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Original Research Article

Neonatal Sequential Organ Failure Assessment (Nsofa) in Early Prediction of Morbidities and Mortality in Neonates with Perinatal Asphyxia – A Prospective Cohort Study

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Conflict of interest: Nil

Abstract:

Background: The most common reason for resuscitation in the delivery room is birth asphyxia. Twenty-five percent of all early postnatal fatalities are related to hypoxic-ischemic encephalopathy (HIE) and subsequent organ failure. In newborns with sepsis, the neonatal Sequential Organ Failure Assessment (nSOFA) takes circulatory, respiratory, and platelet failure into account.

Aim: To evaluate whether nSOFA is also a usefulpredictor for in-hospital mortality in neonates (≥ 36+0 weeks of gestation (GA)) following asphyxia with HIE and therapeutic hypothermia (TH).

Results: nSOFA was documented at ≤ 6 hours of life. 65neonates fulfilled inclusion criteria for TH. All but one infant received cardiopulmonary resuscitation and/or respiratory support at birth. nSOFA was lower in survivors (median 0 [IQR 0-2]; *n* = 56, median GA 39+3, female *n* = 28 (50%)) than in non-survivors (median 10 [4-12], p < 0.001; *n* = 9, median GA 38+6, *n* = 4 (44.4%)). This was also observed for the respiratory (p < 0.001), cardiovascular(p < 0.001), and hematologic sub scores (p = 0.003). The odds ratio for mortality was 1.6 [95% CI = 1.2 – 2.1] per one-point increase in nSOFA. The optimal cut-off value of nSOFA to predict mortalitywas 3.5 (sensitivity 100.0%, specificity 83.9%).

Conclusion: Since early accurate prognosis following asphyxiawith HIE and TH is essential to guide end-of-life decisions, nSOFA (≤ 6 hours of life) offers the potential to identify neonates at risk of mortality.

Keywords: Birth asphyxia; nSOFA; outcome prediction; neonate; Hypoxic-ischemic encephalopathy (HIE); therapeutic hypothermia; resuscitation; organ dysfunction; biomarker; mortality

Introduction

The essential component to neonatal adaptation after birth is the initiation of adequate respiratory effort. Approximately 10-15% of newborns require support for respiratory transition at birth, 3% require positive pressure ventilation by mask, 2% intubation and only < 1% cardiopulmonary resuscitation with chest compressions or ephinephrine to establish cardiorespiratory function. [1] The major cause for delivery room cardiopulmonary resuscitation isbirth asphyxia, a condition of insufficient oxygen supply to vital organs that results in hypoxia, hypercarbia and metabolic acidosis and, if prolonged, may progress to multiorgan failure, includingthe developing brain. [2]

Asphyxia may originate from prenatal, perinatal or postnatal pathology. Prenatal maternal pathologies that increase the risk for birth asphyxia include diabetes mellitus or gestational diabetes, arterial hypertension, placental insufficiency, pregnancy toxemia, eclamptic seizure, infections, or drugs. Perinatal risk factors are e.g., placental abruption, fetomaternal hemorrhage, amniotic fluid embolism, umbilical cord compression (knot or prolapse), insertio velamentosa of the umbilical cord, placenta previa, shoulder dystocia). [3]

Postnatal causes of birth asphyxia are fetal anemia due to twin-to-twin transfusion in monochoriotic twins or fetal isoimmunization, airway anomalies,

neurologic disorders, severe cardiopulmonary disease, infection, congenital malformations, intrauterine growth retardation, medication effects). [4]

Hypoxic-ischemic encephalopathy is classified into three severity grades according to Sarnat et al. based on clinical symptoms. For the diagnosis of moderate or severe hypoxic-ischemic encephalopathy (grade II, III), at least three of the six categories (e.g., vigilance, activity, reflexes, muscle tone, apnea, seizures) must be met. Birth asphyxia accounts for 900.000 neonatal deaths worldwide annually and hypoxic-ischemic encephalopathy is estimated to cause up to a quarter of all postnatal deaths. [5]

