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Vasoactive-Inotropic Score (VIS) is Associated with Outcome After Infant Cardiac Surgery: An Analysis from the Pediatric Cardiac Critical Care Consortium (PC[4]) and Virtual PICU System Registries

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Abstract

Objective—To empirically derive the optimal measure of pharmacologic cardiovascular support in infants undergoing cardiac surgery with bypass, and to assess the association between this score and clinical outcomes in a multi-institutional cohort.

Design—Prospective, multi-institutional cohort study.

Setting—Cardiac intensive care units (CICU) at 4 academic children's hospitals participating in the Pediatric Cardiac Critical Care Consortium (PC[4]) during the study period.

Patients—Children <1 year of age at the time of surgery treated post-operatively in the CICU.

Interventions—None

Measurements and Main Results—Three hundred ninety-one infants undergoing surgery with bypass were enrolled consecutively from 11/2011–4/2012. Hourly doses of all vasoactive agents were recorded for the first 48 hours after CICU admission. Multiple derivations of an

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inotropic score were tested, and maximum vasoactive-inotropic score (VIS) in the first 24 hours was further analyzed for association with clinical outcomes. The primary composite "poor outcome" variable included at least one of mortality, mechanical circulatory support, cardiac arrest, renal replacement therapy, or neurologic injury. High VIS was empirically defined as ≥20. Multivariable logistic regression was performed controlling for center and patient characteristics. Patients with high VIS had significantly greater odds of a poor outcome [OR 6.5, 95% confidence interval (CI) 2.9–14.6], mortality (OR 13.2, 95% CI 3.7–47.6), time to first extubation, and CICU length of stay compared to patients with low VIS. Stratified analyses by age (neonate vs. infant) and surgical complexity (low vs. high) showed similar associations with increased morbidity and mortality for patients with high VIS.

Conclusions—Maximum VIS calculated in the first 24 hours after CICU admission was strongly and significantly associated with morbidity and mortality in this multi-institutional cohort of infants undergoing cardiac surgery. Maximum VIS≥20 predicts an increased likelihood of a poor composite clinical outcome. The findings were consistent in stratified analyses by age and surgical complexity.

Keywords

cardiac surgery; inotrope score; outcomes; illness severity

Introduction

Wernovsky and colleagues proposed the use of an inotrope score to measure pharmacologic cardiovascular support given to infants after cardiac surgery [1]. This score was neither derived from empiric data nor rigorously tested as a measure of illness severity. However, the Wernovsky score and its modifications have often been used as a measure of illness severity following cardiac surgery in children even though the score was not created for this purpose [2–5]. The association between inotrope score and clinical outcomes after pediatric cardiac surgery has remained poorly defined in the literature and clinical practice changes over the past decade suggested the need for a revision to the original inotrope score. Defining clinically relevant predictors of patient risk for morbidity and mortality, like an inotrope score, could help to inform intensivists who might then modify treatment in meaningful ways early in a patient's course.

To address this knowledge gap, we previously developed a vasoactive-inotropic score (VIS) and tested its association with clinical outcomes in a single-center cohort of children <6 months of age undergoing cardiac surgery with cardiopulmonary bypass (CPB). [6] In contrast to the original inotrope score proposed by Wernovsky (IS), this new score incorporates additional medications typically used in contemporary clinical practice. We demonstrated that the maximum VIS in the first 24 hours had a strong and consistent relationship with postoperative morbidity and mortality. Other authors subsequently performed similar analyses in single-center series of infants after cardiac surgery. [7, 8] These studies led to mixed conclusions about the optimal measure of VIS and the strength of association between VIS and clinical outcomes, particularly in neonates.

To further explore remaining questions about VIS, its association with clinical outcomes, and its usefulness as marker of illness severity in postoperative cardiac surgical patients, we performed a multicenter analysis of data reported to the Pediatric Cardiac Critical Care Consortium (PC^4), a new quality improvement collaborative of North American pediatric cardiac intensive care units (CICU) and surgical programs. This study represents the first scientific contribution from the PC^4 collaborative.

Our objective was to assess the association between measures of pharmacologic cardiovascular support and clinical outcomes in this multi-institutional cohort of patients from birth to 1 year of age at the time of surgery with CPB, and specifically in a subgroup of neonates. We hypothesized that maximum VIS in the first 24 hours would perform as well or better than the IS in predicting important clinical outcomes, and that we could define a cut-point that would effectively discriminate patients likely to have morbidity and mortality in the postoperative period.

