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The difficult definition of clinically relevant cardiac surgery-associated acute kidney injury in neonates, infants, and small children

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Abstract

Background

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common feature in pediatric patient population and is associated with major morbidity and mortality. Its definition and grading are still unclear, and 3 different adjudication criteria exist. The aim of this study is to find the best definition for clinically relevant CSA-AKI.

Methods

prospective observational study on 174 pediatric patients < 20 kgs. CSA-AKI was adjudicated based on the Pediatric Risk, Injury, Failure, Loss of Function, and End Stage (pRIFLE), modified Kidney Disease Improving Global Outcomes (mKDIGO) and pediatric reference change value optimized for AKI children (pROCK) definitions. The 3 definitions were compared for association and prediction of a composite outcome.

Results

The incidence of CSA-AKI was different for the different definitions. 43.7% according to the pRIFLE, 14.9% for the mKDIGO and 13.8% for the pROCK. The composite outcome had a rate of 18.4%. At a univariate analysis, the odds ratio for experiencing the composite outcome was 3.0 (95% confidence interval 1.35–6.75, P = 0.007) for the pRIFLE, 4.4 (95% confidence interval 1.79–1.11, P = 0.001) and 5.2 (95% confidence interval 2.06–13.1) for the pROCK. The 3 definitions were significantly discordant. When corrected for other confounders, only the pROCK remained independently associated with the composite outcome (odds ratio 4.29, 95% confidence interval 1.23–14.9, P = 0.022). Prediction of the composite outcome was not significantly better for the pROCK.

Conclusions

the pRIFLE overestimates the incidence of clinically relevant CSA-AKI. The best definition for a clinically relevant CSA-AKI, as well as for its prediction, is obtained by the pROCK.

Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common feature both in adult and in pediatric patient population. It is reported between 10% and 60% in neonates, infants and small children [1–15]. Regardless of its incidence rate, and even in apparently low severity cases, CSA-AKI is associated with a number of additional postoperative morbidity events, prolonged intensive care unit (ICU) stay, and even mortality [4, 6, 13–16].

The large variation in the reported incidence of CSA-AKI in different studies is attributable to differences in type of surgery and age segment, but certainly the criteria for adjudicating a CSA-AKI event are a determinant factor. In the adult population, The Acute Kidney Injury Network (AKIN) [17], the Risk, Injury, Failure, Loss of Function, and End Stage (RIFLE) [18] and the Kidney Disease Improving Global Outcomes (KDIGO) [19] definitions are the most commonly used. They are based on changes in serum creatinine (SCr) or estimated glomerular filtration rate (eGFR) from the baseline (immediately before surgery) to the peak postoperative value measured within the 48 hours following surgery extended to 7 days for some adjudication criteria [20]. The rough application of these well-validated definitions to the pediatric population, and namely to neonates and infants undergoing cardiac surgery has been however criticized, due to the peculiar nature of kidney function and normal SCr ranges in this patient population. Therefore, specific definitions were introduced for tackling pediatric patients. Some are modifications of pre-existent definitions, like the pediatric RIFLE (pRIFLE) [21] and the modified KDIGO (mKDIGO) [19], others are newly developed. In 2018 Xu and associates proposed a pediatric reference change value optimized for AKI in children (pROCK) [22] based on reference change value for SCr. This definition better detected "true" AKI than KDIGO or pRIFLE. However, within the wide (43,982) retrospective patient population, those receiving open-heart surgery were excluded. Additionally, the SCr changes were assessed during a 30-days period. Therefore, the applicability of pROCK as a definition criterion for CSA-AKI remains elusive. Recently, Gao and associates compared pRIFLE, KDIGO, and pROCK in the setting of CSA-AKI in small (< 10 kgs) infants, finding a superiority of pROCK in terms of association with several outcomes [3]. This study, however, included a majority of patients undergoing operations of low or mild complexity, and did not consider the mKDIGO within the CSA-AKI definitions.

The aim of this study is to (a) define the CSA-AKI rate in cardiac surgery patients < 20 kgs according to the different definitions and (b) identify the best definition in terms of association with and prediction of postoperative morbidity and mortality.

