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Original Article

Risk prediction using a neonatal therapeutic intervention scoring system in VLBW and ELBW preterm infants

Nihal Oygur,[1] Hakan Ongun[3] and Osman Saka[2]

[1]*Department of Pediatrics, Division of Neonatology,* [2]*Department of Biostatistics, Akdeniz University Medical School and* [3]*Department of Pediatrics, Medical Park Hospital, Antalya, Turkey*

Abstract ***Background***: The Neonatal Therapeutic Intervention Scoring System (NTISS) is a therapy-based severity-of-illness index, The aim of the present study was to evaluate whether: (i) NTISS can predict the severity of illness with the same accuracy both in very low-birthweight (VLBW) and extremely low-birthweight (ELBW) infants, using all parameters; and (ii) the performance of NTISS can be increased by using only the significant variables.

Methods: All inborns <1500 g, and all outborns <1500 g transferred in the first 12 h of postnatal life, were included. NTISS using 63 variables was assessed for all infants at the 24th hour. Predictive performance for the overall variables was assessed using area under the curve (AUC) for group 1 (500–1499 g), 2 (1000–1499 g) and 3 (500–999 g). Variables with good prediction were identified for each group and a second AUC was assessed using only sensitive variables. Receiver operating characteristic (ROC) curve area for all variables was compared with the ROC area for sensitive variables.

Results: A total of 364 preterm infants fulfilled the eligibility criteria. The AUC of groups 1, 2 and 3 with all variables were 0.851; 0.834 and 0.749, respectively. The number of parameters with good prediction was 33 in group 1, 30 in group 2 and 18 in group 3. The AUC for sensitive variables was 0.848 in group 1; 0.821 in group 2 and 0.823 in group 3. When compared, increase in the description of outcome was significant only for group 3 patients ($P = 0.02$).

Conclusion: NTISS using all parameters seems to be less predictive in ELBW infants. It is probably related to the use of some interventions, done as a routine procedure in almost all ELBW preterm infants, therefore NTISS may be modified according to birthweight in order to obtain a more sensitive prediction.

Key words area under the curve, mortality, neonatal intensive care unit, Neonatal Therapeutic Intervention Scoring System, very low-birthweight.

Measurement of illness severity is useful for assessing mortality risk and making comparisons of outcomes among the neonatal intensive care units (NICUs) of different hospitals or between different years in the same NICU.[1–6]

The Neonatal Therapeutic Intervention Scoring system (NTISS) is a therapy-based severity-of-illness index, which is used as an indicator of neonatal illness severity and resource utilization. It assesses severity, based on the intensity of therapeutic interventions during the first 24 h of life.[2,7] Although it is generally used for prediction in <1500 g preterm infants, it is not clear whether this system can predict mortality with same accuracy in <1000 g preterm infants.

Thus, the aim of the present study was to evaluate whether: (i) NTISS can predict severity of illness with the same accuracy in both very low-birthweight (VLBW) and extremely low-birthweight (ELBW) infants; and (ii) the performance of the NTISS can be increased by using only those variables that have been found to be statistically significant.

Correspondence: Nihal Oygur, MD, Department of Pediatrics, Division of Neonatology, Akdeniz University Medical School, 07070-Antalya, Turkey. Email: nihaloygur@akdeniz.edu.tr

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Methods

Subjects

The study was approved by the Ethics Committee of Akdeniz University. Data were collected by a research fellow using SPSS (SPSS, Chicago, IL, USA). All inborn preterm infants with a birthweight <1500 g and outborns (<1500 g) who were transferred to the NICU at Akdeniz University Medical School in the first 12 h of postnatal life in a 5 year period (2006–2010), were included in the study. Infants who were transferred after the first 12 h of life, or who had lethal congenital anomalies, or who died within 12 h of admittance to NICU were excluded from the study.

Data were collected retrospectively for the first 3 years and prospectively for the last 2 years. All prospective data were abstracted from the clinical records and retrospective data, from the existing medical records. Preterm infants with missing values in their records were also excluded.

