

Early Heart Rate Characteristics Predict Death and Morbidities in Preterm Infants

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Objectives To determine whether an early heart rate characteristics (HRC) index (HeRO score), measured in the first day and week after birth predicts death and morbidities compared with established illness severity scores.

Study design For all very low birth weight infants in a single neonatal intensive care unit from 2004-2014, the average first day HRC index was calculated within 24 hours of birth (aHRC-24h) and the average first week HRC index within 7 days of birth (aHRC-7d). The Score for Neonatal Acute Physiology (SNAP-II) and Clinical Risk Indicator for Babies (CRIB-II) were calculated when data were available. The aHRC was compared with the SNAP-II and CRIB-II for predicting death, late-onset septicemia, necrotizing enterocolitis, bronchopulmonary dysplasia, severe intraventricular hemorrhage, or severe retinopathy of prematurity.

Results All 4 scores were associated with death and severe intraventricular hemorrhage ($P < .01$). The OR and 95% CI for every 1-point increase in aHRC for predicting mortality, adjusted for gestational age, was 1.59 (1.25-2.00) for aHRC-24h and 2.61 (1.58-4.33) for aHRC-7d. High aHRC-7d, SNAP-II, and CRIB-II were associated with bronchopulmonary dysplasia ($P < .001$). High aHRC-7d was associated with late-onset septicemia ($P < .05$). None of the scores predicted necrotizing enterocolitis or severe retinopathy of prematurity.

Conclusions HRC assessed in the first day or first week after birth compares favorably to established risk scores to predict death and morbidities in very low birth weight infants. (*J Pediatr* 2016; ■: ■-■).

Risk prediction scores based on illness severity are important for interinstitutional quality assessment and for clinical research. In the neonatal intensive care unit (NICU), gestational age (GA) alone is a strong predictor of adverse events and outcomes. Adding physiological and laboratory data can improve the accuracy of predictive models and could help identify infants who might benefit from heightened surveillance or preventative measures. Two established risk scores, the Score for Neonatal Acute Physiology (SNAP) and Clinical Risk Indicator for Babies (CRIB) and their updated versions (SNAP-II and CRIB-II), rely on clinical and blood gas data to calculate. A relatively new physiologic measure, the heart rate characteristics (HRC) index, was designed to assess risk of imminent sepsis in very low birth weight (VLBW) infants and is calculated continuously from the bedside monitor electrocardiogram (ECG) signal. Because depressed heart rate variability may occur in both acute and chronic pathologic conditions, we reasoned that a high HRC index shortly after birth might indicate high risk of death or morbidities in VLBW infants in the NICU.

Depressed heart rate variability reflects dysregulation of autonomic nervous system function and occurs in acute conditions such as sepsis or asphyxia.^{1,2} In fetuses, abnormal HRC of transient decelerations on a background of depressed variability are a well-known sign of distress and are associated with adverse outcomes. In neonates, the most common cause of these abnormal HRC is sepsis.^{3,4} A HRC monitor (HeRO Monitor, Medical Predictive Science Corporation, Charlottesville, Virginia) was developed as an early warning system for sepsis in VLBW infants in the NICU, and display of the HRC index (HeRO score) reduces all-cause mortality by 22%⁵ and sepsis-associated mortality by 40%.⁶ Abnormal HRC are not specific for sepsis, and acute or chronic elevations in the HRC index have been reported in a number of other pathologic conditions, including necrotizing enterocolitis (NEC), respiratory failure, and brain hemorrhage.⁷⁻⁹

Although not specifically designed for mortality prediction, a high HRC index throughout the NICU stay was associated with high risk for death.¹⁰ SNAP-II and CRIB-II, which were designed to predict mortality, incorporate a limited number of vital

aHRC-7d	Average first week HRC index	LOS	Late-onset septicemia
aHRC-24h	Average first day HRC index	NEC	Necrotizing enterocolitis
AUC	Area under the ROC curve	NICU	Neonatal intensive care unit
BPD	Bronchopulmonary dysplasia	NRI	Net reclassification improvement
CRIB-II	Clinical Risk Indicator for Babies II	ROC	Receiver operator characteristic
ECG	Electrocardiogram	ROP	Retinopathy of prematurity
GA	Gestational age	SNAP-II	Score for Neonatal Acute Physiology II
HRC	Heart rate characteristics	UVA	University of Virginia
IVH	Intraventricular hemorrhage	VLBW	Very low birth weight

