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Maximum Vasoactive-Inotropic Score and Mortality in Extremely Premature, Extremely Low Birth Weight Infants

Khyzer B. Aziz, MD^{*1}, Orlyn C. Lavilla, MD^{*2}, James L. Wynn, MD^{2,3}, Allison C. Lure, MD², Daniel Gipson, MD², Diemel de la Cruz, MD²

¹Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland

²Department of Pediatrics, University of Florida, Gainesville, Florida

³Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, Florida

Abstract

Objective: To determine the relationship between maximum vasoactive-inotropic (VIS^{max}) and mortality in extremely premature (<29 weeks completed gestation), extremely low birth weight (ELBW, <1000 grams) infants.

Study Design: Single-center, retrospective, observational cohort study.

Results: We identified 436 ELBW, <29 week, inborn infants cared for during the study period. Compared to infants with VIS^{max} of 0, the frequency of mortality based on VIS^{max} ranged from 3.3-fold to 46.1 fold. VIS^{max} >30 was associated with universal mortality. Multivariable modeling that included gestational age, birth weight, and VIS^{max} revealed significant utility to predict mortality with negative predictive value of 87.0% and positive predictive value of 84.8% [adjusted AUROC: 0.90, (0.86-0.94)] among patients that received vasoactive-inotropic treatment.

Conclusion: VIS^{max} is an objective measure of hemodynamic/cardiovascular support that was directly associated with mortality in extremely premature ELBW infants. The VIS^{max} represents an important step towards neonatal precision medicine and risk-stratification of extremely premature ELBW infants.

Keywords

vasoactive-inotropic score; mortality; extremely low birth weight; preterm

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Address Correspondence to: Diemel de la Cruz, MD, Department of Pediatrics, University of Florida, 1600 SW Archer Road, PO Box 100296, Gainesville, FL 32610-0296, ddelacruz@peds.ufl.edu, Tel: 352-273-8985; James L. Wynn, MD, Department of Pediatrics, University of Florida, 1600 SW Archer Road, PO Box 100296, Gainesville, FL 32610-0296, James.wynn@peds.ufl.edu, Tel: 352-273-8985.

*first authors contributed equally

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Conflict of Interest: The authors have no conflicts of interest.

Ethical Approval: This study was approved by the Institutional Review Board at the University Of Florida (IRB201902780). The study was performed in accordance with the Declaration of Helsinki.

Introduction

Premature, extremely low birth weight (ELBW) infants are at high risk for significant morbidity and mortality^{1, 2, 3}. Although the frequency of adverse outcomes in this population are commonly reported, there remains a critical unmet need to identify and quantify the severity of critical illness associated with outcomes of interest to improve clinical care and clinical research. Achievement of this goal is the prerequisite to neonatal precision medicine, where patient-specific factors can be used to provide the right patient with the right treatment at the right time in the neonatal intensive care unit (NICU). Use of vasoactive-inotropic medications is common in the premature, ELBW population, yet outcomes, when reported, are often based on a binary (yes, no) exposure paradigm. Quantification of the pharmacological cardiovascular support provided to this unique population as well as the association with mortality remains unknown.

The inotropic score was initially designed by *Wernovsky et al.* in the Boston Circulatory Arrest Study to quantify the amount of pharmacological cardiovascular support during the postoperative period after arterial switch in term neonates and infants^{4, 5}. Later it was expanded by *Gaies et al.* to include other commonly used medications, such as milrinone, vasopressin, and norepinephrine and subsequently called the vasoactive-inotropic score (VIS)⁶. The inotropic score, VIS, and other similar adaptations that measure cardiovascular support have been used to measure illness severity in neonates and infants undergoing congenital heart surgery, septic pediatric patients admitted to the pediatric intensive care unit (PICU), or septic adult patients admitted the medical intensive care unit (MICU)^{4, 6, 7, 8, 9, 10}. In these studies, the vasopressor dose load, VIS, maximum VIS (VIS^{max}), or various time points pertaining to the VIS have shown a direct relationship between the need for vasoactive-inotropic medications and the risk of morbidity and mortality.

