ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Early Prediction Biomarkers of Contrast Induced Acute Kidney Injury-A single Center experience

Mabrouk I. Ismail[1*], and Lamiaa A. Mohamed[2].

1. Department of Nephrology, Zagazig Faculty of Medicine, Zagazig University, Egypt.
2. Department of Clinical Pathology, Zagazig University hospital, Zagazig University, Egypt.

Manuscript Info

Manuscript History:

Received: 14 January 2016
Final Accepted: 26 February 2016
Published Online: March 2016

Key words:
L-FABP; Cystatin C; AKI; Contrast-induced nephropathy; High osmolar contrast.

Corresponding Author

Mabrouk I. Ismail.

Abstract

Background: Contrast-induced acute kidney injury (CI-AKI) representing the third most common cause of hospital acquired AKI. As serum creatinine (SCr) is an unreliable indicator of acute changes in renal function thus the need for early sensitive biomarkers to detect AKI of utmost value. Urinary Liver type fatty acid binding protein (uL-FABP) and plasma Cystatin C (CysC) is a newly emerging ones.

Objective: To evaluate the significance of urinary L-FABP and plasma Cystatin as early prediction biomarkers of contrast induced AKI.

Patients and methods: This study comprised a total of 33 patients divided into two main groups; Group I: 16 patients underwent coronary angiography for diagnostic and therapeutic purposes and Group II: 17 patients underwent computerized tomography (CT) for various purposes using intravenous (IV) contrast (high osmolar) media (CM). Then the patients reclassified into 2 new subgroups; AKI and non AKI groups accordinting to the change in SCr 24 hours (hs) after CM administration. Full clinical examination, routine investigations and estimation of urinary L-FABP and p- CysC were done.

Results: the basal value of urinary L-FABP and p-CysC was significantly higher in AKI versus non AKI groups. AUC of u L-FABP = 0.837 (95%CI; 0.673 – 1.001); AUC of p-CysC = 0.742 (95%CI; 0.600 – 0.925). Six hs post contrast, both p- CysC and urinary L-FABP showed a highly statistically significant elevation at 6 hours in AKI group as compared to non AKI group, while there was no statistically significant difference in SCr, which showed significant elevation only after 24 hours. AUC of urinary L-FABP =1 (95%CI; 1 – 1); AUC of p-CysC =1 (95%CI; 1 – 1).There was significant positive correlation between uL-FABP and both p-CysC and amount of IV contrast ($r=0.59$, $p<0.05$ &$r=0.53$, $p<0.05$) respectively, negative correlation regarding estimated glomerular filtration rate (eGFR) ($r=-0.52$, $p<0.5$), whereas no significant correlations regarding SCr. Twenty four hs post contrast ,there was significant positive correlations between uL-FABP and each of p- CysC, contrast volume and SCr($r=0.61$, $p<0.05$, $r= 0.56$,$p<0.05$, &$r=0.58$, $p<0.05$) respectively , but negative correlation regarding eGFR($r=-0.52$, $p<0.05$) in AKI group.

Conclusion: Urinary L-FABP and plasma Cystatin C can be considered as predictive biomarkers of contrast induced nephropathy (AKI), basally before contrast exposure and as early as six hours post contrast administration instead of serum creatinine, clearly, as these biomarkers levels start to rise earlier and in advance before any significant change in serum creatinine.

.

Introduction

AKI is defined by an abrupt decrease in kidney function. It is a broad clinical syndrome encompassing various etiologies, including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and vasculitic renal diseases); non-specific conditions (e.g., ischemia, toxic injury); as well as extra renal pathology (e.g., prerenal azotemia, and acute post renal obstructive nephropathy) [1].

The incidence of hospital acquired renal failure is on the rise and contrast induced nephropathy (CIN) is the third most common cause contributing to approximately 11% of hospital acquired renal failure [2]. CI-AKI, previously known as CIN is a syndrome of acute renal dysfunction diagnosed after the intravascular injection of contrast media (CM) [3].The new KDIGO definition of AKI, unify the clinical and research language around this common problem. This definition states that AKI is defined as any of the following: an increase in SCr of ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hs, an increase in SCr to ≥1.5 times the baseline that is known or presumed to have occurred within the prior 7 days, or urine volume < 0.5 ml/kg/h for 6 h [1]**.**

Serum creatinine, the currently accepted 'gold standard' to diagnose AKI, is a delayed and inadequate marker of acute changes in renal function. In AKI, SCr elevation that reflects the development and severity of kidney damage does not occur until days after renal tubular injury has begun [4]; thus, there is a need for new specific biomarkers that identify kidney injury early and replace SCr [5].

