Performance Differences Among Variations Of Systolic, Diastolic, And Mean Arterial Pressures In Prognosticating Mortality In Critically Ill Patients Who Are Taking Norepineprine

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ABSTRACT

Objective: Systolic blood pressure, diastolic blood pressure, and the mean arterial blood pressure are useful markers that can predict morbidity and mortality among critically ill patients and may be used to predict the prognosis of patients with septic shock. Our objective was to compare the ability of percentage variations of the systolic, diastolic, and mean arterial pressures ($\%SBP_{var}$, $\%MAP_{var}$, and $\%DBP_{var}$) to predict the primary outcome of overall 28-day intensive care unit mortality, and the secondary outcomes of early mortality (≤14 days), late mortality (>14 days), and intensive care unit length of stay.

Methods: We performed a retrospective analysis of 163 patients admitted to our adult critical care unit between April 2017 and Sep 2018 who met the inclusion criteria of availability of all required data and who survived or discharged before completing at least 1 week of admission. Independent T-test, Mann Whitney U test, and chi square test were used to express all patient variables. A receiver operating characteristic curve (ROC) followed by sensitivity analysis was generated to determine the predictive performances, and the optimal cut-off values for three propose prognosticators.

Results: The mean overall age was 58.37±9.96 years. 112 subjects (68.71%) were male and 51 subjects (31.29%) were female. The overall 28-day, early, and late ICU mortality rate were 39.26% (64 patients), 9.82% (16 patients), and 29.45% (48 patients), respectively. Our studied three prognosticators of $\%SBP_{var}$, $\%MAP_{var}$, and $\%DBP_{var}$ were significantly lower in survivors in compared with non survivors (8.96%±0.26%, 16.34%±0.65%, and 22.52%±1.10% versus 11.04%±4.61%, 21.17%±7.54%, and 35.18%±29.37%, respectively). The area under curve of ROC $\%MAP_{var}$ (0.818) was significantly greater than those of $\%SBP_{var}$ (0.769) and $\%DBP_{var}$ (0.265).

Conclusion: In summary, $\%MAP_{var}$ and $\%SBP_{var}$ prognosticators were an effective, no-cost bedside modalities, and discriminative prognosticators with realistic, reliable, and readily available red flag bedside assessment tools which had high sensitivity, performance, and accuracy to predict early, late, and overall 28-day ICU mortality in septic mechanically ventilated critically ill patients who were receiving norepinephrine as a vasopressor.

Key words: Blood pressure variations, Critically ill patients, Mortality, Norepinephrine, Septic shock.

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Introduction

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and the mean arterial blood pressure (MAP) are useful markers that can predict morbidity and mortality among intensive care unit (ICU)

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Admitted patients and may be used to predict the prognosis of patients with septic shock. Sepsis is a complex syndrome caused by the body's systemic response to an infection with a major cause of high treatment cost, single or multiple organ dysfunctions.[1-4] C-reactive protein (CRP) is also a useful positive acute-phase reactant marker that can predict morbidity and mortality among critically ill patients. [5,6] However, the results of CRP and other severity indices of sepsis may not be immediately available upon request, potentially delaying effective dynamic risk stratification and goal directed management in these unstable studied cohort. MAP which defined as 1/3 SBP + 2/3 DBP is a readily and affordable attained comprehensive parameter that combines two physiological pressure parameters (SBP and DBP) into a single parameter and previously has been shown to stratify and served as an early warning prognosticator of high risk septic patients from various aetiologies when compared to SBP and DBP.[7-10] Having reliable indicators and markers that would help prognosticate the survival of these patients is invaluable and would subsequently assist in the course of effective treatment.[11,12] Our objective was to compare the ability of %DBP, %SBP, and %MAP variations to predict the primary outcome of overall 28-day ICU mortality, and the secondary outcomes of early mortality (≤14 days), late mortality (>14 days), and ICU length of stay (LOS). Also, our objective was to determine the optimal cut-off point, sensitivity (TPR), specificity (TNR), Youden's index (YI), positive and negative predictive values (PPV and NPV), and accuracy index (AI), of the three tested prognosticators.

Methods

This was a single-centre observational retrospective study conducted in the department of adult ICU of King Hussein Medical Hospital (KHMH) 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 913 critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problems. After excluded all patients who were died or discharged before completed at least 1 week after admission and included all critically ill patients who their anthropometrics, diagnostics, demographics, hemodynamics, nutritional indices, and all required laboratory data were known, 163 critically ill patients were finally included in our study. 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 chi square 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 $\%SBP_{var,}$ $\%MAP_{var,}$ and $\%DBP_{var}$, YI, TPR, TNR, PPV, NPV, and AI 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.