Methods

Study design

This is a preliminary study within the prospective observational study denominated Perfusion Quality Odds 2 (PEQUOD-2), a project financed by the European Union denominated "Next generation EU-PNRR M6C2-investment 2.1 – Valorizzazione e potenziamento della ricercar biomedical del SSN" through the Italian Ministry of Health with the code PNRR-POC-2023-12377023.

The study was approved by the Ethics Committee Lombardia 1 with the code CET 230–2024. The study is conducted at the IRCCS Policlinico San Donato, a Clinical Research Institute partially financed by the Italian Ministry of Health.

Within the PEQUOD-2 there is a pediatric arm aimed to determine the cardiopulmonary bypass (CPB) factors associated with CSA-AKI in neonates and small children (< 20 kgs). The total pediatric patient

population is settled at 200 cases.

The CSA-AKI is the outcome variable of the PEQUOD-2, and therefore a preliminary choice of its definition is required before analyzing the CPB-related factors. The present study is preliminary to the final data analysis, and includes about 90% of the final patient population, that is still to be completed.

Patients

One hundred seventy-four patients were prospectively enrolled in this observational study. All the parents of the patients gave a written informed consent to the participation.

Exclusion criteria were refusal to participate; emergency surgery; preoperative renal replacement therapy. All the patients received cardiac surgery procedures with CPB for correction or palliation of congenital heart defects.

Clinical practice

All the operations were performed by the same congenital cardiac surgical team following institutional standards of anesthesia, perfusion, and postoperative care. CPB was conducted using a non-pulsatile flow at a temperature that could vary between 25°C (in cases with deep hypothermic cardiac arrest and antegrade cerebral perfusion) to 28–30°C in less complex cases, up to 36°C in cases at low complexity. The circuit was primed with red blood cells plus fresh frozen plasma in patients weighing < 10 kgs, and with crystalloid and 5% albumin for patients weighing ≥ 10 kgs. Myocardial protection was achieved with cold blood cardioplegia. Postoperative management, including mechanical ventilation, inotropic support, and intensive care protocols, followed unit guidelines and were not influenced by study participation.

Data collection and definitions

Data were prospectively collected in Research Electronic Data CAPture (RedCAP) platform.

Preoperative data included: age (months), sex, preterm birth, weight (kgs), cyanotic heart defect, positive blood cultures, SCr (mg/dL), eGFR (mL/min/1.73m^2) according to Schwartz equation, hemoglobin (Hb, g/dL), need for mechanical ventilation, use of inotropic drugs (epinephrine, dobutamine, dopamine), vasopressors (nor-epinephrine, vasopressin, argipressin, terlipressin), use of nephrotoxic agents (angiotensin converting enzyme inhibitors, vancomycin, tobramycin, cephalosporin, amikacin, gentamycin, non-steroidal anti-inflammatory drugs), use of furosemide, urgency of surgery.

Intraoperative parameters included: Risk Stratification for Congenital Heart Surgery (RACHS-2) class, duration of CPB (minutes), nadir hematocrit (HCT, %) value on CPB, nadir oxygen delivery (DO_2, mL/min/m^2) on CPB, nadir temperature (°C) on CPB, peak arterial blood lactates (mmol/L) on CPB.

Postoperative data included: time on mechanical ventilation (hours), ICU stay (days), postoperative chest drain output (mL/12 h), surgical re-operation, low cardiac output (need for inotropic drugs > 48 postoperative hours), neurologic damage (stroke, seizures, coma), major infections (bloodstream infections or deep sternal wound infection), and hospital mortality. For the purposes of the present analysis, a composite outcome was defined as prolonged (> 10 days) ICU stay and/or hospital mortality.

