CLINICAL VALUE OF TWO SCORING SYSTEMS, C-REACTIVE PROTEIN AND LACTATE CLEARANCE IN PATIENTS WITH SEVERE SEPSIS AT THE EMERGENCY DEPARTMENT

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ABSTRACT Introduction: More recently the grading system of sepsis was modified to include severe sepsis, septic shock, and refractory septic shock. Sequential organ failure assessment score (SOFA) and the mortality in the Emergency Department Sepsis (MEDS) score have a significant role in related to short-term clinical outcome. **Methods:** An observational cohort study with prospective data collection. The severity of sepsis assessed according to SOFA score, MEDS score. C-reactive protein (CRP) and 6 hours lactate clearance were measured. The outcome of patients noticed according to the detected SOFA score, MEDS score, CRP, and lactate clearance levels in the survivors and non-survivors as well as their correlation with the severity of the disease. **Results:** Fifty patients with an age range from 20 to 92 years. The mortality rate was 24% (12 patients). Six hours lactate mean clearance value was 21.04 $\pm$ 9.48%. Mean SOFA score at presentation was 6.56 $\pm$ 2.99 while after 72 hours, it was 5.28 $\pm$ 3.94. Mean MEDS score was 2.72. Six hours lactate clearance was significantly lower among the dead cases. MEDS score was considerably higher among the mortality cases. SOFA score whether measured at admission or after 72 hours and MEDS score were significantly greater among the dead cases. Both delta SOFA score and 6-hour lactate clearance were found to have the highest predictive characteristics with 100% sensitivity and specificity. There was statistically significant difference between the area under the curve of SOFA 72 hours and 6 hours-lactate clearance when compared to CRP area under the curve. **Conclusion:** Both delta SOFA score and six-hour lactate clearance had the highest predictive characteristics with 100% sensitivity and specificity.

KEYWORDS: SOFA score, MEDS score, 6-hours lactate clearance, severe sepsis.

Introduction

Sepsis is a common and grave disease with substantial morbidity and mortality. It defined as a systemic response to a local infection with concurrent manifestations that are the result of the host response which is known as systemic inflammatory response syndrome (SIRS) [1].The clinical manifestations are the consequence of intense cellular interactions [2]. More recently severe sepsis, septic shock, and refractory septic shock managed by the sepsis grading system. Severe sepsis associated with at least one sign of organ hypoperfusion or dysfunction, such as cardiac dysfunction, acute lung injury, or altered mental status [3]. Clinical trials and observational studies usually use a scor-

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ing system for the assessment of the severity of organ function impairment, the most popular among them are the sequential organ failure assessment score (SOFA) [4] and the mortality in emergency department Sepsis (MEDS) score [5]. The SOFA score is a simple and objective score that 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) [4]. The MEDS score was designed to predict 28-day mortality in patients with suspected sepsis. This scoring system categorizes patients into risk groups based on the presence of nine independent predictors of mortality [6]. Currently, serum lactate clearance shows the most promise as a reasonable biomarker alternative to invasive resuscitation monitoring. Studies have found that septic patients who have not clear serum lactate by 10% in the first 2 to 6 hours have an increased mortality [7]. C-reactive protein (CRP) may be useful in diagnosing the onset of sepsis in acutely ill patients, and some authors have reported that daily measurement of CRP is helpful in the detection of sepsis and that it is more sensitive than currently used markers, such as white blood cell (WBC) count [8]. However, few studies have correlated 6-hours lactate clearance and/or CRP serum concentrations to the severity of sepsis-related conditions at the Emergency Department (ED) represented by SOFA and MEDS scores. However, a clinical score has several advantages that a biomarker does not have. The SOFA and MEDS scores can be rapid, repeatedly, and easily evaluated once the patient's condition changes. It would be interesting to know whether combining the information of either the SOFA or the MEDS scores and 6-hours lactate clearance or CRP may further enhance accuracy in predicting mortality in patients with sepsis at the ED. The present study validates the SOFA and MEDS scores as predictors of mortality in patients with severe sepsis who present to the ED of the Suez Canal University Hospitals. Also, the initial lactate levels and its 6-hours clearance as well as CRP plasma concentrations will be measured in those patients and compare their prognostic value in the assessment of severity and prediction of mortality. Furthermore, we compare the performance of the SOFA and MEDS scores to that of serum CRP and initial arterial lactate levels and clearance.

Aim of the study

To evaluate the clinical utility of the SOFA score, the MEDS score, CRP level and lactate-6h-clearance as early indicators for outcome prediction in patients with severe sepsis attending the ED at Suez Canal University Hospitals.

