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A Systematic Review

The Utility of the Revised Version of the Score for Neonatal Acute Physiology Among Critically Ill Neonates

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ABSTRACT

The revised version of the Score for Neonatal Acute Physiology (SNAP-II) has been used across all birth weights and gestational ages to measure the concept of severity of illness in critically ill neonates. The SNAP-II has been operationalized in various ways across research studies. This systematic review seeks to synthesize the available research regarding the utility of this instrument, specifically on the utility of measuring severity of illness sequentially and at later time points. A systematic review was performed and identified 35 research articles that met inclusion and exclusion criteria. The majority of the studies used the SNAP-II instrument as a measure of initial severity of illness on the first day of life. Six studies utilized the SNAP-II instrument to measure severity of illness at later time points and only 2 studies utilized the instrument to prospectively measure severity of illness. Evidence to support the use of the SNAP-II at later time points and prospectively is lacking and more evidence is needed.

Key Words: neonatal severity of illness, physiologic instability, SNAP-II

Critically ill neonates born every day require the progressively high technologic care that is available in the neonatal intensive care unit (NICU). The demand for neonatal critical care is on the rise. Halpern and Pastores[1] found that neonatal intensive care beds in the United States have increased by 8% and the infant mortality rate still remains high compared with that in other developed countries.[2] Specifically, the 2010 US infant mortality rate of 6.1 deaths per 1000 live births was the highest infant mortality rate among 26 developed countries included in the Organization for Economic Co-operation and Development.[2] Although NICU care has improved over the past 30 years and survival rates are increasing,[3] advances are needed for the improvement of critical care for the most vulnerable newborns.

Clearly decreasing the infant mortality rate is a critical goal; however, neonatal survival is no longer the ultimate goal of neonatal intensive care. Vulnerable neonatal populations, specifically the youngest and smallest babies, are at greatest risk of mortality as well as a lifetime of morbidity following a NICU admission.[4,5] Researchers and clinicians are working diligently to optimize care for these critically ill neonates and thereby decrease the risk of mortality and reduce the risk of lifetime morbidity. Utilization of a tool to operationalize the degree of illness severity for neonates has potential for use as a bedside clinical tool as well as a research tool. Current trends utilizing electronic medical records in the NICU could allow for automation of an illness severity score calculation by using computer code to pull chart data to assign an illness severity score. Operationalizing illness severity scores based on physiologic data points has the potential to help the bedside clinician establish risk at birth and monitor illness severity throughout the patient's admission. It is also important to consider the role of illness severity scores in neonatal research. An illness severity score has the potential to assist researchers in accounting for the level of illness severity at birth and to account for their illness severity when they evaluate for the effectiveness of the

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interventions. Clearly well-designed research studies are needed to generate new knowledge and illness severity scores have the potential to improve the data that are obtained, thereby helping researchers continue to improve the care that is provided for these critically ill newborns.

When designing research studies for this vulnerable population, it is important to consider the concept of neonatal illness severity. Neonatal severity of illness is a concept that is 2-fold: (1) determination of how acutely ill or physiologically unstable the newborn is at that time and (2) assisting in the prediction of future risk of morbidity and mortality for the neonate because of this initial risk.[6]

DERIVATION OF THE SCORE FOR NEONATAL ACUTE PHYSIOLOGY

One of the most common research instruments available to measure the concept of neonatal severity of illness is the revised version of the Score for Neonatal Acute Physiology (SNAP-II). The original SNAP was developed by Richardson et al.[7] One of the greatest reasons for this tool was the need to accurately compare outcomes within and among NICUs. Richardson and colleagues noted that an additional source of variance in NICU cohorts is neonatal illness severity, and without controlling for this initial variation of risk at birth, outcome comparisons would be inaccurate.[7] Therefore, the SNAP measurement tool was created. The SNAP was specifically designed to measure the physiologic instability of the newborn across body systems that are present in the first 24 hours of life. These physiologic measurements change overtime and as such the SNAP instrument was designed to allow for sequential measurement.[7]

Severity of illness is related to risk of mortality; however, there are also perinatal risk factors that influence the risk of mortality that are independent of illness severity. Therefore, the Perinatal Extension (SNAP-PE) was added to the SNAP score to quantify physiologic instability and perinatal mortality risk in one instrument.[8] This instrument contains the full SNAP score and then adds in 3 additional perinatal parameters, including birth weight, small-for-gestational age, and the 5-minute Apgar score, which accounts for additional perinatal risk factors of mortality.[8]

The creators of the original SNAP measurement tool generated initial evidence of validity by demonstrating that increasing SNAP scores were associated with increasing mortality rates ($P < .001$). Additional evidence of validity of the SNAP score was demonstrated by looking for positive relationships between other variables associated with increased illness severity. For example, positive relationships were noted between SNAP scores and additional parameters, including the length of stay ($R^2 = 0.59$), nursing acuity ($r = 0.59$), and increased need for therapeutic interventions ($r = 0.78$).[7] Clearly when babies are more ill, they spend more days as an inpatient in the NICU, they require more interventions in general, which includes a need for a higher level of nursing care. Finally, a positive correlation was noted between SNAP scores and the physician's estimation of mortality risk ($r = 0.65$).[7] The SNAP-PE also demonstrated the ability to predict the combined physiologic and perinatal mortality risk in neonates. The SNAP-PE instrument was a better predictor than SNAP or birth weight alone (area under curve [AUC] ranged from 0.91 ± 0.2 to 0.93 ± 0.2). Furthermore, the Hosmer-Lemeshow (HL) goodness of fit test was poor for the birth weight alone but good for other models ($P = .2$-$.99$).[8]

The SNAP instrument had the potential to assist clinicians and researchers to quantify the concept of illness severity. However, this tool was extensive and required up to 15 minutes to evaluate many parameters including blood pressure, heart rate, respiratory rate, temperature, Po_2, Po_2/FIo_2 ratio, Pco_2, oxygenation index, hematocrit, white blood cell count, immature-to-total ratio, absolute neutrophil count, platelet count, blood urea nitrogen, creatinine, urine output, indirect bilirubin, direct bilirubin, sodium, potassium, ionized calcium, total calcium, glucose, bicarbonate, pH, seizures, apnea, and stool guaiac.[6,7] The authors acknowledged that the SNAP scoring system was cumbersome and their stated goal from the initial instrument development was to eventually make the tool more parsimonious.[7] However, they needed a large cohort of neonates with SNAP data to further analyze and reduce the number of parameters, while still retaining the validity of the illness severity score.

Richardson et al[6] published the initial derivation and validation report of the SNAP-II and SNAPPE-II instruments from a cohort of 25 429 neonates across 30 sites from 3 neonatal networks in the United States and Canada. The revised SNAP-II instrument achieved the authors' goal of creating a more parsimonious tool that could be assessed within 2 to 4 minutes. The SNAP-II retained only 6 items and each item was weighted on the basis of the beta weight from the logistic model. The parameters and possible point values were as follows: lowest mean blood pressure, lowest temperature, Po_2/FIo_2, lowest serum pH, presence of multiple seizures, and low urine output. Just like the SNAP, the SNAP-II is a summative rating scale. The highest possible score is 115. The SNAPPE-II is also the summative rating scale as listed earlier and it adds 3 additional parameters, including birth weight, small-for-gestational

age, and the 5-minute Apgar score. The highest possible SNAPPE-II score is 162. The higher the SNAP-II or SNAPPE-II score is, the more severely ill and physiologically unstable is the neonate. As described by the instrument authors, the SNAP-II was designed to measure the mortality risk due to physiologic instability and the SNAPPE-II was designed to measure the combined physiologic and perinatal mortality risk. Because perinatal factors will not change over time, the SNAPPE-II was only designed to be measured once with data from the first 12 hours following birth. However, the SNAP-II instrument was designed to assess and quantify the physiologic signs of illness that can be assessed clinically. These physiologic derangements can change over time; therefore, the SNAP-II may be useful to measure severity of illness over time.

Parsimony was a strength of this revised tool; however, equally important is that the points assigned to each parameter were empirically derived from the beta weights from the logistic model for SNAP-II.[6] While some tools have been designed to measure illness severity in specific birth weights of neonates, the SNAP-II instrument was designed as a universal tool for critically ill newborns of all gestational ages and birth weights. The SNAPPE-II demonstrated good sensitivity, specificity, and HL goodness of fit across all birth weights. When stratifying the cohort via birth weight, the values were as follows: (1) across all birth weights (AUC 0.91 ± 0.01; HL $P = .9$), (2) less than 1500 g (AUC 0.85 ± 0.01; HL $P = .86$), and (3) 1500 g or greater (AUC 0.87 ± 0.03; HL $P = .63$).[6] No reliability data such as the Cronbach alpha were reported.

PURPOSE

Specifically, this literature review will synthesize all research studies that have utilized the SNAP-II instrument since its creation. As designed, this instrument measures illness severity as physiologic instability of the neonate. While most studies used this instrument to measure illness severity in the first 12 hours of life, some studies used this instrument at later time points and for sequential measurements. While the authors of the tool are clear that the SNAPPE-II is an admission score only, the original SNAP instrument was designed for sequential measurements. However, the utility of the SNAP-II at later time points and for measurements over time is unclear. This literature review seeks to describe how the SNAP-II instrument has been used across neonatal populations within the NICU. In addition, this literature review describes current evidence that is available to support the use of the SNAP-II tool at later time points and for prospective measurements of illness severity beyond the first day of life.

METHODS

All research studies that have utilized the SNAP-II instrument since it was originally derived and validated by Richardson et al[6] will be reviewed. The primary author used 3 search engines to gather potential articles for review: PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. The search terms "neonatal severity of illness" and "SNAP" were used to retrieve relevant articles. The term "SNAP" was used instead of "SNAP-II" to ensure that no relevant studies were overlooked during the initial data retrieval process. Date ranges were omitted since it was feasible to evaluate older papers to understand the full history of the SNAP-II instrument. The inclusion criteria for this comprehensive review included (1) articles available in English, (2) utilization of the SNAP-II instrument, and (3) and original research. The exclusion criteria included (1) duplication of the study from another search engine; (2) articles not available in English; (3) nonresearch articles, including review articles, poster abstracts, conference abstracts, letters to the editor, and commentaries; and (4) studies that did not utilize the SNAP-II instrument in the study.

Once studies were identified, the primary author reviewed each study and data were extracted for synthesis. A table compiled relevant data extraction and included (1) author and year of the publication, (2) study purpose, (3) study location (country), (4) sample size, (5) sample characteristics, (6) research design, (7) utilization of the SNAP-II instrument, (8) research findings, and (9) limitations and potential for bias (see Table 1). Data in the table were compiled to explore the complete utilization of the SNAP-II instrument since the revised instrument was created in 2001.

