Comparative evaluation of AKIN, KDIGO and pRIFLE criteria and urinary biomarkers in prediction of AKI following cardiopulmonary bypass(CPB-AKI) in children

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ABSTRACT:
Introduction: Acute Kidney Injury (AKI) following surgery for congenital heart disease with cardiopulmonary bypass (CPB-AKI) is fairly common. Limited studies have compared newer definitions of AKI in relation to early non-invasive urinary biomarkers for prediction of post CPB AKI. We sought to evaluate a) incidence using pediatric RIFLE, AKIN and KDIGO criteria, b) utility of urinary protein creatinine ratio (UPCR), modified urine microscopy score and NGAL as predictive early AKI biomarkers and c) risk factors for post CPB-AKI in children with CHD.

Material & Methods: Serial blood and urine samples were collected for all children (2 mo-18 y) undergoing congenital heart surgery with cardiopulmonary bypass between Nov 2017 to Apr 2019 at pre surgery,6,24, 48 hrs and day 7, day 30. Incidence of AKI was calculated as per standard definitions. Urine samples were analysed for UPCR and NGAL in the supernatant and the sediments were microscopically analysed to derive a modified urine microscopy score. Risk factors predisposing to AKI were analysed by multivariate analysis. ROC analysis was done for urinary biomarkers taking KDIGO as gold standard definition of AKI.

Results: Amongst 76 children with CHD, incidence of AKI was 51% with AKIN/KDIGO criteria and 55% with pRIFLE criteria. Urinary NGAL rose within 6 hrs of CPB. A cut-off >84 ng/ml had 95% specificity with only 45% sensitivity (AUC-ROC 0.71). At 24 hrs, urine PCR was significantly high (AUC-ROC 0.7686) while urine microscopy score was similar in cases who developed AKI. Ventilation >48 hrs, exposure to multiple antibiotics and sepsis were significantly associated with AKI.

Conclusion: Combination of pRIFLE with AKIN/KDIGO increased detection of post CPB AKI by 4%. In our cohort urinary NGAL at 6 hours and UPCR at 24 hours had a moderate predictive value.

Keywords: Acute Kidney Injury, Urinary Biomarkers, Urinary Protein Creatinine Ratio

INTRODUCTION

Acute kidney injury, a complication after paediatric cardiac surgery with the incidence of 9.6% to 52% [1-6].There are three different classifications based on serum creatinine and urine output to describe AKI in children –paediatric risk, injury, failure, loss, end-stage (pRIFLE),[9] Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcome(KDIGO) [7]. Debates are there in the use of one criteria over another.

Multiple novel biomarkers with traditional biomarkershave been evaluated in past but none proved superior in early prediction of AKI. Sothis study was done to evaluate the incidence of AKI post CPB according to various criteria and the utility of non-invasive urinary biomarkers in early prediction of AKI.

MATERIAL AND METHODS

This was a prospective cohort study conducted inPediatric Cardiothoracic surgery Intensive Care Unit (PCSICU), Army HospitalResearch and Referral, Delhi Cantt between Oct 2017 and Mar 2019. IEC approval granted vides AHRR IRB no 59/2017. Children's with CHD underwent CPB aged between 2 month - 18 years were eligible for recruitment and children's with known CKD, less than 2 months age and parents unwilling to provide consent for follow up were excluded. After enrolment clinical details recorded highlighting the risk factorsof AKI according to KDIGO criteria. Subsequently every child followed up 8 hourly to record clinical parameters in the initial 7 days or upto discharge from the PCSICU and thereafter in the pediatric cardiothoracic ward and advised to review at day 30.

Serial blood (3 ml) and urine (10 ml) samples were collected, aliquoted and archived at -20 ^{0}C for various biochemical investigations using an autoanalyzer system (Vitros 4600 dry chemistry analyser). Serum and urine creatinine (mg/dl) were estimated by enzymatic creatinine assay method using commercial kit from Dimension Vista Enzymatic Creatinine Flex Reagent Cartridge, Siemens. Urine NGAL (ng/ml) estimation was done by ELISA (EDI^{TM} Quantitative urine NGAL ELISA kit of Epitop DiagnosticsSan Diego, CA 92121,USA). Serum uric acid and BUN were measured using commercial kits (Vitros uric acid and BUN slides by colorimetric method).

For urine microscopy score, a fresh urine sample was obtained from the catheter at 6 and 24 hours post surgery and centrifuged at 1500 rpm for 5 min, supernatant discarded and sediment microscopy with scoring was done as per criteria [11].