Table 1 Subject characteristics

	Group 1	Group 2	Group 3
Patients (n)	364	241	123
Gestational age (weeks), mean ± SD	31 ± 3.1	30 ± 4.2	27 ± 2.4
Birthweight (g), mean ± SD	1260 ± 118	1310 ± 106	875 ± 87
Sex (F/M)	251/113	156/85	95/28
Inborn/outborn	246/118	146/95	100/23
Mortality, *n* (%)	103 (28.3)	33 (13.79)	70 (57)

Group 1, birthweight 500–1499 g; group 2, birthweight 1000–1499 g; group 3, birthweight 500–999 g.

Parental consent was obtained for patients with prospective data but not for those with retrospective data, because it would not be possible to find all parents from their old telephone numbers or addresses, written in their records.

The NTISS, consisting of 63 therapeutic interventions, was assessed for all groups of patients in the 24th hour of life. Patients were tracked until death or discharge home. Preterm infants were divided into three groups according to birthweight as follows: group 1, 500–1499 g; group 2, 1000–1499 g; and group 3, 500–999 g.

The predictive performance of NTISS for all variables was assessed using area under the curve (AUC) for group 1, 2 and 3 patients. A receiver operating characteristic (ROC) curve area of 1.0 indicated perfect discrimination, whereas an area of 0.50 was completely random.

In order to understand which variables were more sensitive, each variable was evaluated individually for prediction of outcome in all groups. A second AUC was then assessed for only the variables with good prediction. This AUC was then compared with that for all variables for each group.

Statistical analysis

In order to evaluate the significance of each variable in the NTISS, the χ^2 test was used for all three study groups. Pearson χ^2 test or Fisher's exact test was used depending on the case numbers at each comparison. NTISS variables that predicted survival or death with $P < 0.05$ in preterm infants were identified. These variables were considered as significant variables and they were combined for further ROC curve comparisons. Student's *t*-test was used for the comparison of AUC.

Results

Out of 364 preterm infants with a birthweight <1500 g who were eligible for the study, 241 were between 1000 and 1499 g and 123 were between 500 and 999 g. Gestational age and birthweight were 31 ± 3.1weeks and 1260 ± 118 g for group 1; 30 ± 4.2 weeks and 1310 ± 106 g for group 2; and 27 ± 2.4 weeks and 875 ± 87 g for group 3. Inborn/outborn ratio was 246/118 for group 1, 146/95 for group 2 and 100/23 for group 3. The overall mortality during the 5 year period was 103 (28.3%) for group 1, 33 (13.7%) for group 2 and 70 (56.9%) for group 3 (Table 1).

Leukocyte transfusion in the 'transfusion' item, pacemaker in the 'cardiovascular' item and extensive phlebotomy (>10 blood

Table 2 Significant variables (χ^2 test)