Fatty acid binding proteins are small (15 kDa) cytoplasmic proteins abundantly expressed in tissues with active fatty acid metabolism [6]. The liver type fatty acid binding protein is a newly emerging biomarker that has antioxidant properties, and enhanced expression in proximal tubule cells and subsequent urinary excretion are known to reflect the presence of tubular injury [7]. Urine L-FABP shows promise as an early, accurate biomarker of AKI [8]. Cystatin C (CysC) is a 13-kD cysteine protease inhibitor that is synthesized in all nucleated cells at a steady state. It is freely filtered by glomerulus, not secreted by renal tubules, and completely metabolized at the level of the renal tubules [9]**.** Unlike SCr, non-renal variables (e.g., age, gender, and muscle mass) do not seem to have much effect on CysC levels and many investigations have demonstrated that serum levels reflect GFR better than SCr. [10]**.**

Serum and urinary, CysC measurements are superior to conventional biomarkers, such as urine output, urine protein, urine albumin, blood-urea nitrogen and SCr [11**]**. In intensive care setting, a 50% increase in serum CysC predicted AKI one to two days before rise in SCr [12].This study was carried out to evaluate the significance of urinary L-FABP and plasma Cystatin C as early prediction biomarkers of contrast induced AKI.

Patients and Methods

Study design and population

This cross sectional study carried out in collaboration between Nephrology, Cardiology, Radiology and Clinical Pathology Departments, Zagazig University hospital, during the period from Jan. 2013 to June 2014, in accordance with Helsinki Declaration and the institutional review board of our faculty of medicine, informed written consent was obtained.

Eligible participants included a total 33 patients classified into two main groups:
Group I: included 16 patients (10 males and 6 females) with age ranged from 32 to 55 years, mean age of 42.44 ± 6.45ys, their basal SCr level ranged from 0.7 to 1.1 mg/dl with mean SCr of 0.91±0.16 mg/dl.
These patients underwent coronary angiography for diagnostic and therapeutic purposes using IV (high-osmolar) contrast agent ioxithalamate (Telebrix).
Group II : included 17 patients (9 males and 8 females) ,age ranged from 26 to 50 ys , a mean of 39.05 ± 6.7 ys, their basal SCr ranged from 0.7 to 1.1 mg/dl , mean SCr of 0.87±0.17 mg/dl
These patients underwent CT for various purposes including CT chest (5 patients), CT brain (7 patients), Abdomino pelvic CT (5 patients), using the same IV contrast.
After the process of contrast administration the patients were subdivided into new 2 groups according to SCr.
AKI group A: SCr elevated either by 25% of the basal level or by 0.3 mg/dl above basal level after 24 hours. It included 11 patients (7 males and 4 females), age ranged from 35 to 55 ys, mean age of 42 ± 5.9 ys, BMI ranged from 23 to 27 with a mean BMI of 25.3 ± 2.1. kg/meter.^{2}

Non AKI group B: No rise of SCr level more than 25% of basal level or more than 0.3 mg/dl after 24 hs. It included 22 patients (15 males and 7 females), age ranged from 26 to 50 ys, mean age of 40.04 ± 7.1 ys, BMI ranged from 24 to 27 with mean BMI of 25.5 ± 1.4. kg/meter.^{2}

Exclusion criteria
Participants excluded from the study if had a history of; hepatic diseases, renal diseases (SCr > 1.4 mg/dl), diabetes mellitus, hypertension, autoimmune diseases, sepsis, inflammatory conditions, and malignancy.

All patients included in this study are subjected to the following

Thorough clinical examination with special stress on history of renal diseases. BMI was calculated according to the following formula: BMI=body weight {kg}/ height {in square meter}

Laboratory measurements
Peripheral venous blood samples taken subjected to hematological and biochemical analysis including: Complete blood picture(CBC) [hemoglobin (HB)(g/dl), hematocrit % (HCT)],ESR, uric acid, fasting blood sugar(FBS), serum albumin, BUN, SCr, urinalysis, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP),Calcium(Ca),phosphorus(P),bleeding time , clotting time, electrolytes(sodium &Potassium) , lipid profile according to the standard methods used in routine clinical laboratory**.** Estimation of GFR using MDRD equation,GFR (mL/min/1.73 m2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) [13]. Pelvi-abdominal US, using Acuson 128XP 110 to evaluate kidney size, echogenicity, and cortical thickness and transthoracic echocardiography also done. Specific investigations as Urinary levels of L-FABP in spot urine samples were measured by ELISA before contrast, 6 hours and 24 hours after contrast administration. ELISA [BIOVENDOR Cystatin C is an Enzyme Immunoassay for quantitative determination of Cystatin C levels in human plasma or serum [14].

