

## ACUTE KIDNEY INJURY PREDICTION USING PHOSPHORUS AS A SIMPLE BIOMARKER IN PEDIATRIC CARDIAC SURGERY PATIENTS

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### ABSTRACT

**Background:** Acute kidney injury (AKI) is a strong predictor of morbidity and mortality after cardiac surgery. Lack of valid early biomarkers for predicting AKI has hampered the ability to take therapeutic measures for preventive cause. It was not studied in this context and could be simple marker of AKI. Therefore, we tested role of serum phosphorus in prediction of AKI as a simple biomarker after cardiac surgery in pediatric population. **Methodology:** We prospectively evaluated 113 children aged between 3mo-12yrs undergoing elective cardiac surgery. Serum creatinine and phosphorus were measured preoperatively and postoperatively at 24, 48hrs. As per KDIGO (Kidney Disease Improving Global Outcome) criteria, patients were grouped into AKI and NON AKI on basis of development of AKI within 48hrs postsurgery. **Results:** From 113 children included, 37 developed AKI. In AKI group, serum phosphorus increased significantly from  $4.46 \pm 0.19$  baseline to  $8.60 \pm 0.34$  at 24 hrs postsurgery ( $p < 0.0001$ ). While serum creatinine increased from baseline 0.28 to 0.41 at 24hrs ( $p < 0.0001$ ). Receiver Operating Characteristic Curve analysis showed that serum phosphorus at 24hrs, the area under the curve was 0.72 with sensitivity 80%, specificity 73.15% for a cut off value of 6.4mg/dl. Whereas serum phosphorus at 48hrs, the area under the curve was 0.90 with sensitivity 85.29% and specificity 87.34% for a cut off value of  $> 5.2$  mg/dl. **Conclusion:** Serum phosphorus can be a simple biomarker as early as 24hrs for early prediction of AKI in paediatric cardiac surgery.

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### INTRODUCTION

Acute kidney injury (AKI) is a common complication after paediatric cardiac surgery with the incidence between 9.6% - 52% (Singh, 2016). It is an independent predictor of morbidity and mortality in children who undergo cardiac surgery with mortality rate of 8% compared with 0.9% in patients without AKI (Ibrahim, 2016). Pathophysiology includes decreased renal perfusion, lack of pulsatile flow, oxidative stress, hypothermia, embolism and inflammatory response (Ibrahim, 2016). Variables such as increased duration of surgery, aortic cross clamp, intraoperative hypotension cause AKI. However, serum creatinine is imprecise, suboptimal test as it does not accurately reflect GFR (glomerular filtration rate) in those renal function is constantly changing (Zappitelli, 2015). More than 26 new biomarkers of AKI were studied till now (Munshi, 2014).

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Among the mcystatin C, urine and plasma NGAL (Neutrophil Gelatinase Associated Lipocalin), IL6, L-FABP (Liver Fatty Acid binding Protein), Homovanilic acid sulphate, Kidney Injury Molecule 1 are available to predict and relate to severity of AKI. The scarcity of early and expensive biomarkers of AKI has hindered ability to take therapeutic, prophylactic measures in a timely manner which is potentially reversible cause (Mishra, 2005). Plasma and urine NGAL have shown to raise in 6hrs of ICU stay. In infants  $< 6$  months, low levels of IL18 at 2hrs post-surgery had 91% negative predictive value. Similarly, homovanilic acid sulphate peaked to twice at 4hrs post-surgery. Following AKI, urinary KIM -1 concentration is markedly increased in an hour of surgery. Most of these markers need serial evaluation which is not cost-effective. Since no literature being available on serum phosphorus as biomarker with respect to kidney injury, we initially performed a pilot study on 51 children (Vijitha Burra, 2018). This showed its key role in assessing kidney injury in pediatric cardiac surgery. Therefore, the aim of the present

study was to further validate its role in predicting AKI as compared to serum creatinine in pediatric cardiac surgery.

