Vasoactive-ventilation-renal score in predicting outcome postcardiac surgery in children

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ABSTRACT

Objective: The objective of this study was to evaluate vasoactive-ventilation-renal (VVR) score to predict outcome postcardiac surgery in children and establish the time at which the score is best to predict outcome.

Materials and Methods: This prospective cohort included children ≤18 years recovering from cardiac surgery for congenital heart disease. Data were collected from the Intensive Care Unit (ICU) and vasoactive-inotropic score (VIS) and VVR scores calculated at admission, 24 h, and 48 h postoperatively. Outcome of interest was prolonged length of ICU stay (defined as length of stay [LOS] in the upper 25th percentile) and ICU mortality. Correlation between the outcome and scores was obtained and receiver operating characteristic (ROC) curves generated. Independent association of the scores with the outcome was also established.

Results: One thousand ninety-seven patients were enrolled with a median age of 24 months (range: 2 days–18 years) including 14.6% with single ventricle physiology. Pediatric ICU LOS >89 h was considered prolonged, and mortality was 2.2%. VVR score correlated better with outcome and had greater area under the curve (AUC) for ROC curve than the corresponding VIS at each study time point. The AUC of ROC curve for VVR score was greatest at 48 h for predicting both prolonged LOS (0.87) and mortality (0.92). VVR score at 48 h remains strongly associated with both prolonged LOS (odds ratio [OR] – 1.24; \( P = 0.000 \)) and mortality (OR – 1.16; \( P = 0.000 \)).

Conclusion: VVR score is effective and robust bedside method to predict prolonged LOS and mortality postpediatric cardiac surgery. VVR score at 48 h was the best to predict outcome.

Key Words: Cardiac surgical procedures, critical care outcome, hospital mortality, Intensive Care Unit pediatrics

INTRODUCTION

Children undergoing cardiac surgery are at increased risk for prolonged ventilation and need for hemodynamic support during the postoperative period. Prolonged cardiopulmonary bypass (CPB) time and cardiorespiratory dysfunction post-CPB can result in end-organ damage. The cumulative effect includes prolonged Intensive Care Unit (ICU) stay and increased mortality and morbidity associated with surgery. Scoring indices that can accurately reflect the severity of illness in critically ill patients is extremely valuable in providing guidance for patient care and clinical research. In 1995, Wernovsky created an inotrope score (IS) as part of a study on postoperative
hemodynamics following arterial switch operation. However, no further study could prove a correlation between original IS and clinical outcome. Later, Gaies et al. published a retrospective study using an updated vasoactive-inotropic score (VIS) which has been found to modestly correlate with outcome. Most recently, Miletic et al. developed vasoactive-ventilation-renal (VVR) score and found it more promising to accurately predict outcome postcardiac surgery. Specifically, the VVR score at 48 h postoperatively has been shown to be a robust predictor of short-term clinical outcomes and has consistently outperformed the VIS and serum lactate, which were the important traditional measures. This finding has further been validated by the same author in a different cohort and also by others.

We postulated that VVR score is an effective tool to predict outcome postcardiac surgery and undertook the study to further validate the work of Miletic et al. in a larger population. VVR scores at different postoperative time points were also compared to determine the time point at which the score is best to predict the outcome.

**MATERIALS AND METHODS**

This prospective cohort study was conducted in a 65-bedded cardiac pediatric ICU (PICU) of a tertiary care cardiac center. After the Institutional Ethical Committee approval, children ≤18 years of age undergoing surgery for congenital heart disease between June and November 2015 were enrolled after receiving a written informed consent. Patients who required extracorporeal membrane oxygenation (ECMO) within first 48 h were excluded as their inotrope and ventilator requirement may not represent true value of the disease severity. Patients who died before the cutoff for prolonged length of stay (LOS) were excluded from the analysis of LOS as their length of hospital stay could have been misinterpreted as positive outcome (short LOS). These patients were sickest and would have stayed longer than others.

Data were collected from case records and PICU monitoring charts of the patients. Perioperative data including age, anatomical diagnosis and procedure performed, CPB duration, aortic crossclamp duration, and preoperative serum creatinine were collected. Aristotle basic complexity score and risk assessment for congenital heart surgery (RACHS) score were used to classify the procedures. Acute kidney injury (AKI) was classified using AKI network staging system. Postoperative data of arterial blood gas parameters including PH, partial pressure of carbon dioxide (PaCO2), and partial pressure of oxygen (PaO2) at admission in PICU, 24 h, and 48 h postoperatively along with the corresponding ventilator settings including peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), mean airway pressure, and respiratory rate (RR) in the volume-controlled mode of ventilation were collected. Doses of inotropic and vasopressor agents were also recorded at the time of each blood gas analysis. Postoperative serum creatinine was recorded at admission, 24 h, and 48 h postoperatively. Need for re-exploration for any reason and rhythm abnormality within first 72 h post surgery was also recorded.

