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# Biomarkers of acute kidney injury in children with congenital heart disease after cardiopulmonary bypass

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***Abstract*---**Background: Acute kidney injury (AKI) is a serious postoperative complication after cardiac surgery in children and is a major contributor to patient outcome. This study aims to identify the incidence of AKI in children undergoing cardiac surgery and the role of Interleukin 18 (IL-18) and Kidney Injury Molecule 1 (KIM-1) in diagnosis of AKI in comparison to creatinine. Methods: Forty-four children who underwent open heart surgery using cardiopulmonary bypass) for congenital heart disease were assessed for AKI diagnosis according the

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KDIGO criteria, urinary IL-18 and KIM-1 were determined by Enzyme Linked Immunosorbent Assay in addition to the assessment of length of stay in PICU and outcome and the effect of AKI on these parameters. Results: twenty three percent of the patient developed AKI, there were no statistical correlation between AKI and the factors (Age, gender, CBP and Risk adjustment for congenital heart surgery (RACHS-1) complexity score). Eight of our patients needed peritoneal dialysis (PD), seven of them developed AKI and the 8th patient didn't develop due to the early initiation of PD. There was strong correlation between the development of AKI and the Length of stay in ICU. Both IL-18 and KIM-1 were higher in the patients who didn't develop AKI than the patients who developed AKI. Conclusion: AKI is common among children undergoing open heart surgery. Creatinine is the gold standard biomarker in diagnosis of AKI. Early initiation of PD could prevent the development of AKI. IL-18 and KIM-1 need further studies to assess their value in diagnosis of AKI in children.

***Keywords*---**Acute kidney injury, IL-18, KIM-1, Cardiac surgery, CBP, PD, Children.

## Introduction

Acute kidney injury (AKI) is a one of the most significant complication of cardiac surgery with cardiopulmonary bypass (CBP) in infants and children with congenital heart disease (CHD). It is reported to be about 42% in a recent study done by **Ruf et al.** [1]. AKI is a serious condition characterized by the sudden onset of renal dysfunction, leading to impaired control of acid–base, electrolyte and fluid balance [2].

The mortality following AKI and dialysis in this subset of patients can be as high as 65% and 100% respectively. An increase in serum creatinine of > 0.3mg/dL is associated with a seven-fold increase in mortality in children with acute decompensated heart failure [3].

Postoperative AKI in children is usually diagnosed by measuring urine output and serum creatinine level. It has been reported that serum creatinine is not adequate for the prediction of precise outcome and the evidence of prophylactic treatment because the level of serum creatinine usually increases only after marked decrease of glomerular filtration rate (GFR) (>50% reduction in renal function). Moreover, the level of serum creatinine in children can vary due to various extra-renal factors such as the amount of muscle, diet and drugs [4].

Recently, many novel biomarkers in AKI, rather than serum creatinine, have been developed to directly detect tubular injury at an early stage after pediatric cardiac surgery. Candidate biomarkers in AKI include kidney injury molecule-1 (KIM- 1) and interleukin-18 (IL-18), these biomarkers are increased in the urine within 12 hours of renal dysfunction [5]. In this study, we aimed to early detect AKI after cardiac surgery using CPB in infant and children with CHD by using biomarkers, KIM- 1and IL-18.

**Material and Methods**

This study prospectively enrolled 44 children with CHD who underwent open heart surgery with CPB. The study was enrolled from May 2016 to May 2017 in the postoperative pediatric cardiac intensive care unit (PICU) in Abo Elreesh children hospital (Cairo, Egypt) and Aswan Heart Centre / Magdi Yacoub Foundation, (Aswan, Egypt). This study protocol and the informed consent documents were approved by the Ethical Committee of National Research Centre (NRC), Cairo, Egypt. Informed consent was obtained from all parents. Children aged from one day to 5 years of age after open heart surgery with CPB were included in the study. Patients who had a previous cardiopulmonary arrest or showed a history of renal or hepatic impairment were excluded from the study.

KDIGO (Kidney Disease Improving Global Outcome) AKI criteria were assigned for each patient based on the percent change of the serum creatinine from the baseline (Stage 1= 1.5-1.9 times baseline creatinine, stage 2= 2-2.9 times baseline creatinine and stage 3= 3 times baseline creatinine) [6]. AKI was defined as ≥50% increase from baseline serum creatinine or urine output <0.5mL/kg/hour for 6-12hours according to the kidney disease: Improving Global Outcomes guidelines. [6].

