Journal of Bangladesh College of Physicians and Surgeons
Vol. 33, No. 3, July 2015

# Evaluation of Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL), as an Early Biomarker and Prognostic Factor of Contrast Induced Acute Kidney Injury (CI-AKI) following Cardiac Catheterization

A NESSA[a], MAH FAKIR[a], M MOSTAFI[a], M AHMED[b]

**Summary:**

***Acute kidney injury (AKI) usually detected by s. creatinine, which rises after 48 hrs of insult causes delay in diagnosis and to take preventive or therapeutic measures. Hence amongst many neutrophil gelatinase associated lipocalin (NGAL) is emerging as early, sensitive, and most promising biomarker of AKI both in urine and plasma.***

***This prospective cross sectional observational study was carried out in Combined Military Hospital (CMH) Dhaka from October 2011 to March 2012. A total of willing 100 adult patients undergoing elective coronary angiogram (CAG) with normal kidney function were included in this study. Our study defined contrast induced AKI (CI-AKI) as rise of serum creatinine by ≥25% or e"0.5 mg/dl from baseline after exposure to contrast media and urine NGAL e"100 ng/ml was taken as cut off value to predict AKI as calculated by ROC curve. The main outcome measures were urine NGAL at 4 hrs and serum creatinine at 48 hrs after CAG. Significant elevation of urine NGAL was noted in 9 patients after 4 hrs of CAG, of them 8 (8%) patients developed raised s. creatinine (AKI) after 48 hrs. Patient demographics and procedural factors were although statistically significant in few instances but none was predictive of AKI.***

***Keywords: NGAL, Biomarker, CI-AKI, Cardiac catheterization.***

***(J Banagladesh Coll Phys Surg 2015; 33: 133-139)***

## Introduction:

The incidence of acute kidney injury (AKI) has reached epidemic proportions worldwide, affecting about 7% of hospitalized patients. In the critical care settings, the prevalence of AKI requiring dialysis is about 6% with a mortality rate exceeding 60%.[1,2] A significant increase in morbidity and mortality associated with AKI has been demonstrated in a wide variety of clinical situations including exposure to radio contrast dye, cardiopulmonary bypass, mechanical ventilation, sepsis etc. 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 acute setting.

The search for early specific simple AKI biomarker is an area of intense contemporary research to permit more timely diagnosis of AKI, prediction of injury severity and safety assessment during drug development. Amongst many promising new biomarkers of AKI, NGAL is emerging as excellent biomarker both in urine and plasma, which significantly (more than tenfold) increase within 2-4 hrs of both ischaemic and nephrotoxic AKI in animal models.[3,4]

NGAL also known as lipocalin 2 or Lcn is a 25 KDa protein initially identified bound to gelatinase in specific granules of the neutrophil. It is synthesized during a narrow window of granulocyte maturation in the bone marrow[5] but also may be induced in epithelial cells in the settings of inflammation and malignancy.[6]

Till to date, there is no study regarding NGAL carried out in Bangladesh in any clinical or preclinical settings. So it is imperative to study the significance of NGAL as simple, specific, cheap and early predictors of AKI in various clinical settings. This study will add and strengthen the data already available in the western literature or to have a reference data in this regard home and abroad.

a. Dr. Azizun Nessa, Prof (Brig Gen) Md Amzad H. Fakir, Prof (Brig. Gen.) Mamun Mostafi, Medicine Specialist & Nephrologist, Combined Military Hospital (CMH), Dhaka.

b. Dr. (Lt Col) Masud Ahmed, Anaesthesiologist, Combined Military Hospital (CMH), Dhaka.

**Address of Correspondence:** Dr. (Lt. Col.) Azizun Nessa, Medicine Specialist & Nephrologist, Combined Military Hospital (CMH), Dhaka, Mobile No: 01714256689, E-mail: azizun71@yahoo.com

**Received:** 23 January, 2014 **Accepted:** 23 March, 2015

**Materials and methods:**

This was a prospective cross sectional observational study carried out in combined military hospital (CMH), Dhaka after getting ethical clearance from directorate general of medical services (DGMS) of Bangladesh armed forces between the period of October 2011 to March 2012. A total of willing one hundred patients of both sexes undergoing coronary angiogram for diagnostic or therapeutic procedure were included in the study. Those with known kidney disease as understood by raised serum creatinine or e-GFR <60 ml/min/1.73 $m^2$, peripheral vascular disease, severe chest infection, urinary tract infection, history of contrast allergy or contrast administration within last one month, who developed shock during the procedure and who were receiving aminoglycosides, NSAIDs were excluded from the study.

