.08	1.01-1.17	0.03 (S)	----	-----	-----
SI (bpm/mmHg)	**Overall 28-day mortality**	$1.6*10^{38}$	$5.9*10^{22}$-$4.4*10^{53}$	0.00 (S)	$2.9*10^{124}$	$7.0*10^{27}$-$1.2*10^{219}$	0.01 (S)
	Early mortality (≤ 14 days)	$5.0*10^{28}$	$4.9*10^{10}$-$5.1*10^{48}$	0.01 (S)	$5.0*10^{28}$	$4.9*10^{10}$-$5.1*10^{48}$	0.01 (S)
	Late Mortality (> 14 days)	11.25	8.93-41.71	0.04 (S)	11.25	8.93-41.71	0.04 (S)

OR: Odds ratio.
Yrs: Years.
Kg: Kilogram.
m: Meter.
CI, confidence interval.
BMI: Body mass index.
1: At admission.

Cal: Kcal.
PD: Protein density.
TC: Total calories.
#: Extremely large number.
ALB: Albumin.
CRP: C-reactive protein.

SBP: Systolic blood pressure.
DBP: Diastolic blood pressure.
MAP: Mean arterial pressure.
HR: heart rate.
bpm: Beat per minute.
SI: Shock index.

Prognostic value of the CRP and SI

(Table IV) shows the optimal cut-off point, sensitivity (TPR), specificity (TNR), Youden index (YI), positive and negative predictive values (PPV and NPV), accuracy index (AI), and expected mortality rate of both tested prognostic indicators. The best cut-off values for CRP and SI in our study were 29.5 mg/dl and 1.29 bpm/mmHg, respectively, for early mortality, 34 mg/dl and 1.18 bpm/mmHg, respectively, for late mortality, and 33.60 mg/dl and 1.18 bpm/mmHg, respectively, for overall 28-day ICU mortality. The AUROCs of SI in this study were significantly greater than those of CRP in all mortality groups with 0.996; 95% CI, 0.990-1.00 vs. 0.764; 95% CI, 0.675-0.853, respectively, for early mortality, 0.844; 95% CI, 0.780-0.907 vs. 0.671; 95% CI, 0.583-0.907, respectively, for late mortality, and 0.984; 95% CI, 0.970-0.998 vs. 0.747; 95% CI, 0.672-0.822, respectively, for overall 28-day ICU mortality.The ROC curve analyses and mortality correlations of CRP and SI for early, late, and 28-day ICU mortality are shown in (Fig 2-10)

Table IV. Optimal cut-off point, sensitivity, specificity, positive and negative predictive values, Youdenand accuracy indices, and expected early, late, and 28-day ICU mortality of CRP and SI.

Prognostic Indicator		Cut-off	TPR	FPR	YI	TNR	PPV	NPV	AI	% Mortality
CRP (mg/dl)	Overall 28-day mortality	33.60	68.80 %	26.30 %	42.50 %	73.70 %	62.84 %	78.51 %	71.78 %	37.53%
	Early mortality (≤ 14 days)	29.50	100.00 %	44.90 %	55.10 %	55.10 %	59.01 %	100.00 %	72.73 %	6.11%
	Late Mortality (> 14 days)	34.00	64.60 %	31.30 %	33.30 %	68.70 %	57.16 %	75.01 %	67.09 %	28.80%
SI (bpm/ mmHg)	Overall 28-day mortality	1.18	93.80 %	6.10%	87.70 %	93.90 %	90.86 %	95.91 %	93.86 %	41.59%
	Early mortality (≤ 14 days)	1.29	100.00 %	1.40%	98.60 %	98.60 %	97.88 %	100.00 %	99.15 %	25.33%
	Late Mortality (> 14 days)	1.18	91.70 %	19.10 %	72.60 %	80.90 %	75.63 %	93.78 %	85.14 %	28.53%

CRP: C-reactive protein.
SI: Shock index.
TPR: True positive rate (sensitivity)
PPV: Positive predictive value.
NPV: Negative predictive value.
AI: Accuracy index.

