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Renal resistive index versus cell cycle arrest biomarkers in early detection of cardiac surgery associated acute kidney injury using cardiopulmonary bypass

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Abstract:
Background: A common unfavorable consequence of heart surgeries is cardiac surgery associated acute kidney injury (CSA-AKI). Renal resistive index (RRI) and urinary TIMP-2 with IGFBP7 have been proposed as tools for early CSA-AKI detection.
Patients and Methods: 60 eligible patient's members of the American Society of Anesthesiologists class II or III aged 18 to 75, possessing a Cleveland Clinic score of 0–5, based on evaluation and planned to have elective on-pump cardiac surgery. Assessing RRI and cell cycle arrest biomarkers' efficacy for early identification of AKI was the primary aim of study. The secondary aims intended to assess AKI severity also identify and correlate cut-off values of these biomarkers with the severity of AKI in addition to assess need for renal replacement treatment (RRT).
Results: Ten patients (17.2%) developed CSA-AKI. At end of surgery and 4 hours postoperative, patients with AKI exhibited significantly higher RRI in comparison with those without it (0.73 [0.63-0.76] ,0.72 [0.65-0.75] vs. 0.65 [0.56–0.69], 0.66 [0.57–0.70] P <0.001*). Best results were obtained with a cutoff value of 0.71 at 4 hours postoperatively, with 90% sensitivity and 100% specificity while the cutoff value of 0.72 yielded highest sensitivity (80%) and specificity (100%) at the end of the surgical process. As regard value of [TIMP-2]*[IGFBP7], it was considerably higher in AKI patients at 4 hours after CPB. (0.469, [0.215–0.760] vs. 0.269 [0.108–0.712] P = 0.009). For a cutoff value of 0.3 $(ng/mL)^2/1000$, the best outcomes were attained in terms of sensitivity (70%) and specificity (91.67%).

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Conclusion: RRI has better early diagnostic accuracy (98.28) than urinary cell cycle arrest biomarkers (87.93) but both tools are promising for detect CSA-AKI.

Keywords: CSA-AKI, RRI together with cell cycle arrest biomarkers.

Background:

Among significant side effects that arise during heart surgeries is cardiac surgery associated acute kidney injury (CSA-AKI). Its incidence may increase to 30%, and renal replacement therapy (RRT) is required for 1% to 5% of patients like these.[1, 2] Consequently to CSA-AKI, this complication is beginning to have a substantial impact on society due to the lengthy hospital admissions which are associated with a high financial cost in addition to long-term implications such chronic renal impairment.[3, 4] With several contributing factors, CSA-AKI has a complicated etiopathogenesis. These include inflammatory processes, stress caused by oxidative damage, endogenous and exogenous toxins, ischemia- reperfusion injury, and neurohormonal activation., etc. [5] During the perioperative period, these associated factors frequently coexist rather than occurring separately, which raises the possibility for injury. Additionally, patient-related factors exist that lead to perioperative renal injury. [6]

Acute kidney injury network (AKIN) uses two standards for AKI diagnosis included persistently low urine output (UOP) and high serum creatinine (sCr) level.[7] Because UOP is affected by hypovolemia, dehydration, and the release of anti-diuretic hormone, it is a poor indicator of renal damage. [8] Additionally, the sCr increment is not renal specific and before a spike in sCr is seen, approximately 50% of renal function must be lost. As a result, sCr is a delayed AKI marker.[9] Because of this, these traditional criteria are not specific or accurate enough, and they only become evident when renal lesions have progressed. [10] Nonetheless, a growing corpus of research indicates that novel biomarkers facilitate the early detection of renal damag.[11, 12] Consequently, diagnosis of CSA-AKI has been linked to more recent early AKI markers. Among these markers are renal resistivity index (RRI) based on Doppler imaging [13] and tissue inhibitor of metalloproteinases-2 (TIMP-2) with insulin-like growth factor-binding protein 7 (IGFBP7) as a G1 cell cycle arrest proteins that may be quantified using a specialized urine test [14].

