www.kosmospublishers.com
contact@kosmospublishers.com

Research Article | Advances in Endocrinology and Diabetes | AEAD-105

Time trend of ideal biomarker of acute kidney injury in diabetic patients undergoing Coronary Artery Bypass Graft (CABG)

Rasha Shafie[1]*, Neveen Lewis Mikhael Saad[2], Iman Ezat Elgohary[1], Sherif El Sayed Mahmoud Hegab[3], Nahed Mohamed Baddour[4], Ahmed Gaber Adam[1]

[1]Department of Internal Medicine and Nephrology, Alexandria University, Egypt
[2]Department of Clinical and Chemical Pathology, Alexandria University, Egypt
[3]Department of Diagnostic and Radiology, Alexandria University, Egypt
[4]Department of Internal Medicine and Pathology, Alexandria University, Egypt

Received Date: 11 April, 2019**; Accepted Date:** 21 April, 2019**; Published Date:** 26 April, 2019

***Corresponding author:** Rasha Shafie, Department of Internal Medicine and Nephrology, Alexandria University, Champollion Street, El Azareeta, Egypt. Tel: +201004672146; Email: rasha_shafie@yahoo.com

Abstract

Background: Acute kidney injury (AKI) is an important complication in patients undergoing cardiac surgery. Our study was designed to determine if Tissue Inhibitor Metallo Proteinase (TIMP)-1, 2,3,4 versus Neutrophil gelatinase-associated lipocalin(NGAL)& Procalcitonin can predict AKI early in diabetic CABG patients.

Methods: In 40 diabetic patients undergoing coronary artery bypass graft surgery. Serum TIMP-1,2,3,4, NGAL, procalcitonin & serum creatinine were recorded at four time points: at baseline pre-surgery, 4 hours after cardiopulmonary bypass (CPB), 12h post operative and 24h postoperative day.

Results: 13 of 40 patients developed AKI. Diagnosis based on AKIN criteria & all patients classified as stage 1. Pre operative Serum TIMP- 1,3,4,NGAL, procalcitonin Mean ± SD respectively were 468.97 ± 297.09, 93.17 ± 40.93, 4.13 ± 2.64, 8.43 ± 2.23, 0.01 ± 0.03 ng/ml continue rising to reach respectively 956.88 ± 519.33, 125.99 ± 29.38, 7.66 ± 1.38, 10.69 ± 1.92, 0.11 ± 0.16 ng/ml at 4h post operative before rising of serum creatinine & TIMP2 which delayed at 12h post operative.

Conclusions: Serum TIMP-1,3,4,NGAL & procalcitonin can be used as a predictive test to identify patients at increased risk of AKI very early 4h post CPB before rising of serum creatinine. TIMP-2 increase was delayed 12h post operative as it may not be an early marker in non septic patients. Procalcitonin is not always considered as a marker of sepsis. Most of AKI occurred at 12h post operative. Neither CPB time nor urine output (UOP) has statistical significance in diabetic CABG patients.

Keywords: Acute Kidney Injury, TIMP, NGAL, Procalcitonin, diabetic CABG patients

Introduction

Acute kidney injury (AKI) is a common and serious complication after cardiac surgery **[1]**. It may occur in over 40% of adults, with 1–5% requiring renal replacement therapy (RRT) **[2].** After cardiac surgery, small creatinine increases of 20–25% from preoperative baseline are associated with adverse outcomes **[3].** The mortality in cardiac surgery patients with a severe AKI requiring RRT can be as high as 60% **[4].** Although some clinical tools and scores exist to predict and stratify AKI, we are still lacking biomarkers to predict AKI and recovery from AKI early enough for interventions to be likely effective. The incidence and severity of AKI and patients outcome have not changed in recent years **[1].** Currently, diagnosing and staging of AKI are exclusively based on elevations in serum creatinine and/or decreases in urine output. Serum creatinine, however, is widely known to be insensitive to acute changes in kidney function **[5].** Serum creatinine concentrations neither accurately reflect the glomerular filtration rate nor do they point to the degree of

tubular injury **[4].** Therefore, serum creatinine values are poorly qualified to detect AKI in the early period after cardiac surgery **[6].** The same is true for postoperative oliguria, which can be influenced by a lot of factors including volume status and use of diuretics.