RESULTS

Derivation of included studies

Studies were evaluated on the basis of the inclusion and exclusion criteria. The process of study selection is outlined later and is also depicted in Figure 1. The literature search terms "neonatal severity of illness" and "SNAP" yielded a total of 193 articles. Seventy-eight articles were duplicates and therefore eliminated. Six studies were excluded because of being published in foreign languages, including Chinese,[9] Bulgarian,[10] French,[11] Portuguese,[12,13] and Polish.[14] This yielded a total of 109 abstracts for review. Review of the abstract revealed if the measurement tool for the study included the initial SNAP) or the revised SNAP (SNAP-II). Only studies that included the SNAP-II measurement tool were included; therefore, an additional 59 studies were excluded. The final step in article selection was to exclude any

Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
1. Stanger et al (2014)	To correlate prognostic variables with the intended and actual abdominal closure technique (primary repair vs silo) and assess related outcomes in neonates with gastroschisis	Canada	$N = 679$	Dx gastroschisis from 5/05 to 12/11 GA mean 35.8 BW mean 2557 g CAPSNet 17 perinatal/surgical centers	Observational	SNAP-II used to stratify risk for gastroschisis patients. SNAP-II used as a predictor of treatment method: PR vs silo SNAP-II measured within 12 h of NICU admission SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II scores were higher for patients undergoing primary repair (PR). (11.1 vs 7.21, $P < .001$) SNAP-II score was a predictor of closure type using multivariate analysis ($P = .04$) The authors questioned if the SNAP-II scores were higher due to the course of treatment vs initial severity of illness. Higher SNAP-II scores were not correlated to poor outcomes.	Observational study Duration of silo placement was not obtained; therefore, situational factors vs patient factors for closure decisions may be confounding. There is potential that the higher SNAP-II scores were measuring treatment effect and not initial illness severity. (Should the SNAP-II be limited to a shorter window to decrease treatment effects?) Authors questioned a type 1 error? Authors were concerned of accuracy of SNAP-II as a predictor of treatment.
2. Coleman et al (2013)	To evaluate the 24-h SNAP-II score and highest $Paco_2$ as predictors of ECMO use in neonates with congenital diaphragmatic hernia (CHD)	USA	$N = 47$ ECMO $n = 24$ No ECMO $n = 23$	Dx with CHD from 2007 to 2010 All outborn and tx to tertiary children's hospital *ECMO vs No ECMO* GA 38.5/38.0 BW 3.04/2.90 kg	Retrospective cohort study	Used as a predictor for ECMO tx. SNAP-II measured with data from the first 24 h of admission. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	78% of neonates with SNAP-II >25 needed ECMO SNAP-II predicted ECMO use (AUC = .76, $P = .003$) SNAP-II predicted mortality (AUC = 0.77 [0.63-0.91]; $P = .002$)	Retrospective design Single center Small sample size
3. Capasso et al (2013)	To investigate the effectiveness of IgM-enriched immunoglobulins in reducing short-term mortality rate of neonates with late-onset sepsis.	Italy	$N = 79$ Tx with antibiotic and IgM $n = 40$ Tx with antibiotic only ($n = 39$)	VLBW neonates diagnosed with late onset sepsis from 2008 to 2012 Cohorts split before and after 6/1/2010 *IgM/No IgM* GA 27 ± 2.6/27.6 ± 3.9 (NS) BW 924 ± 277/951 ± 362 (NS) SNAP-II 15 ± 13/12 ± 9 (NS)	Retrospective cohort study	SNAP-II used to assess illness severity /disease severity and establish the 2 groups were homogeneous for this measure. Timing of the SNAP-II score was not reported. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	No statistically significant differences in SNAP-II scores between the 2 groups; therefore, the groups were homogeneous for illness severity. Short-term mortality was significantly less in the group that received both IgM and antibiotics (9 vs 18, OR = 0.16, 95% CI: 0.3-0.7, $P = .005$)	Observational Retrospective Single center Cohorts came from 2 different time points. (Cohort receiving antibiotics alone. Subsequent cohort received both IgM and antibiotics after a practice change occurred routine tx of sepsis in this institution.)

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
4. Iacobelli et al (2013)	To evaluate the association of "severe adverse outcome" (defined as inpatient death or severe neurological injury) and hypoproteinemia (<40 g/L). To compare the predictive ability of hypoprotenemia as compared with other illness severity measurement instruments	France	$N = 761$	Derived from a single-site study over 10.5 y (January 2001 to June 2011). GA 24-31 BW 1203 ± 346 g Cases were excluded if any data were missing for the calculation of the CRIB, CRIB-II, SNAP-II, or SNAPPE-II.	Observational cohort study	Measures of illness severity for comparison included: SNAP-II, SNAPPE-II, CRIB, CRIB-II, and total plasma protein at 12 h of life. Measures of illness severity were compared for their ability to predict poor outcomes including mortality prior to discharge or severe neurological injury. SNAP-II and SNAPPE-II were assessed with data from the first 12 h of life. SNAP-II was not used as a sequential measure.	Total plasma protein was significantly better at predicting the adverse outcome as compared with SNAP-II and CRIB-II ($P < .05$). Total plasma protein had similar predictive capabilities as compared with CRIB and SNAPPE-II. Total plasma protein AUC = 0.849 HL $P = .73$ SNAPPE-II AUC = 0.822, HL $P = .26$ SNAP-II AUC = 0.810, HL $P = .47$ Plasma protein predicted severe adverse outcomes better than CRIB-II and SNAP-II ($P < .05$)	Observational Single center Blood draws for plasma protein levels were not consistent and extended between 12 and 20 h of life.
5. Wilson et al (2013)	To compare patients with congenital diaphragmatic hernia (CDH) who did and did not undergo surgical correction.	Canada	$N = 275$ PSC/NS ($n = 11$) NSC/NS ($n = 24$) Surgery/survivor $n = 224$ Surgery/NS $n = 16$	Derived from prospective CAPSNet database from 2005 to 2009 Dx with CDH GA 26-42 (median = 38) BW 930-4930 (median = 3197.5) LOS 0-135 d (median = 18) SNAP-II 5–63 (median = 21)	Retrospective cohort study	SNAP-II was used to assess mortality risk. Desired to establish a threshold SNAP-II score as a predictor of poor surgical outcome. Timing of the SNAP-II score was not reported. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II predicted neonatal mortality ($P < .001$) Nonsurvivors had higher SNAP-II scores than survivors ($P < .001$) SNAP-II scores were similar between operative nonsurvivors and potential surgical candidates (34 vs 29; $P = .431$). Median SNAP-II scores for these groups was similar at 34 vs 30 ($P < .431$) More than 80% of surgical cases with SNAP-II scores between 30 and 39 survived. 100% mortality rate for potential surgical cases	Observational retrospective The population of interest, PSC, was small. ($N = 11$) Potential for critical information to be omitted from the database including: 1. Confirmed cause of death 2. Undocumented congenital anomalies

(*continues*)

Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
6. Wong et al (2013)	To compare neonatal outcomes of patients receiving a patent ductus arteriosus (PDA) ligation in a pediatric cardiac center vs a pediatric noncardiac care center	Canada	*N* = 990 (Represents 22.9% of total sample dx with PDA) PDA Ligation at CC *n* = 711 PDA ligation at NCC *n* = 279	Dx with PDA and requiring surgical ligation Derived from CNN Database from 2005 to 2009. (18 NICUs with cardiac surgeons/9 NICUs with pediatric surgeons) *Combined cohort/CC/NCC* (Cohort ≤33 wks and <1500 g). GA (*P* = .01) 25.8 (2.0) 25.7 (2.0) 26.0 (2.0) BW (*P* < .01) 846 (279) g 830 (270) g 889 (300) g SNAP-II (*p* = .23) (Median/IQR) 14 (9.28) 16 (9.29) 14 (9.24)	Retrospective Cohort Study	SNAP-II was used as a predictor of mortality risk upon admission SNAP-II was used as a control when assessing mortality rates across this sample. The SNAP-II score was assessed upon admission; however, the time window for measurement was not reported. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	No difference between pediatric cardiac care centers and pediatric noncardiac care center in the SNAP-II adjusted mortality rate (8.7% vs 10.7%; *P* = .32) Overall mortality rate was 9.1% in this study. Increased morbidity including cranial ultrasound abnormalities (OR = 0.55, 95% CI: 0.40-0.77) and sepsis (OR = 0.53, 95% CI: 0.39–0.71) noted for neonates treated at noncardiac care centers.	Observational retrospective
7. Zwicker et al (2013)	To examine the relationships of risk factors (antenatal, perinatal, and postnatal) for abnormal brain development of the corticospinal tract.	Canada	*N* = 126	Derived from current prospective ongoing study (April 2006–September 2010). GA 27.7 (25.9-29.9) BW 1030 (805-1290) SNAP-II 11 (7-22)	Observational	SNAP-II was used to measure early illness severity in first 24 h of life. Early illness severity, operationalized by SNAP-II, was used as the perinatal risk factor in this study. SNAP-II measured with data from the first 24 h of admission. SNAP-II scores were used to stratify the neonate's risk: <10, 10-29, ≥30. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	Increased SNAP-II scores were associated with a slower rise in fractional anisotropy of the corticospinal tract (*P* = .02). This relationship remained significant (*P* = .009) even after controlling for GA and postnatal risk factors. SNAP-II predicted development of the motor pathways of the brain.	Observational Single site

(*continues*)

Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
8. Lucas Da Silva et al (2012)	To assess the validity of the transport risk index of physiologic stability score (TRIPS) score in a NICU sample in Brazil. To compare the performance of the TRIPS, SNAP-II, and SNAPPE-II scores in a NICU sample in Brazil.	Brazil	$N = 175$	Single Regional NICU GA at birth 35.3 (27-42) GA at transport 35.7 (27-42) SNAP-II 10 ± 15.6 (median = 5, IQR = 0-14) SNAPPE-II 14.4 ± 21 (median = 5, IQR = 0-24.7)	Observational prospective	SNAP-II and SNAPPE-II were used as a comparison tool against the TRIPS. (Criterion validity) SNAP-II and SNAPPE-II were evaluated with data from the first 12 h of admission to the NICU after transport. (GA at transport may have been different from GA at birth; therefore, the timing of SNAP-II assessment may vary.) SNAP-II was not used as a sequential measure.	SNAP-II, SNAPPE-II, and TRIPS ROC were not statistically different ($P = .625$) H-L showed good calibration of each instrument. SNAP-II ($P = .29$) SNAPPE-II ($P = .88$) TRIPS ($P = .49$) TRIP–AUC ranged from 0.80 to 0.99 and was most accurate for younger gestations. Overall AUC = 0.80 (95% CI: 0.64-0.95) GA>32 wks–AUC = 0.71 (95% CI: 0.63-0.78) GA <32 wks–AUC = 0.99 (95% CI: 0.85-1) AUC for SNAP-II and SNAPPE-II was not reported.	Observational Single site Small sample size TRIPS score was only measured at one time point, whereas previous studies measured it twice.
9. Nasr et al (2011)	To determine if outborn status is associated with increased mortality for patients with an antenatal diagnosis of congenital diaphragmatic hernia (CDH).	Canada	$N = 140$ Inborn $n = 75$ Outborn $n = 65$	Dx with CDH during antenatal period Derived from all neonates in the CAPSNet (16 pediatric surgical centers) between 2005 and 2008 Inborn/outborn GA 37.7 ± 1.09/37 ± 6.5 ($P = .3$) BW 3079 ± 655/2959 ± 789 ($P = .3$)	Observational Retrospective cohort study	SNAP-II was used to determine severity of illness SNAP-II was used to compare severity of illness between both groups. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	Higher SNAP-II scores were associated with mortality ($P = .005$) NBs in the inborn group (21 [IQR, 7-32]) were sicker than the outborn group. (5 [IQR, 9-12]). ($P = .0001$) Outborn status increased the risk of mortality. (OR 2.8, $P = .04$)	Observational retrospective Inborn and outborn groups were not homogeneous for SNAP-II scores. Potential for critical information to be omitted from the database including prenatal or perinatal risk factors influencing healthcare decisions.