Item (63 NTISS variables)	Group 1	Group 2	Group 3
Respiratory			
Additional O_2	+	+	–
Surfactant	+	+	+
Tracheostomy	–	–	–
Tracheostomy care	–	–	–
CPAP	+	+	+
Entubation	+	+	+
Mechanical ventilation	+	+	+
MV plus muscle relaxant	+	+	–
HFOV	–	–	–
ECMO†			
Cardiovascular			
Indomethacin	+	+	–
Volume expansion (≤15 mL/kg)	+	+	+
Vasopressor (one agent)	+	+	–
Volume expansion (>15 mL/kg)	+	+	+
Vasopressor (>1 agent)	+	+	+
Cardiopulmonary resuscitation	+	+	+
Standby†			
Pacemaker†			
Drug therapy			
Antibiotics (≤2 agents)	–	–	–
Steroids (postnatal)	+	–	+
Anticonvulsant	+	+	+
Aminophylline	+	+	–
Antibiotics (>2 agents)	+	–	–
Diuretic (enteral)	–	+	–
Diuretic (parenteral)	+	+	+
Treatment of metabolic acidosis	+	+	+
Potassium binding resin	+	+	–
Other medications	+	–	–
Vascular access			
Central venous line	+	+	+
Peripheral i.v. line	–	–	–
Arterial line	–	–	–
Monitoring			
Ordinary vital signs	–	–	–
Cardiopulmonary monitoring	–	–	–
Extensive phlebotomy (>10 blood draws)†			
Thermoregulated environment	–	–	–
Non-invasive monitoring	–	–	–
Arterial pressure monitoring	–	–	–
CVP monitoring	+	–	–
Urinary catheter	+	+	–
Quantitative intake–output	–	–	–
Excessive phlebotomy (>10)	–	–	–
Metabolic/nutrition			
Gavage feeding	+	+	+
I.v. lipid solution	+	+	–
I.v. amino acid solution	+	+	+
Phototherapy	–	–	–
Insulin	+	+	–
Potassium infusion	+	+	+
Transfusion			
I.v. gamma globulin	+	+	–
Red blood cell transfusion (≤15 mL/kg)	+	+	+
Red blood cell transfusion (>15 mL/kg)	+	+	+
Partial exchange	–	–	–
Platelet transfusion	+	+	–
Exchange transfusion	–	–	–
Leukocyte transfusion†			
Procedures			
Transportation	+	+	–
Single chest tube	–	–	–
Multiple chest tubes	–	–	–
Minor operation	–	–	–
Dialysis	–	–	–
Pericardiocentesis†			
Pericardial tube†			
Thoracentesis	–	–	–
Major operation†			
No. variables with good discrimination	33	30	18

+, good discrimination; –, not significant. †Not done in any patients during the study period.

Group 1, birthweight 500–1499 g; group 2, birthweight 1000–1499 g; group 3, birthweight 500–999 g.

CPAP, continuous positive airway pressure; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; MV, mechanical ventilation; NTISS, Neonatal Therapeutic Intervention Scoring System.

