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ORIGINAL ARTICLE

Incidence, Risk Factors and Outcomes of Acute Kidney Injury in Neonates Undergoing Open-heart Surgeries: Single Center Experience☆

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Abstract

Background: **Incidence and outcomes of acute kidney injury (AKI) among neonates who underwent open-heart surgery are not well highlighted in the literature. We aim to assess the incidence, risk factors, and outcome of AKI among neonates undergoing open-heart surgery.**

Methods: **This is a retrospective cohort study between 2016 and 2021 for all neonates requiring open heart surgery. The cases were divided into 2 groups: the AKI (index) group and the non-AKI (control) group. The two groups were statistically compared for risk factors, needs for dialysis, and outcomes.**

Results: **100 patients fulfilled the inclusion criteria. Among them, 74 (74%) developed AKI, including 41 (55%), 15 (21%), and 18 (24%) patients in KDIGO stages 1, 2, and 3, respectively. Multivariate analysis comparing both groups demonstrated that low pre-operative creatinine ($p = 0.01$), prolonged bypass time ($p = 0.0004$) and high vasoactive inotropic score (VIS), ($p = 0.0008$) were risk factors for developing AKI post-operatively. Furthermore, in the AKI group, 17 (23%) neonates required renal replacement therapy in the form of peritoneal dialysis. The length of stay was higher in the AKI index group ($p = 0.015$). Patients who had AKI recovered their kidney function at discharge. There was no difference in mortality between both groups.**

Conclusion: **The AKI occurred in 74% of neonates undergoing open-heart surgery, with 23% of them needing peritoneal dialysis. Low pre-operative creatinine, high VIS score, and prolonged bypass time are potential risk factors for AKI development after neonatal open-heart surgery. AKI may lead to prolonged hospitalization, though most affected patients recovered their normal kidney function at discharge.**

Keywords: Acute kidney injury (AKI), Open-heart surgery, Congenital heart disease (CHD)

1. Introduction

Acute kidney injury (AKI), a significant concern in critically ill neonates, is characterized according to modified Kidney Disease Improving Global Outcomes (KDIGO) by changes in serum creatinine or urine output and classified into three stages [1]. Neonates, especially those premature with low birth weight and/or patent ductus arteriosus (PDA), are at higher risk for AKI due to underdeveloped kidneys and low glomerular filtration rate (GFR) [2,4]. Moreover, open-heart surgery is recognized as a prominent risk factor for AKI in neonates [3]. Prolonged exposure to non-pulsatile blood flow during cardiopulmonary bypass (CPB) can lead to renal hypoperfusion and ischemia-reperfusion injury, while the use of the extracorporeal circuit can contribute to renal damage through systemic inflammation and oxidative stress. Additionally, the administration of contrast

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agents prior or during CPB procedures exacerbates the risk of AKI [5,6].

AKI accounts for nearly 30% of neonatal admissions to the neonatal intensive care unit (NICU), emphasizing its significance among critically ill neonates [7]. Prematurity and low birth weight infants are particularly vulnerable due to elevated renal vascular resistance, reduced intercortical perfusion, limited GFR, and underdeveloped kidneys [8–10]. One study reported an AKI incidence rate of 26% among extremely low birth weight (ELBW) infants [8]. They concluded that prematurity, congenital anomalies, acquired renal disorders, cardiac surgeries, and medications are risk factors for AKI in this group of patients [8–10]. Another study estimated a 26.9% prevalence of AKI among critically ill pediatric and young adult patients [11].

AKI is considered an independent burden that increases morbidity and mortality in the NICU and PICU [12]. However, defining AKI in neonates poses challenges due to fluctuations in baseline serum creatinine (SCr) levels and the absence of a consensus definition [13]. A study focusing on pediatric cardiac patients (excluding neonates) identified risk factors such as cyanotic cardiac disease, hyperlactic acidemia, and anemia [14]. A study focusing on AKI risk factors in pediatric cardiac patients indicated that factors including younger age (<12 months), longer CPB time, and low preoperative hemoglobin levels increase AKI risk [15].