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sign metrics and laboratory values from the first 12 hours after birth.^{11,12} Limited studies suggest that high SNAP or CRIB scores are associated with increased risk for other adverse outcomes, including intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD).¹³⁻¹⁵

Prior studies have examined the association of abnormal HRC (a high HRC index) throughout the NICU stay with acute and chronic conditions. In the current study, we determined whether early measurement of the HRC index, in the first day and first week after birth, predicts later adverse events and conditions in VLBW infants, as compared with SNAP-II and CRIB-II.

Methods

The University of Virginia (UVA) Institutional Review Board approved this study. We reviewed HRC monitoring data for all VLBW infants (<1500 g at birth) admitted to the UVA NICU between May 2004 and May 2014. Medical records were reviewed for occurrence of death before NICU discharge, severe IVH (grades III-IV), late-onset septicemia (LOS), NEC, BPD (supplemental oxygen at 36 weeks' post-menstrual age), and severe retinopathy of prematurity (ROP requiring laser or bevacizumab treatment). LOS was defined as clinical signs of sepsis after 3 days of age with a positive blood culture, and antibiotics given for ≥ 5 days. NEC included cases of medical or surgical NEC or intestinal perforation.

HRC Index Monitoring

A commercially available monitor (HeRO, Medical Predictive Science Corporation) calculates the HRC index for all infants throughout their stay in the UVA NICU. The monitor analyzes the ECG signal from bedside monitors using an algorithm designed to detect imminent sepsis, incorporating measures of heart rate variability and decelerations. The 3 measures included in the algorithm are the SD of R-R intervals, sample asymmetry (increased decelerations and few accelerations), and sample entropy.^{1,2} The HRC index is calculated every hour from the previous 12 hours of ECG signal and represents the fold increase in risk that the infant will be diagnosed with sepsis in the ensuing 24 hours compared with the average risk of sepsis for all VLBW infants at all times during the NICU stay.¹⁶ The HRC index was externally validated for sepsis detection² and was tested in a large, multicenter randomized clinical trial.⁵

Calculation of Average First Day HRC Index, Average First Week HRC Index, SNAP-II, and CRIB-II

Average first day HRC index (aHRC-24h) was calculated when ≥ 6 hours of HRC index data were available in the first 24 hours after birth. Average first week HRC index was calculated when ≥ 5 days (120 hours) of HRC index data were available in the first 7 days (average first week HRC index [aHRC-7d]). For infants with either first day or first week

HRC index calculated, medical records were reviewed for clinical and laboratory measurements in the first 12 hours after birth to calculate SNAP-II and CRIB-II Scores. The following components are included in SNAP-II: lowest temperature and blood pressure, lowest PaO₂/FiO₂ ratio, lowest pH, urine output, and seizures. A normal value was assumed for PaO₂/FiO₂ ratio if an arterial blood gas was not obtained. This has been suggested by the authors who developed SNAP and SNAP-II as an acceptable method of calculation when data are unavailable.^{11,17} The following components are included in CRIB-II: GA, birth weight, sex, admission temperature, and highest base deficit.¹²

Statistical Analyses

Differences in scores for infants with and without each adverse outcome were assessed by *t* tests with and without logistic regression to adjust for GA. The additive value of each score compared with GA alone for risk prediction was quantified by the change of the area under receiver operator characteristic (ROC) curve as well as by the net reclassification improvement (NRI). NRI is a measure of the sum of proportions of patients reclassified into the correct risk group by a new risk marker compared with an established risk marker.¹⁷ For example, an NRI of 0.2 with respect to death would indicate that a high HRC index correctly identified survival in 20% more infants compared with the established risk marker of GA. As an additional measure of risk assessment, we calculated the OR and 95% CI for every 1-point increase in aHRC-24h and aHRC-7d over zero for predicting mortality. Statistical analyses were performed in MATLAB (MathWorks, Inc, Natick, Massachusetts) and all *P* values are 2-tailed.

