Predictive ability of neonatal illness severity scores for early death in extremely premature infants

Running title: Neonatal severity scores predict early death

Genichiro Sotodate*[a], MD, Kotaro Oyama[a], MD, Atsushi Matsumoto[a], MD, Yu Konishi[a], MD, Yukiko Toya[a], MD, Nao Takashimizu[a], MD

[a]*Department of Pediatrics, Iwate Medical University Faculty of Medicine Graduate School of Medicine, Morioka, Japan*

*Corresponding to: Genichiro Sotodate, MD, Department of Pediatrics, Iwate Medical University Faculty of Medicine Graduate School of Medicine, 19-1 Uchimaru, Morioka Iwate 020-8505, Japan

Tel. +81 19 651 5111

Fax: +81 19 651 0515

Email: gsotodat@iwate-med.ac.jp

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Abstract

***Background*:** The predictive ability of neonatal illness severity scores for mortality or morbidity in extremely premature infants has not been extensively studied. We aimed to evaluate the ability of neonatal illness severity scores [Clinical Risk Index for Babies II (CRIB II), Score for Neonatal Acute Physiology II (SNAP-II), and SNAP-Perinatal Extension II (SNAPPE-II)] in predicting mortality and short-term morbidity of extremely premature infants.

Methods: This retrospective study involved 171 infants with gestational age (GA) between 22 and 27 weeks who were admitted to the NICU during 2010-2017. Predictive ability of neonatal illness severity scores for mortality and short-term morbidity (bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, necrotizing enterocolitis, and gastrointestinal perforation) was assessed by comparing their area under the receiver operating characteristic curve.

Results: The overall mortality rate was 11.1%. Mortality at 23 weeks' gestation was higher than that at 24-27 weeks' gestation ($p<0.01$, adjusted residual 4.5). Neonatal illness severity scores were significantly higher in infants who died than in those who survived ($p<0.01$). CRIB II (AUC 0.93, 95% CI 0.85-1.00), SNAP-II (AUC 0.90, 95% CI 0.76-1.00), and SNAPPE-II (AUC 0.95, 95% CI 0.91-0.99) appeared to be excellent predictors and were superior to birth

weight (AUC 0.88, 95% CI 0.80-0.95) or GA (AUC 0.84, 95% CI 0.72-0.96) alone in predicting early death (died on <28th postnatal day). CRIB II, SNAP-II, and SNAPPE-II were better predictors of early death than mortality in extremely premature infants. Neonatal illness severity score and short-term morbidity were not strongly associated.

Conclusions: The neonatal illness severity scores were excellent predictors of early death in extremely premature infants and might be useful for selecting extremely preterm infants who need intervention.

Keywords: neonatal illness severity score; extremely premature infant; early death; predictor; perinatal care

Introduction

Given the improvement in perinatal care in recent years, neonatal mortality has markedly decreased; however, the mortality rate among very premature infants is still high (that of infants born at 24-29 weeks' gestation were 70-220 per 1000 live births) [1, 2]. In our neonatal intensive care unit (NICU), the mortality rate of infants born between 23 and 27 weeks' gestation was 76 per 1000 lives; these infants remained at a high risk for adverse outcomes [3].

Mortality rate increased with decreasing birth weight and gestational age (GA) [1]. Birth weight and GA have been used to predict neonatal mortality and morbidity; however, predicting neonatal mortality and morbidity accurately by only these perinatal parameters is difficult. Mortality of premature infants depends on birth weight, GA, and other perinatal factors and physiological conditions[4] of each infant; thus, neonatal illness severity scores are needed to objectively evaluate the risk of adverse outcomes of each very premature infant.

Neonatal illness severity scores could estimate the probability of mortality and morbidity of a particular infant and could identify high-risk infants for a particular intervention [5, 6]. Among the neonatal illness severity scores, Score for Neonatal Acute Physiology (SNAP) and Clinical Risk Index for Babies (CRIB) are widely used. SNAP is known to be predictive of neonatal mortality [7]. SNAP-II has been validated to make the evaluation process simpler and more reliable and to reduce variable numbers. SNAP-II, which is applicable to all infants, is calculated using 6 variables (mean blood pressure, temperature, PaO_2/FIO_2, pH, multiple

seizures, urine output) with the strongest statistical association with neonatal mortality. In SNAPPE-II, 3 more perinatal parameters are added, including birth weight, Apgar score, and small-for-gestational age (SGA). SNAP-II and SNAPPE-II are highly predictive of neonatal mortality [8].