CSA-AKI was adjudicated separately for the 3 definitions that are the focus of this study. The pRIFLE defines 3 stages of AKI in pediatric patients: stage 1 (risk) is adjudicated for an eGFR decrease ≥ 25% within 7 days from surgery; stage 2 (injury) adjudicated for an eGFR decrease ≥ 50%, and stage 3 for an eGFR decrease ≥ 75% or an absolute eGFR < 35 mL/min/1.73 m^2 [21]. mKDIGO applies corrective criteria for neonates (< 30 days) only, adjudicating CSA-AKI stage 1 for an absolute increase in SCr ≥ 0.3 mg/dL within 48 hours from surgery or a relative increase between 1.5 and 2 times the preoperative value within 7 days; stage 2 for an SCr increase 2–3 times the preoperative value; and stage 3 for an SCr value increase > 3 times the preoperative value, or an absolute value > 4 mg/dL, or the need for renal replacement therapy. For any of these adjudications, the postoperative SCr must be > 0.5 mg/dL.

Finally, pROCK considers an AKI stage 1 for an SCr increase of both ≥ 30% and ≥ 20 μmol/L; stage 2 for an SCr increase of both ≥ 60% and ≥ 40 μmol/L; and stage 3 for an SCr increase of both ≥ 120% and ≥ 80 μmol/L; all adjudications within 7 days from surgery.

In our study, we considered both the CSA-AKI stages and the binary variable “CSA-AKI -any stage”.

Statistics

The sample size was based on the primary endpoint (discrimination properties for the composite outcome). Based on institutional data from our records, it was assumed a composite outcome rate of 20%. The negative/positive cases ratio was therefore settled at 5:1. The hypothesized c-statistics at Receiver Operating Characteristics (ROC) analysis was 0.75, and the null hypothesis was a c-statistics of 0.50. With an alpha value of 0.05 and a beta value of 0.20, the sample size was calculated at 174 patients with 28 events.

Continuous variables are reported as median (interquartile interval or range) and compared using the Mann–Whitney U test. Categorical variables are expressed as number (percentage) and compared with the χ^2 or Fisher exact test, as appropriate. Variables associated with the primary endpoint at $P < 0.05$ in univariate analyses were entered into a multivariable logistic regression model with stepwise forward selection to identify independent predictors. The multivariable logistic regression model produced odds ratios with 95% confidence intervals. The discrimination properties of the different CSA-AKI definitions were assessed with an ROC analysis and c-statistics. Separate ROC curves were constructed for each definition, and the statistical difference between definitions was assessed according to the DeLong test. All the statistical analyses were conducted using computerized statistical programs (SPSS 20.0, IBM,

Chicago, IL, GraphPad, GraphPad Software, Inc, San Diego, CA, MedCalc, MedCalc Software, Ostend, Belgium). A P value < 0.05 was considered significant for all the statistical tests.

Results

The general characteristics of the patient population are reported in table 1. Overall, about 50% of the patients received a moderate-to-high complexity procedure, and about 13% a procedure of maximal complexity according to the RACHS-2 grading. The surgical operations were: ventricular septal defects repair (24 cases); arterial switch (20 cases); atrial septal defect repair (16 cases); single ventricle palliation (15 cases); total cavo-pulmonary connection (13 cases); aortic arch procedures (12 cases); pulmonary artery procedure (repair or conduit, 12 cases); tetralogy of Fallot (11 cases); complete atrio-ventricular canal repair (10 cases); Norwood-Sano operation (7 cases); sub-valvular aortic stenosis (6 cases); Fontan operation (6 cases); Ross or Ross/Konno operation (5 cases); Rastelli operation (4 cases); mitral valve repair (4 cases); truncus arteriosus repair (3 cases) and a miscellaneous of other complex operations (6 cases).

Thirty-two (18.4%) patients fulfilled the definition of composite outcome (prolonged ICU stay and/or hospital mortality). In table 2, the differences in perioperative factors between patients with or without the composite outcome are reported. Within the preoperative variables, patients experiencing the composite outcome had a significantly lower age and weight; a higher Hb and eGFR; had a larger rate of bloodstream infections and need for mechanical ventilation; and, finally, they were significantly more likely to receive inotropes, vasopressors, and furosemide.

Within the operative factors, patients experiencing the composite outcome had a significantly higher surgical complexity and longer CPB, lower temperature and DO_2 on CPB, and higher peak lactate on CPB.

