EGYPTIAN JOURNAL OF ANAESTHESIA
2022, VOL. 38, NO. 1, 535–541
https://doi.org/10.1080/11101849.2022.2125249

Sequential estimation of the national early warning score-2 and SERUM PRESEPSIN might discriminate sepsis patients who were vulnerable to death in surgical ICU

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ABSTRACT

Objectives: To evaluate the ability of at-admission (Day 1) estimated serum levels of inflammatory biomarkers and clinical scorings for prediction of survival outcome of sepsis patients admitted to surgical ICU.

Patients & Methods: One hundred and seventy-eight patients were clinically evaluated and gave blood samples for estimation of serum biomarkers' levels (Day 1 data) and re-evaluated on Days 2–3 for the National Early Warning-2 (NEWS-2) score and Day 3 for the Sequential organ failure assessment (SOFA) score and serum level of presepsin (PSP). During 28-day, patients were grouped according to survival outcome as Survivors and Non-survivors.

Results: Day1 clinical scorings and biomarkers' levels were significantly higher in non-survivors (n = 41) than survivors (n = 137). Day 3 SOFA scores of all patients were significantly higher than Day1 scores with significantly higher scores for non-survivors. Through Day1-3, the number of patients with high-grade risk on NEWS2 was significantly higher among non-survivors. Day-3 serum PSP levels were significantly decreased in survivors, while increased in non-survivors. The statistical analyses defined high NEWS2, SOFA, PSP, and procalcitonin serum levels as the significant predictors of mortality. Diagnostic performance characteristics of combined NEWS score and PSP showed high sensitivity, specificity, and accuracy rates with a 99% negative predictive value for survival outcomes.

Conclusion: Sequential estimation of NEWS2 score and serum PSP can discriminate between high-risk patients and those prone to die. Coupling of NEWS-2 scoring and estimation of serum PSP allowed more accurate early identification of patients vulnerable to deterioration with high sensitivity and accuracy rates.

ARTICLE HISTORY
Received 5 July 2022
Accepted 12 September 2022

KEYWORDS
Sepsis; ICU mortality; the new early warning-2 score; serum biomarkers; presepsin

1. Introduction

Sepsis management is still one of the most important challenges in modern clinical practice because the rapid progression of sepsis to septic shock is practically unpredictable [1]. Septic shock patients are prone to altered fibrinolysis, which contributes to microthrombus formation, organ failure, and mortality [2].

The low positivity of traditional diagnostic methods of sepsis and septic shock may be secondary to the influence of the quality and quantity of specimens, the severity of infection, and laboratory sufficiency [3]. This necessitated the search for biomarkers that can help clinicians in the management of sepsis patients to reduce the probability of a fatal outcome [4].

Presepsin (PSP) is a 13 kDa, a small soluble peptide that consists of 64 amino acids [5] and is truncated from a soluble cluster of differentiation 14 (CD14) by circulating plasma proteases [6]. The CD14 is one of the leukocyte differentiation antigens that is present in macrophages, monocytes, granulocytes, and their cell membranes [7].

Failure to recognize a deteriorating patient is a common cause of serious adverse events [8]. Physiological track and trigger systems are designed to help to identify and respond to patients at risk of clinical deterioration [9]. The National Early Warning Score (NEWS) was developed by the Royal College of Physicians in England to standardize early warning scores and is probably the best-validated EWS for recognition of sepsis [10].

2. Objectives

This study targets to evaluate the ability of at-admission estimated serum levels of inflammatory biomarkers and clinical scorings for prediction of survival outcome of sepsis patients admitted to ICU.

2.1. Design

Prospective comparative study

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2.2. Setting

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3. Patients & methods

All patients admitted to the Surgical ICU at Benha University Hospital with manifestations suggestive of sepsis were eligible for evaluation of inclusion and exclusion criteria.

3.1. Exclusion criteria

Patients who had immunosuppressive, cardiac, hepatic diseases, acute kidney injury, hemorrhagic shock, or maintained on immunosuppressant therapy, or renal supplemental therapy were excluded from the study. Also, patients with definite or fulminant infection anywhere in the body who underwent major surgical procedures, especially cancer surgeries, or were suspected to die during their ICU stay were excluded from the study.