Baseline serum creatinine values were obtained as part of routine pre-surgical testing. Demographic data, preoperative serum creatinine, preoperative blood urea, type of surgery, CPB time, aortic cross-clamp time, need for peritoneal dialysis, lengths of ICU stay, echocardiography, type of CHD, preoperative percutaneous oxygen saturation (SpO2) for cyanosis, presence of heart failure (Ross score≥3, which comprise of feeding volume consumed, time taken per feeding, respiratory rate, heart rate, respiratory pattern, peripheral perfusion, S3 or diastolic rumble, and hepatomegaly) transfusion during surgery, and mean arterial pressure during CPB and in-hospital mortality were recorded. Risk adjustment for congenital heart surgery (RACHS-1) category [7] were assigned to each procedure performed. Postoperative serum urea and creatinine values were obtained at 12 and 48 hours. The subjects were divided into 2 groups: AKI group included patients who met AKI criteria described above, and non-AKI group included patients who did not develop AKI.

Peripheral blood samples (3ml) were withdrawn from every participant under complete aseptic condition once preoperatively and twice postoperatively (at 12 and 48 hours). Blood samples were left to clot then centrifuged for separation of sera for immediate assessment of urea and creatinine levels. Urine samples were collected from each patient at 12 and 48 hours postoperatively, followed by centrifugation at 4 C for 15 min at 1500 xg, then transfer the urine to a new Eppendorf and storing at -80 for further

Urinary IL-18 levels were assayed using EIAab enzyme linked immunosorbent assay (ELISA) Kit, (Co., Ltd, USA Cat E0064h) and urinary KIM-1 levels was assayed using EIAab ELISA Kit, (Co.,Ltd , USA Cat E0785h). EIAab quantitative test kit is based on a solid phase enzyme linked immunosorbent assay in which the provided microplate is precoated with an antibody specific to the target antigen.

**Statistical Analysis**

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. For not normally distributed quantitative data, comparison between two groups was done using Mann-Whitney test (non-parametric t-test). Wilcoxon-signed ranks test (non-parametric paired t-test) was used to compare two consecutive measures of numerical variables. The Receiver Operating Characteristic (ROC) curve was used for prediction of cut off values. Evaluation of the biomarkers was done by calculating sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV) and total accuracy. All tests were two-tailed. A p-value < 0.05 was considered significant

**Results**

Our study encompassed 44 participants, their median of age was 9 months (range, 0.27-60), 26 males (59.1%) and 18 (40.9%) females. Five (11.4%) patients of the study group were below 30 days of age, while 26 (59.1%) of our patients were below 1 year of age. Our study cohort presented with variable cardiac lesions illustrated in Figure 1. The study cohort showed a median baseline urea of 19 mg/dl (range, 7-73) and a median baseline creatinine of 0.23 mg/dl (range, 0.2 - 0.6). During the postoperative period patients showed a median level of urea 28.5 mg/dl (range, 11 -70) after 12 hours of CBP, and a higher median level of urea 34.6 mg/dl (range, 11-110) after 48 hours of bypass. Patients also showed a median level of creatinine 0.29 mg/dl (range, 0.2- 0.93) after 12 hours of CPB and also a slightly higher median level of creatinine 0.32 mg/dl (range, 0.20- 0.98) after 48 hours of CPB. Table1.

A comparison of clinical features between the AKI and non-AKI group is illustrated in table 1. Ten patients (23%) of our study cohort developed AKI, while 34 patients (77%) did not develop AKI. AKI of stage 1 was described in 2 (20%) patients whereas 5 (50%) patients and 3 (30%) patients developed AKI of stage II and III respectively. Three patients out of the 10 AKI patients were below 30 days of age while 7 were above 30 days of age. Nine (28.1%) patients of AKI group were cyanotic. There was no statistical association between cyanosis and development of AKI (P= 0.163). In AKI group, the RACHS complexity score for their operations was 2 in 2 patients, 3 in 6 patients and 4 in 2 patients and there was no statistical association between RACHS complexity score and development of AKI (P = 0.372).