FPR: False positive rate.	**TNR: True negative ratio (specificity).**
YI: Youden index.	**bpm: Beat per minute.**

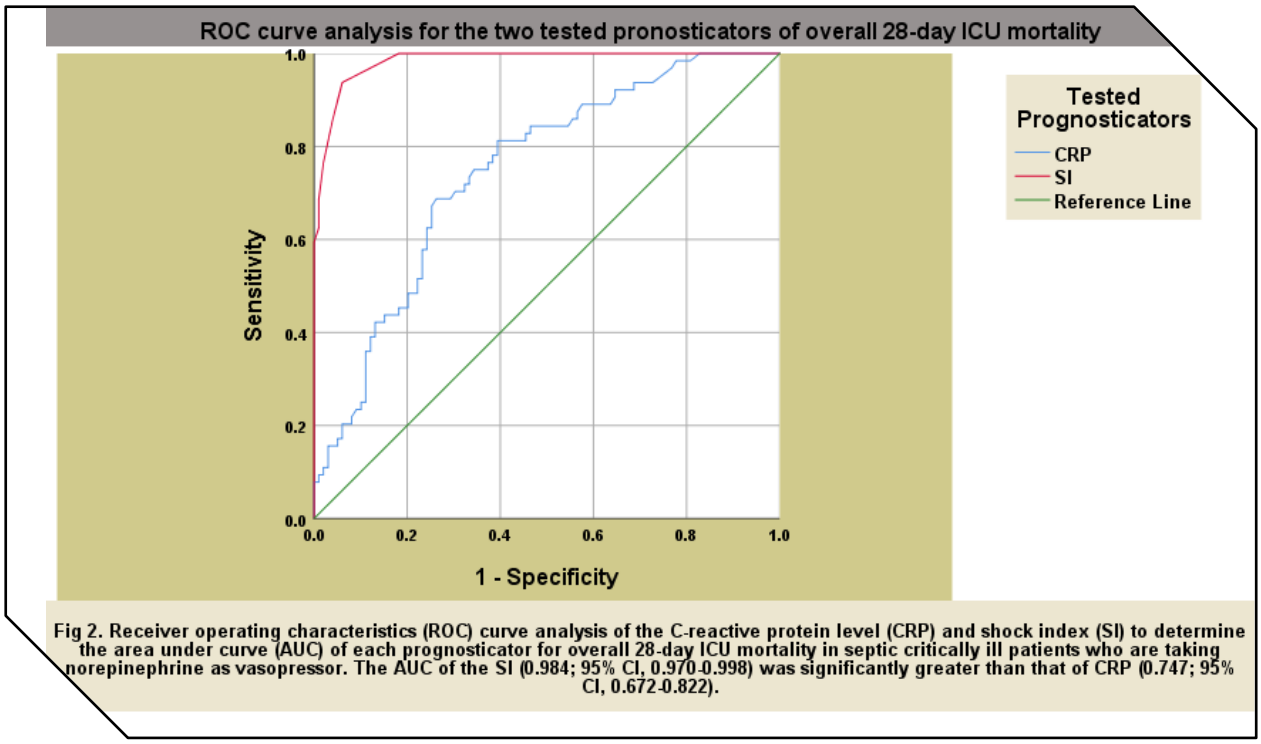

Fig 2. Receiver operating characteristics (ROC) curve analysis of the C-reactive protein level (CRP) and shock index (SI) to determine the area under curve (AUC) of each prognosticator for overall 28-day ICU mortality in septic critically ill patients who are taking norepinephrine as vasopressor. The AUC of the SI (0.984; 95% CI, 0.970-0.998) was significantly greater than that of CRP (0.747; 95% CI, 0.672-0.822).