Therapeutic hypothermia is the only evidence-based neuroprotective therapeutic intervention currently available and is standard of care in high income countries for moderate and severe hypoxic- ischemic encephalopathy (grade II, III). According to guidelines, therapeutic hypothermia is indicated in neonates ≥ 36+0 weeks of gestation if one of the following criteria is met: Umbilical cord pH or pH < 1h: ≤ 7,0; Apgar Score at 10 min ≤ 5; Base excess ≤ -16 mmol/l, ongoing cardiopulmonary resuscitation, ventilatory support at 10 min plus either a clinical sign of hypoxic-ischemic encephalopathy (see above) or pathological background activity on amplitude-integrated electroencephalogram (aEEG), such as low voltage and burst suppression. [6]

The Sepsis-related Organ Failure Assessment (SOFA) Score was designed to quantify organ dysfunction and mortality risk in adult intensive care patients with sepsis. In recent years its use is no longer limited to sepsis and the acronym is sometimes translated into Sequential Organ Failure Assessment, reflecting the broad dissemination of the SOFA score. [7]

The neonatal modification of the SOFA (nSOFA) was proposed to address the need for a consensus definition of neonatal sepsis in 2020. nSOFA uses three objective and broadly available clinical parameters to quantify organ dysfunction: respiratory, cardiovascular, and hematological scores (total scores range from 0 to 15). It has been previously used for predicting mortality and severe morbidity in preterm neonates, preterm neonates with late onset sepsis, respiratory distress syndrome (RDS) [26] and neonates with proven sepsis. [8]

The aim of the present study was to evaluate the accuracy of the nSOFA for predicting in- hospital mortality (sensitivity, specificity) following hypoxic-ischemic encephalopathy and therapeutic hypothermia.

Materials and methods

This prospective study the charts of all neonates with a gestational age of ≥ 36 weeks, who received therapeutic hypothermia for hypoxic-ischemic encephalopathy following birth asphyxia at the level III A NICU of BLDE (DU) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura between January 2022 and December 2022. [IRB approval- BLDE (DU)/IEC/193/2022)]

Contraindications for therapeutic hypothermia were life-threatening congenital malformation (e.g., diaphragmatic hernia, cerebral malformation), suspected metabolic disease, coagulopathy with active bleeding, cerebral hemorrhage, cerebral venous thrombosis, or hemorrhagic infarction, small for gestational age with birth weight < 1800g, severe pulmonary hypertension.

Therapeutic hypothermia was delivered following a standardized protocol. Whole body hypothermia was initiated as early postnatally as possible but within 6 hours after birth. A target temperature of 33.5 to 34.5°C, which was monitored by continuous rectal probe, was considered. It was sustained for 72 hours followed by a rewarming phase. Temperature was increased 0.5°C per hour until 37.0°C were reached. Until 2015 this was done manually. After that a servo-controlled cooling mattress was used.

The nSOFA is calculated from 3 subcategories for respiratory, cardiovascular and hematological status (Table 1). The respiratory category takes the status of mechanical ventilation, oxygen saturation (SpO2) and fraction of inspired oxygen (FiO2) into account (score range 0-8). Cardiovascular status analyses the number of vasoactive drugs necessary to maintain normal blood pressure including the use of corticosteroids (score range 0-4). The hematologic score is based on the presence and severity of thrombocytopenia (score range 0-3). The total score can therefore range from 0 (best) to 15 (worst).[8] Data to calculate nSOFA in our cohort were derived from the patient charts, choosing the worst score value from the first 6 hours of life. Monitoring included continuous amplitude-integrated electroencephalogram (aEEG), Thompson-Score and 1-2 hourly vital signs including changes in ventilator settings was done. A complete blood count is included in the initial blood work on admission.

Statistical Analysis

Analyses were performed using SPSS 25 (IBM Corp., New York, NY, USA). Patient demographics, clinical characteristics and nSOFA scores are presented as medians and ranges or interquartile ranges for continuous variables and for categorical variables as counts and category percentages. Mann-Whitney U tests and Fisher exact Test were used to compare continuous and non- continuous data, respectively. Two-sided p-values < 0.05 were considered statistically significant. Logistic regression was performed to calculate the odds ratio for in hospital-mortality with the nSOFA score as regressor. Positive and negative predictive values were calculated.