Table (1)
A Comparison of between the AKI and non-AKI groups

| Variable | | All (n=44) | Non-AKI group (n=34) | AKI group (n=10) | P- value |
|---|---|---|---|---|---|
| Age (month) | | 9 (0.27-60) | 9.5 (0.27-60) | 2.18 (0.5-60) | 0.286 |
| Weight (kg) | | 6.6 (2.5-19.5) | 6.7 (2.5-19.5) | 4 (2.6-16) | 0.354 |
| RACHS score | | | | | 0.372 |
| 2 | | 9 | 7 (77.8%) | 2 (22.2%) | |
| 3 | | 18 | 12 (66.7%) | 6 (33.3%) | |
| 4 | | 17 | 15 (88.2%) | 2 (11.8%) | |
| Pre-op serum Creatinine (mg/dl) | | 0.23 (0.2-0.6) | 0.25 (0.2-0.6) | 0.2 (0.2-0.3) | 0.206 |
| Serum creatinine / 12 hr (mg/dl) | | 0.29 (0.2-0.39) | 0.27 (0.2-0.65) | 0.5 (0.34-0.93) | <0.001 |
| Serum creatinine / 48 hr (mg/dl) | | 0.32 (0.2-0.98) | 0.31 (0.2-0.98) | 0.55 (0.32-0.83) | 0.005 |
| Urea pre-op (md/dl) | | 19 (7-73) | 19.4 (7-73) | 19 (10-34.7) | 0.591 |
| Urea / 12 hr (mg/dl) | | 28.5 (11-70) | 26.9 (11-60) | 34 (16.9-70) | 0.024 |
| Urea / 48 hr (mg/dl) | | 34.6 (11-110) | 34 (11-110) | 45.2 (20.6-68) | 0.128 |
| CPB time (min) | | 160 (67-740) | 159 (71-270) | 175 (67-740) | 0.261 |
| Cross clamp time (min) | | 99 (38-190) | 98 (47-190) | 99.5 (38-150) | 0.845 |
| Dialysis | | 8 (18.2%) | 1 (12.5%) | 7 (87.5%) | <0.001 |
| LOS (Days) | | 4 (2-124) | 2 (3-18) | 3 (6-124) | 0.15 |
| Outcome | Discharged | 43 | 34 (79.1%) | 9 (20.9%) | |
| | Mortality | 1 | 0 | 1 | |

-Data were expressed as median and range; P-value<0.05 was considered significant; RACHS: Risk Adjustment for congenital heart disease; CPB: Cardio-Pulmonary Bypass; LOS: Length of stay

The AKI group had a median bypass time of 175 minutes and a median cross clamp time of 99.5 minutes, while the non-AKI group had a median bypass time of 159 minutes and a median cross clamp time of 98 minutes. There was no statistical correlation between cardiopulmonary bypass time (P= 0.261) and cross clamp time (P= 0.845) and the development of AKI. Patients who developed AKI showed a higher length of stay in the PICU than the patients who didn't develop AKI with a median length of stay of 6 days (range, 3-124) for the AKI group versus a median of 3 days, (range, 2-18) for the non-AKI group. Results also showed a significant statistical correlation between the AKI and length of stay in the PICU (P= 0.015).

Peritoneal dialysis was indicated in 8 patients (18.2%) of the cohort study, seven of them due to AKI and the 8th patient was dialyzed immediately in the postoperative period due to volume overload and poor systolic function of the ventricles (there is a high possibility that early initiation of dialysis in this patient prevents him from developing AKI). Table 2.