The complexity of neonatal cardiac surgeries arises from the newborn's fragility and organ immaturity [16]. Post-operative complications such as low cardiac output state, sepsis, neurological complications, arrhythmias, pneumonia, lobar atelectasis, and AKI are among well-recognized complications in neonates undergoing cardiac surgery [17–20]. One study revealed that cardiac surgery-associated acute kidney injury (CSA-AKI) is often attributed to post-surgical vasoconstriction, leading to diminished renal perfusion [21,22]. Moreover, prolonged bypass time during cardiac surgery not only contributes to reduced renal perfusion but also amplifies the risk of CSA-AKI by exacerbating vasoconstriction-induced ischemic and reperfusion injury, further compromising kidney function [14,21,22].

The incidence of AKI in neonates following open-heart surgery remains indefinite, primarily due to the diverse definitions used in research and clinical practice. This lack of clarity and a paucity of comprehensive data regarding risk factors and outcomes for this age group specifically emphasizes a knowledge gap [23]. Motivated by these challenges, our study aims to show the neonatal AKI incidence, risk factors, and outcomes in open-heart surgery. It also extends to the incidence across different AKI stages, according to modified KDIGO's criteria, and the requirement for renal replacement therapy in the post-operative period.

Abbreviations

AKI	Acute Kidney Injury
BUN	Blood Urea Nitrogen
CPB	Cardiopulmonary Bypass
CSA-AKI	Cardiac Surgery-Associated Acute Kidney Injury
ELBW	Extremely Low Birth Weight
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
IRB	Institutional Review Board
KDIGO	Kidney Disease Improving Global Outcomes
NICU	Neonatal Intensive Care Unit
OR	Odd Ratio
PDA	Patent Ductus Arteriosus
PD	Peritoneal Dialysis
PICU	Pediatric Intensive Care Unit
RACHS	Risk Adjustment for Congenital Heart Surgery
ROC	Receiver Operating Characteristic
VIS	Vasoactive Inotropic Score

2. Material and method

We conducted a retrospective cohort study on all neonates (0–30 days) who underwent open-heart surgery and were admitted to the pediatric cardiac intensive care unit (PCICU) between October 2016 and December 2021. We first reviewed all neonatal patients who had all types of cardiac surgery for inclusion and exclusion criteria. We included neonates of any gestational age (preterm, term, and post-term) undergoing open-heart surgery requiring cardiopulmonary bypass (CPB) within the specified period. The exclusion criteria were neonates with pre-existing kidney injury as per KDIGO's definition. Institutional review board approval was obtained for this study. The study was approved by the institutional review board (IRB # SP21R/235/05). We used the neonatal KDIGO criteria for AKI classification. Stage 1 AKI is marked by a serum creatinine rise $\geq$0.3 mg/dl or 1.5–1.9 times baseline, and/or urine output <1 ml/kg/h for 24 hours. Stage 2 involves a creatinine increase of 2–2.9 times baseline and/or urine output <0.5 ml/kg/h. Stage 3 is a creatinine rise $\geq$3 times baseline or initiation of renal replacement therapy, and/or urine output <0.3 ml/kg/h. In our study we used both serum creatinine and urine output.

In our study, we gathered data across six main domains: demographics data (e.g., age, height, weight, etc.), congenital cardiac anomalies and surgical complexity. (e.g., disease type, RACHS-1 score, etc.), pre-operative variables (e.g., renal ultrasound,

BUN, etc.), intraoperative variables (e.g., bypass time, etc.), post-operative data (e.g., Vasoactive Inotropic Score VIS, Serum Creatinine, etc.), and outcomes (e.g., mechanical ventilation, hospital length of stay, etc.). Statistical analysis of the variables was executed via John's Macintosh Project (JMP) software version 16.1. Descriptive statistical analysis was carried out using JMP. The statistical tests were based on the Chi-square test for categorical variables, and the independent *t*-test for numerical variables. The Mann-Whitney *U* test was used for the nonparametric variables. We also used logistic regression to assess the influence of different predictors on AKI in neonates after open-heart surgery. The specific variables included in the model, encompassing both patient characteristics and surgical factors, were selected based on literature review and clinical relevance. To ensure an accurate assessment of each variable's unique impact, we adjusted for multiple variables, allowing for the isolation and analysis of individual effects on the outcome. Following the logistic regression analysis results, we examined the sensitivity and specificity of each risk factor identified by the regression to assess their diagnostic accuracy. This was achieved using Receiver Operating Characteristic (ROC) curves, which plot the true positive rates against the false positive rates for different cut points.