Materials and Methods

Setting and study infrastructure

PC^4 is a voluntary quality improvement collaborative originally formed in 2009 with NIH funding (UL1 RR024986). At the time this study was initiated, four centers (C.S. Mott Children's Hospital, Ann Arbor, MI; Boston Children's Hospital, Boston, MA; Children's Hospital of Wisconsin, Milwaukee, WI; and Seattle Children's Hospital, Seattle, WA) were actively contributing data to the registry and all participated in this investigation. PC^4 utilized an established ICU data platform provided by Virtual PICU Systems (VPS, LLC; Los Angeles, CA), and built an additional module specifically to capture data related to the research question. VPS data collectors at each site extracted the mandatory data variables for the PC^4 registry. Additional data necessary for the analysis were prospectively collected for eligible patients (described below) and managed using REDCap electronic data capture tools hosted by the PC^4 Data Coordinating Center (DCC) in Ann Arbor, MI. [9] These two datasets were merged at the DCC prior to analysis.

Study design

This was a prospective cohort study inclusive of consecutive infants up to 1 year of age at the time of surgery with CPB receiving post-operative care in the CICU at the four participating institutions. Patients were enrolled from 11/1/2011 – 4/30/2012. Patients were excluded from the analysis if one of the following criteria were met: 1) the patient returned from the operating room to the CICU on mechanical circulatory support, 2) the patient was transferred to a non-study institution before critical care services were discontinued, or 3) the patient had a previous surgical episode already captured in the study population (i.e. a patient could appear only once in the cohort). Each participating center received Institutional Review Board (IRB) approval to collect data specific to this research study; the need for written informed consent was waived by each institution's IRB.

Data collection and data integrity

Basic demographic and clinical data were collected routinely as part of the PC[4]/VPS databases. Interrater reliability (IRR) testing was performed by VPS/PC4 and each participating institution achieved an IRR >90% on the study variables prior to study initiation and quarterly thereafter. Other surgical data not captured in the PC[4]/VPS databases (e.g. anatomic diagnoses, procedure performed, and bypass times) were extracted from the local Society of Thoracic Surgeons Congenital Heart Surgery Database at each institution. As noted above, additional data necessary for the analysis were prospectively collected at each site in a supplementary data module on all eligible patients. This information included pre-operative and hourly post-operative vasoactive medication use, and the exact time at which clinical endpoints were reached. Operations were categorized using the Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery (STAT) risk stratification system (category 1 = lowest mortality risk; category 5 = highest mortality risk). [10] Data from all sources were linked at the Data Coordinating Center using indirect identifiers (e.g. surgical date, age at surgery). Clinical outcomes were verified with the primary site investigator at each location and crosschecked between data sources. All out-of-range values were also reviewed with each data collection team prior to analysis. All investigators had access to the data presented here and reviewed and approved with the current version of the manuscript.

Measures of Cardiovascular Pharmacologic Support

Our analytic methods mirror those of our original publication. [6] Doses of vasoactive medications were recorded hourly for the first 48 hours after post-operative admission to the CICU. The full list of medications can be viewed in Appendix 1. We calculated the Inotrope Score (IS) and the Vasoactive-Inotropic Score (VIS) as described previously [6] and as shown in Box 1.

We also assessed the sensitivity and specificity of a score including all inotropes, vasopressors, and vasodilators listed in Appendix 1. This formula was inferior to the IS and VIS, and was not further analyzed.

We calculated the maximum and mean IS and VIS in the first and second 24 hour periods after admission to the CICU. To account for vasoactive support over time, and for cases where a patient returned to the CICU on high support only to have it quickly weaned, we studied the mean IS/VIS. Mean IS/VIS was calculated by summing the hourly doses during the 24 hours period and dividing by 24. We also used the IS and VIS at hour 2 and compared this to the other measures. Patients were classified into one of the 5 mutually exclusive groups defined in our previous study [6] based on their scores at the different time points (Table 1), and assigned to the highest group achieved in either frame. For patients who reached a clinical endpoint (see next section below) in the first 48 hours, we did not use any IS or VIS scores after the event to calculate their maximum and mean scores or to classify them into the group framework. We chose to do this because we were interested in using VIS as a metric to predict eventual clinical outcome, and scores collected after an event (e.g. cardiac arrest or initiation of mechanical circulatory support) do not contribute meaningful data for that purpose.