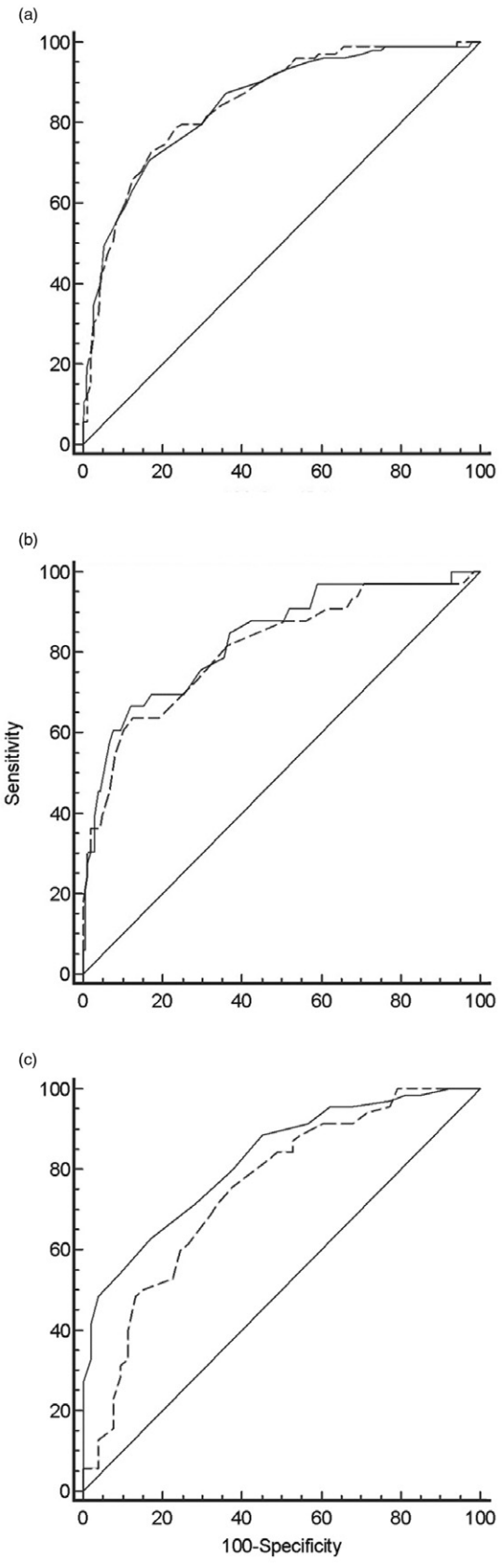

Fig. 1 Comparison of area under the curve (AUC) for (--) all variables and (—) only significant variables of the Neonatal Therapeutic Intervention Scoring System (NTISS) for preterm infants with (a) birthweight 500–1499 g; (b) 1000–1499 g; and (c) 500–999 g. (a) All variables, $n = 62$ variables: AUC, 0.851 (95% confidence interval [CI]: 0.809–0.885); significant variables, $n = 33$ variables: AUC, 0.848 (95%CI: 0.806–0.883), $P = 0.87$. (b) All variables, $n = 62$ variables: AUC, 0.834 (95%CI: 0.781–0.878); significant variables, $n = 30$ variables: AUC, 0.821 (95%CI: 0.756–0.858), $P = 0.32$. (c) All variables, $n = 62$ variables: AUC, 0.749 (95%CI: 0.662–0.822); significant variables, $n = 18$ variables: AUC, 0.823 (95%CI: 0.744–0.886), $P = 0.02$.

draws) in the 'monitoring' item were not performed for any of the NICU patients in the 5 year period. Also, the discrimination of outcome could not be evaluated for extracorporeal membrane oxygenation in the 'respiratory' item because this procedure cannot be performed in our department.

Variables that were found as sensitive for the three groups of preterm infants are listed in Table 2. Thirty-three variables were found to be good discriminators of outcome for group 1 patients, 30 for group 2 and 18 for group 3.

The AUC for NTISS with all variables, was 0.851 (95% confidence interval [CI], 0.809–0.885) in group 1, 0.834 (95%CI: 0.781–0.878) in group 2 and 0.749 (95%CI: 0.662–0.822) in group 3. Although statistically not significant, variables had better discrimination in group 1 and 2 patients when compared to group 3 ($P = 0.32$ for comparison of group 1 and group 3; $P = 0.28$ for comparison of group 2 and group 3).

The AUC for NTISS with only sensitive variables was 0.848 (95%CI: 0.806–0.883) in group 1; 0.821 (95%CI: 0.756–0.858) in group 2 and 0.823 (95%CI: 0.744–0.886) in group 3. Increase in the description of outcome was significant only for group 3 patients when the ROC curve areas of NTISS for all variables were compared with that of NTISS for only the sensitive variables ($P = 0.02$; Table 3; Fig. 1).

Discussion

Neonatal disease severity scoring systems are useful in comparing outcomes across hospitals or NICUs; in obtaining information about population differences when performing studies such as clinical trials; outcome evaluations; and evaluations of resource utilization. An ideal scoring system is accepted as one that is easy to use, has the ability to predict mortality, specific morbidities or cost for various categories of neonates, and is useful for all groups. It is almost impossible, however, to fulfill all these requirements in a single scoring model.[2–8]

The NTISS is based on the treatments received by an infant, rather than on measurement of pathophysiological factors, as in the other scoring system models.[9–12] It is a therapy-based severity-of-illness assessment score, for use in neonatal intensive care, and it has been modified from the Adult Therapeutic Intervention Scoring System. It is a valid measure of therapeutic intensity and can be used as an indicator of neonatal illness severity and resource utilization.[13]

In recent years, increase in *in vitro* fertilization caused also a significant increase in preterm delivery all over the world.