Premature ELBW infants have a high risk for hemodynamic/cardiovascular dysfunction due to: i) less contractile myocardial tissue relative to older children & adults, ii) underdeveloped mechanisms which control myocyte activity, iii) immature adrenergic responses, and iv) limited ability to respond to increases in stress and metabolic demands¹¹. We aimed to determine the association between VIS^{max} and the risk of mortality in premature ELBW infants. We hypothesized that premature ELBW infants who had a higher VIS^{max} would be more likely to experience mortality compared to those who had lower VIS^{max}.

Methods

Patients

This was a single center, retrospective, observational cohort study approved by the University of Florida Institutional Review Board (IRB) prior to the collection of any data. Following IRB approval, an integrated data repository (IDR) of all ELBW, <29 weeks completed gestation infants admitted to the UF Health, level IV NICU between 1/2012 and 1/2020 was created. All clinical data in the electronic health record (EHR) were extracted and deposited into an IDR that was used for this work. Infants born at outside hospitals,

those that survived less than 12 hours, those that had confirmed severe congenital anomalies, or those that completed <22 weeks gestation were excluded.

Case definitions

Chorioamnionitis was defined as histologic evidence of chorioamnionitis or funisitis.

All-cause mortality was reported. Demographic variables and outcomes were defined as

previously reported.² Necrotizing enterocolitis (NEC) was defined as modified Bell's stage

2. Bacteremia was stratified by the timing of onset after birth (early-onset: ≤3 days of life;

late-onset >3 days of life). Severe intraventricular hemorrhage (SIVH) was defined as either

unilateral or bilateral grade 3-4 IVH. Spontaneous intestinal perforation (SIP) was defined

as intestinal perforation without evidence of NEC. Prolonged early antibiotics was defined

as ≥5 days of parenteral broad-spectrum antimicrobial treatment started in the first 3 days of

life.

The maximum vasoactive-inotropic score (VIS^{max})

Vasoactive-inotropic medication exposures during the birth encounter were identified.

Medications considered vasoactive-inotropic included dopamine, dobutamine, epinephrine, milrinone, vasopressin and norepinephrine. For infants with vasoactive-inotropic medication

exposures, the vasoactive-inotropic score (VIS) was calculated as follows: dopamine

dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min)

+ (10 x milrinone dose (μg/kg/min) + 10 x vasopressin dose (mU/kg/min) + 100 x

norepinephrine dose (μg/kg/min)⁸. The VIS^{max} was the maximum VIS score during the

birth hospitalization.

Analytical methods

For descriptive data comparisons, we used Kruskal-Wallis test for continuous data with

Dunn's multiple comparisons test and the χ^2 test for categorical data. Continuous variables

were summarized as medians with quartiles (25th and 75th percentiles). Categorical

variables were presented as percentages. The threshold for statistical significance was less

than 0.05 for 2-sided tests. The area under the receiver operating characteristics curve

(AUROC) for mortality using the VIS^{max} was calculated. Spearman's rank correlation

coefficient was calculated with a 2-tailed p-value and 95% confidence intervals and a

correlation matrix was generated. Logistic regression was performed to determine the

relationship between VIS^{max} and death (unadjusted) as well as comparisons adjusted for

gestational age and birth weight using multiple logistic regression models. Negative and

positive predictive values were calculated based on the multivariable model. All analyses

were performed using Graph Pad Prism version 8 (San Diego).

Results

We identified 559 ELBW, <29 week, infants cared for at UF Health during the study

period. After exclusions [89 out-born, 7 severe congenital anomalies, 7 died in the delivery

room, 11 died <12hours of life (7 received intensive care; 4 received comfort care), 1

transferred to an outside hospital at 24 days of life, and 8 remained hospitalized at the

time of data extraction], 436 infants were available for study. Infants that did not receive

vasoactive-inotropic medications during the birth hospitalization were used as the reference group (n=195). Median VIS^{max} scores were not different by year of admission (p=0.49 by Kruskal-Wallis). The median VIS^{max}, determined to be 10 among 241 patients treated with 1 or more vasoactive-inotropic medications during the birth hospitalization, was used to establish groups for demographic and clinical variable comparisons (Table 1). We did not find significant differences between groups in any maternal variables we examined. Compared to infants with a VIS^{max} of 0 (never received vasoactive-inotropic medications) and those with a VIS^{max} <10, infants that manifested a VIS^{max} ≥ 10 were less mature, smaller, had longer length of stay among survivors, and experienced a greater frequency of complications including SIVH, SIP, prolonged early antibiotic exposure, and death. Apgar scores at 5 minutes were statistically different between patients without vasoactive-inotropic medication exposure (VIS^{max} = 0) and both groups of patients with exposure (VIS^{max} <10; p=0.004 or VIS^{max} ≥ 10; p<0.001), but not between the groups of patients with exposure (p>0.999 by Kruskal-Wallis).

