Sepsis and Septic Shock: Are Initial mSOFA Score, Point-of-Care Lactate, Neutrophil-Lymphocyte Ratio and Platelet Count Good Predictors for Mortality?

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ABSTRACT	ARTICLE DETAILS
Background: Sepsis is a common life threatening medical problem and first leading cause of death in Myanmar. This study was aimed to determine the predictive values of initial mSOFA score, point-of-care lactate, neutrophil-lymphocyte ratio and platelet count for mortality in patients with sepsis and septic shock. **Method:** A hospital based prospective observational study done in No.(1) Defence Services General Hospital, Yangon, from January 2021 to October 2022. All patients above 18 years old admitted with sepsis and qSOFA ≥ 2 were enrolled and sample size was 121 patients. The predictors were mSOFA score, point-of-care lactate, neutrophil-lymphocyte ratio and platelet count, which were assessed within 24 hour of admission and the mortality was observed for 28 days. Logistic regression was used to find out the predictive value and the predictors were compared by receiver operating characteristic curve analysis. **Results:** The initial mSOFA score, point-of-care lactate and neutrophil-lymphocyte ratio of non survivors were significantly higher than survivors (mSOFA score 9 vs 4), (blood lactate 3.3 mmol/L vs 2 mmol/L), (neutrophil-lymphocyte ratio 13.4 vs 8.3). Platelet count was significantly lower in non-survivors than survivors (175 x 10^9/L vs 290 x 10^9/L). The mortality was 33.1%. The mSOFA score and lactate were strongly correlated ($rho = 0.650$, $p < 0.001$). The adjusted odds ratio of mSOFA score was 1.350 (1.135 – 1.606) with adjusted R^2 0.478 and accuracy 80.2%. The adjusted odds ratio of lactate was 1.819 (1.168 – 2.834); NLR, 1.108 (1.023 – 1.200); platelet 0.992 (0.987 – 0.998) with adjusted R^2 0.616 and accuracy 86.8%. Each predictor had moderate prognostic value (AUC > 0.7) and the combinations of mSOFA score and/or lactate with NLR and platelet count, good prognostic value (AUC > 0.8). **Conclusion:** The mSOFA score, lactate, NLR and platelet count had predictive value for mortality assessment in patients with sepsis or septic shock. Lactate level was strongly correlated with disease clinical severity of the sepsis, mSOFA score. The combination of mSOFA score and/or lactate with NLR and platelet count had better predictive value. **KEYWORDS:** Sepsis, septic shock, mSOFA, lactate, neutrophil-lymphocyte ratio, platelet count	**Published On:** **19 January 2023** **Available on:** **https://ijmscr.org/**

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BACKGROUND

Sepsis is a common medical problem causing life threatening condition. There were nearly 50 million of sepsis cases and 11 millions of sepsis related death worldwide in 2017, and the mortality rate was almost 20 % globally (1). Incidence and mortality of sepsis is higher in low income countries. The sepsis related death was 6.6% in all-cause mortality of Myanmar in 2016 (2). Early resuscitation measure and prompt treatment are mandatory in sepsis management to reduce the sequelae and mortality. The modified Sequential Organ Function Assessment (mSOFA) score is a severity assessment score used in critically ill patients; especially in resource-constrained or pandemic settings instead of Sequential Organ Function Assessment (SOFA) score (3). Lactate is a typical biomarker in sepsis and it correlates with disease severity as well as mortality (4). The neutrophil-lymphocyte ratio (NLR) also was described as an independent predictor for mortality in sepsis (5,6). This study was aimed to determine the predictive values of initial mSOFA score, point-of-care lactate level, NLR and platelet count in patients with sepsis or septic shock.

METHODOLOGY

A hospital based prospective observational study done in No.(1) Defence Services General Hospital, Yangon from January 2021 to October 2022. All patients above 18 years old admitted with sepsis and qSOFA ≥ 2 were enrolled and sample size was 121 patients. The parameters were assessed within 24 hour of admission and the mortality was observed for 28 days. Septic shock was defined as systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 65 mmHg or who was having vasopressors to maintain MAP ≥ 65 mmHg.