Statistical analysis
Data were analyzed with SPSS version 15.0 (statistical package for Social Science, Chicago, IL). Quantitative data were expressed as mean ± standard deviation (SD) or standard error (SE). SE=SD/square root of patients number which was used in case of big SD.Also data were analyzed by independent sample, paired t test and one way analysis of variance (ANOVA). While qualitative data were expressed as number and percentage and analyzed by Chi square (χ^2) test. Correlation was done using Pearson correlation test. The receiver operating characteristic (ROC) curve and 95% confidence interval (CI) was performed to determine cutoff values for studied biomarkers. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined. P value considered significant if <0.05 and highly significant if <0.001.

Results

Demographic and laboratory data of studied groups (I & II) shown in table 1. There was significant increase in mean value of amount of IV contrast in Group I (108.12±40.4ml) as compared to Group II(73.5±19.9 ml) (P<0.05), but no significant differences found regarding age, sex, BMI, HB ,basal SCr (mg/dl), basal uL-FABP and basal p- CysC (mg/l),(P>0.05).

Table 1: Demographic and Laboratory data of studied groups.

Variable		Group I Coronary Angiography n=16 / Mean±SD	Group II CT With Contrast n=17 / Mean±SD	t-test	P
Age (ys)		42.44±6.45	39.05±6.7	t= 1.47	0.15
Sex	Male No/%	10 (62.5%)	9 (52.9%)		
	Female No/%	6 (37.5%)	8 (47.1%)	χ^2= 0.31	0.57
HB(g/dl)		13.04±0.5	13.02±0.4	t= 0.12	0.91
BMI (Kg/m^2)		25.3±1.9	25.5±1.5	t= 0.49	0.69
Contrast volume (ml)		108.12±40.4	73.5±19.9	t= 3.15	0.004
Basal SCr (mg/dl)		0.91±0.16	0.87±0.17	t= 0.3	0.76
Basal uL-FABP(ng/ml)		10.12±3.34	9.35±3.12	t= 0.68	0.49
Basal p- CysC(mg/l)		0.875±0.078	0.888±0.082	t= 0.45	0.65
Frequency AKI / No		37.5% / n= 6	29.4% / n= 5	X^2= 0.24	0.62

Post contrast administration , clinical and laboratory data of A -AKI & B -Non AKI groups shown in table2. There was significant difference regarding amount of IVcontrast, basal uL-FABP, and basal p- CysC. (114.09 ±47.89 ml,p=0.005; 12.18±3.06, p= 0.001; 0.94±0.06, p=0.013) respectivelly.Whereas, no significant differences regarding age, BMI, HB, basal SCr.

Table 2: Clinical and Laboratory data of post contrast groups.

Variable	Group A- AKI n=11 Mean±SD	Group B -Non AKI n=22 Mean±SD	t-test	P
Age (ys)	42±5.9	40.04±7.1	0.78	0.43
BMI (Kg/m^2)	25.3±2.1	25.5±1.4	0.47	0.76
HB (g/dl)	12.96±0.52	13.06±0.47	0.57	0.56
Contrast volume (ml)	114.09±47.89	78.4±19.96	3.04	0.005
Basal SCr (mg/dl)	0.92±0.15	0.86±0.16	1.65	0.11
Basal uL-FABP (ng/ml)	12.18±3.06	8.5±2.5	3.66	0.001
Basal p- CysC (mg/l)	0.94±0.06	0.89±0.12	2.6	0.013

Post contrast administration ,time course of studied biomarkers among AKI versus non AKI patients shown in table 3, and illustrated in figures (1, 2, 3); there was a highly significant increase along time course for urinary L-FABP , p- CysC, and SCr in AKI patients.($p<0.001$).Whereas in non AKI patients, there was a highly significant increase along time course for urinary L-FABP) ($p<0.001$), while no significant difference along time course for p-CysC or SCr.

Table 3 : Time-course of studied markers among AKI versus non AKI by ANOVA & LSD

Patients	Biomarker	Basal	6hs	24hs	F	P
AKI	uL-FABP (ng/ml)	12.18±3.06	29.27±5.49 a	63.72±9.35 ab	244.563	0.001
	p- CysC (mg/l)	0.94±0.06	1.352±0.065 a	1.611±0.053 a	456.716	0.001
	SCr(mg/dl)	0.92±0.15	0.93±0.15	1.46±0.15 ab	162.303	0.001
Non AKI	u L-FABP (ng/ml)	8.5±2.5	11.9±3.85 a	14.59±4.86 ab	45.010	0.001
	p- CysC (mg/l)	0.89±0.12	0.867±0.089	0.873±0.11	1.69	0.19
	SCr (mg/dl)	0.86±0.16	0.87±0.11	0.870±0.15	2.36	0.11

a=significance in relation to basal reading b= significance in relation to 6hs post