(*continues*)

Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
10. Nakwan et al (2011)	To evaluate the ability of the SNAP-II instrument to predict mortality in neonates with persistent pulmonary hypertension (PPHN)	Thailand	*N* = 41 *Cohorts*: S *n* = 27 Non-S *n* = 14	Dx with PPHN Cohort derived from a single center from June 2008 to March 2010 *Cohorts*: *S/NS* GA 39.4 ± 1.7/39.5 ± 1.0 (*P* = .89) BW 3042 ± 470 3088 ± 477 (*P* = .88) Males = 73.2% SNAP-II 40.6 ± 18.5	Observational Prospective cohort study	The authors divided the SNAP-II scores into categories: Mild <23 Moderate 24-42 Severe ≥43 SNAP-II measured with data from the first 12 h of admission. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II was able to predict mortality for neonates with PPHN. SNAP-II > 43 greatly increased the risk of mortality The subscales of mean blood pressure (*P* = .03), Pao_2 /FIo_2 (*P* < .01), and urine output (*P* = .03) were individual predictors of mortality risk in this sample. Raising the SNAP-II score by 1 point, raised the odds of mortality by 1.04 (95% CI: 1.01-1.07, *P* < .01) SNAP-II scores were significantly higher in nonsurviving neonates (50.1 ± 18.5 vs 35.7 ± 16.8, *P* = .02).	Observational Single center Small sample size Only 9 neonates had a confirmed dx of PPHN by echocardiography Male/females not equally distributed in the sample. Treatments such as extracorporal membrane oxygenation (ECMO) and nitic oxide were not readily available for use in this NICU.
11. Ter Horst et al (2011)	First aim–To assess if a calculation of aEGG amplitudes is consistent with pattern recognition. Second aim—To assess if there is a relationship between SNAP-II scores and aEEGs of premature infants.	The Netherlands	*N* = 38	Cohort derived from a single center from 2/2006 to 2/2007 GA 29.7 (1.4) Range 26-31.8 BW 1340 (380) g SNAP-II 13.5 (7.8)	Prospective observational study	SNAP-II was used to assess if a relationship exists between illness severity and amplitude integrated EEG (aEEG). SNAP-II was used as a measure of initial severity of illness. SNAP-II was assessed with data from the first 24 h of life. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II scores were inversely correlated with the 5th and 50th aEEG (*r* = −0.34, *P* = .0001/*r* = −0.27, *P* = .001) The strongest correlations between the SNAP-II and aEEG were on the first day of life (*r* = −0.5, *P* = .005/*r* = −0.47. *P* = .018) Relationships were the strongest on day 1 and were nonsignificant by day 5.	Observational Single center Small sample size Equipment limitation created maximum of 3 infants daily who could have EEG testing completed; therefore, all newborns were not included that met inclusion criteria. Authors state that infants were still selected at random. This study evaluated the first 5 days of life only. Long-term follow-up is lacking.

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
12. Brindle et al (2010)	To evaluate the impact of blood gas targets on outcomes for neonates with congenital diaphragmatic hernia (CHD)	Canada	*N* = 147 Target *n* = 63 No target *n* = 84	Dx with CHD (64% with a prenatal dx) Derived cohort from the CAPSNet (11 centers) from May 2005 to November 2007 *Cohorts*: Target/no target GA 38 (Median) 37-40 (IQR) /39 (Median) 37-40 (IQR) (*P* > .05) BW 3.0 (1.2-4.4) kg 3.3 (1.5-4.9) kg (*P* > .05)	Observational cohort study	SNAP-II scores were used to establish that the 2 groups were homogeneous for illness severity. SNAP-II was used to account for mortality risk. SNAP-II scores were obtained in the first 12 h of the NICU admission SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	Infants with established targets were less likely to die (hazard ratio = 0.27; 95% CI: 0.11-0.69; *P* < .05) SNAP-II predicted mortality with multivariate analysis (HR = 1.09; 95% CI: 1.07-1.12; *P* < .0001)	Observational study Small sample size Willingness for the neonatologist to establish blood gas parameters may be a proxy for another variable that affects mortality.
13. Miletin et al (2010)	To assess the relationship between serum cortisol and illness severity and organ dysfunction in VLBW neonates. (SNAPPE-II, CRIB, and NEOMOD)	Ireland (Study conducted in Ireland, but one author was from Czech Republic.)	*N* = 38	Cohort derived from single site from November 2006 through June 2007. BW 1.08 ± 0.3 kg GA 27.8 ± 1.9 SNAPPE-II 16 (Median) 0-80 (range)	Prospective observational cohort study	SNAPPE-II, CRIB and NEOMOD instruments were all used. SNAP-II was measured only with the perinatal extension. SNAPPE-II was used as a measure of illness severity to look for relationships between illness severity and serum cortisol levels. SNAPPE-II was measured, but the time frame for data collection was not clearly reported. SNAP-II was not used as a sequential measure.	Correlation noted between serum cortisol and NEOMOD (*P* = .006, value of the correlation was not reported) No relationship was found between serum cortisol and mean blood pressure. No relationship was found between serum cortisol and SVC blood flow (echocardiography)	Observational Single center Small sample size Echocardiography timing varied between 12 and 24 h of life. Timing of the second dose of antenatal corticosteroids was not reported. Urinary free cortisol may be a better marker of adrenal function; however, serum cortisol was measured. Values for the SNAP-II were not reported.

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
14. Mills et al (2010)	To identify perinatal risk factors that may predict outcomes in neonates born with gastroschisis	Canada	$N = 239$	Dx with gastroschisis Sample recruited from May 2005 to May 2008 period across 14 centers within the CAPSNet database GA 36.2 ± 2.1 BW 2566.3 ± 564.7 SNAP-II 9.2 ± 12.3	Observational study	SNAP-II scores calculated within 12 h of birth SNAP-II was used to predict mortality. SNAP-II score was used as a continuous and categorical variable for statistical analysis. SNAP-II was used to predict course of treatment and treatment failure. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II scores predicted the relative risk of mortality (RR = 1.07; 95% CI: 1.0-1.1) SNAP-II scores predicted mechanical ventilation ($P = .03$ as a continuous variable) and ($P = .001$) as a categorical variable for SNAP-II scores >28. TPN need was predicted by SNAP-II scores ($P = .006$ for continuous variable and $P = .001$ for SNAP scores >28). LOS was predicted by continuous SNAP-II scores ($P = .01$). LOS was also predicted by SNAP-II scores between 17 and 28 ($P = .05$) SNAP-II scores >28 ($P = .0003$) SNAP-II scores >28 has a relative risk of surgical closure failure of 4.9 (95% CI: 1.43-16.8)	Observational Short-term outcomes only
15. MA Xiao-lu et al (2010)	To explore respiratory distress in late preterm/term infants and compare severity of illness instruments (SNAP-II and ACoRN–Acute care of at-risk newborns)	China	$N = 503$ Mild RD $n = 237$ Mod RD $n = 227$ Severe RD $n = 39$	Dx with respiratory distress requiring CPAP or ventilator support Cohort derived from 7 centers in China from November 2008 to October 2009. Cohorts: mild, moderate, and severe RD GA 36.7 ± 2.1 36.7 ± 2.4 37.7 ± 2.1 ($P = .032$) BW 2648.1 ± 573.3 2760.7 ± 604.1 3080.6 ± 643.5 ($P = .000$)	Prospective multicenter cohort study	ACoRN was used to stratify levels of respiratory distress. Then SNAP-II was used as a comparison. ACoRN is easier to obtain. It does not need 12 h of data and does not need an arterial blood gas. SNAP-II assessed 12 h after birth. SNAP-II was used to predict mortality. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II scores were noted as a risk factor for mortality via univariate and multivariate analysis. (OR: 1.071; 95% CI: 1.040-1.103; $P < .01$) (Values for univariate analysis not reported.) ACoRN and SNAP-II were correlated ($r = 0.219$, $P < .01$), but ACoRN was not a predictor of mortality.	Observational

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
16. Dammon et al (2009)[a]	To determine the performance of the SNAP-II and SNAPPE-II in extremely low gestational age newborns.	USA	*N* = 1467	Cohort derived from the ELGAN study across 14 centers and 5 states from 2002 through 2004. GA <28 wks 27% 23-24 wks 45% 25-26 wks 29% 27 wks BW not reported All inborn status.	Prospective cohort study	SNAP-II and SNAPPE-II assed with data from the first 12 h of life. SNAP-II and SNAPPE-II were used to predict mortality. SNAP-II and SNAPPE-II were used to compare mortality outcomes between institutions. SNAP-II and SNAPPE-II scores used as dichotomous variables. Arbitrary cutoffs were explored for SNAP-II and SNAPPE-II scores. SNAP-II was not used as a sequential measure.	All infants received zero points for the SNAP-II subcategory for multiple seizures. When evaluating mortality risk by week of gestation, nonsurviving infants always had higher SNAP-II and SNAPPE-II scores compared to surviving infants at the same gestational age. Newborns with a SNAP-II score of ≥30 were 3.5 times more likely to die and newborns with a SNAPPE-II score of ≥45 were 3.9 time more likely to die when controlling for GA. Without adjustment for gestational age, SNAP-II scores ≥30 were 5.9 times more likely to die and SNAPPE-II scores ≥45 were 6.8 times more likely to die. SNAP-II and SNAPPE-II are population-level predictors of mortality. SNAP-II and SNAPPE-II scores demonstrated an inverse relationship with week of gestation.	Observational