3.2. Clinical assessment tools

(1) Sepsis and septic shock were defined according to the 3rd International consensus definitions; sepsis was defined as life-threatening organ dysfunction secondary to the deregulated host response to infection [11]. Septic shock was defined as sepsis with profound circulatory, cellular, and metabolic abnormalities and was clinically identified by serum lactate level of >18 mg/dl, concurrent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) of ≥65 mmHg in absence of hypovolemia [12] and is associated with an in-hospital mortality rate (MR) of 30–50% [13].

(2) The Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score

SOFA score allows for the calculation of both the number and the severity of organ dysfunction in six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurologic) and the score can measure individual or aggregate organ dysfunction that was defined as individual SOFA score of ≥2 points [14], which is the predetermined cutoff point for in-hospital mortality rate (MR) of >10% [15].

(3) Acute Physiology and Chronic Health Evaluation II (APACHE II) Score

APACHE II score is the severity of disease classification system using point scores for initial values of 12 routine physiological measures, age, and previous health status to provide a score ranging from 0 to 71 with the higher is the score, the higher the mortality risk [16].

(4) The National Early Warning Score (NEWS2)

NEWS2 is based on six vital signs including respiratory rate, oxygen saturation, systolic blood pressure, heart rate, consciousness, and temperature. A NEWS2 score categorizes patients as low, medium, or high-risk patients and guides the frequency of monitoring with a score of zero indicating the need for 12-hr monitoring, a score of 1–4 indicating the need for monitoring every 4–6 h and a score of 5–6 indicates medium risk and potential serious acute clinical deterioration that necessitates hourly monitoring [17], while a NEWS2 score of ≥7 indicates high risk and severe clinical deterioration with the need for continuous monitoring [18].

3.3. Laboratory investigations

At the time of ICU admission, peripheral venous blood samples were obtained by venipuncture under complete aseptic conditions and without the use of a tourniquet by a lab assistant who was blinded about the diagnosis. Blood samples were collected in plain tubes, allowed to clot in a warm water bath at a temp of 37°C for 5 minutes, and then centrifuged at 5000 rpm for 2 minutes to separate serum, which is divided into two parts:

(1) The first part was used for photocolorimeteric estimation of serum lactate levels according to the manufacturer's instructions [19].

(2) The 2nd part was collected in Eppendorf tubes for estimation of serum procalcitonin (PCT), C-reactive protein (CRP), and presepsin (P-SEP) using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions and were read using a 96 well microplate ELISA reader (Dynatech. MR 7000):

a. Human serum PCT level was estimated using an ELISA kit (catalog no. ab221828, Abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique [20].

b. Human CRP level using ELISA kit (catalog no. ab99995, Abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique [21].

c. Human prespesin (PSP) level using ELISA kit (catalog no. MBS766136, MyBioSource Inc., San Diego, California, USA) by quantitative sandwich enzyme immunoassay technique [22].

3.4. Study outcomes

- The primary outcome is the ability of clinical scorings alone or in conjunction with biomarkers for the prediction of the 28-day ICU mortality rate

- Secondary outcomes
  - The extent of change in NEWS-2 and SOFA scores and serum presepsin levels on the 3rd day after ICU admission was calculated as Δ = Day3- Day1
  - Evaluation of the significance of the change concerning mortality.

3.5. Statistical analysis

Obtained data were presented as mean, standard deviation, numbers, percentages, and median and interquartile ranges. Results were analyzed using one-way ANOVA for analysis of variance between groups, paired t-test for analysis within each group, Chi-square test (X^2 test) for analysis of non-numeric data, and Mann–Whitney test for median values. Predictability of studied parameters for discrimination of sepsis patients vulnerable to death was evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) compared versus the null hypothesis that AUC = 0.05. Regression analysis (Stepwise method) was used for the stratification of studied parameters as specific predictors. Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package. P-value <0.05 was considered statistically significant.