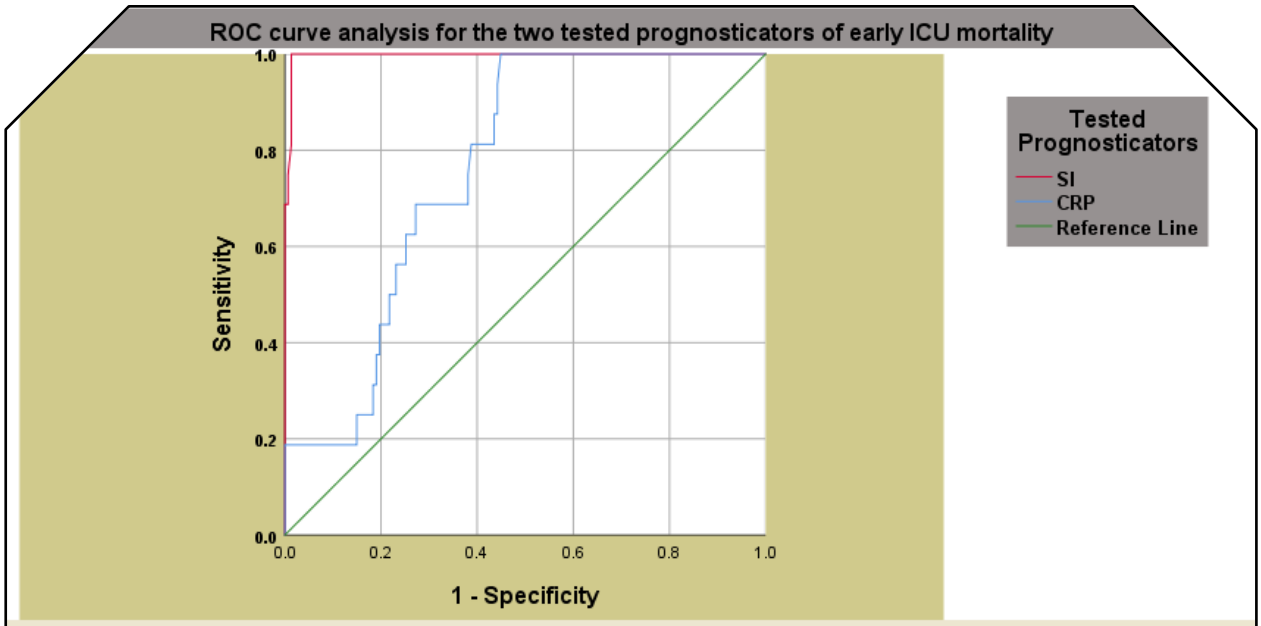

Fig 3. Receiver operating characteristics (ROC) curve analysis of the C-reactive protein level (CRP) and shock index (SI) to determine the area under curve (AUC) of each prognosticator for early ICU mortality in septic critically ill patients who are taking norepinephrine as vasopressor. The AUC of the SI (0.996; 95% CI, 0.990-1.00) was significantly greater than that of CRP (0.764; 95% CI, 0.675-0.853).