Distribution of VIS^{max} by gestational age and birth weight

We found an inverse relationship between the frequency of vasoactive-inotropic medication exposure and gestational age as well as birth weight (Figure 1A-D). Among infants that received vasoactive-inotropic medications, the VIS^{max} was greatest among the most immature and smallest infants.

VIS^{max} timing and mortality

Of the 241 patients with a VIS^{max} > 0, 126 experienced the VIS^{max} within one calendar day of birth; 181 had the VIS^{max} within 7 calendar days of birth. Among the 92 patients that died, four infants did not receive any vasoactive-inotropic medications. Among those that died with a VIS^{max} >0, the median age was 5 calendar days after birth (IQR 2, 15). Overall cohort mortality was 21% (92/436). Among those that did not receive any vasoactive-inotropic medications (VIS^{max} = 0), mortality was 2.1% (4/195). The frequency of mortality increased significantly with VIS^{max} (p<0.001 by Chi-square; Figure 2). Compared to infants with VIS^{max} of 0, the frequency of mortality increased substantially with VIS^{max} > 0 (3.3-fold for VIS^{max} >0-<5; 5.1-fold for VIS^{max} 5-<10; 13.8-fold for VIS^{max} 10-<15; 13.8-fold for VIS^{max} 15-<20; 23.8-fold for VIS^{max} 20-<25; 37.7-fold for VIS^{max} 25-30; and 46.1 fold for VIS^{max} >30). A VIS^{max} > 30 was associated with universal mortality.

Vasoactive-inotropic medication initiation patterns

Among patients that received vasoactive-inotropic medications, dopamine was almost universally (236/241, 98%) the first medication given, and monotherapy with dopamine was the most common treatment (n=102). Pre-episode hydrocortisone followed by dopamine with or without additional vasoactive-inotropic medications occurred in 28 patients. Dopamine with subsequent hydrocortisone (n=23), dopamine with subsequent epinephrine followed by hydrocortisone (n=22), and dopamine with subsequent hydrocortisone followed by epinephrine (n=14) were the most common combinations. Among those 241 patients with VIS^{max} score >0, 118 had concurrent hydrocortisone support (65 died). 123 had no hydrocortisone at the time of the VIS^{max} (23 died).

Modeling mortality risk using VIS^{max}

We measured the utility of the VIS^{max} to predict mortality among all patients (n=436) in our cohort. Unadjusted logistic regression comparing the VIS^{max} and mortality yielded an AUROC of 0.92 (95% confidence intervals 0.88-0.95, p<0.001). A significant positive correlation was found between VIS^{max} and death (Spearman's rank correlation coefficient 0.62; p<0.001). Among all patients, the Spearman rank correlation coefficient between VIS^{max} and death (0.62; p<0.001) nearly approximated the correlation seen between GA and BW (0.65; p<0.001). A multivariable logistic regression model that included birth weight and gestational age alongside VIS^{max} to predict mortality among all patients yielded a negative predictive value (NPV) of 93.2% and a positive predictive value (PPV) of 85% [adjusted AUROC: 0.94, (0.92-0.97)]. Results were very similar when only gestational age [NPV: 92.5%, PPV: 84.4%, AUROC: 0.94, (0.92-0.96)] or only birth weight [NPV: 93.0%, PPV: 84.8%, AUROC: 0.94, (0.91-.96)] were included in the model alongside VIS^{max} to predict mortality.