3. Results

During the study period, a total of 500 children underwent open heart surgery and were filtered through our criteria. One hundred of those met our inclusion criteria and were eligible and included in the final analysis, as shown in Table 1. There were 59 males (59%). Out of the one hundred neonatal patients who were included, 74 (74%) developed acute kidney injury (AKI). Among the index group, 55% were in stage 1, 21% in stage 2, and 24% in stage 3 based on KDIGO's modified criteria as shown in Table 1.

Table 2 demonstrates the types of congenital heart disease and cardiac surgeries with transposition of great arteries being the most common with 61% of those cases developed AKI post-operatively (*p*-Value = 0.021).

In index group, 17 patients (23% of the AKI group) needed peritoneal dialysis ($p = 0.021$) and required a longer hospital stay ($p = 0.015$). Mortality was not different between both groups as shown in Table 3.

The multivariate analysis showed that creatinine pre-operatively (*p*-Value = 0.01) with an odd ratio (OR) of 0.93 (CI = 0.87, 0.98), bypass time (*p*-Value = 0.0004) with an OR of 1.02 (CI = 1.01, 1.03), and maximum vasoactive inotropic score (*p*-Value 0.0008) with an OR of 1.15(CI = 1.04, 1.28) were risk factors for developing AKI as shown in Table 4. ROC identified as the VIS of 13 predicted 80% of AKI cases with sensitivity of 48% and specificity of 85% (AUC = 70%), while bypass time of 127 minutes predicted 78% of AKI cases with sensitivity of 87% and specificity of 54% (AUC = 67%), Fig. 1.

Additionally, the regression analysis within the AKI group showed that high creatinine post-operatively (*p*-value <0.001) with an OR of 1.07 (CI = 1.03, 1.11) and having an open sternum (post-op) (*p*-value <0.011) with an OR of 5.88 (CI = 1.50, 23.07) were associated with the need for PD among AKI cases following open heart surgery (Table 5). ROC curve showed post-op creatinine of 97 μmol/L predicted 46% of AKI cases that required PD with a sensitivity of 65% and specificity of 96% (AUC = 83%) while having a delayed sternal closure predicted 45% of AKI cases that required PD with a sensitivity of 60% and specificity of 86% (AUC = 72%), Fig. 2.

4. Discussion

In our study, we assessed the occurrence of AKI in neonates who had open heart surgeries to be 74%. It is known that neonates have less nephrons and

Table 1. Demographical data for Acute Kidney Injury (Indexed group).

Demographical data	Index AKI group (n = 74)	Control group (n = 26)	P value
Age (days)	13.4 ± 7.7	12.7 ± 7.4	0.67
Height (Cm)	48.8 ± 3.5	48.9 ± 4.6	0.88
Weight (Kg)	3.1 ± 0.5	2.9 ± 0.5	0.38
Male	43 (58%)	16 (61%)	0.75
Preterm	9 (12%)	5 (19%)	0.37
Cyanotic	57 (77%)	17 (65%)	0.24
AKI by KDIGO Stages			
Stage 1	41 (55%[a])		
Stage 2	15 (21%[a])		
Stage 3	18 (24%[a])		

p-Value <0.05 considered significant.

[a] AKI= Acute Kidney Injury, KDIGO= Kidney Disease Improving Global Organization.

Table 2. Disease Types that required open-heart surgery.

Outcome	Index group (n = 74)	Control group (n = 26)	P value
Transposition of great arteries	45 (61%)	9 (35%)	0.021[a]
Coarctation of aorta + (VSD, ASD, AVSD, and/or PDA)	7 (10%)	5 (19%)	0.18
Truncus arteriosus repair	8 (11%)	1 (4%)	0.28
Total anomalous pulmonary vein drainage repair	1 (1%)	5 (19%)	0.001[a]
Hypoplastic aortic arch	4 (5%)	1 (4%)	0.75
Interruption of aortic arch	3 (4%)	2 (8%)	0.48
Others	6 (8%)	3 (11%)	0.6
Risk adjustment for congenital heart surgery score (RACHS)			
RACHs 3 (total cases 26)	17 (23%)	9 (35%)	0.24
RACHs 4 (total cases 73)	56 (76%)	17 (65%)	0.31
RACHs 5 (total cases 1)	1 (1%)	0 (0%)	0.55

p-Value <0.05 considered significant.
[a] RACHS = Risk Adjustment for Congenital Heart Surgery Score. Indexed group = Patients who developed AKI post-operatively, Control group = Patient who did not develop AKI.