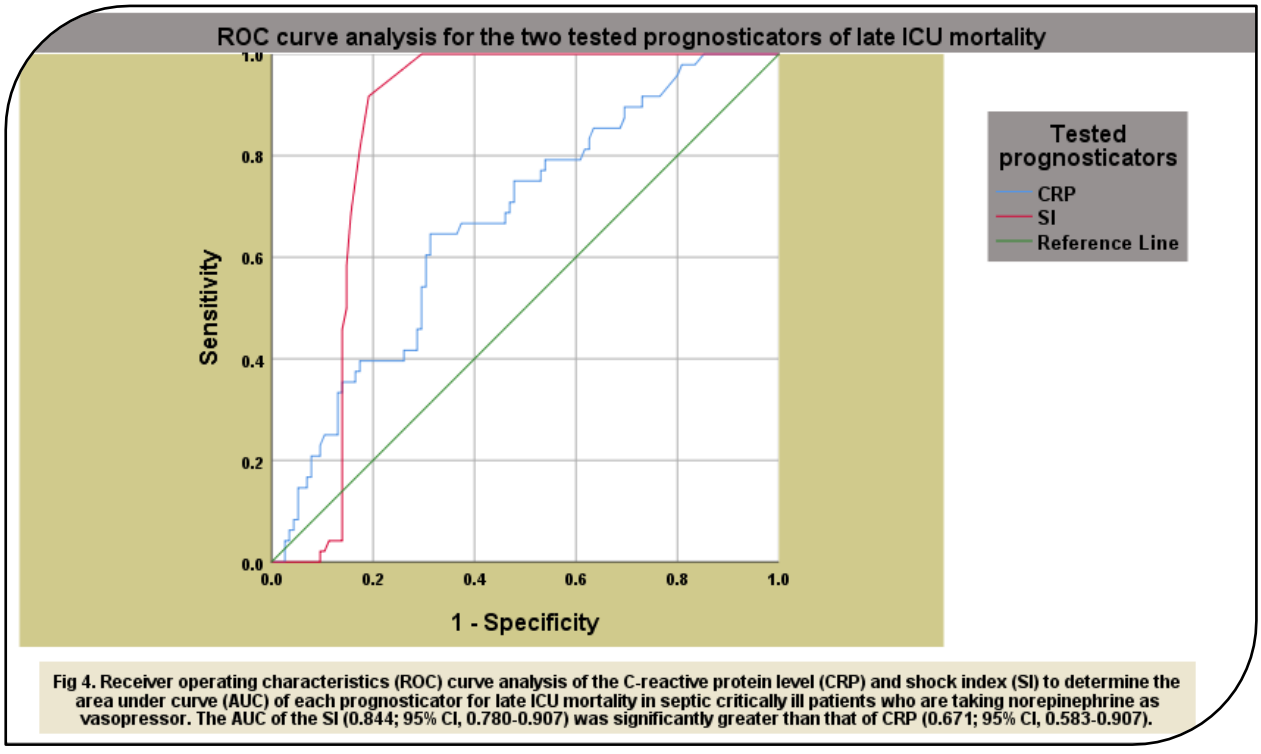

Fig 4. Receiver operating characteristics (ROC) curve analysis of the C-reactive protein level (CRP) and shock index (SI) to determine the area under curve (AUC) of each prognosticator for late ICU mortality in septic critically ill patients who are taking norepinephrine as vasopressor. The AUC of the SI (0.844; 95% CI, 0.780-0.907) was significantly greater than that of CRP (0.671; 95% CI, 0.583-0.907).

