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Kidney Injury Molecule 1 in Children with Heart Failure

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ABSTRACT

Background: Kidney injury molecule-1 (KIM-1) is a novel biomarker that was initially identified and evaluated in patients with acute kidney injury. It predominantly indicates tubular injury and is an earlier and more sensitive indicator of acute kidney injury than plasma creatinine. **Objective:** To evaluate the role of KIM-1 as an early marker of renal dysfunction in children with heart failure and to assess whether KIM-1 concentration is related to heart failure severity and cardiac function. **Patients and Methods:** This case-control study was carried out at the Cardiology Unit, Outpatient Cardiology Clinic, and Clinical Pathology Unit, Zagazig University Hospitals during the period from November 2018 to May 2019 included 93 children. **Results**: KIM-1 was higher in patients with acute and chronic heart failure as compared with controls also it has positive correlations with LVEDD, LVESD, and serum creatinine, while it had a negative correlation with GFR. An optimal admission KIM-1 cut off at >588 ng/ml, with a sensitivity of 85.5%, a specificity of 83.9% for WRF prediction in HF, with an area under the curve (AUC= 0.948, P>0.001). While the sensitivity of GFR and serum creatinine was 67.7%, 72.6% respectively and the specificity was 71%, 90.3% respectively with an area under the curve of 0.773 and 0.875 respectively. **Conclusions:** KIM-1 can be considered as a sensitive diagnostic marker superior to both GFR and creatinine for early detection of impaired renal function in acute and chronic HF even before GFR is markedly reduced and even before serum creatinine is significantly affected.

Keywords: Heart failure, Cardiorenal syndrome, Renal dysfunction.

INTRODUCTION

Pediatric heart failure may be encountered with or without the presence of structural heart disease and at any age from fetal life to late adolescence. It may arise from diverse causes. The most common causes of CHF in infancy are congenital heart diseases. Beyond infancy, myocardial dysfunction of various etiologies is an important cause of CHF [(1)]. Children with heart failure represented 10% to 33% of all cardiac admissions. Slightly more than half of the pediatric heart failure cases reported in both studies were due to congenital heart disease, although the incidence of heart failure in children with congenital heart disease was only 6% to 24%. This reflects the fact that congenital heart disease is considerably more common than other causes of heart failure. In contrast, 65% to 80% of children with cardiomyopathies had heart failure, but this represents only 5% to 19% of total pediatric heart failure cases. Most of heart failure cases (58% to 70%) occurred in the first year of life, with congenital heart disease disproportionately represented compared to older ages [(2)]. Renal dysfunction is a common phenomenon in heart failure and is one of the most potent prognostic indicators in these patients. This mutual interaction shares the common name of the cardiorenal syndrome [(3)].

Renal epithelial cell injury is a feature of many acute and chronic renal diseases. Kidney injury molecule-1(KIM-1), a transmembrane tubular protein, is undetectable in normal kidneys, but it is markedly induced in renal injury including acute kidney injury (AKI) and chronic kidney disease (CKD)[(4)].

AIM OF THE WORK

This study aimed to evaluate the role of KIM-1 as an early marker of renal dysfunction in children with heart failure and to assess whether KIM-1 concentration is related to heart failure severity and cardiac function.

PATIENTS AND METHODS

This case-control study was carried out at the Cardiology Unit, Outpatient Cardiology Clinic, and Clinical Pathology Unit, Zagazig University Hospitals during the period from November 2018 to May 2019. The study included 93 children, who were randomly selected, were included in this study. Our study included (31) cases with acute HF, (31) cases with chronic HF and control group which included (31) age and sex-matched apparently healthy children.

Inclusion Criteria: Age: from 2 months to 12 years.

Gender: male and female. Patients diagnosed with heart failure secondary to CHD. Exclusion Criteria: Age less than 2 months or more than 12 years. Heart failure due to cardiac causes except for CHD as cardiomyopathy. Presence of an underlying lung pathology as a cause of heart failure detected by

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history, clinical examination, and chest X-ray. Endocrinal case, metabolic or renal disease causing heart failure. Diseases affecting the level of KIM-1.
All patients were subjected to full history taking, complete clinical examination including assessment of Modified Ross classification, chest x-ray, ECG, Echocardiography, and laboratory investigations including CBC, serum creatinine, GFR, ALT, AST, Na, K, Ca and serum KIM-1 level.