Results

Out of 2016 neonates screened, 79 neonates received therapeutic hypothermia. We excluded 4 neonates from the analysis, because of a baseline condition with influence on organ function or mortality other than hypoxic-ischemic encephalopathy: two neonates with blood-culture proven early-onset sepsis, one infant with congenital malformation and one infant with chromosomal abnormality. Two neonates had life-threatening congenital malformations, so they were included. Two neonates were excluded since they did not suffer from birth asphyxia, but required resuscitation later than in the delivery room. 45 of 79 neonates were inborn. Out born neonates were transferred to our institution and therapeutic hypothermia was commenced within the first 6 hours of life. From these, 3 neonates were born outside of a hospital, which led to missing data in one case. 7 additional cases of out born neonates had to be excluded, because data to calculate nSOFA were not sufficient. This led to a final cohort of 65 neonates with 21 out born neonates (survival cohort n = 16; non-survival cohort n = 5).

Survivors (n = 56) and non-survivors (n = 9) were similar with respect to gestational age, birth weight, small for gestational age, head circumference, child sex, umbilical cord pH and umbilical base excess (BE) (Table 1). Non-survivors had lower pH and BE in the first infant blood gas analysis, Apgar-Score at 1, 5, and 10 minutes and Thompson-Score. Non-survivors were more often born via c-section, or emergency c-section (Table 2). One surviving infant was born as twin, there were no multiple births in the non-survival cohort. All but one infant received cardiopulmonary resuscitation and/or respiratory support during transition after birth. Non-survivors were more likely to have received cardiopulmonary resuscitation during postnatal care as shown in table 1.

Table 1: Clinical characteristics of survivors and non-survivors

Parameters	Survivors (n = 56)	Non-survivors (n = 9)
Gestational age, weeks [range]	39+3 [36+0 - 41+4]	38+6 [37+2 - 41+2]
Weight at birth, gram [range]	3170 [1745 - 4400]	3380 [2600 - 4400]
Small for gestational age < 10, n (%)	12 (21.4%)	1 (11.1%)
Height at birth, cm [range]	50.0 [42.0 - 58.0]	52.5 [50.0 - 56.0][b]
Head circumference at birth, cm [range]	34.0 [30.0 - 38.0][c]	34.8 [31.5 - 38.0][b]
Female, n (%)	28 (50.0%)	4 (44.4%)
Umbilical cord pH (SD)	6.98 [6.61 - 7.28][d]	7.05 [6.59 - 7.29][e]
First pH from infant[a]	6.93 [6.75 - 7.19][f]	6.74 [6.41 - 7.23]
Umbilical cord base excess	-15.25 [-33.90-4.20][g]	-16.70 [-23.00 - -5.00][h]
First base excess from infant[a]	-17.90 [-28.00--9.10][i]	-25.15 [-31.70 - -8.70][b]
Apgar 1 minute [range]	2 [0 - 6][c]	0 [0 - 1]
Apgar 5 minute [range]	5 [0 - 8][c]	0 [0 - 4]
Apgar 10 minute [range]	7 [1 - 10][c]	3 [0 - 4]
Cardiopulmonary resuscitation, n (%)	13 (23.2%)	7 (77.7%)
Respiratory support, n (%)	55 (98.2%)	9 (100%)
Intubation, n (%)	23 (41.0%)	9 (100%)

nSOFA sum scores were lower in survivors than in non-survivors (Mann-Whitney U test, $p < 0.001$) (Figure 2, Table 3). This also held true for respiratory ($p < 0.001$), cardiovascular ($p < 0.001$), and hematologic sub scores ($p = 0.003$), respectively (Figure 1, Table 2).