STATISTICAL ANALYSIS

Statistical analysis was done by using IBM® SPSS® Statistic version 26. All the continuous variables for both groups were accessed normality by the histograms as well as by the Shapiro-Wilk test. When a variable in either group was in non-normal distribution, the comparative data were expressed as median (interquartile range, IQR) and tested by Mann-Whitney U test, however, both in normal distribution, expressed as mean ± standard deviation (SD) and tested by independent 't' test. All the categorical data were described as frequency (percentage) and determined by Pearson's Chi-square test or Fisher's Exact test. The multivariable binary logistic regression was done to control the demographic parameters, comorbidities and primary source of infection. The predictors were compared by receiver operating characteristic (ROC) curve analysis. The cut off values were determined by product index for the best sensitivity and specificity value. For all the statistical tests, the significant level, alpha was set as p value < 0.05.

RESULTS

A total of 121 patients were listed in this study and mortality was 33.1%. The mortality in patients with septic shock was 42.9%. The comparison of parameters between the survivors and non survivors were showed in (Table 1). The patients with chronic liver disease had higher mortality 27.5% compared with those without disease 7.4%, ($p = 0.003$). The initial mSOFA score, point-of-care lactate and neutrophil-lymphocyte ratio of non survivors were significantly higher than survivors (mSOFA score 9 vs 4) (Blood lactate 3.3 mmol/L vs 2 mmol/L) (neutrophil-lymphocyte ratio 13.4 vs 8.3). Platelet count was significantly lower in non-survivors than survivors (175 x 10^9/L vs 290 x 10^9/L).

Table 1. Comparison of parameters between survivors and non survivors in sepsis patients

Characteristics	Survivors (n = 81)	Non-survivors (n = 40)	p value
Demographic data			
Age (years)	54.52 ± 18.36	58.65 ± 16.73	0.233
BMI (kg/m^2)	23.91 ± 4.52	22.84 ± 4.98	0.247
Female	47 (58.0)	19 (47.5)	0.274
Comorbidity			
Hypertension	37 (45.7)	18 (45.0)	0.944
Diabetes	24 (29.6)	9 (22.5)	0.407
CVA	11 (13.6)	11 (27.5)	0.062
CAD	20 (24.7)	6 (15.0)	0.222
CLD	6 (7.4)	11 (27.5)	0.003
COAD	6 (7.4)	4 (10.0)	0.728
CKD	6 (7.4)	1 (2.5)	0.423
Malignancy	2 (2.5)	3 (7.5)	0.330
SLE	3 (3.7)	1 (2.5)	1.000
Primary source of infection			
RTI	50 (61.7)	27 (67.5)	0.103

Sepsis and Septic Shock: Are Initial mSOFA Score, Point-of-Care Lactate, Neutrophil-Lymphocyte Ratio and Platelet Count Good Predictors for Mortality?

Abdomen & Pelvic	14 (17.3)	10 (25.0)	
S&S infection	9 (11.1)	3 (7.5)	
UTI	6 (7.4)	0 (0)	
CNS infection	2 (2.5)	0 (0)	
Clinical parameters			
Shock	32 (39.5)	24 (60)	0.033
mSOFA	4 (2 – 7)	9 (4 – 11)	< 0.001
Hematological parameters			
TWBC (x 10^9/L)	15.2 (11.0 – 20.3)	16.5 (12.3 – 22.1)	0.105
ANC (x 10^9/L)	11.8 (8.8 – 17.9)	14.8 (10.9 – 20.1)	0.027
ALC (x 10^9/L)	1.5 (1.1 – 2.3)	1.2 (0.9 – 1.6)	0.017
Platelet (x 10^9/L)	290 (196 – 376)	175 (136 – 302)	< 0.001
Hb (g/dL)	10.44 ± 2.20	10.52 ± 2.53	0.868
NLR	8.3 (4.7 – 13.0)	13.4 (9.1 – 21.4)	< 0.001
Bio-markers			
Creatinine (mg/dL)	1.05 (0.74 – 1.95)	1.24 (0.86 – 2.91)	0.336
Lactate (mmol/L)	2 (1.3 – 2.6)	3.3 (2.3 – 5.2)	< 0.001

Data presented as mean ± SD or median (interquartile range) or n of patients (%).