## MATERIALS AND METHODS

Aprospective diagnostic observational study of 113 children aged between 3mo-12yrs undergoing elective cardiac surgery in a tertiary care centre were enrolled in study.Exclusion criteria were preoperative AKI, use of nephrotoxic drugs or contrast material before or during study period, steroids, insulin, diuretics, preoperative inotropic support, children with end stage renal disease, dialyzed, solitary kidney or nephrectomy, hyperbilirubinemia, haemolytic disorders, leukaemia and thyroid disorders. Institutional ethics board approval was taken before study initiation and parental written informed consent was obtained for all participants. Children were recruited during preoperative evaluation. Blood samples were collected for Serum creatinine and phosphorus post anaesthetic induction after central venous access insertion. After surgery, blood samples were collected for serum creatinine and phosphorus at 24,48hrs in postoperative recovery unit.

## Statistical Analysis

All statistical analyses were done using MedCalc (version 12.2.1.0). Continuous variables were expressed as mean±SD. To compare patients with and without acute kidney injury, continuous data were analysed using unpaired T test or Mann Whitney U test.The Shapiro Wilk test was used to confirm normal distribution. Serum phosphorus and serum creatinine were compared between AKI and NON AKI. Sensitivity and specificity of serum phosphorus at 24, 48 hrs to detect AKI were evaluated by the area under the receiver operating characteristics curve(AUC-ROC).Categorical data were analysed by chi square test.  $P < 0.05$  was considered as statistically significant. The percentage of maximum elevation of phosphorus ( $\%Ph = \frac{\text{maximum} - \text{minimum}}{\text{minimum}} \times 100$ ) was calculated at 24, 48 hrs postoperatively.

## RESULTS

Among 113 children aged between 3mo-12yrs who under went elective cardiac surgery,37(32.7%) developed AKI in 48hrs postoperatively according to KDIGO criteria.

**Table 1. Patient Characteristics**

Characteristics	AKI (N=10)	Non-AKI (N=41)	P value
<b>DEMOGRAPIC DATA</b>			
Age in weeks	36.32(23.23-	44.74(34.61-	0.39
Mean(95% CI)	56.77)	57.83)	
Sex			
Female	19	41	0.79
Male	18	35	
Weight (Kg) mean ;95%CI	6.02(5.03-7.19)	6.36(5.72-7.06)	0.57
Cardiac risk score (RACHS 1) median(range)	2 (2.0-2.25)	2 (2.0-2.0)	0.10
<b>PREOPERATIVE DATA</b>			
Serum Creatinine mean(95%CI)	0.29(0.25-0.33)	0.32(0.29-0.35)	0.22
Serum Phosphorus mean(95%CI)	4.46(±1.14)	4.80(±1.25)	0.17
<b>INTRAOPERATIVE DATA</b>			
Duration of surgery (Hours)	4.77(4.39-5.18)	4.16(3.91-4.41)	0.009
ACC time (Mins)	87.83 (±35.75)	58.73 (±29.61)	<0.0001
Urine output (ml/hr/kg)	4.22 (±3.33)	4.68 (±3.07)	0.67
<b>POSTOPERATIVE DATA</b>			
RRT	15	0	<0.0001
ICU stay median(range)	9 (7.00-11.25)	6.00 (5.00-7.00)	<0.0001
Mortality	1	0	0.44
Urine Output (24Hours)	1.99 (±1.06)	2.50 (±1.17)	0.02
Urine Output (48hours)	2.12 (±1.40)	2.57(±1.13)	0.06

**Table 2. Variation of Serum Creatinine and Serum Phosphorus in AKI group at 0,24 and 48 Hours**

AKI GROUP	0 HR	24 HR	P	48 HR	P
SERUM CR	0.28	0.41	<0.0001	0.82	<0.0001
(MEAN& 95%CI)	(0.25-0.33)	(0.34-0.50)		(0.67-1.02)	
SERUM Ph	4.46	8.60	<0.0001	6.86	<0.0001
(MEAN±SE)	(0.19)	(0.34)		(0.38)	

Variables collected include age, sex, weight, RACHS 1 category, duration of surgery, aortic cross clamp time, urine output (intraoperative period, 24hrs, and 48hrs), inotropic score, requirement of RRT, ICU stay, and mortality. Serum creatinine was measured at our laboratory by modified jaffe method. While serum phosphorus is determined photometrically. The primary outcome variable was development of AKI, defined as follows; Stage1 is 0.3 mg/dl rise in 48hr or at least 50%rise from baseline in 7 days, stage 2 is doubling value, stage 3 being tripling/requiring dialysis according to KDIGO criteria (Kidney, 2012). Children were grouped into AKI and NON AKI based on this criteria. Other outcomes included were requirement of RRT, ICU stay and mortality.

