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Critical Organ Dysfunction and Preoperative Mortality in Newborns with Hypoplastic Left Heart Syndrome

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Abstract

Hypoplastic left heart syndrome (HLHS) is fatal without surgical intervention. An important subset of HLHS patients die prior to surgical intervention, but this population is undervalued. The neonatal sequential organ failure assessment score (nSOFA) is an operational definition of organ dysfunction that can identify those with a high risk of mortality among neonatal intensive care unit (NICU) patients. The utility of the nSOFA to predict preoperative mortality in the unique HLHS population is unknown and could inform care, particularly care provided by neonatology staff. We performed a multicenter retrospective cohort study of HLHS cases across three level IV NICUs from January 1, 2009 to December 3, 2023. Patients were classified as either survived or died prior to surgical intervention. Demographic variables were curated from medical records including the maximum nSOFA (nSOFA_{max}) before surgical intervention or death. We identified 265 patients with HLHS over the study period. The nSOFA_{max} was greater in patients who died preoperatively (14/265; 5%) compared with survivors to surgical intervention (median 8 [interquartile range, 6, 12] vs. 2 [0, 4]; $p < 0.001$). The area under receiver operating characteristics curve for the nSOFA_{max} to discriminate for mortality was 0.93 (95% confidence interval, 0.88–0.98; $p < 0.001$). Compared with an nSOFA_{max} of 0, the likelihood ratio for preoperative death doubled at 2, tripled at 4, and was 10-fold at 9. This is the first demonstration of nSOFA utility specific to congenital heart disease and HLHS. The nSOFA_{max} represents a novel, electronic health record-compatible, and generalizable method to identify patient-level organ dysfunction and risk for preoperative mortality in HLHS patients.

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Conflict of Interest

J.L.W. served as a one-time consultant to Sobi for neonatal immunology expertise.

Keywords

congenital heart disease; hypoplastic left heart syndrome; illness severity score; nSOFA score

Introduction

Hypoplastic left heart syndrome (HLHS) is a severe birth defect characterized by underdevelopment of the left heart structures.¹ HLHS is universally fatal without surgical intervention soon after birth. While most progress in HLHS care has focused on operative and postoperative management and outcomes,^{1,2} the preoperative period requires meticulous medical management utilizing tremendous resources and an important subset of HLHS patients die prior to surgical intervention.^{1,2} Therefore, there is a need to closely investigate preoperative HLHS management.

Preoperative HLHS management involves stabilization of patients, often in cardiogenic shock, with respiratory, volume, and inotropic support.^{1,2} Markers of organ dysfunction, including lactate and blood gases, are utilized to monitor and guide care. Similar to the multisystem, categorical sequential organ failure assessment (SOFA) that operationalizes mortality risk in adults and correlative pediatric SOFA in children, the neonatal SOFA (nSOFA) is a validated tool to measure life-threatening organ dysfunction (respiratory, cardiovascular, hematologic) in the neonatal population.^{3–5} The nSOFA has demonstrated utility in multiple subpopulations of critically ill neonates and automated scoring can be integrated into the electronic health record (EHR).^{3–5} However, its utility in the unique HLHS population is unknown and could inform care, particularly care provided preoperatively by neonatology staff. Furthermore, an assessment of preoperative illness severity that would facilitate precise patient classification is not commonly included in HLHS reports. We performed a focused multicenter, retrospective, cohort study to measure the utility of the nSOFA to determine the risk of preoperative mortality in HLHS patients.