BMI, body mass index; CVA, cerebrovascular accident; CAD, coronary artery disease; CLD chronic liver disease; COAD, chronic obstructive airway disease; CKD, chronic kidney disease; SLE, systemic lupus erythematosus; RTI, respiratory tract infection; S&S, skin and soft tissue; UTI, urinary tract infection; CNS, central nervous system; GCS, Glasgow Coma Scale; SpO$_2$, saturation of oxygen; FiO$_2$,fraction of inspired oxygen; RR, respiratory rate; HR, heart rate; AKI, acute kidney injury; Hb, hemoglobin; TWBC, total white cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; mSOFA, modified sequential organ function assessment; NLR, neutrophil-lymphocyte ratio.

Collinearities between the predictor variables were checked by Spearman's correlation method for multivariable binary logistic regression. The mSOFA score was strongly correlated with the lactate level, (*rho* = 0.650, *p* < 0.001), however, other predictors were not strongly correlated (Figure 1). Therefore, mSOFA score couldn't be included in regression analysis of lactate, NLR and platelets, and it was done separately (Table 2).
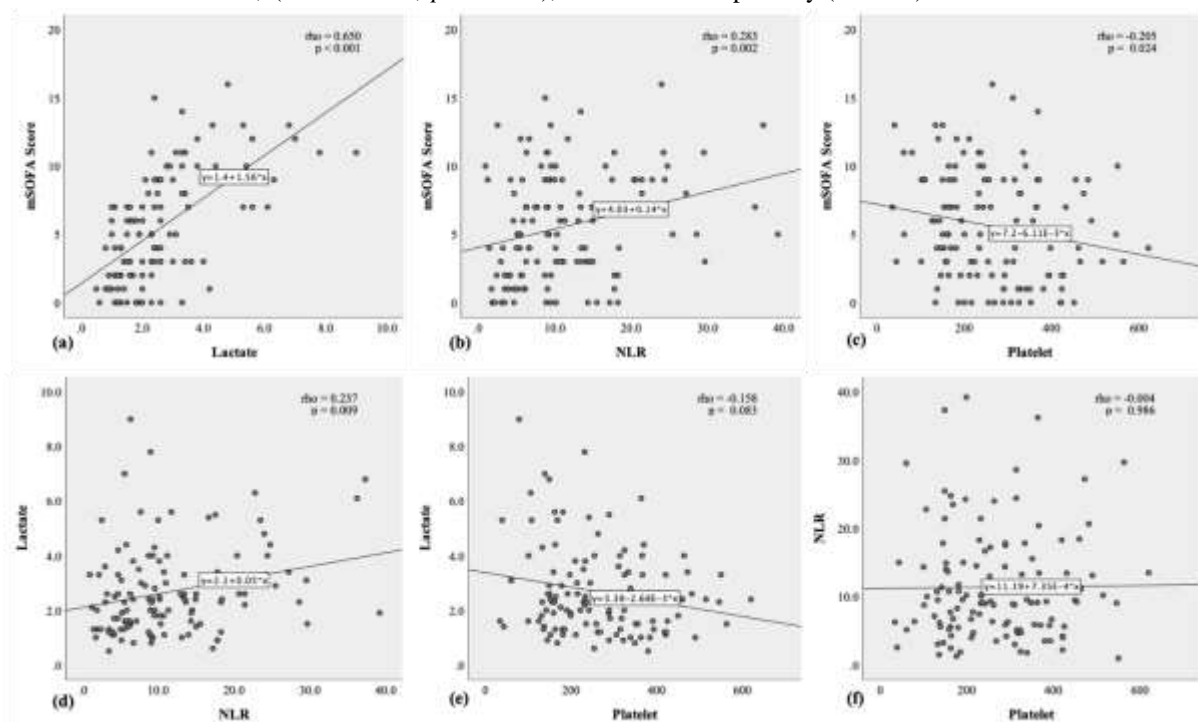