Table (2)
Patients indicated for peritoneal dialysis

| Patient | Diagnosis | Operation | Age | weight | Biomarkers | | | | | | | Indication | Onset & Duration | LOS & Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Creatinine | | | IL-18 | | KIM1 | | | | |
| | | | | | Pre | 12 h | 48 h | 12 h | 48 h | 12 h | 48 h | | | |
| 1 | Taussig Bing | ASO VSD closure | 3 M | 4.5 Kg | 0.2 | 0.68 | 0.61 | 5.4 | 9.2 | 0.1 | 0.2 | Poor LV Volume overload | 18 hours 1 Day | 6 Days Discharged |
| 2 | TOF | TOF repair | 3 Y | 8.8 Kg | 0.2 | 0.34 | 0.8 | 13.2 | 9 | 2.3 | 0.4 | Volume overload | 12 hours 4 Days | 6 Days Discharged |
| 3 | TOF | TOF repair | 2 Y 3M | 10 Kg | 0.3 | 0.39 | 0.6 | 7.5 | 5.3 | 2 | 0.2 | Oliguria Increase KFTs | 25 hours 3 Days | 5 Days Discharged |
| 4 | D-TGA, ASD | ASO ASD closure | 15 Days | 3.3 Kg | 0.2 | 0.55 | 0.3 | 304 | 163 | 17 | 0.9 | Oliguria Poor LV | 10 hours 26 Days | 26 Days Died |
| 5 | D-TGA, ASD, PDA | ASO ASD closure PDA division | 41 Days | 2.6 Kg | 0.29 | 0.44 | 0.45 | 5.2 | 14.5 | 0.1 | 0.1 | Oliguria Poor LV | 40 Hours 5 Days | 13 Days Discharged |
| 6 | PA, ASD, PDA | RVOT opening | 15 Days | 3.5 Kg | 0.29 | 0.67 | 0.83 | 15.5 | 21.7 | 0.1 | 0.1 | Volume overload | 5 Days 7 Days | 124 Days Discharged |
| 7 | D-TGA, ASD, PDA | ASO ASD closure PDA division | 17 Days | 3.1 Kg | 0.2 | 0.77 | 0.6 | 29 | 15.8 | 2.4 | 0.1 | Oliguria Poor LV | 18 Hours 5 Days | 7 Days Discharged |
| 8 | D-TGA, ASD, PDA | ASO ASD closure PDA division | 8 Days | 3.4 Kg | 0.2 | 0.25 | 0.2 | 13.1 | 13.7 | 0.2 | 0.2 | Hyperlactatemia Poor LV Volume overload | On admission 2 Days | 5 Days Discharged |

Data were expressed as median and range; P-value<0.05 was considered significant; ASO: Arterial switch operation; TOF: Tetralogy of Fallot; LV: Left ventricle; ASD: Atrial septal defect; VSD: Ventricular septal defect; PDA: Patent ductus arteriosus; ROVT: Right ventricular outflow tract.

Surprisingly the median levels for both IL18 and KIM1 at the 2 intervals 12 and 48 hours postoperatively were higher in the non-AKI groups than the AKI groups and there was no statistical correlation. Table 3 & 4.

Table (3)
Correlation between the AKI and Non-AKI groups as regards to IL18 Levels

| | | | Valid N | Mean | SD | Median | Minimum | Maximum | P- value |
|---|---|---|---|---|---|---|---|---|---|
| IL18 pg/ml 12 hours postoperative | AKI | No | 34 | 26.3 | 72.8 | 10.4 | 2.8 | 433.5 | 0.989 |
| | | Yes | 10 | 39.8 | 93.1 | 7.7 | 5.2 | 304.0 | |
| IL18 pg/ml 48 hours postoperative | AKI | No | 34 | 52.0 | 136.5 | 20.6 | 2.7 | 809.0 | 0.399 |
| | | Yes | 10 | 27.6 | 47.8 | 14.1 | 5.3 | 163.0 | |

- Pvalue<0.05 was considered significant -IL18: Interlekin 18

Table (4)
Correlation between AKI and Non-AKI groups as regards to KIM-1 levels

| | | | Valid N | Mean | SD | Median | Minimum | Maximum | P- value |
|---|---|---|---|---|---|---|---|---|---|
| KIM1 ng/ml 12 hours postoperative | AKI | No | 34 | .8 | 1.2 | .4 | .1 | 6.1 | 0.591 |
| | | Yes | 10 | 2.5 | 5.2 | .4 | .1 | 17.0 | |
| KIM1ng/ml 48 hours postoperative | AKI | No | 34 | .9 | 1.8 | .4 | .1 | 10.2 | 0.108 |
| | | Yes | 10 | .3 | .3 | .2 | .1 | .9 | |