Methods

In 40 diabetic patients undergoing CABG at cardiothoracic ICU unit over 4 months (24-11-2015 till 14-2-2016), we surveyed individual risk factors for AKI by applying AKIN criteria. Serum ELISA for TIMP-1,2,3,4, NGAL, procalcitonin & creatinine were recorded at four time points: at baseline pre-surgery, 4 hours after cardiopulmonary bypass(CPB), 12h post-operative and 24h postoperative day. Written informed consent was obtained from all patients at the time of enrollment. All patients were prospectively followed from enrollment. Furthermore, we recorded variables known to impact AKI risk: age, sex, CPB time, cross-clamp time, hypertension, COPD, heavy smoking, CKD, previous cardiothoracic surgery, CABG + valve replacement, HCV+ve status, length of ICU stay, LV EF, APACHE II & mortality score on day 1, creatinine clearance by Modification of Diet in Renal Disease equation, serial routine investigations including CBC, BUN, urea, SGOT, SGPT, albumin, TG, cholesterol, FBS, PT, INR, prothrombin activity, Na, K, Ca, P, ALP & Uric acid. 24h urinary proteins measured at day 1 post-operative. UOP recorded hourly all over ICU stay.

Statistical methodology

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Comparisons between groups for categorical variables were assessed using Chi-square test or Fisher Exact. Student t-test was used to compare two groups for normally distributed quantitative variables. ANOVA with repeated measures for comparing between periods for normally distributed data. Mann Whitney test was used to compare two groups for abnormally distributed quantitative variables. Wilxcon Signed rank test for abnormally quantitative periods. Significance of the obtained results was judged at the 5% level.

Results

Forty diabetic patients were eligible for the study. The study population consisted of 30 men (75%) and 10 women (25%) with a mean age 57.27 ± 7.74 years (Table 1). All patients are diabetic & hypertensive. No COPD & CKD. 75% heavy smokers. All patients underwent scheduled elective CABG surgery but two patients underwent CABG surgery plus mitral valve replacement, and only one patient had undergone cardiac surgery before. 2 patients had HCV positive. The mean length of ICU stay was (2 – 18) days. Two patients (5%) died postoperatively one after 48h mostly due to myocardial infarction (MI) & another one after 9 days mostly due to pulmonary embolism and both of them developed AKI. Of 40 patients 13 (32.5%) developed AKI & all classified as stage 1 by AKIN criteria & 27 (67.5%) no AKI. No statistical significance between AKI & no AKI group regarding age, sex, cross clamping time, CPB time, previous heart surgery, LV EF%, HCV positivity, FBS , hemoglobin , WBCs , SGOT , SGPT , TG , cholesterol, Na , k, Ca , P & UOP. There are statistical significance between AKI & no AKI group regarding APACHE II & mortality score on day 1, length of ICU stay, 24h urinary proteins measured at day 1 post-operative and regarding other labs there are statistical significance between both groups in: serum creatinine & creatinine clearance by MDRD equation at 12h post-operative, platelets at pre-operative & 4h post CPB, BUN, urea, albumin & uric acid at 4h post CPB, 12h & 24h post-operative, PT/ INR/ prothrombin activity at 4h post CPB & 24h post-operative. ALP at 12h & 24h post-operative **(Table 1).**