Table 3. Main outcomes (dependents) variables and predictors of AKI based on multi-variable analysis.

Outcome	Index group (n = 74)	Control group (n = 26)	P value
Pre-operative variables			
Kidney abnormality by ultrasound	24 (32%)	11 (42%)	0.66
Serum blood urea nitrogen (mmol/L)	2.7 ± 2.1	3.8 ± 2.6	0.055
Serum Creatinine (μmol/L)	42.7 ± 8.7	45.6 ± 9.5	0.17
Urine out-put (mL/kg/h)	5.1 ± 1.9	5.1 ± 2.3	0.98
Intra-operative variables			
Bypass time (Minutes)	129.3 ± 51.8	90.9 ± 64.1	0.009*
Cross-Clamp time (Minutes)	89.9 ± 39.9	66.3 ± 47.4	0.032*
Delayed sternal closure (Minutes)	20 (27%)	2 (7.7%)	0.059
Post-operative variables			
Need for furosemide administration	74 (100%)	23 (88%)	0.003*
Maximum vasoactive inotropic score (VIS)	13.3 ± 10.4	7.7 ± 5.8	0.0013*
Serum blood urea nitrogen (mmol/L)	6.7 ± 9.3	3.9 ± 2.0	0.019*
Serum creatinine (μmol/L)	76.0 ± 19.4	52.8 ± 10.9	<0.0001*
Urine output (mL/kg/h)	3.0 ± 1.9	4.9 ± 2.2	0.0006*
Lactic acid (mmol/L)	6.7 ± 3.3	4.6 ± 2.5	0.0022*
Need for peritoneal dialysis	17 (23%)	0 (0%)	0.021*
Duration of mechanical ventilation (Days)	6.3 ± 7.9	4.0 ± 5.1	0.093
Outcome			
Hospital length of stay (Days)	24 ± 20.3	17 ± 16.2	0.015*
Mortality	2 (3%)	1 (4%)	0.48

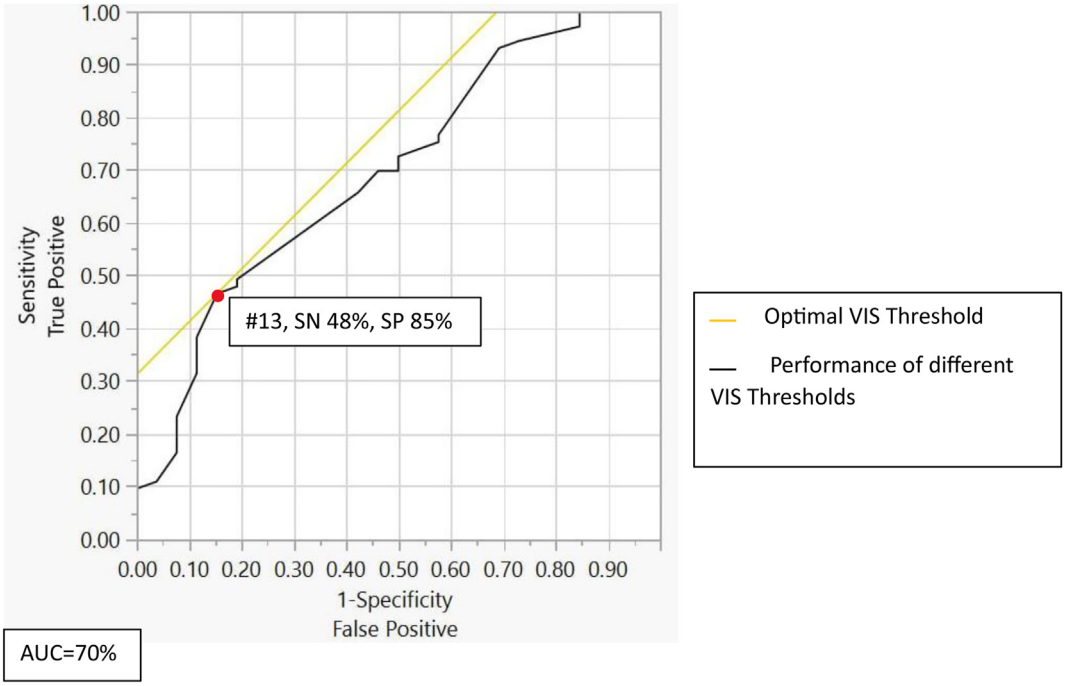
p-Value <0.05 considered significant.