4. Results

During the study duration from June 2019 to Nov 2021, 231 sepsis patients were admitted to the surgical ICU at Benha University Hospital, 53 patients were excluded for not fulfilling the inclusion criteria, and 178 patients were enrolled in the study. Throughout the 28-day follow-up at ICU, 41 patients (23%) died, non-survivors were significantly older (p = 0.048) and showed a significantly (p = 0.037) higher frequency of the need for mechanical ventilation than survivors. At-admission data of all patients categorized according to 28-day survival outcome is shown in Table 1.

During the duration since ICU admission (Day-1) till D-3, all the clinical scorings of non-survivors were significantly higher in comparison to the scorings of survivors. Day-3 SOFA score was significantly higher compared to the Day-1 score of all patients, but the ΔSOFA was significantly higher in non-survivors than in survivors. As regards the NEWS-2, from Day1 to Day3, patients' distribution according to the risk grades of NEW-2 score showed a significant (p < 0.0001) difference between survivors and non-survivors with a significantly higher frequency of patients of high-risk grade among non-survivors. The median values of NEWS-2 scores were significantly higher among non-survivors than the survivors during days 1-3 with significantly higher ΔNEWS2 for non-survivors (Table 2).

Table 1. At-admission data of studied patients categorized according to 28-day survival.

Parameters		Survivors (n = 137)	Non-survivors (n = 41)	P
Age		53.9 ± 10.3	57.4 ± 8.6	**0.048**
Sex	Males	81 (59.1%)	26 (63.4%)	**0.623**
	Females	56 (40.9%)	15 (36.6%)	
Approximate BMI (Kg/m^2)		30.2 ± 2.3	30.7 ± 2.9	**0.284**
Temperature (°C)		37.9 ± 1.1	38 ± 1.4	**0.414**
Need ventilation	Yes	18 (13.1%)	11 (26.8%)	**0.037**
	No	119 (86.9%)	30 (73.2%)	
Associated medical problems	Yes	35 (36.5%)	15 (73.2%)	**0.168**
	No	102 (63.5%)	26 (44.4%)	

Data are shown as mean, standard deviation, numbers, percentages; BMI: Body mass index; p-value indicates the significance of the difference between both groups; p < 0.05 indicates the significant difference; p-value >0.05 indicates the non-significant difference.

Estimated levels of sepsis-associated laboratory variables were significantly higher in non-survivors compared to the levels estimated in survivors. On Day-3 serum, presepsin levels were significantly decreased in survivors (p < 0.0001), while were significantly (p = 0.0001) increased in non-survivors with significantly (p < 0.0001) higher levels in sera of non-survivors compared to survivors. Moreover, the median value of ΔPSP of non-survivors was significantly higher in comparison to that of survivors (Table 3).

Correlation analysis showed a negative significant correlation between survival rate and patients' age and at-admission APACHE II, SOFA, and NEWS-2 clinical scorings and total leukocytic count, plasma lactate levels, and serum levels of CRP, PCT, and PSP. At-admission, the NEWS-2 score showed a positive significant correlation with the APACHE II score, plasma lactate levels, and serum PSP levels. Serum PSP levels estimated at ICU admission showed a positive significant correlation with APACHE II, SOFA, and NEWS-2 clinical scores and with plasma lactate levels and serum CRP levels (Table 4).

Regression analysis of variables correlated with mortality defined high at-admission NEWS-2 score, serum PSP, SOFA score, and serum PCT as the significant independent variables for the prediction of mortality. ROC curve analysis defined high at-admission NEWS-2 score and serum PSP as positive independent predictors for mortality with moderate accuracy, while high at-admission SOFA score and serum PCT levels as positive predictors for mortality with weak accuracy as judged by the area under the curve (Table 5, Figure 1).

The diagnostic performance characters of NEWS-2 score and serum PSP estimated at-admission using the median value for each (5 for NEWS-2 and 432 for PSP) separately and in combination were improved on the application of both variables as a diagnostic tool with sensitivity and negative predictive value for mortality of 97.6 and 99%, respectively, and specificity of 73.7% and accuracy rate for prediction of mortality by 79.2% (Table 6).