STATISTICAL ANALYSIS:

All data recorded and stored in MS Excel format as master sheet.Baseline comparisons were performed using the Mann–Whitney Utest.A comparison of the AKI grades according to KDIGO, pRIFLE and AKIN criteria was performed using the Kruskal–Wallis test for continuous variables and two-sided $\chi2$ analysis for categorical variables. A multivariate logistic regression analysis was performed to identify the risk factors for AKI. Receiver–operator characteristic (ROC) area under the curve (AUC) and 95% confidence interval analysis was performed. Tests were considered significant at $p < 0.05$. Data were analyzed using the STATA, version 13.0 (StataCorp. 2013).

RESULTS

Total 78 children underwent CPB during the study period, of these 76recruited& 2excluded being below 2 months of age. Demographic characteristics showed male preponderance (67%) and almost equal percentage of cyanotic&acyanotic heart disease children, Table 1.

Table 1: Baseline characteristics of CHD patients

Characteristics	N (%)
Age distribution	
<1 year	37 (49%)
1 – 2 year	14 (18%)
2 – 14 year	25 (33%)
Sex	
Male	51(67%)
Female	25 (33%)
Type of congenital heart disease	
Cyanotic	35 (46%)
Acyanotic	41 (54%)

Post surgery 50 (65%) kids were inmechanical ventilation, of these 4 (8%) required for < 6 hrs, 23 (46%) for 6-24 hrs, 12 (24%) for 24 – 48 hrs and 11 (22%) for >48 hrs. Total 50 (66%)children required vasopressor support to maintain the hemodynamics, of which 12 (16%) received 1-2 inotropes and 38 (50%) >2 inotropes.

Duration of CPB ranged from < 90 min in 22 (29%), 90-120 min 28 (38%), 120-180 min21 (28%) &>180 min4 (5%) children.Post surgery all received intravenous antibiotics, 41 (54%)received cefoperazone, 4 (5%)meropenam, 24 (32%) meropenam with colistin, 6 (8%) meropenam with colistin and tigycycline.Total 19 (25%) developed post CPB blood culture positive sepsis among them 9 (12%) was positive for Klebsiella and 10 (13%) for Burkholderia.

Incidence of post CPB AKI

Total of 39/76 (51%) children developed AKI as per KDIGO criteria. Staging of children with post CPB AKI according to KDIGO & AKIN criteria given in Table 2

Table 2: Staging of children developed AKI according to KDIGO & AKIN criteria

Criteria	Based on rise of serum creatinine	Based on decrease of urine output	Total
KDIGO – Stage I	22 (29%)		
Stage II	11 (14%)	2 (3%)	39 out of 76 (51%)
Stage III	6 (8%)		
AKIN – Stage I	22 (29%)		
Stage II	11 (14%)	2 (3%)	39 out of 76 (51%)
Stage III	6 (8%)		
pRIFLE criteria	Based on fall of eGFR	Based on decrease of urine output	Total
Risk	26 (34%)	2 (3%)	
Injury	12 (16%)		42 out of 76 (55%)
Failure	4 (5%)		

As per pRIFLE criteria26 children had a fall of eGFR >25%, 12 children >50%, and 4 children >75% within 48 hrs of CPB.After combining KDIGO, AKIN and pRIFLE criteria total 42 (55%) children developed AKI (Table 2).

Among 39 children who had AKI as per KDIGO criteria, 6 needed RRT, 12 (16%) died within 1 month post CPB.On follow up of survivorsafter 30 days of discharge nonedeveloped acute kidney disease (AKD)& beyond 3 months none progressed to CKD.

Various biomarkers in prediction of post CPB AKI
Various biomarkers studied were urine protein creatinine ratio, BUN, serum creatinine, serum uric acid, FeNa, urine microscopy score and urine NGAL.There was a significant rise of serum creatinine within 24 hrs post CPB in AKI group. Amongst the different biomarkers, urine protein creatinine ratio and urinary NGAL showed a significant predictive ability for AKI within 6 hrs of CPB as compared with serum creatinine. Urine microscopy score at 24 hrs of CPB had no significant change with respect to 6 hrs of CPB (Table 3).

