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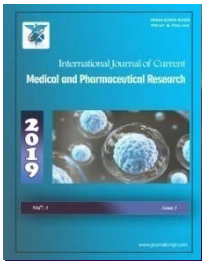

THE PREDICTIVE PERFORMANCE OF BODY TEMPERATURE PROGNOSTICATORS AND THERE'S CORRELATIONS WITH MAJOR CLINICAL OUTCOMES ON SEPTIC CRITICALLY ILL PATIENTS WHO ARE TAKING NOREPINEPHRINE AND ANTIPYRETIC

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ABSTRACT

Objectives: Hyperthermia (>38∘C) or hypothermia (<36∘C) are one of the clinical diagnostics septic patients which may results in poor outcomes. The aim of our study is to investigate the predictive efficacy of maximum temperature (Tmax), average temperature (Tavg), and temperature variance (%Tvar) on the early, late, and overall 28-daymortalityin critically ill patients who are taking norepinephrine and intravenous (IV) paracetamol.

Methods: A retrospective analysis was conducted in our adult ICU between April 2017 and Sep 2018 who were their tested temperature variables (Tmax, Tavg, %Tvar)can be obtained.All patient's continuous variables were expressed as mean± SD by using the independent samples T-test or as numbers with percentages by using $\chi 2$ test.A receiver operating characteristic (ROC) and sensitivity analyses will be conducted to compare the prognostic ability, optimal cutoff points of the 3 tested prognosticators

Results: The mean overall age was 58.37±9.96 years, and 112 subjects (68.71%) were male. 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. Survivors had also significantly lower Tavg, Tmax, and %Tvar (37.38±0.40 ℃, 38.35±0.47 ℃, and 7.78%±2.53%) than nonsurvivors (37.99±0.57 ℃, 38.35±0.47 ℃, and 10.48%±1.91%).The AUROCs of %Tvar in this study were significantly greater than those of Tmaxand Tavgamong all stratified mortalities.

Conclusion: %Tvar is an effective, no-cost bedside modality, realistic, reliable, and discriminative prognosticator with high sensitivity, specificity, performance, and accuracy when compared with the other 2 analogue temperature prognosticators to predict early, late, and overall 28-day ICU mortality.

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INTRODUCTION

Temperature is routinely monitored in all hospitalized patients especially in critically ill patients in which extremes and fluctuations of temperature have been reported to be frequent and associated with negative economic and clinical impacts of high treatment cost, organ dysfunction, morbidity, and mortality.[1-3]Fever is one of the most prominent symptoms and part of acute phase reactant to a variety of infectious and non-infectious insults.[4-5]Hyperthermia (>38∘C) or hypothermia (<36∘C) are one of the clinical diagnostics septic patients. The importance of having reliable, cost effective, and easily attainable clinical prognostic indicators that would help to predict and differentiate the mortality risk of these critically ill patients is invaluable within an Intensive Care Unit (ICU).The aim of our study is to investigate the predictive efficacy of T_{max}, T_{avg}, and $\%T_{var\ on}$ the early, late, and overall 28-day ICU mortality in septic mechanically ventilated critically ill patients who are taking norepinephrine and intravenous (IV) paracetamol.

MATERIALS AND METHODS

This was a single-centre observational 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. Data of the critically ill patients who were admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problems were recruited from our institutional electronic medical records (EMR). These data were considered as part of the routine clinical examinations without any medical intervention. Flow chart of critically ill patient's

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selection and data collection process is fully illustrated in Figure 1.

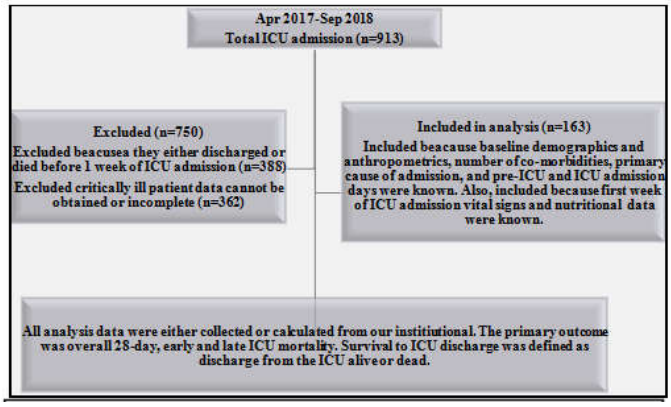

Fig 1 Flow chart of critically ill patient's selection and data collection process. Apr: April.Sep: September.ICU: Intensive Care Unit.