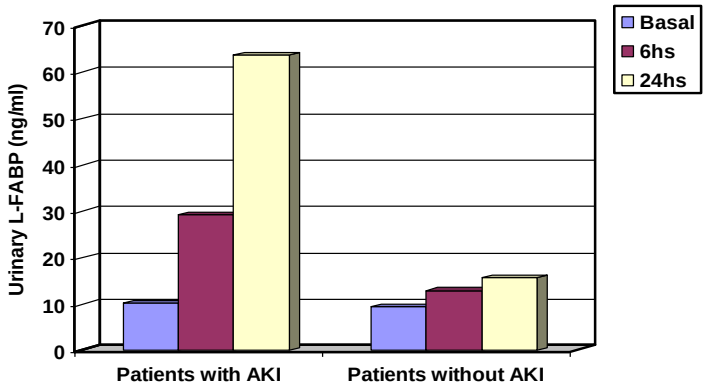

Figure1: Time-course of uL-FABP among patients with AKI versus non AKI.

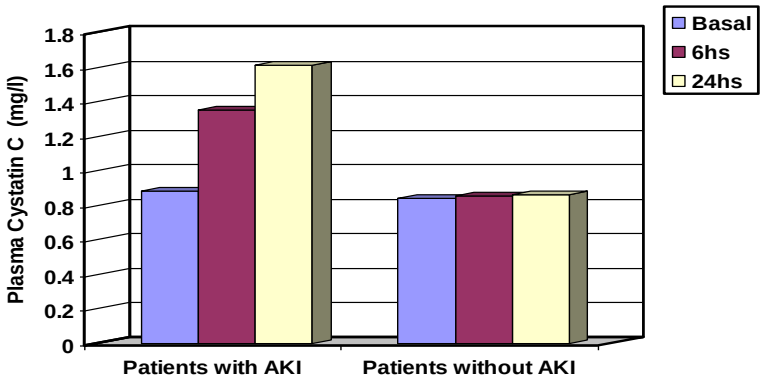

Figure2: Time-course of p- CysC among patients with AKI versus non AKI.

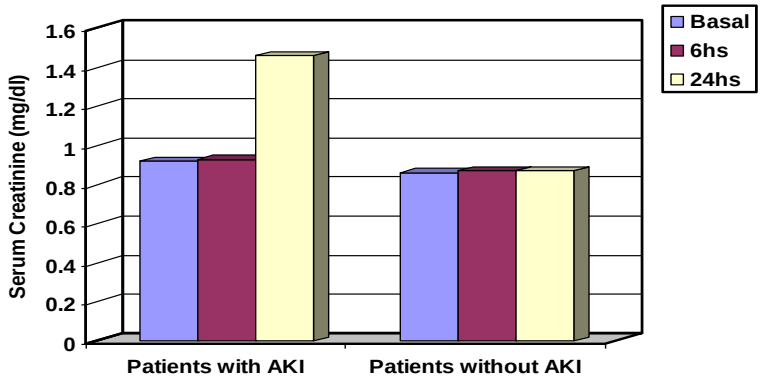

Figure 3: Time-course of SCr among patients with AKI versus non AKI.

Six hs post contrast, table 4; demonstrated significant positive correlations between uL-FABP and p- CysC and amount of IV contrast , similarly on comparing p- CysC.; negative correlation regarding eGFR ; whereas non-significant correlations regarding SCr in AKI group.

Table 4: Correlation of uL-FABP and p- CysC, 6 hs post contrast in AKI versus non AKI groups.

uL-FABP (ng/ml) versus	p- CysC (mg/l) * versus	AKI				Non AKI			
		r	p	r*	p*	r	p	r*	p*
1-p- CysC	u L-FABP	0.59	<0.05	0.59	<0.05	0.39	NS	0.35	NS
2-Contrast volume	contrast volume	0.53	<0.05	0.55	<0.05	0.33	NS	0.35	NS
3-eGFR (ml/min)	eGFR(ml/min)	-0.52	<0.05	-0.57	<0.05	-0.32	NS	-0.39	NS
4-SCr (mg/dl)	SCr	0.28	>0.05	0.34	>0.05	0.18	NS	0.28	NS

24 hs post contrast, tables 5, demonstrated significant positive correlations between uL-FABP and p- CysC, amount of IV contrast and SCr; but negative correlation regarding eGFR in AKI group. Similar correlations, obtained on comparing p- CysC with previous parameters.