2. Methods

2.1. Study design: This is a diagnostic prospective cohort study.

2.2. Participants

We studied 60 patients of both genders planned for on-pump cardiac surgeries using ofcardiopulmonary bypass (CPB) at Main Alexandria University Hospital, Egypt, between May 2022 and September 2023. The Declaration of Helsinki's guiding principles were followed during the trial. Approval of the Medical Ethics Committee of Alexandria Faculty of Medicine was obtained (IRP NO: 00012098).

Because the collection of urine specimens and renal ultrasonography data is non-invasive and was done in accordance with our institution's standard of care, participants' written informed consent was required, as per the Research Ethics Board's ruling. [15, 16]

Patients in our study aged of 18 to 75 and members of class II or III of the American Society of Anesthesiologists, possessing a Cleveland Clinic score of 0–5. [17] Exclusion criteria were as follow: patients with endocarditis or using intra-aortic balloon pump (IABP), off pump heart surgery, urgent or redo cardiac surgery or combined surgery, chronic renal dysfunction (confirmed by elevated serum urea and sCr level ≥2.1 mg/dl at time of admission), renal artery stenosis or kidney malformations. Additionally, those who have previously needed dialysis due to advanced renal disease.

2.3. Data collection

Preoperatively, the following data was gathered: demographic data, patients' medical and surgical history. Also patients' drug therapy and preoperative basal renal function (serum urea, sCr, creatinine clearance). The following data was obtained during surgery: type of surgery, timing of CPB and cross-clamp, MAP after CPB termination, total number of patients treated with diuretics and the dosages used. As well as intraoperative complication (bleeding, arrhythmia, difficult separation from CPB, the need for inotropes or vasopressors and their doses and durations, and the need for IABP. Postoperative data were recorded: The time when mechanical ventilation is weaned off, the proportion of patients who got blood products and the number of patients requiring RRT and percentage of patients who got diuretics in ICU.

2.4.1. Conventional markers assessments for early identification of AKI (AKIN)

During study, sCr was measured every 12 hours for 3 days postoperatively. UOP was checked every hour and recorded every 4 hours for 72 hours. Timing of AKIN criteria assessment and staging of AKI patients were at time of ICU admission and every 12 hours for 3 days.

2.4.2. Novel markers and metrics for early AKI identification

Data were collected and evaluated preoperatively as a baseline, after induction of general anesthesia, at the end of surgery, 4 hours and 24 hours after termination of CPB to identify the earliest elevation of the markers.

2.4.2.1. Sonographic marker: Three measurements of the end diastolic and peak systolic velocities were made on each kidney using a pulsed-wave Doppler to interrogate the interlobar or cortico-medullar arteries in order to determine RRI values. Peak systolic velocity – end diastolic velocity / peak systolic velocity is the formula used for calculating the RRI value. All RRI readings taken at each time-point were averaged to provide the final time-point value. [18]

2.4.2.2. Biologic biomarkers: Using the ELISA method, urinary TIMP-2 and IGFBP7 levels were assessed. TIMP-2 and IGFBP7 indexes in $(ng/mL)^2/1000$ units were provided and AKI risk was considered to be moderate if the index was less than 0.3, high if it was between 0.3 and 2.0, and extremely high if it was greater than 2.0. [19]

2.5. Outcome data

Evaluation of RRI and cell cycle arrest biomarkers' effectiveness for CAS-AKI early identification was the main aim of the study. The secondary aims were to assess severity of AKI and the occurrence of its severe forms (i.e. stage II or III), as well as the need to RRT within 72 hours after surgery as well as, identify and correlate cut-off values of these biomarkers with the severity of AKI.