Patients who developed postoperative AKI were comparable to the non AKI group with regard to age,weight,cardiac risk score (RACHS-1 Risk Adjustment for Congenital Heart Surgery), preoperative serum creatinine (cr), serumphosphorus (Ph).

### Roc Curves for Serum Phosphorus (24hrs, 48hrs)

AUC of the ROC curve for serum phosphorus to predict AKI at 24hrs was 0.72 as shown below in Figure 1. Sensitivity and specificity of serum Ph at 24hrs:80%, 73.15% with cut off value of >6.4. AUC of the ROC curve for serum phosphorus to predict AKI at 48hrs was 0.90 as shown below in Figure 2. Sensitivity and specificity of serum Ph at 48hrs:85.29%, 87.34% with cut off value of >5.2

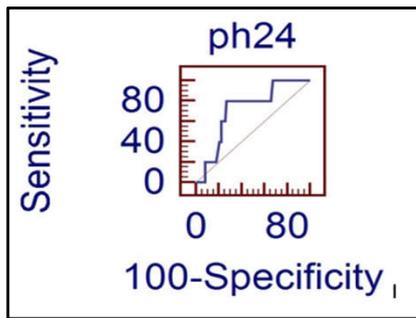


Fig. 1. ROC curve for serum phosphorus to predict AKI at 24hrs (ph\_24)

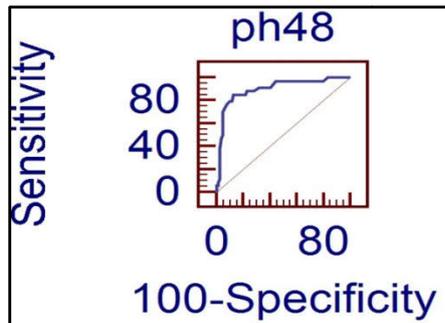


Fig. 2. ROC curve for serum phosphorus to predict AKI at 48hrs (ph48)

**Comparison of prediction of aki using serum creatinine and phosphorus:** Preoperative serum creatinine and phosphorus levels in children with and without AKI were within normal ranges and did not differ between those two groups. In AKI group, Serum Ph levels increased significantly at 24hrs from baseline (6.29 vs 4.47) with  $p=0.003$ . However, serum Cr at same point in AKI group was not statistically significant ( $p=0.14$ ). Serum Ph at 48hrs could not show statistically significant increase ( $p=0.07$ ) although serum Cr had significant increase statistically at 48hrs in AKI ( $p=0.02$ ).

Table 3. Variation of serum Creatinine and Phosphorus between AKI and Non-AKI group

Value	AKI	Non-AKI	P-value
24 Hours Cr (mean:95%CI)	0.41(0.34-0.50)	0.28(0.26-0.30)	<0.0001
Serum Phosphorus (mean ± SD)	8.60 ± 2.05	4.64 ± 1.16	<0.0001
48 Hours (Mean±SD) Serum Creatinine (mean: 95%CI)	0.82 (0.67-1.01)	0.27(0.25-0.31)	<0.0001
Serum Phosphorus (mean ± SD)	6.86 ± 2.16	3.90 ± 1.16	<0.0001

## DISCUSSION

AKI is an independent predictor of mortality in children undergoing cardiac surgery under cardiopulmonary bypass (CPB) (Singh, 2016). The factors involved in paediatric AKI are preoperative, cardiopulmonary bypass, postoperative, inflammatory and neuroendocrine responses. It is common post cardiac surgery in children due to renal hypoperfusion, reperfusion injury, and inflammatory responses (Ibrahim, 2016). Thus, early AKI diagnosis is of great significance for prognosis of patients. Serum creatinine and urine volume are nonspecific indicators of staging criteria of AKI and susceptible to external factors (Wang, 2017). Serum creatinine