Results

In the years of the study, 566 VLBW infants had ≥ 6 hours of HRC index data within 24 hours of birth for aHRC-24h analysis and data available for calculation of SNAP-II and CRIB-II, and 480 had >120 hours (5 days) of HRC monitoring data available in the first week for calculation of aHRC-7d. Mean GA was similar for infants in the aHRC-24h and aHRC-7d groups (28.6 ± 2.9 and 28.9 ± 2.8 weeks, respectively). Of the 566 infants, 52% were male and 32% were <1000 g. During the same time period, approximately 1300 VLBW infants were admitted to the UVA NICU (mean GA, 27.5 ± 3.0 weeks; 51% male). Infants without early HRC data available for analysis were either born at another institution or did not have ECG leads placed in the first days after birth owing to poor skin integrity. The incidences of death, severe IVH, LOS, NEC, BPD, and severe ROP of the 566 infants included in the analysis are shown in **Table I**.

Predictive Performance of aHRC-24h, aHRC-7d, SNAP-II, and CRIB-II

Higher aHRC-24h and aHRC-7d were associated with death and severe IVH, with the difference remaining significant after accounting for GA ($P \leq .01$; **Figure 1, A**). The OR and 95% CI

Table I. HRC index, SNAP-II, and CRIB-II scores based on outcomes

Outcomes	N (%)	GA (mean, SD)	aHRC-24 hr, median (IQR)	aHRC-7d, median (IQR)	SNAP-II, median (IQR)	CRIB-II, median (IQR)
Died	51 (9)	27 ± 3	1.60 (0.84, 2.81)	1.44 (0.68, 1.88)	25 (14, 44)	9 (6, 15)
Survived	515 (91)	29 ± 3	0.79 (0.53, 1.37)	0.77 (0.53, 1.28)	14 (9, 19)	7 (5, 9)
sIVH	47 (8)	27 ± 3	1.87 (1.02, 3.21)	2.01 (0.98, 2.39)	25 (14, 38)	9 (6, 14)
No sIVH	519 (92)	29 ± 3	0.79 (0.53, 1.36)	0.77 (0.53, 1.16)	14 (9, 19)	6 (5, 9)
LOS	63 (12)	27 ± 2	1.30 (0.68, 1.8)	1.00 (0.72, 1.75)	14 (9, 30)	8 (6, 10)
No LOS	471 (88)	29 ± 3	0.76 (0.51, 1.29)	0.75 (0.51, 1.16)	14 (8, 19)	6 (5, 9)
NEC	37 (7)	28 ± 2	1.02 (0.64, 1.55)	0.93 (0.59, 1.59)	14 (9, 22)	7 (6, 9)
No NEC	497 (93)	29 ± 3	0.79 (0.52, 1.37)	0.77 (0.53, 1.17)	14 (9, 19)	6 (5, 9)
BPD	98 (20)	27 ± 2	1.15 (0.70, 2.08)	1.28 (0.77, 1.74)	20 (14, 29)	9 (7, 13)
No BPD	405 (80)	29 ± 3	0.73 (0.46, 1.21)	0.69 (0.47, 1.00)	9 (8, 16)	6 (5, 7)
Severe ROP	15 (3)	25 ± 2	1.48 (0.84, 2.46)	1.65 (0.78, 2.11)	30 (14, 40)	11 (8, 14)
No severe ROP	488 (97)	29 ± 3	0.77 (0.51, 1.32)	0.75 (0.51, 1.16)	14 (8, 19)	6 (5, 9)

sIVH, severe IVH.

Scores were calculated for 566 VLBW infants (480 with aHRC-7d) for GA, survival, and morbidities. Death and sIVH were assessed for all infants, LOS and NEC for all infants except for those that died at <30 days old without LOS or NEC, and BPD and severe ROP for infants still hospitalized in our unit at 36 weeks' postmenstrual age. Median and IQR of aHRC-24 and aHRC-7d and SNAP-II and CRIB-II are shown.

for every 1-point increase in aHRC for predicting mortality after adjustment for GA was 1.59 (95% CI, 1.25-2.00) for aHRC-24h and 2.61 (95% CI, 1.58-4.33) for aHRC-7d. The aHRC-7d was higher in those who developed both LOS and BPD, but the aHRC-24h was not. GA was negatively correlated with aHRC-24h and aHRC-7d (Figure 1, B and C). Higher SNAP-II was associated with death, severe IVH, and BPD after adjustment for GA ($P \leq .01$), but not with LOS. None of the 4 scores was associated with development of NEC or ROP after adjustment for GA (all $P > .05$). Median and IQRs of all 4 scores and GA for infants with and without each outcome are compared in Table I.