Demographic characteristics, baseline investigations reports, procedural factors were recorded in a preformed data sheet for each patient. Low osmolar, nonionic radiocontrast agent iohexol (Imiro-350) was used for all patients. Urinary NGAL and s creatinine tests were done in the following sequence-

$t_0$- baseline (just before procedure).

$t_1$ – 4 hrs after the procedure.

$t_2$ - 48 hrs after the procedure.

Urine NGAL samples were analyzed by human NGAL rapid ELISA kit (037). Lot no: NR- 1006 FCE: BIOPORTO Diagnostics, Denmark.

The rise of serum creatinine from baseline by either ≥ 0.5 mg/dl (≥44.2micromol/L) or ≥25% occurring 48 hrs of contrast administration was defined as CI-AKI.[7]

The data collected were tabulated and analyzed using SPSS (statistical package for the social sciences) package version 13 software. Quantitative data were expressed as mean & standard deviation ($\bar{x}$ ±SD) and analyzed by applying student's t- test (paired and unpaired) for comparing two groups of variables .Qualitative data were expressed as number and percentage (no & %) and analyzed by applying chi-square test. Results were considered as significant at $p<0.05$.

**Results and observations:**

The receiver operating characteristics curve at different cut off values in relation to s. creatinine were evaluated. With a cut-off value of 100 ng /ml, the 4 hr u-NGAL revealed the highest sensitivity and specificity (100% and 98.91% respectively) in predicting AKI with area under the curve (AUC) 0.995.(Fig-1)

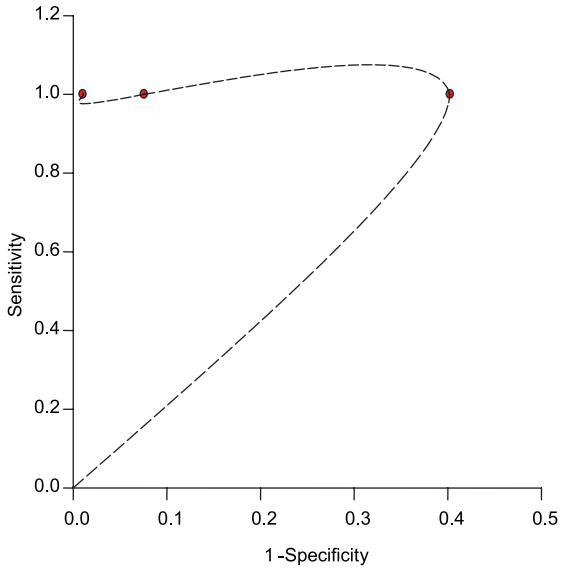


**Fig.-1:** *ROC curve at different cut off values of u-NGAL in relation to serum creatinine*

There was a sharp rise of mean urine NGAL (150±29.52 ng/ml) at 4 hrs time point in AKI group, whereas there is no significant change in non- AKI group (21.16±18.55) (Fig.-2) and it was statistically significant (p=0.0001). But at 48 hrs the level of uNGAL in AKI group although still higher than baseline but dropped below the cut off value (100 ng/ml).