Pre-operative Serum TIMP- 1,3,4,NGAL,procalcitonin Mean ± SD respectively were 468.97 ± 297.09, 93.17 ± 40.93, 4.13 ± 2.64, 8.43 ± 2.23, 0.01 ± 0.03 ng/ml continue rising to reach respectively 956.88 ± 519.33, 125.99 ± 29.38, 7.66 ± 1.38, 10.69 ± 1.92, 0.11 ± 0.16 ng/ml at 4h post-operative before rising of serum creatinine & TIMP2 which delayed at 12h post-operative **(Table 2) (Figure 1).**

Discussion

At the very least, several hours are needed to define oliguria. Several attempts to treat AKI have failed, perhaps in part because therapies were initiated too late in the presence of an already established acute tubular necrosis (ATN). Therefore, identifying biomarkers to predict the development and severity of AKI early after cardiac surgery has been an important goal for over a decade. Several biomarkers including interleukin (IL)-18, neutrophil gelatinase-associated lipocalin (NGAL), cystatin c, and kidney injury molecule-1 (KIM 1) have been studied. However, the area under the curve (AUC) and therefore the suitability of these biomarkers to predict AKI after cardiac surgery were fairly low (0.65 for KIM-1, 0.67 for NGAL, and 0.71 for cystatin c0). A recent study showed that renal tubular cells enter a period of G1 cell-cycle arrest after inducing ischemia **[7]** or sepsis **[8].** IGFBP7 and TIMP-2 are both involved in G1 cell cycle arrest during the early phase of cell injury **[9–11].** The G1 cell cycle arrest may prevent the division of cells with damaged DNA until the DNA damage is repaired **[10].** In the Sapphire study **[12],** it was demonstrated that the AUC values to predict the development of AKI (AKIN stage 2 or3) in critically ill patients within 12 hours were 0.76 for IGFBP7 and 0.79 for TIMP-2. Multiplication of the two marker ([TIMP2]*[IGFBP7]) resulted in an even higher AUC (0.80) and was significantly superior to all previously described markers of AKI. Moreover, [TIMP-2]*[IGFBP7] significantly improved risk prediction when added to clinical scoring systems. Cardiac surgery with CPB triggers an inflammatory response involving pro inflammatory cytokines such as TNF-α, IL-6, and IL-8 as well as activation of the complement system because of exposure of the blood to artificial surfaces. Increased levels of IL-6, IL-8, and the soluble TNF receptors,

as more stable indicator of TNF-α release, have been reported [13]. Alterations in homeostasis may also initiate alterations in inflammation at the molecular level & this will lead to a slight and transient increase in PCT levels was observed in the first postoperative day after cardiac surgery.

Our study included forty diabetic patients undergoing CABG surgery at Alexandria university cardiothoracic unit, we surveyed individual risk factors for AKI & by applying AKIN criteria 13 of them classified as stage 1 according to rise of serum creatinine & not based on UOP. It is not coincide with what mentioned by Meersch et al **[14]** which studied 50 patients & 26 of them classified AKI by AKIN criteria into stage 1: 19 patients (9 according to rise of serum creatinine & 10 according to UOP change) stage 2: 6 patients (all according to UOP change) stage 3: 1 patient(according to UOP change). We found that no statistical significance between AKI & no AKI group regarding age, sex, cross clamping time, CPB time, previous heart surgery, LV EF%, (table 1). This is coincide with Meersch et al **[14]** which also mentioned that no statistical significance between AKI & non AKI group regarding age,sex,CPB & cross clamping time, pre-operative serum creatinine, diabetic status, HTN, estimated GFR. In contrast to Meersch et al we didn't find any difference regard UOP. We found that no statistical significance between AKI & no AKI group regarding HCV positivity, FBS, hemoglobin, WBCs, SGOT, SGPT, TG, cholesterol, Na, k, Ca & P (table 1). In contrast to Grayson AD et al **[15]** who found that the mean CPB time of patients who developed AKI compared to those who did not develop AKI was significantly longer & Isolated CABG has the lowest incidence of AKI, followed by valvular surgery and combined CABG with valvular surgery we didn't find similar results possibly due to different patient population.

