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ORIGINAL ARTICLE

Urinary NGAL on First Day of Admission and Adverse Events in Infants with Acute Congestive Heart Failure.

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ABSTRACT

Background: Acute heart failure (AHF) is frequently associated with worsening renal function in pediatric patients. Neutrophil gelatinase-associated lipocalin (NGAL) serves as an early marker for acute kidney injury.

Objective: To improve survival and health outcomes of infants with acute congestive heart failure through detection of the role of U-NGAL in predicting patient outcomes.

Methods: A prospective follow-up study of 30 patients presented with acute congestive heart failure from December 2018 to May 2019 in the pediatrics department, Zagazig University Hospitals were recruited. Patients were divided into two groups: group (A): patients with AKI and group (B): patients without AKI. An echocardiographic examination was performed on admission. Urea, serum creatinine, estimated glomerular filtration rate (eGFR), and Urinary NGAL were measured on 1st day of admission, 3rd day, and at the end of recompensation therapy.

Results: Fifty (50%) patients developed AKI within the follow-up period. On the 1st day, 3rd day, and end day of recompensation therapy, urinary NGAL level was significantly elevated in infants who developed AKI. For prediction of AKI, admission urinary NGAL level >152.37 ng/ml had sensitivity and specificity of 100% and 93.3%, respectively. The area under the receiver–operator curve was 0.97. At a cut-off value > 173.2 ng/ml, the sensitivity was 100% and the specificity was 75.29% to detect mortality and adverse outcome among studied patients.

Conclusion: Admission urinary NGAL level can predict AKI and in-hospital outcome (mortality and adverse events) in infants hospitalized for AHF.

Keywords: AHF, AKI, urinary NGAL.

INTRODUCTION

In pediatric cardiac patients, Acute kidney injury (AKI) is a very common adverse event. it is the main risk factor for increased morbidity and mortality in the short run and repeated episodes of AKI lead to chronic kidney disease (CKD) especially in patients with multiple risk factors, such as heart transplant recipients **[1].** In acute and chronic heart failure there is simultaneous or sequential cardiac-renal dysfunction with bidirectional nature called cardio-renal syndrome has been recently described in adults but scarcely reported in children **[2].**

Proteinuria, serum creatinine, and blood urea nitrogen (BUN) are the most used biomarkers for early detection in acute kidney injury and chronic kidney diseases, lately. **[3]**. However, they are not sensitive for the early detection of kidney injury when therapies may be more effective**[4]**.

Doctors can change their treatment strategies to protect the kidney from damage and reduce the risk of the adverse event if a new marker provides earlier detection of chronic kidney diseases and AKI than BUN, creatinine, and proteinuria. **[5].**Neutrophil gelatinase-associated lipocalin (NGAL), is a lipocalin protein synthesized by renal tubular epithelial cells. After ischemia or nephrotoxic injury in

renal tubular epithelial cells, it was synthesized in kidney tubules within hours, and NGAL is released into the urine in an experimental model **[6]**. There were a lot of publications about using NGAL as a marker for prediction and diagnosis of AKI in adult patients with AHF, But there we, not enough information about using NGAL as a marker of prediction or diagnosis of AKI in pediatric patients.

Our study aimed to detect the role of U-NGAL in predicting patient outcomes in children with AHF.

PATIENTS AND METHODS

This prospective follow-up study was conducted in the pediatrics department, Zagazig University Hospitals from December 2018 to May 2019. This study has been carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Thirty children aged two to 48 months and presenting with symptoms and signs of AHF were enrolled in the study. AHF was diagnosed according to Ross **[7]**. The development of AKI is defined as an increase in serum creatinine by 0.3 mg/dl within 48 hours or a 50% increase in serum creatinine from the level on admission during hospitalization **[8]**. The estimated filtration rate (eGFR) was calculated using the Schwartz formula **[9]**. Infants with previous surgical cardiac correction, non-cardiac systemic chronic diseases, pre-existing renal insufficiency, or suffering from peripheral vascular diseases, or on nephrotoxic drugs before the study were excluded from the study.

Patients were divided into two groups: group (A): patients with AKI and group (B): patients without AKI. Informed consent was obtained prior to enrolment in the study from the children's guardians. The study protocol was approved by the Pediatric Ethical Committee of Zagazig University.

