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Severity Index of Neonatal Septicemia in Neonatal Intensive Care units Using Score for Neonatal Acute Physiology-II

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ABSTRACT

Background: This study aimed to evaluate the competence of the score for neonatal acute physiology (SNAP-II) as a tool to anticipate morbidity and mortality of neonates with early or late sepsis in neonatal intensive care units (NICUs).
Methods: This prospective cohort study was conducted on all neonates of > 32 weeks with sepsis in tertiary NICUs at Cairo University Children Hospital and El Galaa Hospital For Armed Forces Officers Families, Cairo, Egypt, within May-October 2019. The eligible samples consisted of 100 neonates with septicemia who met inclusion and exclusion criteria and were enrolled. the score for neonatal acute physiology-II was calculated within 24 h of sepsis onset and followed up for 2 weeks for mortality and organ dysfunction (OD). The collected data were analyzed in SPSS software (version 25).
Results: It was revealed that SNAP-II was significantly higher in neonates who passed away, compared to the survived neonates (46±17 vs. 12±10, respectively; P<0.001). Moreover, SNAP-II was significantly higher in neonates who developed OD within 14 days of sepsis onset, compared to those without OD (37±17 vs. 9±7, respectively; P<0.001). The score for neonatal acute physiology-II at 14.5 was considered the best cut-off point in predicting OD with a sensitivity of 100%, positive predictive value of 70.4%, specificity of 81.2%, and negative predictive value of 100%. In addition, SNAP-II at 23.5 was considered the best cut-off point in predicting overall mortality with 100% sensitivity, 58.6% PPV, 85.5% specificity, and 100% NPV.
Conclusion: Higher SNAP-II within 24 h of the early- or late-onset neonatal sepsis was a reliable predictor of OD and death.

Keywords: Mortality, Neonates, Organ dysfunction, Sepsis, SNAP-II

Introduction

Neonatal sepsis is highly prevalent in developing countries. The overall incidence of sepsis was estimated at 32.9% in neonatal intensive care units (NICUs) of Cairo University, Egypt, with a higher incidence of late-onset, compared to early-onset sepsis (1). Considering neonatal sepsis-related mortality rate, which was at the range of 33%-51% in several studies performed by Shehab El-Din et al. (2), Helal et al. (3), and Awad et al. (4), and due to the insufficient amount of resources and lack of reliable investigations to validate sepsis, it is required to have a tool for early anticipation and treatment of sepsis to avoid its long-term burden on neonates and pediatric health.

Prediction scores with clinical frameworks have been developed to facilitate the diagnosis of preliminary sepsis and commencement of antimicrobial treatment (5). The score of neonatal acute physiology (SNAP) and its second-generation (i.e., SNAP-II) have been firstly used in NICUs, where neonates are admitted shortly after birth. The SNAP-II is a validated illness severity

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and mortality risk score, which is accurate and simple (6). Based on what is discussed earlier, the current study aimed to use the SNAP-II as a predictor tool for morbidity and mortality of neonates with proved early or late sepsis in NICUs at El Galaa Hospital For Armed Forces Officers Families and Cairo University Children Hospital, Cairo, Egypt.

Methods

Design and patients

This prospective cohort study was conducted on all newborns with sepsis admitted to NICUs at El Galaa Hospital For Armed Forces Officers Families and Cairo University Children Hospital, within 6 months. The study aimed to follow up all septic neonates in NICUs for 14 days to predict morbidity/mortality or improvement. Both NICUs are referral tertiary units located in Cairo, serving people from all over Egypt and use the same protocol in sepsis diagnosis, management, and follow-up. This study was approved by the Ethics Committee of the Faculty of Medicine, Cairo University.

This study was conducted over 6 months from May-October 2019 and enrolled all cases with neonatal sepsis. The average rate of admission to both units was about 45-55 babies monthly (about 15-20 and 30-35 at NICUs of El Galaa Hospital For Armed Forces Officers Families and Cairo University Children Hospital, respectively). The incidence of sepsis in admitted cases was 40%-50%. Only 100 neonates fulfilled the inclusion and exclusion criteria and completed the study.

