

Urinary Tissue Inhibitor of Metalloproteinases-2 as Early Biomarker of Acute Kidney Injury after Cardiac Surgery

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ABSTRACT

Background: Tissue inhibitor of metalloproteinase-2 (TIMP-2) is a member of the matrix metalloproteinase family, inducer of G1 cell cycle arrest, it is a marker of cellular stress in the early phase of tubular cell injury caused by a wide variety of insults

Aim and objectives: The aim of this work was to study if urinary TIMP-2 can be used as one of early biomarkers of acute kidney injury after cardiac surgery.

Subjects and Methods: This was cross sectional study was conducted in collaboration between the Internal Medicine, Cardiothorathic and Clinical pathology departments, Faculty of Medicine, Zagazig University Hospitals. A total number of 50 patients were included and classified into two main groups: Group I: included 25 patients who undergone coronary artery bypass graft. Group II: included 25 patients who undergone valve replacement surgery. The patients were reclassified after the procedure into two groups: AKI group: defined on 24 h creatinine level elevation either by 25% of the basal level or by 0.3 mg/dl above the basal level. No AKI group: No rise of the serum creatinine level after 24 hours of the operation. The duration of the study ranged from 12- 18 months.

Results: There was highly significant difference regard urinary TIMP-2 and serum Cystatin C after 24 hours post operative in AKI group than non AKI group. Also we

found that all markers significantly increased postoperatively than preoperative in AKI group only. But Cr, and BUN postoperative were significantly higher at AKI group later after 48 H and 72 H, and GFR significantly decreased than No AKI group.

Conclusion: On the basis of recent evidence, urinary TIMP-2 is an effective predictive factor of AKI.

Keywords: Tissue inhibitor of metalloproteinase-2, Cystatin C, acute kidney injury, cardiac surgery.

Introduction

The most common severe complication of cardiac surgery is acute kidney damage (AKI). Throughout 2 million cardiac procedures are conducted each year around the world, with the incidence of cardiac surgery-associated AKI (CSA-AKI) ranging from 5% to 42%. After sepsis, CSA-AKI is the second most prevalent cause of AKI in the intensive care unit, and it is linked to higher morbidity and mortality [1].

CSA-AKI is a common wide term expressing variable pathologies. It can be considered as type 1 of cardiorenal syndrome (CRS), according to the CRS classification which was implemented in 2008 [2]. CRS is a bidirectional condition known as a pathophysiologic disorder of the heart and kidneys, whereby a sudden rapid deterioration of the function of one organ might induce acute or chronic dysfunction of the other organ. Type I CRS means that deterioration of cardiac function, leading to AKI [3].

Diagnosing and grading of AKI is still depending on changes of creatinine level and /or decreases in output urine. On the other hand, serum creatinine is well known to be insensitive to acute or minimal changes of kidney function, as it doesn't neither accurately reflect the glomerular filtration rate nor do they point to the severity of tubular injury [4].

The search for biomarkers for early AKI detection that might allow direct intervention and renal protection measures which could alter renal outcomes especially in critically ill patients.

Cystatin C is a low-molecular-weight protease inhibitor freely filtered by glomeruli and completely reabsorbed by tubules and has been shown to reliably reflect changes in GFR. Cystatin C detects AKI 2 days earlier than creatinine, As it may be noted within 2–6 h after surgery and correlate to the extent and duration of AKI [5].

Tissue inhibitor of metalloproteinase-2 (TIMP-2) is a 21 kDa protein expressed in melanoma and renal tubular cells. TIMP-2 irreversibly inactivates metalloproteinases (MMP) by binding to their catalytic zinc cofactor [6].

Both TIMP2 and IGFBP7 are involved in the G1 cell-cycle arrest phase that occurs during the very early phases of cellular stress. Detection of cell-cycle arrest may serve as a biomarker of impending tubular damage in AKI. It is also believed that manipulation of the cell cycle may have therapeutic potential [7].

Therefore, it is of worth developing a more sensitive or specific indicator to detect acute kidney injury after cardiac surgery.

Subject and Methods

This study has been done in collaboration between the Internal Medicine, Cardiothorathic and Clinical pathology departments, Faculty of Medicine, Zagazig University Hospitals during the period between January 2020 and January 2021. All the patients have signed an informed written consent.

A total number of 50 patients were included and classified into two main groups: **Group I:** 25 patients who undergone coronary artery bypass graft. **Group II:** 25 patients who undergone valve replacement surgery.

