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Urinary Neutrophil Gelatinase Associated Lipocalcin (uNGA|L) as an early marker for contrast induced acute kidney injury after cardiac catheterization.

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Abstract

Background: The incidence of acute kidney injury(AKI), previously referred to as acute renal failure, has reached epidemic proportions world-wide, affecting about 7% of hospitalised patients. In the critical care setting, the prevalence of AKI requiring dialysis is about 6%, with a mortality rate exceeding 60%**.** The early diagnosis of AKI currently depends on detection of reduced kidney function by the rise in serum creatinine concentration, which is a delayed and unreliable measure in the acute setting. In general, there are several non-renal factors influencing the serum creatinine concentration. Therefore, experimental studies have identified interventions that may prevent or treat AKI if instituted early in the disease process, *well* before the serum creatinine rises. Neutrophil gelatinase-associated lipocalin (NGAL), small inflammatory cytokine, is a 25-kDa protein belonging to the lipocalin superfamily. Since serum creatinine is known to be an inadequate and late marker of acute kidney injury (AKI), NGAL might soon emerge as an early marker for AKI. **Objective:** The aim of this study is to evaluate urinary NGAL as an early marker of contrast induced acute kidney injury after cardiac catheterization and as a predictor of clinical outcomes. **Methods:** This case control study was conducted on 40 patients with symptoms suggestive of coronary heart disease undergoing diagnostic cardiac catherization and with different relating diseases were compared with 40 healthy individuals selected from Ain-Shams University Hospitals. **Results:** Among the 40 patients and controls 28 were males 12 were females, with mean age of 49.9+/-8.8 years and 50+/-7.6 years respectively. In group I 20 patients had hypertension, 10 had diabetes, and 12 were dyslipidemic. While in the control group II 17 individuals had hypertension, 11 had diabetes, and 16 had dyslipidemia. The mean value of the urinary neutrophil gelatinase- associated lipocalcin 0, 2, 4 hours in the acute kidney injury group (9 patients) shows a statistically significant difference in comparison to the non AKI group (31 patients). Also, there is a statistically significant difference between the mean value of serum creatinine and creatinine clearance between the AKI and Non AKI groups when assessed on day 0, 1, 2, 3 respectively. **Conclusion:** Urinary **(**NGAL) has recently emerged as a sensitive, specific, and early marker of AKI**.**

Keywords: AKI, serum creatinine, NGAL, dyslipidemia, AKI.

Introduction

Acute kidney injury is a syndrome of varied severity. It is characterized by a rapid decline in the glomerular filtration rate (GFR) and retention of nitrogenous waste products such as blood urea nitrogen and creatinine. [(1)]**.** In recent years it has been recognized that the old term acute renal failure fails to describe the dynamic process of ongoing changing GFR. [(2)]**.** Serum creatinine does not accurately reflect the GFR in a patient who is not in steady state. Creatinine is removed by dialysis. [(3)]**.**

Recognizing the need for a uniform definition for ARF, the ADQI group proposed a consensus graded definition, called the RIFLE criteria [4]. The RIFLE criteria consists of three graded levels of injury (Risk, Injury, and Failure) based upon either the magnitude of elevation in serum creatinine or urine output, and two outcome measures (Loss and End-stage renal disease).[5] [6][7] ([8]

Contrast-induced nephropathy (CIN) is a widely recognized and clinically significant problem in patients undergoing invasive procedures that require contrast administration. The major risk factor for developing CIN is preexisting renal dysfunction, particularly in association with diabetes[9]

Contrast-induced nephropathy is broadly defined as acute kidney dysfunction occurring after exposure to intravascular contrast media that is not attributable to other causes .[10] The most commonly used definition of CIN, therefore, is either a relative increase in serum creatinine from baseline value of 25% or an absolute increase of 0.5 mg/dL within 48 to 72 hours after contrast exposure [11]

A useful AKI biomarker should be specific for renal injury and provide insight into the cause and location of injury, rather than just a nonspecific marker of glomerular filtration [11]
Studies have shown that uNGAL may be an early biomarker of contrast induced nephropathy (CIN) occurring after coronary angiography [12] [13]

In addition to overall sensitivity and specificity in the prediction and diagnosis of AKI, a useful biomarker also must be appropriate for widespread clinical use.[14]

Neutrophil gelatinase associated lipocalin (NGAL) is a 25-kDa protein originally isolated from neutrophil secondary granules and is now known as a prevalent epithelial cell protein with wide distribution throughout the body.