Finally, 100 neonates were enrolled in the study with proven sepsis and were categorized into two groups (n=50 each) of full-term neonates (37-41 weeks) and preterm neonates (32-36 weeks). In the current study, eligible neonates (0-28 days old) were born at a gestational age of 32-41 weeks of both genders with proved septicemia according to laboratory and clinical signs. On the other hand, the cases presenting with sepsis-like manifestations were excluded, including preterm neonates with a gestational age of < 32 weeks, neonates with a proven inborn error of metabolism, neonates with severe perinatal hypoxia (5-minute Apgar score of < 4), and neonates with complex congenital anomalies.

All included patients were subjected to a record of careful history, complete clinical examination of all systems, including complete blood count with differential white cell count (using Siemens Sysmex XS-500 Hematology Analyzer), C-reactive protein (CRP) (using latex agglutination assay of CRP Flex reagent cartridge), arterial blood gases, blood culture, sensitivity (using BACT/ALERT 3D system by bioMerieux), and chest X-ray. Moreover, SNAP-II was conducted within 24 h of sepsis onset according to Richardson et al. parameters (Table 1) (6). In addition, follow-up was carried out for 14 days from sepsis onset for organ dysfunction (OD) (by clinical and/or investigations follow-up) and mortality.

Sepsis was diagnosed when the baby had the

Table 1. Score for neonatal acute physiology-II for individual parameters

Variable	Value	Score
Lowest mean blood pressure	≥30	0
	20-29	9
	<20	19
Lowest temperature (°F)	>96	0
	95-96	8
	<95	15
PaO_2/FiO_2 Ratio	≥2.5	0
	1.0-2.49	5
	0.3-0.99	16
	<0.3	28
Lowest serum pH	≥7.20	0
	7.10-7.19	7
	<7.1	16
Multiple seizures	None	0
	Yes	19
Urine output (cc/kg/h)	>0.9	0
	0.1-0.9	5
	<0.1	18

Mild illness (0-20), Moderate illness (21-40), Severe illness (≥40) (Richardson et al., 2001)

following criteria: clinical signs, investigations, evidence of systemic inflammatory response syndrome, or OD (7).

Sepsis was suspected clinically by at least having one of the following criteria: 1) General condition: temperature instability, poor feeding, not doing well; 2) Central nervous system: irritability, lethargy, hyporeflexia, hypotonia, and seizures; 3) Cardiovascular system (CVS): pallor, mottling, delayed capillary refill time, tachycardia, bradycardia, and hypotension; 4) Respiratory system: apnea, tachypnea, retraction, grunting, cyanosis; 5) Gastrointestinal tract: abdominal distension, feeding intolerance, and hepatomegaly; 6) Urinary system: oliguria and anuria; and 7) Hematology system: splenomegaly, bleeding tendency, and pallor (8).

Investigations had to include at least one of the following: positive blood culture, radiological signs of pneumonia, positive sepsis screen (at least 2 of the following: C-reactive protein of > 6 mg/L, total leucocytic count (TLC) of < 5000/mm3, immature/total ratio of > 20 %).

At least two of the following pieces of evidence were indicative of systemic inflammatory response syndrome: (one of which had to be temperature or TLC)

1 Core temperature of > 38.5°C or < 36.0°C.
2 Bradycardia of < 100 beats/min or Tachycardia of > 180 beats/min.
3 Tachypnea of > 50 /min or need for a mechanical ventilator.
4 TLC elevated (>34000/mm^3 in the 1st week or >19500/mm^3 after 1 weak) or depressed (<5000/mm^3) or > 10% immature neutrophils.

The development of OD was diagnosed according to the criteria proposed by Goldstein et al. (9) and thorough clinical examination and follow-up investigations. Severe sepsis was diagnosed when sepsis was accompanied by one of the following: CVS dysfunction or $\geq$ 2 of other organ dysfunctions (9).