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Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
17. Dammon et al (2010)[a]	To assess if SNAP-II and SNAPPE-II scores for extremely low GA newborns (ELGANS) were predictive of neurological sequella.	USA	*N* = 1399	Cohort derived from the ELGAN study across 14 centers and 5 states from 2002 through 2004. GA <28 wks BW not reported All inborn	Observational study	SNAP-II and SNAPPE-II assigned within the first 12 h of life. SNAP-II and SNAPPE-II were used to predict neurological sequella. Dichotomies of SNAP-II (>30) and SNAPPE-II (>45) scores were used. SNAP-II was not used as a sequential measure.	High SNAP-II (>30) and SNAPPE-II (>45) scores were predictive of interventricular hemorrhage (IVH), moderate to severe ventriculomegaly and echodense lesions in cerebral white matter. High SNAP-II and SNAPPE-II did not predict cerebral palsy, positive autism screen, and small head circumference at 24 mo corrected age. SNAP-II and SNAPPE-II were inversely correlated with GA. Discussion concerning whether SNAP-II and SNAPPE-II are part of the causal chain to brain damage or if they are a marker for developmental vulnerability.	Observational study The newborns in the ELGAN study that did not complete the 24-mo follow-up had heterogeneous socioeconomic backgrounds as compared with the group that completed the follow-up. Missing data—Not all neonates in the study participated in every assessment, so the denominator changes between different outcomes of interest.
18. Sundaram et al (2009)	To evaluate the relationship between the SNAP-II score and mortality as well as organ dysfunction in a cohort of newborns with severe sepsis over a 14-day period.	India	*N* = 40 Survivors *n* = 15 Non-S *n* = 25	Dx with severe sepsis and <28 d old GA 30.2 ± 2 BW 1188.3 ± 282.8 Day of onset of septicemia 4 (Median) 3-6 (IQR)	Prospective cohort study	SNAP-II scores were obtained with data for the 12 h following the onset of severe septicemia. SNAP-II was used as a prognostic tool after the dx of sepsis. SNAP-II score was assigned arbitrary cut off values: Mild: 1-20 Moderate: 21-40 Severe: >40 SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II scores > 40 were associated with more dysfunctional organs (3.8 ± 0.4 vs 2.9 ± 0.8; *P* = .001). Median SNAP-II score was higher in babies who died within 14 d of study enrolment (43 [36-53.5] vs 18 [16-37]; *P* <.001). AUC = 0.82 (95% CI: 0.68-0.95; *P* <.001) SNAP-II scores <40 were associated with fewer dysfunctional organs (3.8 ± 0.4 vs 2.9 ± 0.8; *P* = .001) Three category's on the SNAP-II score (MAP <29 mmHg, lowest	Observational study Single center Small sample size A large number of potential participants were excluded from the study. [Inclusion criteria met (*n* = 75), yet 45.9% (*n* = 34) were excluded because of various reasons.]

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
							blood pH, and urine output) demonstrated a statistical difference between neonates who died versus survived ($P = .009$, .009, .01) and organ dysfunction persisted vs improved ($P = .03$, .007, .004), respectively.	
19. Soraisham et al (2009)	To explore the effects of chorioamnionitis on the morbidity and mortality of preterm neonates less than 33 wks' gestation while controlling for initial illness severity.	Canada	$N = 3094$ E-Chorio $n = 477$ NE-Chorio $n = 2617$	Cohort derived from the CNN database among 24 centers from January 2005 through December 2006. *Cohorts*: *E-Chorio* *NE-Chorio* GA 27.7 ± 2.7 29.1 ± 2.4 ($P < .001$) BW 1174 ± 439 1347 ± 460 ($P < .001$) SNAP-II 10 (5-20) 8 (0-14) ($P < .001$)	Observational retrospective cohort study	SNAP-II used as a control to adjust for severity of illness in the neonates. The score was calculated with data from the first 12 h of admission in the NICU. Used the SNAP-II score as continuous and dichotomous variable. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	Mortality was higher for neonates exposed to chorioamnionitis (10.6% vs 6.1%) but did not remain so after controlling for illness severity with the SNAP-II Chorioamnionitis was associated with early sepsis (OR = 5.84; 95% CI: 3.03-11.25) and IVH (OR = 1.6; 95% CI: 1.16-2.21). After controlling for severity of illness, this relationship continued with early sepsis (OR = 5.54; 95% CI: 2.87-10.69) and with severe IVH (OR = 1.62; 95% CI: 1.17-2.24).	Observational retrospective Dx of chorioamnionitis may be difficult and some chart information was not available.
20. Lim et al (2008)	To determine if daily SNAP-II scores identify risk of sepsis, necrotizing enterocolitis, and death.	USA	$N = 141$	Cohort derived from all NICU admission at a single center from July to October 2004. BW 2289 ± 938 g GA 34 ± 4 wks LOS 19 ± 20 d	Prospective observational study	SNAP-II and SNAPPE-II were calculated for the first 12 hours of admission to the NICU. SNAP-II was assessed daily until death or discharge. SNAP-II missing data was assumed to be normal (zero points).	SNAP-II 0 (Median) (85% CI: 0-9) 92% SNAP-II were 0 66% of SNAP-II scores >10 were not related to any adverse event. Only 34% were within 5 d of dx of sepsis or NEC. Majority of the patients with morbidity had a score of 0 within 5 d of the event.	Single center Absence of some variables needed for calculation of the SNAP-II score.

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
						Authors state that illness severity measures are sometimes used to council parents.	Authors advised caution concerning the use of the SNAP-II scores for sequential measurements	
21. Madan et al (2008)	To describe factors associated with patent ductus arteriosus (PDA) and gastrointestinal (GI) complications associated with indomethacin treatment	USA	*N* = 210 PDA closure *n* = 157 PDA no closure *n* = 53 NEC or IP *n* = 32 No NEC or IP *n* = 178	Cohort derived from a single center from 1997 to 2003. Dx with patent ductus arteriosus (PDA) and tx with indomethacin GA All ≤30 26 (mean) BW All <1500 g 915g (mean) SNAP-II 22 (mean)	Retrospective cohort study	SNAP-II Measured at 2 time points: Birth and with the first dose of indomethacin The exact timeframe of data assessed for SNAP-II measurement is not clear. SNAP-II was used to predict treatment failure of PDA closure. SNAP-II was used to predict potential complications including NEC and IP. SNAPPE-II was not measured.	SNAP-II at birth and at first dose of indomethacin was not associated with PDA closure (*P* = .22, *P* = .82) SNAP-II at birth and at first dose of indomethacin was not associated with GI complications (*P* = .24, *P* = .61). As gestational age increased: PDA closure rates increased (OR 1.51 per wk, 95% CI: 1.14-2.01; *P* = .004) GI complication rates decreased (OR = 2.41; 95% CI: 0.52-0.84) Male newborns were more likely to experience GI complications. (OR = 2.41; 95% CI: 1.07-5.45) An association was found between gestational age and ductal closure with indomethacin. (AUC = 0.71; 95% CI: 0.63-0.79)	Observational retrospective Single center Small sample of newborns with PDA closure failure, NEC, or IP.

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Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
22. Figueras-Aloy et al (2007)	To determine if intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, L-selectin, and P-selectin can be used to help diagnosis sepsis To determine if there is a relationship between these markers and severity of illness in septic neonates	Spain	$N = 37$ HC− $n = 10$ HC+ $n = 15$ Control $n = 12$	Dx with R/O sepsis Cohort derived from consecutive admissions in a single center over a 21-mo period. (actual dates not reported) Age of the newborns ranged from within 1 h of birth to 32 d. *Cohorts*: Control HC− HC+ GA 38.5 (37-40) 40 (36-40) 37 (32-39) ($P = .113$) BW 3037 (2625-3835) 3365 (2840-3612) 2350 (1390-3120) ($P = .124$) Day of life at initial blood draw (Median/IQR) 1 (1-1) 2.5 (2-3) 10 (3-14) ($P = .001$)	Prospective observational cohort study	SNAP-II was measured at the moment of highest clinical illness. The exact timeframe of data collection for SNAP-II measurement was not clearly reported. SNAP-II was used to quantify severity of illness for potential septic patients. SNAP-II was used as a comparison tool to assess for relationships between severity of illness and ICAM-1, VCAM-1, L-selectin, and P-selectin. Baseline SNAP-II was not measured upon admission for comparison. SNAPPE-II was not measured.	Soluble ICAM-1 demonstrated a positive correlation ($r = 0.537$, $P = .006$) with SNAP-II scores. ICAM-1 levels >274 μg/L were associated with HC+ sepsis Positive correlation between sICAM-1 and gestation age ($r = 0.623$, $P = .041$) The day of life for the initial blood draw was significantly different between the 3 groups ($P < .001$). Mean day of life was 1 for the control group, 2.5 for the HC− group and 10 for the HC+ group.	Observational Single center Small sample size
23. Kadivar et al (2007)	To determine if the SNAPPE-II instrument is a predictor of neonatal mortality among the neonates admitted in a single NICU in Iran.	Iran	$N = 213$	Recruited September 2003 to August 2004 Mean SNAPPE-II = 21.6 Mean BW = 2479.8 g Mean 5-min Apgar score = 7.71 Day of life 7.6 (0.5) GA 35.8 (0.2) BW 2479.8 (29.4) SNAPPE-II 21.6 (1.1)	Prospective observational	SNAP-II was measured only with the perinatal extension. SNAPPE-II was measured within 12 h of NICU admission. (This was not always the day of birth.) SNAP-II was not used as a sequential measure.	Factors associated with mortality: SNAPPE-II ($P = .04$) 5-min Apgar score ($P = .01$) GA ($P = .03$) BW ($P = .02$) Logistic regression demonstrated that SNAPPE-II and Apgar at 5 min were significant predictors of mortality. (Chi-square results not reported.)	Observational Single-site study