-Pvalue<0.05 was considered significant -KIM-1: Kidney injury molecule 1

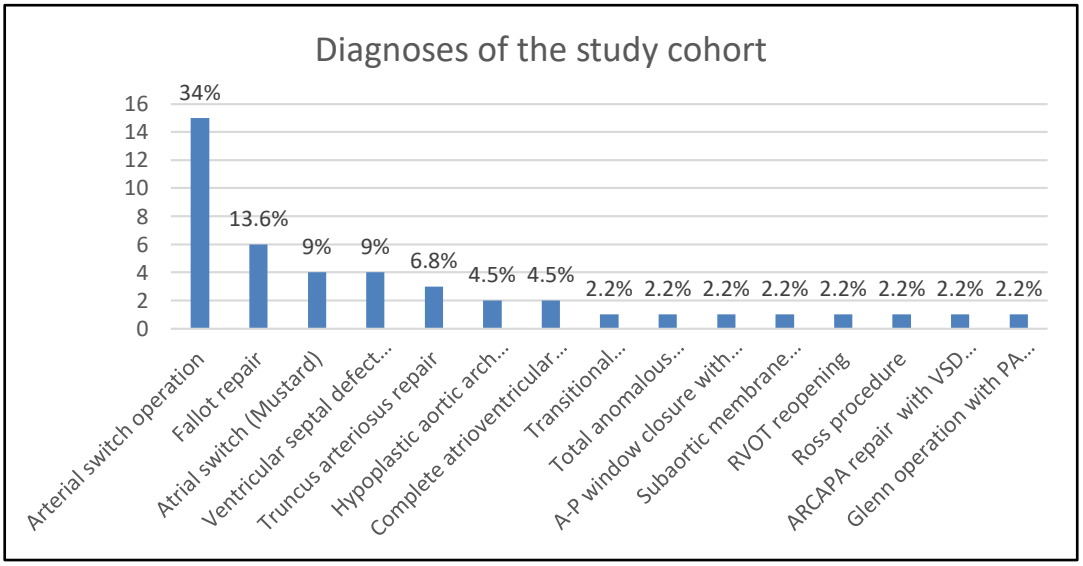


Figure 1: Distribution of cardiac lesion in the cases of the study

**Discussion**

Cardiac surgery with CPB is used to treat children with congenital heart diseases. However, reduced perfusion and non-pulsatile renal blood flow during CPB cause hypoxic-ischemic renal injury, leading to tubular and endothelial cell injury. [8,9].

The incidence of AKI after cardiac surgery using CPB in children is reportedly as high as 50% and is related to younger age, single ventricle status, higher RACHS-1 category, higher baseline serum creatinine level, and longer CPB time. [10,11]. Postoperative AKI causes an increase in the length of ICU stay and use of intensive treatments such as mechanical ventilation and continuous renal replacement therapy. Furthermore, children with postoperative AKI are more likely to progress to end stage renal disease and are more prone to the hazard of mortality. [12]. Therefore, early diagnosis and continuous follow-up of these patients are recommended. For the early recognition of AKI, several biomarkers have been introduced in the recent decades to overcome the challenges posed by traditional methods based on serum creatinine level and urine output. Although many cohort studies have been conducted to date to determine effective AKI biomarkers, no definitive results have been produced in pediatric studies as opposed to adult studies. This may be owing to the maturity of renal tubular function and structure being significantly different across different age group. [9].

Especially among young infants, the cutoff range of urine AKI biomarkers is known to be significantly different from individuals of other age groups because the renal tubules are immature to function appropriately and cannot optimally concentrate urine. However, few studies have been conducted to identify the age-specific differences in children under the age of 2 years. [9, 13, 14]. We have studied a cohort of 44 children with congenital heart disease who had an open-heart surgery and went on cardiopulmonary bypass. In our study we addressed the incidence of AKI, perioperative factors that can increase or decrease the incidence of AKI and 2 new biomarkers (IL-18, KIM-1) and their role in diagnosis and monitoring of AKI post open heart surgery.

The incidence of AKI in our cohort study was (23%), literatures showed a wide range for the incidence of AKI in children after cardiac surgery ranging from 3-42% and 27-50% respectively [15,16]. Other studies showed a higher incidence of AKI after CPB than our study (36.6%) and (37.9%) respectively, this higher incidence may be due to the higher number of the cohort study group in comparison to our study 525 and 145 patients respectively [16,17]. In our study we had 5 patients below 30 days of age, (60%) of them had AKI while (40%) didn't have AKI and we had 39 patients above 30 days of age, (82%) of them didn't have AKI and (18%) of them had AKI. This goes with the results that showed the lower the age of the patient undergoing cardiac surgery the more liability of AKI to occur. **Morgan et al.** showed that (64%) of their cohort study which were neonate had AKI post operatively, this is due to the immaturity of the kidneys in the younger age groups than the elder children [18].