Table 2. Clinical scorings of studied patients categorized according to 28-day survival.

Scoring systems Group			Survivors (n = 137)	Non-survivors (n = 41)	P-value
At-admission APACHE II score			22.5 ± 4.1	24.4 ± 6.8	**0.028**
SOFA score		Day-1	9.5 ± 2.5	10.5 ± 2.7	**0.0215**
		Day-3	10.4 ± 3.1	14.4 ± 3.7	**<0.0001**
		P1 value	0.012	<0.0001	
		ΔSOFA	1 [0–1]	4 [2–5]	**<0.0001**
NEWS-2 score	**Day-1**	Low risk	72 (52.6%)	7 (17.1%)	**<0.0001**
		Moderate risk	51 (37.2%)	14 (34.1%)	
		High risk	14 (10.2%)	20 (78.8%)	
		Score	4 [2–5]	6 [5–8]	**<0.0001**
	Day-2	Low risk	80 (58.4%)	5 (12.2%)	**<0.0001**
		Moderate risk	48 (35%)	14 (34.1%)	
		High risk	9 (6.6%)	22 (53.7%)	
		Score	3 [2–5]	7 [6–8]	**<0.0001**
	Day-3	Low risk	102 (74.5%)	0	**<0.0001**
		Moderate risk	33 (24%)	5 (12.2%)	
		High risk	2 (1.5%)	36 (87.8%)	
		Score	3 [2–5]	7 [7–8]	**<0.0001**
		ΔNEWS	0 [(−1)- 0]	1 [0–2]	**<0.0001**

Data are shown as mean, standard deviation, numbers, percentages, median & interquartile range [IQR]; APACHE II: Acute Physiology And Chronic Health Evaluation II, SOFA: sequential organ failure assessment, ΔSOFA: the change of Day3 SOFA concerning Day1 SOFA score; NEWS: The National Early Warning score; p-value indicates the significance of the difference between both groups; P1 indicates the significance of the difference between Day1 and Day3 SOFA scores; $p < 0.05$ indicates the significant difference; p-value >0.05 indicates a non-significant difference.

Table 3. Laboratory findings of studied patients categorized according to 28-day survival.

Parameter Group		Survivors (n = 137)	Non-survivors (n = 41)	P-value
At-admission (Day 1)	Total leucocytic count (10^3/cc)	8.24 ± 3.13	9.8 ± 3.86	**0.0078**
	Plasma lactate level (mg/dl)	25.2 ± 6	39.5 ± 16.7	**<0.0001**
	C-reactive protein (ng/ml)	226.5 ± 86.8	267.1 ± 93	**0.009**
	Procalcitonin (ng/ml)	0.87 ± 0.47	1.26 ± 0.91	**0.0003**
Presepsin (pg/ml)	Day-1	436.4 ± 180.3	687.5 ± 240.6	**<0.0001**
	Day-3	308.3 ± 161.8	896 ± 272.7	**<0.0001**
	P1	<0.0001	0.0001	
	ΔPSP	−122 ([−157]-38.7)	207 (164–238)	**<0.0001**

Data are shown as mean, standard deviation; ΔPSP: serum levels estimated in a sample of Day3 minus that of Day1; P1 indicates the significance of the difference between serum PSP in samples of Day1 and Day3; p-value indicates the significance of the difference between both groups; $p < 0.05$ indicates the significant difference; p-value >0.05 indicates the non-significant difference.

Table 4. Spearman's correlation between survival rate, NEWS-2 clinical scores, serum P-SEP levels, and other studied variables studied in patients admitted to surgical ICU.

