

# Prediction of Preterm Mortality with Late Onset Sepsis using the Neonatal Sequential Organ Failure Assessment Score in Suez Canal University Hospitals

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## ABSTRACT

**Background:** The fatal condition known as neonatal sepsis is characterized by life-threatening organ dysfunction brought on by a dysregulated immune response to infection, but there is no operational definition of organ dysfunction that is relevant to newborns and may foretell infection-related death.

**Objective:** The aim of the current study was the prediction of mortality risk factors in low birth weight (LBW) preterm infants with Late Onset Sepsis (LOS) in Neonatal Intensive Care Unit (NICU).

**Patients and methods:** A cross sectional analytical study conducted on LBW preterm newborns admitted at Neonatal Intensive Care Unit in Suez Canal University Hospitals, between June 2020 to May 2021 and diagnosed to have LOS; nSOFA scores were derived for those patients at multiple time points first at the time of sepsis evaluation then at 48 hours interval till death or discharge then comparing the peak score with the outcome. The score assesses respiratory, cardiovascular and hematological systems, with scores ranging from (0-8) (0-4) and (0-3) respectively.

**Results:** The study included 102 neonates; 30 (29%) non-survivors and 72 (71%) survivors. Males were affected more than females (58.82% vs 41.18%). At a cut-off point of more than 7, which was selected as the optimum criterion; the sensitivity obtained was 86.67%, the specificity was 98.61% and accuracy 94%. The area-under-ROC-curve was equal to 0.981 (95% CI: 0.933 - 0.998) with positive statistical significance ( $P < 0.001$ ).

**Conclusion:** NSOFA score can be used to predict death in LBW babies who have LOS. One of the most important steps towards better newborn sepsis outcomes is the prediction of LOS mortality.

**Keywords:** SOFA score, LOS, Sepsis, LBW, Cross sectional study, Suez Canal University.

## INTRODUCTION

Even in high-income nations, neonatal sepsis is a serious issue that has an influence on morbidity and death. Prematurely born babies are those in whom neonatal sepsis occurs and has the highest effects <sup>(1)</sup>.

Infectious illness frequency was high in low- and middle-income nations, which may be a result of limited access to well stocked and staffed medical facilities <sup>(2)</sup>. An estimated 5.3-8.7 million neonates died in sub-Saharan Africa alone in 2014 as a result of neonatal sepsis and subsequent long-term morbidity <sup>(3)</sup>. In Egypt, neonatal sepsis affected 33% of neonates admitted to Neonatal Intensive Care Unit (NICU) <sup>(4,5)</sup>.

Neonatal sepsis is characterized by neurological, cardiovascular, pulmonary, and hematological symptoms as a result of dysregulated host response to infection <sup>(6)</sup>.

Neonatal sepsis can manifest as either an early (EOS) or a late LOS start of symptoms. EOS appears within the first three days of life (about 72 hours), whereas LOS appears between days four and thirty, or after the first seven days <sup>(7)</sup>.

The incidence of EOS ranges from 1 to 5 per 1000 births while the incidence of LOS varies between 0.61% and 14.2%. There is inverse relation between LOS and birth weight; 51.2% in infants between 501-750 grams, newborns under 1500 grammes, 15–25%, and infants above 2500 grammes, 1.6% <sup>(8)</sup>.

Clinically diagnosing LOS can be difficult due to the nonspecific signs and symptoms and negative blood cultures, the diagnostic gold standard, which can be

caused by a small sample size, the mother's use of antibiotics, the dose of antibiotics taken prior to sampling, low blood bacterial counts, or short-term bacteremia <sup>(9)</sup>.

Difficulties in early diagnosis and the unexpected course of LOS that can lead to septic shock and death need assessment of LOS depending on presence and progression of organ dysfunction and this can be done using the nSOFA which also can predict mortality in these patients <sup>(10)</sup>.

During the progression to death with LOS, there was a considerable rise in the demand for mechanical breathing, oxygen use, cardiovascular support (in the form of vasoactive medications), and the incidence of thrombocytopenia. These data served as the basis for the development of the nSOFA score system, which was created to forecast death from LOS in preterm, very low birth weight (VLBW) children <sup>(11,12)</sup>.

The current study was aiming at using the nSOFA score as a predictor of mortality in premature LBW neonates with clinical or proven LOS to define mortality risk factors; for early detection of high risk neonates and trial of modifying management plan for better outcome.

## PATIENTS AND METHODS

A cross sectional analytical study was conducted at NICU in Suez Canal University Hospitals. The study included 102 preterm infants (less

than 37 weeks) who were admitted at NICU during the period of June 2020 to May 2021.