Table 3 : Prediction of AKI by different biomarkers within 24 hrs of CPB

Biomarker	Baseline			At 6 hrs			At 24 hrs		
	AKI (n=39)	Non-AKI(n=37)	P value	AKI (n=39)	Non-AKI(n=37)	P value	AKI (n=39)	Non-AKI(n=37)	P value
Urine Protein Creatinine ratio, Mean ± SD	1.9 ± 2.3	1.2 ± 0.9	0.95	2.47 ± 2.44	1.44 ± 0.99	**0.009**	2.9 ± 1.9	1.5 ± 1.0	**0.0001**
FeNa Mean ± SD	0.01 ± 0.02	0.16 ± 0.23	0.99	0.03 ± 0.03	0.02 ± 0.03	**0.07**	0.05 ± 0.13	0.03 ± 0.04	0.18
BUN (mg/dl) Mean ± SD	10.6 ± 5.7	10.4 ± 6.4	0.44	13.6 ± 5.2	13.2 ± 5.5	0.37	16.4 ± 4.8	15.7 ± 5.7	0.28
Serum creatinine (mg/dl), Mean ± SD	0.29 ± 0.1	0.33 ± 0.1	**0.04**	0.39 ± 0.13	0.35 ± 1.1	**0.05**	0.53 ± 0.27	0.39 ± 0.1	**0.003**
Serum Uric acid (mg/dl), Mean ± SD	3.7 ± 0.8	3.6 ± 0.8	0.70	4.1 ± 1.1	3.9 ± 0.9	0.19	4.2 ± 0.8	4.2 ± 1.2	0.50
Urine microscopy score Mean ± SD	-	-	-	1.1 ± 0.3	1.1 ± 0.2	0.5	1.1 ± 0.3	1.2 ± 0.2	**0.04**
NGAL (ng/ml), Mean ± SD	-	-	-	142.4 ± 230.1	6.7 ± 36.6	**0.0003**	-	-	-

Other biomarkers like BUN (p= 0.28), FeNa (p= 0.18) and serum uric acid (p= 0.50) showed no statistically significant association in predicting AKI post CPB within 24 hrs (Table 3).
On ROC-AUC analysis, after 6 hrs of CPB urine NGAL had a moderate AUC of 0.714 as compared to serum creatinine (AUC ROC 0.60), Urine protein creatinine ratio (AUC 0.6)(Fig 1).Urine NGAL at 6 hours at a cutoff of 84 ng/ml had the best specificity (95%) and sensitivity of 45% for prediction of AKI(Fig 1). At 24 hrs after CPB, urine protein creatinine ratio and serum creatinine had significant AUC ROC for prediction of AKI (Fig 1).
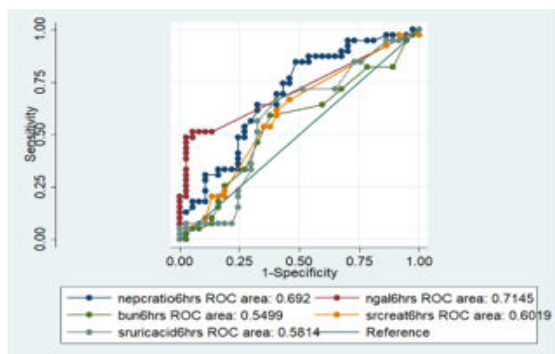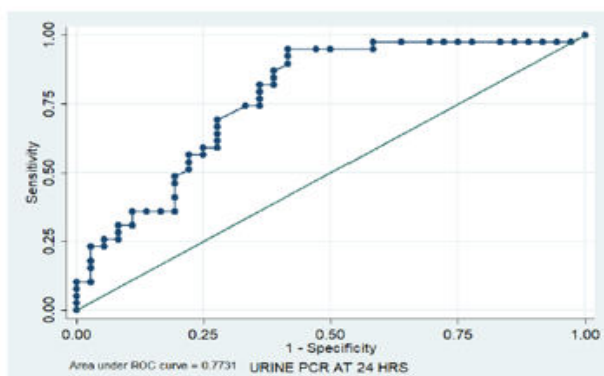
AUC ROC of biomarkers at 6 hrs of CPB
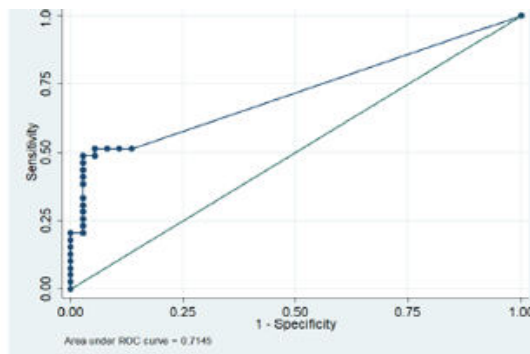
NGAL Value = 84 ng/ml

Sensitivity 45%, Specificity 95%

AUC ROC of urine PCR at 24 hrs

Fig 1 : AUC ROC analysis of biomarkers at 6 hrs and 24hrs of CPB

Risk factors for post CPB AKI

There was no significant difference observed with sex, anthropometry, duration of CPB and inotropes exposure. Children who developed AKI were more likely to have mechanical ventilation for >48 hrs (p= 0.003), had sepsis and received >2 antibiotics (Inj. Meropenam with collistin and tigecyclin) (p= 0.02) (Table 4).