CRIB is calculated using 6 variables [9]. CRIB II, which is applicable to infants with GA <32 weeks, is an updated version of CRIB that was calculated using 4 variables (birth weight, base excess, body temperature, sex) and is highly predictive of neonatal mortality [10]. Neonatal illness severity scores (CRIB, CRIB II, SNAP, SNAP-II, SNAPPE-II) are used to assess mortality risk [4, 11-15], poor neurodevelopmental outcome [16-18], and morbidity of bronchopulmonary dysplasia (BPD) [19-21] and retinopathy of prematurity (ROP) [19] in premature and very low birth weight infants. Few studies have evaluated the predictive ability of neonatal illness severity scores for mortality or morbidity in extremely premature infants [16, 22]. Perinatal care has improved over the last years, but the association between mortality and morbidity of extremely premature infants and neonatal illness severity scores may alter in recent years. Thus, we aimed to evaluate the ability of CRIB II, SNAP-II, and SNAPPE-II for predicting mortality and short-term morbidity (IVH, NEC, BPD, ROP) of extremely premature infants.

Materials and Methods

This retrospective cohort study was conducted at Iwate Medical University of Medicine, Iwate, Japan. Infants with GA between 22 and 27 (extremely premature infants) weeks who were admitted to the NICU between October 2010 and December 2017 were included. Antenatal corticosteroids were administered in women with anticipated preterm delivery (<34 weeks' gestation) in our hospital to reduce neonatal death risk. The exclusion criteria were as follows: admission was beyond 1 hour post-delivery and congenital malformation incompatible with life. We collected all clinical data (GA, birth weight, sex, lowest temperature, SGA, Apgar score, seizure, urine output, lowest pH, PAO_2, FIO_2, worse base excess, lowest mean blood pressure) needed to calculate the CRIB II, SNAP-II, and SNAPPE-II scores from the NICU database and medical records. CRIB II, SNAP-II, and SNAPPE-II scores were calculated according to the method previously mentioned [8, 10].

The association between neonatal illness severity scores and morbidity of BPD and ROP was analyzed in infants who survived more than 36 weeks' corrected age. The association between neonatal illness severity scores and mortality, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and gastrointestinal perforation was analyzed in all infants. The primary outcome was the predictive ability of the neonatal illness severity scores (CRIB II, SNAP-II, SNAPPE-II) for mortality and short-term morbidity in extremely preterm infants.

Terminology

GA was determined by the maternal last menstrual period and confirmed on ultrasonography.

Chorioamnionitis was diagnosed clinically based on the presence of fever of 38.3 °C or higher and leukocytosis (> 18,000/μL). Mortality was defined as death prior to discharge home. BPD was defined as requiring supplemental oxygen or positive pressure ventilation at 36 weeks' corrected age [23]. IVH was defined as grade III or IV[24]. NEC was defined as modified Bell's stage II and III [25]. Gastrointestinal perforation was defined as a radiologic finding of free air. ROP was defined as requiring laser coagulation according to the International Committee for Classification of Retinopathy of Prematurity [26, 27]. In the study period, intraocular injection of anti-VEGF was not performed in our hospital.

Ethics

This study adhered to the Japanese ethical guidelines concerning epidemiological studies and conducted with approval of the ethics committee of Iwate Medical University of Medicine (approval number MH 2018-588). Informed consent was obtained from the parents of the infants by opt-out.

Statistical analysis

Continuous variables are expressed as mean±standard deviation and median (range). Categorical variables are expressed as number and percentage. Statistical analysis for baseline group comparisons was performed by X^2 or Fisher's exact for categorical variables and

Mann-Whitney U test for continuous variables. Analysis of the area under curve (AUC) of the receiver operating characteristic (ROC) curve was constructed to assess the predictive ability of these scores for mortality and morbidity. The AUC results were considered excellent, good, fair, poor, and failed for AUC values between 0.9 and 1, 0.8 and 0.9, 0.7 and 0.8, 0.6 and 0.7, and 0.5 and 0.6, respectively [11]. Logistic regression was utilized to assess the independent effects of various risk factors for mortality. CRIB II, SNAP-II, and SNAPPE-II were not included in the multivariate logistic regression analysis because of multicollinearity. Data were analyzed using SPSS version 21 (IBM, Armonk. NY, USA). Statistical significance was set at p-value<0.05.