Figure 1. Correlation analysis between predictor variables: (a) mSOFA score and lactate, (b) mSOFA score and NLR, (c) mSOFA score and platelet count, (d) lactate and NLR, (e) lactate and platelet count, and (f) NLR and platelet counts

Sepsis and Septic Shock: Are Initial mSOFA Score, Point-of-Care Lactate, Neutrophil-Lymphocyte Ratio and Platelet Count Good Predictors for Mortality?

The prediction of mortality on initial mSOFA score was statistically significant ($X^2(17) = 48.843$, $p < 0.001$), explained 47.8% variation and correctly predicted 80.2% of deaths. The odds of death increased by 35% (95% CI, 13.5% – 60.6%) for each mSOFA score increased, ($p = 0.001$), after adjusting demographic parameters, comorbidities and primary source of infection. The prediction on lactate, NLR and platelet count was also statistically significant ($X^2(19) = 70.792$, $p < 0.001$), explained 61.6% variation and correctly predicted 86.8% of deaths. The odds of death increased by 81.9% (95% CI, 16.8% – 183.4%) for each mmol/L of lactate increased, 10.8% (95% CI, 2.3% – 20.0%) for 1 unit of NLR increased; and 0.8% (95% CI, 0.2% – 1.3%) for each platelet count decreased, after adjusting the other parameters.

Table 2. Multivariable binary logistic regression analysis on MSOFA score, lactate, NLR and platelet count for prediction of mortality in patients with sepsis and septic shock after adjusting the demographic parameters, underlying comorbidities and primary source of infection

Predictors	Adjusted R^2	Adjusted OR (95% CI)	p value
mSOFA	0.478	1.350 (1.135 – 1.606)	0.001
Lactate	0.616	1.819 (1.168 – 2.834)	0.008
NLR		1.108 (1.023 – 1.200)	0.012
Platelet		0.992 (0.987 – 0.998)	0.008

mSOFA, modified sequential organ function assessment; NLR, neutrophil-lymphocyte ratio; OR, odds ratio; CI, confident interval. The results are adjusted for age, sex, BMI, comorbidities and primary source of infection. The odds ratio is the change in odds of mortality within 28 days for each increasing unit of the predictor.