All patient continuous variables were expressed as mean± standard deviation by using the independent samples T-test for comparison between survivors group and nonsurvivors group or using dependent T-test for comparison within survivors and nonsurvivors groups. 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 wasused to determine the area under the ROC curves (AUROCs), predictive performances, and the optimal cut-off values for T_{avg}, T_{max}, $\%T_{var}$. Youden's indices, sensitivities, specificities, positive and negative predictive values, and accuracy indices were also calculated. Statisticalanalyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

RESULTS

The mean overall age was 58.37±9.96 years, and 112 subjects (68.71%) were male. 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. Mortality was significantly higher in medical (85.94%) than surgical (14.06%) critically ill patients. Pre-ICU, ICU, and overall hospital stay days were also significantly higher in non-survivors (7.42±4.57 days, 17.30±4.14 days, and 24.72±1.98 days, respectively)than survivors (2.23±1.06 days, 9.23±1.06 days, and 11.46±2.12 days, respectively). Survivors had significantly higher average administered human albumin dose, average protein density (PD), and average albumin level (18.89±3.16 g/day, 3.72±0.74 g/100 Cal, and 2.64±0.12 g/dl, respectively) than non-survivors (14.06±6.09 g/day, 3.50±0.36 g/100 Cal, and 2.57±0.13 g/dl, respectively). Survivors had also significantly lower T_{avg}, T_{max}, $\%T_{var}$, and paracetamol dependency (37.38±0.40 ℃, 38.35±0.47 ℃, 7.78%±2.53%, and 0.85±1.36 g/day, respectively) than nonsurvivors (37.99±0.57 ℃, 38.35±0.47 ℃, 10.48%±1.91%, and 2.77±0.81 g/day, respectively). There were insignificant differences between the two groups regarding average child-Pugh score, average Glasgow coma scale (GSC), and average norepinephrine infusion rate.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.

The best cut-off valuesfor T_{avg}, T_{max}, and $\%T_{var}$in our study were (37.51 ° C, 38.48 ° C, and 7.94%) for overall 28-day ICU mortality prediction, (37.59 ° C, 39.35 ° C, and 11.25%) for early ICU mortality forecasting, and (37.30 ° C, 38.48 ° C, and 7.94%) for late ICU mortality prognosticating. The AUROCs of $\%T_{var}$ in this study were significantly greater than those of $T_{max}$and T_{avg}in all mortality groups with (1.00; 95% CI, 1.00-1.00) vs (0.911; 95% CI, 0.870-0.952) and (0.831; 95% CI, 0.771-0.891) for overall 28-day ICU mortality. The ROC curve analyses of the three tested prognosticators early, late, and 28-day ICU mortality are shown in Fig 2-4.

DISCUSSION

The present study included critically ill patients who were took 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 address the sensitivity and performance comparison between the average, maximum, and variation of fast, affordable, valid, reliable, and easily attainable mortality prognosticator such as Temperature for forecasting the mortality and stratified it as overall, early, and late in septic mechanically ventilated critically ill patients taking norepinephrine as vasopressor and IV paracetamol as antipyretic. In the context of ever-shrinking resources, early stratification with discriminative predictive tools are critically needed in this dynamic and unstable patients with high acuity and uncertainty status to avoid any potentialdelay or under-triaging while appropriately assigning a higher priority to sicker patients.$\%T_{var}$ emphasises current physiologic no-cost bedside triage dynamic rather than static tools that 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).[6-8] After careful analysis of the data, $\%T_{var}$ shows higher sensitivity, performance, specificity, positive and negative predictive value, and accuracy than T_{max} and T_{avg} among the three stratified mortalities. Table 4 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 three tested prognostic indicators among early, late, and 28-day overall mortality. In summary, $\%T_{var}$is an effective, no-cost bedside modality, realistic, reliable, and discriminative prognosticator with high sensitivity, specificity, performance, and accuracy when compared with the other 2 analogue temperature prognosticators to predict early, late, and overall 28-day ICU mortality in septic mechanically ventilated critically ill patients who are taking norepinephrine as a vasopressor and IV paracetamol as antipyretic and 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 is an experienced and high-volume unit, so our data maybe useful in other centres. A larger, multisite, and prospective study is needed to control for multiple confounders.