Table 5: Correlation of uL-FABP and p- CysC, 24 hs post contrast in AKI & non AKI groups.

uL-FABP (ng/ml) versus	p- CysC (mg/l) * versus	AKI				Non AKI			
		r	p	r*	p*	r	p	r*	p*
1-24hs p- CysC	u L-FABP	0.61	<0.05	0.61	<0.05	0.37	NS	0.37	NS
2-Contrast volume	Contrast Vol.	0.56	<0.05	0.59	<0.05	0.32	NS	0.32	NS
3-eGFR (ml/min)	eGFR(ml/min)	-0.52	<0.05	-0.63	<0.05	-0.12	NS	-0.35	NS
4-SCr (mg/dl)	SCr(mg/dl)	0.58	<0.05	0.59	<0.05	0.31	NS	0.23	NS

The validity at the basal values and six hs post contrast of studied biomarkers as predictors of AKI, showed in table 6. Basally, setting a cutoff value of 10.5 (ng/dl) for u-FABP yielded a sensitivity and specificity of 81.8% and 77.3% respectively with positive predictive value (PPV) of 64.3% and negative predictive value (NPV) of 89.5%; whereas, setting a cutoff value of 0.875 (mg/l) for p- CysC yielded a sensitivity and specificity of 81.8% and 59.1% respectively with PPV of 50% and NPV of 86.7%. Whereas, at six hs post contrast, setting a cutoff value of 17.5 (ng/dl) for urinary L-FABP yielded a sensitivity and specificity of 100% and 90.9% respectively with PPV of 84.6% and NPV of 100%; whereas setting a cutoff value of 1.025 (mg/l) for p- CysC yielded a sensitivity and specificity of 100% and 95.5% respectively with PPV of 91.7% and NPV of 100%.

Table 6: Validity of studied markers as predictors for AKI 6 hours after contrast administration.

Time	Biomarker	Cutoff value	Sensitivity	Specificity	PPV	NPV
Basal values	u L-FABP(ng/ml)	10.5 ng/dl	81.8%	77.3%	64.3%	89.5
	p- CysC (mg/l)	0.875 mg/l	81.8%	59.1%	50.0%	86.7
6 hs post contrast	u L-FABP(ng/ml)	17.5 ng/dl	100%	90.9%	84.6%	100%
	p- CysC (mg/l)	1.025 mg/l	100%	95.5%	91.7%	100%

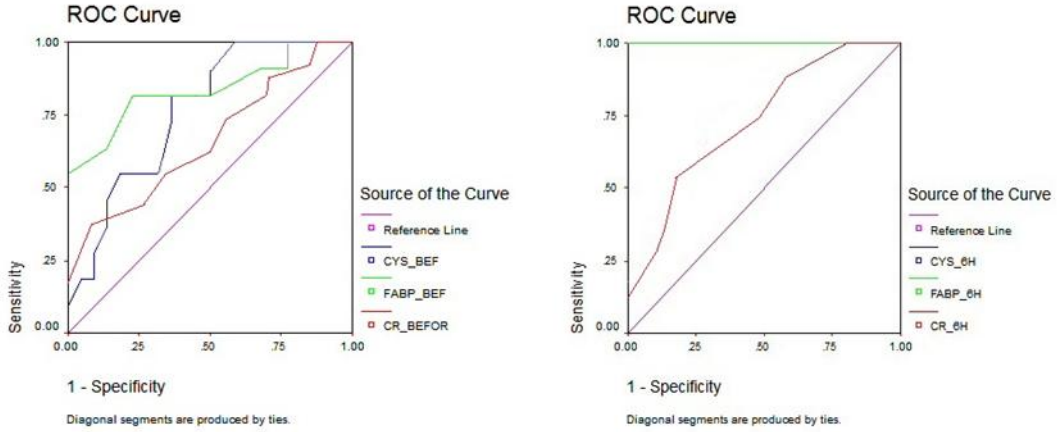

Figure 4&5: ROC curve of p- CysC, uL-FABP, and SCr , basal and 6 hs post contrast.

Discussion

Contrast media (CM) are increasingly used in diagnostic and interventional procedures. This results in raising the incidence of contrast induced nephropathy (CIN) [15]. Acute renal injury is typically diagnosed by measuring serum creatinine. Unfortunately, SCr is an unreliable indicator during acute changes in kidney function [16]. In intensive care setting, a 50% increase in p- CysC predicted acute kidney injury 1 to 2 days before the rise in SCr [17].

In this study regarding demographic and some laboratory parameters, no significant differences found regarding age, sex, BMI, HB, basal SCr, uL-FABP and p- CysC between groups I &II; while there was a statistically significant difference regarding amount of IVcontrast media, due to nature of both procedures; which results in higher frequency of AKI in group I (37.5%) as compared to group II (29.4%) with a relative risk (RL) of 1.28. After contrast administration , patients were reclassified according to occurrence of AKI, into other two groups : Group A -AKI, 11 patients experienced elevation of SCr either by 25% of basal level or by 0.3 mg/dl above basal level after 24 hs post contrast and group B -Non AKI, 22 patients who didn't experience an elevation of SCr. There was about 33 % of patients (11) fulfilled the criteria of contrast nephropathy with more cases in groups I (6 patients, 54.5%) than group II (5 patients, 45.5%).