Methods

We performed a retrospective cohort study of HLHS cases in the level IV neonatal intensive care units (NICUs) at the Riley Hospital for Children at the Indiana University Health (IU; January 1, 2009–November 1, 2022), University of Florida Health (UF; January 1, 2012–March 1, 2020), and Johns Hopkins University (JHU; July 1, 2016–December 3, 2023). Following site-specific Institutional Review Board approval, International Classification of Diseases (ICD) codes for HLHS (ICD9: 746.7; ICD10: Q23.4) were used to identify HLHS with confirmation via echocardiogram report review. Patients without confirmed classical HLHS or who were redirected to palliative care were excluded. Included patients were classified as either survived or died prior to surgical intervention. Demographic variables were curated from medical records alongside the maximum nSOFA (nSOFAmax) that occurred before surgical intervention or death. Variables were assessed for data distribution and compared using the Mann–Whitney or chi-square test. Calculations were based on available data only. Area under receiver operating characteristics curves (AUROC) were

calculated using nSOFAmax for the outcome of preoperative mortality. Calculations were performed using GraphPad Prism (v10).

Results

ICD code screening yielded 427 potential subjects. After exclusions (158 not HLHS, 4 palliative care post-HLHS diagnosis), we identified 265 patients with HLHS over the study period (174 patients from IU, 52 from UF and 39 from JHU; Table 1). As expected, preoperative death (14/265; 5%) was associated with established risk factors in the newborn population, including gestational age and Apgar score and with laboratory surrogates of organ dysfunction including minimum pH, maximum lactate, and maximum base deficit. Preoperative mortality was not associated with birthweight, sex, or mode of delivery. We analyzed the nSOFAmax score in all HLHS patients across the hospitalization from birth to death or initial operation. Compared with patients who survived to an operation, nSOFAmax was greater in patients who died preoperatively (median 2; [interquartile range, 0, 4] vs. 8; [6, 12]; $p < 0.001$). The AUROC for the nSOFAmax to discriminate for mortality was 0.93 (95% confidence interval, 0.88–0.98; $p < 0.001$). Center-specific AUROCs were similar for IU (0.94 [0.89–0.99; $p < 0.001$]) and UF (0.95 [0.89–0.99; $p < 0.001$]). Cases of mortality JHU ($n = 3$) were excluded due to redirection to palliation. Compared with an nSOFAmax of 0, the likelihood ratio for preoperative death doubled at 2, tripled at 4, and was 10-fold at 9.

Discussion

This is the first demonstration of nSOFA utility in congenital heart disease and specifically HLHS.^{3–5} The nSOFAmax score showed excellent, generalizable discrimination of preoperative mortality in the high-risk HLHS population. The distinct physiology of HLHS requires meticulous preoperative medical management, including careful limitation of oxygen supplementation to balance systemic and pulmonary blood flow.² Despite the weight of the nSOFA respiratory scoring component, which can account for as much as 8 of the maximum 15 points, we found the nSOFA had excellent accuracy for preoperative death. HLHS patients often die from cardiogenic shock due to unmanageable pulmonary overcirculation or restrictive atrial septum with associated pulmonary hypertension and cardiogenic shock. The nSOFA score has been validated in the entire NICU population, as well as in multiple subsets of NICU patients, as an excellent tool to identify organ dysfunction and discern all-cause mortality, and our data reinforce this finding, demonstrating similar utility in the HLHS population, likely succumbing to cardiogenic shock.

Although this report is focused on the relationship between the nSOFAmax score and preoperative mortality, serial nSOFA measures can reveal individual clinical trajectories and may serve as objective measures of effective therapeutic intervention (Figure 1). Many high-performing centers caring for HLHS patients have moved to aggressive management, with surgical pulmonary artery banding or catheter-based internal pulmonary artery banding, balloon atrial septostomy, or atrial septal stenting, along with rapid progression to surgical Norwood, in a subset of high-risk HLHS patients. The nSOFA provides an ideal marker to identify these high-risk patients that may benefit from this early intervention strategy. The

nSOFA score may also be used to measure improvement postintervention and pre-Norwood procedure. Given the increasing availability of automated, EHR-compatible nSOFA scoring, it may be a valuable tool for multidisciplinary clinical teams managing this complex patient population, especially as health care incorporates artificial intelligence and machine learning for neonatal precision medicine.