Preterm infants presumed or proven to have LOS in Suez Canal University Hospital NICU were included in the study, while infant diagnosed to have neonates with birth asphyxia, congenital immunodeficiency syndromes, congenital deformities, serious congenital heart disease, and inborn metabolic abnormalities were excluded from the study.

LOS was defined as an event that met all of the following criteria: (1) the event occurred after the third day of life, (2) A blood culture was performed, empiric antibiotic therapy was started at the time of evaluation, continued for at least 7 days, or until death, depending on the clinician's suspicion for a serious infection caused by the presence of multiorgan dysfunction (MOD), and (3) All C-reactive protein (CRP) measurements taken throughout the episode were gathered to conclusively prove the presence of inflammation.

#### **Data collection tools:**

A case sheet was created using information gathered from the research population, including:

#### **- History taking from the parents and NICU residents:**

♦ Parental history: Maternal history including Name, Age, date of last menstrual period, type of delivery, Risk for neonatal infections e.g. Urinary tract infections, Premature rupture of membranes more than 18 hours and chorioamnionitis and Paternal history including name and age.

♦ Patient history: Name, Birth weight, History of perinatal hypoxia, time and cause of admission, time of LOS suspicion, any invasive procedures before LOS suspicion e.g mechanical ventilation (MV), umbilical catheterization and if they received parenteral nutrition therapy (PNT).

- **Examination:** Assessment of gestational age (GA), Weight, General examination, Vital signs including Temperature, respiratory rate, Blood pressure, Heart rate and oxygen saturation (SpO<sub>2</sub>) for calculation of SpO<sub>2</sub>/FiO<sub>2</sub> ratio which is indicator for respiratory distress syndrome, Chest examination, Cardiac examination, Neurological examination.

#### **- Investigations:**

♦ **Radiological:** Chest X-ray (CXR) where Plain posteroanterior CXR was done to prove or exclude chest infection.

♦ **Laboratory:** For CBC with differential, CRP, ABG and blood culture.

♦ **nSOFA score:** Preterm LBW neonates with clinical (-ve blood culture) or proven (+ve blood culture) LOS

were assessed using nSOFA scoring system at evaluation and at 48 hours interval.

Assessment was done for respiratory, cardiovascular and hematological systems as prognostic factors for LOS. To characterize dynamic changes in the nSOFA uses category scores (total score range: 0–15):

- If the patient requires mechanical ventilation and needs oxygen, the score ranges from (0 to 8):

- Isn't intubated or intubated and SpO<sub>2</sub>/FiO<sub>2</sub> ≥300= 0.
- Is intubated and SpO<sub>2</sub>/FiO<sub>2</sub> <300= 2.
- Is intubated and SpO<sub>2</sub>/FiO<sub>2</sub> <150= 4.
- Is intubated and SpO<sub>2</sub>/FiO<sub>2</sub> <150= 6.
- Is intubated and SpO<sub>2</sub>/FiO<sub>2</sub> <100= 8.

- The requirement for inotropic support, which may involve the administration of corticosteroids (for suspected adrenal insufficiency or catecholamine-resistant shock) (score range 0-4) where:

- No systemic steroids AND no inotropes= 0.
- No inotropes and systemic steroid therapy= 1.
- One inotrope plus no systemic steroids= 2.
- One inotrope AND systemic steroid therapy OR two or more inotropes= 3.
- Systemic steroid therapy AND two or more inotropes= 4.

- Thrombocytopenia's existence and severity (score range: 0-3) where:

- Platelet count ≥150 × 10<sup>3</sup>= 0.
- Platelet count 100–149 × 10<sup>3</sup>= 1.
- Platelet count <100 × 10<sup>3</sup>= 2.
- Platelet count < 50 × 10<sup>3</sup>= 3.

To determine the relationship between the peak nSOFA score and the outcome (survivor/non-survivor), data were put into an Excel sheet and examined. Data were then examined to determine the prediction power of the nSOFA cut-off point.

#### **Ethical consent:**

**This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Suez Canal University [reference number 4082# at 24/2/2020]. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.**

#### **Statistical analysis**

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows.

Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for

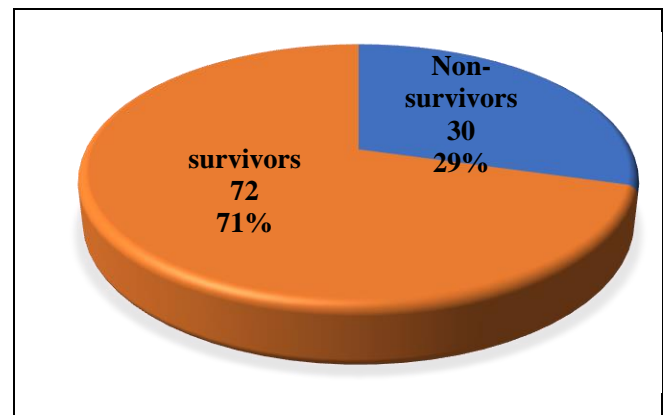
normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD).