Table 3 AUC and no. sensitive parameters

Birthweight groups (g)	$AUC_{all\ parameters}$ (95%CI)	No. sensitive parameters†	$AUC_{sensitive\ parameters}$ (95%CI)	*P*
1 (1499–500)	0.851 (0.809–0.885)	33	0.848 (0.806–0.883)	0.87
2 (1499–1000)	0.834 (0.781–0.878)	30	0.821 (0.756–0.858)	0.32
3 (999–500)	0.749 (0.662–0.822)	18	0.823 (0.744–0.886)	**0.02**

†χ^2 test. **Bold**, $P < 0.05$.
AUC, area under the curve; CI, confidence interval.

Although two-thirds of preterm infants with a birthweight <1000 g were not able to survive in the past, advances in neonatal intensive care over the past decade, such as use of high-frequency oscillatory ventilation, nitric oxide and antenatal corticosteroids, have resulted in a significant decrease in the mortality of ELBW infants.[14–16] Life-threatening conditions, treatment modalities, interventions and causes of mortality in >1000 g preterm infants are very different to those in <1000 g preterm infants, therefore they should not be evaluated in the same group as <1500 g preterm infants. This suggestion may also be true for risk prediction models, therefore we investigated whether risk prediction using NTISS also differed due to birthweight. We also identified those parameters significant in risk prediction in the different birthweight groups and investigated whether it was possible to increase the prediction by using only the significant parameters.

We used mortality to validate the severity of illness measure, because mortality could be clearly defined and used in almost all types of prediction models. According to the present results, risk prediction using NTISS seemed to be significant for preterm infants <1500 g, and the prediction accuracy could not be changed by using only the sensitive variables ($AUC_{all\ variables}$, 0.851 vs $AUC_{significant\ variables}$, 0.848 in group 1; $P = 0.87$). The prediction accuracy was also good in preterm infants with birthweight between 1000 and 1499 g and the sensitivity could not be changed by using only the significant parameters ($AUC_{all\ variables}$, 0.834 vs $AUC_{significant\ variables}$, 0.831 in group 2; $P = 0.32$). In group 3, however, risk prediction using NTISS for all variables seemed to be less sensitive for <1000 g preterm infants when they were evaluated as a separate group, and significant increase was obtained when only the sensitive variables were used for NTISS ($AUC_{all\ variables}$, 0.749 vs $AUC_{significant\ variables}$, 0.823 in group 3; $P = 0.02$). These results suggest that the significance of variables for risk prediction may change due to birthweight. Some variables such as vasopressor use, indomethacin, i.v. lipids, platelet transfusion, and i.v. immunoglobulin are common procedures, done for almost all <1000 g preterm infants, while these procedures may be indicative of a worse prognosis or more invasive disease for those with birthweight >1000 g.

It is common opinion that the risk of intraventricular hemorrhage, necrotizing enterocolitis, hypothermia, hypotension, metabolic disturbances and mortality increases as prematurity increases. Therefore it is logical to increase the number of therapeutic interventions and supportive therapies in NICUs, as the gestational age of the preterm baby decreases. Also, therapeutic interventions may vary with the different NICUs. As an example, it is common to give prophylactic indomethacin or ibuprofen to all preterm infants <1000 g in the NICU at Akdeniz University Medical School, therefore indomethacin is not a significant risk predictor for ELBW preterm infants in that center. Similarly, using gavage feeding for a preterm infant under 34 weeks gestation or total parenteral nutrition in the early postnatal days of a small preterm infant are also common procedures for most NICUs, but when gavage feeding or total parenteral nutrition is used for a near-term baby it means that the newborn has a severe neurologic, cardiovascular or respiratory problem. Therefore, predictors of mortality differ in number and variety according to gestational age, and the number of predictors of mortality decreases as gestational age decreases.

In conclusion, a good neonatal mortality risk prediction model should consist of only variables that have high discriminatory ability. Before decreasing the number of variables in the NTISS, however, further multicenter studies with a larger number of preterm infants are necessary.

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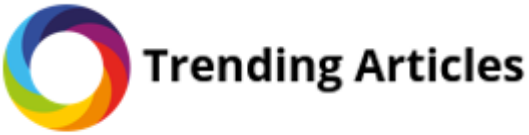

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