is the main diagnostic test of AKI which is suboptimal and raising late in course of disease, leading to delay in evaluation, treatment, and application within narrow therapeutic window (Zappitelli, 2015). Although various criteria have been used for the diagnosis of AKI, KDIGO classification has recently been introduced as a standard diagnostic tool. Using KDIGO criteria for the diagnosis of AKI, the present study found that hyperphosphatemia at 24 hrs could be used as an early predictor of AKI after cardiac surgery in children. In the present study, incidence of AKI was 32.7%. While in Zappitelli et al found incidence being as high as 40% following cardiac surgery in children. In the present study, authors evaluated the performance of serum phosphorus as AKI biomarker in paediatric post cardiac surgery cohort. The AUC-ROC value for serum phosphorus at 24hrs after surgery ( $AUC=0.72$ ;  $p=0.04$ ) with a sensitivity of 80%, specificity of 73.15%. The cut off value at this time was 6.4mg/dl. While at 48hrs ( $AUC=0.90$ ;  $p<0.0001$ ) cut off value was 5.2 mg/dl. Ihab A et al found that plasma reninase with  $AUC=0.375$  while for serum NGAL, 24hrs after surgery to predict AKI were 0.66 (Ibrahim, 2016). Wang et al investigated diagnostic role of urinary IL-18 after CPB with  $AUC=0.90$  as early as 2hrs after CPB and with  $AUC$  of urinary NGAL being 0.83 (Wang, 2017). The  $AUC$  of urine albumin ranges 0.57-0.76 for AKI detection (Sugimoto, 2016).

Risk factors of AKI after paediatric cardiac surgery are low body weight, young age, increased RACHS-1 score, preoperative pulmonary hypertension, preoperative inotrope, preoperative mechanical ventilation. In the present study, we found duration of surgery in AKI vs NON AKI (4.77 vs 4.16;  $p=0.009$ ) is significant. Acute kidney injury (AKI) is associated with systemic complications including volume overload, electrolyte and metabolic disturbances (Zappitelli, 2015). Hyperphosphatemia is a common complication of AKI, developing as a direct consequence of decreased renal excretion. Persistent hyperphosphatemia (>12hrs) occurs in impaired kidney function. Normal values of phosphorus in infant 6-8, child 4.5-5.5, adolescent 2.7-4.5. It is the sixth most abundant element in the human body. Levels are expressed in terms of mg/dl. Removal of phosphate by dialysis may vary by >400 mg per treatment. Estimation of serum phosphorus is a simple, easily available and cost-effective (Ridolfo, 2015). Using KDIGO criteria for the diagnosis of AKI, the present study showed increase in serum creatinine (Sr Cr) and serum phosphorus (SRPH) in AKI group which is significant ( $p<0.05$ ). Therefore SRPH can be used as a biomarker similar to Sr Cr in detecting AKI. There was significant decrease in urine output in AKI vs NON AKI ( $p=0.01$ ) at 24hrs.

In AKI group at 24hrs, 48 hrs significant ↑ in Sr Cr noted ( $p<0.0001$ ). On retrospective analysis of SRPH levels, authors found the statistical significant increase in SRPH at 24hrs in AKI group with  $p<0.0001$ . At 24hrs -when there was an increase in SRPH along with Sr Cr, there was decrease in urine output significantly in AKI ( $P=0.02$ ). While at 48hrs, both Sr Cr and SRPH showed significant change with urine output being not significant ( $P=0.06$ ) between AKI and NON AKI. Apart from absolute serum Ph values, percentage increase in serum Ph levels could also implicate AKI. SRPH showed 85% change from baseline to 24hrs while it reduced to 51% at 48hrs in AKI group. This is due to therapeutic interventions undertaken that reduced SRPH levels therefore, it helps to know its efficacy. Apart from absolute serum Ph values, percentage increase in serum Ph levels could also

implicate AKI. The present study showed 55% increase in serum Ph levels in AKI when compared with 0.87% in NON AKI with  $p=0.0011$  at 24hrs. While at 48hrs, 62.95% increase in serum Ph in AKI in comparison with -15.8% in NON AKI with  $p=0.0007$ .

### Limitations

Sample volume analysed could be insufficient to stage AKI and determine the predictable cut off value of serum phosphorus at each stage for defining AKI criteria earlier than serum creatinine. To determine patterns of change in serum phosphorus at various time points and its importance in AKI was not analysed.

### Conclusion

Serum phosphorus level estimation being simple, easy and cost-effective predicts AKI as early as 24hrs in comparison with serum creatinine level in children undergoing cardiac surgery. Future research on its evaluation for its association with other new biomarkers is required and determine the specific value of serum phosphorus to extent to which its elevation leads to changes in patient management.

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