T-test was used to compare means of normally distributed variables, and Mann-Whitney test was used to compare means of non-normally distributed data. Correlation and regression tests were done for the relation between variables.

Area under the curve (AUC) analysis was performed on ROC curves. Calculating sensitivity, specificity, positive predictive value, negative predictive value, and accuracy will help establish the utility of the best cut-off value for nSOFA scores associated with greater mortality that was discovered on the curve. P value  $\leq 0.05$  was considered to be statistically significant.

**RESULTS**

A total number of 102 neonates were diagnosed to have LOS and according to their outcomes, they were classified into survivors (72 neonates) and non survivors (30 neonates) (Figure 1).



**Figure (1): The ratio between the number of survivors and non-survivors.**

Males were affected more than females (58.82 % vs. 41.18%). Non survivors had lower Mean gestational age and mean birth weight compared to survivors. At time intervals when the score was analyzed, non-survivors had higher total and individual component nSOFA scores than survivors (2.54±2.1 vs. 9.63±1.97 for survivors and non-survivors, respectively). At a cut-off point >7, which was selected as the optimum criterion; the sensitivity obtained was 86.67%, the specificity was 98.61% and accuracy 94%. The area-under-ROC-curve was equal to 0.981 (95% CI: 0.933 – 0.998) with positive statistical significance (P $\leq 0.001$ ).

**Table (1): Baseline characteristics of the study population.**

Variable	Non-survivors (n=30)	Survivors (n=72)	P-value	Sig. test
<b>Male (n=60)</b>	20 (66.67%)	40 (55.56%)	0.298	Chi-square test
<b>Female (n=42)</b>	10 (33.33%)	32 (44.44%)		
<b>Gestational age (weeks)</b> Mean $\pm$ SD	32.2 $\pm$ 2.02	32.86 $\pm$ 2.02	0.142	Mann-Whitney test
<b>Birth weight (kg)</b> Mean $\pm$ SD	1.57 $\pm$ 0.39	1.68 $\pm$ 0.42	0.253	
<b>Time of LOS onset (days)</b> Mean $\pm$ SD	6.33 $\pm$ 3.76	8.65 $\pm$ 5.34	<b>0.008*</b>	

\*Highly Significant at P<0.01. Non-significant at P>0.05

Table 2 shows that there were no statistically significant differences between study groups regarding the culture results whether positive or negative. Sputum culture wasn't done in 48 cases due to its contamination with the patients' saliva and fear of false positive results. It can be deduced from the table that, between research groups, there were no statistically significant changes in the blood C-reactive protein values, whether they were positive or negative.

**Table (2): Culture results of the study groups.**

Group		Non-survivors (n=30)	Survivors (n=72)	P-value	Sig. test
<b>CRP</b>	<b>Negative (n=12)</b>	5 (16.67%)	7 (9.72%)	0.321	Chi-square test
	<b>Positive (n=90)</b>	25 (83.33%)	65 (90.28%)		
<b>Blood culture</b>	Negative (n=15)	4 (13.3%)	11 (15.5%)	0.138	Fisher's exact test
	Positive (n=87)	26 (86.7%)	61 (85.9%)		
<b>Sputum culture</b>	Not valid	12 (40%)	36 (50.7%)	0.540	
	Negative	9 (30%)	20 (28.2%)		
	Positive	9 (30%)	16 (22.5%)		

Non-significant at P>0.05.

**Figure 2** shows the more prevalence of gram negative organisms mainly klebsiella pneumoniae in both groups, also klebsiella was responsible for death of 25 (83.3%) cases in non-survivors group (P-value <0.001).