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Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
24. Mathur et al (2007)	To assess the ability of new tool (TOPS) to assess for illness severity in neonates and to compare the TOPS instrument to SNAP-II.	India	*N* = 175 NS *n* = 60 Survivor *n* = 115	Cohort derived from outborn infants transported to a tertiary NICU in India from a single center from March to December 2003. *Cohorts*: NS Survivor Age at admission 5.57 (0.89) 7.01 (0.72) (*P* = .14) Weight at admission 2045 (693) 2193 (709) (*P* = .29) GA 37.4 (4.83) 36.5 (4.25) (*P* = .25)	Prospective observational cohort study	SNAP-II was determined with data from the first 12 h of admission SNAP-II was used as a predictor of mortality. SNAP-II was used as a comparison tool. (Criterion validity) SNAP-II was not used as a sequential measure. SNAPPE-II was not measured. TOPS score was assessed upon NICU admission. *TOPS* temperature Oxygenation Proxy for perfusion Blood sugar	TOPS and SNAP-II performed similarly. TOPS AUC = 0.89 SNAP-II AUC = 0.88 Goodness of Fit Test was 0.75 (TOPS)/ 0.80 (SNAP-II) TOPS is a simplified score and eliminates the need for expensive equipment	Observational Single center
25. Zupancic et al (2007)	To revalidate the performance of the SNAP-II and SNAPPE-II	USA Canada	*N* = 9897 ≤1500 g (*n* = 5617) >1500 g (*n* = 5280)	The cohort was derived from 58 self-selected from the Vermont Oxford Network from January to December 2002. *Cohorts*: ≤1500 g >1500 g Total BW 1021 ± 305 2826 ± 783 2375 ± 1048 GA 28 ± 3 36 ± 3 34 ± 5 SNAPPE-II 28 9 13 SNAP-II (total sample) 11.7 (mean) 5 (median)	Prospective observational study	SNAP-II was calculated in the first 12 h of admission. SNAP-II was used as designed as a measure of illness severity. SNAP-II was being compared with the VON-RA. SNAP-II was not used as a sequential measure.	Discrimination of SNAP-II and SNAPPE-II was best for neonate's ≤ 1500 g. Discrimination of the instrument improved when congenital anomalies were accounted for. Combined weight SNAP-II AUC = 0.86 SNAPPE-II AUC = 0.89 ≤1500 g SNAP-II AUC = 0.82 SNAPPE-II AUC = 0.86 >1500 g SNAP-II AUC = 0.79 SNAPPE-II AUC = 0.82 H-L *P* values ranged from .184 to .965	Observational No reliability data reported.

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
26. Lam et al (2006)	To describe the cost for hospital care for neonates diagnosed with CDH. To compare costs between neonates with CDH vs non-CDH in 2 cohorts with similar SNAP-II scores upon admission. To identify any correlations between the SNAP-II score and cost for NICU care.	Canada	*N* = 32 CDH *n* = 32 Control *n* = 27	Cohort derived from a single-center NICU/PICU between 1999 and 2003. The cohort of interest included patients diagnosed with CDH. The control group consisted of patients with similar SNAP-II scores. Mean BW 3.1 kg Mean GA 38.2 wks SNAP-II 12.5 (mean) 13 (median) 0-34 (range)	Retrospective cohort study	SNAP-II scores were completed within 12 h of NICU admission. SNAP-II was used as a control to ensure the 2 groups were homogeneous for severity of illness. SNAP-II scores were also used to group surviving infants into 3 terciles of risk. Group 1 (0-5) Group 2 (6-23) Group 3 (>23) SNAP-II was not used as a sequential measure.	Admission SNAP-II score correlates to the total cost of care for the neonate with CDH. (The actual correlation is not reported.) Mean total cost per CDH survivor = $54 102 (range $9608-$244 734) Mean total cost per nonsurvivor -CDH was $9761 (range $943-$25 888) Mean total cost for control group (non-CDH) was $13 722 (range = $1544-$83 945) CDH cohort vs the control group had significantly greater costs per survivor (*P* = .002) and longer length of stay (*P* = .006)	Single center Small sample size Underestimation of costs due to (1) unavailability of some provider costs, (2) estimation of nursing costs based on units of service vs actual salary, and (3) cost of continuing care after discharge is unavailable.
27. De Felice et al (2005)	To evaluate the relationships among histologic chorioamnionitis (HCA), illness severity, and outcomes in a sample of very low BW (VLBW) infants.	Italy	*N* = 116 HCA+ *n* = 67 HCA− *n* = 49	Cohort derived from 2 centers in Italy. *Cohorts*: HCA+ HCA− BW 928 ± 322 g 1044 ± 264 (*P* = .001) GA 26.91 ± 2.61 29.63 ± 2.29 (*P* = .0001)	Prospective observational study	SNAP-II and SNAPPE-II were assessed during the first 12 h of admission. SNAP-II and SNAPPE-II were used to assess severity of illness and mortality. SNAP-II and SNAPPE-II along with other illness severity indexes were used to help predict the possibility of HCA. Comparisons between the different illness severity tools were made.	HCA+ compared to HCA− status was associated with: Earlier GA at birth (*P* < .0001) Lower BW (*P* = .0010) Higher illness severity scores (*P* ≤ .0001) Increased mortality rate (*P* = .0018). HCA was an independent predictor of severe illness. SNAP-II >22 (OR = 43.05; 95% CI: 11.9-155.7; *P* < .0001) SNAPPE-II >42 (OR = 48.95; 95% CI: 10.18-235.4; *P* <.0001) CRIB >5 (OR = 21.37; 95% CI: 6.24-73.21)	Observational Two study centers Small sample size

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
						Instruments utilized included SNAP-II, SNAPPE-II, CRIB, CRIB-II, and NTISS. SNAP-II was not used as a sequential measure.	CRIB-II >10 (OR = 56.17; 95% CI: 6.75-467.2)	
28. Skarsgard et al (2005)	To validate the SNAP-II score as a predictor of mortality in a sample of neonates diagnosed with CDH. To compare the SNAP-II with the new predictive equation developed by the Congenital Diaphragmatic Hernia Study Group (CDHSG).	Canada	*N* = 88	Dx with CDH The cohort was derived from the 19 507 neonates admitted through the CNN (17 centers) from January 1996 through October 1997. GA 37.4 ± 3.3 BW 2939 ± 735	Observational retrospective	SNAP-II was measured with data collected during the first 12 h of admission. SNAP-II was used as a measure of illness severity. SNAP-II was compared with the performance of a new research instrument (CDHSG). SNAP-II measured as a continuous variable. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	SNAP-II (OR 1.057; 95% CI: 1.019-1.097) and GA (OR = 0.838; 95% CI: 0.703-1.000) were predictive of mortality. AUC/H-L Gestational age 0.68/0.75 SNAP-II 0.76/0.7 Combined Model with GA and SNAP-II 0.81/0.88 CDHSG Model 0.83/0.06	Observational retrospective Small sample size CDH was defined by the *ICD-10* code 456.6, which could be used for a variety of defects.
29. Figueras-Aloy et al (2004)	To determine if plasma endothelin-1 (ET-1) is associated with signs and symptoms of sepsis in newborns.	Spain	*N* = 35 HC− *n* = 13 HC+ *n* = 22	Dx with sepsis Cohort derived from single-center admissions from March 1998 to March 2000. *Cohorts*: HC− HC+ GA (Median/IQR) 40 (39-40) 32 (30-38) (*P* = .002) BW (Median/IQR) 3450 (3120-3660) 1630 (1230-28 000) (*P* < .001)	Observational Prospective cohort study	SNAP-II was measured at the moment of highest clinical illness. The exact timeframe of data collection for SNAP-II measurement was not clearly reported. SNAP-II score was used to assess severity of illness specifically for the septic newborn.	SNAP-II scores were higher in the HC+ newborns compared with newborns who were HC− The total SNAP-II scores were correlated with ET-1 (*r* = 0.373; *P* = .027). Concentrations of ET-1 rose significantly as SNAP-II subcategories: blood pressure (*P* = .030), pH (*P* = .048), seizures (*P* = .010), and urine output (*P* = .013) increased.	Observational Single center Small sample size

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Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
						SNAP-II was used as a comparison tool to assess for relationships between severity of illness and plasma endothelin-1 (ET-1)	The most accurate subcategories of the SNAP-II were blood pressure ($R^2 = 0.519$, accuracy = 91.4), pH ($R^2 = 0.649$, accuracy-85.7), and urine output ($R^2 = 0.711$, accuracy = 91.4). The least accurate subcategory was Po_2/Flo_2 ($R^2 = 0.453$, accuracy = 60%).	
30. Lee et al (2003)	To examine the variation in mortality occurrences within 7 d of admission for neonates < 32 wks' gestation.	Canada	*N* = 5192 Day admit *n* = 2061 Night admit *n* = 3131	Preterm cohort derived from admissions to the CNN NICUs between January 1996 and October 1997. *Cohorts*: Day admit Night admit GA Range = 24-32 29.2 ± 2.4 29.0 ± 2.5 (*P* > .05) BW 1340 ± 462 1330 ± 474 (*P* > .05) SNAP-II 12.0 ± 13 13.0 ± 13.5 (*P* < .01)	Prospective observational cohort study	SNAP-II was measured with data collected during the first 12 h of admission. SNAP-II scores were used as risk adjustments for the day vs night admission. SNAP-II was used to assess for homogeneous groups. SNAP-II was not used as a sequential measure. SNAPPE-II was not measured.	Mortality odds were 60% higher in NICU night admissions as compared to day time admissions. Factors that predicted early neonatal death included male, outborn status, Apgar score <7 at 5 min of life, congenital anomalies, early gestations, high SNAP-II scores. Night admission (OR = 1.6) and in-house neonatologist at night (OR = 0.6) predicted early mortality. Mortality rates were significantly higher at night (5.4% vs 4%; *P* < .05). SNAP-II scores were significantly different between daytime (12.0 ± 13) and nighttime (13.0 ± 13.5) admissions.	Observational study Delivery room deaths were not included; therefore, the mortality rate is underestimated. Obstetrical care data were not available. This omission of information can skew the data as perinatal conditions will affect neonatal outcomes. Data on nursing experience between shifts were not available and controlled for. Authors questioned if the 12-h data collection period could be confounded by treatments or quality of care during the initial hours of life instead of initial illness severity alone.

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Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
31. Figueras-Aloy et al (2003)	To determine variation in plasma nitrite/nitrate and endothelin-1 in neonatal sepsis.	Spain	*N* = 128 Control *n* = 68 HC− *n* = 35 HC+-Mod *n* = 21 HC+ Severe *n* = 4	Dx with sepsis and control group without sepsis. Cohort derived from a single center from 1998 to 2000. Newborns ranged in age from 1 to 15 d. *Cohorts*: Control HC− HC+ Mod HC+ Severe GA 37.8 (2.0) 38.2 (2.8) 35.1 (4.8) 29.8 (2.1) (*P* < .001 for all except 1 and 2) BW 2995 (602) 3071 (717) 2343 (981) 1336 (439) (*P* < .001 for all except 1 and 2) SNAP-II None for controls 1.1 (3.8) 7.1 (10.7) 73.7 (31.8) (*P* < .001) SNAPPE-II None for controls 1.4 (4.2) 7.7 (10.9) 73.7 (31.8) (*P* < .001)	Prospective cohort study	SNAP-II and SNAPPE-II were assessed when the newborn displayed the greatest severity of illness from sepsis. The exact timeframe of data collection for SNAP-II and SNAPPE-II measurement was not clearly reported. SNAP-II was used as a comparison tool to assess for relationships between severity of illness, nitrite/nitrate, and plasma endothelin-1 (ET-1). SNAP-II scores were used to stratify patients according to severity of illness levels. SNAP-II was not used as a sequential measure.	Endothelin-1 and SNAP-II were positively correlated (*r* = 0.305; *P* = .018). SNAPPE-II and endothelin-1 were positively correlated (*r* = 0.288; *P* = .026).	Observational study Single center Control and study groups were not homogeneous for GA and BW. SNAP-II not assessed in the control group, so illness severity homogeneity/heterogeneity of the sample is unknown.