**Parolari et al.** and **Parikh et al.** reported a much lower incidence of AKI following cardiac surgery in adult patients (8.9%) and (5%) respectively, those results support that the younger patients have immature kidneys and more liable to develop AKI than older patients [19,20]. Our study showed no statistical association between the RACHS score and the development of AKI. **Park et al.** stated the same results and mentioned that it may be due to the relative absence of high category surgery stage 5 and 6 which is the same situation in our study [21]. **Pedersen et al.** reported that the incidence of AKI increases with the increase of the RACHS scoring system and this was due to that the patients which had a RACHS score 5 and 6

develop higher incidence of AKI than the patients with lower RACHS score operations [22].

There was no statistical correlation between CBP time, aortic cross clamp time and the development of AKI in our study. The study carried by Li et al. figured out that patients who had a CPB time more than 180 minutes were more liable to develop AKI than patients with less CPB time. They stated also that the CPB time was a reflection of complexity of the surgery and not a direct factor for the development of AKI [23], so this may explain why in our study there was no relation between the CPB time and the development of AKI as the overall complexity of our cases were mild to moderate, also the differences in protocols among centers regarding CPB which maybe a confounding factor that limits generalization of results between centers.

In our study peritoneal dialysis was indicated for 8 patients, seven of them developed AKI and the 8th patient didn't develop AKI due to early initiation of peritoneal dialysis that prevented the development of AKI. **Leow et al.** agreed with the same results in their study as they mentioned that children at risk of developing AKI after cardiac surgery should be considered for early peritoneal dialysis, they found that the early peritoneal dialysis was associated with greater net negative fluid balance and higher urine output in the 1st 24 and 48 hours post cardiac surgery [24]. **Sasser et al.** found that the initiation of prophylactic peritoneal dialysis after cardiopulmonary bypass in children was associated with less development of AKI and improved clinical outcome. They concluded that the prophylactic peritoneal dialysis decreases the circulating inflammatory cytokines that can develop AKI [25].

Our study showed a strong correlation between the development of AKI and increase the length of stay in the PICU. The results showed that the patients who developed AKI had a median length of stay double to the patients who did not develop AKI. There was no difference in other literatures than our results as they mentioned that AKI is associated with longer Stay in the PICU and more complications [16,26].

Our results showed that there was no statistical correlation between the development of AKI and both biomarkers IL-18 and KIM-1 we used for diagnosis in our study. **Wang et al.** mentioned that the IL-18, a proinflammatory cytokine produced in the renal proximal tubule, level reaches the peak after 2 hours from the CPB and this peak level lasted for 10 hours, this might explain that our results didn't show a high level of IL-18 in the AKI group in comparison with the AKI group as we obtained our samples at 12 and 48 hours after the CPB [27]. Also 7 patients from the AKI group needed peritoneal dialysis, this could have been a factor in decreasing the levels of the biomarkers IL-18 and KIM-1. KIM-1 production is low in a normal kidney, whereas its upregulation and production significantly increase in renal proximal tubule cells owing to ischemic injury.

**Elmedany et al.** also stated that the urinary KIM-1 levels increase very early after cardiac surgery and reaches a peak after 12 hours and this also explains that the levels of KIM-1 in our study were equal in both groups at 12 hours, earlier levels at 2 or 4 or 6 hours could have been better for early detection in the AKI group [28].

**Hazle et al.** also showed that there was no statistical correlation between the levels of the AKI-1 and the development of AKI in his study, they also mentioned that KIM-1 poorly differentiated patients with either good or poor outcomes [29].

## Conclusion

AKI is common among children undergoing cardiac surgery on CPB for management of congenital heart disease especially below 30 days of age. AKI is associated with increase morbidity, length of stay in PICU and poor outcome. Creatinine is still the gold standard biomarker for diagnosis of AKI, it is reliable, available and cheap biomarker. Early postoperative peritoneal dialysis may have a role in preventing the development of the post cardiac surgery AKI in children.IL-18 and AKIM-1 needs more studies as a biomarker for diagnosis of AKI.

## Study limitations

This study had several limitations. First, the small sample size of patients in comparison to other studies. Second, the absence of RAHCS score 5 and 6 surgeries in our study. These types of surgeries are not done in Egypt. Norwood protocol will be implemented soon in our center. Lastly, the limited intervals for biomarkers sampling at 12 and 48 hours after surgery due to high cost of the biomarkers.

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