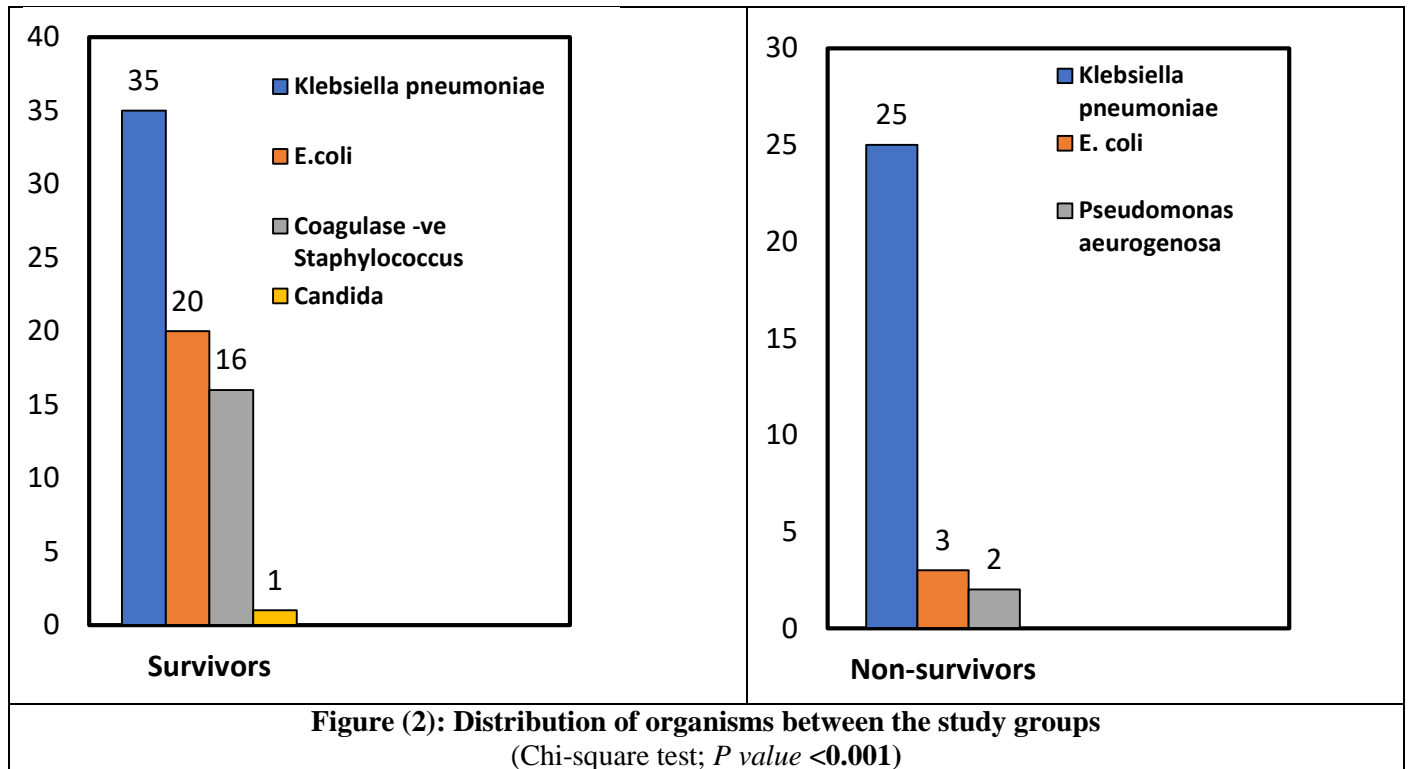


Table 3 showed that the peak nSOFA score had statistically significant difference between study groups with a higher value for the non-survivors.

**Table (3): Peak nSOFA score for study population**

Group	Non-survivors	Survivors	P-value	Sig. test
Variable	Mean ± SD	Mean ± SD		
<b>Total nSOFA score</b>	9.63 ± 1.97	2.54 ± 2.1	<b>&lt;0.001***</b>	Mann-Whitney U test.

Highly significant at P<0.01.

Regarding the diagnostic accuracy of the peak nSOFA score of the study were calculated as follows; the dependent variable was the occurrence of a death event. At a cut-off point >7, which was selected as the optimum criterion; sensitivity obtained was 86.67%, specificity was 98.61% and accuracy 95.03%. The area-under-ROC-curve was equal to 0.981 with positive statistical significance (Table 4 and Figure 3).