(*continues*)

Table 1. **Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)**

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
32. Zardo et al (2003)	To compare birth weight and illness risk scores for prediction of neonatal mortality	Brazil	$N = 494$ Survivor $n = 450$ NS $n = 44$ (8.9%)	Cohort derived from NICU admissions in a single center from March 1997 to June 1998. *Cohorts*: Survivor NS BW 2354 g (mean for all neonates) 2418 (median) 1775-3070 (IQR) 860 (median) 643-1690 (IQR) GA 36 (mean)	Cohort/ retrospective cross-sectional study	SNAP, SNAPPE, and birth weight were measured prospectively. Data were collected with the first 24 h after admission. SNA-P-II, SNAPPE-II, and CRIB, were measured retrospectively upon chart review. SNAP-II and SNAPPE-II were assessed using data collected within the first 12 h after admission. All illness severity measures were used as comparisons to determine the best prediction of mortality. SNAP-II was not used as a sequential measure.	All risk scores performed better than BW alone (AUC = 0.81). AUCs SNAP0.85 SNAPPE 0.90 SNAP-II 0.88 SNAPPE-II 0.91	Observational retrospective Single center
33. Chien et al (2002)	To determine the ability of the SNAP-II to improve prediction of grade III or IV IVH and chronic lung disease (CLD).	Canada	$N = 4226$ CLD $N = 4226$ IVH $N = 3778$ (77% had cranial U/S for evaluative)	GA ≤32 wks Cohort derived from admissions to 1 of 17 Canadian NICUs in the CNN between 1996 and 1997. Cohorts: IVH CLD BW 1190 ± 426 1390 ± 457 GA 29 ± 2 29 ± 2 SNAP-II 14 ± 13 11 ± 11	Prospective observa-tional	SNAP was used as the "criterion" to assess for criterion validity for the SNAP-II. SNAP-II was used to predict outcomes including IVH and CLD. SNAP-II was assessed using data collected within the first 12 h after admission. SNAPPE-II was not measured.	Prediction of IVH: SNAP AUC = 0.73 ± 0.01 $\chi^2 = -222$ SNAP-II AUC = 0.73 ± 0.02 $\chi^2 = -219$ Prediction of CLD SNAP AUC 0.74 ± 0.01 $\chi^2 = 381$ SNAP-II AUC = 0.78 ± 0.01 $\chi^2 = 470$ In model with gestational age, small for gestational age and SNAP-II the AUC improved. (IVH 0.78/CLD 0.82). Goodness of fit was demonstrated with a H-L (IVH $P = .16$/CLD $P = .51$)	Observational Limitations of the SNAP-II: It takes 12 h to complete It may measure initial illness severity and treatment response. Discrepancy between reported GA for IVH group (29 vs 31 wks).

(*continues*)

Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
34. Chien et al (2001)	To examine if newborns born outside of a tertiary care facility have an increased risk of morbidity and mortality after controlling for illness severity and perinatal risk factors for preterm infants	Canada	*N* = 3769 Outborn *n* = 605 (16%) Inborn *n* = 3164	Cohort was derived from preterm infants (≤32 wks) admitted to a NICU in the CNN from January 1996 to October 1997. *Cohorts*: Inborn Outborn GA 20-26 wk = 21%/27% 27-28 wk = 17%/18% 29-30 wk = 24%/23% 31-32 wk = 38%/32% SGA 6%/2% SNAP-II 0-9 points 53%/45% 10-19 points 23%/28% 20-29 points 12%/13% ≥30 points 12%/14%	Prospective observational cohort study	SNAP-II was measured within the first 12 h of admission to the NICU. SNAP-II was used to measure illness severity. SNAP-II was used to compare for homogeneity vs heterogeneity illness severity between the 2 groups.	Outborn infants had statistically higher incidence of mortality, IVH, CLD, PDA, respiratory distress, and hospital-acquired infections. After controlling for initial illness severity, the statistical significance remained for everything above except CLD. Outborn infants had higher SNAP-II scores compared to inborn infants.	Observational Mortality is underestimated because delivery room deaths and transport deaths were not included in the study.

(*continues*)

Table 1. Review of the relevant research articles for utilizing the score for neonatal acute physiology (*Continued*)

Authors and date of publication	Purpose	Country of origin	Sample size (*N*)	Sample characteristics	Research design	SNAP-II	Findings	Limitations and potential for bias
35. Richardson et al (2001)	To empirically derive and validate the second-generation Score for Neonatal Acute Physiology (SNAP-II) and the second-generation Score for Neonatal Acute Physiology-Perinatal Extension (SNAPPE-II)	USA Canada	$N = 25\,429$ Derivation cohort $n = 10\,819$ Canada ($n =$ 5588) California ($n = 5530$) New England ($n = 3492$)	Cohort was derived from newborns of all birth weights and gestational age admitted to the NICU in 30 different study sites from 3 neonatal networks (Canada, California, New England). Newborns were recruited from January 1996 to October 1997.	Prospective observational	SNAP-II and SNAPPE-II were assessed with data from the first 12 h of admission. Points for each subcategory of the SNAP-II were empirically derived from the beta weights in the logistic model. SNAP was used as a control for group homogeneity. SNAP was used as the criterion for criterion validity of the SNAP-II.	Total sample AUC = 0.91 ± 0.01 Goodness of Fit 0.90 Correlation between SNAPPE and SNAPPE-II 0.91 Birth weights <1500 g AUC = 0.85 ± 0.01 Goodness of fit = 0.86 SNAPPE and SNAPP-II ($r = 0.86$) Birth weights ≥1500 g AUC = 0.87 ± 0.03 Goodness of fit = 0.63 Correlation between SNAPPE and SNAPPE-II $r = 0.88$ ≥1500 g = 0.87 ± 0.03 H-L = 0.90.	Observational Some values of 0 were assigned because of the unavailability of test results. In the absence of a test result, tests were assumed to be normal (zero points).

Abbreviations: ACoRN, acute care of at risk newborns; aEEG, amplitude integrated EEG; AUC, area under the receiver operator characteristic curve; BW, birth weight; CAPSNet, Canadian Pediatric Surgery Network; CC, cardiac center; CDH, congenital diaphragmatic hernia; CDHSG, Congenital Diaphragmatic Hernia Study Group; CNN, Canadian Neonatal Network; Dx, diagnosed; E-Chorio, exposed to chorioamnionitis; ELGAN, extremely low gestational age newborns; ET-1, plasma endothelin-1; GA, gestational age in weeks; HC−, hemoculture negative; HCA−, histologic chorioamnionitis negative; HCA+, histologic chorioamnionitis positive; HL, Hosmer-Lemeshow goodness of fit test; HM+, Hemoculture positive; ICAM-1, intercellular adhesion molecule; IP, intestinal perforation; IQR, interquartile range; IVH, Intraventricular hemorrhage; LOS, length of stay; Mod, moderate; NCC, noncardiac center; NEC, necrotizing enterocolitis; NE-Chorio, not exposed to chorioamnionitis; non-S, nonsurvivor; NS, nonsurvivor; NSC, nonsurgical candidate; NTISS, Neonatal Therapeutic Intervention Scoring System; PSC, potential surgical candidates; RD, respiratory distress; S, survivor; SGA, small for gestational age; SNAP-II, Score for Neonatal Acute Physiology-II; SNAPPE-II, Score for Neonatal Acute Physiology Perinatal Extension-II; R/O, rule out; Tx, treatment; VCAM-1, vascular cell adhesion molecule; VLBW, very low birth weight; VON-RA, Vermont Oxford Network risk adjustment.

[a]Same study; multiple publications (ELGAN study).

nonresearch articles. Fourteen studies were excluded including 12-conference meeting or poster abstracts, one commentary, and one letter to the editor. This left a total of 36 papers for full review; however, one additional study was eliminated because the SNAP-II instrument was not used as an instrument for the study. Therefore, a total of 35 articles remained for inclusion in this review.

Characteristics of included studies

The SNAP-II is one of the most widely used measurement instruments used to operationalize the concept of neonatal illness severity. It has been used internationally in countries, including the United States,[15–19] Canada,[20–32] Spain,[33–35] Italy,[36,37] Brazil,[12,38] India,[39,40] France,[41] Thailand,[42] the Netherlands,[43] Ireland,[44] China,[45] and Iran.[46] Two studies had cohorts that were derived from populations across 2 countries, including the United States and Canada.[6,47] It is important to note that of the 35 studies meeting inclusion criteria, 20 studies were conducted in Canada, the United States, or both. This includes the initial study of derivation and validation of the SNAP-II measurement tool.[6]

Research studies were almost equally divided between multicenter and single-center studies. Three large neonatal networks, including the Canadian Pediatric Surgery Network,[20,21,24–26] Canadian Neonatal Network,[6,22,27,29–32] and the Vermont Oxford Network,[6,16,17,47] participated in several studies. The sample sizes varied greatly among the studies as shown in Table 2. Samples ranged from the smallest sample of 32[28] to the largest cohort of 25 429.[6] Nine studies included sample sizes fewer than 100[15,28,33,34,36,39,42–44]; however, there were 8 larger studies with sample sizes more than 1000.[6,16,17,27,30–32,47] Newborns in the studies varied greatly across gestational age and birth weight. While the 2 large validation studies included newborn cohorts across the entire continuum of gestational ages and birth weights,[6,47] most studies focused on preterm, late preterm, or term newborns. Some studies specifically focused on very low-birth-weight newborns[19,44,48] and extremely low-gestational-age newborns[16,17] which are premature populations with expected risk of illness severity. Not only was the SNAP-II used across all gestational ages and birth weights, it was also used across many specific morbidities, including congenital diaphragmatic hernia (CDH),[15,21,24,25,28,29] chorioamnionitis,[27,48] sepsis,[33–36,39] gastroschisis,[20,26] patent ductus arteriosus (PDA),[19,22] persistent pulmonary hypertension,[42] and respiratory distress.[45]