We can say that not always we can depend on UOP to classify AKI hence not always we can depend on it. Neither CPB time nor UOP has statistical significance in diabetic CABG patient.

The mean length of ICU stay & APACHE score in AKI group were higher than non AKI group (table 1). It is coinciding with what mentioned by Meersch et al **[14]:** mean length of ICU stay in AKI group was 12 ± 3 days versus non AKI group 4 ± 1 days & APACHE score also was higher in AKI group 12 ± 5 versus non AKI group 8 ± 3 days.

Hence APACHE score & length of ICU stay are higher in AKI patients.

Serum NGAL increased early 4h post-operative before serum creatinine **(Table 2-3) (Figure 1)** while other studies showed that level of urinary NGAL one hour post-CPB significantly predicted the risk of AKI after cardiac surgery [6]. Others mentioned that plasma NGAL levels two hours after CPB were strongly correlated with the duration and severity of AKI. Other studies showed that NGAL levels were predictive of cardiac surgery associated AKI when measured both in urine and plasma **[16-18].** Other studies **[19, 20]** showed that NGAL can predict AKI 24–72 h before serum creatinine increase; one might consider repetitious NGAL levels during the first 24 h to provide a projection to the clinician regarding AKI development in the first 3–4 postoperative days. In the 26 patients studied by Meersch et al **[14]:** who developed AKI, urinary NGAL significantly increased at 4 h after CPB ($p = 0.001$) followed by a rapid decrease back to baseline at 12 h after CPB. The usefulness of NGAL in early detection as regard sampling & timing is more controversial.

However we still can depend on serum NGAL a certain extent to predict AKI 4h post CPB before rising of serum creatinine.

Serum procalcitonin increased early 4h post-operative before serum creatinine & all patients known non septic patients **(Table 2-3) (Figure 1)** while Lecharny et al **[21]** described higher mean PCT levels in patients who developed postoperative myocardial infarction than in those with an uneventful postoperative course. Meisner et al **[22]** demonstrated a correlation between postoperative PCT levels in terms of the development of SIRS, respiratory failure, and the need for positive inotropic support. Procalcitonin levels were also found to be related to the development of postoperative complications **[21-24].** Likewise, Dörge et al **[23]** reported that higher PCT levels in patients who developed postoperative organ failure than in those with an uncomplicated postoperative course. Adamik et al **[24]** reported that after CPB, PCT levels remained unchanged in patients with an uneventful recovery and increased in patients with complications, especially in those who developed renal and hepatic dysfunction in addition to respiratory and circulatory insufficiency. Using a cut off value of just 2 ng/ml, the positive and negative predictive values for postoperative complications were 100%/93% and 100%/87% on the first and second postoperative days, respectively **[24].** Rothenburger et al **[25]** reported that PCT was useful in discriminating between acute phase response following cardiac surgery with CPB or local problems and systemic infections, and found the additional CRP measurement useful in increasing the specificity. The usefulness of PCT as regard its level being measured alone not with CRP in distinguishing infectious versus non-infectious complications is more controversial.

In this regard we can say that procalcitonin is not always marker of sepsis.

Serum TIMP-1, 3, 4 increased early 4h post-operative before TIMP 2 **(Table 1, 2) (Figure 1),** other study showed that urine concentration of [TIMP-2]*[IGFBP7] rose from a mean of 0.49 at baseline to 1.51 4 h after CPB in patients who developed AKI [26]. No studies about TIMP 1, 3, 4 in CABG patients. Only studies about TIMP2 in general ICU patients which found that serum TIMP 2 got higher more with septic patient while IGFB7 more in surgical patients **[27].** Gunnerson KJ et al mentioned that for postoperative surgical intensive care unit patients, a single urinary TIMP2•IGFBP7 test

accurately identified patients at risk for developing AKI within 12 hours **[27].** Cuartero M et al mentioned that TIMP-2 and IGFBP-7 can predict AKI in both septic and non-septic critically ill patients **[28].**

For 1st time in diabetic patients undergoing CABG without evidence of sepsis serum TIMP2 can predict AKI 12h post-operative mostly due to these groups were different while serum TIMP-1,3,4 increased early 4h post-operative.