Table 1 Baseline and follow-up comparison data of the study's critically ill patients

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	62.31±11.12	56.69±9.38	0.917NS
Gender	Male	112 (68.71%)	67 (67.68%)	45 (70.31%)	11 (68.75%)	34 (70.83%)	0.796NS
	Female	51 (31.29%)	32 (32.32%)	19 (29.69%)	5 (31.25%)	14 (29.17%)	
BW_1 (Kg)		74.17±10.24	74.63±10.06	73.45±10.56	69.44±9.34	74.79±10.69	0.609NS
BMI_1 (Kg/m²)		25.92±4.00	26.19±3.85	25.50±4.22	24.11±4.28	25.97±4.14	0.311NS
Admission class	Medical	105 (64.42%)	50 (50.51%)	55 (85.94%)	14 (87.5%)	41 (85.42%)	0.002S
	Surgical	58 (35.58%)	49 (49.49%)	9 (14.06%)	2 (12.5%)	7 (14.58%)	
Norepinephrine Rate $_{avg}$ (mcg/min)		9.53±1.79	9.27±1.68	9.94±1.89	9.94±2.49	9.94±1.67	0.724NS
Human Albumin Dose $_{avg}$ (g/day)		16.99±5.11	18.89±3.159	14.06±6.09	9.38±6.80	15.63±5.01	0.000S
Albumin level $_{avg}$ (g/dl)		2.61±0.13	2.64±0.12	2.57±0.13	2.55±0.11	2.57±0.14	0.442NS
TC $_{avg}$ (Cal/day)		1327.32±261.96	1357.56±270.23	1280.54±243.32	1181.86±269.47	1313.43±227.52	0.581NS
PD $_{avg}$ (g/100Cal/day)		3.64±0.63	3.72±0.74	3.50±0.36	3.46±0.42	3.52±0.35	0.002S
Day(s) Pre-ICU admission (day(s))		4.27±3.91	2.23±1.06	7.42±4.57	13.31±5.89	5.46±1.10	0.000S
ICU Stay day(s)		12.40±4.79	9.23±1.06	17.30±4.14	10.56±1.97	19.54±1.10	0.000S
Hospital Stay day(s)		16.67±6.81	11.46±2.12	24.72±1.98	23.87±3.93	25.00±0.00	0.003S
T_{avg} (ºC)		37.62±0.56	37.38±0.40	37.99±0.57	38.46±0.64	37.84±0.45	0.001S
T_{max} (ºC)		38.78±0.80	38.35±0.47	39.46±0.72	40.08±0.73	39.25±0.59	0.001 S
T_{min} (ºC)		35.84±0.49	36.09±0.32	35.47±0.47	34.92±0.42	35.66±0.32	0.022 S
$\%T_{var}$ (ºC)		7.78%±2.53%	6.04%±0.62%	10.48%±1.91%	13.42%±0.97%	9.50%±0.82%	0.000 S
Paracetamol $_{avg}$ (g/day)		1.60±1.50	0.85±1.36	2.77±0.81	3.00±0.00	2.69±0.93	0.000S
28-day ICU Mortality	28-day ICU Survival			99 (60.74%)			
	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 (%).

ICU: Intensive care unit.
S: Significant (P-Value <0.05).
TC: Total calorie.
PD: Protein density in g/100 Cal.
NS: Nonsignificant (P-Value >0.05).
BW: Body weight in kilogram.
BMI: Body mass index in Kg/m.^{2}
T_{avg}: Average Temperature during 1st week of admission.
T_{max}: Maximum temperature during 1st week of admission.
$\%T_{var}$: variation of temperature during 1st week of admission.

Table 2 Sensitivity, specificity, positive and negative predictive values, youden's and accuracy indices of the 3 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	T_{avg}	37.51	79.70%	26.30%	53.40%	73.70%	66.21%	84.89%	27.54%	76.06%
	T_{max}	38.48	100.00%	29.30%	70.70%	70.70%	68.81%	100.00%	0.00%	82.20%
	$\%T_{Var}$	7.94%	100.00%	0.00%	100.00%	100.00%	100.00%	100.00%	0.00%	100.00%
Early mortality (≤14 days)	T_{avg}	37.59	100.00%	38.10%	61.90%	61.90%	62.92%	100.00%	0.00%	76.86%
	T_{max}	39.35	100.00%	17.00%	83.00%	83.00%	79.18%	100.00%	0.00%	89.67%
	$\%T_{Var}$	11.25%	100.00%	0.00%	100.00%	100.00%	100.00%	100.00%	0.00%	100.00%
Late mortality (>14 days)	T_{avg}	37.30	89.60%	48.70%	40.90%	51.30%	54.33%	88.41%	20.27%	66.34%
	T_{max}	38.48	100.00%	39.10%	60.90%	60.90%	62.31%	100.00%	0.00%	76.25%
	$\%T_{Var}$	7.94%	100.00%	13.90%	86.10%	86.10%	82.30%	100.00%	0.00%	91.56%

T_{avg}: Average temperature during first week of ICU admission.
T_{max}: Maximum temperature during first week of ICU admission.
$\%T_{var}$: Variation of temperature values during first week of ICU 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.