2.6. Statistical assessment

The computer was fed data, and Version 20.0 of the IBM SPSS software was utilized for analysis. (IBM Corp, Armonk, NY). The qualitative data was described using percentages and numbers. We used the Shapiro-Wilk test to verify the normality of the distribution. Quantitative data was described using the terms range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). When comparing two investigated groups for usually quantifiable variables, we utilized the Student's t-test; when comparing more than two periods, we employed an ANOVA with repeated measures. In order to compare two groups under study using quantitative variables that were not regularly distributed, we employed the Mann Whitney test. Fisher's exact test or the Chi-square ($\chi 2$) test were used to statistically examine the categorical data, depending on the situation. Significance of the achieved results considered at the 5% level. Plotting receiver-operating characteristic curves (ROC) allowed for evaluation of prediction power of the newly measured AKI biomarkers. The area under the ROC curves was computed with the 95% confidence intervals (CI) when contrast between patients with and without AKI. An area of more

than 50% indicates an acceptable performance, while an area of around 100% shows the test's best results. Furthermore, a performance comparison between two tests was made possible via the ROC curve.

3. Results

3.1. Patients

Two of these patients were eventually excluded from the trial, leaving 58 patients total. Evaluation and measurements were conducted during the first three postoperative days. Based on the AKIN criteria, patients divided into two groups that included AKI and non-AKI at the end of the trial and following data collection and analysis. The AKIN staging criteria further split the AKI group into 3 severity levels. (Figure 1).

Characteristics of the patient and perioperative data did not demonstrate any statistically significant differences between patients who have and do not have AKI, with the exception of a few risk factors. (Table 1).

Table (1): Characteristics of patients and perioperative data.

	AKI (n= 10)	No AKI (n = 48)	P-value
Anthropomorphic and preoperative data			
Age (year)	53.10 ± 14.72	51.65 ± 13.75	0.765
Sex (F/M)	**3/7**	**22/26**	**0.490**
BMI (kg/m2)	30.32 ± 4.13	**32.51 ± 9.21**	**0.466**
LVEF (%)	59.90 ± 9.15	59.63 ± 8.59	**0.928**
Carotid occlusion >70% (%)	2 (20)	4 (8.3)	**0.274**
Coronary angiography (%)	2 (20)	-	**0.027***
pre-operative Cleveland clinic score	2.7 ± 1.94	1.73 ± 0.92	**0.025***
Preoperative serum creatinine (mg/dl)	**0.96 ± 0.17**	**0.91** ± 0.15	**0.330**
Comorbidities			
IHD	**4 (40)**	**27 (56.3)**	**0.489**

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Diabetes, n (%)	**7 (70)**	**37 (77.1)**	**0.691**
Hypertension, n (%)	**8 (80)**	**35 (72.9)**	**1.000**
Peripheral vascular disease, n (%)	**3 (30)**	**2 (4.2)**	**0.032***
Acute MI	**2 (20)**	**-**	0.027*
Drug history			
ACEIs/ ARBs, n (%)	**7 (70)**	**16 (33.3)**	**0.040***
NSAID, n (%)	**6 (60)**	**4 (8.3)**	0.001*
Anticoagulants	**5 (50)**	**9 (18.8)**	
Intraoperative data			
Types of surgery (CABG/ Valve)	**4/6**	**27/21**	**0.489**
CPB duration (min)	**133** ±33.2	**111.16 ±16.56**	**0.069**
Cross-clamp duration (min)	**95.50 ± 20.34**	**85.79 ±14.33**	**0.076**
MAP post CPB (mmHg)	**77.50 ± 8.90**	**79.94 ±7.22**	**0.335**
Diuretic consumption, n (%)	**8 (80)**	**17 (35.4)**	**0.014***
Diuretic dose (mg)	**140 ±46**	**70.59**±34.44	<0.001*
Difficult off-bypass (%)	**2 (20)**	**1 (2.1)**	0.074
Post-bypass ST-changes (%)	**4 (40)**	**4 (8.3)**	0.024*
Postoperative data			
Duration of MV weaning (hr.)	**7.55± 2.8**	**5 ±1.12**	**0.019***
Bleeding in chest tube (ml)	**607.5 ± 218.6**	**493.8 ±164.1**	**0.096**
RBCs transfusion (units)	**2.5 ± 0.85**	**1.98 ± 0.76**	**0.083**
ICU stay (days)	**7.7 ± 2.36**	**4.35 ± 0.86**	**0.001***