Distribution of AKI group according to time of AKI 15.4% (2 patients) 4h post CPB, 53.8% (7 patients) 12h post-operative, 15.4% (2 patients) 24h post-operative, 15.4% (2 patients) 48h post-operative **(figure 2).**

In summary most of AKI in this group of patients occur at 12h post-operative

Conclusions

Serum TIMP-1,3,4, NGAL & procalcitonin can be used as a predictive test to identify patients at increased risk of AKI very early 4h post CPB before rising of serum creatinine. TIMP-2 increase was delayed 12h post-operative as it may not be an early marker in non-septic patients. Procalcitonin is not always considered as a marker of sepsis. Most of AKI occurred at 12h post-operative. Neither CPB time nor UOP has statistical significance in diabetic patients undergoing CABG.

	Total (n = 40)	No AKI (n=27)	AKI (n=13)	p
Sex				
Male	30 (75%)	20 (74.1%)	10 (76.9%)	**1.000**
Female	10 (25%)	7 (25.9%)	3 (23.1%)	
Age (years)	57.27 ± 7.74	56.11 ± 7.72	59.69 ± 7.48	**0.173**
Cross clamping time	77.5 (30 - 145)	75 (30 - 145)	90 (50 - 120)	**0.340**
CPB Time	120 (60 - 300)	120 (60 - 240)	120 (80 - 300)	**0.342**
Short duration (<118min)	13 (32.5%)	11 (40.7%)	2 (15.4%)	**0.157**
Long duration (>118min)	27 (67.5%)	16 (59.3%)	11 (84.6%)	
HTN	40(100.0%)	27(100.0%)	13(100.0%)	-
DM	40(100.0%)	27(100.0%)	13(100.0%)	-
COPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
CKD	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Heavy smoker	30(75.0%)	20(74.1%)	10(76.9%)	**1.000**
Previous heart surgery	1(2.5%)	0(0.0%)	1(7.7%)	**0.325**
LV EF%	60(38 – 75)	62(38 – 75)	62(40 – 74)	**0.612**
Length of ICU stay in days	3(2 – 18)	3(3 – 7)	7(2 – 18)	**0.007***
HCV	2(5.0%)	0(0.0%)	2(15.4%)	**0.100**
CABG + valve replacement	2(5.0%)	0(0.0%)	2(15.4%)	**0.100**
APACHE score on day one	5(1 – 12)	4(1 – 11)	9(2 – 12)	**0.002***
Mortality score %	8(4 - 15)	4(4 – 15)	8(4 – 15)	**0.002***
24h urinary proteins	130(30 – 170)	130(30 – 140)	130(50 – 170)	**0.036***
UOP	3034.2 ± 1156.5	3171.1 ± 1265.8	2750± 863.13	**0.287**
Input	3100(1200–5550)	3000(1700–4800)	3600(1200 – 5550)	**0.036***
*: Statistically significant at p ≤ 0.05				