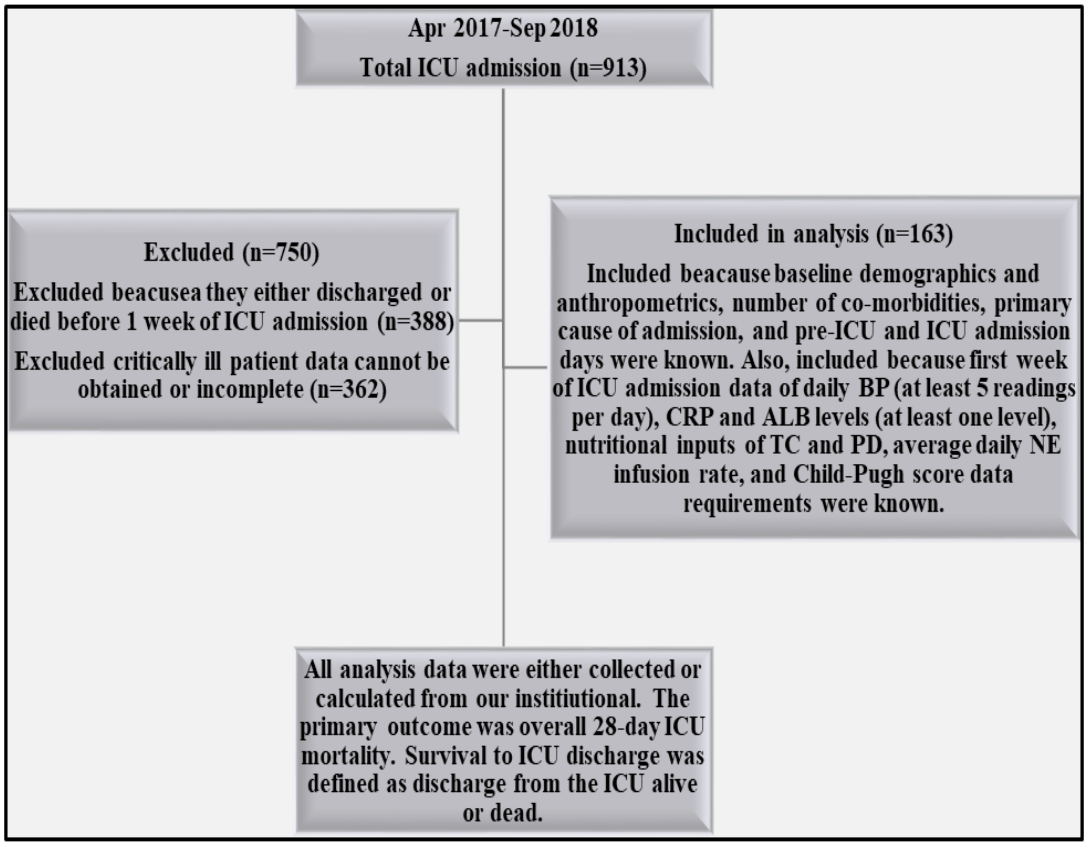

Fig 1. Flow chart of critically ill patient's selection and data collection process.

Apr: April.	**CRP: C-reactive protein.**	**PD: Protein density.**
Sep: September.	**BP: Blood pressure.**	**ALB: Albumin.**
ICU: Intensive Care Unit.	**NE: Norepinephrine.**	**TC: Total calorie.**

Result

The mean overall age was 58.37±9.96 years. 112 subjects (68.71%) were male and 51 subjects (31.29%) were female. The overall 28-day, early, and late ICU mortality rate were 39.26% (64 patients), 9.82% (16 patients), and 29.45% (48 patients), respectively. 28-day ICU mortality was significantly higher in medically than surgically admitted patients (85.94% (55 medically patients) versus 14.06% (9 surgically patients), respectively). Baseline pre-ICU admission days and number of co-morbidities >1 were also significantly higher in non-survivors than survivors (7.42±4.57 days versus 2.23±1.06 days and 65.63% (42 subjects) versus 47.47% (47 subjects), respectively). Despite baseline albumin level (ALB_1) was 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 (H.ALB) doses and nutritional protein density (PD) inputs and significantly lower CRP (18.89±3.16 g/day and 3.72±0.74 g/100 Cal and 28.38±14.38 mg/dl, respectively) than non-survivors (14.06±6.09 g/day and 3.50±0.36 g/100 Cal and 43.09±19.28 mg/dl, respectively) which ultimately resulted in significantly higher average ALB during ICU admission in survivors (2.87±0.12 g/dl) than in non survivors (2.57±0.13 g/dl). The ICU and overall hospital LOS were also significantly lower in survivors non survivors (9.23±1.06 days and 11.46±2.12 days versus 17.30±4.14 days and 24.72±1.98 days, 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/m^2)		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 using one sample T-test and independent T-test or as number (%) using chi square test.
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.