In addition to the limitations inherent to a retrospective cohort study, another limitation is our focus on the preoperative period. Future studies could also expand to the postoperative period. We present hourly nSOFA scores in three HLHS patients to demonstrate that the nSOFA score is an excellent real-time marker of organ dysfunction in the HLHS population. Future studies could expand this analysis with a comparison, at hourly intervals, to other components traditionally used as markers of organ dysfunction in HLHS, such as pH and lactate. Future studies may also expand on this schema, to identify nSOFA score thresholds that might prompt an intervention to prevent preoperative death in HLHS patients. We did not examine the utility of individual nSOFA component scores. Future studies may consider developing a unique score for HLHS, using individual components of the nSOFA included or excluded, or new components added. However, the nSOFA score has broad utility in many NICU populations, as a composite score, and is currently displayed within the EMR and accessible to many centers caring for HLHS patients.

This study demonstrates a novel, generalizable method to identify organ dysfunction and risk for preoperative mortality in patients with HLHS.

Acknowledgment

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References

1. Ohye RG, Schranz D, D'Udekem Y. Current therapy for hypoplastic left heart syndrome and related single ventricle lesions. *Circulation* 2016;134(17):1265–1279. [PubMed: 27777296]
2. Feinstein JA, Benson DW, Dubin AM, et al. Hypoplastic left heart syndrome: current considerations and expectations. *J Am Coll Cardiol* 2012;59(1, suppl):S1–S42. [PubMed: 22192720]
3. Lavilla OC, Aziz KB, Lure AC, Gipson D, de la Cruz D, Wynn JL. Hourly kinetics of critical organ dysfunction in extremely preterm infants. *Am J Respir Crit Care Med* 2022;205(01):75–87. [PubMed: 34550843]
4. Aziz KB, Schles EM, Makker K, Wynn JL. Frequency of acute kidney injury and association with mortality among extremely preterm infants. *JAMA Netw Open* 2022;5(12):e2246327. [PubMed: 36512358]
5. Fleiss N, Coggins SA, Lewis AN, et al. Evaluation of the neonatal sequential organ failure assessment and mortality risk in preterm infants with late-onset infection. *JAMA Netw Open* 2021;4(02):e2036518. [PubMed: 33538825]

Key Points

- An important subset of HLHS patients die preoperatively.
- nSOFA can be used to measure preoperative HLHS severity.
- nSOFA predicts preoperative mortality risk in HLHS patients.

