RESEARCH PAPER

# Score for Neonatal Acute Physiology II Predicts Mortality and Persistent Organ Dysfunction in Neonates with Severe Septicemia

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**Objective:** To investigate the relationship between score for neonatal acute physiology II (SNAP II) applied within 12 hours from the onset of severe sepsis, and death and persistent organ dysfunction (OD).

**Design:** Prospective cohort study.

**Setting:** Level III neonatal intensive care unit.

**Participants:** Neonates with severe sepsis.

**Intervention**:SNAP II was applied within the first 12 hours from the onset of severe sepsis. Neonates with major malformations, severe asphyxia and prior blood products were excluded.

**Major outcome measure:** Death at day 14 from enrolment.

**Results:** Forty neonates completed the study. Twenty-five died within 14 days. The median SNAP II was significantly higher in babies who died versus those who survived [median (IQR): 43 (36 – 53.5) *vs* 18 (16 - 37), *P*<0.001]. A SNAP II greater than 40 had 88% positive predictive value for death and persistent OD each, and 86.6% and 86% specificity for death and persistent OD, respectively. On day 14 from enrolment, more organs normalized/improved in the subjects with SNAP II of ≤40. Perfusion related SNAP II parameters were significantly associated with death and organ dysfunction.

**Conclusions:** Severely septicemic neonates with high SNAP II scores (>40) have a higher risk of dying and persistent organ dysfunction. Individual SNAP II parameters do not contribute equally in prediction of mortality.

**Keywords:** *Mortality, Neonate, Organ dysfunction, Sepsis, SNAP II.*

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Neonatal septicemia may lead to a systemic inflammatory response syndrome (SIRS) and untreated, progresses to severe septicemia, and organ dysfunction (OD)(1). Application of severity scores in this condition may be useful for prognostication and evaluation of the effectiveness of therapeutic protocols in the Neonatal Intensive Care Unit (NICU). Various scoring systems *viz.* score for neonatal acute physiology (SNAP)(2), the SNAP perinatal extension (SNAP-PE)(3), and clinical risk index for babies (CRIB)(4) have been used to assess the severity of illness in newborns.

The SNAP, SNAP-PE and their next generation variants SNAP II and SNAP-PE II have been primarily used in NICUs, where newborns are admitted immediately after delivery(5). No study has attempted to use SNAP or SNAP II parameters as prognostic markers among neonates after the onset of sickness in the NICU. This study investigates the relationship between SNAP II applied within 12 h from the onset of severe septicemia, and outcome in the form of mortality and persistent organ dysfunction, separately, at day 14 from enrollment in neonates less than 28 days age.

*Accompanying Editorial: Pages 765-766*

## METHODS

This prospective cohort study was conducted in the level III neonatal intensive care unit of a referral institute in Northern India. The data presented here was obtained as part of another study on the association between low plasma protein C values and mortality, the details of which are available elsewhere(6). Neonates (<28 days), diagnosed to have septicemia (defined as clinical signs and either blood culture or sepsis screen positive or radiological evidence of pneumonia) with evidence of SIRS and OD were eligible for enrolment(6). Sepsis screen consisted of C reactive protein (CRP), micro erythrocyte sedimentation rate (mESR), total leukocyte count (TLC), absolute neutrophil count (ANC) and immature to total ratio (ITR), and was considered positive if any two or more out of these five were abnormal. CRP was considered positive above 10 mg/L, mESR above 10 mm in first hour or 'age in days +3' mm in the first 7 days, TLC less than 5000 per $mm^3$, ANC according to Manroe's and Zipursky's charts and ITR above 20% (7,8).

Presence of at least 2 of the 4 criteria defining SIRS and evidence of at least one OD within the 24 hour period preceding entry into the study was deemed essential along with evidence of septicemia. SIRS criteria framed by Adams-Chapman and Stoll(9) were adapted for newborns, with age-appropriate changes introduced for temperature, hypoxemia and oliguria. Organ dysfunction criteria were adapted from a previous study done for the safety assessment of activated protein C (APC) administration in severely septic children(10).