Repeated analyses restricted to only those that received vasoactive-inotropic treatment using the outcome of mortality revealed comparable results for analyses using unadjusted logistic regression [VIS^{max} and mortality; AUROC 0.88 (0.83-0.93)]. Among only the patients that received vasoactive-inotropic medications, the Spearman's rank correlation coefficient between VIS^{max} and death (0.64; p<0.001) exceeded the correlation seen between GA and BW (0.61, p<0.001). A multivariable logistic regression model that included birth weight and gestational age alongside VIS^{max} to predict mortality among only the patients that received vasoactive-inotropic medications yielded a NPV (86.9%), PPV (84.8%) and AUROC: 0.90, (0.86-0.94) (Figure 3). Results were very similar when only gestational age [NPV: 86.0%, PPV: 84.4%, AUROC: 0.90, (0.85-0.94)] or only birth weight [NPV: 87.7%, PPV: 86.1%, AUROC: 0.90, (0.85-0.94)] were included in the model alongside VIS^{max} to predict mortality. Repeat analyses that included hydrocortisone treatment had no effect on the model.

Discussion

This study represents the largest, most comprehensively studied cohort of extremely premature, ELBW infants for which a VIS^{max} was calculated. We found that mortality varied significantly with VIS^{max} and was universal with a VIS^{max} > 30. The VIS^{max} was an easily quantifiable measure of vasoactive-inotropic support that was highly-associated with the risk of mortality within this vulnerable population. The ability to objectively and reproducibly characterize patient-specific hemodynamic support is a critical first step in neonatology that may be used in future clinical studies to improve patient classification and patient care.

The direct association between VIS^{max} and death risk in our extremely premature ELBW cohort was similar to studies in children and adults. *Gaies et al.* found that a VIS^{max} of 20-24 in the first 24 hours or VIS^{max} of 15-19 in the subsequent 48 hours post congenital heart surgery in infants was associated with a higher risk of death (in-hospital or within 30 days of discharge), cardiac arrest, need for mechanical circulatory support, need for renal replacement therapy, or central nervous system injury relative to the "low risk" group

($VIS^{\max} < 3$)⁶. Among pediatric patients with sepsis admitted to the PICU, *Haque et al.* found that a $VIS^{\max} > 20$ was associated with 100% mortality¹². The VIS^{\max} scores in our cohort were higher than those of infants and children from previous studies^{6, 8, 12}. We found 87% (58/67) of patients with a $VIS^{\max} > 20$ died and universal mortality occurred with a VIS^{\max} of > 30 . Furthermore, we saw an inverse relationship between vasoactive-inotropic support relative to gestational age and birth weight. Taken together, our VIS^{\max} and associated mortality data are similar to results in adults and children, and the higher scores seen in our cohort do not readily support an early path to palliation or comfort care in this population.

As expected, we found a greater frequency of complications of extreme prematurity associated with critical illness including hemodynamic instability among those with higher VIS^{\max} scores. SIVH, SIP, and NEC are often associated with hemodynamic dysfunction^{13, 14, 15}. Although the presence or absence of hypotension is included in the staging of NEC¹⁶, and a requirement for vasoactive-inotropic support is a criterion for septic shock^{17, 18, 19}, neither the extent nor the severity of hemodynamic support required in most neonatal conditions are routinely reported. Notably, over half (52%) of the extremely premature ELBW infants that received vasoactive-inotropic medications experienced VIS^{\max} within one calendar day of birth, suggesting that the indication for vasoactive-inotropic therapy was temporally associated with the complex interplay of antenatal factors, transitional events, and post-natal stressors immediately following delivery^{20, 21}. Based on our results, patients with significant differences in mortality risk may be grouped together based on gestational age, birth weight, or a diagnosis that lacks severity classifiers. Use of the VIS^{\max} would facilitate severity of hemodynamic dysfunction classification among babies that require vasoactive-inotropic medications.