In this study on comparing the baseline criteria of the new 2 groups , the amount of contrast administered, basal p-CysC and basal u L-FABP were significantly higher in AKI group as compared to non-AKI group, this implies that each of these parameters has a predictive value for the occurrence of contrast nephropathy . Whereas, there was no

significant difference regarding age, BMI, HB, and Basal SCr, in agreement with Nakamura et al [18], who reported that before angiography, uL-FABP levels were significantly high in CIN group (18.5 ±12.8 microg/g Cr), than non CIN (7.4 ±4.4 microg/g Cr; $P < 0.01$) or healthy volunteers (5.4 ± 4.4 microg/g Cr; $P < 0.01$); whereas SCr and Cr. clearance slightly differed.

Our study showed a statistically highly significant differences between 6hs and 24hs post contrast reading of u L-FABP and p- CysC as compared to the basal one, in AKI group. Whereas no significant diffferancece found regarding SCr at 6hs post contrast, but there was highly significant increase of SCr after24hs in agreement with the results obtained by Ozdemir et al. [19].

Surpassingly, there was a statistically highly significant differences regarding uL-FABP in Non AKI group at 6h and 24hs post contrast as compared to their basal levels; whereas no signifant difference regarding both SCr and p- CysC ,which could be explained by the fact that u L-FABP expression in proximal tubules may be up regulated under tubular stress (e.g., tubular ischemia &toxic insult), and excretion of uL-FABP from proximal tubules may increase before occurrence of cellular structural damage [20], in agreement with Kato et al.,[21],who found that uL-FABP levels were significantly increased after coronary angiography, suggesting transient proximal tubular damage by contrast medium, although SCr were not useful for predicting or detecting CIN and in agreement with Bachorzewska-Gajewska et al.,[22] who reported 25 patients underwent PCI; none of them fulfilled the criteria of CIN, despite the highly significant elevation of uL-FABP as early as 4 hs post contrast (25.90±21.93 pg/ml) and 24 hs (33.49±26.41 pg/ml) as compared to a baseline value of (3.76±1.52 pg/ml).

Also, similar result obtained by Ohta et al., [23], who reported that in patients without CIN, on the day following angiography, urinary excretion of L-FABP was markedly increased by 578 %, then swiftly returned to basal level on the second day, but no increase in SCr. These results suggest that urinary excretion of L-FABP, sensitively reflects injurious stress on renal tubules. Contrary to these findings, Nakamura et al., [18], reported that one and two days post contrast, uL-FABP levels in CIN group increased significantly to 46.8 ± 30.5 μg/g Cr and 38.5 ± 28.5 μg/g Cr, respectively; while little change in non CIN group.

In this study there was highly significant statistical difference regarding both u L-FABP and p- CysC in AKI group in comparison to Non AKI group at 6hs and 24hs after contrast. While there was no statistically significant difference as regard SCr at 6hs, but, there was highly significant statistical difference at 24h after contrast. These results agreed with Manabe et al., [24], who confirmed that SCr and u L-FABP levels in CI-AKI group were significantly higher as compared to non-CI-AKI group, on days 1 and 2 after contrast, and study reported by Shaker et al., [25], who found that p- CysC and u NGAL could be valuable in early detection CIN, and p- CysC increased significantly only 24 hs post contrast not at 4 hs.

In contrary to these findings, conflicting results, regarding the time course of L-FABP, were obtained by Malyszko et al., [26],who conducted his study on 140 patients (70 , type 2 diabetes mellitus (DM) in comparison to 70 non DM) with normal SCr, undergoing cardiac catheterization; they evaluated SCr, urinary NGAL, p- CysC, urinary KIM-1, IL- 18, and u L-FABP before and 2, 4, 8, 24, and 48 hs after contrast, and observed a significant rise in L-FABP 24 and 48 hrs. after PCI in both groups without any significant changes in 2–8hs (in diabetics: baseline=6.39 (0.96–7.21) pg/ml, 8h value=10.43 (2.31–51.33) pg/ml, 24h value=18.92 (5.43–112.12) pg/ml; in non-diabetics: baseline=5.32 (0.64–5.43) pg/ml, 8h value=6.38 (0.88–22.27) pg/ml, 24h value=16.01 (4.17–98.45) pg/ml); on the other hand, p- CysC increased significantly after 8 hs, reaching its peak 24 hs in both groups. In patients with CIN, p- CysC was higher only at 8 and 24 hs after contrast, whereas uL-FABP was significantly higher only after 24 hs.