The means (SD), medians, and frequencies (proportions) of the data are displayed. When comparing groups (AKI against No AKI), the P-value is used. The statistical

significance of the comparative results was determined using P-values of 0.05, and all significance tests were two-tailed.

3.2. Clinical outcomes

Ten patients (17.2%) developed AKI, according to the AKIN definition. So patients who fell in a stage higher than stage "0" during the first 72 hours postoperatively were categorized as AKI patients. Others who remain in stage "0" throughout the same time were categorized as non AKI patients. No patients needed RRT. (Figure 1).

The AKI group reported a significantly higher rise in mean sCr. by the end of the third day mainly at 60 hr and 72 hr in AKI patients (p 0.017, 0.003 respectively).

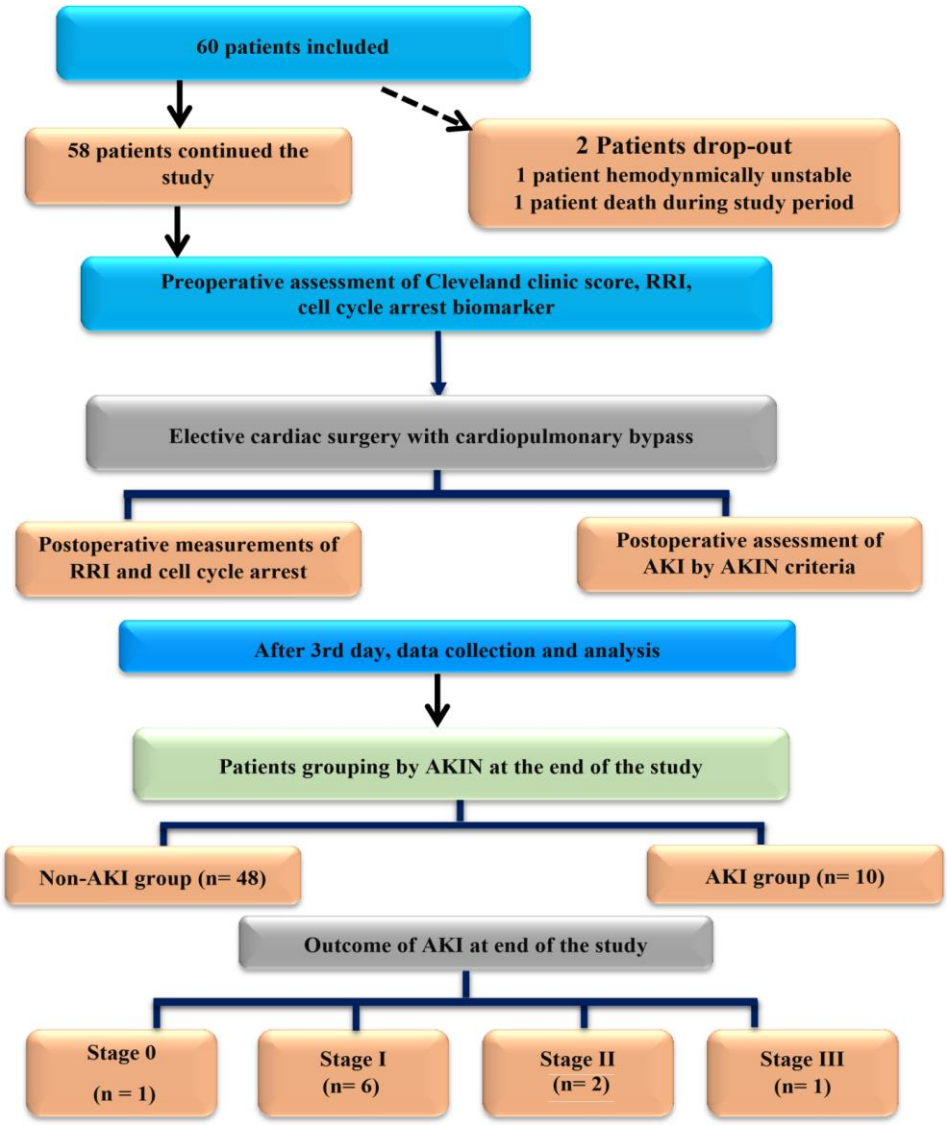

Fig 1. Flowchart of the trial.

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3.3. Doppler-based RRI's perioperative kinetics

With this rather small cohort, preoperative RRI measurements revealed no significant difference between both groups (p= 0.658) and the values still not significant different after induction of general anaesthesia. Then at end of surgery, at 4 and 24 hours after termination of CPB, values of RRI in the AKI group increased significantly (p< 0.001), and failed to go back to the baseline reading. (Table 2)

Table (2): Perioperative kinetic of urinary cell cycle arrest biomarkers and RRI