We found dopamine was nearly universally the first medication started, and dopamine was included in 99% (239/241) of treatment patterns we studied. Medication selection for initial vasoactive-inotropic therapy in this cohort was similar to previous studies in very low birth weight infants (< 1500 grams)^{20, 22, 23, 24, 25}. Given the varied initiation and combination of vasoactive-inotropic medications administered coupled with an inability to determine the indication for vasoactive-inotropic support, no particular medication combination or pattern was a reliable indicator of adverse outcomes and mortality. There is significant opportunity for improvement in neonatal clinical care and research that would accompany a determination of active disease state, phase of physiologic transition, and competing interventions prior to and after initiating vasoactive-inotropic therapy via added use of targeted neonatal point-of-care echocardiograms, increased use of biological markers of perfusion (i.e. lactates), and other noninvasive modalities such as near-infrared spectroscopy (NIRS)^{26, 27, 28, 29, 30}.

Our objective was to determine the relationship between VIS^{\max} and mortality in extremely premature (< 29 weeks completed gestation), extremely low birth weight (< 1000 grams) infants. Our results highlight the strong association of the VIS^{\max} score and mortality risk and underscore the inclusion of the VIS^{\max} as an opportunity to use an underutilized metric in a fragile population lacking objective, quantifiable, replicable tools. In stark contrast to data-rich care guidelines available for pediatric and adult ICU patients to address multiple

etiologies of hypotension, the definition of hypotension, including evidence-based thresholds for when to intervene, the characterization and dynamics of hypotension including cardiac function as well as the effects of specific medications and dosing, and therapeutic endpoints of when to stop treatment, remain unclear in the extremely preterm infant^{31, 32}. Many reasons may be given for this lack of consensus including the impact and overlap of a variety of antenatal factors, transitional events, and post-natal disease states^{20, 33}. The lack of verified clinical definitions and predictors of outcomes complicates neonatal care. The conduct of clinical trials to determine if benefit or harm occurs with a specific intervention or therapy is hampered by the variability in practices across centers and insufficient detail in publications including the extent of support. The VIS^{max} could allow for risk stratification of patients, assist with study design, help to more clearly describe populations being investigated, and serve as an important control variable when analyzing the impact of therapies intended to stabilize the cardiovascular system in unique patient populations. Due to the potential variability in hemodynamic support practices between centers based on the lack of evidence-based approaches for hypotension, use of the VIS^{max} in future clinical studies represents a substantial advance in this population in that it may be used independently or in concert with severity of illness scores, such as the neonatal sequential organ failure assessment (nSOFA)³⁴, to help identify and quantify the extent of hemodynamic/cardiovascular dysfunction.

Our study is not without limitations inherent to any retrospective single-center study. Our objective was to determine the relationship between the VIS^{max} and mortality in this unique population. We did not perform a matched propensity analysis aimed to determine the impact of vasoactive-inotropic drugs on mortality. These data neither support modification of an individual patient's treatment to avoid a high VIS^{max}, nor that vasoactive-inotropic medications cause adverse outcomes. We chose to focus on inborn, extremely premature ELBW infants due to the variability in neonatal outcomes based on hospital of birth, adverse outcomes related to neonatal transport, and inability to accurately quantify vasoactive-inotropic medication administration at outside hospitals and during transport^{35, 36, 37, 38}. Future studies that include out-born infants may produce different results that are influenced by the greater likelihood of complications associated with transport of this fragile patient population. We were unable to identify the specific etiology or specific criteria in this cohort that prompted intervention with vasoactive-inotropic medications by the clinical provider. The rationale for vasoactive-inotropic medication including need, selection, and dosing is an area of much debate in neonatology. There is neither a consensus definition of hypotension in this population, nor guidelines on which medications and doses should be used, thus the prescriptive practice for vasoactive-inotropic medications may be unique between centers. Prospective, multi-center studies are planned to determine the generalizability of our results. We did not collect data on the use of volume expansion, which is routinely contraindicated in the ELBW population given the risk of IVH unless there is a clear volume loss mechanism. Between the groups that received vasoactive-inotropic medications, we did not see a difference in the 5 minute Apgar score, which may reflect the need for and response to resuscitation following potentially impactful variables at the time of delivery (i.e. prenatal care, cord accident, placental abruption). Vasoactive-inotropic drugs were the first-line interventions at the institution in this population over the study period

for hypotension (defined as less than the gestational age at birth), consistent with many academic center's approaches^{39, 40, 41, 42, 43, 44, 45}. Despite these limitations, this is the largest descriptive study of VIS^{max} in extremely premature, ELBW infants in the absence of consensus guidelines for management of hypotension in this population.