NGAL is freely filtered at the glomerulus and almost completely reabsorbed in the proximal tubule. Thus, increased urinary excretion suggests proximal tubular damage with impaired reabsorption or increased primary synthesis and excretion by distal nephron segments [14]

A role for NGAL as a marker of AKI was first suggested by ***Supavekin et al,*** whom they were the first to show increased NGAL gene expression in a mouse model of renal ischemia-reperfusion injury [15].

The utility of NGAL may not be limited for reaching an early diagosis of AKI but could extend to the excellent ability of this marker to assess the risk of an unfavourable clinical course in patients with established AKI [16] There are several commonly accepted strategies in the management of a patient with newly diagnosed AKI.

They include a restoration of adequate kidney perfusion, the avoidance of potential nephrotoxins (e.g. nephrotoxic antibiotics, contrast media) and therapeutic efforts that target the cause of AKI. It appears reasonable to speculate that an earlier institution of these measures will improve clinical outc0mes. [17] [18] Several investigators have examined the role of NGAL as a predictive biomarker of nephrotoxicity following contrast administration [19] [20]

Patients and Methods

Our study was conducted on 40 patients with different relating diseases were selected from Ain-Shams University Hospitals compared with 40 healthy individuals. Informed consent was obtained from all participants. The study subjects were arranged in two groups as follows:

A) **Group I:** included 40 patients with symptoms suggestive of coronary heart disease undergoing diagnostic cardiac catheterization using iopromide (a Low Osmolar, Non-Ionic contrast media) in amount ranging from 40 cc up to 150 cc.

B) **Group II**: included 40 apparently healthy individuals without symptoms of coronary heart disease. They are matched with the group 1 patients for age and gender.

Exclusion criteria

1- Preexisting renal insufficiency
2-Administration of the following drugs within 48 hours prior to or after contrast: Aminoglycosides - Amphotericin B – Nephrotoxic chemotherapeutic agents (platinum-based agents, methotrexate, ifosfamide)-Non-steroidal anti-inflammatory drugs (NSAIDs)-ACEI.
3-A documented episode of hypotension (MAP<60) within 48 hours prior to or after contrast administration,Sepsis.
4-After renal transplantation,Peripheral vascular disease.
5-Elderly (age >65 years).

Precatheter preparation and catheter technique:

The patients were asked not to eat or drink anything for 6-8 hours before the procedure.
An angiogram took from 45 minutes to one hour. As the procedure began, a nurse inserted an IV (intravenous line) into a vein in the patient arm to receive fluids and medications easily.
During the angiogram as the patients lie on the table, they were mildly sedated but awake throughout the procedure.
A specially trained cardiologist performed the procedure.

After the patients were relaxed, the doctor used a small needle to inject lidocaine**,** a local anesthetic, to numb an area in the groin.The femoral artery is the blood vessel doctor used to insert a catheter and thread it through the arteries to the heart to perform the angiogram.

The x-ray camera helps the physician guide the catheter to the heart. When the catheter was properly positioned, the cardiologist injected a radiographic contrast agent through the catheter into the heart and its arteries.

All the Individuals included in the study were subjected to:

I) Full medical history, examination including Body mass index and urine output estimation.
II) Laboratory Measurements:
i) CBC
ii) BUN, S.Na^+, S.K^+, S. corrected calcium, S. phosphate, Random blood sugar, Lipid profile and cardiac enzymes.
iii) Serum creatinine: immediately before and daily for 3 successive days after the procedure for group I.
iv) Urine analysis, protein / creatinine ratio.
v) NGAL measured in the urine (immediately before , 2 hours and 4 hours after the contrast administration for group I) using the ELISA commercially available kit, according to the manufacturer's instructions. Its levels expressed as ng/ml (with normal value up to 65 ng/ml).