The patients were subjected to full history taking and thorough clinical examination and imaging studies. Imaging studies included echocardiography. Blood urea, serum creatinine, eGFR, and urinary NGAL levels were measured immediately after enrollment for day 1 measurements. Subsequent samples were collected on day 3 and at the end of the recompensation therapy. All patients underwent echocardiographic examination to assess cardiac function. Echocardiography was performed using Esaote My Lab class C Jenoe Italy systems with different probe sizes. Each child was examined according to the recommendations of the American Society of Echocardiography**[10].** The echocardiographic examination included M mode, two-dimensional, and Doppler modes. The left ventricular end-systolic and diastolic diameters, ejection fraction (EF), and fractional shortening (FS) were measured using the M mode echocardiography in the left parasternal view. Blood samples were obtained, spun, separated, and frozen at -20°C until analysis. The urinary NGAL level was measured by the enzyme-linked immunosorbent assay (ELISA) using the commercially available ELISA test kit (Cat. No. KIT 036, BioPorto Diagnostics, Gentofte Denmark/Human Lipocalin-2/NGAL-ELISA).

STATISTICAL ANALYSIS

Data were analyzed using the Statistical Package for Social Sciences (SPSS) release 16. Data showing normal distribution were presented as the means and standard deviation. The non-parametric values were tested using the Mann-Whitney test. Qualitative data are represented by frequency and relative percentage and a chi-square test was used for testing the association of the qualitative data. Receiver–operating characteristic (ROC) analyses were performed to compare the potential of admission urinary NGAL to predict the occurrence of AKI and to predict in-hospital outcome (mortality and adverse events) among infants with heart failure. In all analyses, *P* values <0.05 were considered statistically significant.

RESULTS

There was no statistically significant difference between cases with AKI and cases

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without regarding sex, etiology of heart failure, or ROSS classification. Regarding outcome, all improved cases had no AKI, however, 20% of cases with AKI died and 33.3% of them were complicated (Table 1).

The laboratory markers are presented in Table 2. There was a statistically significant difference between cases with AKI and cases without urea, creatinine, e GFR, and U-NGAL at 1st day, 3rd day, and end day of recompensation therapy (Table 2).

The sensitivity of NGAL at cut-off 152.37 ng /ml was 100%, specificity was 93.3% and the accuracy was 96.7% to detect AKI among studied patients. (Table 3).

The sensitivity of NGAL at cut-off 173.5 ng /ml was 100%, specificity was 77.3% and the accuracy was 83.3% to detect mortality and adverse outcome among studied patients (Table 4).

Table (1): Comparison between cases with AKI and cases without regarding sex, etiology of heart failure, ROSS classification, and outcome of cases.

	AKI	No AKI	P-value (Sig.)
Count	15	15	
Sex			
Female	6 (40%)	10 (66.7%)	0.14 (NS)
Male	9 (60%)	5 (33.3)	
Etiology of heart failure:			
DCM	7 (46.7%)	8 (53.3%)	0.90 (NS)
ECD	4 (26.7%)	3 (20%)	
VSD	4(26.7%)	4 (26.7%)	
Ross:			
Class: II	5 (33.3%)	3 (20%)	0.54 (NS)
Class: III	6 (40%)	9 (60%)	
Class: IV	4 (26.7%)	3 (20%)	
Outcome:			
Improved	7 (46.7%)	15 (100%)	<0.001 (HS)
Complicated	5 (33.3%)	0 (0%)	
Died	3 (20%)	0 (0%)	

DCM: dilated cardiomyopathy. ECD: endocardial cushion defects. VSD: ventricular septal defect

Table (2): Comparison between cases with AKI and cases without regarding laboratory data.

Laboratory data	AKI	No AKI	P-value (Sig.)
Count	31	31	
Urea X±SD			
1st day	20.27±6.86	9.73±3.71	<0.001 (HS)
3rd day	16.53±4.93	9.73±3.54	<0.001 (HS)
End day	13.47±3.56	9.73±3.73	0.02 (S)
Creatinine X±SD			
1st day	1.21±0.67	0.33±0.07	<0.001 (HS)
3rd day	0.85±0.56	0.34±0.06	<0.001 (HS)
End day	0.58±0.38	0.33±0.06	<0.001 (HS)

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Laboratory data	AKI	No AKI	P-value (Sig.)
Count	31	31	
eGFR X±SD			
1st day	29.53±18.19	76.80±17.75	<0.001 (HS)
3rd day	39.20±17.14	75.93±14.82	<0.001 (HS)
End day	51.07±14.62	76.47±17.09	<0.001 (HS)
U-NGAL X±SD			
1st day	206.38±68.80	81.59±52.45	<0.001 (HS)
3rd day	146.12±32.48	83.01±36.68	<0.001 (HS)
End day	111.42±28.77	83.25±32.92	0.02 (S)

Table (3): Validity of Urinary NGAL level in 1st day in the prediction of AKI among studied patients.