Conclusions

VIS^{max} is a quantifiable, objective marker of hemodynamic/cardiovascular support that was directly associated with mortality in extremely premature ELBW infants. VIS^{max} > 30 was associated with universal mortality in this population. The VIS^{max}, alone or in conjunction with other acuity of illness scores, such as the nSOFA, represents an important step towards neonatal precision medicine that may aid clinicians in risk stratifying extremely premature ELBW infants.

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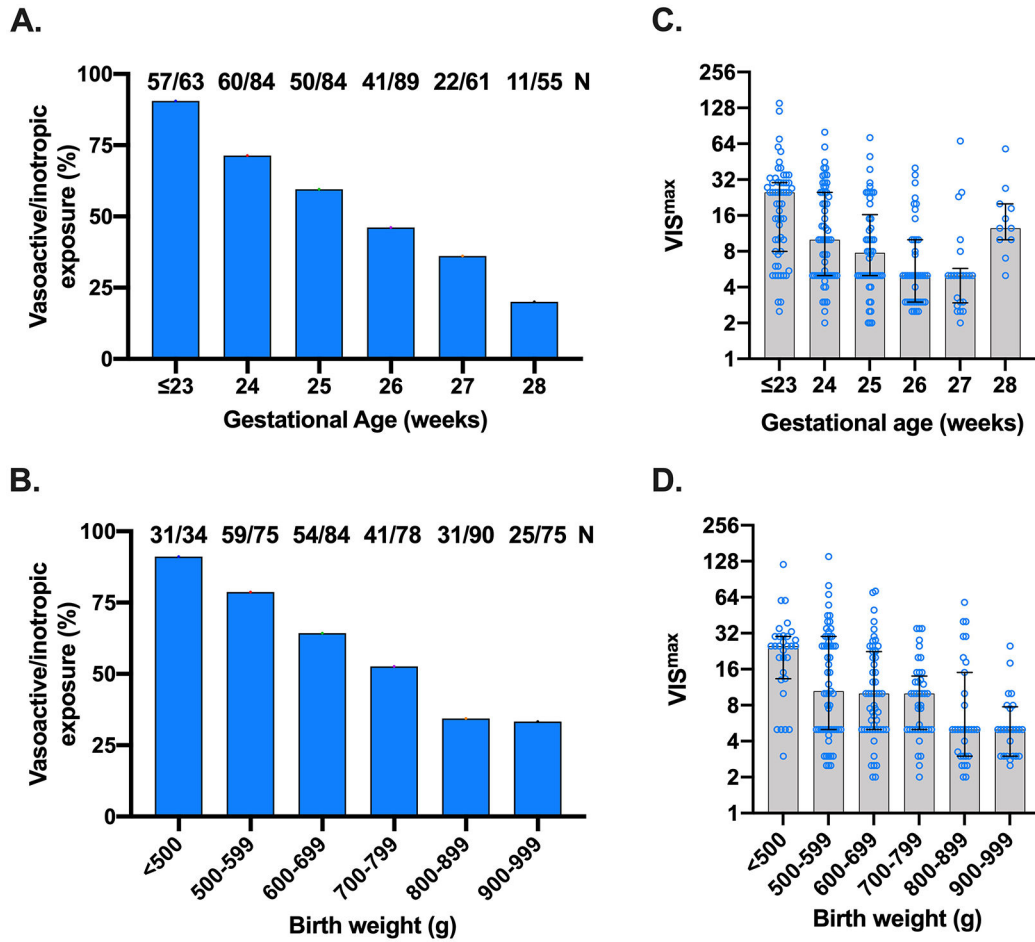


Figure 1. Vasoactive-inotropic medication exposure and VIS^{max} by gestational age and birth weight.