Technique of urine sample processing for NGAL:

In the BioVendor Human Lipocalin-2/NGAL ELISA, the Standards, Quality controls and samples are incubated in microtiter wells pre-coated with polyclonal anti-human Lipocalin-2 antibody. After 60 min incubation and a washing, biotin-labelled polyclonal anti-human Lipocalin-2 antibody is added and incubated with captured Lipocalin-2 for 60 min.
After another washing, the streptavidin-HRP conjugate is added.

After 30 min incubation and the last washing step, the remaining conjugate is allowed to react with the substrate solution (TMB). The reaction is stopped by addition of acidic solution, and absorbance of the resulting yellow product is measured spectrophotometrically at 450 nm.

The absorbance is proportional to the concentration of Lipocalin-2.

A standard curve is constructed by plotting absorbance values against concentrations of Standards, and concentrations of unknown samples are determined using this standard curve.

III) Estimated creatinine clearance: by Cockcroft-Gault formula [(140-age)x(Wt in kg)x(0.85 if female)/(72xCr)] immediately before and daily for 3 successive days after the procedure for group I.

IV) ECG, Echocardiography to show Ejection fraction and Pelvi-abdominal ultrasound to exclude preexisting kidney disease.

V) Results collected, verified, revised then analyzed statistically for correlation between the study parameters in the different groups using SPSS (statistical program for social science version 12) as follows:

I. Descriptive statistics: Description of quantitative variables as mean, SD and range. **Description** of qualitative variables as number and percentage.

II. Analytic statistics: Paired sample T test, Pearson correlation coefficient**,** Chi square test for comparison of qualitative data.

III. P value: > 0.05 considered non significant (NS), P<0.05 significant (S), P <0.01 considered highly significant (HS).

Results

Our study included 2 groups:

Group I (Cases) included 40 patients, 28 males and 12 females with mean age 49.9± 8.8 years.

Group II included 40 individuals as a control group, 28 males and 12 females with mean age 50 ± 7.6 years.

Group I included 20 patients had HTN (50%) and group II included 17 patients had HTN (42.5%).

Group I included 10 patients had DM (25%) and group II included 11 patients had DM (27.5%).

Group I included 12 patients had Dyslipidemia (30%) and 28 didn't have Dyslipidemia (70%) and group II included 16 patients had Dyslipidemia (40 %) and 24 didn't have Dyslipidemia (60 %).

Group I included 9 smokers (22.5%) and 31 non-smokers (77.5%) and group II included 10 smokers (25%) and 30 non-smokers (75%).

And there is no significant difference between the 2 groups regarding demographic and premorbid conditions (**Table 1).** There is no significant relation between laboratory data and both case and control group.

		Group I Cases (40)	Group II Control (40)	P value
Age		49.9 ± 8.8	50 ± 7.6	0.9 (NS)
Sex (male :female)		28:12	28:12	1 (NS)
Comorbid conditions	**HTN**	20	17	0.5 (NS)
	DM	10	11	0.8 (NS)
	Smoking	9	10	0.7 (NS)
	Dyslipidemia	12	16	0.4 (NS)

Table (1) Demograghic data and premorbid conditions between the cases and control groups:

u-NGAL (ng/ml)	**Group I** (Mean±SD)	**Group II** (Mean±SD)	**P Value**
Baseline	57.08 ± 12.5	61.45 ± 13.02	0.5 (NS)
After 2 hours	122 ± 122.7	----------	----------
After 4 hours	150.5 ± 174	----------	----------

Table (2) The mean value of group I and II for u-NGAL.

Table (2) shows the mean value of group I for u-NGAL (immediately before) is 60.47±12.88 , u-NGAL (2 hours post) is 121.97± 122.73 and u-NGAL (4 hours post) is 150.5± 174.01 ng/dl with no significant difference between the 2 groups regarding the baseline u-NGAL (immediately before the catheter).