Clinical endpoints and outcome variables

The primary outcome for analysis was the dichotomous composite morbidity and mortality variable, termed "poor outcome," used in our previous analysis. [6] This outcome was reached if any of the following occurred: mortality (in-hospital or 30-day out of hospital), cardiac arrest, use of mechanical circulatory support, renal replacement therapy, or neurologic injury (stroke or seizure). Secondary outcomes included CICU length of stay, time to first extubation, and need for reoperation requiring CPB. Patients with length of stay or time to extubation ≥ 75^{th} percentile for the cohort were categorized as "prolonged" for analyses testing the association between IS/VIS and these metrics.

Statistical analysis

Demographic and clinical characteristics were compared between two composite outcome groups as well as between centers, using Chi-square test for categorical variables and t-test, Wilcoxon rank sum test, analysis of variance, or Kruskal-Wallis test, as appropriate, for continuous variables. To determine the best metric in relation to poor outcome, the AUC (area under the receiver operating characteristic (ROC) curves) of each maximum and mean value for each score formula (IS, VIS, and derivations) were compared. Optimal cut points for "high VIS" designation were then chosen utilizing sensitivity and specificity from the ROC curve of the selected best metric. Odds ratios (OR) with 95% confidence interval (CI) were estimated using logistic regression to evaluate the relative odds of each clinical outcome, including the composite poor outcome variable, in the high VIS group compared to the low VIS group. In addition to analyzing the association between VIS and the composite clinical outcome, we also assessed the relationship between VIS and each of the individual endpoints separately.

Variables found to be significantly associated with the composite poor outcome in the univariate analyses ($p<0.05$) were included in the multivariable analysis; age at surgery, surgical complexity category, stage 1 single ventricle repair, and weight-for-age z-score. Model fit was evaluated by Hosmer-Lemeshow goodness-of-fit test and a C-statistic. Posterior predicted probabilities of the composite outcomes at each VIS group were calculated using the fitted model with other covariates fixed at their mean values. Stratified analyses were performed by age [neonates (0–29 days) and infants (1 month – 1 year)] and by surgical complexity [low (STAT categories 1–3) vs. high (STAT category 4–5)]. We controlled for center by including it as a fixed effect in each model to account for unmeasured practice differences between hospitals including extubation and CICU discharge criteria.

All analyses were performed with SAS Version 9.3 (SAS institute Inc., Cary, NC) with statistical significance set at p-values <0.05 using two-sided tests. Descriptive statistics are presented as mean ± standard deviation or median (interquartile range) as appropriate for continuous variables and frequency (percentage) for categorical variables. Statistics by center are not shown to prevent identification of the individual hospitals.

Results

Patient characteristics and center variation

Three hundred and ninety-one consecutive infants meeting eligibility criteria were enrolled in the study cohort. Demographic and clinical characteristics of the study population are shown in aggregate and based on composite outcome status in Table 2. The cohort included 141 neonates (36%) and 132 (34%) in STAT categories 4 or 5. Patients meeting the composite clinically derived “poor outcome” were younger, had frequent pre-operative vasoactive support, and were more likely to be in STAT categories 4 or 5 (all $p<0.05$).

The frequencies of patient characteristics and utilization of therapies at each center were tabulated and the ranges across centers are presented in Table 3. Table 3 demonstrates the wide variation between centers in the use of individual vasoactive agents.

Comparing VIS and IS for predicting poor outcome

The performance characteristics of IS and VIS for predicting a poor outcome are displayed in Table 4. Though both scores performed similarly, maximum VIS in the first 24 hours was selected for additional study based on the ease of calculation of a maximum value compared to a mean, inclusion of commonly used vasoactive agents not included in the IS, and being calculable within the first 24 postoperative hours. Other derivations of VIS and IS were not tested further.

Defining a “high VIS” cutpoint

Sensitivity and specificity from the ROC curve for predicting a poor outcome at each maximum VIS group in the first 24 hours suggested either group 3 or group 4 would be an appropriate metric to define high VIS (Supplemental Digital Content - Table 5). Though the group 3 cutpoint yielded the highest combined sensitivity and specificity, we opted to use group 4 and above to define high VIS because we wanted to maximize the specificity of our group designation. In subsequent analyses, patients with a maximum VIS in the first 24 hours of ≥20 (groups 4 or 5) were categorized as “high VIS.”