All enroled neonates had their illness severity assessed using SNAP II(5). This score consists of 6 physiological parameters, namely lowest mean arterial pressure (MAP), worst ratio of partial pressure of oxygen ($PaO_2$) to fraction of inspired oxygen ($FiO_2$), lowest temperature (in ºF), lowest serum pH, occurrence of multiple seizures, and urine output (<1mL/kg/hr). The data collection window was the first 12 hours from the onset of severe septicemia, during which period the above parameters were prospectively recorded. Weighted scores were given based on the presence or absence of each parameter. Higher scores indicate more severe illness. Severity of the illness was arbitrarily graded according to the SNAP II score as follows: Mild: 1-20, moderate: 21-40, and severe: >40.

Neonates with major congenital malformations, severe birth asphyxia (Apgar <4 at 5 minutes) or who had received blood products before sampling for plasma protein C activity assay were considered not eligible for the study. Neonates who satisfied the eligibility criteria were enrolled after explaining the nature of the study to the parents and obtaining a written informed consent. The study had the approval of the Institute Ethics Committee.

All subjects were followed up until remission of OD or death, whichever was earlier, up to a maximum of 14 days. Evolution of OD was evaluated using the same OD criteria used at enrollment(6). Investigations of OD were repeated during the study period as per a pre-defined protocol. Sampling was coordinated with routine sampling, to minimize needle pricks and trauma. A sample size of 40 was recruited to suit the requirements of our primary study(6).

The key outcome measure was difference in SNAP II between survivors and non-survivors. Secondary outcomes were difference in SNAP II between neonates with and without persistent OD on day 14 from enrollment, and discriminatory ability of SNAP II for death and persistent OD on day 14 from enrolment.

Categorical variables were analyzed by Chi square test with continuity correction or Fisher's Exact test and continuous variables by Student's *t* test or Mann Whitney U test, depending on distribution. Receiver-operator characteristic (ROC) curves were constructed for SNAP II to identify the best trade off for SNAP II value to predict the risk of mortality as well as for the individual SNAP II parameters to assess their diagnostic accuracy.

## RESULTS

Seventy-four neonates met inclusion criteria. Thirty four were excluded (7 for receiving prior blood products, 6 for severe birth asphyxia, 2 for major congenital malformations, 2 for hemolysed blood sample and 17 for logistic reasons like patient not

accessible to the investigator and non-functioning status of the analyzer), thus leaving 40 babies to complete the study.

The characteristics of the enroled neonates are described in ***Table* I**. Blood culture was positive in 33 babies (82.5%), septicemia screen in 35 babies (87.5%) and chest *X*-ray in 24 (60%) neonates. All 7 culture negative subjects had a positive sepsis screen. The etiologic organisms are described in ***Table* II**.

Twenty-five babies died within the 14-day observation period due to septicemia. The study population had a median SNAP II score of 37 (IQR 18.5-47.5) at enrollment. Thirty five percent of the study subjects had moderate illness (SNAP II=21-40) and 40% had severe illness (SNAP II>40). The median SNAP II was significantly higher in the babies who died versus those who survived [median (IQR) 43 (36 – 53.5) *vs* 18 (16 - 37), respectively; *P*<0.001]. The death rates by SNAP II category were 20% for mild, 64% for moderate, and 87.5% for severe. Sensitivity, specificity, and predictive values of a SNAP II greater than 40 is documented in ***Table* III**. The area under the Receiver-Operator characteristic (ROC) curve for SNAP II curve was 0.82 (95% CI 0.68-0.95, *P*<0.001).

The median number of organs involved at enrollment was 3.5 (IQR 3.0-4.0) whereas the median number of organs involved at day 14 was low [3.0 (IQR 2.0-4.0), *P*=0.004]. In 14 babies (35%), the OD improved by day 14. Lungs were the most frequently involved organ at enrollment (97.5%), followed by the hematologic system (90%) with 32.5% of these cases having disseminated intravascular coagulation (DIC). Seventy five percent had cardiovascular involvement. Shock requiring vasoactive drug support was present in 30 babies (75%) and renal failure was diagnosed in 26 babies (65%) at enrollment.