Another surprise, Ribichini et al., [27], claimed that no additional diagnostic value of p- CysC over SCr in determination of CIN, they found, that p- CysC levels did not reach a statistically significant differences in CIN versus non CIN groups, up to 48 hs, while SCr was significantly higher in CIN group only after 48 hs. Moreover, they found that absolute changes in SCr proved more accurate than p- CysC for predicting CIN at an early stage (12 hs after renal insult). The change in SCr at 12 hs from baseline was a strong predictor of CIN, while p- CysC at 12 hs was not predictive of CIN.

In this study , the six hs post contrast profile, demonstrated a significant positive correlations between uL-FABP each of p- CysC and amount of IV contrast , similarly on comparing p- CysC with uL-FABP & contrast volume; negative correlation regarding eGFR ; whereas non-significant correlations regarding SCr in AKI group. Whereas,

24hs post contrast profile demonstrated a significant positive correlations between uL-FABP and each of p- CysC, amount of IV contrast and SCr; but negative correlation regarding eGFR in AKI group. Similar correlations obtained on comparing p- CysC with previous parameters.

In our study, it was found that basal values of both p- CysC and L-FABP were equally sensitive as predictors of CI-AKI before contrast administration (sensitivity= 81.8%), however, L-FABP was more specific than p- CysC at cutoff values of (0.875 mg/l for p- CysC and 10.5 ng/ml for L-FABP); while combined p- CysC and L-FABP had higher sensitivity and less specificity than either one of them (sensitivity=90.9%; specificity=45.5%) as predictors of CN before exposure.

AUC of basal uL-FABP = 0.837 (95%CI; 0.673 – 1.001), indicating good performance as a predictor for CIN before contrast exposure; basal p- CysC had a fair predictive ability ,while contrast volume had an AUC of =0.812, indicating a also good predictive of CIN. Whereas basal SCr was a poor predictor of CIN with AUC = 0.636 (95%CI; 0.470 – 0.856).This results come in agreement with Nakamura et al., [18], who reported that uL-FABP level, the best predictor of CIN among multiple predictive variables. Also in agreement with Manabe et al., [23]; who found AUC (= 0.70 before contrast administration for uL-FABP. Through multivariate analysis, L-FABP level of $\geq$ 24.5 μg/g Cr was found to be an independent predictive biomarker of CI-AKI before contrast administration.

It is worth noting that the aforementioned studies didn't include p- CysC as a biomarker for detection of CIN, in contrast to the conflicting result obtained by Kato et al., [21], who found that p- CysC, at a cut-off level of >1.2 (g/l) exhibited 94.7% sensitivity and 84.8% specificity for detecting CIN, p- CysC level was the only independent variable factor to detect CIN. This could be explained by the small patients number (33 patients) in our study compared to 87 patients in their thesis, all of them underwent coronary angiography with more IV contrast volumes.

The sensitivity and specificity of u L-FABP at 6hs post contrast ,was 100% and 90.9% respectively at a cut-off value of 17.5 ng/ml. p- CysC had similar sensitivity and more specificity (100% and 95.5 % respectively) at a cut-off value of 1.025 mg/l. Combined p- CysC and L-FABP had 100% sensitivity but less specificity of 86.4%. On analyzing ROC curve for biomarkers values at 6hs after contrast, there was an excellent performance of both urinary L-FABP and p- CysC with an AUC for L-FABP = 1 (95% CI, 1-1) and that of p- CysC = 1 (95% CI, 1-1), while AUC of was 0.683, indicating poor ability of SCr for detecting CIN at 6hs post contrast. Logistic regression analysis was done among variables predicting AKI before contrast exposure; urinary L-FABP at a cut-off value of 10.5 ng/ml was the best independent variable factor to predict CI-AKI.

The limitation of our study is it's relatively shortage of cases, thus, the predicted cutoffs for studied biomarkers may be different from that obtained in other wide scale samples studies. So further prospective in depth studies on large sample population, focusing on patient's outcome with determination of mortality independent risk factors, of sure will yield more accurate, conclusive and beneficial results.

Conclusion

Urinary L-FABP and plasma Cystatin C can be considered as predictive biomarkers of contrast induced nephropathy (AKI), basally before contrast exposure and as early as six hours post contrast administration instead of serum creatinine, clearly, as these biomarkers levels start to rise earlier and in advance before any significant change in serum creatinine.

Acknowledgment

The authors acknowledge Prof.Dr. Khaled Lakouz, Prof.of intervention radiology, Prof.Dr. Magdi Abdelsamei, Prof.of intervention cardiology, Prof.Dr. Essam Lotfy and Dr.Aly Shindy, of internal medicine department , for their kind help and unlimited support in this work.