Materials and methods

Research design and population

Observational cohort study with prospective data collection.It received approval from the Institutional Research Review Board Ethical Committee of the Suez Canal University, Faculty of Medicine, Ismailia, Egypt. Population included both gender and above eighteen years patients attended to the ED at Suez Canal University Hospital with criteria of severe sepsis which is:

1. Presence of the criteria of Systemic Inflammatory Response Syndrome (SIRS) according to American College of Chest Physicians [9], when two or more of the following criteria are present,
   (a) Heart rate less than 90 beats per minute,
   (b) Body temperature less than 36°C or more than 38°C,
   (c) Tachypnea more than 20 breaths per minute or, on blood gasses a $PaCO_2$ more than 32 mmHg.,
   (d) White blood cell count less than 4000 cells/mm^3 or more than 12000 cells/mm^3 or the presence of greater than 10% immature band neutrophils [10],
2. Signs of circulatory shock [3] when there is one of these,
   (a) Systolic BP less than 90 mmHg or MAP less than 70 mmHg or hypotension requiring volume resuscitation or vasopressor / inotropic agents,
   (b) Altered sensorium,
   (c) Acute oliguria (urine less than 0.5 ml/kg/hr.),
3. Evidence of infection [11] when there is one of these
   (a) Tentative diagnosis of sepsis documented by physicians in the ED,
   (b) Clear laboratory evidence (e.g. pneumonia on chest radiographs, abscess formation, bacterial cultures, and others.).
4. Arterial metabolic acidosis (pH < 7.35 and HCO_3^- < 20 mEq/l),

   We excluded patients known to have organ chronic failure; patients are known to have a history of cancer, patients known to have the previous history of fever of unknown origin and refusal to participate in the study.

Sample size:

The sample size calculated through the width of the confidence interval (CI). The formula for a confidence interval for Sn or Sp would be:

$$Sn \pm z\frac{1-\alpha}{2}\sqrt{Sn}\frac{(1-Sn)}{naSp} \pm z\frac{1-\alpha}{2}\sqrt{Sp}\frac{1-Sp}{nn}$$

According to 95% CI of$\pm$ 0.12 for Sn and $\pm$ 0.083 for Sp; The sample size = 50 patients.

Data Collection

Data collected in pre-organized data sheet by the researcher; from patients fulfilling inclusion and exclusion criteria. These data included clinical evaluation of the patients upon arrival to ED regarding full medical history, vital signs, radiological, laboratory investigations including 6hs lactate clearance and CRP, and severity of sepsis which assessed according to the SOFA score. SOFA score did at presentation and after 72 hours to calculate delta SOFA score. Another score applied to each patient, the MEDS score which designed to predict 28-day mortality in patients with suspected sepsis. Our patients were followed up daily during hospitalization for the efficacy of management and survival status, and after discharge, a telephone call with the patient or with his family was conducted to inquire about the patient's one-month survival status. The fate of the patient recorded whether ICU admission, inpatient admission operative intervention or died. The outcome of the patients noticed according to the detected SOFA score, MEDS score, CRP and lactate clearance levels in the survivors and non-survivors as well as their correlation with the severity of the disease.

Data Management and Statistical Analysis

Data collected throughout history, clinical examination and laboratory investigations were coded, entered and analyzed using Microsoft Excel software. Data were imported into SPSS (Statistical Package for Social Sciences) software program version 10.0 for analysis. According to the type of data, the following tests were used to test differences for significance; Chi-square, t-test, and one-way ANOVA with least significance difference. Chi-square test and non-parametric tests were used to compare categorical variables. P value set at <0.05 for significant results.

Table 1 Demographic characteristics of the studied patients:

Age	**Mean ± SD**	58.76 ± 19.39	
Age	**Range**	20 – 92	
		Number	**Percentage**
Sex	**Male**	20	40%
Sex	**Female**	30	60%
Outcome among the studied patients	**Died***	**Survive**	**Total**
Number (Percentage)	12 (24%)	38 (76%)	50 (100%)
ICU admission	6 (50%)	10 (26%)	16 (32%)
Inpatient admission	4 (33%)	10 (26%)	14(28%)
Operative intervention	2 (17%)	18 (48%)	20 (40%)
Total	12 (100%)	38 (100%)	50 (100%)
*All dead cases died early (5-days) mortality.			