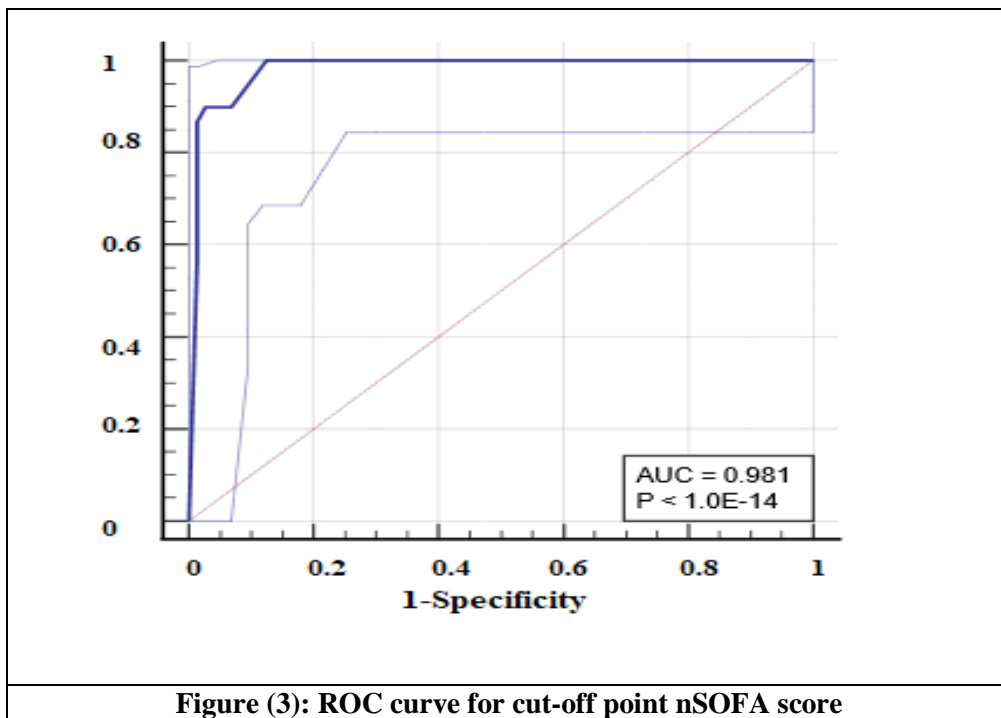


Figure (3): ROC curve for cut-off point nSOFA score

Table (4): Diagnostic accuracy parameters for cut-off point of nSOFA score

Variable	Cut-off point of nSOFA score
Area under curve	0.981
P-value	<b>&lt;0.001</b>
95% CI	0.933 - 0.998
Optimal criterion	>7
Sensitivity	86.67
95% CI	69.3 - 96.2
Specificity	98.61
95% CI	92.5 - 100.0
+Likelihood Ratio	62.4
95% CI	8.9 - 439.2
-Likelihood Ratio	0.14
95% CI	0.05 - 0.3
+Predictive Value	96.3
95% CI	78.7 - 99.5
-Predictive Value	94.7
95% CI	87.7 - 97.8
Accuracy	95.03%

Highly significant at P<0.01.

Figure 4 and table 5 show the relations between peak nSOFA score and its components. The peak score showed the highest R and R-squared values and the highest change per unit value of the respiratory nSOFA score.

Table (5): Prediction of components of nSOFA score.

Component	Equation	R	R-squared
<b>Respiratory score</b>	0.6041x - 1.1094	0.9236	0.8524
<b>cardiovascular score</b>	0.1947x + 0.2068	0.7522	0.5659
<b>Hematologic score</b>	0.1995x + 0.9496	0.6386	0.4078