Our study showed that among (group I): 9 of 40 (22.5%) had AKI while the remaining 31 (77.5%) hadn't AKI . Among the 9 patients who developed AKI 1 patient (11.11%) had DM and 8 patients (88.89%) didn't have DM. While, regarding the frequency of hypertension 2 patients (22.22%) had HTN and 7 patients (77.78%) didn't have HTN.

In our study the the mean age for AKI group 54.7± 5.5 while that of Non AKI group 48.5± 9.2 with statistically significant difference for the mean value of age between the 2 groups.

This study also showed a statistically significant difference between the AKI and non AKI patients regarding sex as female patients are more susceptible to AKI than males as shown in t**able (3)**

		AKI(9)	Non AKI (31)	P value
Age		54.7±5.5	48.5± 9.2	**0.02 (S)**
Sex (male:female)		3:6	25:6	**0.01 (S)**
Comorbid conditions	**HTN**	2	18	0.06 (NS)
	DM	1	9	0.3 (NS)
	Smoking	0	9	0.07 (NS)

Table (3) Demograghic data and premorbid conditions between the AKI and Non AKI groups.

S.Creatinine (mg/dl)	AKI (9) (Mean±SD)	Non AKI(31) (Mean±SD)	P Value
Day 0	1.13±0.14	1.09 ± 0.11	0.384 (NS)
Day 1	1.17±0.11	1.08± 0.1	0.052 (NS)
Day 2	1.44±0.19	1.1±0.09	**0.000 (HS)**
Day 3	2.47±0.19	1.1 ± 0.09	**0.000 (HS)**

Table (4) The mean value of serum creatinine in AKI and Non AKI groups.

Table (4) shows the mean value of creatinine level at day 0 , 1, 2 , 3 in the AKI and non AKI patients with statistically significant difference between the groups regarding the mean value of creatinine level at day 2 and day 3 (P= 0.000).

Creat Clearance (ml/min/1.73m^2)	AKI (9) (Mean±SD)	Non AKI(31) (Mean±SD)	P Value
Day 0	66.55 ± 5.81	68.13 ± 5.21	0.479 (NS)
Day 1	66 ± 5.68	68.06 ± 5.06	0.345 (NS)
Day 2	59.89 ± 6.53	67.8 ± 5.33	**0.006 (HS)**
Day 3	47.11 ± 9.03	67.32 ± 5.48	**0.000 (HS)**

Table (5) The mean value of creatinine clearance in AKI and Non AKI groups.

Table (5) shows the mean value of creatinine clearance at day 0 , 1, 2 , 3 in the AKI and non AKI patients with statistically significant difference between the groups regarding the mean value of creatinine clearance at day 2 and day 3 (P=0.006, 0.000 respectively).

u-NGAL (ng/ml)	AKI (9) (Mean±SD)	NonAKI(31) (Mean±SD)	P Value
Baseline	57.08 ± 12.5	61.45 ± 13.02	0.376 (NS)
After 2 hours	330.89 ± 97.3	61.32 ± 12.71	**0.000 (HS)**
After 4 hours	456.11±107.21	61.77 ± 12	**0.000 (HS)**

Table (6) The mean value of u-NGAL in AKI and Non AKI groups.

Table (6) shows the mean value of uNGAL at 0 , 2 , 4 hours in the AKI and non AKI patients with statistically significant difference x between the groups regarding the mean value of uNGAL at 2nd and 4th hour (P=0.000).

In this study the risk factors for AKI show a statistically significant difference between AKI and non-AKI patients regarding these risk factors of MAP (p 0.0) HS and for serum albumin (0.05).