Results

A total of 178 infants were screened for the study; of these, 171 infants met the inclusion criteria. Seven infants were admitted beyond 1 hour post-delivery. No infant had congenital malformation. We collected the clinical data retrospectively, and all infants had sufficient data for calculating the neonatal illness severity scores (CRIB II, SNAP-II, SNAPPE-II). None was lost to follow-up.

Population characteristic

Characteristics of the study population are shown in Table 1. Among the 171 infants (one infant was born at 22 weeks' GA, 33 infants at 23 weeks' GA, 33 infants at 24 weeks' GA, 34 infants at 25 weeks' GA, 25 infants at 26 weeks' GA, and 45 infants at 27 weeks' GA), the overall

mortality rate of extremely premature infants was 11.1% in the study period. Seven (4.1%) died on the <28th postnatal day (early death) and 12 (7.0%) died between the 28th postnatal day and day of discharge (late death). Compared with surviving infants, infants who died had significantly lower GA and birth weight ($p<0.01$) and significantly higher incidence of SGA, NEC, and gastrointestinal perforation ($p<0.01$). Neonatal illness severity scores were significantly higher in infants who died than in surviving infants ($p<0.01$). Mortality was 33% (11/33) in infants born at 23 weeks' GA, 6% (2/33) at 24 weeks' GA, 6% (3/34) at 25 weeks' GA, 8% (2/25) at 26 weeks' GA, and 2% (1/45) at 27 weeks' GA. Among the 7 infants with early death, 5 were born at 23 weeks' GA, 1 at 24 weeks' GA, and 1 at 25 weeks' GA.

Mortality and early death at 23 weeks' gestation were higher than those at 24-27 weeks' gestation ($p<0.01$, adjusted residual 4.5).

Logistic regression of mortality

Univariate analysis revealed that CRIB II (OR 1.60 (95% CI 1.28-1.99), $p<0.01$), SNAP-II (OR 1.07 (95% CI 1.04-1.11), $p<0.01$), and SNAPPE-II (OR 1.07 (95% CI 1.04-1.10), $p<0.01$) scores were independent risk factors for mortality and that CRIB II (OR 2.34 (95% CI 1.42-3.86), $p<0.01$), SNAP-II (OR 1.11 (95% CI 1.05-1.18), $p<0.01$), and SNAPPE-II (OR 1.11 (95% CI 1.05-1.08), $p<0.01$) scores were risk factors for early death. In the multivariate logistic regression analysis among variables of neonatal illness severity scores (GA, birth weight, Apgar score at 5 min, mean blood pressure, PaO_2/FIO_2, body temperature, pH, base excess, urine

output), birth weight (OR 0.99 (95% CI 0.987-0.996), p<0.01) and pH (OR 0.58 (95% CI 0.37-0.93), p=0.023) were shown to be independent risk factors for mortality. Birth weight (OR 0.99 (95% CI 0.977-0.996), p<0.01) and base excess (OR 0.72 (95% CI 0.56-0.93), p=0.012) were shown to be independent risk factors for early death.

Predictive ability of the neonatal illness severity scores

Table 2 presents the AUC for the predictive ability for mortality and short-term morbidity predictive ability of the neonatal illness severity scores. CRIB II, SNAP-II, and SNAPPE-II appeared to be good or fair predictors of mortality. CRIB II and SNAPPE-II were superior to SNAP-II in predicting mortality. Predictive ability of neonatal illness severity scores was similar to that of birth weight (AUC 0.84, 95% CI 0.75-0.93), but superior to that of GA (AUC 0.77, 95% CI 0.65-0.89) in predicting mortality. CRIB II, SNAP-II, and SNAPPE-II appeared to be excellent predictors and were superior to birth weight (AUC 0.88, 95% CI 0.80-0.95) or GA (AUC 0.84, 95% CI 0.72-0.96) alone in predicting early death. AUC of all neonatal illness severity scores indicated fair or failed ability for predicting short-term morbidity in extremely premature infants.