All haemodynamic parameters of SBP_{max}, SBP_{min}, and SBP_{avg} versus MAP_{max}, MAP_{min}, and MAP_{avg} versus DBP_{max}, DBP_{min}, and DBP_{avg} versus were significantly higher values in survivors (113.77±3.15 mmHg, 103.77±3.15 mmHg, and 111.77±3.15 mmHg versus 87.04±3.16 mmHg, 73.77±3.15 mmHg, and 81.77±3.15 mmHg versus 73.44±3.30 mmHg, 58.64±3.23 mmHg, and 66.65±3.20 mmHg, respectively) than in non-survivors (98.41±16.13 mmHg, 88.41±16.13 mmHg, and 96.41±16.13 mmHg versus 72.14±14.81 mmHg, 58.99±13.98 mmHg, and 66.76±14.70 mmHg versus 57.26±17.02 mmHg, 42.99±16.46 mmHg, and 51.03±16.47 mmHg, respectively).

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)	
NE (mcg/min)	9.53±1.79	9.27±1.68	9.94±1.89		0.72
			9.94±2.49	9.94±1.67	(NS)
GCS (3-15)	12 (12-13)	12 (12-13)	12 (12-13)		0.34
			12 (12-13)	12 (12-13)	(NS)
Child-Pugh Score (5-15)	6 (6-8)	6 (6-8)	6 (6-7)		0.09
			6 (6-7)	6 (6-7)	(NS)
ALB_1 (g/dl)	2.75±0.32	2.63±0.20	2.94±0.39		0.00
			3.28±0.46	2.82±0.28	(S)
H.ALB (g/day)	16.99±5.11	18.89±3.16	14.06±6.09		0.00
			9.38±6.80	15.63±5.01	(S)
ALB (g/dl)	2.72±0.13	2.87±0.12	2.57±0.13		0.04
			2.55±0.11	2.57±0.14	(NS)
CRP (mg/dl)	34.16±17.93	28.38±14.38	43.09±19.28		0.01
			50.55±21.88	40.61±17.89	(S)
SBP_{min} (mmHg)	97.56±12.94	103.77±3.15	88.41±16.13		0.00
			54.50±20.69	93.55±6.09	(S)
SBP_{max} (mmHg)	107.56±12.94	113.77±3.15	98.41±16.13		0.00
			64.50±20.69	103.55±6.09	(S)
SBP_{avg} (mmHg)	105.56±12.94	111.77±3.15	96.41±16.13		0.00
			62.50±20.69	101.55±6.09	(S)
$\%SBP_{var}$	9.79%±3.10%	8.96%±0.26%	11.04%±4.61%		0.00
			18.67%±10.00%	9.88%±0.64%	(S)
DBP_{min} (mmHg)	52.31±13.19	58.64±3.23	42.99±16.46		0.00
			38.40±21.09	48.23±6.25	(S)
DBP_{max} (mmHg)	66.89±13.64	73.44±3.30	57.26±17.02		0.00
			21.50±21.87	62.68±6.44	(S)
DBP_{avg} (mmHg)	60.34±13.19	66.65±3.20	51.03±16.47		0.00
			16.40±21.09	56.27±6.24	(S)
$\%DBP_{var}$	27.64%19.64%	22.52%±1.10%	35.18%±29.37%		0.00
			90.11%±56.98%	26.86%±3.36%	(S)
MAP_{min} (mmHg)	67.79±11.71	73.77±3.15	58.99±13.98		0.00
			28.90±14.22	63.55±6.09	(S)
MAP_{max} (mmHg)	81.02±12.15	87.04±3.16	72.14±14.81		0.00
			40.40±16.28	76.95±6.14	(S)
MAP_{avg} (mmHg)	75.70±12.13	81.77±3.15	66.76±14.70		0.00
			35.20±16.06	71.55±6.09	(S)
$\%MAP_{var}$	18.29%±5.36%	16.34%±0.65%	21.17%±7.54%		0.00
			36.96%±11.48%	18.77%±1.78%	(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 using one sample T-test and independent T-test, as number (%) using chi square test, or us median (range) using Mann Whitney U-test.