Table 4. Multivariate analysis.

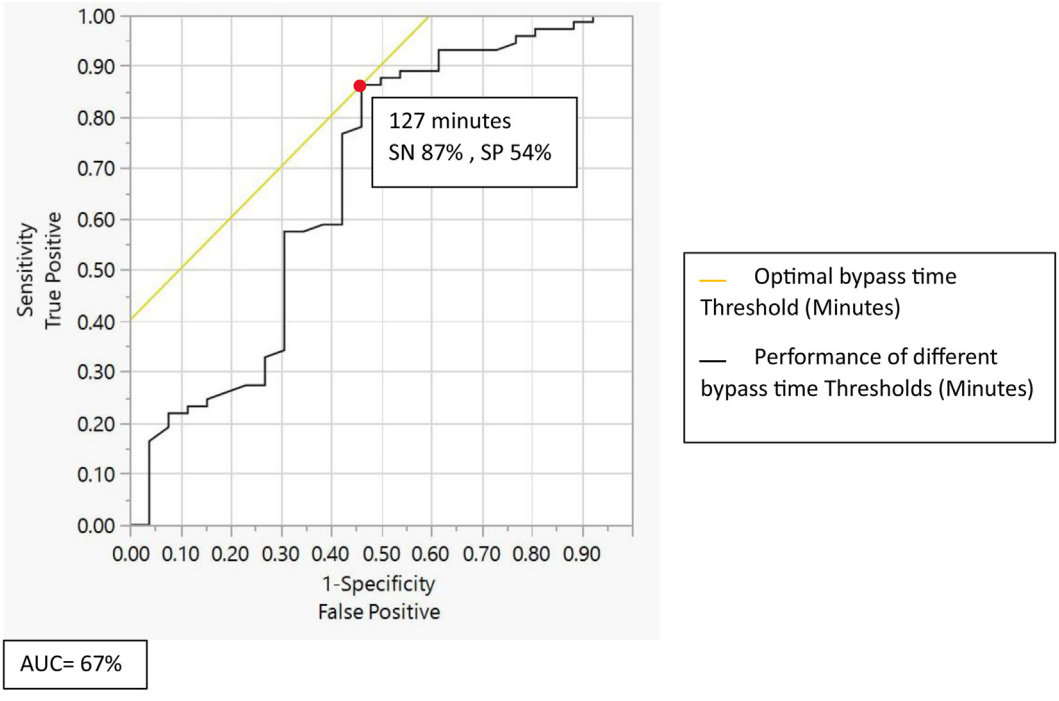
Multivariant analysis	*P* Value	Odd ratio (Confidence interval)
Creatinine pre-operatively (μmol/L)	0.01[a]	0.93 (0.87, 0.98)
Bypass time (Minutes)	0.0004[a]	1.02 (1.01, 1.03)
Maximum vasoactive inotropic score	0.0008[a]	1.15 (1.04, 1.28)

p-Value <0.05 considered significant.
[a] RACHS= Risk Adjustment Congenital Heart Surgery Score, *VIS= Vasoactive-Inotropic Score.

compensatory reserve in case of any insults. As a result, they are at higher risk for developing AKI compared to older children especially under ischemic conditions like open-heart surgery. Despite the scarcity of studies on this population, the AKI incidence obtained from our sample was relatively higher compared to the 15%–64% incidence rate reported by published literature [14,25]. In a study by Shalaby et al.



A)



B)

*Fig. 1. A) ROC of AKI and VIS. *ROC= Receiver operating characteristic curve, AKI= Acute Kidney Injury, *VIS= Vasoactive-Inotropic Score, AUC= Area under the curve, SN= Sensitivity, SP= Specificity. B) ROC for AKI and bypass time. *SN= Sensitivity, SP= Specificity, AUC= Area under the curve.*

Table 5. Multivariate analysis For PD.