Estimating the strength of association between high VIS and clinical outcomes

Results of a multivariable logistic regression are shown in Table 6. High VIS was significantly associated with the poor composite outcome (OR 6.5, 95% CI 2.9 - 14.6), with adequate model calibration (Pearson Chi-square statistic = 7.5; $p=0.48$) and good discrimination (C-statistic = 0.82). The observed and posterior predicted probabilities of a poor outcome based on group assignment using maximum 24 hour VIS is shown in Figure 1. High VIS was also significantly associated with prolonged CICU length of stay (OR 3.8, 95% CI 2.0 - 7.2) and prolonged time to first extubation (OR 5.3, 95% CI 2.8 - 10.1), but not with need for reoperation ($p=0.58$). Patients with high VIS had significantly higher risk of mortality (OR 13.2, 95% CI 3.7 - 47.6) and each of the morbidities in the composite outcome variable when analyzed separately (all $p<0.05$).

In stratified analyses by age at surgery and by STAT category, high VIS remained significantly associated with greater odds of having a poor outcome in both neonates and

infants, and in patients with low and high surgical complexity (Table 7). Patients with high VIS also had increased risk of mortality in each stratified group.

Discussion

This analysis demonstrated an association between maximum VIS in the first 24 hours after CICU admission and postoperative morbidity and mortality in children <1 year of age following surgery with CPB. The metric we derived performs as well or better as a predictor of clinical outcome when compared to the IS or other derivations of an inotrope score. Maximum VIS in the first 24 hours has biologic plausibility as a measure of illness severity and predictor of outcome as previously literature demonstrates a nadir in cardiac output after bypass [1], higher risk of cardiac arrest [11], and peaking serum markers of inflammation [12] and myocardial injury [13, 14] during this time period.

We further determined a cutpoint for high VIS that discriminated patients with significantly greater odds of a poor clinical outcome and greater resource utilization compared to those with low VIS. The relationship between VIS and clinical outcome was demonstrated in a population of patients spanning a wider age range than previously reported, and the association remained in stratified analyses by age and surgical complexity. Most importantly, our analysis demonstrates that the association between VIS and clinical outcomes holds in a multicenter cohort controlling for center effects.

Though we could not analyze every possible score for pharmacologic cardiovascular support, we tested several that can be calculated easily and early in the post-operative course, and found results similar to our previous single center cohort study. Another investigative team suggested that the optimal measure of VIS is the value at 48 hours after admission,[8] reasoning that sustained cardiovascular support over time may be more predictive of clinical outcome than a single maximum value. We tried to account for this possibility by calculating a mean VIS over the first 48 hours, but found that this metric performed no better than the maximum VIS in the first 24 hours. We favor metrics that can be calculated as early in the post-operative course as possible in efforts to develop population- and individual-level risk prediction methods for CICU patients, similar to APACHE. [15] These are desirable candidate variables because risk prediction calculated early in a patient’s course may give clinicians the opportunity to change their therapeutic strategy based on predicted outcome. However, current models used for population-based risk adjustment are not necessarily adequate to predict individual patient risk [16], and no illness-severity or risk-adjustment method currently applied to critically-ill pediatric cardiac patients has been evaluated for this purpose.

Studies performed after our original VIS publication raised doubt about the strength of association between VIS and outcomes in the neonatal population. Butts et al. showed that VIS was at most only modestly correlated with clinical outcomes and resource utilization in a cohort of neonates from a single center series.[7] In the current study, we analyzed a larger group of neonates from multiple centers and demonstrated strong associations between maximum VIS in the first 24 hours and clinical outcomes, including ventilator and CICU length of stay. The reasons for the discrepancy between the two studies are not immediately

clear, other than the methodological differences in the analytic approach. There will be even greater opportunities in the future to define the association between VIS and outcomes in this important age subgroup as registries continue to develop and amass greater numbers of unique patient populations.

One of the inherent values of multicenter research, demonstrated in this study, is the ability to observe and describe practice variation among peer institutions. All four centers participating in this investigation are well-established programs with busy cardiac surgical services where children undergoing cardiac surgery are cared for in dedicated CICUs. Despite the similarities, it is clear from the descriptive data that institutional preferences for certain combinations of vasoactive agents vary widely.

Practice variation is likely driven in part by the lack of evidence to guide therapy around even the most basic pediatric CICU practices, like prescribing vasoactive drugs in the perioperative period. This lack of evidence emphasizes the need for focused efforts to develop an evidence-base for common practices through sequential analyses. In this study, we utilized an existing clinical registry to provide standard patient and outcome data, and then added a specific set of data variables to answer a hypothesis-driven research question. This approach markedly improves efficiency for data collection by using information for research that was already being collected with high fidelity as part of routine ICU operations. Future efforts to link critical care databases with other clinical and administrative registries [17] hold promise to provide answers to many questions related to best practice, value, and comparative effectiveness in the CICU. The next crucial step is to bridge the gap from data collection to quality improvement. Quality improvement collaboratives have played a key role in understanding the drivers of variation between hospitals around adult cardiac surgical outcomes, and intervening to raise quality.[18] If datasets like those employed in this study can be used effectively by quality improvement collaboratives focused on perioperative care for pediatric surgical patients then similar advances may be within reach in the near future.