Group I	u-NGAL after 2hours	
	Pearson Correlation	Sig. (2-tailed)
Age	0.286	0.073 (NS)
MAP mmHg	-0.349	**0.029 (S)**
Pulse /min	0.023	0.888 (NS)
Hb g/dl	-0.348*	**0.028 (S)**
BUN mg/dl	-0.195	0.227 (NS)
Na$^+$ mmol/l	0.068	0.675 (NS)
K$^+$ mmol/l	-0.004	0.979 (NS)
Ca^{++} mg/dl	0.156	0.337 (NS)
PO4^{++} mg/dl	0.055	0.736 (NS)
Pr/Cr R g/g creat	-0.229	0.155 (NS)
EF %	-0.173	0.287 (NS)

Table (7): Correlations of u-NGAL at 2 hours among all cases patients.

Table (7) shows statistically significant correlation between u-NGAL after 2 hours and both Hb level and MAP among all the cases.

AKI group (9)	u-NGAL after 2hours	
	Pearson Correlation	Sig. (2-tailed)
Age	0.005	0.989 (NS)
MAP mmHg	0.038	0.925 (NS)
HR /min	-0.590	0.095 (NS)
Hb g/dl	-0.329	0.388 (NS)
BUN mg/dl	0.071	0.856 (NS)
Na^+ mmol/l	0.507	0.163 (NS)
K^+ mmol/l	0.011	0.978 (NS)
Ca^{++} mg/dl	0.117	0.764 (NS)
$PO4^{++}$ mg/dl	0.036	0.927 (NS)
Pr/Cr R g/g creat	-0.042	0.914 (NS)

Table (8): Correlations of u-NGAL after 2 hours in AKI group.

Table (8) shows the correlation between u-NGAL at 2 hours, age, clinical data and some laboratory data among AKI patients.

AKI group (9)		u-NGAL after 2hours	
		Pearson Correlation	Sig. (2-tailed)
Echo	**EF %**	-0.760*	**0.018 (S)**
	LVH	-0.192	0.151 (NS)

Table (9): Correlations of u-NGAL after 2 hours with echocardiography findings in AKI group.

Table (9) shows significant correlation between u-NGAL at hours and echocardiography (Ejection fraction) among AKI patients with (P value 0.018).

AKI group (9)	u-NGAL after 2hours	
	Pearson Correlation	Sig. (2-tailed)
Contrast amount cc	-0.290	0.450 (NS)

Table (10): Correlations of u-NGAL after 2 hours with IV contrast amount in AKI group.

Table (10) shows no significant correlation between u-NGAL after 2 hours and IV contrast amount among AKI patients.

	Cut off	AUROC	Sensitivity	Specificity	PPV	NPV
S.Creat (mg/dl)	≥ 1.15	72.2%	66.7%	74.2%	42.9%	88.5%
uNGAL (ng/ml)	≥203.5	100%	100%	100%	100%	100%

Table (11): The difference between s.creatinine and u-NGAL

Table (11) shows that the cut off value of serum creatinine after 1 day post catherterization is ≥ 1.15 mg/dl while that of u-NGAL after 4 hours is ≥ 203.5 ng/ml, also shows that the sensitivity and specificity of s.creatinine is 66.7% and 74.2% respectively with a positive predictive value 42.9% and a negative predictive value 88.5% while both sensitivity and specificity of u-NGAL is 100% and both PPV and NPV 100%.

Discussion

The proposed diagnostic criteria for ARF are an abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥0.3 mg/dL (26.4 micromol/L) from baseline, a percentage increase in the serum creatinine concentration of ≥50 percent, or oliguria of less than 0.5 mL/kg per hour for more than six hours. Recent studies have demonstrated the utility of early NGAL measurements for predicting clinical outcomes of AKI. The 2-h urine NGAL levels were highly correlated with duration and severity of AKI, length of hospital stay, dialysis requirement and death [21]

Serum creatinine levels or glomerular filtration rate (GFR), as well as urinary output, are the most commonly used markers of renal function and are used to determine the magnitude of renal injury[22] .