	Preoperative	After induction of GA	At end of surgery	4 hours after CPB	24 hours after CPB
Cell cycle arrest biomarkers					
AKI (n = 10)					
Mean	0.212	0.234	0.255	0.469	0.293
± SD.	0.061	0.068	0.080	0.189	0.103
Non AKI (n = 48)					
Mean	0.203	0.217	0.222	0.269	0.224
± SD.	0.045	0.045	0.047	0.117	0.052
T	0.524	0.942	1.724	3.219*	2.063
P	0.603	0.350	0.090	0.009*	0.066
RRI					
AKI (n = 10)					
Mean	0.64	0.65	0.73	0.72	0.71
± SD.	0.01	0.02	0.04	0.03	0.03
Non AKI (n = 48)					
Mean	0.63	0.65	0.65	0.66	0.63
± SD.	0.03	0.02	0.02	0.03	0.02
T	1.622	0.459	7.835	5.464	10.473
P	0.114	0.648	<0.001*	<0.001*	<0.001*

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Data are displayed as mean (SD). When comparing groups (AKI against No AKI), the P-value is used. A 0.05 P-value was utilized to assess statistical significance for comparison results, and all significance tests were two-tailed.

The AUC of the postoperative RRI that measured at different times in comparison to the preoperative value is displayed in (Figure 2) along with the ROC curve. The results revealed that the best diagnostic performance and accuracy for RRI to diagnose AKI was achieved at 4 hours postoperatively at an optimal cut-off value of >0.71 with sensitivity and specificity of 90% and 100%, respectively and diagnostic accuracy was 98,28% at this period. We found that numeric results of postoperative RRI did not correlate to AKI severity.