Multivariant analysis	*P* Value	Odd ratio (Confidence interval)
Creatinine post-operatively (μmol/L)	<0.001[a]	1.07 (1.03,1.11)
Delayed sternal closure (Minutes)	0.011[a]	5.88 (1.50,23.07)

p-Value <0.05 considered significant.
[a] PD= Peritoneal Dialysis, RACHS= Risk Adjustment Congenital Heart Surgery Score, VIS= Vasoactive-Inotropic Score.

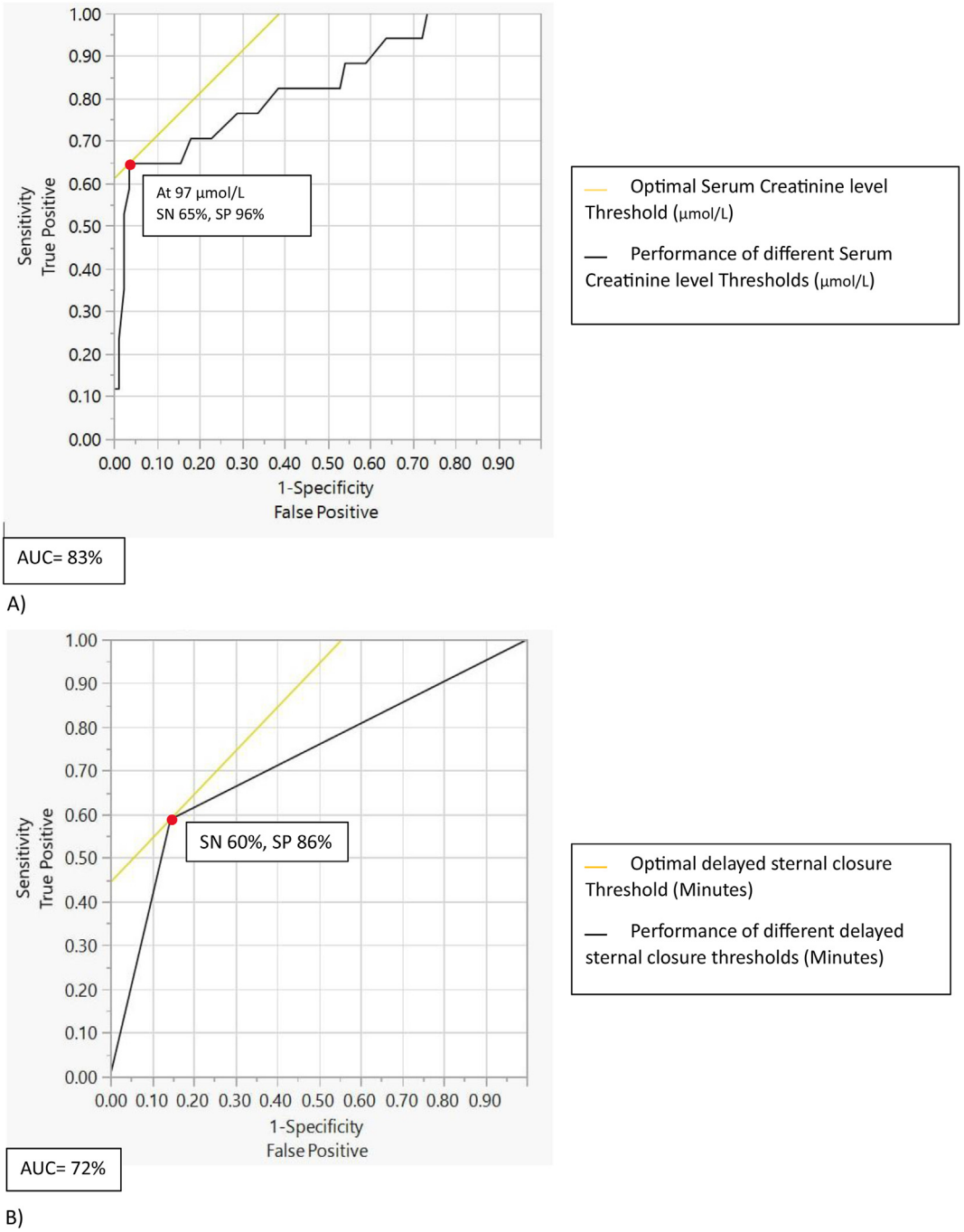


*Fig. 2. A) ROC of PD and serum creatinine level (post-op). *SN= Sensitivity, SP= Specificity, PD= Peritoneal dialysis, AUC= Area under the curve. B) ROC of PD and delayed sternal closure (post-op). *SN= Sensitivity, SP= Specificity, PD= Peritoneal Dialysis, AUC= Area under the curve.*