Neonates with SNAP II greater than 40 had more organs involved at enrollment compared to neonates with SNAP II less than or equal to 40 (3.8±0.4 *vs* 2.9 ±0.8, *P*=0.001). The median SNAP II was significantly higher in the babies in whom the OD persisted or worsened versus in whom it normalized [Median (IQR): 42.5 (36.5-53) *vs* 18 (15.5-34) respectively; *P*<0.001]. On day 14 from enrolment, more organs normalized/improved in the subjects with SNAP II of ≥40 (2.96±0.8 *vs* 2.13±1.6; *P*=0.008) in comparison with the subjects with

**TABLE I** BASELINE CHARACTERISTICS OF STUDY SUBJECTS (*N*=40)

| Baseline characteristic | | Values |
|---|---|---|
| Gestation in wks (mean ± SD) | | 30.2 ± 2 |
| Birth weight in gms (mean ± SD) | | 1188.3 ± 282.8 |
| Growth status* (%) | AGA | 28 (70) |
| | SGA | 12 (30) |
| Males (%) | | 27 (67.5) |
| Day of onset of illness (median, IQR) | | 4 (3-6) |

** SGA – small for gestational age; AGA – appropriate for gestational age*

**TABLE II** DISTRIBUTION OF ORGANISMS IN BLOOD CULTURE AND THEIR RELATION WITH SNAP II SCORES

| Organism | Total culture positive (*n*=33) | SNAP II scores Mean ± SD |
|---|---|---|
| *Alcaligenes fecalis* | 8 (24.2) | 34.6±17.8 |
| *Klebsiella pneumoniae* | 8 (24.2) | 35+17 |
| *Escherichia coli* | 7 (21.2) | 31.8 ± 14 |
| MRSA* | 4 (12.1) | 41±24.6 |
| *Enterobacter aerogenes* | 4 (12.1) | 40.7±6.9 |
| LFGNB* | 1 (3.1) | 53 |
| *Enterococcus fecalis* | 1 (3.1) | 42 |

*Figures in parentheses are percentages. P value for one way analysis of variance (ANOVA) was >0.05. *MRSA – methicillin resistant staphylococcus aureus, LFGNB-lactose fermenting gram negative bacilli.*

**TABLE III** SNAP II MORE THAN 40 AS A PROGNOSTIC TEST FOR DEATH AND ORGAN DYSFUNCTION

| Factors | % Predictive value (95% CI) for death | % Predictive value (95% CI) for OD |
|---|---|---|
| Sensitivity | 60 (40.7-76.6) | 58 (39-74.5) |
| Specificity | 86.6 (62.1-96.3) | 86 (60-95.9) |
| PPV | 88 (65.6-96.7) | 88 (65.6-96.7) |
| NPV | 56.5 (36.8-74.4) | 52 (33-70.7) |

*PPV: Positive predictive value, NPV: Negative predictive value.*

**TABLE IV** SNAP II PARAMETERS AND OUTCOME

| Parameter | Died (*n*=25) | Survived (*n*=15) | *P* | OD* persisted (*n*=26) | OD* improved (*n*=14) | *P* |
|---|---|---|---|---|---|---|
| MAP ≤29 mmHg | 22 | 7 | 0.009 | 22 | 7 | 0.03 |
| Lowest blood pH (<7.20) | 22 | 7 | 0.009 | 23 | 6 | 0.007 |
| $PaO_2/FiO_2$ ratio (<2.50) | 24 | 13 | 0.2 | 25 | 12 | 0.2 |
| Urine output (<1mL/kg/hr) | 20 | 6 | 0.01 | 21 | 5 | 0.004 |
| Lowest temperature (≤96ºF) | 4 | 2 | 0.7 | 5 | 1 | 0.5 |
| Multiple seizures | 1 | 0 | — | 1 | 0 | — |

**OD – Organ dysfunction*

SNAP II of greater than 40 (3.76±0.4 *vs* 3.53±0.7; *P*=0.1).