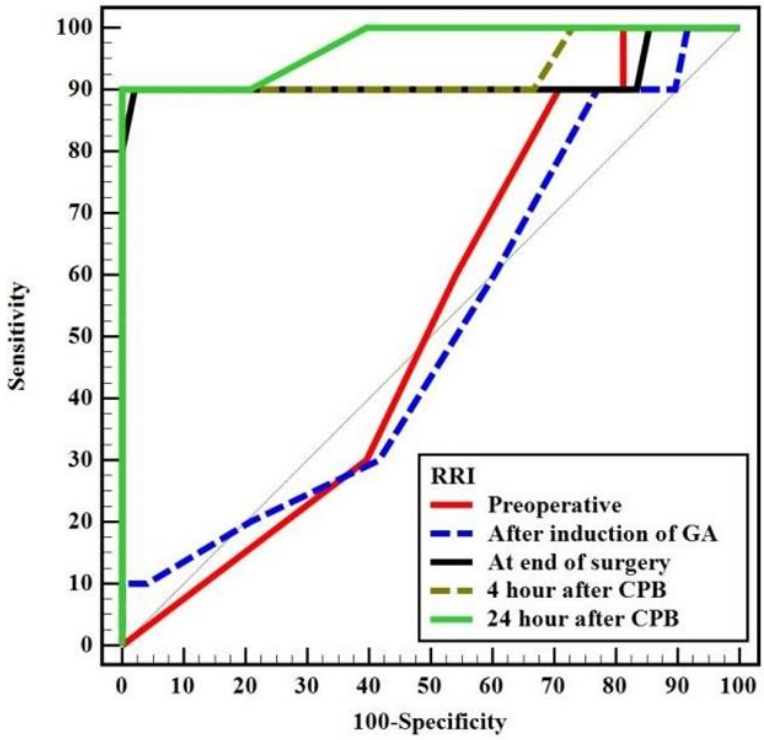

Fig. 2. This figure depicts the receiver operating characteristic (ROC) curve for the detection of AKI using RRI measured preoperative, after induction of general anaesthesia, at end of surgery, 4 hours and 24 hours after termination of CPB.

3.4. Urinary perioperative kinetics [TIMP-2]*[IGFBP7]

There was no significant difference in preoperative urine [TIMP2]*[IGFBP7] in this relatively small cohort between those with and without postoperative AKI. (Table 3). Comparing both groups postoperatively, cell cycle arrest biomarkers in the AKI group increased statistically significantly at the 4 hours after CBP (p= 0.009) which

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returned to be insignificant but the reading not retuned to preoperative values at the 24 hours after CPB (p= 0.066). (Table 2)

Postoperative AUC for [TIMP-2]*[IGFBP7] measured at various research periods in comparison to the preoperative value is shown in the ROC curve in (Figure. 3). The best diagnostic performance and accuracy for cell cycle arrest biomarkers for identification of CAS-AKI were found at 4 hours postoperatively at an optimal cut-off value of >0.3 $(ng/mL)^2/1000$ with a corresponding sensitivity and specificity of 70% and 91.67%, and a diagnostic accuracy of 87.93%. We found that numeric results of postoperative [TIMP2]*[IGFBP7] were correlated to AKI severity.

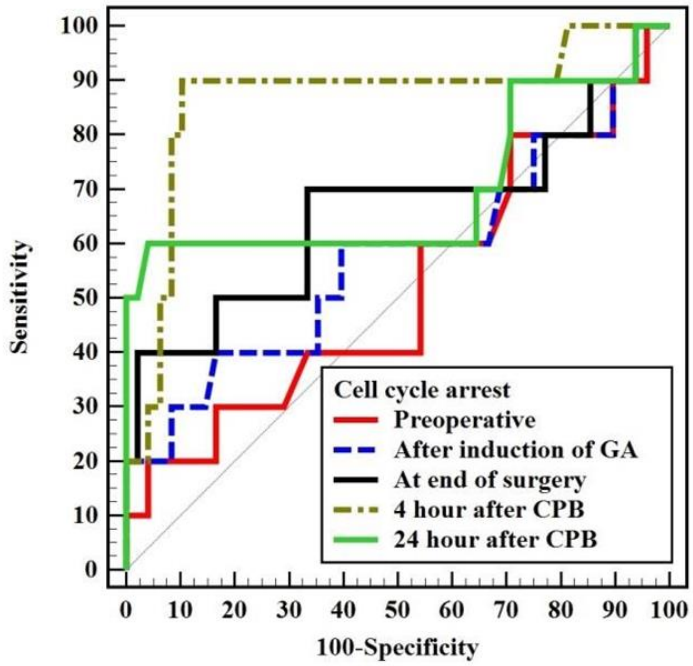

Fig. 3. This figure depicts the receiver operating characteristic (ROC) curve for the detection of AKI using the urinary [TIMP-2]*[IGFBP7] measured preoperative, after induction of general anaesthesia , at end of surgery, 4 hours and 24 hours after termination of CPB.