VIS and VVR scores were calculated for all patients at study time point. VIS was calculated using formulae; VIS = Dopamine dose (µg/kg/min) + Dobutamine dose (µg/kg/min) +100 × Epinephrine dose (µg/kg/min) +10 × Milrinone dose (µg/kg/min) +10000 × Vasopressin dose (µg/kg/min) +100 × Norepinephrine dose (µg/kg/min). Ventilation index (VI) was calculated using formula: VI = RR × (PIP−PEEP) × PaCO₂/1000; ∆Cr was calculated by subtracting serum creatinine (in mg/dl) at the time of each measurement with preoperative serum creatinine and VVR using formula: VVR = VIS + VI + (ΔCr × 10).

For patients whose postoperative serum creatinine values were less than preoperative values, ΔCr was taken as 0. For patients not requiring ventilator support at the time of measurement, VI was taken as 0.

All statistical analysis was performed using SPSS 22 software (Armonk, NY: IBM Corp). Median with range was used to describe continuous data whereas absolute count with percentage was used for categorical data. The primary outcome of interest was LOS and hospital mortality. Data were analyzed for correlation between the scores and outcome using Spearman’s rho. For further analysis of LOS, data were dichotomized as the upper (worst) 25th percentile versus lower (best) 75th percentile. LOS in the upper 25th percentile was considered prolonged LOS. Receiver operating characteristic (ROC) curve was generated, and the ability of VIS and VVR score (at 0, 24, and 48 h) to correctly predict prolonged LOS and mortality was analyzed using area under the curve (AUC) value. AUC of individual curves at each time point was compared using z-statistics. Best cutoff value for the VVR score was derived having maximum accuracy and minimal weighted error.

Univariate analysis was performed for demographic and clinical characteristics of patients to predict prolonged LOS and mortality using Mann–Whitney U-test, Chi-square test, or Fisher’s exact test as appropriate for individual variables. Significance variables were included in the multivariate logistic regression model, and odds ratio (OR) was calculated. P < 0.05 was considered significant.

**RESULTS**

A total of 1103 patients were screened in the study. Six patients were transferred to PICU on ECMO or required...
ECMO within first 48 h and were excluded from the study. One thousand and ninety-seven patients were enrolled in the study with a median age of 24 months (range: 2 days–18 years) and 615 (56.1%) male. Ventricular septal defect (24.2%) and Tetralogy of Fallot (19.8%) were the most common diagnosis, and single ventricle physiology included 14.6% (n = 160) of the study population. Baseline characteristics of the patients are depicted in Table 1. Median LOS was 64 h (range: 46 h to 23 days). Prolonged LOS was defined as >89 h (upper 25th percentile of LOS). Overall mortality was 2.2% (n = 24). Nine patients who died before the cutoff for prolonged LOS were excluded from the analysis of prolonged LOS.

Median VIS and VVR scores with maximum and minimum values are presented in Table 2. VVR score was higher compared to the corresponding VIS at each point of measurement. Analysis of Spearman’s correlation coefficient showed VVR score correlate better with outcomes than the corresponding VIS at all the study time point. VVR at 48 h correlated best with both prolonged LOS and mortality with a correlation coefficient of 0.63 and 0.23, respectively [Table 2]. Analysis with ROC curve to predict prolonged LOS [Figure 1] and mortality [Figure 2] is depicted in Table 2. AUC for VVR scores was higher than the corresponding VIS at all the study time point. AUC was highest at 48 h for both prolonged LOS (0.87) and mortality (0.92).

Correlation with other variables (age, CPB time, RACHS category, and Aristotle complexity grade) was also evaluated, but none these factors were superior to 24 and 48 h VIS or VVR score in predicting the outcomes. AUCs of these variables shown in Table 2 were inferior to VIS or VVR at all the time point. The AUCs for the VVR score at different study time points were also compared. No significant difference was found between 24 and 48 h VVR (Z = 0.79; P = 0.430) in predicting mortality, whereas both 24 (Z = 3.03; P = 0.002) and 48 h VVR (Z = 3.62;
P = 0.001) were significantly better than 0 h VVR. In predicting prolonged LOS, 48 h VVR was significantly better than 24 h VVR (Z = 2.45; P = 0.015) and 0 h VVR (Z = 7.28; P = 0.001); also, VVR at 24 h was significantly better than VVR at 0 h (Z = 4.93; P = 0.001).