GA alone was highly predictive of death and each morbidity (Table II). Each score resulted in a significant increase in the area under the ROC curve (AUC) compared with GA alone for prediction of death and severe IVH (Table II and Figure 2). The change in ROC area was also

significant for aHRC-7d predicting LOS and BPD (Table II). SNAP-II and CRIB-II increased the ROC area over GA alone for predicting BPD but not LOS.

We also used a relatively new metric, the NRI, to compare the 4 risk indices with GA, which is a well-established, major risk predictor for death and morbidities in neonates. The NRI is a measure of fraction of cases reclassified into the correct category with the new test compared with the old one. The NRI demonstrated that aHRC-24h, aHRC-7d, and SNAP-II but not CRIB-II added information to risk prediction for death and IVH compared with GA alone (NRI > 0.30; $P \leq .01$). The NRI was also significant for BPD prediction using aHRC-7d, SNAP-II, and CRIB-II (NRI > 0.40; $P < .001$) and for septicemia prediction using aHRC-7d (NRI = 0.30; $P = .03$).

There was no additive value to combining aHRC with SNAP-II or CRIB-II for risk assessment based on change in ROC area or NRI.

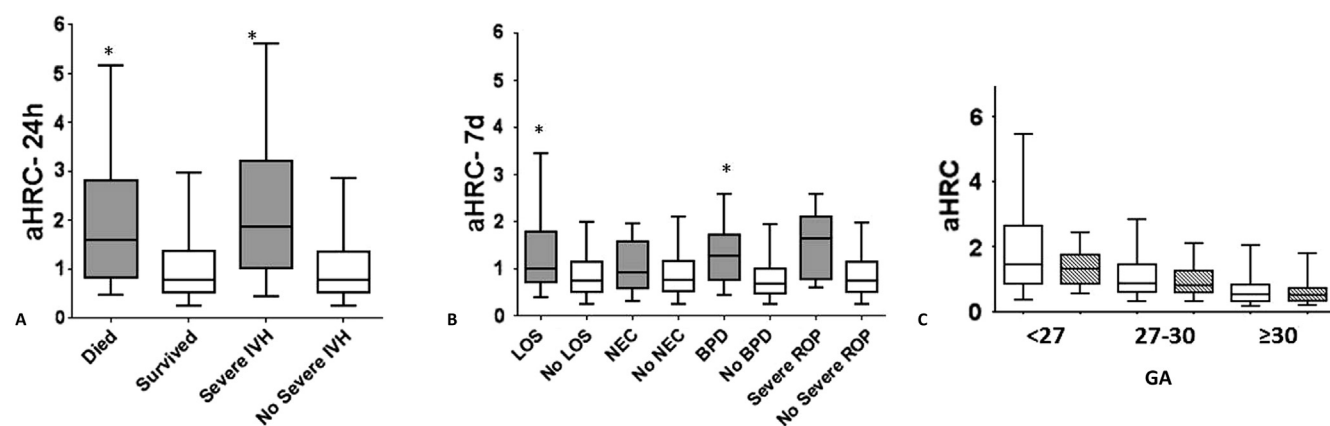


Figure 1. **A**, Median, IQR, and 5th and 95th percentile aHRC-24h for infants who died or had severe IVH (gray) compared with infants who survived or did not have severe IVH (white). **B**, Median, IQR, and 5th and 95th percentile aHRC-7d for infants who had LOS, NEC, BPD, or ROP (gray) compared with those who did not have the outcome (white). * $P < .01$ using logistic regression to adjust for GA. **C**, Median, IQR, and 5th and 95th percentile aHRC-24h (white) and aHRC-7d (stripes) by GA. The correlation coefficient of aHRC-24h and aHRC-7d with GA was -0.3999 and -0.4276 , respectively.