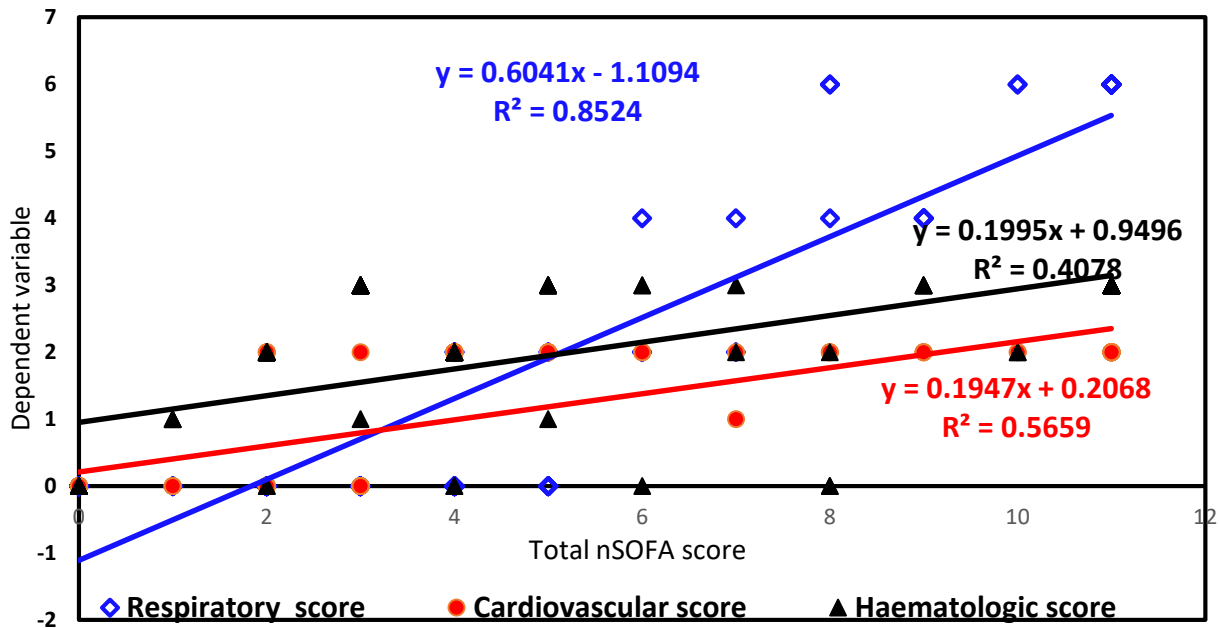


Figure (4): Relations between total nSOFA score and its components

Table 6 shows the significant best-fit multiple logistic regression model for the prediction of fatal outcome. The odds of occurrence of a death event changes by changes in the odds of the dependent variables. Significant Chi-squared test of the model indicates a good goodness of fit.

Table (6): Best-fit logistic regression model for nSOFA score prediction

Variable	Beta	P-value	OR	95% CI OR
Lowest SpO2/FiO2 ratio	-0.016	0.018*	0.984	0.971 - 0.997
Total nSOFA score	-1.687	<0.001***	0.185	0.078 - 0.437
Constant	15.251	<0.001***	4202791.817	

Multiple logistic regression. Best-fit model. \*Highly Significant at P<0.01. Non-significant at P>0.05.

Figure 5 shows the ROC curves constructed for variables that showed statistically significant difference when all of the study variables had their ROC curves constructed. The dependent variable was the occurrence of a death event. Optimum criteria are the cut-off points or values at which the best combination of sensitivity and specificity occurs. The sensitivity of an age of less than or equal 5 days of life to the occurrence of death in the study population was 70% and the specificity was 60%. Regarding the components of the nSOFA score, the components to be mentioned later; proved significance. The first significant component was "Cardiovascular score" which showed sensitivity and specificity of 100% and 62.5%, respectively, at an optimum value of more than zero. Lowest SpO2/FiO2 ratio at a value of less than or equal 175, as an optimum criterion, showed a sensitivity of 83.33%, specificity of 98.61% and accuracy of 93.5%. Respiratory score showed a sensitivity of 90.00%, specificity of 97.22% and accuracy of 94.84% at an optimum criterion of a value of more than 2. Hematologic score at a cut-off value of more than 2 showed a sensitivity of 80.00% and a sensitivity of 75.00%.

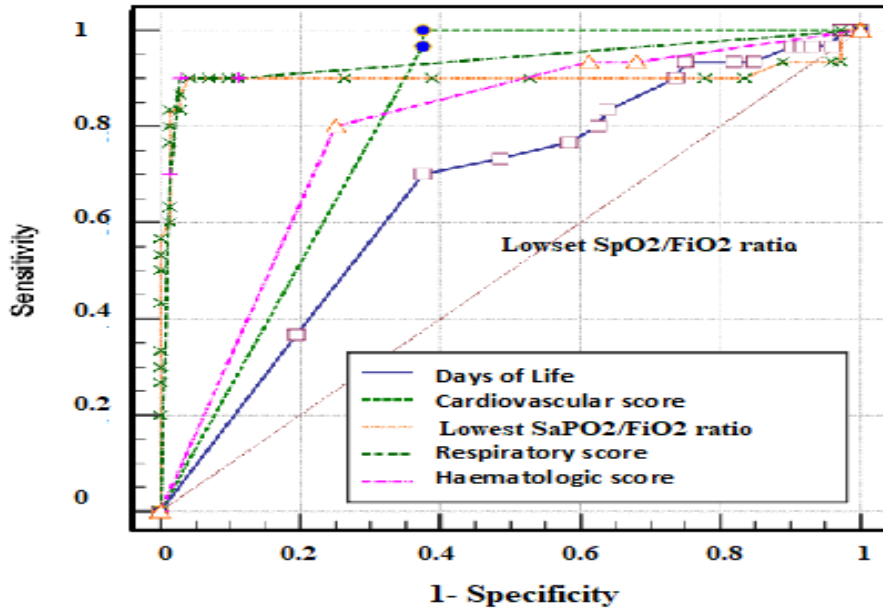


Figure (5): ROC curves for ROC-analysis of significant variables other than the peak nSOFA score

Table 7 and figure 6 show Kaplan-Meier curve for study population for the survival of the population. Mean and median values of survival time were slightly more than 19 days and 21 days respectively. It is worth mention that the survival probability at 0 days is 100% and at 30 days was 41.67%; which is the maximum value reached on the Kaplan-Meier curve.