N: Number of study's critically ill patients.
ALB: Albumin level.
H.ALB: Human albumin.
DBP: Diastolic blood pressure.
SBP: Systolic blood pressure.
MAP: Mean arterial pressure.
S: Significant (P-Value <0.05).
GCS: Glasgow coma scale.
Cal: Kcal.
NE: Norepinephrine.
TC: Total calories.
PD: Protein density.
CRP: C-reactive protein.
NS: Non-significant (P-Value >0.05).

Our studied three prognosticators of $\%SBP_{var}$, $\%MAP_{var}$, and $\%DBP_{var}$ were significantly lower in survivors in compared with non survivors (8.96%±0.26%, 16.34%±0.65%, and 22.52%±1.10% versus 11.04%±4.61%, 21.17%±7.54%, and 35.18%±29.37%, respectively). There were insignificant differences between the two tested groups regarding average child-Pugh score, average Glasgow coma scale (GSC), average NE infusion rate, and total calories (TC) inputs. Demographics, admission co-morbidities and class, anthropometrics, and follow-up comparison data of the study's critically ill patients are fully summarised in Table 1 and Table 2, respectively. Table 3 shows the optimal cut-off point, TPR, TNR, YI, PPV, NPV, and AI of the tested prognostic indicators. The best cut-off values for $\%SBP_{var}$, $\%MAP_{var}$, and $\%DBP_{var}$ in our study were 12.26%, 18.49%, and 105.11% for overall 28-day ICU mortality. The area under curve of (ROC) AUROC of $\%MAP_{var}$ (0.818; 95% CI, 0.738-0.897) was significantly greater than those of $\%SBP_{var}$ (0.769; 95% CI, 0.678-0.859) and $\%DBP_{var}$ (0.265; 95%, 0.179-0.350). Fig 1 illustrates the ROC curve analysis for the three tested prognosticators of the overall 28-day ICU mortality.

Table III: Optimal cut-off point, sensitivity, specificity, positive and negative predictive values, Youden and accuracy indices of the three tested prognosticators of $\%SBP_{var}$, $\%MAP_{var}$, and $\%DBP_{var}$ for overall 28-day ICU mortality.

Prognosticator	Cut-off	TPR	FPR	YI	TNR	PPV	NPV	AI	AUCROC	p-value
$\%SBP_{var}$	12.26%	83.90%	38.90%	45.00%	61.10%	58.23%	85.44%	70.05%	0.769	<0.05 (S)
$\%MAP_{var}$	18.49%	87.10%	28.20%	58.90%	71.80%	66.63%	89.59%	77.81%	0.818	<0.05 (S)
$\%DBP_{var}$	105.11%	15.60%	0.00%	15.60%	100%	100%	64.70%	66.86%	0.265	<0.05 (S)

$\%SBP_{var:}$ Percentage variation of systolic blood pressure.
$\%MAP_{var:}$ Percentage variation of mean arterial pressure.
$\%DBP_{var:}$ Percentage variation of diastolic blood pressure.
TPR: True positive rate (sensitivity)
FPR: False positive rate.
YI: Youden index.
PPV: Positive predictive value.
NPV: Negative predictive value.
AI: Accuracy index.
TNR: True negative ratio (specificity).
AUCROC: Area under curve of receiver operating characteristic.
ICU: Intensive care unit.

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 the prognosticating performance of three pressure parameters of SBP, MAP, and DBP using there's percentage variations based on the concept of dynamic changes, instabilities, and high acuities of septic critically ill patients.[13-16] Vital sign dependent on blood pressure (BP) emphasises current physiologic no-cost bedside triage dynamic rather than static tools that can be used at any time for triage decisions and appropriately assigning a higher priority to sicker septic patients in the context of ever-shrinking resources, early stratification with fast, affordable, valid, reliable, and discriminative predictive tools while waiting for the results of other diagnostics.[17-20] After careful analysis of the data, $\%MAP_{var}$ demonstrated significantly higher sensitivity, performance, negative

predictive value, and accuracy than $\%SBP_{var}$ followed by $\%DBP_{var}$ (87.10%, 58.90%, 89.59%, and 77.81% versus 83.90%, 45.00%, 85.44%, and 70.05% versus 15.60%, 15.60%, 64.70%, and 66.86%, respectively). This study demonstrates a vast difference in predictive values of BP percentage variations, possibly due to the fact that fluid resuscitation and norepinephrine, which were primarily used in these septic mechanically ventilated critically ill studied patients, gives rise to alterations of physiological parameters of heart rate (HR), stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR), making the BP percentage variations especially $\%MAP_{var}$ indicator a realistic reflection of the septic patients and a more reliable predictive prognosticator compared to with other non-dynamic indicators such as CRP and pro-calcitonin, lactate, and white blood cells (WBCs).[21-24]