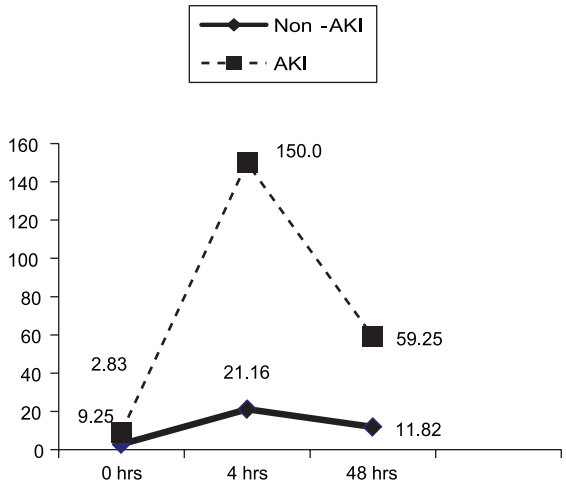


**Fig.-2:** *u NGAL vs time*

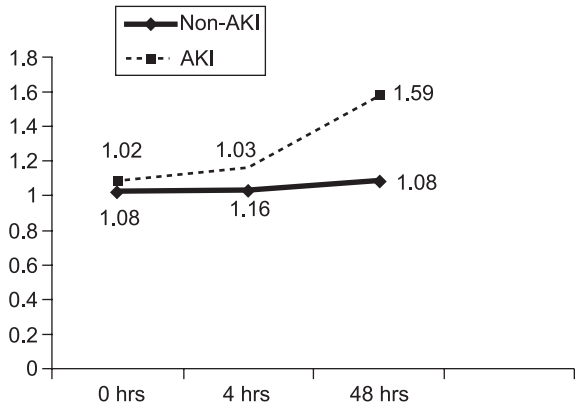


**Fig.-3:** *Serum Creatinine vs time.*

Patients having no AKI (rise of serum creatinine <25% or rise<0.5 mg/dl) (n=92) and AKI (rise of serum creatinine ≥25% or rise ≥0.5 mg/dl) (n=8) mean baseline and at 4 hrs s. creatinine didn't differ significantly (Fig-3). But at 48 hrs, the mean change of serum creatinine in AKI group (1.59±0.19) was statistically significant (p= 0.0001) than non AKI group (1.08±0.15).

**Table-I**

*Prediction of CI-AKI by uNGAL and s. creatinine at different time point (n=100).*

| Time (hrs) | Marker | No AKI | AKI |
|---|---|---|---|
| 0 | - | 100 | - |
| 4 | u-NGAL | 91 | 09 |
| 48 | s. creatinine | 92 | 08 |

Prediction of AKI basing on raised u-NGAL (>100 ng/ml) and s. creatinine(≥25%or e"0.5mg /dl from base line)

**Table-II**

*Comparison of patients characteristics with CI-AKI and Non-AKI as predicted by uNGAL(>100ng/ml) at 4 hrs time* point(n=100).

| Parameters | Non-AKI(n=91) | AKI(n=09) | P value |
|---|---|---|---|
| Age (yrs) | | | |
| Mean±SD | 51.76±8.98 | 61.38±11.01 | (0.005)[a] |
| Range | (30-75) | (36-70) | |
| Sex(M/F) | 72/19 | 7/2 | (0.01)[b] |
| DM(+/-) | 23/68 | 8/1 | (0.0001)[b] |
| HTN(+/-) | 50/41 | 7/2 | (0.069[ns])[b] |
| Hb% (gm/dl) | | | |
| Mean±SD | 12.16±1.64 | 12.01±1.08 | (0.515 [ns])[a] |
| (Range) | (10.80-14.70) | (10.2-13.80) | |
| Body weight(kg) | | | |
| Mean±SD | 67.37±6.88 | 69.88±5.65 | (0.306 [ns])[a] |
| (Range) | (50-80) | (60-77) | |
| e-GFR(ml/min/1.73m$^2$) | | | |
| (CG method) | | | |
| Mean±SD | 80.87±15.63 | 76.76±13.67 | (0.474 [ns])[a] |
| (Range) | (60.00-152.77) | (60.30-93.55) | |
| Vol of Contrast media(ml) | 89.67±42.77 | 125.00±23.15 | (0.024)[a] |
| (mean ±SD) | (50.00-300.00) | (100.00-150.00) | |
| (Range) | | | |
| Dose of Iodine(gm) | 31.39±14.97 | 43.75±8.10 | (0.024)[a] |
| (mean ±SD) | (17.50105.00) | (35.00-52.50) | |
| (Range) | | | |
| Duration of procedure(min) | 45.27 ±14.25 | 58.13±5.30 | (0.013)[a] |
| (mean ±SD) | (30.00-90.00) | 45.27±14.25 | 0.013[*](45.00 60.00) |

(Range)
[a]Unpaired Student's 't' test
[b]Chi square test
ns = Not significant
CG method=Cockroft Galt formula.