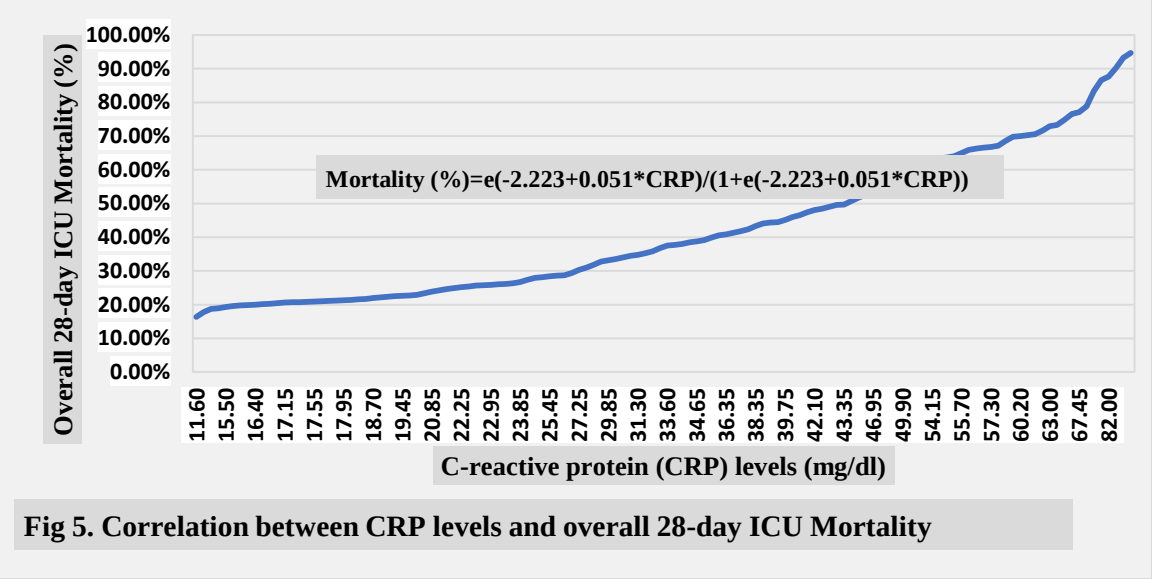

Fig 5. Correlation between CRP levels and overall 28-day ICU Mortality

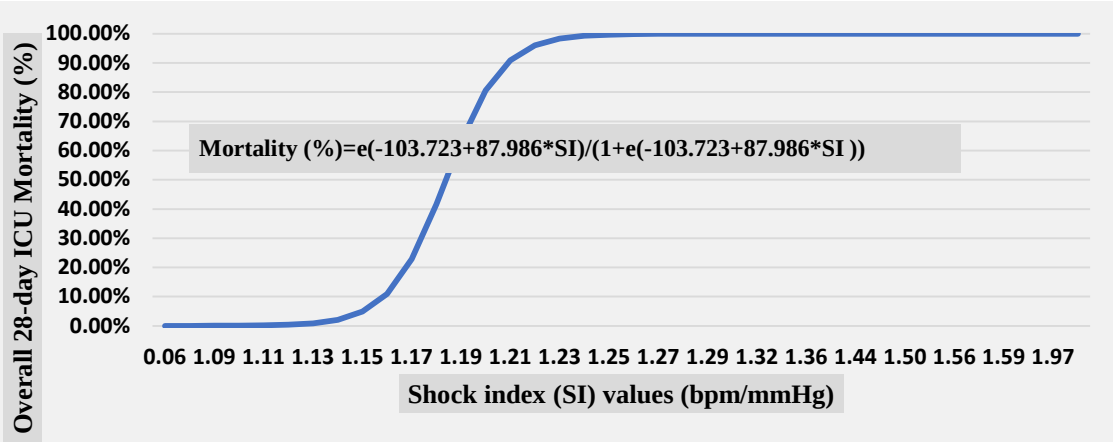

Fig 6. Correlation between SI and overall 28-day ICU Mortality

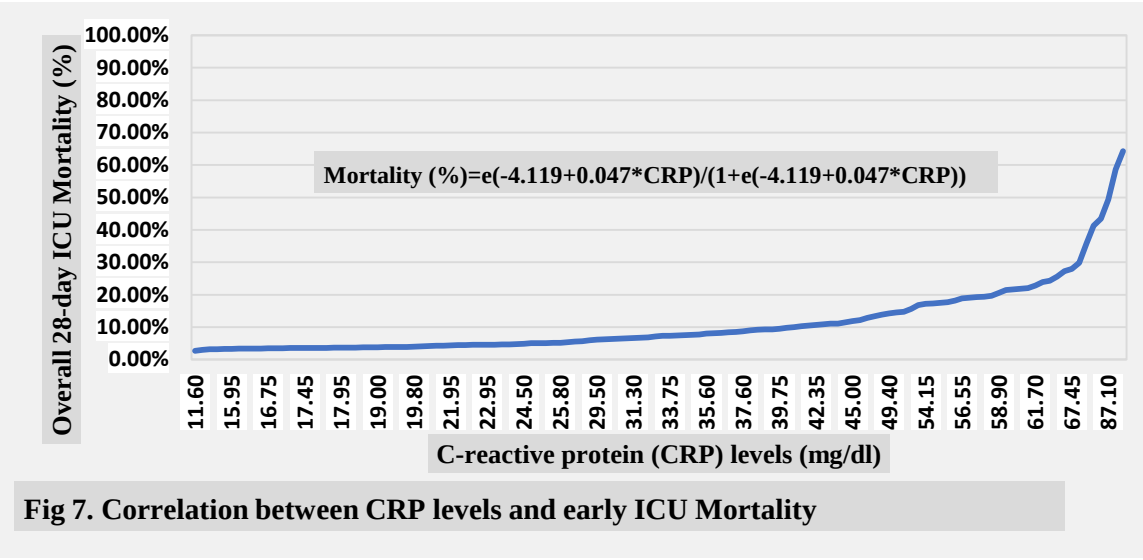

Fig 7. Correlation between CRP levels and early ICU Mortality

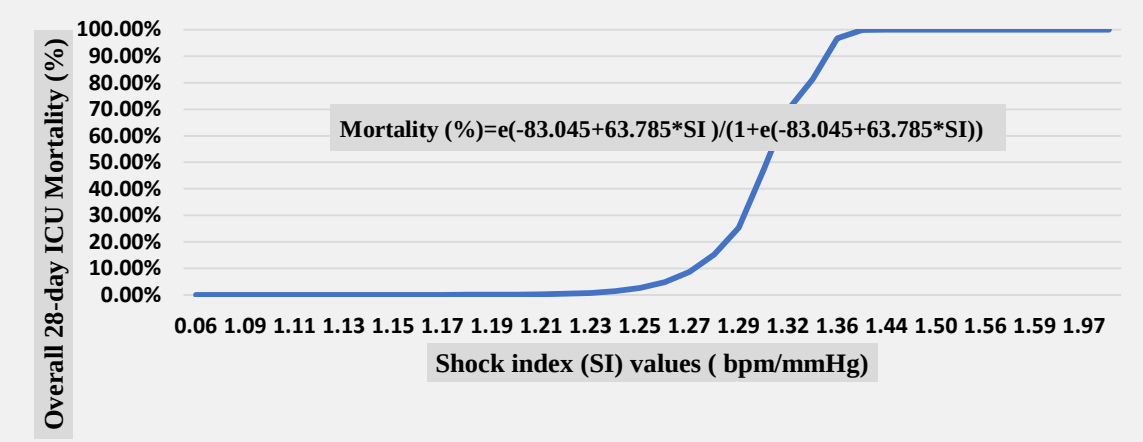

Fig 8. Correlation between SI and early ICU Mortality

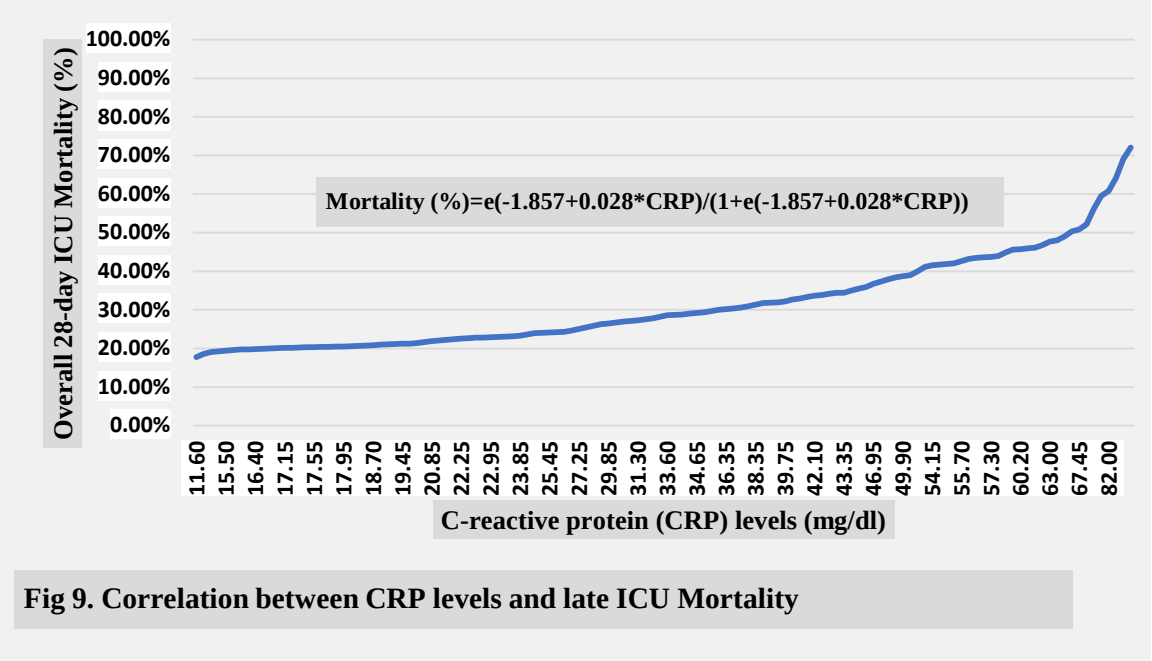

Fig 9. Correlation between CRP levels and late ICU Mortality

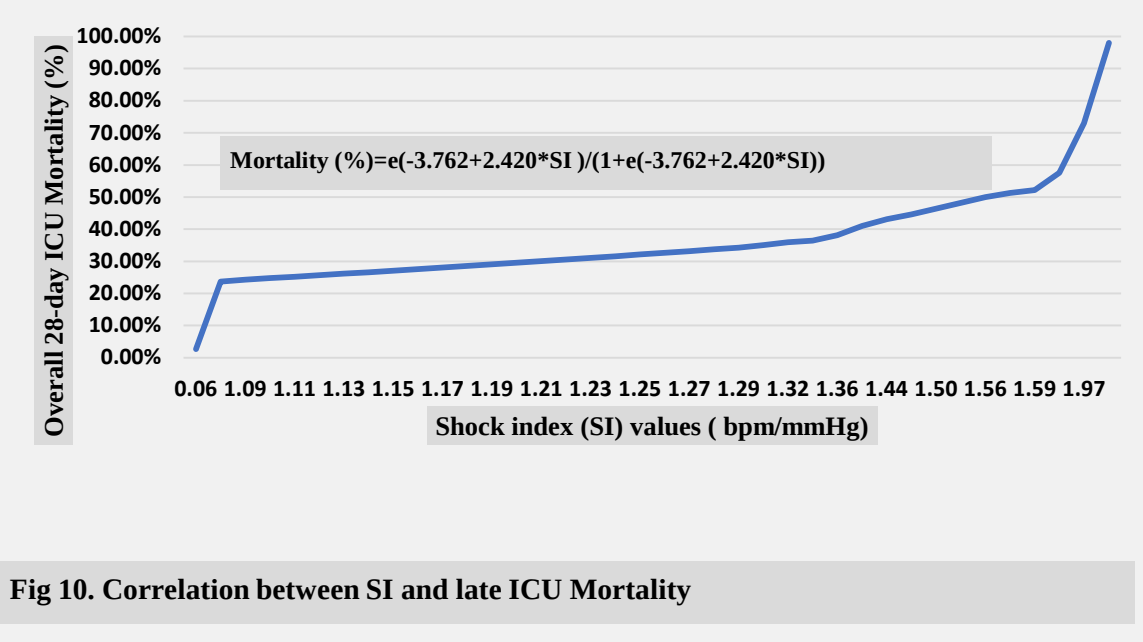

Fig 10. Correlation between SI and late ICU Mortality

Discussion

The present study included septic mechanically ventilated critically ill patients who are 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 to address the correlations between SI, CRP, and mortality. In the context of ever-shrinking resources, early stratification with fast, affordable, valid, reliable, and discriminativepredictive tools are critically needed in this unstable, high acuity, and high uncertainty status of the septic critically ill to avoid any potentialdelay or under-triaging while appropriately assigning a higher