Table II. Performance of scores and GA by AUC

	GA	aHRC-24 hr	aHRC-7d	SNAP-II	CRIB-II
Death	0.725	0.741*	0.719*	0.771*	0.723*
sIVH	0.726	0.778*	0.782*	0.765*	0.724
LOS	0.734	0.738	0.738*	0.733	0.737
NEC	0.630	0.628	0.627	0.642	0.643
BPD	0.820	0.827	0.827*	0.839*	0.840*
Severe ROP	0.931	0.930	0.931	0.935	0.933

AUC of GA and aHRC-24 hr, aHRC-7d, SNAP-II, and CRIB-II, adjusted for GA.

*Significant change in ROC area compared with GA alone ($P \leq .01$).

Discussion

In this large study of VLBW infants, we found that an HRC index assessed in the first day or first week after birth predicts adverse outcomes. The average HRC index compared favorably with SNAP-II and CRIB-II scores and, based on assessment of change in ROC area and NRI, added information beyond GA alone for predicting death, severe IVH, and the development of BPD. The first week aHRC index was also associated with LOS, but none of the scores was associated with development of NEC or ROP.

The HRC index was designed to detect imminent sepsis, incorporating measures of heart rate variability and transient heart rate decelerations, which can be indicative of an acute inflammatory response.¹⁸ An earlier study also showed that a higher HRC index throughout the NICU stay was associated with death,¹⁰ and the current study shows that abnormal HRC shortly after birth also indicate increased risk of death. In contrast with the HRC index, SNAP-II and CRIB-II scores

were developed for mortality risk prediction and incorporate both physiologic and laboratory data in the first 12 hours after birth. We found that first day HRC performed similarly to SNAP-II and similarly or slightly better than CRIB-II for predicting mortality in this population, although previous studies have reported higher AUCs for both SNAP-II and CRIB-II.^{11,12,19-22} Because GA alone strongly influences mortality and morbidity risk with a high AUC, we analyzed the change in AUC and a newer measure, the NRI, and showed that each score added to GA, but HRC did not add to SNAP-II or CRIB-II for predicting death or morbidities.

Our results add to the limited number of studies evaluating the ability of illness severity scores to predict outcomes other than death in preterm infants.¹³⁻¹⁵ SNAP-II incorporates measures of oxygen administration and blood oxygen levels (lowest PaO₂/FiO₂ ratio) and predicted development of BPD in a large study of preterm infants (<32 weeks' GA).¹³ Although the HRC index does not factor in tests directly related to respiratory status, we found previously that an acute increase in the HRC index may occur in preterm infants with acute respiratory deterioration,⁸ which may be related to effects of hypoxia or acidosis on heart rate variability, or frequent heart rate decelerations during apnea spells. The aHRC-7d was predictive of BPD whereas the aHRC-24h was not, which may reflect transient abnormalities of HRC shortly after birth or procedures or medications given in the first day. For example, if atropine is given for intubation, it greatly and transiently depresses heart rate variability.

We found that infants with severe IVH have higher HRC index values in the first day and first week. IVH occurs most often during the first 3 days after birth and we did not have serial brain ultrasound examinations during this period to determine whether a high HRC index actually predicts or simply reflects occurrence of severe IVH. In a prior study, we found severe IVH to be associated with chronically abnormal HRC for the first month, which may represent ongoing autonomic nervous system dysfunction or neuroinflammation.⁹ Chronic elevation of the HRC index during the NICU stay was also found to be associated with neurodevelopmental impairment at 1 year of age in 2 studies.^{9,23} Association of high SNAP and CRIB scores with adverse neurodevelopmental outcomes has been reported in some studies, but not in others.^{24,25}

None of the early illness severity scores analyzed in this study correlated with increased risk of NEC or severe ROP after adjustment for GA. GA alone is a very strong predictor of severe ROP. With regard to NEC, we showed previously that an acute increase in the HRC index occurs in some infants in the 24-hour period before NEC diagnosis,⁷ but in the current study we did not find that first day or first week HRC index predicted later development of NEC or intestinal perforation. A prior small study found that low heart rate variability in the high-frequency spectrum (thought to represent parasympathetic tone) occurring during the first week identifies preterm infants at increased risk for development of NEC.²⁶ We found no association between SNAP-II or CRIB-II and NEC, similar to another study showing that neither first