Discussion

The present study showed that the neonatal illness severity scores (CRIB II, SNAP-II, SNAPPE-II) appeared to be good predictors of mortality in extremely premature infants, similar

to birth weight, but superior to GA. Moreover, it is highly possible that the neonatal illness severity scores were excellent predictors of early death in extremely premature infants (CRIB II: AUC 0.93; SNAP-II: AUC 0.90; SNAPPE-II: AUC 0.95). However, neonatal illness severity scores were poor predictors of short-term morbidity.

Predicting mortality of extremely premature infants is helpful for clinical decision making; however, it is difficult to do this accurately. The present study demonstrated that neonatal illness severity scores proved to be good predictors of mortality, and there is little difference in the predictive ability between neonatal illness severity scores and birth weight. Greenwood et al. [16] reported that CRIB II was superior to GA or birth weight alone in predicting mortality of infants born at <29 weeks' GA. Dammann et al. [22] reported that infants with SNAP-II score ≥ 30 were almost 6 times more likely to die than those with lower SNAP-II score, and infants with SNAPPE-II score ≥ 45 were almost 7 times more likely to die than those with lower SNAPPE-II, among infants born at <29 weeks' GA.

To the best of our knowledge, this is the first study demonstrating that CRIB II, SNAP-II, and SNAPPE-II were better predictors of early death than mortality in extremely premature infants. Generally, 82.7% of deaths occurred within 28 days of birth in extremely premature infants [2]. We speculated that early death prediction and early therapeutic intervention of extremely premature infants with high mortality risk will improve mortality in these infants. However, Park et al. [11] demonstrated that CRIB II was not effective in predicting early death in

extremely low birth infants. CRIB II scores were higher in our infants born at 23 and 24 weeks' GA with early death (18.3±2.2) than in Park et al.'s infants born at 23 and 24 weeks' GA who died on <7th postnatal day (16.1±1.1). Infant characteristics may differ between Park et al.'s study and ours.

Previously, SNAP-II predicted the mortality risk of infants with severe septicemia [28] and congenital diaphragmatic hernia [29], and SNAP-II was better in predicting illness severity in very low birth weight infants than in those who weighed more than 1,500 g [30]; neonatal illness severity scores might be appropriate for evaluating mortality of high-risk populations. We believe that further analysis will be required to evaluate the relationship between neonatal illness severity scores and mortality in extremely premature infants.

CRIB II and SNAPPE-II had similar predictive ability, which is superior to that of SNAP-II. In the present study, multivariate analysis revealed that birth weight, pH, and base excess were independent risk factors for mortality and early death; therefore, SNAPPE-II, in which the variables include perinatal factors, showed better predictive ability of mortality than SNAP-II. Variables of CRIB II and SNAPPE-II include birth weight and blood gas (pH, base excess); therefore, CRIB II showed similar predictive ability of mortality with SNAPPE-II. In previous reports, predictive ability of CRIB II was slightly superior to SNAPPE-II in infants born at <32 weeks' GA [4], and CRIB II showed greater predictive ability of mortality than SNAPPE-II in very low birth weight infants [15]. The different results might be due to the different populations

being studied.

Neonatal illness severity scores were poor predictors of short-term morbidity in extremely premature infants in the present study. Özcan et al. [19] reported that SNAPPE-II was an independent risk factor for BPD and ROP. Yanhong et al. [21] reported that high SNAP scores were significantly associated with increased risk for BPD; however, predictive accuracy of SNAP was not superior to that of GA. Carvalho et al. [14] reported that SNAPPE-II was proved to predict severe morbidities, including IVH, NEC, and ROP; however, the AUC demonstrated fair-to-poor predictive ability. The present study suggested that the association between neonatal illness severity scores and short-term morbidity in extremely premature infants was not strong. We suggested that predicting short-term morbidity risk of extremely premature infants depends not only on neonatal illness severity scores but also on the interaction of medical factors after 12 hours of birth. CRIB II, SNAP-II, and SNAPPE-II were poorly calibrated for extremely premature infants. Short-term morbidity of extremely premature infants is especially higher than that of the general population; thus, the neonatal illness severity scores should be re-validated in predicting short-term morbidity of extremely premature infants.

The rapid medical evolution might have altered the association between mortality and severity scores. Nevertheless, neonatal illness severity scores were still excellent predictors of mortality in extremely premature infants. Although even the best scoring systems are not completely accurate, neonatal illness severity scores might be useful for selecting infants who need

intervention, such as whether to perform resuscitation, mechanical ventilation, and other intensive treatments to reduce early death in extremely premature infants.