4. Discussion

The current prospective observational trial's findings demonstrate that RRI can more accurately and promptly anticipate the establishment of AKI just at end of surgery that more earlier than the traditional criteria for AKI diagnosis that depends on sCr. Furthermore, out of all the measurements obtained during the first 24 hours after CPB termination, our findings demonstrated that the only the [TIMP-2]*IGFBP7] measurement, taken 4 hours after CBP, was substantially higher in AKI group in comparison Non-AKI group.

As regards RRI, numerous studies conducted since the 1990s have highlighted how easily RRI may be used to diagnose and characterize AKI in a variety of clinical situations. [20-22] Dawood et al. [23] found that AKI patients had significantly higher 1 h and 6 h RRI. The diagnostic accuracy at 1 h was 93.0%, AUC was 0.991, using a cut-off value of 0.72. The diagnostic accuracy at 6 h was 94.8%, AUC 0.995 at a cut-off value of 0.71. Also Qin et al.[24] proved the effectiveness of RRI in accurately predicting AKI in patients undergoing repair of aortic dissection. The maximum RRI was obtained at 6 hours postoperatively with cutoff value of 0.71, a sensitivity of 76.9% and specificity of 95.5%.

In line with our study, Cherry et al. [25] concluded that routine intraoperative transesophageal echocardiography exam should include RRI assessment as there is a strong correlation between AKI and intraoperative RRI among patients that had cardiac surgeries.

Similarly, Tublin et al. [22] showed that better RRI performance when assessed just after surgery and proved that renal Doppler is beneficial for noninvasively monitoring of renal function after heart surgery for predicting long-term AKI using RRI. Additionally, Guinot et al.[26] concluded that Doppler-based RRI has a desirable cut-off of 0.73 and a gray area spanning 0.72 and 0.75. It could be beneficial for the noninvasive evaluation of the restoration of kidney function following heart surgery.

As regards validity of cell cycle arrest biomarkers for early detection of AKI, values of the cell cycle arrest biomarkers increased statistically significantly four hours after the CPB termination in the AKI group.

There were several studies evaluating the predictive power of urine [TIMP-2]*I[GFBP7] for AKI diagnosis that carried out in adult patients planned for on-pump cardiac procedures.

According to Meersch et al. [27], [TIMP-2]*[IGFBP7] had a significantly higher value at 4 hours after CPB ended. Its average increased from 0.49 preoperatively to 1.51 at that point, and its AUC at 4 hours postoperative was 0.81, recommending that [TIMP-2]*[IGFBP7] has a greater significance in order to predict CAS-AKI.

Also, our results were perfectly matching with Wang et al. [28] confirmed that [TIMP-2]*IGFBP7] could anticipate AKI risk within 4 hours following heart surgery, with an AUC of 0.80. The prognostic value of [TIMP-2*[IGFBP7] was significantly higher in AKI patients.

In agreement with our results, Pilarczyk et al.[29] showed that urinary [TIMP-2]* [IGFBP7] in AKI group compared to non-AKI group increased considerably as early as 4 hours after CABG. As regard accurateness for AKI's anticipation, the [TIMP-2]*[IGFBP7] showed higher sensitivity (0.89) and specificity (0.81) using cut-off 0.817

which was substantially superior than that of sCr with sensitivity (0.50), specificity (0.52) and cut-off value 1.17 mg/dl.

Furthermore, Oezkur et al.[30] examined the correlation between [TIMP2]*[IGFBP7] at various intervals following cardiac surgery, and they found that the optimal period to predict the AKI risk was just after surgery.