	Survival rate		NEWS-2 score		P-SEP serum level	
Variables	Rho	P	Rho	P	Rho	P
Age	−0.177	**0.018**	0.132	**0.079**	0.076	0.314
Body temperature	−0.065	**0.386**	0.104	**0.165**	0.054	0.314
APACHE II score	−0.231	**0.002**	0.164	**0.029**	0.239	0.001
SOFA score	−0.284	**<0.0001**	0.061	**0.416**	0.1770	0.023
NEWS-2 score	−0.496	**<0.0001**			0.548	<0.0001
Total leucocytic count (10^3/cc)	−0.190	**0.011**	0.040	**0.592**	0.261	<0.0001
Plasma lactate level (mg/dl)	−0.472	**<0.0001**	0.310	**<0.0001**	0.235	0.002
C-reactive protein (ng/ml)	−0.190	**0.011**	0.095	**0.206**	0.143	0.058
Procalcitonin (ng/ml)	−0.170	**0.023**	0.117	**0.119**	0.292	<0.0001
Presepsin (pg/ml)	−0.469	<0.0001	0.548	<0.0001		

Rho: Spearman's correlation coefficient; APACHE II: Acute Physiology And Chronic Health Evaluation II, SOFA: sequential organ failure assessment; NEWS: The National Early Warning score; p-value indicates the significance of Rho value; $p < 0.05$ indicates the significant difference; p-value >0.05 indicates the non-significant difference.

Table 5. Statistical analyses of at-admission clinical and lab variables of studied patients for prediction of the upcoming 28-day mortality of sepsis patients.

	Regression analysis		ROC curve analysis			
Independent variables	β	P-value	AUC	Std E	P	95% CI
SOFA	0.173	**0.005**	0.693	0.044	**<0.001**	0.606–0.780
NEWS-2	0.332	**<0.001**	0.834	0.034	**<0.001**	0.768–0.900
Procalcitonin (ng/ml)	0.150	**0.017**	0.617	0.054	**0.024**	0.511–0.722
Presepsin (pg/ml)	0.245	0.002	0.822	0.043	<0.001	0.737–0.906

ROC: Receiver operating curve; AUC: Area under the curve; Std E: Standard deviation; CI: Confidence interval; β: Standardized coefficient; SOFA: sequential organ failure assessment; NEWS: The National Early Warning score; p-value indicates the significance of result; $p < 0.05$ indicates the significant difference; p-value >0.05 indicates the non-significant difference.

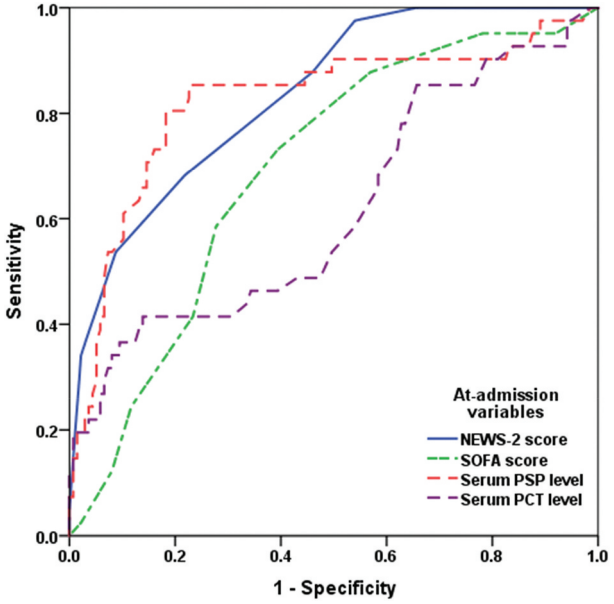

Figure 1. ROC curve analysis of at-admission clinical scorings and lab parameters of studied patients for prediction of upcoming 28-day ICU mortality of sepsis patients.

Table 6. The diagnostic performance characters of at-admission NEWS-2 score and serum PSP levels as predictors for mortality of sepsis patients admitted to surgical ICU.

Character	NEWS-2 score	PSP level	NEWS2 + PSP
Sensitivity (%)	82.9 (67.94–92.85)	85.4% (70.83–94.43)	97.6 (87.1–99.9)
Specificity (%)	52.55 (43.85–61.14)	60.6 (51.9–68.8)	73.7 (65.5–80.9)
Positive predictive value (%)	34.3 (28.5–39.6)	39.3 (33.7–45.3)	52.6 (45.5–59.6)
Negative predictive value (%)	91.1 (83.7–95.4)	93.3 (86.7–96.7)	99 (93.6–99.9)
Positive likelihood ratio	1.75(1.40–2.19)	2.21 (1.7–2.76)	3.71 (2.79–4.94)
Negative likelihood ratio	0.32 (0.16–0.65)	0.24 (0.11–0.51)	0.03 (0.0–0.23)
Accuracy (%)	59.6 (52–66.83)	66.3 (58.8–73.2)	79.2 (72.5–84.9)