A. Exposure to vasoactive-inotropic medications was inversely proportional to gestational age and ranged from 20 to 91% ($p < 0.001$ by Chi square). **B.** Exposure to vasoactive-inotropic medications was inversely proportional to birth weight and ranged from 33 to 91% ($p < 0.001$ by Chi square). **C.** VIS^{max} among only patients that received vasoactive-inotropic medications was inversely proportional to gestational age with range median values from 5 to 25 (23 vs all except 28; 24 vs 26, 24 vs 27; 27 vs 28; $p < 0.05$ by Kruskal-Wallis). **D.** VIS^{max} among only patients that received vasoactive-inotropic medications was inversely proportional to birth weight with range median values from 5 to 25. (<500 vs all groups except 500-599; 500-599 vs 800-899, 500-599 vs 900-999; 600-699 vs 900-999; $p < 0.05$ by Kruskal-Wallis).

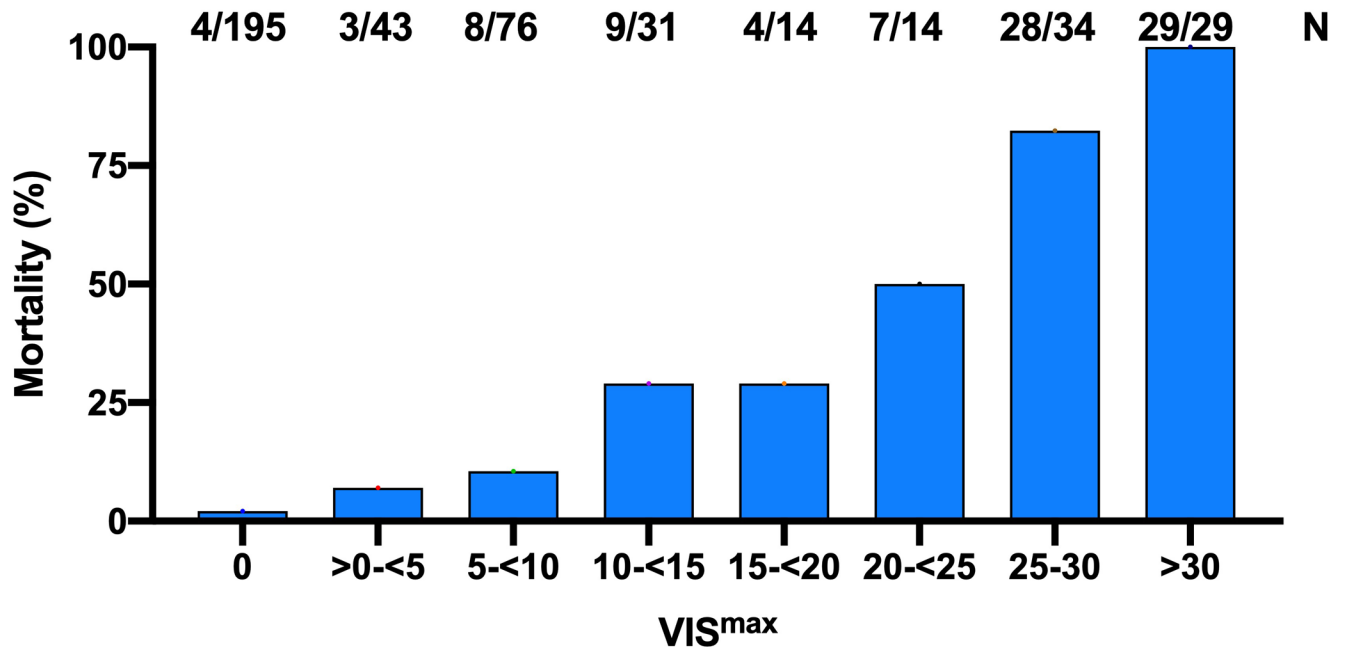


Figure 2. Mortality by VIS^{max} range.

All-cause mortality varied significantly by 5 point VIS^{max} intervals and ranged from 2.1% (VIS^{max} = 0) to 100% (VIS^{max} >30) ($p < 0.001$ by Chi square).