Table 2: Descriptive characteristics of nSOFA total score and sub scores in survivors and non- survivors

	Survivors(n = 56)	Non-survivors (n= 9)	P value
nSOFA total score	0 [0 - 2]	10 [4.5 - 11.5]	< .001
Respiratory score	0 [0 - 0]	8 [4 - 8]	< .001
Intubation, n (%)	23 (41.1%)	9 (100.0%)	< .001
SpO2/FiO2	447.6 [246.9 - 461.9][a]	79.0 [55.0 - 178.3]	< .001
Cardiovascular score	0 [0 - 0]	2 [2 - 3]	< .001
One inotrope, n (%)	9 (16.1%)	2 (22.2%)	0.642
Two or more inotropes, n (%)	0 (0%)	4 (44.4%)	< .001
Systemic steroids, n (%)	0 (0%)	1 (11.1%)	0.138
Hematologic score	0 [0 - 0]	1 [1 - 1]	0.003
Platelet count	237 [180 - 279]	132 [110 - 242]	0.077

A significant relationship of nSOFA and mortality was confirmed with an odds ratio for mortality of 1.61 [95% CI = 1.24 - 2.08] per one-point increase in nSOFA score (X2 (1) = 25.98, p < 0.001, Nagelkerkes R2 = 0.53). The ROC curve for risk of death by nSOFA (Figure 3) had an area under the

curve (AUC) of 0.94 (95% CI = 0.88 - 1.00). The optimal cut-off value of the nSOFA score according to Youden-Index and closest top left method was 3.5 (sensitivity 100.0%, specificity 83.9%). Using a cut-off of 3.5 points on the nSOFA score, the positive and negative predictive values were 50.0% and 100.0%, respectively (cross-tabulation in Table 3).

Table 3: Cross-tabulation of nSOFA cut-off value of 3.5 in survivors and non-survivors

Parameters		Survivors	Non-survivors	Total
nSOFA at least 3.5	no	47	0	47
	yes	9	9	18
		56	9	65

Discussion

The nSOFA proved useful for predicting in-hospital mortality in neonates with hypoxic- ischemic encephalopathy undergoing therapeutic hypothermia. Non-survivors showed significantly higher sum scores, as well as respiratory, cardiovascular, and hematologic sub scores. [9] A one-point increase in nSOFA increased the odds for in-hospital mortality by 1.6. None of the neonates with nSOFA score < 3.5 died in this cohort (negative predictive value: 100%). Thus, the nSOFA serves well as an operational definition of organ dysfunction identifying neonates at risk for death following birth asphyxia.

Despite the excellent negative predictive value of nSOFA scores< 3.5 several survivors had nSOFA scores of 8, limiting the positive predictive value of the cut-off value. This is likely due to the fact that the respiratory sub score has the highest weight in the nSOFA sum score, with mechanical ventilation contributing 8 points of the possible total of 15. [10] All non-survivors and 41% of survivors were intubated and received mechanical ventilation within the first 6 hours of life, which resulted in respiratory sub scores of 2 to 8 points.

In a previous study it was shown that the need for mechanical ventilation was significantly higher in the group with severe asphyxia and unfavorable outcome (death and severe brain injury on MRI) compared to neonates with better short term outcome. [11,12] However, in this cohort, the need for mechanical ventilation without another sign of organ dysfunction was not inextricably associated with death, calling for caution when interpreting nSOFA scores in neonates on mechanical ventilation who are otherwise stable. [13]

A neonate who experiences birth asphyxia may still develop multi-organ failure and become life-threateningly ill due to the redistribution of cardiac output to vital organs such as the brain, myocardium, and adrenal gland. Reduced perfusion to the other organs may cause local hypoxia/ischemia and may result in organ failure. [14] If birth asphyxia is prolonged, cardiovascular deterioration occurs that eventually causes myocardial dysfunction. The fact that the cardiovascular sub score showed fewer differences between survivors and non-survivors in this study may indicate that this cohort was less affected, or that cardiovascular impairment in asphyxia is less common than in sepsis, for which the nSOFA was originally developed for.