The CSA-AKI rate was different depending on the type of definition: 24 cases (13.8%) according to the pROCK; 26 cases (14.9%) according to the mKDIGO; and more than double rate (76 cases, 43.7%) according to pRIFLE. However, CSA-AKI was significantly associated with the composite outcome regardless of the definitions used for adjudication. When considered separately, CSA-AKI (any stage) defined according to pRIFLE had an odds ratio for the composite outcome of 3.0 (95% confidence interval 1.35–6.75, P = 0.007); when defined according to the pROCK criteria, the odds ratio was 5.2 (95% confidence interval 2.06–13.1, P = 0.001), and when defined according to mKDIGO the odds ratio was 4.4 (95% confidence interval 1.79–11.1, P = 0.001).

A concordance/discordance matrix is reported in table 3. Overall, the CSA-AKI adjudication was significantly (P = 0.001) different when compared for couples of criteria. In particular, the “liberal” definition of the pRIFLE led to the fact that when CSA-AKI was denied by the pRIFLE, it was by the pROCK and mKIDGO too. Conversely, when CSA-AKI was adjudicated by the pRIFLE, it was denied in 68% of the cases by the pROCK and 66% by the mKDIGO. pROCK and mKDIGO, even if producing similar rates of CSA-AKI adjudication, still demonstrated significant differences, especially for pROCK-based CSA-AKI adjudication, that was denied in 42% of the cases by mKDIGO.

The higher rate of CSA-AKI adjudication for pRIFLE was due to its eGFR-based criterion: out of the 72 pRIFLE-adjudicated CSA-AKI cases, 52 were denied by the pROCK (in 25 cases there was no critical change in absolute or relative SCr values, and in 27 there was only the relative change ≥ 30%) and 50 were denied by the mKDIGO (in 42 cases because the peak SCr was not > 0.5 mg/dL, and in 8 cases because, despite a peak SCr > 0.5 mg/dL, there was not a critical absolute nor relative change). The 40 patients where CSA-AKI was adjudicated based on pRIFLE but not pROCK and mKDIGO had a median peak postoperative SCr of 0.33 mg/dL (interquartile range 0.33–0.46 mg/dL).

Table 5 shows the association of different outcome components between patients with or without CSA-AKI according to the 3 definitions tested in our study. Due to the low incidence of mortality, no definition found a statistically significant difference for this outcome. pRIFLE-adjudicated CSA-AKI had a higher rate for all the bad outcomes excepted bleeding; pROCK-adjudicated CSA-AKI had a higher rate for all the bad outcomes excepted bleeding and neurologic damage; and mKDIGO-adjudicated CSA-AKI had a higher rate of bleeding, ICU stay, and surgical re-operation.

Given the multifactorial association of preoperative and operative factors with the composite outcome, a logistic regression analysis (stepwise forward) was applied, including all the factors being associated with the composite outcome at a level of $P < 0.05$, together with the 3 CSA-AKI definitions (table 5). Only 4 factors remained independently associated with the composite outcome, and after adjustment for the other co-variates, CSA-AKI defined according to pROCK remained independently associated with the composite outcome with an odds ratio of 4.3. Based on the equation reported in table 5, a multivariable model for association with the composite outcome was built.

The discrimination capacity of the CSA-AKI staging as predictor of the composite outcome was tested with an ROC analysis separately for the different definitions and for the multivariable model with pROCK adjusted for preoperative mechanical ventilation, RACHS-2, and CPB duration (Fig. 1). No CSA-AKI definition reached a good degree of discrimination, with a c-statistics of 0.692 (95% confidence interval 0.618–0.760) for the pROCK, 0.625 (95% confidence interval 0.549–0.697) for the mKDIGO and 0.624 (95% confidence interval 0.547–0.696) for the pRIFLE. When tested for significant differences, there was no difference between the 3 definitions of CSA-AKI. Conversely, the multivariable model including the pROCK yielded an excellent discrimination (c-statistics 0.884, 95% confidence interval 0.827–0.928) outperforming ($P < 0.001$) the staging of CSA-AKI based on pRIFLE, mKDIGO, and pROCK.

Discussion

Within the wide scenario of retrospective studies addressing CSA-AKI definitions in pediatric patients, our study presents the only prospective series aimed at defining CSA-AKI incidence according to the 3 published definitions and addressing their association with postoperative outcomes.