When the individual SNAP-II parameters were analyzed, it was found that parameters related to perfusion (MAP, acidosis, and oliguria) were significantly associated with death as well as organ dysfunction at day 14 (***Table* IV**). Hypothermia and hypoxia were observed more commonly in babies who died but did not attain statistical significance. The area under ROC of lowest MAP, lowest pH, lowest $PaO_2/FiO_2$ ratio, urine output less than 1mL/kg/hour, and lowest temperature were 0.75 (95% CI 0.58-0.92, *P*=0.009), 0.78 (95% CI 0.63-0.93, *P*=0.004), 0.68 (95% CI 0.49-0.87, *P*=0.06), 0.70 (95% CI 0.53-0.88, *P*=0.03), and 0.62 (95% CI 0.44-0.79, *P*=0.2), respectively.

## DISCUSSION

This study is the first of its kind in neonates where SNAP-II has been applied to neonates after onset of severe septicemia to predict mortality and OD. Like other illness severity scores, SNAP II was originally developed to predict the risk of dying(5) at admission to NICU and for baseline risk adjustment to facilitate comparison of mortality between NICU's(11). Most previous studies have applied SNAP II to assess the illness severity within the first 12 hours after admission in the NICU(11-13). We felt that many babies may not be very sick at admission to NICU and may develop severe sickness later in the course of NICU stay. The SNAP-II at admission to NICU may not be able to capture the events when the baby becomes sicker. Hence, we attempted to apply SNAP II within 12 hours from the diagnosis of severe septicemia in babies who were already admitted in the NICU.

Our study cohort was different from that of the previous studies by being sick to begin with, with a high median SNAP II of 37(11-13). The median SNAP II was significantly higher in babies who died in comparison with those who survived. An earlier study done in mechanically ventilated term infants reported a significantly high mean SNAP in babies who died in the first 2 weeks of life(13). Maiya, *et al*.(14) from India have reported the mean SNAP in babies who survived versus who died as 4.88 *vs* 17.38 (*P*<0.001). Both the above studies used the older generation SNAP in babies at the point of admission to the NICU. Being a physiological score of severity of illness, the higher the score, the greater would be the physiologic derangement and hence greater would be the organ involvement. Consistent with that we observed a higher SNAP II in babies in whom the organ dysfunction persisted/worsened and *vice versa*. This indicates that organ function recovery was better in babies with a lower severity of illness.

Each parameter of SNAP II was derived by assigning weighted points based on the relative risk of mortality conferred by the presence of that parameter(5). We evaluated the individual parameters of the score as they may not contribute equally to the risk prediction(13). In our study, only those parameters indicating circulatory instability like low mean arterial pressure, lowest blood pH and urine output were significantly associated with death and/or organ dysfunction. There was no difference in respiratory system involvement between those

**WHAT IS ALREADY KNOWN?**

- SNAP II can predict mortality in neonates at admission to the Intensive Care Unit.

**WHAT THIS STUDY ADDS?**

- SNAP II can predict mortality as well as organ dysfunction in severely septic neonates; individual components of the score do not have equal predictive ability.

died and survived which indicates that individual parameters of the SNAP II did not contribute equally to the risk of dying. Shock predicted death but hypoxia did not. This was observed despite lungs being the most common organ to be involved. When we constructed ROC curves individually for each of the SNAP II parameter, apart from the total SNAP II score, only the circulation related parameters were associated with death with a moderate predictive accuracy.

A limitation of this study was that the study group was selected to satisfy the inclusion criteria for the primary study on Protein C, hence, the data of the neonates who were excluded could not be analyzed.

We conclude that neonates with severe septicemia are at significantly higher risk of dying if they have high SNAP II scores. A SNAP II greater than 40 has a moderate diagnostic accuracy in predicting death as well as organ dysfunction and hence may be useful to clinicians as an adjunct to other prognostic indicators. Individual SNAP II parameters do not contribute equally in prediction of mortality with circulatory parameters contributing the most to the total score.

*Contributors:* SD and VS conceptualized and designed the study and also analyzed and interpreted the data. VS drafted the manuscript. SD and AN substantially revised the manuscript for important intellectual content. AN also helped in interpretation of the data. JA conducted the hematological investigations and helped in manuscript writing. SD will act as guarantor of the manuscript. The final manuscript was approved by all the authors.

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