Ethical Clearance:

Written Informed consent was taken from the patient parents to participate in the study. **Approval for performing the study was obtained from Pediatrics and Clinical Pathology Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval.** The work has been carried out following the code of ethics of the world medical association (Declaration of Helsinki) for studies involving humans.

Statistical Methods

Statistical analysis was performed using Microsoft® Excel® version 2010 and Statistical Package for Social Sciences (SPSS®) for Windows® version 15.0. Continuous data are to be presented as a range, mean and standard deviation (if parametric); or range, median and interquartile range (if non-parametric). Dichotomous or categorical data are to be presented as numbers and percentages. Repeated measures in the same group will be compared using two way ANOVA (analysis of variance), Wilcoxon rank test (for non-parametric continuous variables) and Chi-squared test and McNemar's test (for categorical variables). The significance level is set at 0.05.

RESULTS

Table (1): Comparison between the studied groups regarding the kidney function

Kidney function	Control	Acute HF	Chronic HF	Test	P-value (Sig.)
No.	31	31	31		
Creatinine (mg/dL)					
Median (IQR)	0.31 (0.27– 0.4)	1.4 (0.5 – 1.8)	1.1 (0.4 – 1.8)	34.86^{K}	**<0.001(HS)**
GFR (ml/min)					
Median (IQR)	126 (117–136)	82 (62 – 132)	80 (65 – 130)	18.32^{K}	**<0.001(HS)**

GFR: Glomerular filtration rate IQR: Interquartile range
^{K}Kruskal Wallis test. p< 0.05 is significant.

There was a statistically significant difference between acute and chronic HF cases when compared with the control group regarding GFR and creatinine. Table (1)

Table (2): Comparison between the studied groups regarding the echocardiographic data

Echo data	Control	Acute HF	Chronic HF	Test	P-value (Sig.)
No.	**31**	**31**	**31**		
LVEDD (mm)					
Mean ± SD	**21.5 ± 2.3**	**32.8 ± 3.4**	**31.5 ± 3.1**	**130.4***	**<0.001(HS)**
LVESD (mm)					
Mean ± SD	**15.6 ± 1.4**	**24.1 ± 2.7**	**24.4 ± 2.6**	**143.6***	**<0.001(HS)**
IVS (mm)					
Mean ± SD	**5.7 ± 0.4**	**5.7 ± 0.5**	**5.8 ± 0.6**	**0.476***	**0.623(NS)**
PW (mm)					
Mean ± SD	**5.8 ± 0.3**	**5.9 ± 0.3**	**5.8 ± 0.4**	**0.754***	**0.473(NS)**
EF (%)					
Mean ± SD	**75.0 ± 3.0**	**74.1 ± 3.2**	**73.3 ± 3.2**	**2.276***	**0.109(NS)**
FS (%)					
Mean ± SD	**39.2 ± 2.3**	**39.0 ± 2.3**	**38.2 ± 2.2**	**1.645***	**0.199(NS)**

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter,
IVS: interventricular septum thickness, PW: Left ventricular posterior wall thickness,
EF: ejection fraction, FS: fraction shortening. * One-way Anova test. p< 0.05 is significant.

Values of LVEDD and LVESD were significantly different among acute and chronic HF cases as compared to their controls while there was no significant difference regarding IVS, PW, EF, and FS. Table (2)

Table (3): Comparison between the studied groups regarding the KIM-1

KIM-1	Control	Acute HF	Chronic HF	Test	P-value (Sig.)
No.	31	31	31		
KIM-1 (ng/g creatinine)					
Median (IQR)	435 (377 – 555)	1087 (672 – 1523)	1169 (685 – 1682)	49.22[K]	**<0.001(HS)**

KIM-1: Kidney injury molecule-1 IQR: Interquartile range
[K]Kruskal Wallis test. p< 0.05 is significant.

There was a statistically significant difference in KIM-1 regarding acute and chronic HF cases when compared with the control group**.** Table (3)

Table (4): comparing KIM-1 levels with different indices of HF severity

HF severity indices	KIM-1 (ng/g creatinine)	Test	P-value (Sig.)
No.	Median (IQR)		
Ross classification			
Control	435 (377 – 555)	55.354 [K]	**<0.001(HS)**
Mild	809 (596 – 1483)		
Moderate	1097 (647 – 1628)		
Severe	1437 (1218 – 1710)		

IQR: Interquartile range [K]Kruskal Wallis test. p< 0.05 is significant.