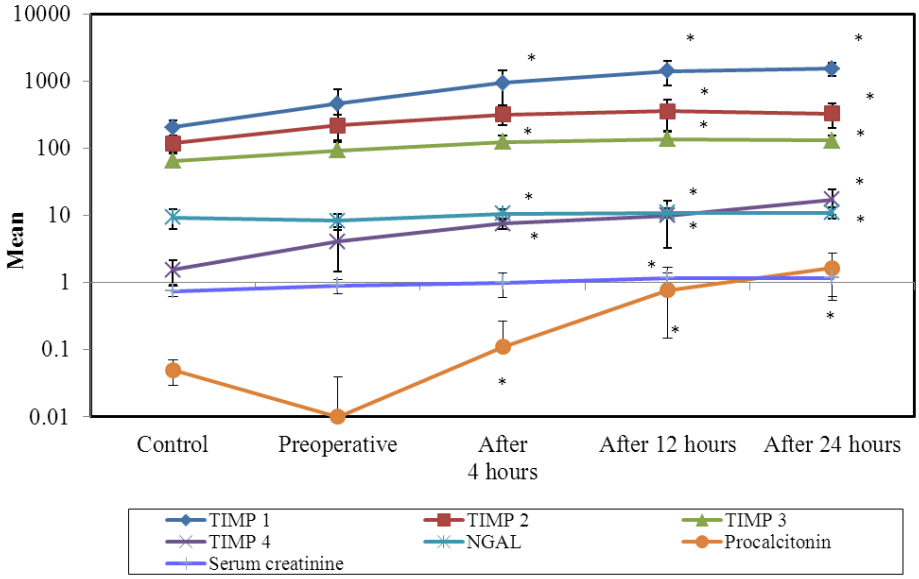
Table 1: Baseline characteristics of the study.

Qualitative data were described using number and percent and was compared using Fisher Exact for Chi square test .Normally quantitative data was expressed as Mean ± SD and compared using student t-test. Abnormally distributed data was expressed using Median (Min. – Max.) and was compared using Mann Whitney test.

	AKI (n=13)	Delta change (n=13)	% of change (n=13)	P_{pre}
Serum creatinine				
Preoperative	0.91 ± 0.22			
Postoperative (after 4 hours)	1.0 ± 0.40	↑0.09 ± 0.26	↑7.77 ± 25.31	**0.291**
Postoperative (after 12 hours)	1.18 ± 0.52	↑0.28 ± 0.37	↑27.62 ± 36.18	**0.046***
Postoperative (after 24 hours)	1.18 ± 0.56	↑0.27 ± 0.46	↑30.47 ± 50.05	**0.064**

NGAL				
Preoperative	8.43 ± 2.23			
Postoperative (after 4 hours)	10.69 ± 1.92	↑2.26 ± 2.27	↑33.32 ± 36.56	**0.022***
Postoperative (after 12 hours)	10.98 ± 1.79	↑2.55 ± 2.44	↑38.03 ± 39.37	**0.016***
Postoperative (after 24 hours)	11.0 ± 2.12	↑2.57 ± 2.51	↑37.58 ± 38.48	**0.019***
Procalcitonin				
Preoperative	0.01 ± 0.03			
Postoperative (after 4 hours)	0.11 ± 0.16	↑0.10 ± 0.16	↑1003.4 ± 1990.9	**0.001***
Postoperative (after 12 hours)	0.77 ± 0.62	↑0.76 ± 0.60	↑8396.6 ± 5800.6	**0.001***
Postoperative (after 24 hours)	1.66 ± 1.11	↑1.65 ± 1.11	↑18439.8±13105.3	**0.001***
TIMP 1				
Preoperative	468.97 ± 297.09			
Postoperative (after 4 hours)	956.88 ± 519.33	↑487.92 ± 587.86	↑198.29 ± 213.22	**0.007***
Postoperative (after 12 hours)	1426.33 ± 565.31	↑957.37 ± 625.24	↑398.40 ± 443.64	**0.002***
Postoperative (after 24 hours)	1548.88 ± 330.35	↑1079.9 ± 403.82	↑451.98 ± 484.96	**0.001***
TIMP 2				
Preoperative	222.43 ± 96.42			
Postoperative (after 4 hours)	322.86 ± 99.30	↑100.43 ± 143.56	↑80.57 ± 104.71	**0.055**
Postoperative (after 12 hours)	359.45 ± 177.99	↑137.02 ± 191.81	↑95.95 ± 128.37	**0.016***
Postoperative (after 24 hours)	333.13 ± 131.11	↑110.70 ± 164.49	↑96.44 ± 186.54	**0.033***
TIMP 3				
Preoperative	93.17 ± 40.93			
Postoperative (after 4 hours)	125.99 ± 29.38	↑32.82 ± 34.85	↑83.59 ± 147.34	**0.010***
Postoperative (after 12 hours)	137.43 ± 42.95	↑44.26 ± 60.49	↑129.12 ± 255.13	**0.039***
Postoperative (after 24 hours)	131.27 ± 23.76	↑38.09 ± 48.11	↑131.17 ± 306.30	**0.019***
TIMP 4				
Preoperative	4.13 ± 2.64			
Postoperative (after 4 hours)	7.66 ± 1.38	↑3.53 ± 2.47	↑176.46 ± 181.95	**0.001***
Postoperative (after 12 hours)	9.96 ± 6.66	↑5.82 ± 6.34	↑250.23 ± 288.21	**0.006***
Postoperative (after 24 hours)	17.49 ± 7.25	↑13.35 ± 6.89	↑550.87 ± 702.52	**0.001***
P_{Pre}: p value for comparing between pre operative with each other period				