(2018), the authors reported an incidence of 54% of AKI among all neonates with a non-renal anomaly admitted to neonatal ICU [26]. The difference is possibly due to a more selective inclusion criteria in our cases focusing exclusively on neonates undergoing open heart surgery with cardiopulmonary bypass which by itself is a recognized risk factor for neonatal AKI compared to non-cardiac surgeries [3]. Furthermore, in the multi-center AWAKEN study that investigated incidence of AKI in neonates, the authors identified various risk factors among critically ill neonates including lower birth weight, the use of extracorporeal membrane oxygenator (ECMO) and having cardiac surgeries [27]. As such, our findings further corroborate previous studies by demonstrating how common AKI and how susceptible neonates post open heart surgery are to develop AKI. Accordingly, perioperative monitoring and preparation for renal replacement therapy should be intra-operatively considered and timely instituted post-operatively.

Furthermore, among our population of AKI cases in our study 55% were in stage 1, 21% in stage 2 and 24% in stage 3. In another study investigating neonatal AKI, Park et al. (2016) reported 25.9% (stage 1), 12.3% (stage 2) and 3.6% (stage 3) [15]. The difference between our report and Park et al.'s can be attributed again to different study designs and patients' selection criteria as they recruited children older than 1 month of age in their study, which in turn diluted the overall incidence of AKI.

Through bivariate analysis, we found that among neonates who developed AKI, 61% had arterial switch operation. Using the RACHS score to stratify the risk of AKI post cardiac surgeries, we found most of our cases ranked as RACHS 3 (23%) and 4 (76%) with one patient (1%) in RACHS 5 categories. This goes in line with a multi-center study reporting comparable results [28]. Our study suggests that increasing complexity of cardiac surgery is associated with linear increase in AKI development.

Regarding intra-operative factors, the AKI group had significantly longer bypass and cross-clamp times compared to the controls. Similarly, Auon et al.'s single center and both NEPHRON's and Li et al.'s multi-center studies showed similar bypass times; however, only the latter showed statistical significance compared to controls [14,25,32]. Our cross-clamp times (89.9 ± 39.9 min), on the other hand, were longer compared to the studies included in our literature review. Longer bypass and cross-clamping increase the hypoperfusion period and the likelihood of developing AKI in these vulnerable individuals [3]. The higher lactic levels post-surgery (Table 3) in the AKI group supports this hypothesis.

In addition to prolonged bypass time, among the post-operative variables max VIS scores and lactic acid were significantly greater in the AKI group. These findings are also comparable to previous reports in the literature. For instance, Rhone et al. (2014) showed in their retrospective study, that infants with AKI were more likely to receive inotropes or vasopressors during their hospital stay [24,29]. A similar result was found by Park et al. (2016) and Li et al. (2011) [15,25]. These together point to the potential nephrotoxicity of vasopressors/inotropes when attempting to stabilize the hemodynamics of a patient following cardiac surgery. These drugs typically work by increasing systemic resistance to enhance systemic perfusion, but simultaneously can limit blood flow to some organs including the kidneys [24].

On top of that, children only after 2 years of age can reach maximum glomerular filtration rates, hence medications are more likely to remain in neonates' bodies for longer periods adding more injury to the already offended kidneys [24]. Worth mentioning also, another retrospective chart review showed urine output after furosemide administration in the first 24 hours could be a potential marker for AKI following cardiac surgeries [29,30]. In line with the study, we found the AKI group had significantly lower urine production despite the more frequent use of furosemide compared to the controls. We hypothesize diuretics (e.g. furosemide) are not able to work efficiently in neonates in the setting of AKI due to the age-related differences in pharmacokinetics and suboptimal excretory ability [31], and as a result, neonates with AKI were more likely to need renal replacement therapy (23%).