Results

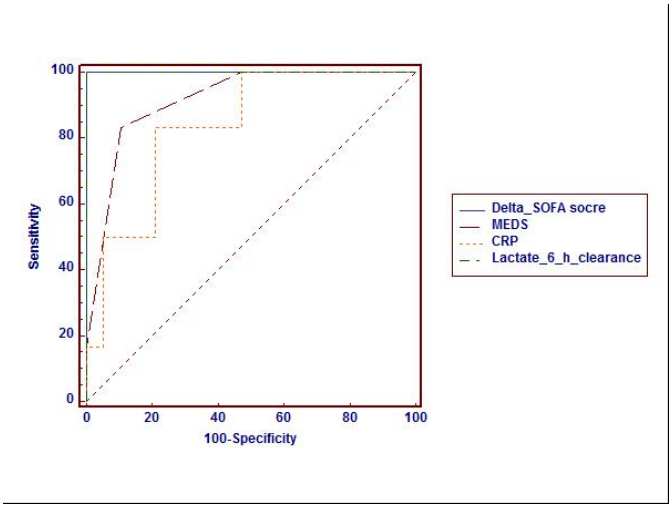
Socio-demographic data of the study population

The current study conducted on 50 patients presented to the ED, Suez Canal University Hospitals with the diagnosis of severe sepsis. The mean age of the patients was 58.76 years with a range of 20 to 92 years. Most of the patients in the present study were females (60%). The mortality rate was 24%. Thirty-two % of the patients were admitted to ICU while 28% admitted to the inpatient ward and 40% went to the operative room. (Table 1).

Clinical evaluation

The mean was 74.42 with a broad range from 29.91 up to 147.8 mg/L. As regarding 6 hours lactate clearance, it ranged from 7.81 to 37.24% with a mean value of 21.04 %. Mean SOFA score at presentation was 6.56 ± 2.99 while after 72 hours, it was 5.28 ± 3.94. Mean MEDS score was 2.72. Dead cases had significantly higher CRP levels compared to the survived cases. Six hours lactate clearance was significantly lower among the dead situations. MEDS score was substantially greater among the mortality cases (4 versus 2.32). SOFA score whether measured at admission or after 72 hours was significantly higher among the mortality cases. Delta sofa score (the difference between sofa score after 72 hours and initial sofa score) was considerably greater among dead cases. (Table 2).

Our study showed that Delta SOFA sensitivity 100%, specificity 100%, positive predictive value 100% and negative predictive value 100%. MEDS sensitivity 83.3%, specificity 89.47%, positive predictive value 71.4% and negative predictive value 94.4%. CRP sensitivity 83.3%, specificity 78.95%, positive predictive value 55.6% and negative predictive value 93.8%. 6h Lactate Clearance sensitivity 100%, specificity 100%, positive predictive value 100% and negative predictive value 100%. Both Delta SOFA score and lactate 6-hour clearance were found to have highest predictive characteristics with 100% sensitivity and specificity. There was statistically significant difference between the area under the curve of SOFA 72 hours and lactate 6 hours clearance when compared to CRP area under the curve. (Graph 1).



Graph 1: ROC curves analysis for value of Delta SOFA score, MEDS score, CRP and 6 hours lactate clearance to predict mortality among patients with severe sepsis.

Discussion

Sepsis persists as a major health care problem and a serious disease with high mortality and immense financial burden on the health care system despite ongoing research to improve overall outcomes [11]. Severity assessment is necessary for the management of patients, including decision-making regarding choice of treatment and patient disposition. These scoring systems can help to determine the chances of survival [13]. Also, several serum biomarkers are purported to have diagnostic and prognostic values in patients with sepsis, they have the ability to reflect the severity of sepsis and septic shock and can be used to tailor antimicrobial therapies [14]. The current study conducted on 50 patients presented to the ED at Suez Canal University Hospitals, Egypt with severe sepsis. All patients were evaluated in

Table 2 CRP, 6 hours lactate clearance, SOFA score and MEDS score among the studied patients and according to mortality:

		Total Studied Patients (n=50)		Survived Cases (n=38)	Died Cases (n=12)	p-value
		Rang	Mean ± SD	Mean ± SD	Mean ± SD	
CRP (mg/L)		29.91-147.8	74.42±35.03	64.65±30.45	105.39±31.17	0.001*
serum lactate (mmol/L)	Initial serum lactate	2.15 – 6.9	4.59 ± 1.39	4.11 ± 1.2	6.12 ± 0.65	0.001*
serum lactate (mmol/L)	6h. lactate clearance %	7.81–37.24	21.04±9.48	24.79±7.64	9.17±1.38	0.001*
SOFA score	Initial	1 –12	6.56±2.99	5.78±2.86	9±2	0.002*
SOFA score	After 72 h.	1 –14	5.28±3.94	3.31±1.77	11.5±1.78	0.001*
SOFA score	Δ score			-2.47±1.37	2.5±0.52	0.001*
MEDS score		1 –5	2.72±1.16	2.32±0.99	4±0.6	0.001*
*Statistically significant difference.						