Cut-off value of	SN % (0.91-1 CI)	SP % (0.91-1 CI)	PPV % (0.91-1 CI)	NPV % (0.91-1 CI)	Accuracy% (0.91-1 CI)	AUC (0.91-1 CI)	P-value (Sig.)
≥152.37	100%	93.3%	93.8%	100%	96.7	0.97	<0.001 (HS)

ROC curve: Receiver Operating Characteristic curve. SN: Sensitivity. SP: Specificity. PPV: Positive Predictive Value. NPV: Negative Predictive Value. AUROC: Area Under Receiver Operating Characteristic curve. CI: Confidence Interval.

Table (4): Validity of urinary NGAL on the first day of admission in predicting in-hospital outcome (mortality and adverse events) among infants with heart failure.

Cut-off value of	SN % (0.77-1 CI)	SP % (0.77-1 CI)	PPV % (0.77-1 CI)	NPV % 0.77-1 CI)	Accuracy% (0.77-1 CI)	AUC (0.77-1 CI)	P-value (Sig.)
> 173.5	100%	77.3%	61.5%	100%	83.3	0.89	<0.001 (HS)

ROC curve: Receiver Operating Characteristic curve. SN: Sensitivity. SP: Specificity. PPV: Positive Predictive Value. NPV: Negative Predictive Value. AUROC: Area Under Receiver Operating Characteristic curve. CI: Confidence Interval.

DISCUSSION

In our study, we found that about half of our AHF cases had AKI. **Aghel et al [11]** foundthat35(38%)patients with AHF developed WRF during follow-up for five days in hospital when investigating 91 patients with AHF. Also, **Metra et al [12]** found that 34% of the patients who developed WRF during hospitalization for AHF developed WRF.

the mechanisms of WRF explain that using overzealous diuresis in the setting of AHF, leads to reduced renal perfusion, and low cardiac output heart failure, resulting in acute tubular injury. Leading to excessive neurohormonal activation and altered tubule-glomerular feedback. and more recent studies found an association between venous congestion with WRF more than low cardiac output with WRF in cases with AHF**[13].**

In our study, the patients who developed AKI had significantly higher admission urinary NGAL, serum creatinine, and urea levels and significantly lower e GFR values. This came in agreement with **Soyler et al. [14]** who investigate 91 ADHF patients for serum NGAL level and found worsening of renal function (defined as creatinine level increase ≥0.3 mg/dL). when serum NGAL level was elevated on admission.

Breidthardt et al [15] had observed that in AHF cases with AKI all renal function tests including serum creatinine, BUN, and NGAL were significantly increased, while e GFR values were significantly decreased compared with cases without AKI. **Aghel et al [11]** and **Macdonald et al [3]** found the same results according to NGAL levels.

A ROC curve analysis was performed to evaluate the individual diagnostic value of NGAL for the prediction of AKI among the studied patients. The sensitivity of NGAL at cut-off 152.37 ng/ml was 100%, specificity was 93.3% and the accuracy was 96.7% to detect AKI among studied patients. **Macdonald et al. [3]** found that NGAL level > 89 ng/ml on admission had a sensitivity of 68% and specificity of 70% with AUC of 0.71 in the prediction of AKI in patients with ADHF. Also, **Shrestha et al. [16]** used both serum and urine NGAL as sensitive markers for prediction of AKI prediction with AUC of 0.67 and 0.64 respectively.

Regarding the outcome among our patients admitted with acute congestive heart failure (22 cases improved clinically, there were 3 deaths and 5 cases developed complications as cardiogenic shock, 3 of them were in need for mechanical ventilation). All the improved cases had no AKI, however, 20% of cases with AKI died and 33.3% of them had complications.

Urinary NGAL at a cut of 173.2 ng /ml on admission conferred a higher hazard ratio for death and adverse outcome among our patients with a sensitivity of 100%, specificity of 75.29%.

Nakada et al. [17] (2017) reported the development of clinical acute kidney injury is related to elevation of U-NGAL level on the first day of admission and associated with poor prognosis in acutely decompensated heart failure patients.

CONCLUSION

Urinary NGAL can be considered as a sensitive diagnostic and prognostic marker superior to both GFR, urea, and creatinine for early detection of AKI in AHF even before GFR is markedly reduced and even before serum urea and creatinine are significantly affected.

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