However, it must be recognized that such markers are Serum creatinine levels or glomerular filtration rate (GFR), as well as urinary output, are the most commonly used markers of renal function and are used to determine the magnitude of renal injury[23] *;(24)*

However, it must be recognized that such markers are imperfect. They cannot be used to distinguish between hemodynamically mediated changes in renal function, such as prerenal azotemia as opposed to intrinsic renal failure or obstructive uropathy. Similarly, changes in volume states can significantly influence the levels of serum creatinine, further minimizing the true relative change in renal function. Furthermore, there may be a significant time lag (in hours or days) between the change in the above markers and the actual onset of anatomic or structural damage.[25] [26]

Knowing the above limitations of currently used kidney function markers, it is accepted that they may be unable to detect any acute injury or process; in fact, their levels may rise coincident with a late period in the injury process. This has led to research to find more accurate kidney function biomarkers (serum and/or urine) [27] .

The goal of biomarker research is the early diagnosis of AKI (within hours, rather than within days or weeks). In that way, appropriate preventive and preemptive strategies, as well as treatment regimens, can be rendered at a phase whereby permanent loss of function can be avoided, making AKI truly reversible.[28]

NGAL is a 25-kD protein, remains a mystery. One possibility, however, is that it is involved in renal morphogenesis, such as induction of repair and reepithelialization. It has been shown to be elevated in the plasma and urine of animal models of ischemic and nephrotoxic acute kidney injury and, hence, is considered by some to be a novel urinary biomarker for ischemic injury [29]

Our study included forty patients diagnosed with different relating diseases and compared them with forty normal individuals.

Our study showed that of 40 patients had coronary catheterization 9 patients developed AKI and 31 patients didn't develop AKI.

All the 9 patients who developed AKI had elevated u-NGAL after 2 hours with more elevations after 4 hours, This elevation was detectable at an earlier time (after 2 hours) with respect to serum creatinine (after day 1 post cardiac catheter).

We found that the cut off value of serum creatinine after 1 day post catherterization is ≥ 1.15 mg/dl with sensitivity and specificity (66.7% and 74.2% respectively) and an AUC **of 72.2%.**

While the cut off value of u-NGAL after 4 hours is ≥ 203.5 ng/ml with both sensitivity and specificity 100% and an AUC of 100%.

Also there is statistically significant difference between u-NGAL after 2 hours between the patients who developed AKI and the patients who didn't develop AKI (P = 0.000).

In agreement with Sargentini et al. study, in which uNGAL levels were measured with an automated immunoassay in urine samples from patients undergoing cardiac surgery using cardiopulmonary bypass, patients developing AKI displayed a significant increase (P=0.011) in uNGAL levels

compared to u-NGAL at the time of admission. This increase was detectable at an earlier time point (after 4 hours) with respect to serum creatinine (measured after 24 hours). Confirming its utility as a biomarker, at 4 hours the uNGAL levels were significantly higher in AKI patients than in non-AKI patients (P=0.021) [30].

Also consistent with Torregrosa et al. study, they evaluated the usefulness of NGAL and IL-18 in urine samples and cystatin-C in serum samples for the early (within 12 hours of the intervention) detection of AKI in a group of emergency patients in the ICU with acute coronary syndrome or heart failure, who underwent cardiac surgery or coronary angiography with or without angioplasty or endoprosthesis implantation with the following results:they found that uNGAL is useful for the early detection of AKI with an AUC of 0.881 and Of all the biomarkers for AKI that are being studied, NGAL has probably inspired the greatest amount of interest and they observed a significant difference in the values of NGAL from urine samples between patients that developed AKI and those that did not, allowing us to clearly distinguish them both. The mean urine level of NGAL in the control group (healthy volunteers) was 18 (5) ng/ml and they observed a significant difference in NGAL (P<.001) between patients with AKI and the control group between the two groups (P<.001). [31] In addition, both urine and plasma NGAL were excellent independent predictors of AKI, with an area under the curve (AUC) of >0.9 for the 2–6-h urine and plasma NGAL measurements [32]

The mean urine level of NGAL in the control group (healthy volunteers) was 18 (5) ng/ml and they observed a significant difference in NGAL (P<.001) between patients with AKI and the control group between the two groups (P<.001) [31]. Also NGAL has also been shown to be useful for the early diagnosis of AKI following coronary angiography according to ***Malyszko and colleagues***[33]

Our study showed statistically significant correlation between u-NGAL after 2 hours and both Hb level and MAP among all the cases (P value : 0.028), and this result match with that was found by Hryniewieckaa et al. they stated that uNGAL/Cr was inversely correlated with hematocrit (Htc) and hemoglobin (Hb) ($r = -0.35$ and $P = 0.0002$; $r = -0.39$ and $P = 0.00004$; respectively) .