Illness severity as a predictor of mortality

Illness severity is closely tied with the concept of mortality risk. Clearly, as neonatal severity of illness increases, physiologic instability increases, and therefore the risk of neonatal death also increases. Not all of the included studies included analysis for this specific point, but much evidence is available to support that higher illness severity does lead to a higher mortality rate. Many of the included studies evaluated and reported the ability of the SNAP-II instrument to predict mortality in their study sample. Some researchers used the area under the receiver operating characteristic curve (AUC) to demonstrate the sensitivity and specificity of the SNAP-II. A result of 1 would be perfect discrimination, while a result of 0.5 would be completely random. The AUCs reported in these studies included 0.76,[29], 0.77,[15] 0.81,[41] 0.82,[39,47] and 0.88.[12,40] Zupancic et al[47] further divided the study sample into birth weight more than and less than 1500 g and found that the AUC was more accurate for the smaller babies (AUC 0.82 vs 0.79). Each of the results in the studies would be considered acceptable to good. It is interesting to note that the seminal article for the SNAP-II and SNAPPE-II instrument did not report an AUC for the SNAP-II, but reported only an AUC of 0.91 for the SNAPPE-II instrument across all birth weights.[6]

Some researchers used odds ratios (ORs) to describe how the risk of mortality increased along with increasing illness severity. Nakwan et al[42] found that in a sample of neonates with persistent pulmonary hypertension, the odds of death increased by 1.04 for every 1-point increase in the SNAP-II score (OR = 1.04; 95% CI: 1.01-1.07; $P < .01$). Another study described the OR of mortality for newborns with respiratory distress (OR = 1.071; 95% CI: 1.040-1.103; $P < .01$). The third and final study described the increased risk of mortality in a cohort of neonates with CDH (OR = 1.057; 95% CI: 1.019-1.097).[29] Risk of mortality was also described as a hazard ratio (HR = 1.09; 95% CI: 1.07-1.12; $P < .0001$)[25] as well as the relative risk of mortality (RR = 1.07; 95% CI: 1.0-1.1).[26] Nasr and Langer[24] demonstrated that higher SNAP-II scores are associated with mortality ($P = .005$). Wilson et al[21] demonstrated that illness severity scores (SNAP-II) predicted neonatal mortality ($P < .001$). Sundaram et al[39] found that median SNAP-II scores were higher in the nonsurviving cohort (43 [36-53.5] vs 18 [16-37]; $P < .001$). Some studies used cutoff values to define mortality risk. For example, Dammann et al[16] found that an SNAP-II score greater than 30 demonstrated that the newborn was 3.5 times more likely to die. Furthermore, when they adjusted for gestational age, the risk increased to 5.9.[16]

Illness severity and morbidity

Illness severity and morbidity are also closely related. Neonates who are sicker manifest increased illness severity scores and greater organ dysfunction.[34,39] Neonates who are extremely low gestational age are

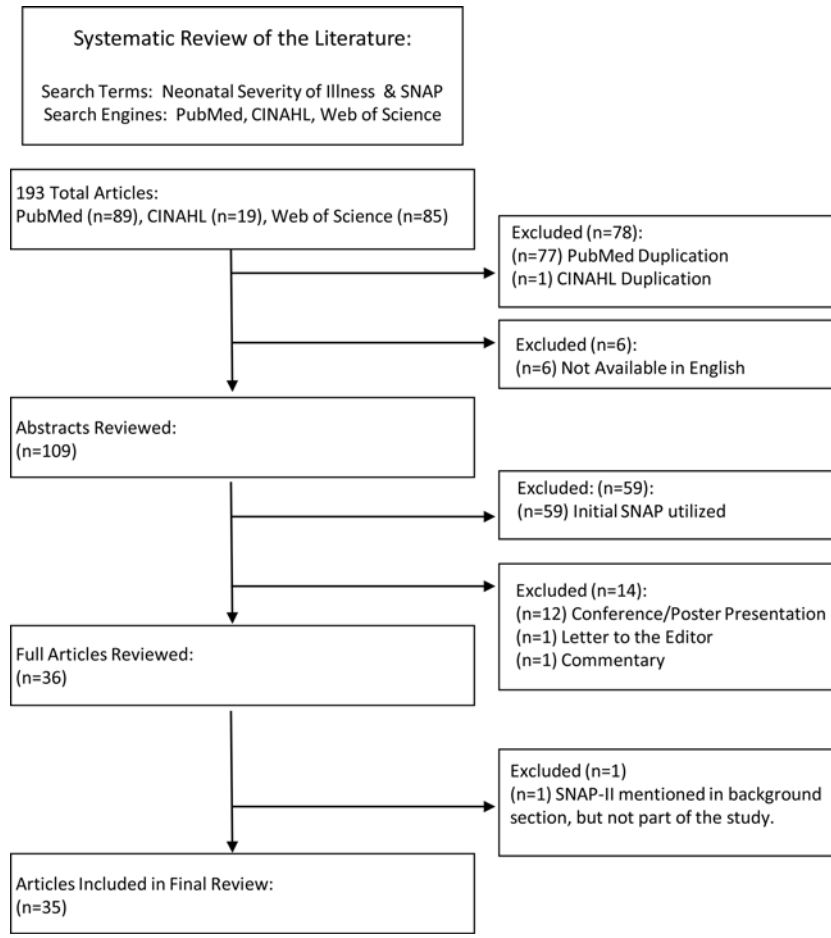

Figure 1. Flowchart for the inclusion of articles in the review of the literature.

also very much at risk for increased illness severity due to immaturity.[16,17] When considering the relationship between illness severity and morbidity for neonates, researchers are also interested in the possibility of illness scores helping predict future morbidity, future treatment needs, and treatment outcomes.

Prediction of future morbidity

Critically ill newborns have common illnesses that occur perhaps because of immaturity or illness severity such as intraventricular hemorrhage (IVH) and necrotizing enterocolitis. Dammann et al[17] found that SNAP-II scores greater than 30 were predictive of IVH and ventriculomegaly and echodense lesions in the brain; however, they did not see a relationship with cerebral palsy, autism, or microcephaly at 24 months corrected age of life. Chien et al[31] found that the SNAP-II performed similarly to the original SNAP instrument and was able to predict IVH (AUC 0.73 $\pm$ 0.02, $\chi^2 = 219$) and chronic lung disease (AUC 0.78 $\pm$ 0.01 $\chi^2 = 470$).

Table 2. **Sample size for included studies using the SNAP-II**

Sample size between 1 and 49	15, 28, 33, 34, 39, 42, 43, 44
Sample size between 50 and 99	29, 36
Sample size between 100 and 499	12, 18, 19, 21, 23, 24, 25, 26, 35, 37, 38, 40, 46
Sample size between 500 and 999	20, 22, 41, 45
Sample size between 1000 and 4999	16, 17, 27, 31, 32
Sample size between 5000 and 9999	30, 47
Sample size $\geq$10 000	6

Treatment needs

One study looked at severity of illness as a means to predict treatment needs for severely ill neonates. Specifically, Coleman et al[15] found that 78% of CDH patients with SNAP-II scores greater than 25 required extracorporeal membrane oxygenation. Furthermore, SNAP-II scores were able to predict the use of extracorporeal membrane oxygenation (AUC 0.76; $P = .003$).

Treatment outcomes

A major area of focus is the relationship between illness severity and treatment outcomes. Wilson et al[21] evaluated surgical treatment outcomes of CDH patients. He used the SNAP-II scores to compare the groups of patients offered surgical treatment and those who were not. Since more than 80% of the surgical cases with SNAP-II scores between 30 and 39 survived, and the potential surgical candidates had a 100% mortality rate, the authors were advocating for more specific guidelines of when to withhold surgical treatment from the newborn.[21] Nasr and Langer[24] worked to compare illness severity among CDH neonates who were inborn versus outborn, indicating whether the neonate was born in that facility or whether the newborn was born in another facility and later transported to the NICU. Although the inborn group was sicker than the outborn group (21 [IQR, 7-32] vs 5 [IQR, 9-12]; $P = .0001$]; outborn status was still associated with increased risk of mortality (OR = 2.8; $P = .04$).[24] This seems to indicate that perhaps the quality of care in referral centers is not as optimal as within a tertiary center that routinely cares for the most critically ill infants. Capasso et al[36] focused on outcomes of septic newborns who did and did not receive immunoglobulin along with antibiotic therapy. The SNAP-II was used to demonstrate that the groups were homogeneous for severity of illness prior to comparison of the outcomes with varying treatments. The weakness of this study is that they did not clearly report when SNAP-II scores were assessed.[36] Madan et al[19] sought to discover if severity of illness was related to successful PDA treatment; however, she discovered that treatment success or failure was related to gestational age. As gestational age increased, PDA closure rates increased (OR = 1.51 per week; 95% CI: 1.14-2.01; $P = .004$) and gastrointestinal complication rates decreased (OR = 2.41; 95% CI: 0.52-0.84).[19]

Illness severity as a control

As noted earlier, neonatal illness severity is a predictor of mortality and morbidity and because of this influence illness severity must be controlled when assessing outcomes between cohorts within and among NICUs. As the need for evidence-based practice continues, staff nurses will be called on to participate in more performance improvement projects as well as research studies. Accounting for and controlling for illness severity when evaluating outcomes in the NICU are a critical step to ensure accurate data interpretation. Eight of the included studies used the concept of illness severity, operationalized by the SNAP-II scores, as a means to establish group homogeneity or heterogeneity for illness severity before assessing outcomes between the groups. Included studies used illness severity as a control between septic newborns receiving antibiotics and immunoglobulin versus antibiotics alone,[36] newborns receiving surgical ligation for a PDA at a cardiac versus noncardiac pediatric surgical center,[22] newborns who had documented specific blood gas targets versus those who did not have specific blood gas targets established,[25] neonates admitted to the NICU during the daytime versus nighttime,[30] and finally 2 studies focused on inborn versus outborn status for neonates.[24,32] One study used illness severity scores along with birth weight to match the control group to a group of neonates who were diagnosed with CDH. Since the purpose of the study was to compare costs between CDH and non-CDH patients, it was important to ensure that homogeneous samples were recruited for the comparison to be accurate.[28] Finally, the extremely low-gestational-age newborn study used severity of illness, operationalized by SNAP-II scores, to adjust for NICUs that had a greater percentage of sicker newborns as this would skew the mortality rates for comparison.[16]

SNAP-II scores have also been used as a control when evaluating relationships between other variables. For example, Soraisham et al[27] found a relationship between chorioamnionitis and early sepsis (OR = 1.6; 95% CI: 1.16-2.21) and IVH (OR = 1.6; 95% CI: 1.16-2.21). After controlling for illness severity, the relationships remained (sepsis: OR = 5.54; 95% CI: 2.87-10.69; and IVH: OR = 1.62; 95% CI: 1.17-2.24).