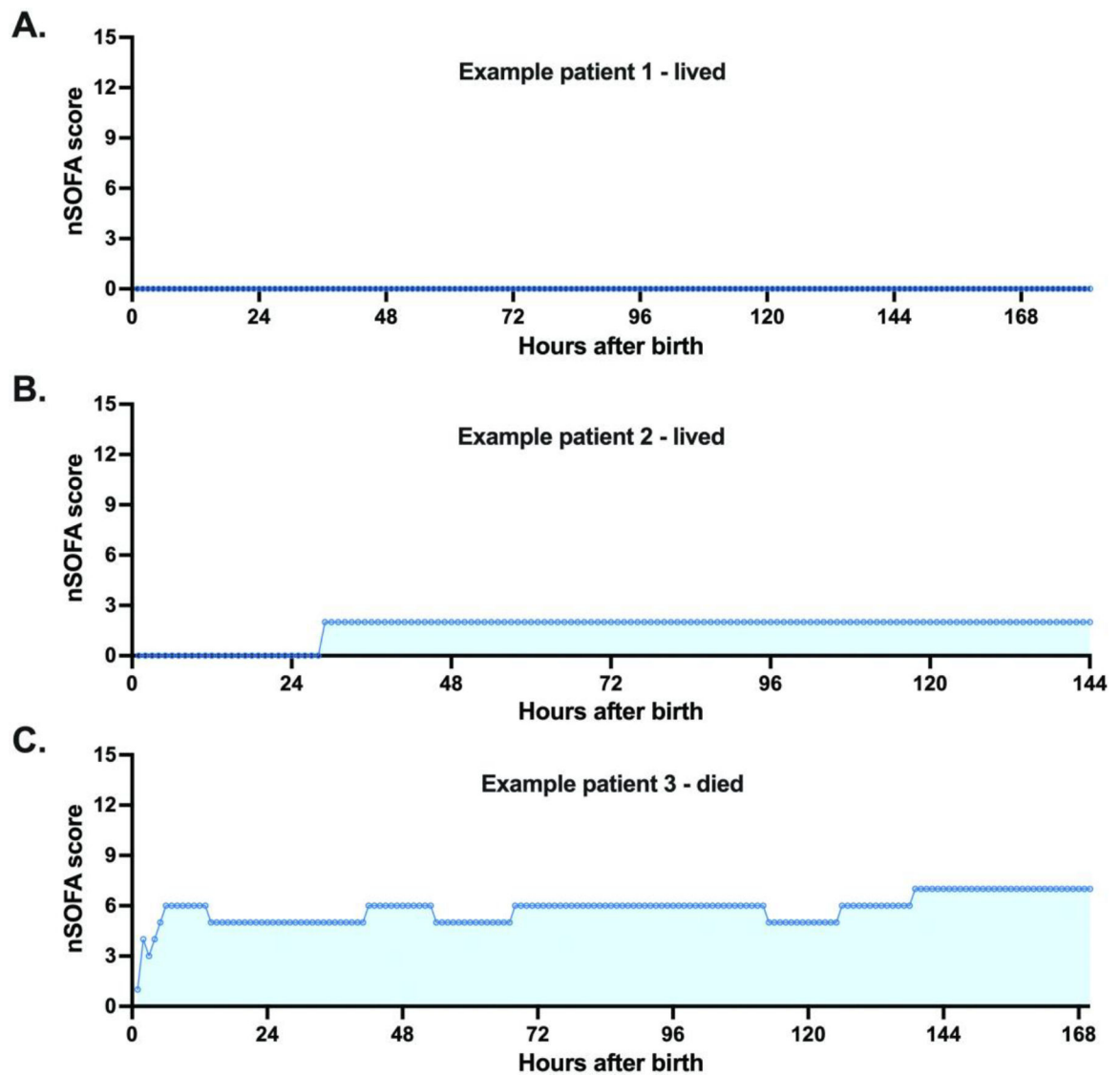


Fig. 1. Example hypoplastic left heart syndrome neonatal sequential organ failure assessment score (nSOFA) score profiles for individual patients who survived (A, B) and those who died (C).

Table 1

Hypoplastic left heart syndrome cohort characteristics

Characteristic	Lived (n = 251)	Died (n = 14)	p-Value
GA (wk), median (IQR)	39 (38, 39)	38 (37, 39)	0.002
BW (g), median (IQR)	3,128 (2,838, 3,390)	3,145 (2,183, 3,291)	0.32
Male, n (%)	161 (64)	8 (57)	0.60
Vaginal delivery, n (%) ^a	140 (57)	8 (57)	0.99
5-min Apgar, median (IQR) ^b	9 (8, 9)	6 (5, 7)	<0.001
Minimum pH, median (IQR) ^c	7.26 (7.17, 7.30)	7.00 (6.93, 7.15)	<0.001
Minimum base deficit (mEq/L), median (IQR) ^d	-6 (-8, -3)	-12 (-20, -10)	<0.001
Maximum lactate (mmol/L), median (IQR) ^e	3.0 (2.2, 5.0)	10.8 (6.5, 14.3)	<0.001
Maximum nSOFA score, median (IQR)	2 (0, 4)	8 (6, 12)	<0.001

Abbreviations: BW, birthweight; GA, gestational age; IQR, interquartile range; nSOFA, neonatal sequential organ failure assessment.

^aMissing delivery mode in 5 survivors.

^bMissing 5-minute Apgar score in 15 survivors; 2 died.

^cMissing pH in 4 survivors; 1 died.

^dMissing base deficit in 4 survivors; 1 died.

^eMissing lactate in 29 survivors; 1 died.