The patients were reclassified after the procedure into two groups:AKI group: which was defined on 24 h creatinine level elevation either by 25% of the basal level or by 0.3 mg/dl above the basal level. It includes 26 patients (18 male and 8 female) with age ranged from 39 to 59 years with mean values \pm SD 50 \pm 9.54years. Their weight ranges from 65 to 86 kg with mean values \pm SD 76.26 \pm 10.1.**No AKI group:** No rise of the serum creatinine level after 24 hours of the operation. It includes 24 patients (17 male and 7 female) with age ranged from 37 to 59 years with mean values \pm SD 50.7 \pm 9.21 years. Their weight ranges from 62 to 83 kg with mean values \pm SD 72.62 \pm 11.2.

Inclusion criteria: All subjects were enrolled after their written consent, all subjects were aged between 30 – 65 years old, all subjects were chosen with no history of liver disease, renal disease or malignancies and all subjects were with normal basal creatinine level.

Exclusion criteria: Overt infectious complications, pregnancy, autoimmune diseases, malignancy, renal disease, liver cell failure.

Tools and instruments: All subjects of the study were submitted to the following:

- 1- **Full clinical assessment including:** History taking and clinical examination: according to work sheet with special stress on history of renal diseases.
- 2- **Routine laboratory investigations:** They were all done according to the methods applied in the clinical pathology laboratories of Zagazig university

hospitals and include: Complete blood count, blood urea and serum creatinine, liver function tests, random blood glucose level, lipid profile and transthorathic echocardiography.

- 3- **Calculation of glomerular filtration rate using MDRD equation** $GFR (ml/min/1.73 m^2) = 175 \times (S cr)^{-1.145} \times (Age)^{-0.203}$. Multiply 0.742 if female.
- 4- **Specific investigations:** Measurement of urinary TIMP-2, and Measurement of seum Cystatin C. They measured by ELISA technique (ELISA is a sandwich enzyme immunoassay for the quantitative measurement of the biomarker).
- 5- **Sampling:** We collected 10 ml of urine and 2 ml of peripheral venous blood from each subject under complete aseptic conditions. This process was done preoperative and repeated after 24 hours after coming of the surgery. Then samples centrifuged for 15 minutes and stored at -20°C till being assayed

Statistical Analysis: Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. Differences between quantitative independent groups by t test or Mann Whitney, P value was set at <0.05 for significant results & <0.001 for high significant result. To assess the diagnostic value of the parameters, receiver operating characteristic (ROC) and the area under the curve (AUC) were calculated.

Results

Age was distributed as 48.8±10.1 and 50.1±8.9 respectively between studied groups without significant difference also weight was distributed as 76.35±9.26 and 72.96±11.3 without significant difference between groups, regarding sex male were majority at both groups without any significant difference between groups. **Table (1)**

There were no significant difference regard Cr, BUN and GFR preoperative between AKI and No AKI groups but Cr, and BUN postoperative were significantly higher at AKI group later after 48 H and 72 H, and GFR significantly decreased than No AKI group. Also Cr, and BUN postoperative were significantly higher at AKI group later after 48 H and 72 H, and GFR significantly decreased than pre intervention. No AKI group showed no significant different Cr, BUN and GFR pre and postoperative. **Table (2)**

There was no significant difference regarding Pre-Cyst C between the AKI and No AKI groups, but Post-Cyst C was significantly higher in the AKI group than the No AKI group. It was also significantly higher among AKI cases than pre-Cyst C, but not significantly different among No AKI cases than pre-Cyst C. **Table (3)**

Regarding Cystatin C, Significant area under curve 0.986 with significant cutoff >0.82 with sensitivity 90% and specificity 89.0% **Figure (1)**

There were very high significant increase regarding TIMP-2 ($p=0.000$) in post operative than preoperative in AKI group. Also there was high significant difference in TIMP-2 between the AKI group and No AKI group. While no significance difference in no AKI group. **Table (4)**

Significant area under curve for TIMP-2 was 0.817 with significant cutoff >1.9 with sensitivity 83.5%, and specificity 80.8%. **Table (5)**

This table shows that there were high significant difference ($p=0.000$) in duration of operation (min) between two types of cardiac surgery. **Table (6)**

Table (1): Age, Weight and sex distribution between studied groups

			AKI (N=26)	No AKI (N=24)	t/X ²	P
Age			48.8±10.1	50.1±8.9	-0.267	0.403
Weight			76.35±9.26	72.96±11.3	1.212	0.250
Sex	Male	N	18	17		
		%	69.2%	70.8%		
	Female	N	8	7	0.015	0.9
		%	30.8%	29.2%		
Total		N	26	24		
		%	100.0%	100.0%		