Thombocytopenia may result from both asphyxia and therapeutic hypothermia. There is a reduced release of platelets from the bone marrow and an increased destruction of circulating platelets in birth asphyxia, platelet dysfunction under therapeutic hypothermia. The nadir of platelet count is on the 3rd day of life following asphyxia and 5th day of life under therapeutic hypothermia, suggesting an additive effect of therapeutic hypothermia. [15] An influence of therapeutic hypothermia on the early nSOFA score is therefore unlikely. It is reasonable to assume that cardiovascular and hematological sub scores of the nSOFA increase during the acute phase of post- resuscitation treatment before dropping again. However, early determination of organ dysfunction and risk of mortality is desirable. All neonates in this study had hypoxic-ischemic encephalopathy as an expression of moderate to severe brain injury. [16]

Redirection of care is common on (N)ICUs for critically ill patients with poor prognosis either for survival, severe disabilities and a high burden of treatment or poor quality of life. The window ofopportunity for decisions to limit therapy in severe hypoxic-ischemic encephalopathy exists while the infant is critically ill and physiologically unstable and therefore highly likely to die when treatment is withheld or withdrawn. The extend of the time window depends on the severity of the injury, the extent of cerebral edema, and the use of sedatives and anticonvulsants. Sarkar et al. [13] demonstrated that 40% of neonates with hypoxic-ischemic encephalopathy were extubated within thefirst 3 days. Physicians must consider the competing factors of prognostic certainty and this time window. [17] In the cooling era, most deaths after elective extubation occurred within the first 72 hours in very unstable neonates, whereas withdrawal of nutrition and hydration was a more difficult option in neonates who survived the acute phase with severe brain damage and palliative care. Decisions about life-sustaining treatments or withdrawal of support are among the most sensitive and difficult conversations parents ever

must face about their infant. [18] Medico-ethical guidelines recommend shared decision making with parents in these situations and parents appreciated being fully informed about the medical situation and possible options, and especially appreciated being encouraged to ask questions. A recent study showed that both parents and physicians share the wish for certainty in end-of-life decisions. [19] However, prognosis in hypoxic-ischemic encephalopathy is challenging.

First-hour clinical parameters, such as umbilical cord pH and Apgar scores have limitedreliability in predicting individual mortality. In addition, the Apgar includes subjective componentswith high inter-observer variability. Currently available biomarkers, physical examination, chemical, electrophysiological, and imaging studies, all have specific limitations. [20] Electrophysiology has a good predictive marker for abnormal brain activity, but itnecessitates equipment, resources, and expertise.[21] MRI examinations also involves a large amount of time and effort, the risk of transporting a critically ill infant and limited accuracy of early scans compared to those obtained at the end of the first week of life.[22] The fact that only 4 of the non- surviving neonates in this study received MRI highlights that they presented with such severe symptomatology that the extent of cerebral damage was either not necessary for decision making todiscontinue therapy or the neonates died despite full therapy.

Strengths and Limitations

The strength of our study lies in the fact that we were able to show for the first time that the nSOFA offers the potential to identify neonates at risk of mortality following birth asphyxia and hypoxic-ischemic encephalopathy within the first 6 hours of life. The nSOFA is easy to apply, does not require a large number of human resources and no technical equipment. It is based on variables that can be objectified and measured even in low-resource settings. The nSOFA may serve as a valuable tool in the discussion of treatment termination after severe birth asphyxia with hypoxic- ischemic encephalopathy and therapeutic hypothermia.

Future aspects and conclusions

Therefore, the results of this study should be prospectively replicated in multiple centers and larger samples to investigate influencing factors such as maternal diseases, delivery mode, socio- economic status, and fetal factors e.g., child sex, small for gestational age and sepsis. In addition, it may be of interest to explore the extent to which the nSOFA is helpful in future decision making andin counseling with parents. The nSOFA is easy to apply, measurable even in low-resource settings and can be used to identify neonates at risk of in-hospital mortality due to asphyxia with hypoxic- ischemic encephalopathy and therapeutic hypothermia. Early accurate prognosis after asphyxia withhypoxic-ischemic encephalopathy and therapeutic hypothermia is essential to guide end-of-life decisions.

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