Data are presented as percentage and 95% confidence interval in parenthesis; NEWS: The National Early Warning score; PSP: Presepsin;

5. Discussion

The application of the National Early Warning score-2 (NEWS-2) for daily evaluation of sepsis patients at ICU allowed discrimination of patients improving and those deteriorating using a cutoff point of ≥5 on the at-admission NEWS-2 score. The selected cutoff point for differentiation coincided with the recently documented that NEWS2 is an effective predictor of mortality for emergency department patients and suggested a maximum NEWS2 score of ≥4 as the best trigger point for escalation of treatment [23].

At-admission, the NEWS-2 score showed higher specificity and negative predictive value than at-admission APACHE II and SOFA scores. Moreover, sequential NEWS-2 evaluation for 3 days allowed identification of 34 patients of the 41 patients who died at the end of 28-ICU stay, thus it provided a correct prediction of mortality by a rate of 82.9%. This high predictive ability of NEWS-2 score for deterioration and mortality was assured statistically by ROC curve analysis (AUC = 0.834) and by regression analysis.

In line with these findings, a recent study found NEWS-2 could predict admission to ICU and mortality of a high percentage of those admitted to ICU for their disease severity with an AUC = 0.9 [24]. Another study documented that NEWS2 at a cutoff point of ≥7 had significantly greater AUC than other screening tools at Emergency Triage for the prediction of sepsis among ambulance patients with clinically suspected infection [25]. In a similar comparison of NEWS2 and SOFA scores, a recent study reported that the 3-day NEWS2 had good discrimination for predicting 7-, 14-, 21-, and 28-day mortalities and was not inferior to the SOFA [26].

The ability of at-admission serum presepsin to discriminate ICU sepsis patients vulnerable to die was superior to the ability of TLC, CRP, and PCT, with an AUC = 0.822. In line with these findings, multiple studies assured the superiority of estimated serum presepsin over other biomarkers as an early marker for discrimination of septic patients who are vulnerable to progression to septic shock or deterioration and death [27–29]. Moreover, two recent studies documented that PSP has a reliable early diagnostic ability for sepsis comparable to that of PCT [30] and could be a useful marker for prognosis of sepsis severity and mortality risk [31].

Estimation of diagnostic performance characters assured the sensitivity and negative predictive value of high day-1 presepsin levels as an early predictor of mortality of sepsis patients admitted to surgical ICU with high accuracy rate than the NEWS-2 score. Similarly, a recent study assured the higher accuracy of early presepsin measurement in ICU patients for the diagnosis of sepsis and the prediction of mortality in comparison to quick SOFA or systemic inflammatory response syndrome scores [32]. Moreover, the performance characteristics of NEWS-2 as a predictor for mortality were increased when combined with presepsin and both could predict mortality with a sensitivity rate of 97% and negative predictive value of 99%, and specificity and accuracy rates of 73.7% and 79.2%, respectively. In line with these findings, one recent study found that combined estimation of serum presepsin levels with the Glasgow Prognostic Score increased the specificity of clinical scoring for predicting septic acute respiratory distress syndrome [33]. Another recent study suggested that NEWS2 score and laboratory illness severity as calculated by a frailty index were independently associated with post-discharge survival of older adults admitted to ICU with acute clinical conditions [34].

6. Conclusion

At-admission high NEWS-2 clinical score and serum PSP could discriminate sepsis patients who were prone to death with high sensitivity and negative predictive value. Coupling of NEWS-2 scoring and serum PSP allowed more accurate early identification of patients vulnerable to deterioration with high-performance characters. Sequential estimation of both variables can discriminate high-risk patients and thus allows early modification of management plans.

6.1. Limitation

The study was a single-center study and results need multicenter comparative studies to be established.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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