Table (2): Comparison of mean± SD of serum Cr, BUN and GFR distribution at different times between studied groups:

		AKI (N=26)	No AKI (N=24)	t	P
Pre Cr		0.89±0.33	0.821±0.235	0.943	0.764
Post Cr		0.99±0.35	0.861±0.185	1.48	0.124
Cr 48 hours		1.57±0.50	0.864±0.189	6.46	0.001*
Cr 72 hours		2.80±0.55	0.867±0.195	16.19	0.0005**
P pre and post		0.052	0.404		
P pre and 48 h		0.00**	0.358		
P pre and 72 h		0.00**	0.319		
Pre BUN		12.85±2.64	12.13±1.7	1.538	0.131
Post BUN		27.93±11.39	12.22±1.4	6.97	0.000**
P		0.00**	0.154		
Pre GFR		112.38±34.35	105.33±32.93	0.740	0.463
Post GFR		88.00±21.77	104.92±33.03	-2.154	0.036
P		0.00**	0.057		

Table (3): Cystatin C distribution between studied groups at different times:

	AKI (N=26)	No AKI (N=24)	t	P
Pre cyst_C	0.71±0.83	0.67±0.67	0.146	0.037
Post cyst_C	0.99±0.12	0.68±0.09	10.66	0.00**
P	0.001*	0.069		

Table (4): Comparison of mean ±SD TIMP2 between AKI cases and No AKI cases at different times.

	AKI (N=26)	No AKI (N=24)	Mann- Whitney U	P
Pre TIMP2	2.265±3.26 2.32 (0.1-11)	2.15±3.26 1.15 (0.1-11)	264.5	0.354
Post TIMP2	7.51±7.96 4.80 (0.25-30)	2.67±5.69 0.69 (0.1-20)	107.0	0.000*
P	0.00**	0.358		

Table (5): Validity of TIMP2, as predictor of AKI:

Test Result Variable(s)	Area	Cutoff	P	95% C I		Sensiti vity	Specifi city
				Lower Bound	Upper Bound		
post TIMP2	0.817	>1.90	0.00*	0.745	0.956	83.5%	80.8%

Table (6): Comparison of mean ± SD of duration of operation (min) in studied groups.

	Coronary artery bypass surgery (N=25)	Valve replacement (N=25)	t	P
Duration of operation (min)	191.4±12.18	90.4±7.85	34.85	0.000**