The incidence of CSA-AKI in the pediatric patient population

From our results, CSA-AKI in children weighing < 20 kgs is about 14–15% according to the [27] range is not a novelty when addressing pediatric CSA-AKI, and there are many reasons for this. A first important issue is that, despite having specific definitions for the pediatric segment of the cardiac surgery population since 2007 [21], in many subsequent studies the standard definitions based on KDIGO and AKIN were applied to children, infants, and neonates. CSA-AKI incidence according to the standard KDIGO definition was reported quite homogeneously between 33% and 56% [7, 9, 16, 23–26]. Studies that applied the standard AKIN criteria provided similar rates (36%) [27]. These limited differences are not surprising, since the differences between definitions are very little.

Conversely, studies applying specific CSA-AKI definitions for pediatric patients, report a heterogeneous scenario. pRIFLE-based CSA AKI incidence is reported at 15–45% in unselected patient population from neonates to 18 years [2, 3, 14, 27], 52% in neonatal arterial switch operation [4, 13], up to 60–70% in other reports [10, 12]. When the mKDIGO criteria were applied, the CSA-AKI incidence was reported in a smaller range of 20–38% [2, 10, 15], with a high rate at 55% for the complex neonatal Norwood procedure [6].

There are few reports addressing pROCK in the setting of cardiac surgery, with a reported rate of about 18% [3].

Our results are in agreement with the other studies with respect to the pRIFLE-based and pROCK-based incidence of CSA-AKI, while when found lower rates for mKDIGO-based incidence. Overall, it seems that the standard definitions (RIFLE, AKIN, KDIGO) and the pRIFLE adjudicate CSA-AKI at a higher rate than pROCK and, to some extent, mKDIGO. There is a reasonable explanation for this. The pRIFLE adjudicates CSA-AKI based on the changes in eGFR, regardless of the peak value or relative changes of postoperative SCr. Doing this, it includes a number of patients who actually had a good preoperative eGFR, suffered a limited decrease, and did not reach truly abnormal postoperative SCr. As a matter of fact, in patients where the CSA-AKI was adjudicated based on pRIFLE but denied by both the pROCK and the mKDIGO, the median SCr peak did not exceed 0.33 mg/dL. Actually, both the pROCK and the mKDIGO include conditions that limit the possibility of adjudicating a CSA-AKI in patients with subclinical patterns of AKI: the pROCK, by requiring the double simultaneous presence of an absolute and a relative increase of SCr above defined thresholds; and the mKDIGO by requiring that for any CSA-AKI staging the peak postoperative SCr should exceed 0.5 mg/dL.

What is a clinically relevant CSA-AKI and its definitions

The above interpretation leads to the problem of defining what is clinically relevant CSA-AKI. The main problem when trying to define which of the various pediatric CSA-AKI definitions is the most convincing and which one we should use in clinical practice as well as in clinical research, is that there is not a “gold standard" for CSA-AKI. Every definition is arbitrary, exactly as it happens for other morbidity events like perioperative myocardial infarction or excessive bleeding. So, studies trying to identify the best definition

of pediatric CSA-AKI based their methodology on clinical relevance, i.e. on the level of association (and even prediction) of other bad outcomes.

Ueno and associates [10] chose 3 outcome measures (need for renal replacement therapy, ICU length of stay, and mortality) finding an association with pRIFLE and mKDIGO. Gao and associates [3] tested a composite outcome (at least one of the following: peritoneal dialysis, re-operation, re-intubation, pulmonary infection, extracorporeal membrane oxygenation) finding an association with pRIFLE, pROCK and AKIN. Wu and associates [15] and Eberle and associates [6] used hospital mortality for testing the mKDIGO definition of CSA-AKI, while Tanyildiz and associates [12] used the same criterion for testing pRIFLE; these authors found a significant association of CSA-AKI with mortality. pRIFLE and mKDIGO were tested in other series [4, 13, 27] finding an association with longer ICU stay, mechanical ventilation time, various morbid events, and mortality. pRIFLE yielded a good (c-statistics = 0.80) discrimination for mortality in a large population of neonates [2].