Table (7): Means and Medians for Survival Time

Mean			Median		
Estimate	Standard error	95% Confidence Interval	Estimate	Standard error	95% Confidence Interval
19.110	1.780	15.620 - 22.599	21.000	6.634	7.997 - 34.003

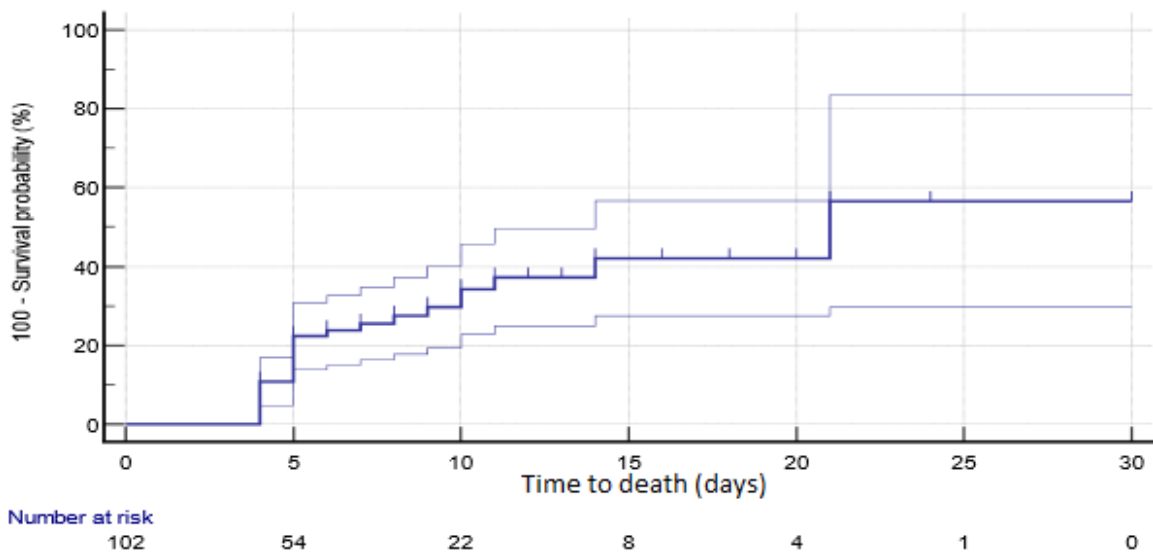


Figure (6): Kaplan-Meier curve for the studied population.

## DISCUSSION

The nSOFA was created to address the lack of a neonatal-specific consensus definition for sepsis. The nSOFA functions as an operational definition of organ failure that can identify those with a high risk of death among preterm babies with infection, much as the adult SOFA and pediatric SOFA <sup>(10)</sup>.

The current study was aiming at using the nSOFA score as a predictor of mortality in premature LBW neonates with clinical or proven LOS to define mortality risk factors; for early detection of high risk neonates and trial of modifying management plan for better outcome.

In the study, 30 (29%) neonates didn't survive while 72 (71%) survived LOS episode showing that LOS is associated with low mortality rate. This is in agreement with a study conducted in Egypt where Compared to EOS, LOS was associated with less mortality <sup>(13)</sup>. Another Egyptian research done at Mansoura University found that EOS mortality was 51 percent and LOS mortality was 42.9% <sup>(4)</sup>.

Males were affected more than females (58.82% vs. 41.18%), but there was no discernible gender difference between survivors and non-survivors.

This is in agreement with a study conducted by Fleiss *et al.*, <sup>(12)</sup> where (56%) of LOS cases were males and (44%) were females and also found no significant difference between LOS survivors and non-survivors regarding gender, also a study conducted in Rotterdam where 51.9% of men had LOS, showing that host susceptibility may be influenced by variables related to sex <sup>(14)</sup>. The statically significant difference was in the days of life when the infection manifested which was earlier in non-survivors than survivors (P-value 0.008).

This is similar to that was found by Fleiss *et al.*, <sup>(12)</sup> where infection occurred at (median, 13 days) in non survivors and (median, 16 days) in survivors and also to that found by a study conducted by **Wynn and Polin**, <sup>(10)</sup> who discovered that non-survivors developed sepsis more quickly than survivors (median day of life, 11 vs. 19), Additionally, a Singaporean research indicated that, in comparison to LOS survivors, those who died experienced LOS sooner (median age, 17 vs. 10 days, respectively) <sup>(15)</sup>.

Our study showed significant difference in mean CRP which was higher in non-survivors than survivors (63.39±58.88 and 32.33±28.13, respectively).

The Iraq study found that the mean platelets, WBC, and ANC levels were significantly lower in neonates with sepsis who died compared to those who survived, which wasn't in agreement with us. However, they also found that a significantly higher percentage of neonates with sepsis who died had a CRP level  $\geq 10\text{mg/dl}$  (77.5%) than neonates who survived <sup>(17)</sup>.