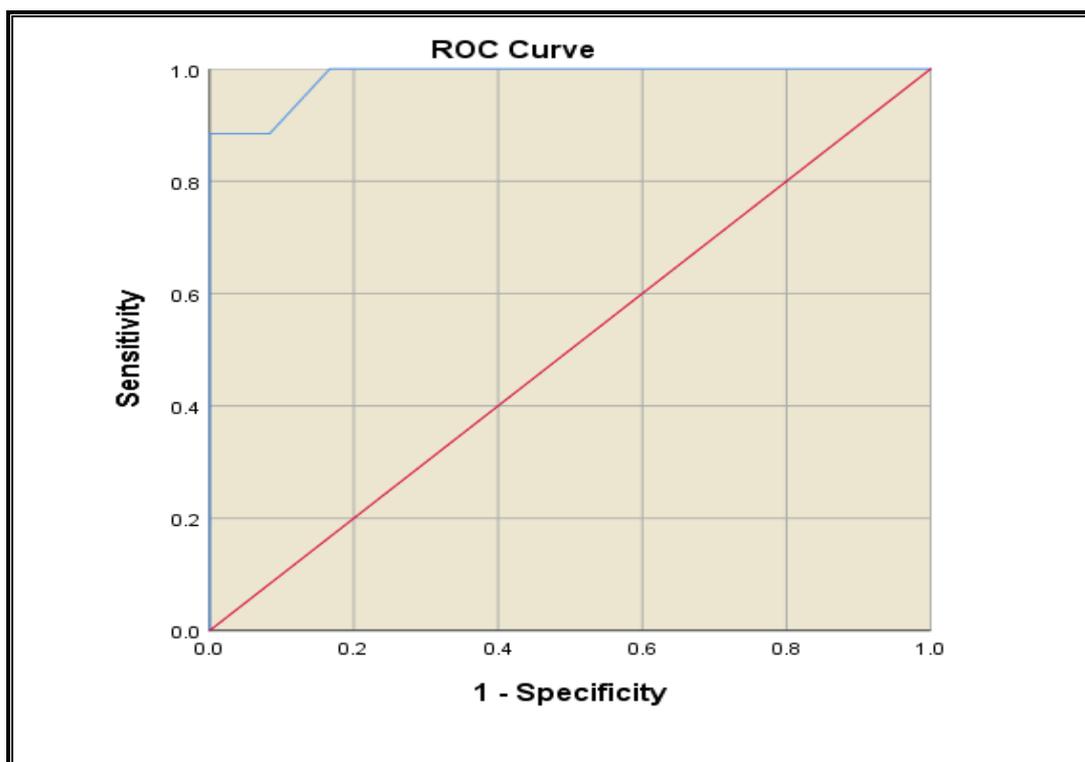


Fig. (1): Roc curve of s. cystatin C as a biomarker to detect AKI post operative.

Discussion

Acute kidney damage (AKI) is linked to a high rate of death and poor long-term results. It can also cause chronic kidney disease (CKD), aggravate pre-existing CKD, and hasten the progression of CKD to end-stage renal disease (ESRD). Although epidemiological studies have shown that AKI survivors who require temporary dialysis are at an exceptionally high risk of developing CKD, there is no mechanism to predict renal recovery with certainty [8].

It is well known that during critical illness patients can develop sepsis, heart failure, or shock, they may incur additional exposure to nephrotoxins (e.g. drugs, iodinated contrast materials, contrast CT, ...) [9].

So development of easy and rapid applicable biomarkers for prediction of renal injury also predictive of renal recovery is of great value.

The main aim of this study was to study if urinary TIMP-2 can be used as early biomarker of acute kidney injury after cardiac surgery.

A cross sectional study was conducted in collaboration between the Internal Medicine, Cardiothorathic and Clinical pathology departments, Faculty of Medicine, Zagazig University Hospitals. A total number of 50 patients were included and classified into two main groups: Group I: included 25 patients who would undergo

coronary artery bypass graft. Group II: included 25 patients who would undergo valve replacement surgery.

The patients were reclassified after the procedure into two groups: AKI group: defined on 24 h creatinine level elevation either by 25% of the basal level or by 0.3 mg/dl above the basal level. No AKI group: No rise of the serum creatinine level after 24 hours of the operation. The duration of the study ranged from 6-12 months.

Age was distributed as 48.8 ± 10.1 and 50.1 ± 8.9 respectively between studied groups without significant difference also weight was distributed as 76.35 ± 9.26 and 72.96 ± 11.3 without significant difference between groups, regarding sex male were majority at both groups without any significant difference between groups.

Honore et al., [10] supported our study by revealing that there was no statistically significant difference between the AKI group and the control group in terms of age and gender. In the study, they looked at 232 sepsis patients, with 40 (17%) of them developing AKI within 12 hours of testing.

Serum creatinine and urine output are the gold standards in diagnosis and staging of kidney injury. However creatinine is unspecific marker of changes in GFR as it cannot express the aetiology and location of kidney insult (e.g. prerenal versus intrinsic ; affected renal tubule segment; nephrotoxic versus ischemic AKI) also the extent of renal damage are not accurately reflected by SCr concentrations. [11]

Our study showed that, there were no significant difference regard Cr, BUN and GFR preoperative between AKI and No AKI groups but Cr, and BUN post were significantly higher at AKI group later after 48 H and 72 H, and GFR significantly decreased than No AKI group. Also, Cr and BUN post were significantly higher at AKI group later after 48 H and 72 H, and GFR significantly decreased than pre intervention. No AKI group showed no significant different Cr, BUN and GFR pre and post.

In the study of **Westhoff et al., [12]**, the AKI group displayed significantly higher values for Cr, and they compared urinary protein concentration and urinary protein-to-creatinine ratio compared to the non-AKI group I ($P < 0.001$) which supported and matched with our study.

According to, **McCullough et al., [13]**, the major risk for AKI, 29% had diabetes mellitus, 24% with $eGFR < 60$ mL/min/1.73 m², and 2.6% had $eGFR < 30$ mL/min/1.73 m².

New AKI diagnostic biomarkers have been identified and studied in recent years, mostly consisting of urine markers of renal tubular injury [14].

Serum cystatin C (CysC), a filtration marker of GFR, is an endogenous protease inhibitor produced at a constant rate by nucleated cells and its concentration is not affected by age, gender, or muscle mass in children. In children, CysC is a more accurate estimate of GFR than SCr and is more diagnostic of reduced chronic kidney function. Thus, it is possible that acute CysC change may be more effective at detecting acute GFR changes with AKI than SCr.