In summary, $\%MAP_{var}$ prognosticator and $\%SBP_{var}$ were an effective, no-cost bedside modalities, and discriminative prognosticators with realistic, reliable, and readily available red flag bedside assessment tools which had high sensitivity, performance, and accuracy to predict early, late, and overall 28-day ICU mortality in septic mechanically ventilated critically ill patients who are taking norepinephrine as a vasopressor.[25-27] This study is limited by its retrospective design, 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.

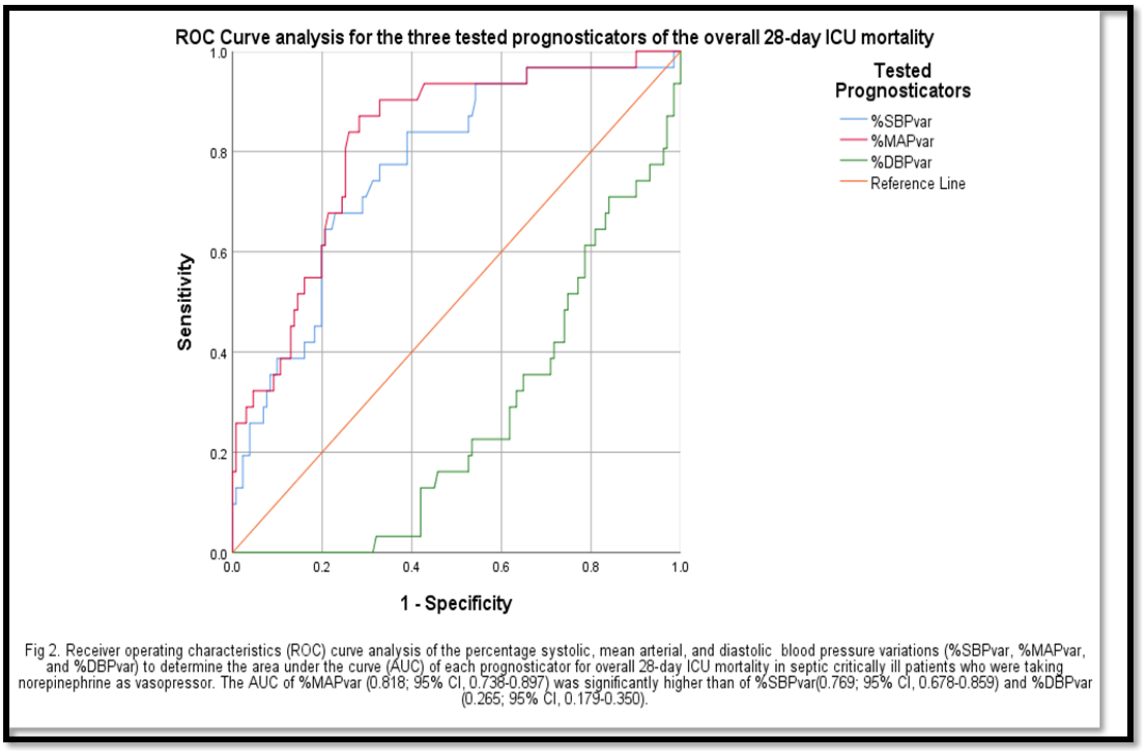

Fig 2. Receiver operating characteristics (ROC) curve analysis of the percentage systolic, mean arterial, and diastolic blood pressure variations (%SBPvar, %MAPvar, and %DBPvar) to determine the area under the curve (AUC) of each prognosticator for overall 28-day ICU mortality in septic critically ill patients who were taking norepinephrine as vasopressor. The AUC of %MAPvar (0.818; 95% CI, 0.738-0.897) was significantly higher than of %SBPvar(0.769; 95% CI, 0.678-0.859) and %DBPvar (0.265; 95% CI, 0.179-0.350).

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