Table 2: Delta change of different AKI biomarkers along different periods



*: Significant values with preoperative

Figure 1: Comparison between TIMP 1, TIMP 2, TIMP 3, TIMP 4, NGAL, procalcitonin and serum creatinine according to different periods.

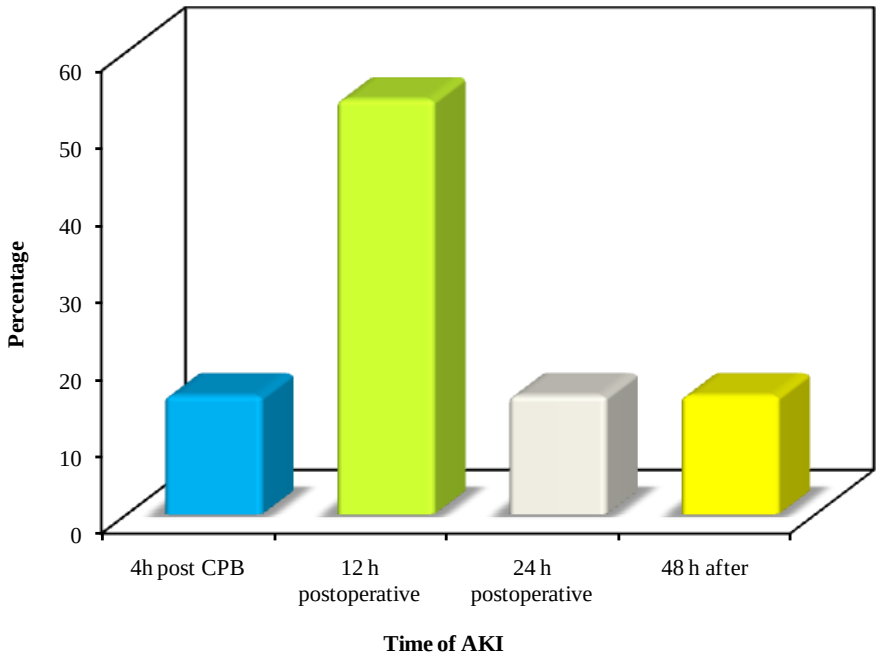


Figure 2: Distribution of the cases according to Time of AKI (n=13).