Statistical analysis

The collected data were coded and entered into the SPSS software (version 25). The information was summed up using the mean and the standard deviation in quantitative data and frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were implemented using the non-parametric Kruskal-Wallis and Mann-Whitney U tests. Chi-square ($\chi 2$) test was used for comparing categorical data. An accurate test was utilized if the expected frequency was less than 5. Correlations between quantitative factors were evaluated using Spearman's correlation coefficient. A receiver operating characteristic (ROC) curve was created with the analysis of the area under the curve (AUC) performed to identify the best cut-off value of scores for detecting death and OD. Standard diagnostic indices, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic efficacy were calculated as described by Galen. The p-values less than 0.05 were considered statistically significant.

Results

In this study, 100 neonates were enrolled, 50% of among whom were preterm (PT) and the rest 50% were full-term; moreover, 56% and 44% of the cases were male and female, respectively. The mean scores of birth weight and gestational age (GA) were estimated at 2.46±0.8 Kg and 36.1±2.59 weeks. It was found that 46% of cases were diagnosed with sepsis, while 54% of them had severe sepsis. In addition, 83 (83%) cases were discharged; however, 17 (17%) of them passed away.

The initial clinical manifestations of sepsis among the studied neonates, in descending order, were mainly respiratory (90%), CVS and neurologically (77%), and urinary manifestations (3%). Considering the severity of SNAP-II, it was reported to be mild in 62% (score 0-20), moderate in 27% (score 21-40), and severe in only 11% (scores of >40) of cases. The score of neonatal acute physiology-II was significantly higher in PT and severe sepsis groups. Furthermore, it was significantly higher in neonates with gram-negative blood cultures, compared to those with gram-positive cultures (Table 2).

Among the studied neonates, 57% had positive blood cultures with Klebsiella pneumonia as the most common organism (Table 3). It was revealed that SNAP-II had a positive correlation with the number of systems affected after 14 days and a negative correlation with GA and birth weight (Table 4). The newborns who developed OD after 14 days had significantly higher SNAP-II (especially moderate and severe categories) with the development of sepsis (37.45±16.7), compared to those without OD (9.14±7.82; P<0.001).

The neonates who passed away in our study

Table 2. Comparison between the score for neonatal acute physiology-II and other parameters

		Total score (SNAP-II)		P-value
		Mean	SD	
Gestational age	Preterm	22.26	19.65	*0.013
	Full-term	13.58	13.45	
Sepsis or severe sepsis	Sepsis	6.48	6.07	*<0.001
	Severe sepsis	27.67	17.83	
Blood culture	Negative	17.23	20.32	0.157
	Positive	18.44	14.81	
Organism (if positive blood culture)	Gram-positive organism	11.50	15.77	*0.007
	Gram-negative organism	21.67	13.79	
	Fungal (*Candida*)	21.33	8.02	
Outcome	Discharge	12.11	10.22	*<0.001
	Death	46.29	16.98	

SNAP: Score for neonatal acute physiology. *P-value < 0.05

Table 3. Blood culture of studied babies

		n=100	%
Blood culture	Negative (no growth)	43	43.0%
	Positive (organism)	57	57.0%
		n=57	%
Organism	Gram-positive organism	18	31.6%
	Gram-negative organism	36	63.2%
	Fungal (*Candida*)	3	5.3%
Organism type	*Staphylococcus aureus*	7	7.0%
	Staphylococcus haemolyticus	1	1.0%
	Staphylococcus hominis	4	4.0%
	Staphylococcus epidermidis	5	5.0%
	Streptococcus agalactia	1	1.0%
	Pseudomonas	4	4.0%
	Escherichia coli	2	2.0%
	Klebsiella	30	30.0%
	Candida	3	3.0%

Table 4. Correlation between the score for neonatal acute physiology-II and other parameters

		Total score (SNAP-II)
Gestational age	Correlation Coefficient	-0.335-
	P-value	0.001
	n	100
Birth weight	Correlation Coefficient	-0.205-
	P-value	0.041
	n	100
Number of systems affected after 14 days	Correlation Coefficient	0.773
	P-value	*<0.001
	N	100

SNAP: Score for neonatal acute physiology. *P-value < 0.05

had significantly higher SNAP-II (46.29±16.98), compared to those who were discharged. (12.11±10.22; P<0.001). Deceased neonates had also significantly higher SNAP-II severity

(moderate and severe categories). High scores of all individual parameters of SNAP-II were statistically significant with OD that occurred after 14 days of sepsis, and with mortality; nevertheless, SNAP-II parameters did not equally affect organ dysfunction or mortality (Table 5).