One limitation of this study is its retrospective design. However, all infants had sufficient data for calculating the neonatal illness severity scores, and no infant was lost to follow-up. The other limitation is that only a small number of infants were included and the study was performed in a single institution. Our hospital is the only tertiary medical facility in the region; therefore, almost all extremely premature infants are admitted to our hospital. However, our study population might not reflect the infant characteristics seen elsewhere. Further studies involving a larger population and multiple institutions are needed to confirm our findings.

In conclusion, the neonatal illness severity scores were excellent predictors of early death in extremely premature infants and might be useful for selecting extremely preterm infants who need intervention,

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Table 1. Population characteristics, and CRIB II, SNAP-II, SNAPPE-II in the study population.

			total	survived	expired	p value
			n=171	n=152	n=19	
Gestational age		mean±SD	25.5±1.6	25.7±1.5	24.2±1.4	<0.01
Birth weight		mean±SD	741.3±208.2	767.5±200.6	532.0±141.7	<0.01
Sex	male	n (%)	97 (56.4)	85 (55.9)	12 (63.2)	0.548
SGA		n (%)	23 (13.5)	17 (11.2)	6 (31.6)	0.025
chorioamnionitis		n (%)	41 (24.0)	35 (23.0)	6 (31.6)	0.403
antenetal CS		n (%)	96 (56.8)	84 (56.0)	12 (63.2)	0.707
PDA		n (%)	43 (25.3)	41 (27.0)	2 (11.1)	0.163
IVH	grade3-4	n(%)	9 (5.3)	6 (3.9)	3 (15.8)	0.134
NEC	grade II-III	n (%)	5 (3.0)	1 (0.7)	4 (23.5)	<0.01
Intestinal perforation		n (%)	6 (3.6)	2 (1.3)	4 (23.5)	<0.01
BPD		n (%)	74 (45.7)	69 (42.6)	5 (83.3)	0.053
ROP		n (%)	31 (19.8)	29 (19.1)	2 (50.0)	0.177
CRIB Ⅱ		median (range	12 (7-21)	12 (7-19)	16 (9-21)	<0.01
SNAP-Ⅱ		median (range	25 (0-74)	23 (0-74)	42 (9-66)	<0.01
SNAPPE-Ⅱ		median (range	49 (0-109)	43 (0-109)	76 (37-101	<0.01

SGA small for gestational age, CS corticosteroid, PDA patent ductus arteriosus, INDO indomethacin, IVH intraventricular hemorrhage, NEC necrotizing enterocolitis, BPD bronchopulmonary dysplasia, ROP retinopathy of prematurity

Table 2. Area under receiver operating curve for mortality and complication predicting ability of the neonatal severity scores.

	CRIB Ⅱ	SNAP-Ⅱ	SNAPPE-Ⅱ
mortality	0.81 (0.69-0.93)	0.77 (0.65-0.90)	0.85 (0.77-0.93)
early death[§]	0.93 (0.85-1.00)	0.90 (0.76-1.00)	0.95 (0.91-0.99)
PDA	0.49 (0.39-0.59)	0.55 (0.45-0.65)	0.50 (0.39-0.59)
IVH	0.74 (0.57-0.90)	0.77 (0.62-0.93)	0.74 (0.56-0.90)
NEC	0.64 (0.40-0.88)	0.73 (0.56-0.91)	0.74 (0.55-0.93)
Intestinal perforation	0.72 (0.50-0.93)	0.71 (0.57-0.85)	0.74 (0.58-0.91)
BPD[¶]	0.80 (0.73-0.87)	0.63 (0.55-0.72)	0.67 (0.59-0.76)
ROP[¶]	0.66 (0.56-0.77)	0.64 (0.51-0.73)	0.60 (0.47-0.68)

Data is presented as area under reciever operating curve (95% confidence interval)
§ early death: infants who died on the <28th postnatal day.
¶ BPD and ROP were analyzed in the infants who survived more than 36 weeks' corrected a
PDA patent ductus arteriosus, IVH intraventricular hemorrhage, NEC necrotizing enterocolitis, BPD bronchopulmonary dysplasia, ROP retinopathy of prematurity