These data should not be used to infer a causal relationship between high vasoactive support and clinical outcomes. There is usually important confounding by indication occurring when observing the relationship between vasoactive medication use and morbidity and mortality; the sickest patients receive the highest doses of drugs and more frequently receive third- and fourth-line agents. Our study design is inadequate to determine whether certain agents or drug combinations actually cause the observed morbidity and mortality, though that possibility certainly exists. An important question for future research is whether initiation of particular therapies (e.g. ECMO cannulation, therapeutic hypothermia) at a lower VIS is beneficial to patients compared to treatment with greater pharmacologic support.

It is a reasonable question whether therapy metrics are the most appropriate markers of disease severity. Most cardiac intensivists would likely prefer objective measurements of cardiac output or oxygen delivery, rather than the amount of vasoactive pharmacologic support, to describe the degree of cardiovascular dysfunction after surgery with CPB. However, these physiologic measurements are either unobtainable or subject to measurement error in most cases. Further, in most instances the agents used to calculate the

VIS are only prescribed when cardiovascular support is indicated; it is logical to infer that if a patient is receiving vasoactive infusions the treating clinician felt that treatment was required, and that higher doses were necessary to treat a greater degree of dysfunction. Thus, we believe the VIS is an appropriate surrogate for illness-severity based on the data presented herein.

In addition to the limitations noted previously regarding the exhaustiveness of score derivation and testing, there are other limitations in interpreting these data. While this is the first multicenter cohort to study the association between vasoactive support and outcomes, the institutions participating in this study may not be representative of the entire CICU community. Further, the results cannot be generalized to non-CPB cases or to older children undergoing surgery. While our model showed good calibration and discrimination, the observed and predicted probabilities for a poor outcome in group 2 were higher than in group 3, which cannot be easily explained. Future analyses will determine whether this is a chance finding in this cohort or a real phenomenon. Though this represents the largest cohort of patients undergoing cardiac surgery in which granular data on vasoactive agent use was collected, the relatively small study group limits the precision of our effect size estimates, though we were still able to show significant associations between high VIS and mortality alone, along with the individual morbidities.

Finally, we chose to approach this analysis using a standard methodology described above, culminating in a multivariable logistic regression. Other complementary and alternative methods exist for mining datasets to assess associations between independent variables and outcomes including, but not limited to, random forest, support vector machine, and nearest-neighbor interpolation. Datasets are likely to become more extensive in the future than the one used for this analysis through linkages between registries and incorporation continuously captured information from bedside monitors and devices. Analyses of these larger databases may rely on these newer techniques listed here.

Conclusions

This study confirms the association between VIS and clinical outcomes after pediatric cardiac surgery for the first time in a multi-institutional cohort. VIS remains an attractive candidate variable for inclusion in a multivariable risk-adjustment or risk-prediction model in the CICU. Further work with larger datasets is necessary to understand more precisely how VIS functions as a predictor of outcome, how it performs in other important patient subgroups, and whether it can be combined with other candidate variables to create a unique illness-severity index for this patient population that predicts important clinical outcomes. This may be enhanced with more sophisticated “big data” analytic techniques appropriate for data structures more complex than those used in this study.

This study also demonstrates how efficient multicenter collaborative research can be in the pediatric CICU domain. In addition to shortening the timeline to achieve adequate sample size for analysis, a collaborative research environment reveals variation in practice patterns that should stimulate discussion and future scientific efforts to define an evidence base for CICU practice. Our method included supplementing an existing registry with additional data

variables to answer a specific research question. Similar use of registries in future observational research and in clinical trials holds promise for facilitating scientific efforts in pediatric cardiac surgery and critical care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Box 1

Inotrope Score (IS) =

Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100 x Epinephrine dose (mcg/kg/min)

Vasoactive-Inotropic Score (VIS) =

IS + 10 x Milrinone dose (mcg/kg/min) + 10,000 x Vasopressin dose (units/kg/min) + 100 x Norepinephrine dose (mcg/kg/min)