Table 4 : Association of different risk factors with post CPB AKI

Variables	Parameters	AKI (n=39)		Non-AKI (n=37)		P value
		No	(%)	No	(%)	
Sex	Male	26	67%	25	68%	0.97
	Female	13	33%	12	32%	0.95
Weight	0 to +2Z	8	21%	5	14%	0.49
	0 to -2Z	11	28%	14	38%	0.52
	<-2Z	20	51%	18	48%	
Height	0 to +2Z	4	10%	6	16%	0.89
	0 to -2Z	9	23%	7	19%	0.50
	<-2Z	26	67%	24	65%	0.71
Ventilation	<6 hrs	01	3%	3	4%	0.94
	6-24 hrs	12	31%	10	14%	0.30
	24-48 hrs	6	15%	7	9%	0.73
	>48 hrs	11	26%	0	0%	**0.003**
Inotropes	1-2 inotropes	5	13%	7	9%	0.53
	>2 inotropes	24	62%	14	18%	0.23

CPB time	<90 min	10	26%	13	35%	0.51
	90-120 min	13	33%	15	40%	0.65
	121-180	13	33%	08	21%	0.38
	>180 min	03	8%	01	3%	0.35
Antibiotics	Cefoperazone	17	42%	25	67%	0.20
	Mero + Vanco	01	3%	4	11%	0.17
	Mero +Collistin	15	39%	8	22%	0.33
	Mero +Collistin+ Tigy	06	16%	0	0%	**0.02**
Sepsis	Blood culture positive	15	20%	4	5%	0.02

Discussion

Thiswas a single centre prospective cohort study & aimed to determine the incidence of AKI post CPB by KDIGO, AKIN, and pRIFLE criteria in children and evaluate the role of selected urinary biomarkers (NGAL, urine PCR and urine microscopy score) vis-a-vis traditional (BUN,uric acid, FeNA, creatinine) for early prediction of AKIwithin 24 hours of surgery. Overall calculated sample size of 150 cases could not be met during the study period owing to temporary cessation of pediatric cardiac surgery in our hospital following an outbreak of nosocomial sepsis.

High incidence (51%) of AKI noted in our study population using KDIGO and AKIN criteria.In previous studies by Haase et al and Piggott et al, incidence of AKI post cardiac surgery according to KDIGO criteria was44.7% and 52% respectively [6,12]. Incidence of AKI using AKIN criteria in published literature has ranged between 25.9-44.7% [13-15]. Using pRIFLE criteria, we noted a higher incidence of AKI of 55% (42 of 76) with additional 3 cases. Haase et al and Robert et al noted an incidence of 45.7% and 30.6% for AKI according to pRIFLE criteria in children undergoing CPB [14, 15]. Expectedly in our study there was no significant difference in the incidence of AKI by KDIGO and AKIN criteria owing to the similarity of both criteria. Since change in eGFR is the basis for pRIFLE criteria and it is inverse of serum creatinine the difference in incidence of AKI using this criteria is plausible.

Majority of cases of AKI in our study remained non-oliguric with urine output criteria of <0.5 ml/kg/hr for at least 6 hours being met in only 2 cases. However in 31/76 (41%) cases urine output did fall to <1 ml/kg/hr. The relative lower sensitivity of urine output criteria is well documented in literature [13-15]. Liberal usage of diuretic infusions in the postoperative phase may be the reason. Though multiple biomarkersexplored and published in world literature for early detection of AKI, we chosen3 novel urinary markers (urine protein creatinine ratio, urine microscopy score, NGAL) alongside traditional blood metabolites (BUN, uric acidand FeNa).

No significant rise of BUN was observed within 24 hrs in AKI group as compared to non AKI group in our study. A trend towards rise of serum uric acid level observed in AKI group in our study but was not statistically significant. Though we noted a rise of FeNa at 6 hrs and 24 hrs in post CPB AKI group, it was not statistically significant (p=0.07 at 6 hrs; p=0.18 at 24 hrs). In previous studies too, no significant change in FeNa was observed within 24 hrs of postCPB AKI [17].