Also our results found positive correlation between cell cycle arrest biomarkers and AKI severity and this relation became significant during second and third postoperative 24 hours found that stage 2-3 AKI risk assessment was the test's intended purpose.

In concordance with our results, Kashani et al. [31] also suggested using [TIMP-2]*[GFBP7] to classify AKI risks. They demonstrated that detrimental impact on the kidneys (dialysis, death, persistent renal insufficiency, etc.) and advanced stages of AKI that developed within 12 hours was significantly increased. As risk of AKI and detrimental impact on the kidneys increased to two times and five times when [TIMP-2]*[IGFBP7] was > 0.3(ng/mL)^2/1000 and at 2 (ng/mL)^2 /1000 respectively.

Hoste et al. [32] found that when a cutoff of 2 (ng/mL)^2 /1000 was applied, [TIMP-2]*[IGFBP7] showed highest specificity of 95% and PPV of 49%, and when a cutoff of 0.3 (ng/mL)^2 /1000 was applied, maximum sensitivity was 89% and the NPV was 97%.

Additionally, Wetz et al. [33] found that patients who had AKI had greater urinary [TIMP-2]*[IGFBP7] levels than those who did not. Furthermore, Yamashita et al. [34] showed that urinary [TIMP-2]*[IGFBP7] has a ROC with AUC ranged from 0.81 to 0.84, indicating that it is a reliable diagnostic of AKI in critically septic patients.

As contrary to our study, Mayer et al. [35] concluded that [TIMP2]*IGFBP7] values were considerably greater in AKI group at 24 hours after CPB weaning and 1 hour after CPB start ($p < 0.05$). According to Wetz et al. [33], patients with AKI showed noticeably greater amounts of [TIMP-2]*[IGFBP7] on the day one following operation with no discernible difference in concentration on the day of surgery.

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Conclusion:

RRI is an easy, promising, bed-side, reproducible tool that can be beneficial to early detect CSA-AKI with better early diagnostic accuracy than urine cell cycle arrest proteins but both tools are promising for detect CSA-AKI.

Limitations:

Despite several meaningful findings, our study has several limitations. First, our current monocentric study was conducted with a limited number of patients, which may have resulted in a lack of power in some statistical analyses. In contrast, the

predictive value of RRI and urine [TIMP-2]*[IGFBP7] for AKI detection needs to be assessed in a multicenter study with a larger sample size. Second, it's crucial to keep in mind that urinary cell cycle arrest biomarkers and RRI should be viewed as tools rather than as ends in and of themselves. Even though clinical trials produced positive results, more innovative diagnostic tools are needed to address the pathophysiological characteristics of AKI. This may make it possible to provide goal directed care for AKI and to halt the pathological process early by concentrating on the site and etiology of the pathology. Third, because all of our criteria had a 72-hour time window, we concentrated on the renal impact of the index cardiac surgical procedure (and very early possible complications) rather than later consequences. So enlarging the time window, i.e., using a more sensitive definition (KDIGO definition), could have yielded higher incidence of CS-AKI and, possibly, different performance of the tested biomarkers. Fourth, we did not consider the effect of positive end-expiratory pressure and peak airway pressure on RI, which would lead to a high RI value. Finally, the results of this study are generalizable only for patients at risk to develop AKI scheduled to undergo cardiac surgery using CBP. So more studies are needed to determine if RRI and cell cycle arrest biomarkers would show the same predictive ability in off-pump cardiac surgeries.

Abbreviations:

CSA-AKI: Cardiac surgery associated-acute kidney injury, AKIN: Acute Kidney Injury Network, RRI: Renal Resistivity Index, IGFBP7: insulin-like growth factor-binding protein 7, TIMP-2: tissue inhibitor of metalloproteinases-2, CPB: cardiopulmonary bypass, ELISA: enzyme-linked immunosorbent assay.

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Conflict of Interest: The authors report there are no competing interests to declare.

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