Illness severity on the first day of life

Most of the studies focused on assessing initial illness severity on the first day of life. Clinically this makes sense as one is establishing initial risk at birth. Specifically, this review seeks to establish the utility of the SNAP-II instrument, but it is important to note that many times when the researchers desire to report initial illness severity, they will report the SNAP-II with the perinatal extension (SNAPPE-II). This instrument accounts for 3 additional perinatal risk factors that will remain constant. That is why this is assessed only at 1 time point and not sequentially. Furthermore, most of the studies used a 12-hour data collection window for the SNAP-II score per the initial instrument design.[6,16,18,20,25–32,41,42,45,47,48] However, 3 studies

expanded the data collection period to 24 hours.[15,23,43] Finally, 3 studies did not clearly report when the assessment was done and how many hours were used for the data collection window.[21,22,36]

Illness severity at later time points

Conceptually, illness severity is not only appropriate to evaluate on the first day of life. In fact, illness severity is something that will change over time. This was a primary reason why the author of the instrument separated the SNAP-II from the SNAPPE-II. The SNAP-II measures the physiologic state of the newborn and has the ability to capture the continuum of illness severity as it relates to physiologic instability. Therefore, it makes sense that a measurement instrument is needed that can quantify illness severity across the entire NICU length of stay. However, only 8 studies included severity of illness measurements after the first day of life. Two of those studies included more than 1 measurement; therefore, they will be discussed in the following section.

Two of the studies focused on illness severity assessment after a transport.[38,40] Although the assessment of severity of illness could occur on the first day of life, oftentimes the assessment occurred later (gestational age at birth 35.3 vs gestational age at transport 35.7). Both studies also compared another instrument for severity of illness against the SNAP-II score. One study demonstrated that the SNAP-II, SNAPPE-II, and TRIPS (The Transport Risk Index of Physiologic Stability) performed equally well ($P = .625$).[38] The goodness of fit was also tested across models and demonstrated a good fitting model using the HL goodness of fit (SNAP-II, $P = .29$; SNAPPE-II, $P = .88$; TRIPS, $P = .49$).[38] The second study split the sample into surviving and nonsurviving neonates. The mean age of transport and subsequent admission to the NICU was 7.01 and 5.57 days, respectively, meaning that these assessments took place sometimes 5 and 7 days after birth. It is important to note that both instruments performed well. The AUC for the SNAP-II and TOPS (temperature, oxygenation, proxy for perfusion—capillary refill, and sugar—blood sugar) was .88 and .89, respectively.

The remaining 4 studies dealt with the assessment of illness severity with septic newborns. Sundaram et al[39] sought to measure severity of illness for 12 hours after the onset of septicemia. The median age of these study participants was 4 days with an interquartile range of 3 to 6. Although the severity of illness assessment (SNAP-II) scores were delayed by 4 days for most babies, this study still demonstrated the ability to predict mortality (AUC 0.82; 95% CI: 0.68-0.95).[39] This study also demonstrated that with SNAP-II scores more than 40, there was more organ dysfunction (3.8 ± 0.4 vs 2.9 ± 0.8; $P = .001$).[39] This supports that the SNAP-II instrument was able to discriminate between varying levels of severity of illness. The final 3 articles sought to measure severity of illness at the highest level of clinical illness.[33–35] The participants in the studies ranged in age between 1 and 15 days,[35] within 2 days of sepsis diagnosis (range of diagnosis = 3-264 hours),[34] and between 1 hour and 32 days.[33] There is much diversity within the actual day of assessment for these studies. Not only is there variation among the 3 studies, but also there is variation within each study. The main purpose of these 3 studies was to assess relationships between SNAP-II scores and other biomarkers that could potentially provide additional information about illness severity.

Illness severity as a sequential measure

The main purpose of this article was to synthesize the available evidence measuring severity of illness prospectively. Of 35 studies, this review found only 2 studies that measured severity of illness over time. The first study measured the concept at 2 time points. Specifically, the author sought to determine whether there was a relationship with illness severity and outcomes associated with the treatment of PDA closure and indomethacin treatment.[19] SNAP-II scores were measured at birth and then again with the first dose of indomethacin administration. No relationship was found between SNAP-II scores at either time point (birth and with first dose of indomethacin) related to failed closure of the PDA ($P = .22$; $P = .82$) or gastrointestinal complications ($P = .24$; $P = .61$).[19] The relationships that they found indicated the critical influence that gestational age plays when considering treatment success and treatment complications for this population.

The final study that measured severity of illnyesess over several time points used initial severity of illness scores with the SNAP-II and SNAPPE-II for the first 12 hours of life and then continued to measure daily SNAP-II scores until the baby was discharged or died. The authors were specifically evaluating the relationship between severity of illness as measured by the SNAP-II and sepsis, necrotizing enterocolitis, and death. The study failed to demonstrate a relationship between SNAP-II scores as an accurate predictor of these later adverse events. In fact, results demonstrated that the majority (66%) of the SNAP-II scores greater than 10 were not related to any adverse events.[18] And, the majority of patients who experienced a complication had a score of 0 within 5 days of the event. Furthermore, 92% of the total SNAP-II scores were 0; thus, the median SNAP-II score was 0.[18]

DISCUSSION

Clearly, the SNAP-II instrument has evidence to support its utility in neonatal research. Quantifying illness severity is helpful in research studies because it allows (1) quantification of the baseline risk of mortality and morbidity for the neonate, (2) quantification of how physiologically ill or unstable the newborn is at the time it is measured, (3) evaluation for homogeneous versus heterogeneous samples within and among research studies, (4) stratification of patients based on level of risk, and (5) the ability to determine initial risk at birth and then subsequent improvement or decline in the health of the neonate.

Neonatal severity of illness as operationalized by the SNAP-II has the majority of evidence available to support its sensitivity, specificity, and utility as a measure of illness severity measured during the first 12 hours of life or upon admission to the NICU. Although there is a recommended 12-hour data collection period for the SNAP-II,[6] subsequent researchers have expanded this back to the original 24-hour window utilized by the original SNAP instrument.[15,23,43] There is concern that treatment effects may be measured as well as initial illness severity with such a long data collection window. Although the data supported the validity of the SNAP-II instrument across all gestational ages and birth weights, Zupancic et al[47] demonstrated that the SNAP-II is better at discriminating illness severity in very low-birth-weight neonates (≤1500 g).

The specific research interest of this review was to determine whether the SNAP-II instrument could be used to measure neonatal illness severity at a later time point (after the initial day of birth) and as a sequential measure. Two studies evaluated severity of illness after transport and provided evidence of validity and discrimination.[38,40] The 4 remaining studies evaluated severity of illness in relationship to neonatal sepsis. Each of the studies found relationships that provided evidence of measurement of severity of illness. Sundaram et al[39] found that SNAP-II scores were higher in babies who died and specifically SNAP-II scores greater than 40 were associated with more organ dysfunction.[39] The other 3 studies were conducted by Figueras-Aloy et al[33] and examined relationships between illness severity and various biomarkers associated with sepsis. Each of these studies demonstrated positive relationships to indicate that the SNAP-II does have some utility as an adequate measure after the first day of life. However, these were all single-center studies and involved only transported and septic newborns. There is potential that these newborns were sick enough to pass a threshold of discovery by the SNAP-II instrument.

Only 2 studies evaluated neonatal severity of illness over time in a prospective manner. Both Madan et al[19] and Lim and Rozycki[18] were not successful at finding hypothesized relationships. Only 1 study measured severity of illness daily and specifically sought to evaluate the ability of the SNAP-II instrument to measure illness severity over time.[18] An interesting phenomenon surfaced concerning null values. Lim and Rozycki[18] found that 92% of the SNAP-II scores were 0 and that null values often surrounded major morbidity events. One possible explanation is that if a specific test, for example, an arterial blood gas, has not been performed, then the assumed value is normal and therefore zero points are earned for the neonate. Treating missing data as normal values is questionable.

Strengths and weaknesses

A major strength of this review is that it included all of the research studies that utilized the SNAP-II instrument and was not limited to a specific age or date range. This is the first review article evaluating the utility of the SNAP-II instrument. However, the major limitation of this review is that it does not contain a review of all instruments that have been used to operationalize the concept of illness severity.

The strength of the evidence is supported by several large studies conducted across multiple hospitals. For many of the studies, this included neonatal networks that are working to promote research across the hospitals within specific geographic locations. The greatest benefit of this collaboration includes recruiting patients from different NICUs, so that the recruited sample might be more representative of the general population, thus more generalizable research findings. However, when recruiting patients across multiple hospitals, it is important to consider the effects that the environment may have on each subset of neonates. If the environmental effect is not controlled for, an ecologic fallacy error can be made when interpreting results and population-level findings are mistakenly attributed to individuals.[49] As a minimum standard, the interclass correlations should be reported and provide justification as to why multilevel modeling approaches were not used. Perhaps the greatest weakness of the studies is that they were observational in nature with mostly convenience samples. This study type limits the ability of researchers to assess for cause-and-effect relationships among the study variables. However, the studies provide useful data within the ethical constraints of human subject research on vulnerable neonatal populations. Finally, although the studies provide measures of validity for the SNAP-II instruments, no reliability measures were reported.

Implications for research and practice

The SNAP-II instrument has been used successfully to quantify the concept of illness severity upon admission to the NICU; however, more evidence is needed concerning the sensitivity and specificity of

the SNAP-II instrument when measuring illness severity sequentially and at later time points. Caution is advised when utilizing the SNAP-II for sequential measurements.[18] Although there is evidence to support the validity of the SNAP-II instrument, reliability data are still lacking. Future studies using the SNAP-II instrument should report measures of reliability such as the Cronbach alpha for this purpose.

To date, the SNAP-II instrument has been used only to generate population-level data for research purposes.[16] One author mentioned that illness severity scores can be used to counsel parents[18]; however, other authors have advised caution and recommended that SNAP-II scores not be used to guide decisions for individual patients.[6,47] However, there is a need for further development of this tool so that it can provide individual patient-level data and it can be utilized as a clinical decision-making tool. Furthermore, researchers need to work with informatics specialists to automate the scoring process using data that are already routinely entered by neonatal nurses into an electronic medical record.[47]

CONCLUSION

Neonatal severity of illness is a key concept when caring for critically ill neonates. The SNAP-II has assisted researchers and clinicians in quantifying this concept to control varying severity of illness when evaluating outcomes at the population level. Although severity of illness is something that changes over time, more evidence is needed to determine if the SNAP-II instrument is able to accurately measure this at a later time point and as a sequential measure. Furthermore, the need for a precise measurement tool that can measure this concept at the individual patient level as well as the population level is the ultimate goal for improving neonatal critical care.

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