**Table-III**

*Clinical outcome of patients basing on uNGAL*

| Outcome | Non-AKI (n=91) | AKI (n=09) | P value* |
|---|---|---|---|
| | (uNGAL<100ng/ml) | (uNGAL >100ng/ml) | |
| Duration of AKI (days) | - | 5.25±0.71 | - |
| Hospital Stay after CAG(days) mean ±SD (Range) | 3.70±1.44 2.00-3.00 | 6.25±1.16 4.00-7.00 | 0.0001 |
| Dialysis requirement | No | No | - |
| Mortality | None | None | - |

*Unpaired student's 't' test

at different time points(0,4,48 hrs) revealed at 04 hrs, 09 patients (9%) had significantly raised u-NGAL(suspected AKI) whereas no patient had significantly raised s. creatinine at that time point. But at 48 hrs, 08 of them had also raised s. creatinine and confirming AKI. One patient with clinically significant uNgal at 04 hrs but normal s creatinine at 48 hrs considered as false positive.(Table-1)

When the demographic features and procedural factors were compared between patients with non-AKI and AKI groups it was found that mean age of the patient in AKI group was significantly higher than non- AKI group (61.38±11.01 yrs vs 51.76±8.98 yrs). Seven (07) male and two (02) female patients had significantly high u-NGAL at 4 hrs after contrast exposure, which is also statistically significant (p value=0.01) .08(eight) patients were diabetic and 01(one) was non-diabetic in high NGAL group whereas 23 diabetic patients and 68 non-diabetic patients had normal u-NGAL and this finding is statistically significant (p=0.0001). 07 patients with AKI were hypertensive and 02 had normal BP in AKI group whereas 42 out of 92 had no history of hypertension in normal u-NGAL (non-AKI) group, which has no statistical significance($p=0.069^{ns}$). Mean e-GFR was 76.76±13.67 ml/min/1.73m$^2$ in suspected AKI (high NGAL) group compared to 80.87±15.63 in patients with non AKI group. Mean volume of contrast media (CM) in AKI group was 125.00±23.15 ml whereas it was 89.67 ±42.77 ml in non AKI group (p=0.024). Mean duration of procedure in AKI & non AKI group were 58.13±5.30 and 45.27±14.25 min respectively (p=0.013*). Both pre angiogram urine NGAL and 4 hrs post angiogram urine NGAL were significantly positively correlated with the volume of contrast, duration of the procedure and 48 hrs post angiogram serum creatinine level but had significant negative correlation with HTN, Hb%, body wt and e-GFR level.

Mean duration of AKI (n=09) was 5.25±0.71 days and mean hospital stay after CAG of this group of patients was 6.25±1.16 days compared to 3.70±1.44 days in non AKI group. The difference was statistically significant (P=0.0001). No patient required renal replacement therapy or dialysis and there was no case of mortality in study subjects because of the procedure itself or its complication (AKI).

**Discussion:**

The incidence of both acute kidney injury (AKI) and chronic kidney disease (CKD) is reaching epidemic proportions.[2] In both situations, early intervention can significantly improve the prognosis. However the paucity of early predictive non invasive biomarkers has impaired our ability to institute potentially effective therapies for these common clinical conditions in a timely manner. A troponin like biomarker of AKI that is easily measured, unaffected by other biological variables and capable of both early detection and risk stratification would represent a tremendous advance in clinical medicine.[8] NGAL is now being evaluated as a novel biomarkers in human AKI in different clinical setting including exposure to radio-contrast dye, cardiopulmonary bypass, mechanical ventilation, sepsis etc. In this study, NGAL is evaluated as an early biomarker of AKI in patients following administration of contrast dye during cardiac catheterization.