Also in agreement with Liu et al. they studied the increase risk of AKI with a decreasing lowest hematocrit during CPB in their asian population (relative risk, 0.933; 95%; P < .001), in particular with the lowest hematocrit of ≤ 22% and a 23% increased risk of AKI was found for preoperative anemia (relative risk, 1.225; P = .028) so the lowest hematocrit and preoperative anemia were potentially modifiable risk factors independently associated with AKI [34]

Recently, research has focused on the association of neutrophil gelatinase–associated lipocalin (NGAL) with acute and/or active kidney injury. However, it should be remembered that NGAL is involved in iron metabolism and antimicrobial defense mechanisms[35]

Our study showed statistically significant difference between AKI patients and non-AKI patients regarding age (P value 0.02) as old patients were more liable to have AKI.

Also there is statistically significant difference between the AKI and non AKI patients regarding sex (P value: 0.01), we found that female patients were more susceptible to develop AKI than males.

In agreement with Hryniewieckaa et al. pNGAL inversely correlated with patient's age ($\beta = -0.18$ and $P = 0.02$) with $R = 0.67$ and $R2 = 0.45$, Plasma and urine NGAL levels are strongly correlated not only with kidney function parameters, but also with red and white blood cell parameters and patient's age and sex [35]

Our study showed significant correlation between u-NGAL after 2 hours and Ejection fraction in AKI patients (P value: 0.018) making a low ejection fraction a major risk factor for AKI thus a rise in u-NGAL levels.

In consistent with Thanakitcharu and Jirajan u-NGAL level may be a useful marker for predicting AKI in adult patients undergoing open cardiac surgery. Lower ejection fraction and longer CPB time were two major risk factors for AKI development.[36]

Larger volumes of contrast agents are used in coronary angiography than in other imaging studies therefore patients who undergo coronary angiography (these patients usually have one or more comorbid conditions) have AKI more frequently than other patients.[37]

But our study showed that there is no correlation between u-NGAL after 2 hours and the amount of the intravenous contrast in the AKI group (P value: 0.450).

In consistent with Perrin et al. who stated that since the amount of Contrast Material (CM) correlates with tubular toxicity and uNGAL is a marker of acute tubular injury, they hypothesised that these two parameters may correlate. However and in accordance to their study and other studies, their data clearly indicate that uNGAL is not related to the amount of CM. *(38) (39(40))*

Conclusion

NGAL is one of the most intensively investigated novel renal biomarkers with promising data from animal experiments and clinical studies comprising the populations at risk for AKI. Within minutes to a few hours after a renal insult, NGAL is induced in and released from the injured distal nephron. So, it appears to fulfill many characteristics of an appropriate 'real-time' biomarker for AKI detection. The early diagnosis of AKI currently depends on detection of reduced kidney function by the rise in serum creatinine concentration, which is a delayed and unreliable measure in the acute setting. In general, there are several non-renal factors influencing the serum creatinine concentration. Since serum creatinine is known to be an inadequate and late marker of acute kidney injury (AKI), NGAL might soon emerge as an early marker for AKI. Recent studies have demonstrated the utility of early NGAL measurements for predicting clinical outcomes of AKI. Further studies are needed to study the correlation between uNGAL and other contributing factors for AKI either separately or in conjunction.

In addition to early diagnosis and prediction, it would be desirable to identify biomarkers capable of discerning AKI subtypes, identifying etiologies, predicting clinical outcomes, allowing for risk stratification and monitoring the response to interventions.

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