Actually, the association of CSA-AKI with other bad outcomes should follow a temporal sequence (i.e. the outcome should follow and not anticipate the CSA-AKI adjudication). To this respect, mortality and prolonged ICU length of stay appear as reasonable outcomes to be associated with and predicted by CSA-AKI. Conversely, a number of other outcomes might be the cause, rather than the consequence of CSA-AKI. This applies to pneumothorax, infections, low cardiac output, severe bleeding and others that have been used in previous studies. In our study, we have arbitrarily applied a composite outcome of prolonged (> 10 days) ICU stay and mortality, both being events that follow the CSA-AKI adjudication. The definition of prolonged ICU stay as > 10 days was applied in other studies [3]. Hospital mortality in our series was very low (3 cases) and did not allow us to use this outcome for testing association nor prediction, but we incorporated it in the adjudication of the composite outcome. In their study proposing the pROCK definition of CSA-AKI [22], the authors used the term “true AKI”, but they tested the pROCK for association with mortality. In general, every time the clinical researchers try to assess the performance of different definitions of CSA-AKI, the objective is not finding associations with the “true AKI” but with the “clinically relevant AKI”.

Comparison of the 3 pediatric CSA-AKI definitions.

In our study, we could find that the pRIFLE, mKDIGO, and pROCK definitions of pediatric CSA-AKI were all associated with a number of bad outcomes. With respect to the composite outcome, the level of statistical association was < 0.001 for all the definitions. However, once adjusted for the other independent covariates, only the pROCK remained significantly associated with the composite outcome. This suggests that it probably outperforms the pRIFLE and the mKDIGO.

There are few studies comparing different definitions of CSA-AKI. Anuk and associates [27] did not find any difference between pRIFLE and mKDIGO. Different findings are reported by other authors: Lu and associates [2] compared pRIFLE with mKDIGO (and other definitions used in adults) and found that the incidence of CSA-AKI was 34% according to the pRIFLE and 22% according to the mKDIGO; mKDIGO was superior to pRIFLE in terms of prediction of postoperative mortality. Ueno and associates [10] confirmed

these results, founding a CSA-AKI rate of 76% according to pRIFLE and 38% according to mKDIGO, with a superiority of mKDIGO in terms of association with morbidity and mortality.

The most relevant study is certainly from Gao and associates [3] who compared pRIFLE, unmodified KDIGO, and pROCK in a retrospective study on 413 infants who underwent cardiac operations. Again, the CSA-AKI incidence was greater for the pRIFLE (45%) than for the pROCK (18.6%). The composite postoperative outcome was significantly ($P < 0.01$) associated with the pROCK but not with the pRIFLE or the unmodified KDIGO. Of notice, when adjusted for age, weight, CPB duration and RACHS, the pROCK maintained its association with the composite outcome, but not with the prolonged ICU stay.

This study is certainly important for the numerosity of the reported series, and for its homogeneity in terms of age (neonates and infants). However, it is partially applicable to the real world of pediatric cardiac surgery, due to a selection bias: patients with preoperative complications and those requiring a deep hypothermic cardiac arrest were excluded; only 17–18% of the patients received surgery at moderate-to-high risk (RACHS-2 ≥ 3, and no patient received the complex surgery represented by the Norwood or arterial switch operations. Our series included 50% of patients with RACHS-2 ≥ 3, and no exclusion criteria were applied. However, even considering these differences, our results are similar to those from Gao and associates, both in terms of CSA-AKI incidence and superiority of the pROCK.

This finding is certainly important and deserves other studies to be confirmed. And it is somehow surprising, because in the original study proposing the pROCK, a very large (almost 100,000) series was included, but this was not limited to surgical patients. And cardiac surgery patients were excluded from the development of the pROCK. Despite this, it seems that the pROCK performs better than the other definitions of CSA-AKI.

There are limitations and strengths in our study. The main limitations are (i) the relatively low sample size, and (ii) the very low mortality rate, making impossible to use this outcome alone. The strengths are the prospective design, the inclusion of patients undergoing high-risk surgery, and the pragmatic nature of the study, without any major preoperative exclusion criteria.

Declarations

Conflict of interest:

The authors have no conflict of interest to declare.