This table displayed a median of KIM-1 among studied patients concerning heart failure severity by Ross classification. A statistically significant difference was found between the classes of heart failure as regards the median values of the KIM-1 level (P<0.001) when compared with control. Table (4)

Table (5): Correlation analysis between KIM-1 and other variables

Variable	KIM-1 (ng/g creatinine)	
	r	p
LVEDD (mm)	0.663	**<0.001**
LVESD (mm)	0.595	**<0.001**
IVS (mm)	-0.072	0.492
PW (mm)	0.100	0.339
EF (%)	-0.190	0.078
FS (%)	-0.129	0.219
Hb (gm/dL)	-0.583	**<0.001**
TLC (*1000/cc)	-0.171	0.101
PLT (*1000/cc)	0.032	0.758
Serum Na (mmol/L)	-0.065	0.539
Serum K (mmol/L)	-0.118	0.261
Serum Ca (mg/dL)	0.060	0.567
Creatinine (md/dL)	0.789	**<0.001**
GFR (ml/min)	-0.631	**<0.001**
ALT (U/L)	-0.028	0.792
AST (U/L)	0.020	0.847
Duration of illness (months)	0.038	0.770

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, IVS: interventricular septum thickness, PW: Left ventricular posterior wall thickness, EF: ejection fraction, FS: fraction shortening, Hb: Hemoglobin, TLC: total leukocytic count, PLT: platelet,Na: Sodium, K: potassium Ca: calcium, GFR: Glomerular filtration rate ALT: Alanine aminotransferase, AST: aspartate aminotransferase, HF: Heart failure.

There were significant positive correlations between KIM-1 level and LVEDD and LVESD, while there was a significant negative correlation with Hb in HF cases. There were significant positive correlations between KIM-1 level and creatinine while there was a significant negative correlation with GFR in HF cases. There were non-significant correlations between KIM-1 level and IVS, PW, EF, FS, TLC, platelet, Na, K, Ca, ALT, AST, and duration of illness in HF cases. Table (5)

Table (6): The cut-off values of KIM-1 (ng/g creatinine), creatinine (mg/dl) and GFR (ml/min) for worsening renal function prediction in HF; ROC curve analysis

Cut-off value of KIM-1	SN % (95% CI)	SP % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy % (95% CI)	AUC (95% CI)	P-value (Sig.)
KIM-1 (ng/g creatinine)							
≥ 588 ng/ml	85.5%	83.9%	91.4%	74.3%	85%	0.948	<0.001 (HS)
Creatinine (mg/dl)							
≥ 0.5mg/dl	72.6%	90.3%	93.8%	62.2%	78.5%	0.875	<0.001 (HS)
GFR (ml/min)							
≤117ml/min	67.7%	71%	82.4%	52.4%	68.8%	0.773	<0.001 (HS)

ROC curve: Receiver Operating Characteristic curve.
AUROC: Area Under Receiver Operating Characteristic curve.
SP: Specificity. PPV: Positive Predictive Value.
NPV: Negative Predictive Value. SN: Sensitivity.
95%CI: 95% Confidence Interval. p< 0.05 is significant.

A receiver operating characteristic (ROC) curve showed an optimal KIM-1 cut off at >588 ng/g creatinine, with a sensitivity of 85.5%, a specificity of 83.9% for worsening renal function prediction in HF, with an area under the curve (AUC= 0.948, P<0.001). Table (6)

A receiver operating characteristic (ROC) curve showed an optimal admission creatinine cut off at ≥ 0.5 mg/dl, with a sensitivity of 72.6%, a specificity of 90.3% for worsening renal function prediction in HF, with an area under the curve (AUC= 0.875, P<0.001). Table (6)

A receiver operating characteristic (ROC) curve showed an optimal admission GFR cut off at ≤ 117 ml/min, with a sensitivity of 67.7%, a specificity of 71% for worsening renal function prediction in HF, with an area under the curve (AUC= 0.773, P<0.001). Table (6)

DISSECTION

Renal function is usually assessed from serum creatinine concentrations and predominantly reflects glomerular filtration but not tubular function, because tubular secretion of creatinine occurs to only a small extent at high creatinine concentrations [(5)]. In our patients with acute and chronic HF, the median GFR was decreased (82 and 80 ml/min respectively compared to control group the median of GFR was in normal (126 ml/min) while creatinine was significantly higher in acute and chronic HF cases as compared with their controls.