Here Urine NGAL & serum creatinine level is measured just before ($t_0$) ,4 hrs ($t_1$) and 48 hrs ($t_2$) after contrast administration and AKI was defined as rise of serum creatinine $\geq$0.5 mg/dl or 25% from baseline[7] and the cut off value of uNGAL indicating AKI as 100ng/ml[9,10] as proved by receiver operating characteristic (ROC) curve analysis also.

The diagnostic performance of NGAL varied considerably among different studies depending on the clinical setting at the assay being used. ROC analyses are frequently used to determine the discriminatory ability of a diagnostic test at a different cut off values to predict AKI. The area under the ROC (AUC- ROC) is a measure of the ability of a test to separate patients with the diagnosis from unaffected individuals.

The AUC – ROC for NGAL in the diagnosis of AKI across different studies has varied between 0.61 (a poor test) and 0.998 (a magnificent test).

The predictive performance of NGAL also depends on the severity of AKI as classified by RIFLE criteria.[11,12] Despite these numerous potential variables, a meta analysis revealed an overall AUC of 0.78 for prediction of AKI when NGAL measured within 6 hrs of initiation of CPB and AKI was defined as a >50% increase in serum creatinine.[9]

Several studies in which patients developed AKI have demonstrated the use of NGAL in the early diagnosis of AKI and proposed cut off value for optimum utility of the test ranging from 100-270 ng/ml[9] reported an optimum value of 104 ng/ml which is close to the value (95$^{th}$centile of 107 ng/ml) proposed by M.Rachel Cullen.[10]

For patients receiving iodinated contrast media, the development of contrast induced AKI (CI-AKI) is associated with adverse in- hospital outcomes and increased risk of death.[13] In 439 patients with CKD (S.creatininee"158 mmol/L) undergoing percutaneous coronary revascularization, 37% of patient developed CI AKI as defined by an increase in s. creatinine e"25%. The in-hospital mortality for the AKI group was three times higher than those without AKI (14.9% vs. 4.9%), with an almost two fold increase in one year mortality.[14]

In this study, 9 patients had significantly raised uNGAL at 4 hrs of CAG. Eight of them were diabetic (8 out of total 31 diabetic patients). This agreed with Malyszako et al[15] who concluded that diabetic patients are more vulnerable and prone to develop contrast nephropathy. Toprak reported that the most important and well established patient- related risk factors for CIN are CKD particularly CKD combined with diabetes mellitus and advanced age.[16]

Comparing patients who developed CIN (CI-AKI) and those who did not develop AKI it was found in this study that volume of contrast was significantly higher in those who developed AKI. This agreed with Morabito et al[17] who concluded that contrast media volume is a strong modifiable risk factor for AKI. This was also in agreement with Sanaei-Ardekani et al[18] who reviewed 931 cases of coronary angiography and found increased CIN with increased volume of contrast.

CI AKI has been associated with longer hospital stays[19] and requirement for renal replacement therapy in 1-4 % of patients depending on the presence or absence of underling renal impairment or the type of contrast used (high or low osmolar vs. iso-osmolar contrast media).[20]

In this study mean duration of hospital stay in patient (n=09) with CI -AKI was 6.25±1.16 days in comparison to 3.70±1.44 days in non AKI group and the difference is statistically significant. The rise of s. creatinine was subtle and reversible with volume expansion only. No patient of this study required dialysis or there was no case of mortality.

In a retrospective study of 7586 patients undergoing percutaneous coronary intervention, CI-AKI was associated with baseline renal impairment, the presence of acute myocardial infarction, haemodynamic instability and the volume of contrast administered.[21] In contrary to this study Morabito et al[17] reported that lower levels of basal haemoglobin appeared to be related to a higher risk of CI-AKI. Baseline eGFR was significantly lower in patients who developed CI- AKI as also found by Ling et al.[22]

This study has got several strengths. First, we prospectively recruited a relatively homogenous cohort of adult subjects without any preexisting renal pathology whom the only obvious etiology for AKI would be the result of contrast administration. Second, the study design allowed for the precise temporal definition of altered urine NGAL concentration and a direct comparison with subsequent changes in serum creatinine. Results of this study clearly indicate that

urine NGAL is a powerful early biomarker of AKI that precedes the increase in serum creatinine by several hours to days. The magnitude of rise supports the notion that urine NGAL is a highly discriminatory biomarker with a wide dynamic range and cut off values that allow for easy risk stratification. Third, use of urinary sample have certain advantages like noninvasive nature of sample collections and the reduced number of interfering proteins although leucocyturia can be a confounding variables. Fourth the results obtained using the ARCHITECT® Platform were independent of changes in urinary concentration and were equally applicable after correction for urine creatinine measurements.