Unlike our study, a study conducted by **Wynn et al.** <sup>(18)</sup> showed that sepsis survivors had a higher CRP peak than non-survivors (152 mg/L vs 91 mg/L, P=0.003). This finding was probably influenced by the fact that non-survivors had a longer median time from

evaluation to death (54 hours), or by the fact that providers may not have repeated CRP in non-survivors because they felt there was no clinical reason to do so.

In our study, culture positive cases were 85.2% while culture negative ones were 14.9%. Additionally, the media employed in our investigation, which included pathogens from viruses (such as rubella and CMV), protozoa (such as *Toxoplasma gondii*), and treponemes (such as *Treponema pallidum*), may not have been able to extract the etiological agent. Gram-negative bacteria made up to 97.7% and Gram-positive bacteria made up to 18% of the positive blood cultures, we discovered. *Klebsiella pneumoniae* was the most often isolated strain and caused 83.3% of non-survivor deaths (P-value <0.001).

Early exposure to antibiotics may modify the newborn mucosal colonization and result in a majority of Gram-negative bacteria, increasing the risk of Gram-negative infections <sup>(19)</sup>.

In our study, at all time periods analyzed, the non-survivors exhibited higher peak and individual component nSOFA scores than the survivors did, with mean and standard deviations of the scores being 2.54 (SD 2.1) vs. 9.63 (SD 1.97) for non-survivors and survivors, respectively.

This is agreement with a research by **Srikanth and Kumar** <sup>(20)</sup>, the mean nSOFA score of LOS patients among survivors at admission was 1.96 (SD 1.69), and at 24 hours it was 1.16 (SD 1.48). Among contrast, the nSOFA score among non survivors was 7.6 (SD 2) at admission and 10 (SD 2) at 24 hours, with a statistically significant (P value <0.001).

At a cut-off point of more than 7, which was selected as the optimum criterion; sensitivity obtained was 86.67% and specificity was 98.61% with accuracy of 95%. The area-under-ROC-curve (AUROC) was equal to 0.981 (95% CI: 0.933 - 0.998) with positive statistical significance (P<0.001).

This is close to what was found by **Srikanth and Kumar** <sup>(20)</sup> where the outcome (survivor/non-survivor) was substantially correlated with mortality of 90% when compared to the nSOFA cut-off score of  $\geq 6$ .

In our study, we found statistically significant differences between study groups regarding all of the components of the nSOFA score. The following components' means and standard deviations were higher for the non survivors: "Respiratory, CVS and Hematologic score" vice versa was seen for "Lowest SpO<sub>2</sub>/FiO<sub>2</sub> ratio", and "Lowest Platelet Count" whose means and standard deviations were lower in non-survivors.

CVS score" showed sensitivity and specificity of 100% and 62.5%, respectively, at an optimum value of more than zero. Respiratory score showed sensitivity of 90.00% and specificity of 97.22% at an optimum criterion of a value of more than 2 and Lowest SpO<sub>2</sub>/FiO<sub>2</sub> at a value of less than or equal 175, as an optimum criterion, showed sensitivity of 83.33% and specificity of 98.61%.



It makes sense that low values were related with increased mortality since SpO<sub>2</sub>/FiO<sub>2</sub> is a solid non-invasive indication of acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure that can aggravate LOS <sup>(21)</sup>.

Hematologic score at a cut-off value of more than 2 showed a sensitivity of 80.00% and a sensitivity of 75.00%. In our study, we found that lowest SpO<sub>2</sub>/FiO<sub>2</sub> ratio and peak nSOFA score were the significant best-fit multiple logistic regression model for the prediction of death outcome (P<0.001).

In both pediatric and adult ICU populations, organ dysfunction ratings are often employed as metrics for predicting clinical outcome as well as death, and they have been validated across a variety of illness conditions <sup>(22,23)</sup>.

Our work has shown that the nSOFA might predict mortality in a manner comparable to that of the pediatric and adult SOFAs, but it still requires confirmation in multicenter studies with significant sample sizes. Future studies must validate the nSOFA cut-off score used in our study to predict death.

## LIMITATIONS

The small sample size of our study precluded us from classifying the patients according to the infection location, such as pneumonia, NEC, and so forth, which may have had an impact on prognosis. It was challenging to compare the score before and after the diagnosis of sepsis for greater accuracy due to the absence of an automated electronic health form for data collection and assessment.

## CONCLUSION

The nSOFA would, if validated in further studies, address a critical unmet need for a useful, objective operational definition of organ dysfunction that is applicable to this particular population and predicts their outcome while alerting healthcare professionals to revise and modify their treatment plans in the hopes of improving outcomes. Future studies for assessing changes in the NSOFA score after modifying the management plan depending on score more than or equal to 7.

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**Competing interests:** Nil.

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