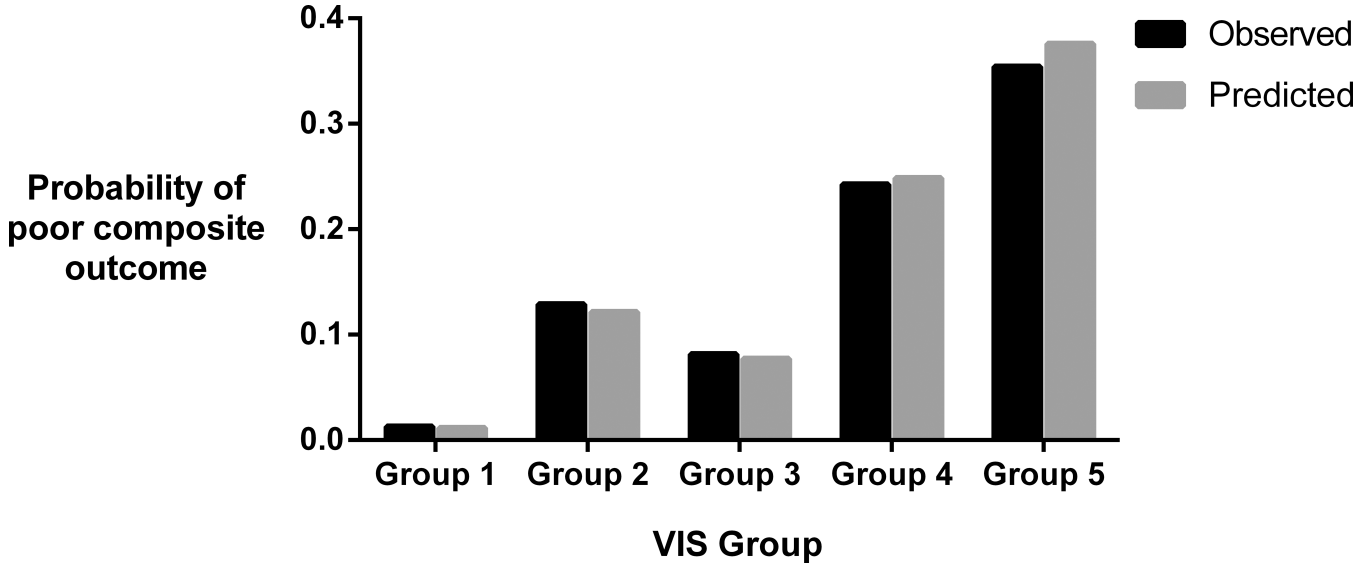

Figure 1.

The observed (black bars) and predicted (gray bars) probability of reaching the composite clinical (poor outcome) are shown according to VIS group based on maximum VIS in the first 24 hours. Predicted probabilities are those calculated from the multivariable model controlling for center and patient characteristics.

Table 1

Classification system based on inotropic score

Group†	IS or VIS 1st 24 hours	IS or VIS 24–48 hours
1	<10	<5
2	10–14	5–9
3	15–19	10–14
4	20–24	15–19
5	≥25	≥20

†Group assignment based on highest support level in either time period.

(Example: Patient with maximum IS 22 in first 24 hours, and 14 in the subsequent 24 hours, would be classified as group 4. Similarly, a patient with maximum IS 10 in the first 24 hours and maximum IS 25 in the second 24 hours would be classified as group 5.)

Table 2

Comparison of patient and clinical characteristics by composite outcome status (N=391)