The excellent performance of uNGAL in this study can probably be attributed to the exclusion of patients with co morbidities (e.g. known kidney diseases) and tend to the fact that we studied a homogenous population undergoing routine CAG. Similar to several previous investigations we didn't normalize u-NGAL for urinary creatinine excretion but this approach did not seem to affect the performance of the test in this study.[23]

Despite the optimism in the field, there are important limitations that exist in the published AKI biomarker literature that must be acknowledged. First, majority of studies reported were from single centers. Second, most studies like this study didn't include patients with CKD. Third, only a few studies have investigated biomarkers for the prediction of AKI severity, morbidity and mortality. Fourth, biomarker combinations are likely to improve clinician's ability to predict AKI and its outcomes and these studies are only beginning to surface.

Finally, and perhaps most importantly the definition of AKI in the published studies was based largely on elevations of serum creatinine, which raises the challenge of using a flawed outcome variable to analyze the performance of a novel assay. This definition of AKI set up the biomarkers assay for lack of accuracy due to either false positive or false negative results. Indeed a recent multicenter pooled analysis of published data on 2322 critically ill children and adults revealed the surprising finding that approximately 20% of patients display early elevations in NGAL concentration but never develop increase in serum creatinine.[24]

Importantly this subgroup of NGAL positive -creatinine negative subjects encountered a substantial increase in adverse clinical outcome including mortality, dialysis requirement, ICU Stay and overall hospital stay.[24] In this study, we found, one patient had raised uNGAL at 4 hrs but his serum creatinine was all through normal.

Thus early NGAL measurements can identify patients with subclinical AKI, who have an increased risk of adverse outcomes even in the absence of diagnostic increase in serum creatinine and should alert clinicians to the need for close clinical monitoring of kidney function and facilitate timely initiation of renal protective therapies. Since the gold standard for true AKI (tissue biopsy) is highly unlikely to be feasible in humans and the current absence of gold standard criteria of AKI and universally accepted cut off value, a level of uncertainty will remain for near future.

**Conclusion:**

NGAL has entered the final phases of the biomarker development process, facilitated by the development of commercial tools for its measurements in larger populations with different settings. Till to-date including in this study, urinary NGAL represent novel, sensitive, specific and highly predictive early biomarker of AKI when compared to other conventional biomarkers. In this study, a significant rise in urine NGAL was demonstrated 04 hours after contrast administration which significantly correlated with the rise in serum creatinine 48 hours after contrast. Thus rise of urine NGAL (>100 ng/ml) can be used as early predictor of contrast induced acute kidney injury. If current prospective multicentre studies with well defined patient cohorts measuring NGAL levels using standardized laboratory platforms provide promising result, NGAL may qualify as 'Troponin' of not only in contrast induced but in all types of AKI, which will definitely prove to be useful in facilitating early diagnosis, guiding targeted intervention and monitoring disease progression and resolution.

**Acknowledgement:**

This work was funded and supported by Directorate General of Medical Service (DGMS),Bangladesh Armed Forces.

**References:**

1. Parikh CR, Devarajan P. New biomarkers of acute kidney injury. Crit Care Med. 2008; 36(4 suppl) S.159-65.
2. Devarajan P. NGAL in acute kidney injury: Fro serendipity to utility. Am J kidney Dis. 2008; 52: 395-399.

3. Mishra J, Ma Q, Prada. Identification of neutrophil gelatinase associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol. 2003 14: 2534-2543.

4. Mishra J, Mori k, Ma Q, Kelly C, Barasch J, Devarajan P. Neutrophil Gelatinase Associated lipocalin (NGAL): a novel urinary biomarker for cisplatin nephrotoxicity. Am J Nephrol. 2004; 24: 307-315.