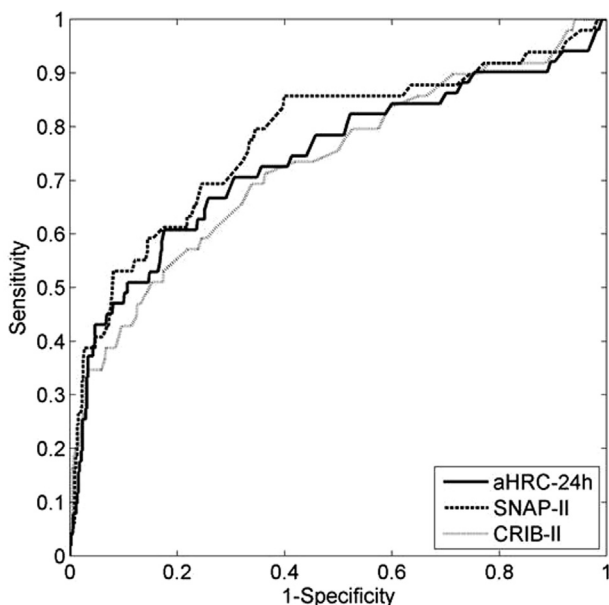


Figure 2. ROC curves for predicting death using aHRC-24h, SNAP-II, and CRIB-II, all adjusted for GA.

day nor daily assessment of SNAP-II scores predicts NEC.¹⁵ Because NEC is uncommon and its pathophysiology complex, larger studies would be needed to develop physiologic predictive scores.

Interestingly, a high average HRC index in the first week was associated with later development of septicemia, occurring on average about 4 weeks after birth. It is possible that decreased heart rate variability soon after birth reflects autonomic nervous system dysfunction and because the autonomic nervous system plays a role in host defense this might indicate vulnerability to later infection.²⁷ Alternatively, abnormal HRC in the early postnatal period may simply serve as a marker of high overall illness severity and need for interventions such as prolonged mechanical ventilation or intravascular catheters, which increase sepsis risk. Prior small studies have reported a higher incidence of LOS in neonates with high first day SNAP¹ and SNAP-II with perinatal extension,¹⁵ but in our larger study sample we did not find this association. We also did not find the first day aHRC index to be predictive of LOS, which may reflect events or procedures occurring at or shortly after birth that transiently affect HRC.

Generally, the HRC index and SNAP-II and CRIB-II scores performed similarly for risk prediction in this study, and there was no additive benefit. There are some differences in acquisition and other aspects of the scores that deserve consideration. Measurement of the HRC index requires specialized equipment not available in most NICUs, and requires placement of ECG leads immediately after birth, which may not always be done for extremely preterm infants with very fragile skin. Also, administration of anticholinergic medication before endotracheal intubation, which is common practice in some NICUs, depresses heart rate variability and increases the HRC index. An advantage of SNAP-II and CRIB-II is that they integrate demographic and laboratory data with vital sign data to identify infants with high mortality risk. Another advantage to these scores is that no specialized equipment is required. On the other hand, these illness severity scores require time and effort to calculate and thus are not available readily or continuously. A consideration for all of these scores is that they were not designed specifically to identify infants at high risk for many of the serious adverse events and outcomes common to very preterm infants, such as NEC and ROP. Addition of physiologic data beyond HRC such as pulse oximetry data might result in more sensitive and specific predictive algorithms. A small study found that a “PhysiScore” incorporating multiple vital signs and oxygen saturation in the first 3 hours after birth performed well for identifying preterm infants at high risk for various morbidities.¹⁹ Advances in “big data” analytics may allow the development of optimized scores incorporating both vital signs and demographic and laboratory data to help clinicians identify high-risk or deteriorating patients, and this in turn might lead to earlier therapies and improved patient outcomes.

Abnormal HRC soon after birth are associated with mortality and multiple morbidities in VLBW infants in the

NICU. Risk scores such as the HRC index may be useful for interinstitutional outcomes research, stratification in clinical trials, and identifying infants that might benefit from heightened surveillance or targeted therapies. ■

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