Demographic and clinical variables for patients were compared between the outcome groups [Table 3]. Variables with P < 0.05 were included in the multivariate regression analysis [Table 4]. Patients with genetic abnormality and those requiring re-exploration were excluded in the multivariate analysis due to the small number of such patients. VVR at 48 h remains strong predictor for both prolonged LOS (OR: 1.24; 95% confidential interval [CI]: 1.19–1.29; P = 0.000) and mortality (OR: 1.16; 95% CI: 1.10–1.22; P = 0.000). Other variables independently associated with mortality in the multivariate model were RACHS category ≥3 and AKI stage ≥2, and variables associated with prolonged LOS were age, RACHS category ≥3, and postoperative rhythm abnormality.

VVR score at 48 h was further dichotomized in high and low to simplify its interpretation. The cutoff value of 5 was chosen for prolonged LOS with sensitivity of 81% and specificity of 77% and 12 for mortality with sensitivity of 92% and specificity of 89%.

**DISCUSSION**

The current study validated the work of Miletic et al. who found a strong association between the VVR score and outcome postcardiac surgery in heterogeneous group of children with mixed cardiac lesion<18 years of age. The authors found the finding really exciting and suggested further studies exploring the application of VVR score in children recovering from cardiac surgery. In the current study, they took their word and validated it in a larger population. We also established the association of VVR score with mortality. This study also included heterogeneous group of patients irrespective of diagnosis, including repair of cyanotic heart disease, and those with single ventricle physiology and residual right to left shunt.

### Table 3: Univariate analysis of outcome indicators (prolonged length of stay and mortality) with patient variables

| Variable | Prolonged LOS (n = 270) | No prolonged LOS (n = 818) | P |
|----------|-------------------------|---------------------------|---|
| Age (months) | 49.7±48.1 | 21.8±37.7 | 0.000 |
| Male sex | 148 | 460 | 0.684 |
| Genetic abnormality | 24 | 34 | 0.003 |
| RACHS ≥3 | 100 | 100 | 0.000 |
| Aristotle complexity grade ≥3 | 142 | 186 | 0.000 |
| CPB (min) | 94.9±73.6 | 65.4±40.1 | 0.000 |
| AXC (min) | 62.2±52.2 | 38.8±28.7 | 0.000 |
| AKI stage ≥2 | 62 | 64 | 0.000 |
| Postoperative rhythm abnormality | 84 | 30 | 0.000 |
| Re-exploration within 24 h | 20 | 12 | 0.000 |
| VVR score at 48 h | 12.6±9.3 | 2.4±3.5 | 0.000 |

### Table 4: Multivariate logistic regression analysis of the variables associated with outcome

| Variable | Prolonged LOS | P | OR (95% CI) |
|----------|---------------|---|-------------|
| Age | 0.000 | 0.99 (0.98–0.99) |
| RACHS category ≥3 | 0.000 | 2.82 (1.76–4.52) |
| Aristotle complexity grade ≥3 | 0.342 | 0.79 (0.49–1.29) |
| CPB time | 0.765 | 1.00 (0.99–1.01) |
| AXC time | 0.639 | 1.00 (0.99–1.02) |
| AKI stage ≥2 | 0.142 | 1.51 (0.87–2.63) |
| Postoperative rhythm abnormality | 0.000 | 4.90 (2.71–8.85) |
| VVR 48 h | 0.000 | 1.24 (1.19–1.29) |

**Mortality**

| Variable | P | OR (95% CI) |
|----------|---|-------------|
| Age | 0.155 | 0.99 (0.97–1.01) |
| RACHS category ≥3 | 0.000 | 7.68 (2.55–23.13) |
| Aristotle complexity grade ≥3 | 0.121 | 3.07 (0.74–12.68) |
| CPB time | 0.074 | 1.02 (0.99–1.04) |
| AXC time | 0.065 | 0.97 (0.95–1.00) |
| AKI stage ≥2 | 0.028 | 3.15 (1.13–8.76) |
| Postoperative rhythm abnormality | 0.247 | 1.89 (0.64–5.56) |
| VVR 48 h | 0.000 | 1.16 (1.10–1.22) |

OR: Odds ratio, CI: Confidence interval, RACHS: Risk assessment for congenital heart surgery, CPB: Cardiopulmonary bypass, AXC: Aortic cross-clamp, AKI: Acute kidney injury, VVR: Vasoactive-ventilation-renal
shunt, who were excluded by Miletic et al. in their earliest study. The VI is known to be better than oxygenation index as it is not affected by mixing of oxygenated and deoxygenated blood due to shunting. This justifies the inclusion of cyanotic patients and those with single ventricle physiology and residual right to left shunt in the present study. In fact, the strength of association between VVR score and outcome improved after including this cohort of patients. Scherer et al. further validated the score including heterogeneous patients irrespective of their physiology in their cohort.