In the present study, with the application of the ROC curve for predicting OD, SNAP-II at 14.5 was considered as the best cut-off point in predicting OD with a sensitivity of 100%, PPV of 70.4%, specificity of 81.2%, NPV of 100%, AUC of 0.962, and P-value of < 0.001 (Figure 1). In our analysis of the ROC curve for mortality prediction, SNAP-II at 23.5 was considered as the best cut-off point in predicting overall mortality with a sensitivity of 100 %, PPV of 58.6%, specificity of 85.5%, NPV of 100%, AUC of 0.971, and P-value of < 0.001 (Figure 2).

Table 5. Comparison between organ dysfunction and mortality with Score for neonatal acute physiology-II for individual parameters

		Organ dysfunction after 14 days					Outcome				
		Organ dysfunction		No organ dysfunction		P-value	Discharge		Death		P-value
		n=31	%	n=69	%		n=83	%	n=17	%	
Lowest mean blood pressure score	0	14	45.2%	61	88.4%	*<0.001	71	85.5%	4	23.5%	*<0.001
	9	14	45.2%	8	11.6%		12	14.5%	10	58.8%	
	19	3	9.7%	0	0.0%		0	0.0%	3	17.6%	
Worst ratio of Pao2/fio2 score	0	1	3.2%	15	21.7%	*0.006	16	19.3%	0	0.0%	*<0.001
	5	24	77.4%	51	73.9%		64	77.1%	11	64.7%	
	16	6	19.4%	3	4.3%		3	3.6%	6	35.3%	
Lowest temperature score	0	16	51.6%	59	85.5%	*0.001	68	81.9%	7	41.2%	*0.001
	8	13	41.9%	9	13.0%		14	16.9%	8	47.1%	
	15	2	6.5%	1	1.4%		1	1.2%	2	11.8%	
Lowest serum Ph score	0	1	3.2%	53	76.8%	*<0.001	54	65.1%	0	0.0%	*<0.001
	7	15	48.4%	15	21.7%		26	31.3%	4	23.5%	
	16	15	48.4%	1	1.4%		3	3.6%	13	76.5%	
Occurrence of multiple seizures score	0	19	61.3%	67	97.1%	*<0.001	75	90.4%	11	64.7%	*0.013
	19	12	38.7%	2	2.9%		8	9.6%	6	35.3%	
Urine output<1 ml/kg/hr score	0	20	64.5%	67	97.1%	*<0.001	79	95.2%	8	47.1%	*<0.001
	5	11	35.5%	2	2.9%		4	4.8%	9	52.9%	

*P-value<0.05

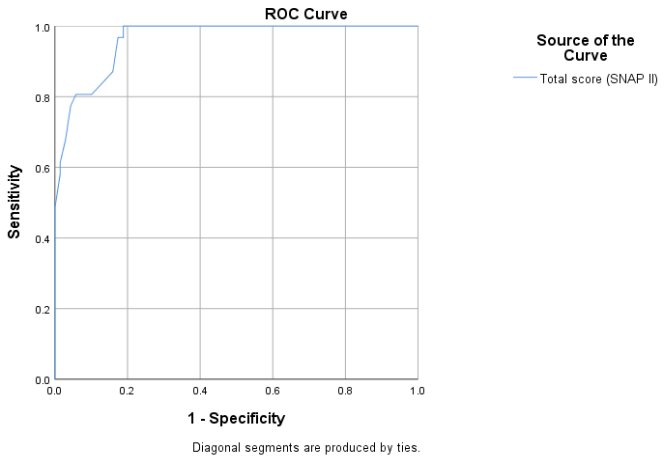

Figure 1. Receiver operating characteristic curve for detection of organ dysfunction using the score for neonatal acute physiology-II