5. Borregaard N, Schested M, Nielsen BS, Sengelov H, Kjeldsen L. Biosynthesis of granule proteins in normal human bone marrow cells. Gelatinase is a marker of terminal neutrophil differentiation. Blood. 1995; 85: 812-17.

6. Nielsen BS, Borregaard N, Bundgaard JR, Timshel S, Schested M, Kjeldsen L. Induction of NGAL synthesis in epithelial cells of human colorectal neoplasia and inflammatory bowel disease. Gut. 1996; 38: 414-20.

7. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012; 2:1 – 38.

8. Devarajan P. Neutrophil gelatinase associated lipocalin a promising biomarker for human acute kidney injury Biomarker Med. 2010; 4: 265-280.

9. Hasse M, Bellomo R, Devarajan. Accuracy of neutrophil gelatinase associated lipocalin(NGAL) in diagnosis and prognosis in acute kidney injury: a systematic and met analysis. Am J Kidney Dis.2009 54: 1012-24.

10. Rachel Cullen M, Patrick T Murray, Maria C, Fitgibbon. Establishment of a reference interval of urinary neutrophil gelatinase associated lipocalin. Annals of Clinical Biochemistry. 2012; 49: 190-193.

11. Hasse-Fielitz A, Haase M, Bellomo R. Instability of urinary NGAL during long term storage. Am J kidney Dis.2009; 53: 564-65.

12. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure- definition, outcome measures, animal models, fluid therapy and information technology needs. The Second International Consensus Conference of Acute Dialysis Quality Initiative (ADQI) Group. Crit Care.2004; 8: R 204-12.

13. Mc Cullough PA. Contrast induced acute kidney injury. J Am Coll Cardiol 2008; 51(15):1419-28.

14. Gruberg L, Mintz GS, Mehran R. The prognostic inplications of further renal function deterioration within 48 hrs of interventional coronary procedures in patients with preexistent chronic renal insufficiency. Am J Cardiol.2000; 36 (5): 1542-8.

15. Malyszako J, Bachorzewska-Gazewska H, Poniatowski B, Malyszako JS and Dobrzycki S. Urinary and serum biomarkers after cardiac catheterization in diabetic patients with stable angina and without severe chronic kidney disease .Renal Fail. 2009; 31(10):910-19.

16. Toprak O. Conflicting and new risk factors for contrast induced nephropathy.J Urol. 2007; 178(6):2277-83.

17. Morabito S, Pisoleri V, Benedetti G, Di Poma A,Colantonio R, Mancone M, et al: Incidence of contrast induced acute kidney injury associated with diagnostic or interventional coronary angiography . J Nephrol. 2012; 1:0.

18. Sanaei-Ardekani M, Movahed MR, Movafagh S and Grahamm N. Contrast induced nephropathy. a review. Cardiovascular revascularization medicine. 2005; 6(2): 82-88.

19. Dangas G, Jakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN,et al: Contrast induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol. 2005; 95 (1): 13-19.

20. Nikolsky E, Mehran R, Turcot D. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. Am J Cardiol. 2004; 94(3): 300-305.

21. Keely EC, Kadakio R, Soman S. Analysis of long term survival after revascularization in patients with chronic kidney disease presenting with acute coronary syndrome. Am J Cardiol. 2003; 92(5):509-14.

22. Ling W, Zhaoni N, Ben H, Ley G, Jianping L, Huili D, et al; Urinary IL-18 and NGAL as early predictive biomarkers in contrast induced nephropathy after coronary angiography. Nephron Clin Prac.2008; 108(3):176-181.

23. Wagener G. Gubitosa G. wang S, Borregaard N, Kim M and Lee HT. Increased incidence of Acute Kidney Injury with Aprotinin use during cardiac surgery with urinary NGAL . Am J Nephrol.2008; 28(4): 576-82.

24. Haase M, Devarajan P, Fielitz -Hasse A. The outcome of neutrophil gelatinase associated lipocalin (NGAL)-positive subclinical acute kidney injury:a multicenter pooled analysis of prospective studies.J Am Coll Cardiol. 2011; 58(22):2310-2312.