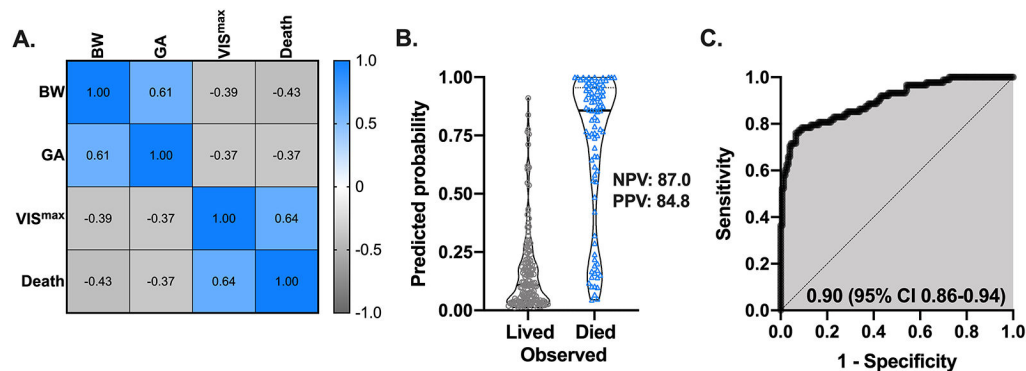


Figure 3. Modeling mortality risk using VIS^{max} among those that received vasoactive-inotropic medications.

A. Spearman's rank correlation coefficients between variables included in the multivariable regression model. A coefficient of 0.64 was found between death and VIS^{max} ($p < 0.001$).

B. Multivariable logistic regression to determine the relationship between death and VIS^{max} adjusted for gestational age and birth weight yielded a negative predictive value of 87.0% and positive predictive value of 84.8%.

C. Adjusted AUROC for mortality was 0.90, (95% confidence intervals 0.86-0.94).

Table 1.

Cohort demographics

	Total (n=436)	VIS ^{max} = 0 (n=195)	VIS ^{max} <10 (n=119)	VIS ^{max} 10 (n=122)	p-value
Maternal					
Age	27 (22, 33)	26 (22, 33)	28 (23, 32)	27 (22, 33)	0.67
Race					0.78
Black	190	83	55	52	
White	189	89	46	54	
Other	57	23	18	16	
Pregnancy induced hypertension ¹	134 (31%)	58 (30%)	35 (29%)	41 (34%)	0.72
Chorioamnionitis ²	215/427 (50%)	103/194 (53%)	56/115 (49%)	58/120 (48%)	0.64
Preterm labor	273 (63%)	125 (64%)	72 (61%)	76 (62%)	0.81
C-section	287 (66%)	125 (64%)	87 (73%)	75 (61%)	0.13
Antenatal steroids	409 (94%)	187 (96%)	109 (92%)	113 (93%)	0.25
Neonatal					
Birth weight	725 (594, 860)	825 (699, 904)	714 (590, 845)	600 (509, 709)	<0.001
GA	26 (24, 27)	27 (26, 28)	25 (24, 27)	25 (24, 26)	<0.001
5 minute Apgar	6 (4,7)	7 (5,8)	6 (4,7)	6 (3,7)	<0.001
Male	227 (52%)	99 (51%)	62 (52%)	66 (54%)	0.85
SIVH	88 (20%)	16 (8%)	28 (24%)	44 (36%)	<0.001
SIP	30 (7%)	1 (<1%)	11 (9%)	18 (15%)	<0.001
5 days early antibiotics ³	291 (67%) EOB (n=11)	106 (54%) EOB (n=4)	86 (72%) EOB (n=2)	99 (81%) EOB (n=5)	<0.001
Necrotizing enterocolitis	68 (16%)	23 (12%)	25 (21%)	20 (16%)	0.09
Late-onset bacteremia	108 (25%)	38 (19%)	36 (30%)	34 (28%)	0.07
Death	92 (21%)	4 (2%)	11 (9%)	77 (63%)	<0.001
Death <4 days	41 (9%)	3 (2%)	4 (3%)	34 (28%)	<0.001
Length of stay, days ⁴	97 (82, 119)	90 (77, 109)	106 (88, 127)	112 (97, 131)	<0.001
VIS ^{max} timing (days from birth)	NA	NA	0 (0, 4)	2 (1, 10)	<0.001
VIS ^{max} to death interval (days)	NA	NA	3 (1, 15)	1 (1, 3)	0.18

¹ maternal diagnosis of pre-eclampsia or gestational hypertension

² histologic only; 6 without records

³ or death with intention to treat

⁴ among survivors

EOB – early-onset bacteremia