In chronic HF, reduced GFR is mainly dependent on reduced renal perfusion, which may serve as a hypoxic trigger for tubular damage. Chronic renal hypoxia has not only been proposed as the final common pathway to end-stage renal disease but may also be the initiating trigger for a vicious circle between tubulointerstitial injury and chronic renal insufficiency. This hypothesis may be one of the pathways by which chronic renal insufficiency may develop in patients with chronic HF[(6)].

This result was in agreement with **Nymo *et al.* [(7)], Jungbauer *et al.* [(8)] and Shrestha *et al.* [(9)],** who found that GFR was lower in heart failure (HF) patients and it was an independent risk factor for cardiovascular disease (CVD), in particular for heart failure (HF). Also, **Shrestha *et al.* [(10)] and Aghel *et al.* [(11)]** demonstrated that serum creatinine levels on admission were significantly higher, while admission eGFR values were significantly lower in acute HF cases as compared with their controls.

Traditional explanations regarding the mechanisms of WRF in the setting of acute HF include overzealous diuresis, leading to reduced renal perfusion, and low cardiac output heart failure resulting in acute tubular injury. These can lead to excessive neurohormonal activation and altered tubuloglomerular feedback. Also, more recent studies have demonstrated the association between venous congestion rather than low cardiac output with WRF in ADHF. Clearly, no single mechanism can explain this complex pathophysiologic interaction between the failing heart and the impaired kidneys [(12)].

Echocardiography is a very important tool in the diagnosis of HF, it can confirm enlargement of ventricular chambers and impaired left ventricular systolic functions including EF and FS [(13)].

Our study showed a significant increase in LVEDD and LVESD in AHF and CHF groups than the control group, while there was no significant difference in left ventricular functions as measured by EF and FS in cases of AHF and CHF in comparison with normal children. Our results were in agreement with **Kindermann *et al.* [(14)]** who reported that congenital heart diseases can cause congestive HF symptoms despite normal systolic ventricular function.

Also, **Tsutsui *et al.* [(15)]** found that all patients with symptomatic CHF have been reported to have relatively normal or preserved left ventricular (LV) ejection fraction (EF). ‘‘HF with preserved EF (HFpEF)’’ has been defined as the presence of typical

CHF symptoms and signs with an EF of more than 40% or 50%. There might be an area of overlap between HFpEF and HFrEF.

There are different histopathological pathways of tubulointerstitial injury induced by glomerular damage. This damage is associated with hypoxia and oxidative stress on a tubular level, and eventually, nephron loss, which, in turn, impose hemodynamic stress and damage in the remaining nephron units. Therefore, a sensitive marker of tubular injury, which can be used to identify or confirm the presence of glomerular injury would be helpful in the evaluation of the time course of renal function and renal damage in CHF patients [16]. So, we examined the relation of Kidney injury molecule (KIM)-1, as a marker of renal inflammation with other parameters of renal function, including serum creatinine and eGFR.

In the present study, KIM-1 was higher in patients with acute and chronic heart failure (median = 1087 and 1169) as compared with controls (median 435 ng/g creatinine with the P-value <0.001). This came in agreement with **Jungbauer *et al.*** [8] who found the same results. **Damman *et al.*** [17] found that patients with heart failure have higher urinary KIM-1 compared with healthy controls. KIM-1 is also a sensitive marker for kidney injury in children undergoing cardiac surgery [18].

Singhal and Saha [19] found that KIM -1 has the potential of being an excellent marker of AKI in the pediatric emergency setting. **Han *et al.*** [20] found that Kidney injury molecule 1 {KIM-1} is a promising marker for early detection of AKI, and its concentration is markedly increased within hours following kidney injury.

Hence, KIM-1, the new biomarker of kidney injury and glomerular filtration, holds the promise of substantially improving the diagnostic approach to acute kidney injury [21].

In the present study, KIM-1 showed a significant increase in KIM-1 with increasing the severity of the clinical condition (P-value of Ross classification <0.001). This came in agreement with **Jungbauer *et al.*** [8] who found that KIM-1 showed a significant correlation with a more severe clinical condition (NYHA r ¼ 0.50, P, 0.001).

In the present study, patients with severe Ross classification presented with higher KIM-1 concentrations as compared with those patients with moderate Ross classification. Also, patients with moderate Ross classification presented with higher KIM-1 concentrations as compared with those patients with mild Ross classification but this difference was non-significant.