References

1. Wijeysundera DN, Karkouti K, Dupuis JY. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. JAMA 2007; 297: 1801–9.
2. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998; 104(4):343-8.
3. Lassnigg A, Schmidlin D, Mouhieddine M. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 2004; 15: 1597–605.
4. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006; 1: 19–32.
5. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiological principles. Intensive Care Med 2004; 30: 33–7.
6. Wagener G, Jan M, Kim M. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology 2006; 105: 485–91.
7. Tang IY, Murray PT. Prevention of preoperative acute renal failure: what works? Best Pract Res Clin Anaesthesiol 2004; 18: 91–111.
8. Yang QH, Liu DW, Long Y, Liu HZ, Chai WZ, Wang XT. Acute renal failure during sepsis: potential role of cell cycle regulation. J Infect 2009; 58: 459–64.
9. Devarajan P. Update on mechanisms of ischemic acute kidney injury. J Am Soc Nephrol 2006; 17: 1503–20.
10. Rodier F, Campisi J, Bhaumik D. Two faces of p53: aging and tumor suppression. Nucleic Acids Res 2007; 35: 7475–84.
11. Boonstra J, Post JA. Molecular events associated with reactive oxygen species and cell cycle progression in mammalian cells. Gene 2004; 337: 1–13.
12. Kashani K, Al-Khafaji A, Ardiles T. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013; 17: R25.
13. Cremer J, Martin M, Redl H. Systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg 1996; 61: 1714-20.
14. Struber M, Cremer JT, Gohrbandt B. Human cytokine responses to coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 1999;68:1330-5.
15. Meersch M, Schmidt C, Van Aken H. Urinary TIMP-2 and IGFBP7 as Early Biomarkers of Acute Kidney Injury and Renal Recovery following Cardiac Surgery. PLoS One 2014;9(3):e93460.
16. Grayson AD, Khater M, Jackson M, Fox MA. Valvular heart operation is an independent risk factor for acute renal failure. Ann Thorac Surg 2003;75:1829–35.

17. Dent CL, Ma Q, Dastrala S. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care 2007; 11: R127.
18. Haase-Fielitz A, Bellomo R, Devarajan P. The predictive performance of plasma neutrophil gelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. Nephrol Dial Transplant 2009; 24: 3349-54 .
19. Parikh CR, Coca SG, Thiessen-Philbrook H. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 2011; 22: 1748–57.
20. Haase M, Bellomo R, Devarajan P. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009; 54: 1012–24.
21. Lecharny JB, Khater D, Bronchard B. Hyperprocalcitoninemia in patients with preoperative myocardial infarction after cardiac surgery. Crit Care Med 2001; 29:323-5.
22. Meisner M, Rauschmayer C, Schmidt J. Early increase of procalcitonin after cardiovascular surgery in patients with postoperative complications. Intensive Care Med 2002; 28:1094-102.
23. Dörge H, Schondube FA, Dorge P, Seipelt R, Voss M, Messmer BJ. Procalcitonin is a valuable prognostic marker in cardiac surgery but not specific for infection. Thorac Cardiovasc Surg 2003; 51:322-6.
24. Adamik B, Kubler-Kielb J, Golebiowska B, Gamian A, Kubler A. Effect of sepsis and cardiac surgery with cardiopulmonary bypass on plasma level of nitric oxide metabolites, neopterin, and procalcitonin: correlation with mortality and postoperative complications. Intensive Care Med 2000; 26:1259-67.
25. Rothenburger M, Markewitz A, Lenz T. Detection of acute phase response and infection. The role of procalcitonin and C-reactive protein. Clin Chem Lab Med 1999; 37: 275-9.
26. Price PM, Safirstein RL, Megyesi J. The cell cycle and acute kidney injury. Kidney Int 2009; 76: 604–13.
27. Gunnerson KJ, Shaw AD, Chawla LS. TIMP2•IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. The J Trauma Acute Care Surg 2016;80(2):243-9.
28. Cuartero M, Betbesé A, Sabater J, Ballús J, Ordóñez J. Urinary TIMP2 and IGFBP7 as early biomarkers of acute kidney injury in septic and nonseptic critically ill patients. Crit Care 2015;19 (Suppl 1):P288.

Citation: ***Shafie R, Saad NLM, Elgohary IE, Hegab SESM, Baddour NM, Adam AG (2019) Time Trend of Ideal Biomarker of Acute Kidney Injury in Diabetic Patients Undergoing Coronary Artery Bypass Graft (CABG). Advn Endoc and Diabet: AEAD-105.***