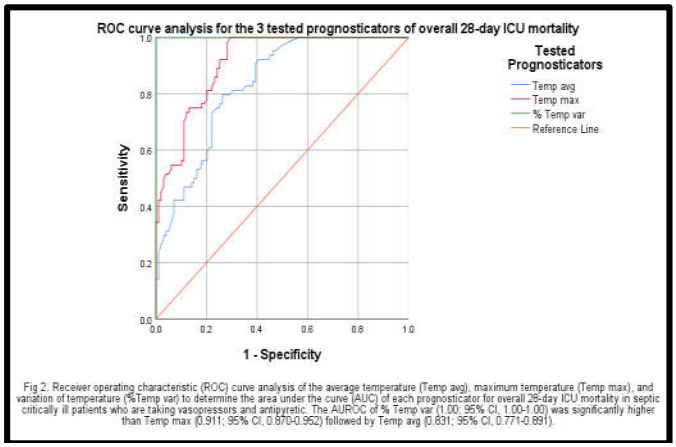

Fig 2. Receiver operating characteristic (ROC) curve analysis of the average temperature (Temp avg), maximum temperature (Temp max), and variation of temperature (%Temp var) to determine the area under the curve (AUC) of each prognosticator for overall 28-day ICU mortality in septic critically ill patients who are taking vasopressors and antipyretic. The AUROC of % Temp var (1.00; 95% CI, 1.00-1.00) was significantly higher than Temp max (0.911; 95% CI, 0.870-0.952) followed by Temp avg (0.831; 95% CI, 0.771-0.891).

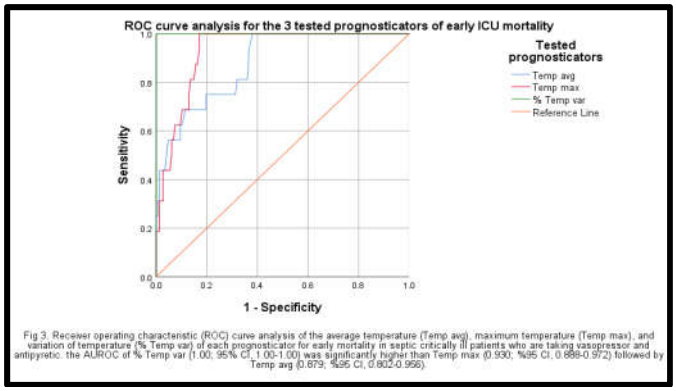

Fig 3. Receiver operating characteristic (ROC) curve analysis of the average temperature (Temp avg), maximum temperature (Temp max), and variation of temperature (% Temp var) of each prognosticator for early mortality in septic critically ill patients who are taking vasopressor and antipyretic. the AUROC of % Temp var (1.00; 95% CI, 1.00-1.00) was significantly higher than Temp max (0.930; %95 CI, 0.888-0.972) followed by Temp avg (0.879; %95 CI, 0.802-0.956).

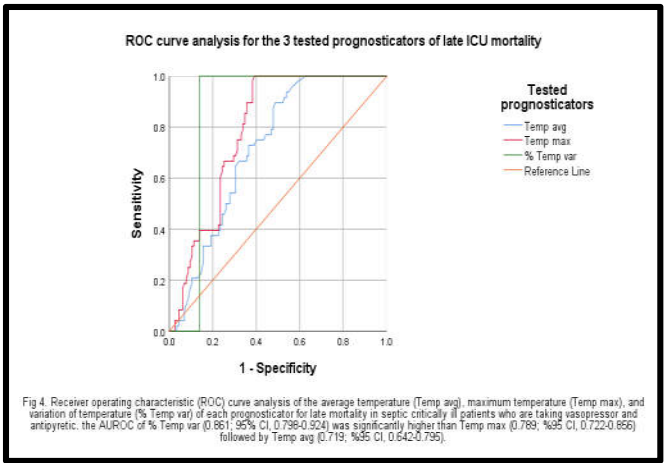

Fig 4. Receiver operating characteristic (ROC) curve analysis of the average temperature (Temp avg), maximum temperature (Temp max), and variation of temperature (% Temp var) of each prognosticator for late mortality in septic critically ill patients who are taking vasopressor and antipyretic. the AUROC of % Temp var (0.861; 95% CI, 0.798-0.924) was significantly higher than Temp max (0.789; %95 CI, 0.722-0.856) followed by Temp avg (0.719; %95 CI, 0.642-0.795).

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