Characteristics	Overall	Composite poor outcome		P-value[§]
		Yes (N=45)	No (N=346)	
Male sex	215 (55.0)	25 (55.6)	190 (54.9)	0.94
Age at surgery, days	84 (9–165)	14 (6–120)	91.5 (9–168)	0.005
Neonates (age at surgery < 30 days)	141 (36.1)	25 (55.6)	116 (33.5)	0.004
Weight at CICU admission, kg	4.3 (3.3–5.8)	3.7 (3.2–4.6)	4.4 (3.3–6.0)	0.05
Weight-for-age z-score, Mean ± SD	−1.6 ± 1.6	−1.2 ± 1.8	−1.7 ± 1.5	0.04
Preoperative use of vasoactive agents Any	69 (17.6)	15 (33.3)	54 (15.6)	0.003
Dopamine	27 (6.9)	5 (11.1)	22 (6.4)	N/A
Epinephrine	8 (2.0)	4 (8.9)	4 (1.2)	
Vasopressin	0 (0.0)	0 (0.0)	0 (0.0)	
Milrinone	42 (10.7)	9 (20.0)	33 (9.5)	
Dobutamine	2 (0.5)	0 (0.0)	2 (0.6)	
Norepinephrine	1 (0.3)	0 (0.0)	1 (0.3)	
Stage 1 single ventricle repair	47 (12.0)	12 (26.7)	35 (10.1)	0.001
STAT risk category				
1 to 3	256 (65.5)	22 (48.9)	234 (67.6)	0.01
4 or 5	132 (33.8)	23 (51.1)	109 (31.5)	
missing	3 (0.8)	0 (0.0)	3 (0.9)	
Cardiopulmonary bypass time, minutes	121 (84–158)	140 (108–191)	120 (81–154)	0.01
Aortic cross-clamp time, minutes	75 (47–106)	85.5 (60–127)	73 (45–104)	0.02
Deep hypothermic circulatory arrest time, minutes	19.5 (10–42)	22 (15–42)	18 (9–40)	0.31
Regional cerebral perfusion time, minutes	52 (39–68)	59 (46–103)	51 (33–64)	0.11

Abbreviations: CICU, cardiac intensive care unit; STAT, Society of Thoracic Surgeons– European Association for Cardiothoracic Surgery risk category; SD, standard deviation.

[*] Data are presented as N (%) for categorical variables and Median (25th percentile – 75th percentile) for continuous variable and otherwise indicated.

[§] p-value from Chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables for the comparison of each characteristics between two outcome groups.

Table 3

Center variation: patient characteristics, practice, and outcomes

	Range across centers
Patients enrolled, N	67–130
Age, days (median)	56–143
Neonates, %	26–47
Patients in STAT category 4 or 5, %	27–47
Stage 1 single ventricle repair, %	7–17
Use of deep hypothermic circulatory arrest, %	20–33
Use of regional cerebral perfusion, %	0–25
Pre-operative vasoactive infusion, %	7–31
Vasoactive agents used post-operatively, %	
Dopamine	0–88
Epinephrine	10–89
Norepinephrine	1–42
Vasopressin	1–50
Milrinone	46–100
Nitroprusside	0–43
Mechanical ventilation at start of post-operative admission, %	82–100
Maximum VIS, median	7.5–14.5
Maximum IS, median	3–10
Composite poor outcome, %	6.2–14.8
Died in-hospital or within 30 days of hospital discharge	2.5–7.8
Cardiac arrest requiring CPR	1.5–9.6
Mechanical circulatory support	3.5–6.3
Need for renal replacement therapy	0–1.7
Neurologic injury	0.8–6.3
Time to first extubation, hours (median)	24–92
Post-operative CICU length of stay, days (median)	4–9

Abbreviations: CICU, cardiac intensive care unit; STAT, Society of Thoracic Surgeons– European Association for Cardiothoracic Surgery risk category; IS, inotropic score; VIS, vasoactive-inotropic score

Table 4

. Performance characteristics of VIS and IS (controlling for center)

	In the first 2 hours			In the first 24 hours			In the first 48 hours		
Scoring method	**AUC**	**se**	**95% CI**	**AUC**	**se**	**95% CI**	**AUC**	**se**	**95% CI**
Maximum VIS	0.76	0.04	0.69, 0.83	0.79	0.03	0.73, 0.85	0.77	0.03	0.71, 0.84
Mean VIS	0.76	0.04	0.69, 0.83	0.76	0.04	0.68, 0.84	0.79	0.03	0.72, 0.85
Maximum IS	0.72	0.04	0.64, 0.81	0.79	0.04	0.72, 0.86	0.76	0.04	0.68, 0.84
Mean IS	0.74	0.04	0.65, 0.82	0.77	0.04	0.69, 0.84	0.77	0.04	0.70, 0.85

Abbreviations: VIS, vasoactive-inotropic score; IS, inotrope score; AUC, area under the receiver operative characteristic (ROC) curve; se, standard error of AUC; CI, confidence interval

Table 5

Sensitivity and specificity for predicting poor composite outcome to maximum VIS cut points in the first 24 hours (controlling for center)

Maximum VIS group	1	2	3	4	5
Sensitivity	1.00	0.98	0.77	0.57	0.41
Specificity	0.00	0.37	0.68	0.82	0.91

Abbreviations: VIS, vasoactive-inotropic score

Table 6

Association of maximum VIS with outcomes (multivariable logistic regression[‡])