Receiver operating characteristic curves were used to evaluate the prognostic value of the predictors and their combinations (Figure 2). Each predictor was found to be having moderate prognostic value (AUC > 0.7) and the combinations of mSOFA score and/or lactate with the two hematological parameters (NLR and platelet count), good prognostic value (AUC > 0.8). The cut off values were determined by product index and their sensitivity, specificity, likelihood ratios, post-test odds ratios and post-test probability were calculated (Table 3).
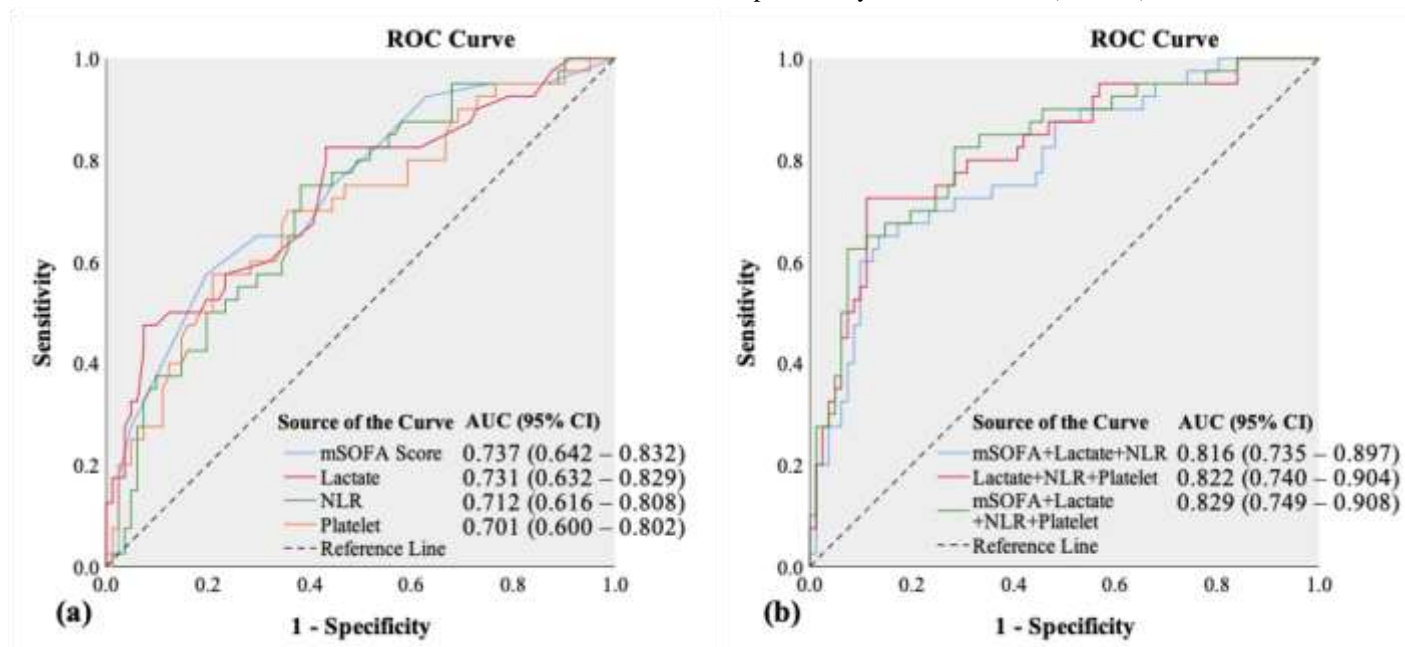
Figure 2. Receiver operating characteristic (ROC) curve analysis of prognostic value of predictors for 28-day mortality in patients with sepsis and septic shock; (a) mSOFA score, lactate and NLR and platelet count and, (b) the best combinations of the predictors.

Sepsis and Septic Shock: Are Initial mSOFA Score, Point-of-Care Lactate, Neutrophil-Lymphocyte Ratio and Platelet Count Good Predictors for Mortality?

AUC, area under curve; CI, confident interval

Table 3. The predictors and cut-off values with sensitivity, specificity and accuracy according to the receiver operating characteristic (ROC) curve analysis

Predictors	Cut off	Sensitivity	Specificity	LR+	LR-	Post-test OR	Post-test Probability
mSOFA	8	0.575	0.802	2.904	0.530	5.480	0.490
Lactate	2.15	0.825	0.566	1.901	0.309	6.198	0.387
NLR	9.24	0.750	0.617	1.958	0.405	4.833	0.393
Platelet	184	0.575	0.790	2.728	0.538	5.090	0.475

mSOFA, modified sequential organ function assessment; NLR, neutrophil lymphocyte ratio; LR, likelihood ratio; OR, odds ratio

DISCUSSION

It was a prospective observational study done on 121 patients with sepsis or septic shock. The overall mortality was 33.1% and 42.9% in patients presenting with septic shock. Age, body mass index (BMI) and sex distribution were not significantly different between survivors and non survivors, however, mean age was increased among non survivors compared with survivors, [(58.65 ± 16.73 vs 54.52 ± 18.36 years), respectively, ($p = 0.233$)]. The patients with chronic liver disease had higher mortality 27.5% compared with those without chronic liver disease 7.4%, ($p = 0.003$). Among them, majority of patients were cirrhosis of liver with alcohol used disorder. The pre-existing chronic liver disease was an independent risk factor for sepsis associated mortality (7). Cirrhosis patients had increased risk of respiratory failure and death during sepsis (8). Patients with alcohol used disorder were prone to get sepsis (9).