Conflict of interest

No conflict of interest has been declared by the authors.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter. (2012); 2: 1–138.
2. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. Am J Kidney Dis. (2002); 39: 930–936.

3. Ronco C, Stacul F, McCullough PA: Subclinical acute kidney injury (AKI) due to iodine-based contrast media. Eur Radiol (2012); 23(2):319-23.
4. Rosner MH, Okusa MD: Acute kidney injury associated with cardiac surgery. Clin J Am Soc Neprol (2006); 1: 19–32.
5. Hawkins R: New Biomarkers of Acute Kidney Injury and the Cardio-renal Syndrome. Korean J Lab Med. (2011); 31(2): 72–80.
6. De Geus H, Betjes M, Bakker J: Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges. Clin Kidney J. (2012); 5: 102–108
7. Cho E, Yang H, Jo S: The Role of Urinary Liver-Type Fatty Acid-Binding Protein in Critically Ill Patients J Korean Med Sci. (2013); 28(1): 100–105.
8. Moore E, Bellomo R, Nichol A.: Biomarkers of acute kidney injury in anesthesia, intensive care and major surgery: from the bench to clinical research to clinical practice. Minerva Anestesiol (2010); 76(6):425-40.
9. Stevens LA, Coresh J, Schmid CH: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: A pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis (2008); 51: 395–406.
10. McIlroy DR, Wagener G, Lee HT: Biomarkers of acute kidney injury: an evolving domain. Anesthesiology (2010); 112: 998-1004.235
11. Khan E, Batuman V, Lertora JJ: Emergence of biomarkers in nephropharmacology. Biomark Med. (2010); 4(6):805-14
12. Herget-Rosenthal S, Marggraf G, Husing J: Early detection of acute renal failure by serum cystatin C. Kidney Int. (2004); 66:1115-22.
13. Levey AS, Coresh J, Greene T: Chronic Kidney Disease Epidemiology Collaboration Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. (2006); 15; 145(4):247-54
14. Hossain M, Emara M, El moselhi. H: Comparing measures of Cystatin C in human sera by three methods. Am J Nephrology (2009); 29(5): 381 – 391
15. Mehran R Nikolsky E: Contrast-induced nephropathy: Definition, epidemiology, and patients at risk. Kidney International. (2006); 69, S11–S15.
16. Bellomo R, Kellum JA, Ronco C: Defining acute renal failure: physiological principles. Intensive Care Med. (2004); 30:33-37.
17. Herget-Rosenthal S, Marggraf G, Husing J: Early detection of acute renal failure by serum cystatin C. Kidney Int. (2004); 66:1115-22.
18. Nakamura T, Sugaya T, Node K: Urinary excretion of liver-type fatty acid-binding protein in contrast medium-induced nephropathy. Am J Kidney Dis. (2006); 47:439–444.
19. Ozdemir O, Oguz A D, Eren A: Cystatin C as biomarker of contrast-induced nephropathy in pediatric cardiac angiography. Turkish journal of Medical science (2014); 44:178-185.
20. Kamijo-Ikemori A, Sugaya T, Kimura K: Urinary fatty acid binding protein in renal disease. Clin Chim Acta (2006); 374: 1–7.
21. Kato K, Sato N, Yamamoto T: Valuable Markers for Contrast-Induced Nephropathy in Patients Undergoing Cardiac Catheterization. Circ J (2008); 72: 1499–1505
22. Bachorzewska-Gajewska H, Poniatowski B, Dobrzycki S: NGAL (neutrophil gelatinase-associated lipocalin) and L-FABP after percutaneous coronary interventions due to unstable angina in patients with normal serum creatinine Adv Med Sci. (2009); 54(2):221-4.
23. Ohta S, Ishimitsu T, Minami J: [Effects of intravascular contrast media on urinary excretion of liver fatty acid-binding protein]. [Article in Japanese] (Abstract). Nihon Jinzo Gakkai Shi. (2005); 47(4):437-44.
24. Manabe K, Kamihata H, Motohiro M: Urinary liver-type fatty acid-binding protein level as a predictive biomarker of contrast-induced acute kidney injury. Eur J Clin Invest. (2012); May; 42(5):557-63.
25. Shaker OG, El-Shehaby A, and El-Khatib M: Early diagnostic markers for contrast nephropathy in patients undergoing coronary angiography. Angiology. (2010); 61(8):731-6.
26. Malyszko J, Bachorzenwska-Gajewska H, Poniatowski B: Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and without severe chronic kidney disease. Ren Fail. (2009); 31(10):910-9.
27. Ribichini F, Gambaro G, Graziani MS: Comparison of serum creatinine and cystatin C for early diagnosis of contrast-induced nephropathy after coronary angiography and interventions. Clin Chem. (2012); 58(2):458-64.