Proteinuria reflects injury and derangement of the glomerulotubular balance and serves as an early AKI biomarker [18]. Significant rise of urine protein creatinine ratio was observed by Zappitelli et al in post CPB AKI patients within 6 hrs with a AUC-ROC of 0.71 (p <0.001) [19]. In our study too UPCR was elevated in the postoperative phase and at 24 hrs had a AUC

ROC of 0.7686.According to the above finding urine protein creatinine ratio, can predict AKI within 24 hrs of CPB [18].

The increased number of renal tubular epithelial cells (RTE) and granular cast signifies cell death and apoptosis that would be associated with more severe form of AKI [16]. There have been attempts to eliminate subjectivity in assessment with introduction of objective scoring of the urine microscopy findings [11]. In our study we found rise of urine microscopy score within 24 hrs of CPB in the patients who further developed advanced stages of AKI according to KDIGO criteria.In previous studies Kanbay et al, Gay et al and Perazella et al also showed an increase in urine microscopy score in the established and worsened cases of AKI [20, 11, 16] and after 5 days of onset of AKI. It is plausible that we could also get change in urine microscopy score if we measured the same in later time period but the aim of our study was early prediction of AKI prior to the rise of serum creatinine.

We chose urinary NGAL, a non invasive sample instead of blood. A rise as early as 2 hours was noted with peak by 6-12 hours and persistence till 5 days [21]. Mishra et al demonstrated a linear relationship between 1-1000 ng/ml rise of the serum values and a rise at 2 hours much before the rise (after 1-3 days) of serum creatinine. According to Mishra et al, at 2 hr plasma NGAL AUC of 0.91 and urine NGAL AUC of 0.99 could predict AKI. Multiple pediatric and adult studies till date with multifactorial etiologies of AKI have validated this marker.Our study showed significant increase in urine NGAL with best cut off of 84 ng/ml with sensitivity of 45% and specificity of 95%. Our observed AUC of 0.71 at 6 hrs of CPB suggests a moderate predictive value for AKI. Previous studies too have had similar AUCs and cut offs for significant prediction of AKI. It suggests urine NGAL is a early predictor of AKI post CPB [17, 22, 23].

CPB itself induces inflammation and haemolysis and is an independent risk factor for AKI.Blinder et al, Piggott et al, Sethi et al showed significant association of AKI with prolonged duration of CPB [4-6, 24]. We did not find an association with increasing CPB duration. Our study was underpowered to detect this effect owing to the small sample size.

In our study significant association of post CPB AKI with duration of ventilation more than 48 hrs observed (Table 4). In previous study Sethi et al and Simon Li et al suggested significant association of post CPB AKI with the prolonged duration (>48hrs) of ventilation. In our study, total 50 (66%) out of 76 patients received different vasopressor agents to maintain the hemodynamics. Out of these total 12 (16%) children received 1-2 inotrope and rest 38 (50%) received >2 inotropic support. Amongst those who received > 2 inotropes, 24 (62%) developed AKI, but statistically not significant. Multiple drug exposure is associated with AKI. Matthieu et al showed significant association of post CPB AKI with the use of aminoglycoside and vancomycin [66]. In our study too, like meropenem with colistin &tigecycline showed, 10 (13%) out of 76 patients who exposed to the above combination of antibiotic developed AKI, which was statistically significant (p =0.006).

Sepsis associated AKI becomes a important confounder. There was a higher prevalence of infections in our setup with 19 (25%) out of 76 children developed blood culture positive sepsis, out of which 9 (12%) was positive for Klebsiella and 10 (13%)for Burkholderia. Among these 19 children who developed blood culture positive sepsis, 15 had AKI. Sethi et al [4] showed significant association of sepsis with post CPB AKI, which correlates with our study. However our study remains underpowered to look into the interplay of sepsis and CPB associated factors.

We did have certain limitations. Firstly it was a single centre study in a referral centre of armed forces hospital with limited clientele as against a busy civilian practice which limits the number available for study purposes. Secondly Sample size of the study (N= 78), not fulfil the proposed sample size (N=150) as mentioned in the protocol due to less number of patients underwent cardiac surgery during the study period.Thirdly, the risk of AKI may also

be influenced by the type of cardiac lesion. We are underpowered to assess these factors and dissect it out from independent effects of the CPB. Finally, none of our children except for obvious syndromic features underwent a routine screening ultrasonography of abdomen. Children with structural abnormality of Kidney were not excluded which may be associated with more chance of AKI post CPB.

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