Table 3 Significance difference between AUC of different parameters:

Parameter	AUC	Sensitivity	Specificity	PPV	NPV
Delta SOFA	100%	100%	100%	100%	100%
MEDS	92%	83.3%	89.47%	71.4%	94.4%
CRP	83%	83.33%	78.95%	55.6%	93.8%
6h Lactate Clearance	100%	100%	100%	100%	100%
*Statistically significant difference.					

Table 4

Parameter	Delta SOFA score	MEDS	CRP
MEDS	0.1 (NS)	-	-
CRP	0.03*	0.3 (NS)	-
6h Lactate Clearance	0.9 (NS)	0.1 (NS)	0.03*
NS: No statistically significant difference.			

the ED and followed up to one month from their presentations. The mortality rate between our patient was 24% (12 patients), six of them died in ICU, four in inpatient ward and two of them died early postoperative. While 76% (38 patients) survived, ten admitted to ICU, another ten admitted to inpatient ward and eighteen patients admitted for surgical intervention. The results showed that the mean age of the studied patients was 58.76 years old with a range from 20 to 92 years old. Most of the patients were females 60%. Our results are comparable with the study of Desai S et al., (2013) who studied 50 patients with severe sepsis 54% were females with a mean age 47.52 years [15]. Also, the present study also agrees with another study by Jones AE et al., (2009) in which most of the patients were females 52% with a mean age of 57 years [12]. In accordance, Chen CC et al., (2006) studied 276 patients with severe sepsis 55.4% of them were females with a mean age 62 years [16]. The present study showed that there was no statistically significant difference between survived and dead cases regarding the history of chronic illness. However, it was found that the patients presented with a disturbed level of consciousness represented a significantly higher incidence (91.67%) in the former group than those in the survived group (25%). The current study showed that 50% of the dead cases presented with a GCS score of less than eight versus 10.53% of the survived cases with a significantly higher incidence of low GCS in the former group. In our study, the results showed that the mean CRP was 74.42 mg/L with a broad range from 29.91mg/L up to 147.8 mg/L and the best cut-off value was >88mg/L. **Chan YL et al., (2002)** reported that the mean CRP was 100.3 mg/L with also a broad range of 35.7 mg/L up to 170 mg/L in a study that evaluated the feasibility of using CRP levels as an indicator of bacterial infection of adult patients in the emergency department