priority to sicker patients [9].SI emphasises current physiologic no-cost bedside triage dynamic rather than static toolsthat can be used at any time for triage decisions regarding septic patients while waiting for the results of other diagnostics, especially white blood cells (WBCs) with differential, CRP, and procalcitonin (PCT) [10-19]. After careful analysis of the data, SI shows higher sensitivity, performance, specificity, positive and negative predictive value, and accuracy than CRP in both late (91.70% vs. 64.60%,72.60% vs. 33.30%, 80.90% vs. 68.70%, 75.63% vs. 57.16%, 93.78% vs. 75.01%, and 85.14% vs. 67.09%, respectively) and 28-day ICU mortality (93.80% vs. 68.80%,87.70% vs. 42.50%,93.90% vs. 73.70%,90.86% vs. 62.84%, 95.91% vs. 78.51%, and 93.86% vs. 71.78%, respectively),while in the case of early mortality, SI shows higher performance, specificity, positive predictive value, and accuracy than CRP (98.60% vs. 55.10%, 98.60% vs. 55.10%, 97.88% vs. 59.01%, and 99.15% vs.72.73%, respectively).This study demonstrates a vast difference insignificance and predictive values of SI when compared with CRP, possibly due to the fact that norepinephrine, which was used as a vasopressor in these septic mechanically ventilated critically ill studied patients, givesrise to alterations of physiological parameters of HR and SBP, making the SI indicator a realistic reflection of the septic patients and a more reliable predictive prognosticator compared to CRP.

In summary, SI is an effective, no-cost bedside modality, realistic, reliable, and discriminativeprognosticator with high sensitivity, specificity, performance, and accuracy when compared with CRP to predict early, late, and overall 28-day ICU mortality in septic mechanically

ventilated critically ill patients who are taking norepinephrine as a vasopressor. SI may be used as an additional or readily available red flag bedside assessment tool for severe disease. This study is limited by its retrospective design, using single-centre data, including only septic mechanically ventilated ICU patients. Nonetheless, our centre isan 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 causation between SI, CRP, and mortality and therole in resource utilisation, and risk stratification of septic patients.

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