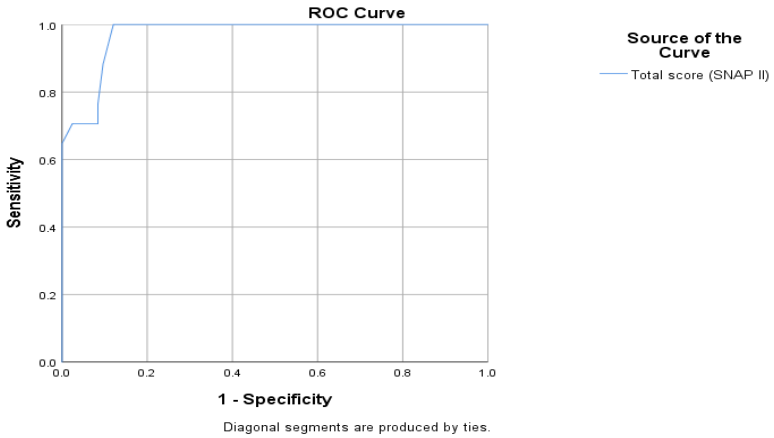

Figure 2. Receiver operating characteristic curve for prediction of death using the score for neonatal acute physiology-II

Discussion

The score of neonatal acute physiology was established by Richardson et al. (10) and authorized as a predictor of mortality and OD. It is a score based on physiological parameters that use 28 vital signs and routinely available laboratory test results and is evaluated during the worst time of the first day after admission (11). Richardson et al. (6) produced the second-generation SNAP, in which they reduced the data collection time from 24 h to 12 h for newly admitted neonates to decrease the effects of treatment bias. They also reduced the number of variables to six, which had the strongest statistical association with mortality; therefore, SNAP-II was originally established to predict the risk of mortality at NICU admission.

This study was conducted to determine the effect of using SNAP-II as a simple predictor of mortality and morbidity after 14 days of sepsis onset in neonates with septicemia. This research was the first study that used SNAP-II within 24 h of sepsis onset, not from admission. As some of the neonates were normal on admission and acquired infection throughout the hospital stay, the researchers needed to assess the value of scores in predicting sepsis outcome, rather than in comparing different units.

Our study was comparative to that conducted by Sundaram et al. (7); they included only 40 low-birth-weight neonates with severe sepsis and applied SNAP-II within 12 h from the sepsis onset; however, a larger number of neonates (n=100) was included in the present study and subjected to SNAP-II within 24 h of diagnosis of neonatal sepsis of both categories (sepsis or severe sepsis).

Our study included 100 newborns with sepsis (50 preterms [32-36 weeks] and 50 full-terms [37-42 weeks]), divided into 56 males and 44 females. Based on the results, 90% of the cases were appropriate for gestational age, while 10% of them were small for gestational age. The mean scores of gestational age and birth weights were estimated at 36.3±2.5 weeks and 2,460±800 g, respectively. The median day of sepsis onset was the 4th day of admission, 46% of included newborns had sepsis, while 54% of them had severe sepsis; moreover, there were 57% positive cultures among the subjects.

The score of neonatal acute physiology-II was significantly higher in lower gestational age (mean SNAP-II in preterm vs. full term was 22.2 vs. 13.5, respectively). This may be explained by that preterm neonates are at higher risk of developing sepsis complications because of deficiencies in humoral and cellular immunity and they are exposed to invasive life support systems and So more derangement of physiological parameters of SNAP II.

The median SNAP-II of neonates was obtained at 12.5 at enrollment, while in a study performed by Sundaram et al. (7), the median was as high as 37, as they included only severely septicemic low birth weight neonates. In the present research, the results of SNAP-II obtained for the enrolled neonates into 3 illness severity categories, namely mild, moderate, and severe with 62%, 27%, and 11% of cases infected (scores of 0-20, 21-40, and >40), respectively. It was revealed that organ dysfunction was statistically higher in moderate and severe categories (>20).

In our study, OD occurred in 31% of neonates after 14 days, with respiratory and renal OD as the most and least common incidence in 24% and 7%

of affected cases, respectively. It was found that SNAP-II was significantly higher with the number of systems affected after 14 days. Median SNAP-II in those who developed OD was significantly higher, compared to those who improved without developing OD (31 vs. 7.8, respectively; P<0.001). This indicated that recovery from OD was better in neonates with a lower score. In agreement with our results, Sundaram et al. (7) showed that the median SNAP-II in neonates with persistent OD was higher than in those lacking OD (42.5 vs. 18, respectively). Furthermore, Helal et al. (3) demonstrated nearly the same results (21 for OD vs. for no OD).