[17]. In contrast, **Ugarte et al.**, (2000) investigated 190 critically ill patients and reported the optimal cut-off level for CRP using the Youden's index was 79 mg/l [18]. Also, **Chan YL et al., (2002)** found that the best cut-off value for CRP using Youden's index was only 60 mg/L [17]. As a prognostic marker, some have reported that serum CRP on admission associated with higher mortality [19].In our study, the dead cases had significantly higher CRP levels compared to the survived cases (105.39 mg/L versus 64.65 mg/L respectively). In the current study, the results showed that mean initial serum lactate level was 4.59 $\pm$ 1.39 mmol/L while after 6 hours, it was 3.73 $\pm$ 1.49 mmol/L. Initial and 6-hour serum lactate levels were significantly higher among the dead cases compared to the survived cases. As regarding 6 hours lactate clearance, it ranged from 7.81 to 37.24% with a mean value of 21.04%. Six hours lactate clearance was significantly lower among the dead cases compared to the survived cases. The area under the ROC curve of 6 hours lactate clearance for prediction of mortality was 100% (95% confidence interval 0.928-1). Our results showed that 6 hours lactate clearance significantly correlated with mortality (P-value= 0.001). Six hours lactate clearance$\leq$ 11.38% had a sensitivity and specificity 100% for prediction of death. Lactic acid levels have become a useful marker for tissue hypoperfusion and may also serve as an endpoint for resuscitation in patients with sepsis and septic shock [20, 21].**Zanaty OM et al., (2012)** reported that the initial serum lactate level was 6.28$\pm$ 2.18 mmol/L while after 6 hours, it was 3.36$\pm$ 1.15 mmol/L. Six hours lactate clearance also was significantly lower among the dead cases compared to the survived situations in a study included 53 patients with severe sepsis [20]. **Bakker et al. (1996)** defined "lactime" as the time during which lactate remains > two mmol/L and observed that this duration of lactic acidosis was predictive of organ failure and survival [21].Serial lactate measurements may be more important as an outcome prognostic indicator than a single lactate measurement [22]. **Nguyen et al. (2004)** concluded that higher Lactate clearance in the most presentation of severe sepsis and septic shock is associated with improved morbidity and mortality rates, which is consistent with current efforts that emphasize the importance of identifying and treating tissue hypoperfusion during the first six h of resuscitation [23]. **Scott S. et al (2010)** concluded that, the systematic monitoring of lactate clearance at 2 h should be clinically useful in cases of acute cardiac or respiratory insufficiency to identify patients at a high risk of negative outcome and, potentially, to increase the intensity of the therapeutic approach and finally suggested that, a 2-h lactate clearance >15% is highly predictive of positive outcome and may reassure the clinicians that the therapeutic approach is appropriate [24]. **Nguyen et al., (2010)** studied six h lactate clearance as a surrogate for the resolution of global tissue hypoxia in sepsis. They found that there was a significant decrease in-hospital, 28-day, and 60-day mortality in the higher lactate clearance quartiles ($P < 0.01$). Also, the higher lactate clearance was significantly associated with decreased levels of biomarkers, an improvement in organ dysfunction and outcome in severe sepsis and septic shock [25]. As regarding SOFA score, the present study showed that Mean SOFA score at presentation was 6.56 $\pm$ 2.99 points while after 72 hours, it was 5.28 ± 3.94 points. Delta SOFA score (the difference between sofa score after 72 hours and initial sofa score) was significantly higher among dead cases. The area under ROC curve of the delta SOFA score for prediction of mortality was 100% (95% confidence interval 0.93-1). Delta SOFA score significantly correlated with mortality (P-value= 0.001). **Jones AE et al., (2009)** in their study found that the mean SOFA score at presentation was 7.1 $\pm$ 3.6 points and after 72 hours was 7.4 $\pm$ 4.9 points. The area under the receiver operating characteristic curve of SOFA for predicting in-hospital mortality at presentation was 0.75 (95% confidence interval 0.68 - 0.83) and after 72 was 0.84 (95% confidence interval 0.77-0.90). The delta SOFA was found to have a positive relationship with in-hospital mortality [26]. Another study by Desai S and **Lankhani JD (2013)** showed that the mortality rate of patients with SOFA score after 72 hours less than nine was 9.1% while the death rate of patients with a score more than nine was 78%. The trend of mean SOFA score was progressively declining in the survivor group [15]. In contrast, **Acharya SP et al., (2007)** in their study found that the delta SOFA score did not correlate with mortality (p-value = 0.117) and only the initial mean and highest SOFA score were the reliable predictors of mortality in severe sepsis and septic shock [27]. Our study showed that the average MEDS score was 2.72 $\pm$ 1.16. MEDS score was significantly higher among the mortality cases (4 versus 2.32). The results also proved that MEDS score significantly correlated with mortality (P-value = 0.001). MEDS score >3 had a sensitivity of 83.33% and specificity of 89.47% in the prediction of death. The area under ROC curve of MEDS score was 92% (95% confidence interval 0.803 – 0.976). It was in agreement with **Jeffrey D et al., (2008)** who found in their study that the mean MEDS score was 2. The area under ROC curve of MEDS score regarding the prediction of mortality was 88% (95% confidence interval 0.83-0.92) [28]. **Chen CC et al., (2006)** showed in their study that the MEDS score may serve as a quick and straightforward triage tool in the identification of a subset of ED patients with the highest mortality risk from sepsis [16]. **Nathan I et al., (2007)** also, concluded in their study that the MEDS score is are a liable predictor of patient survival at one year after an indexed hospital visit with suspected infection. Although the score initially derived for 28-day in-hospital mortality, it was proven to be a valid predictor of 1-year survival [29].

The current study showed the comparison between evaluated different parameters regarding prediction of mortality among the studied patients. Both delta SOFA score and 6-hour lactate clearance were found to have the highest predictive characteristics with 100% sensitivity and specificity. There was statistically significant difference between the area under the curve of SOFA 72 hours and 6 hours-lactate clearance when compared to CRP area under the curve.

Conclusion

Six hours lactate clearance had a higher sensitivity, specificity, and predictive values compared to the CRP in the prediction of mortality in severe sepsis. Both delta SOFA score and six-hour lactate clearance had the highest predictive characteristics with 100% sensitivity and specificity.

Authors' Statements

Competing Interests

The authors declare no conflict of interest.

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