From our sample, we found that mortality rates were higher among the AKI group but did not reach statistical significance as with Li et al.'s (2011) report [25]. Using multi-variate analysis, we found prolonged bypass times, high vasopressor and inotrope use, and low baseline/preoperative creatinine to be significant risk factors for AKI. Similarly, Li et al. also indicated prolonged bypassing times (more than 120 minutes) were independently associated with AKI development after surgery. Unfortunately, vasopressor/inotrope use was not a consistently reported variable, hence VIS scores were difficult to compare to other reports. In NEPHRON's study, AKI cases had a (median) VIS score of 5 compared to our 13 (mean). Both our larger VIS score (more nephrotoxicity) and longer cross-clamping times could explain our larger incidence of AKI, and correspondingly a longer length of hospital stay compared to other single and multicenter studies investigating AKI post-cardiac surgery. Regarding baseline creatinine, the lower levels observed in the

AKI group could be explained by several interplaying factors – among these are underlying heart conditions, maternal creatinine levels and gestational age (GA) [33]. Our AKI group had a greater proportion of cyanotic CHDs - typically more debilitating than acyanotic CHDs [34], hence they were more prone to fluid retention and consequential dilution of creatinine levels. Studies have shown a strong correlation between maternal and neonatal creatinine levels, especially in preterm (GA <37 weeks) [33]– our AKI group had a greater proportion of preterm babies; hence these levels could be reflecting their maternal counterparts – which unfortunately was not accounted for in the current study's analysis.

Using ROC curves, we found VIS of 13 predicted 80% of AKI with sensitivity of 48% and specificity of 85%, and Bypass time of 127 minutes predicted 78% of AKI with sensitivity of 87% and specificity of 54% were good positive predictive values to anticipate which neonates would develop AKI, hence both variables could be potential surrogate markers for AKI occurrence.

Regarding the need for renal replacement therapy, a nominal logistic fit model for peritoneal dialysis (PD) showed high creatinine levels or delayed sternal closure after surgery significantly increased the likelihood for the need for PD. Accordingly, we utilized ROC curves to compare the two variable's discriminant capacity to predict the need for PD. As shown in Table 5, both a creatine level of 97 μmol/L and having a delayed closure of the sternum post-operatively were statistically significant to specify the need for PD among AKI cases.

The authors recognize that our study is not free of limitations. First, the retrospective nature of our study design prevents us from making causal inferences about our reported risk factors. Second, our study is limited to a single institution, which means generalizing to other institutions and populations is not feasible – especially when our small sample size is taken into consideration. Lastly, our definition and calculation of AKI incidences were based on serum creatinine levels – which has been shown to be not the best marker for detecting kidney damage in younger populations [9,13], hence our reports might be underestimating the true rate of AKI in neonates.

5. Conclusion

In conclusion, our study showed an AKI incidence of 74% (55% in stage one, 21% in stage two, and 24% in stage three). Among AKI cases, 23% required peritoneal dialysis as a form of renal replacement therapy. Multiple variable analysis demonstrated that serum creatinine preoperatively, the need for high inotropic support (VIS), and bypass time are considered potential predictors for developing AKI in neonates undergoing open-heart surgery. Hospital length of stay was higher in the AKI group compared to control group. However, the difference in mortality rates between the AKI and the control group was insignificant.

Furthermore, our findings suggest the insertion of peritoneal dialysis during the operation of those neonates who underwent open-heart surgery will allow passive peritoneal drainage and early institution of renal replacement therapy as needed.

We recommend future studies to include multiple institutions as part of their study to have a better understanding of AKI's risk factors among this specific group and to be able to generalize the results to a wider population. Lastly, we believe that a prospective study design with more standardized monitoring of kidney function and longer follow-up duration post-surgery is needed to detect any further changes in these patients.

Author's contribution

Conception and design of Study: FAA, MABM. Literature review: FAA, MABM, HFA, NSA, KEA, OMK. Acquisition of data: FAA, MABM, HFA, NSA, KEA, OMK. Analysis and interpretation of data: FAA, MABM, HFA, NSA. Research investigation and analysis: FAA, MABM, HFA, NSA, KEA, OMK. Data collection: FAA, MABM, HFA, NSA, KEA, OMK. Drafting of manuscript: FAA, MABM, HFA, NSA, KEA. Revising and editing the manuscript critically for important intellectual contents: FAA, MABM, HFA, NSA, KEA, OMK. Data preparation and presentation: FAA, MABM, HFA. Supervision of the research: MSK. Research coordination and management: MSK.

Conflict of interest

We declare that there is no conflict of interest regarding the publication of this paper.

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