Our current study found that there was no significant difference between the AKI and No AKI groups in terms of Pre-Cyst C, but that Post-Cyst C was significantly higher in the AKI group than the No AKI group. It was also significantly higher in AKI cases than pre-Cyst C, but not significantly different in No AKI cases than pre-Cyst C. Significant area under curve 0.986 with significant cutoff >0.82 with sensitivity 90% and specificity 89.0%.

Our results were supported by study of **Bongiovanni et al., [15]** as they reported that when considering serial measurements and the comparison of AKI versus non-AKI, CysC and sCr showed significant differences between the two groups at each measurement time until 48 hours. The AUC of CysC compared to sCr and to eGFR showed a higher predictive power (CysC = 0.72, sCr = 0.70, ;eGFR = 0.71). The AUC of CysC + sCr and of CysC + eGFR showed a good high diagnostic value for AKI (resp., AUC 0.70, and AUC 0.70) but lower than that of CysC alone.

Urinary biomarker, tissue inhibitor of metalloproteinases-2 (TIMP-2), has been validated for predicting moderate and severe AKI (classified as AKI stage 2 and 3 according to the Kidney Disease Improving Global Outcome [KDIGO] 2012 classification) in critically ill patients. Both TIMP-2 and IGFBP7 are markers of cellular stress in the early phase of tubular cell injury caused by a wide variety of insults (inflammation, ischemia, oxidative stress, drugs, and toxins) ., [16].

Furthermore, tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7) both molecules can initiate G1 cell-cycle arrest that prevents cells from dividing when potentially injured. Importantly, both biomarkers also act as “alarm” proteins exerting paracrine effects on adjacent cells. The product of these two biomarkers ([TIMP-2] X [IGFBP7]) outperformed all other known biomarkers or biomarker combinations for predicting moderate-severe AKI, and the test has been validated using a clinical adjudication committee as a gold-standard for AKI. [17].

In the study in our hands, as regard TIMP2 , AKI cases were significantly higher regard pre and postoperative measurement.while it had no significane difference in no AKI group

Our results were supported by study of **Honore et al., [11]** as they reported that patients with AKI had significantly higher levels of [TIMP-2] X [IGFBP7] than patients without AKI ($p < 0.001$). This effect of AKI on [TIMP-2] X [IGFBP7] levels was not modified by nonrenal SOFA (Sequential Organ Failure Assessment) ($p = 0.70$).

However, in the study of **Dekker et al., [18]**, levels of TIMP-2 ($P = 0.24$) was comparable between patients with ADPKD (Autosomal dominant polycystic kidney disease) and healthy controls, as was the product of both markers (TIMP-2xIGFBP7, $P = 0.33$). Normalized to urine creatinine, both TIMP-2 ($P = 0.02$) was significantly lower in patients with ADPKD as compared with controls. Urine protein levels were higher in patients with ADPKD than in controls (median 0.07 [IQR 0.04–0.12] g/l vs. 0.05 [IQR 0.04–0.08] g/l, respectively, $P = 0.003$).

The present study showed that as regard ROC curve for TIMP2 ,significant area under curve was 0.81, with significant cutoff >1.9 , with sensitivity 83.5% and specificity 80.8%.

Honore et al., [11] revealed that the area under the receiver operating characteristic curve (95% CI) of tissue inhibitor of metalloproteinase-2 was 0.84 (0.73–0.92), in low and high nonrenal Sequential Organ Failure Assessment score subgroups. Performance of the tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 test was not modified by nonrenal Sequential Organ Failure Assessment ($p = 0.70$).

There were significant difference between acute kidney injury and Coronary Artery Bypass Surgery as regard duration of operation.

Conclusion

On the basis of our research serum cystatin C and urinary [TIMP2] are effective predictive factors of AKI. A combined use of biomarkers with clinical characteristics of patients may help predict AKI in the future.

Conflict of interest

It should be noted that there was no association between the authors and any organization or institution. The Authors report no declarations of interest.

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Authors' contributions:

Esam El-Din Mahmoud Lotfy Omar and Adel Abd El-Mohsen Ghorab, Made substantial contributions to the conception and share with design of the work; **Heba S. Abdel-Aziz Assal Lamiaa Abd El-Wahab Mohamed and Emad A. William** made substantial contributions to the conception, design of the work; the acquisition, analysis, interpretation of data; the creation of new software used in the work, had drafted the work and substantively revised it. All authors have read and approved the manuscript.

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The authors are responsible for all parts of the work. All statements contained in the article are true and any formula or instruction contained in the article will not if followed accurately ,cause any injury, illness or damage to the user

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