Data Availability Statement:

Data will be shared under reasonable request.

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Tables

Tables are available in the Supplementary Files section.

Figures

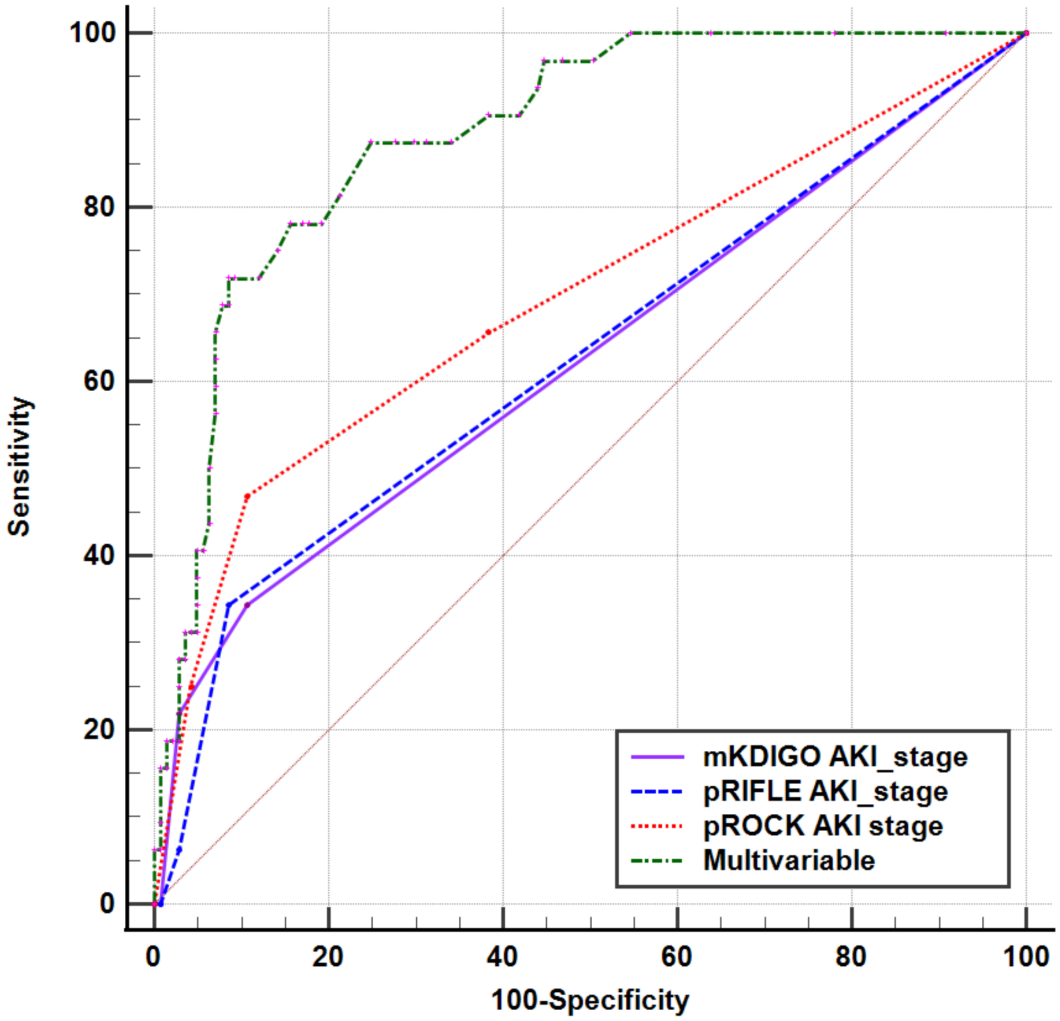


Figure 1

Receiver Operating Characteristics analysis for predictivity of the composite outcome for the 3 different definitions of Cardiac Surgery associated Acute Kidney Injury (AKI) and for the multivariable model. Data in the text.

mKDIGO: modified Kidney Disease Improving Global Outcomes; N/A: not applicable; pRIFLE: pediatric Risk, Injury, Failure, Loss of Function, and End Stage; pROCK: pediatric reference change value optimized for AKI in children.

Supplementary Files

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