Outcome	N	Percent	OR[a]	95% CI	p-value[§]
Poor outcome	45	11.5	6.5	2.9, 14.6	0.001
Prolonged time to first extubation	94	24.0	5.3	2.8, 10.1	<.0001
Prolonged CICU length of stay	101	25.8	3.8	2.0, 7.2	<.0001
Need for reoperation requiring CPB	14	3.6	1.4	0.4, 5.2	0.58
Died in-hospital or within 30 days of hospital discharge	19	4.9	13.2	3.7, 47.6	<.0001
Cardiac arrest requiring CPR	23	5.9	4.3	1.5, 12.5	0.01
Mechanical circulatory support	17	4.3	34.1	5.9, 197	<.0001
Neurologic injury	17	4.3	4.8	1.4, 15.9	0.01
Cardiac arrest requiring CPR or mechanical circulatory support	31	7.9	10.0	3.6, 27.3	<.0001

Abbreviations: VIS, vasoactive-inotropic score; OR, odds ratio; CI, confidence interval; CICU, cardiac intensive care unit; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation.

[a]OR represents odds of a poor outcome in “high VIS” group (with maximum VIS in groups 4 and 5) relative to “low VIS” group (with maximum VIS in groups 1, 2, and 3) after controlling for centers, patient age, single-ventricle repair, STAT risk category, and weight-for-age z-score.

[‡]includingcenter, patient age, single-ventricle repair, STAT risk category, and weight-for-age z-score.

[§]p-value from multivariable logistic regression after controlling for centers, patient age, single-ventricle repair, STAT risk category, weight-for-age z-score.

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Table 7a

Association of maximum VIS with outcome stratified by age group (controlling for center)

Age at surgery	**Outcome**	**N**	**Percent**	**OR**[a]	**95% CI**	**p-value**[§]
Neonate (≤30 days)	Poor outcome	25	17.7	4.9	1.8, 13.5	0.002
	Prolonged time to first extubation	59	41.8	7.2	3.2, 16.2	<0.001
	Prolonged CICU length of stay	57	40.4	3.1	1.5, 6.5	0.003
	Need for reoperation requiring CPB	7	5.0	2.0	0.4, 12.1	0.42
	Died in-hospital or within 30 days of hospital discharge	11	7.8	22.6	2.7, 191	0.004
Infant (1 mo – <1yr)	Poor outcome	20	8.0	9.6	2.9, 31.5	<0.001
	Prolonged time to first extubation	35	14.0	5.1	1.9, 13.6	0.001
	Prolonged CICU length of stay	44	17.6	9.8	3.5, 27.2	<0.001
	Need for reoperation requiring CPB	7	2.8	1.3	0.1, 13.2	0.81
	Died in-hospital or within 30 days of hospital discharge	8	3.2	12.3	2.0, 84.6	0.01

Table 7b Association of maximum VIS with outcome stratified by STAT risk category (controlling for center)

STAT Category	Outcome	N	Percent	OR[a]	95% CI	p-value[§]
1 to 3	Poor outcome	22	8.6	5.7	1.9, 16.6	0.002
	Prolonged time to first extubation	37	14.5	6.1	2.4, 15.8	<0.001
	Prolonged CICU length of stay	41	16.0	4.4	1.8, 10.7	0.001
	Need for reoperation requiring CPB	8	3.1	6.1	1.1, 33.1	0.04
	Died in-hospital or within 30 days of hospital discharge	9	3.5	13.4	2.6, 93.0	0.002
4 to 5	Poor outcome	23	17.4	6.0	2.1, 17.4	0.001
	Prolonged time to first extubation	55	41.7	6.1	2.7, 14.0	<0.001
	Prolonged CICU length of stay	57	43.2	4.1	1.9, 9.2	<0.001
	Need for reoperation requiring CPB	6	4.5	0.3	0.04, 3.0	0.33
	Died in-hospital or within 30 days of hospital discharge	10	7.6	9.1	1.9, 67.7	0.004

Abbreviations: VIS, vasoactive-inotropic score; STAT, Society of thoracic surgeons– European association for cardiothoracic surgery risk category; OR, odds ratio; CI, confidence interval; CICU, cardiac intensive care unit; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation.

[a] OR represents odds of a poor outcome in "high VIS" group (with maximum VIS in groups 4 and 5) relative to "low VIS" group (with maximum VIS in groups 1, 2, and 3) after controlling for centers.

[§] p-value from multivariable logistic regression after controlling for centers and other covariates.