According to the results, SNAP-II was also higher in the severe sepsis group, compared to the sepsis group (mean SNAP-II=27.6 vs. 6.4, respectively; P<0.001); in other words, more severely ill and physiologically unstable neonates had higher physiological parameters of SNAP-II. The use of the ROC curve showed that SNAP-II was excellent in predicting OD with an AUC of 0.962 and a P-value of < 0.001. Based on that, SNAP-II at 14.5 was considered the best cut-off point in predicting OD with a sensitivity of 100 %, PPV of 70.4%, specificity of 81.2%, and NPV of 100%. Helal et al. (3) created ROC curves for the SNAP-II of ≥ 40, the area under the ROC curve was 0.829 with a sensitivity of 23.1%, PPV of 100%, specificity of 100%, and NPV of 41.2% for OD. Moreover, Sundaram et al. (7) found that the area under the ROC curve for SNAP-II of > 40 in predicting OD was 0.82 (P<0.001) with a sensitivity of 58%, PPV of 88%, specificity of 86%, and NPV of 52%.

Based on the findings, death was statistically higher in moderate and severe categories of SNAP-II. Mortality rates in the SNAP-II category were obtained at 0%, 22%, and 100% for mild, moderate, and severe cases, respectively. Mean SNAP-II in those who passed away was significantly higher, compared to those who survived (46.2 vs. 12.1, respectively; P<0.001), with the median of SNAP-II obtained at 48 vs. 8, respectively. The same studies were carried out by Helal et al. (3) (23 vs. 10 respectively; P=0.003), Sundaram et al. (7) (median 43 vs. 18, respectively), and by Nakwan et al. (12) (mean 36 vs. 22, respectively).

The use of the ROC curve revealed an excellent prognostic effect of SNAP-II in predicting mortality, with an AUC of 0.971 and a P-value of < 0.001. Based on that, SNAP-II at 23.5 was considered as the best cut-off point in predicting mortality with a sensitivity of 100 %, PPV of 58.6%, specificity of 85.5%, and NPV of 100%. Helal et al. (3) created ROC curves for the SNAP-II score of ≥ 40, which demonstrated moderate predictive accuracy. The area under the ROC curve was obtained at 0.699 with 29.6% sensitivity, 66.7% PPV, 92.5% specificity, and 72.1% NPV for mortality. In addition, Sundaram et al. (7) established that the area under the ROC curve for SNAP-II of > 40 in predicting mortality was 0.82 with a sensitivity of 60%, PPV of 88%, specificity of 86.6%, and NPV of 56.5%.

Conclusion

Higher SNAP-II within 24 h of the early- or late-onset neonatal sepsis was a reliable predictor for OD and death, especially in moderate and high severe categories (SNAP-II score of >20). Higher SNAP-II showed that more organs were affected after 14 days. According to the results, SNAP-II at 14.5 was considered the best cut-off point in predicting OD with a sensitivity of 100 %, PPV of 70.4%, specificity of 81.2%, and NPV of 100%.

The mortality rate was statistically higher in moderate and severe categories of SNAP-II (>20). The score of neonatal acute physiology-II at 23.5 was considered the best cut-off point in predicting overall mortality with a sensitivity of 100 %, PPV of 58.6%, specificity of 85.5%, and NPV of 100%.

Limitations

In the current study, only moderate preterm neonates were entered into the research and extremely preterm newborns were excluded. In this regard, it is required to perform studies with a larger sample size, especially among extremely preterm newborns.

Recommendations

It is recommended to perform more studies to establish these findings, and perhaps a multi-institutional study will be a beneficial next step to conduct the study on a larger sample size including extremely preterm neonates and with different center policies. Moreover, it is required to use SNAP-II daily in a septic neonate for follow-up sepsis improvement or deterioration and response to treatment.

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Conflicts of interest

All authors have no financial disclosure or conflict of interest regarding the publication of this study.

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