Median VVR score at all the time points was higher than the VIS. This indicates the significant contribution of ventilation and renal parameters in the postoperative outcome of the patients. Median VIS and VVR scores were maximum at admission and decreased significantly during the next 48 h. This could be related to the peak support required at the time of cessation of CPB when the body is still adapting to the new physiology of circulation post surgery and also due to the significant physiological effects of CPB. VVR score at all the time points correlated better than the corresponding VIS and also had greater AUC-ROC to predict LOS and mortality. Earlier studies support these findings although the outcomes studied in those studies were mainly LOS and duration of mechanical ventilation. None of the earlier studies have evaluated the score in predicting mortality. The current study showed a significant association of both VIS and VVR scores with mortality; VVR score being the better one.

This study showed 48 h VVR to best correlate with outcome and had greatest AUC-ROC, which is consistent with the studies by Miletic et al. This finding was also applicable to VIS which was also best at 48 h to predict outcome; result being consistent with reports by Davidson et al. Scherer et al. found 12 h VVR score to be best in predicting prolonged LOS in their cohort. The score at admission performed worst in the current study; this finding has been consistently reported in other studies. The AUC of VVR at admission was significantly lower than those at 24 and 48 h in predicting the outcomes. This could be explained by the fact that ventilator and hemodynamic support at admission mostly reflects the dynamic process following the cessation of CPB and adaptation to the new cardiac physiology postsurgery in addition to the changes during transport and less likely reflects severity of organ dysfunction. Furthermore, using serum creatinine in the score which is a poor early marker of kidney injury makes the contribution of renal parameter minimal at admission. No significant difference in AUC-ROC was found between VVR at 24 and 48 h for predicting prolonged LOS; however, to predict mortality, VVR at 48 h performed significantly better than at 24 h. VVR score at admission was significantly inferior to those at 24 and 48 h in predicting both the outcomes. Scherer et al. found VVR score at all the time points equally predictive of prolonged LOS as no statistically significant difference was found between VVR scores at different time points.

Apart from VVR score, we found RACHS category ≥3 to be independently associated with both mortality and prolonged LOS. The finding is consistent with many earlier reports which have shown direct association between complexity of the procedure and outcome. The ability of VVR to predict outcome in individual risk categories was not performed in the current study which needs to be evaluated. AKI ≥ Stage 2 was also found to be independently associated with mortality which further emphasizes the need to include renal parameter in the score; however, association with prolonged LOS could not be established. Younger age group and rhythm abnormality were independently associated with prolonged LOS. Younger age has been consistently associated with prolonged LOS as is arrhythmias in previous reports.

VVR score has been proven to be simple, easy to calculate, and a robust predictor of outcome postcardiac surgery. Being an easy bedside method and cost-effective than newer experimental biomarkers, this method could definitely be a useful research as well as prognostic tool. The efficiency of VVR compared to other disease severity indices such as the pediatric logistic organ dysfunction score, pediatric risk of mortality III score, and pediatric index of mortality II score is still debatable and need to be evaluated. All these scores involve complex calculations which give VVR a clear advantage over them.

More recently, VVR has been under some criticism for calculating the parameter of renal dysfunction by subtracting postoperative value from preoperative value which many suggest as inaccurate. As serum creatinine varies greatly depending on age and is not an accurate marker for renal injury, the value may underestimate the true effect of kidney injury. The inclusion of percentage increase of estimated glomerular filtration rate may help to eliminate these shortcomings and needs to be evaluated. Furthermore, the utility of VI is questioned as it includes the difference between PIP and PEEP. PIP rises with airway resistance, which in mechanically ventilated children is not an accurate indicator of lung mechanics. It is the increase of both PIP and plateau pressure (PLAT) which suggests decreased compliance. Inclusion of PLAT in place of PIP may improve the accuracy of VI and need further evaluation.

The current study included 6.6% of patients with RACHS 4 and none of RACHS 5 and 6 whereas the study population of Miletic et al. included 18.4% of patients with RACHS 4–6. The difference could be
due to the different cohort involved. Furthermore, our center located in a developing country has less number of patients with higher complexity due to poor referral system and infrastructure. The validity of the score in higher complexity procedure could not be determined by the current study. The ventilation time in the current study was higher than that of Miletic et al. which could be explained by the higher case burden and lack good infrastructure and workforce. The other limitation of the study is that it was a single-center study. Although ventilation protocol of the PICU is defined and volume-controlled ventilation was the preferred mode, individual variation cannot be ruled out.

CONCLUSION

Despite the limitation, VVR score remains an effective and robust bedside tool to predict outcome postcardiac surgery in children. VVR score calculated at 48 h was the best to predict outcome.

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Conflicts of interest
There are no conflicts of interest.

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