In this study, the prediction of mortality on mSOFA score showed that each mSOFA score increase resulted in 1.35 times higher odds of death; [adjusted OR, 1.350 (95% CI, 1.135 – 1.606), $p = 0.001$]. This finding was consistent with a study done by Fuchs et al. (10), in which each SOFA score increasement resulted in 1.35 times higher risk of death ($p = 0.001$), and Li et al. (11), in which odds ratio was 1.434 (95% CI, 1.293– 1.591). According to Sipahioglu & Bahcebası (12), the odds ratio of death in sepsis by SOFA score increase was 1.886 (1.410-2.510), ($p < 0.001$) in geriatric population.

This study showed that the odds of death increased by 81.9% (1.8 times) for each mmol/L of lactate increased and it was consistent with Villar et al. (13), there, the odds ratio of lactate was 1.5 (95% CI: 1.1-2.1), however the odds ratio of lactate level was contradict to Charoentanyarak et al. (14), in which the odds ratio of lactate was 1.025 (1.002 – 1.048), ($p = 0.029$), although the lactate was a significant predictor.

The NLR was also found to be a significant predictor and the odds ratio was 1.108 (1.023 – 1.200), ($p = 0.012$), and it was a discrepancy with the previous studies; 1.043 (1.012– 1.083), (p = 0.016) in Liu et al. (15); 1.01 (1.00–1.02), (p =

0.015) in Gameiro et al. (16); 1.054 (95% CI, 1.032– 1.076) in Li et al. (11).

The platelet counts also had predictive value and odds ratio 0.992 (0.987 – 0.998), ($p = 0.008$) and it was comparable with a recent study done by Schupp et al. (17), in which the mortality risk was higher in patients with low platelet counts. However, there was a contradict that the initial platelet count was not significant in study done by Al Saleh & AlQahtani (18), [adjusted OR, 1.000 (95% CI, 0.997 – 1.002), p = 0.837] and only the percent reduction of platelet was significant, [adjusted OR, 1.028 (95% CI, 1.012 – 1.045), p = 0.001].

The prognostic values of mSOFA score, lactate, NLR and platelet count were compared by using the receiver operating characteristic curves. Each predictor was found to be having moderate prognostic value (AUC > 0.7) and the combinations of mSOFA score and/or lactate with the two hematological parameters (NLR and platelet count), good prognostic value (AUC > 0.8). The cut off values were determined by choosing the highest value of multiplication of sensitivity and specificity (product index). According to the calculation, the mSOFA score, lactate, NLR and platelet at their respective cut off values had 5 to 6 times higher odds of death compared with their respective counterparts, independently.

LIMITATION OF STUDY

This study has some limitations. The first limitation was that although the demographic data, comorbidities and the primary source of infection were controlled in multivariable logistic regression, the causal organisms with their virulency and the treatment factors couldn't be controlled. The second limitation was that this study was carried out during the era of COVID-19 pandemic and variation in limitation of resources could be a confounding factor that we couldn't control. The third limitation was that we were able to use the modified SOFA score instead of SOFA score and there would be some discrepancies between the use of these two scoring systems.

Sepsis and Septic Shock: Are Initial mSOFA Score, Point-of-Care Lactate, Neutrophil-Lymphocyte Ratio and Platelet Count Good Predictors for Mortality?

CONCLUSIONS
The mSOFA score, lactate, NLR and platelet count had predictive value for mortality assessment in patients with sepsis or septic shock. Lactate level was strongly correlated with disease severity of the sepsis, mSOFA score. The combination of mSOFA score and/or lactate with NLR and platelet count had better predictive value.

RECOMMENDATION
Point-of-care lactate can be used interchangeably with mSOFA score for severity assessment in emergency setting. The initial mSOFA score, lactate, NLR and platelet count are good independent predictors for mortality in patients with sepsis or sepsis shock. Further prospective studies are recommended to validate these results.

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