This agreed with **Jungbauer *et al.*** [8] who found that patients in NYHA classes 3 and 4 presented with higher KIM-1 concentrations as compared with those patients with NYHA ≤ 2 but their results were statistically significant.

Jungbauer *et al.* [8] found that assessment of tubular markers, particularly KIM-1, may help to identify heart failure patients at risk for developing renal dysfunction, the cardio-renal syndrome, and impaired survival. **Emmens *et al.*** [22] found that Kidney Injury Molecule-1(KIM-1) is a marker of tubular damage and associated with worse outcomes in heart failure (HF).

Carlsson *et al.* [23] found that participants who had a combination of high KIM-1 and low GFR appeared to have the highest heart failure risk, indicating that different aspects of kidney pathology may portray additive prognostic information.

Carlsson *et al.* [23] reported that higher urinary KIM-1 is associated with an increased risk for incident heart failure hospitalizations in the community-based ULSAM cohort.

In patients with acute HF, renal insufficiency is frequent; the early identification of such patients may represent an opportunity to develop strategies aiming for the preservation of kidney function. For example, careful titration of loop diuretic doses and avoidance of potential nephrotoxins such as intravenous radiographic contrast media [24].

In the present study, (KIM)-1 level had significant positive correlations with serum creatinine, while it had a significant negative correlation with GFR. This result runs in parallel with observations reported by **Emmens *et al.*** [22] who found that in chronic HF, plasma KIM-1 was associated with GFR (P < 0.001) and creatinine. And in acute HF, higher plasma KIM-1 levels were associated with higher creatinine (P = 0.001). But in disagreement with our study, **Jungbauer *et al.*** [8] found that there was no significant correlation between KIM-1 and each of creatinine with GFR.

Kramer *et al.* [25] found that KIM-1 is an important biomarker of AKI and acute tubular necrosis (ATN) and showed a correlation between its concentration and the degree of renal dysfunction. Renal and urinary Kim-1 correlated with proteinuria and interstitial damage.

Mårtensson *et al.* [26] found that the diagnostic value of urinary KIM-1 significantly exceeded traditional biomarkers (serum creatinine and urea) as predictors of kidney tubular histopathological changes in rats.

Recent data suggest the importance of monitoring this marker for early diagnosis, prognosis, and the therapy effects not only in patients with various forms of AKI and other renal diseases but also in patients with heart failure after cardiopulmonary bypass, various forms of the cardiorenal syndrome, cardiothoracic surgical interventions in the pediatric emergency setting, and so forth[27].

In the present study, A receiver operating characteristic (ROC) curve showed an optimal admission KIM-1 cut off at >588 ng/g creatinine, with a sensitivity of 85.5%, a specificity of 83.9% for

worsening renal function prediction in HF, with an area under the curve (AUC= 0.948, P<0.001). The sensitivity, specificity, and area under the curve were higher in KIM-1 when compared with creatinine and GFR. So, KIM-1 can be used as a predictor for worsening renal function in HF, better than creatinine and GFR.

Our result agreed with **Liang *et al.* [28] and Liangos *et al.* [29],** who showed more than 90% sensitivity in the diagnosis of AKI when KIM-1 was tested.

Khreba *et al.* [30] found that the ROC analysis of KIM-1 for early detection of AKI was done. They found the sensitivity was 48% and specificity was 94% with AUC 0.715.

Higher levels of KIM-1 have been reported in patients with impaired GFR **Nauta *et al.* [31] and Vaidya *et al.* [32],** two aspects of kidney disease that are shown to be closely associated with an increased cardiovascular risk **Matsushita *et al.* [33] and Nerpin *et al.* [34].** The fact that KIM-1 predicted cardiovascular death beyond these established markers of kidney damage and dysfunction indicates that KIM-1 portrays an aspect of kidney pathology that is not fully reflected by levels of eGFR. It is also possible that KIM-1 predicts the deterioration of kidney function, which in turn leads to an increased cardiovascular risk [35].

CONCLUSION

The conclusions of this study were limited by sample size may be considered relatively small, which restricts the power of conclusions, the lack of data on albuminuria and proteinuria as alternative markers of impaired kidney function. that the timing of biomarker measurement has an important impact on the ability of KIM-1 to predict the development of WRF since the latter was also time-dependent.

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