Role of Urinary Chitinase 3 Like Protein 1 for Early Detection of Acute Kidney Injury in Adult Critically Ill Patients

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ABSTRACT

Background: AKI is a common problem in ICU patients and is mostly multifactorial. Also, it is known to increase mortality, duration of ICU and hospital stay and increase the cost of care in critically ill patients. Early diagnosis in these settings helps in decreasing the outcome of AKI. Multiple biomarkers have developed concentrating on early diagnosis of acute kidney injury. Urinary Chitinase 3 like protein 1 is a novel biomarker studied for early detection of acute kidney injury.

Objectives: the current study was aimed to assess the role of urinary chitinase 3 like protein 1 (CHI3L1) as an early biomarker for detection of acute kidney injury in adult critically ill patients.

Patients and methods: this was a prospective cohort study that was conducted in Ain Shams University Hospital. This study included 30 adult critically ill patients with normal kidney function and they were observed for 48 hours. The development of Acute Kidney Injury was based on serum creatinine and urine output criteria according to KDIGO criteria. Urine samples, for assessment of urinary CHI3L1, urine creatinine and urine CHI3L1/Cr ratio were collected under aseptic techniques at 3 times intervals (0, 12 and 24hrs).

Results: our results showed that, of these 30 patients, 15 patients developed acute kidney injury using KDIGO criteria and 15 patients had normal kidney function. Our results showed the percentage of patient who developed AKI according to KDIGO, stage I 60.0%, stage II 33.3% and stage III 6.7%. Of these patients 80% developed AKI based on serum creatinine and 20% based on serum creatinine and urine output. Our results showed that there is statistically significant difference between AKI group and non-AKI group as regards urine chitinase 3 like protein 1(CHI3L1) at 0hour, 12 hours and 24hours (P≤0.05). As the higher level of urine CHI3L1 was found in AKI group which ranges from 35-135ng/ml with mean 94±34.02 at 0 hour, from 70-200ng/ml with mean 126.80±43.77 at 12 hours and from 105-200ng/ml with mean 160.57±28.02 which means that urine CHI3L1 level increases with AKI. Our results showed that there is statistically significant difference as regards urine CHI3L1 between non-AKI group and the 3 stages of AKI in AKI group at 0hr, 12hrs and 24hrs (P≤0.05).

Conclusion: Urinary chitinase 3 like protein 1 is a highly sensitive early marker in prediction of acute kidney injury in adult critically ill patients.

Key words: acute kidney injury, biomarkers, chitinase 3 like protein 1, critically ill patients.

INTRODUCTION

Acute Kidney Injury is a clinical syndrome with sudden decline in kidney function that occurs over a period of hours to days leading to retention of nitrogenous and metabolic waste products [1]. AKI is common in patients in the ICU. AKI is mostly multifactorial, but it is known to increase mortality, duration of ICU and hospital stay and increase the cost of care in critically ill patients. It changes the outcome of patients, especially those needing RRT [2]. AKI is considered a prevalent and serious problem worldwide. The incidence ranges from 3-20% in hospitalized patients and 30-60% in ICU patients. The mortality rates among AKI patients are still high despite the efforts done for elucidating the mechanism and introduction of RRT [3]. Now, the standard diagnostic tools for AKI diagnosis are observation of serum creatinine concentration and urine output, both of which are indicators of renal function but not kidney injury. SCr is an integrator of multiple intrarenal and extra-renal functions, and its concentration shows the balance between creatinine generation and excretion. SCr not only is a late and insensitive biomarker of changes in kidney function, but its concentration does not distinguish between structural kidney damage and functional hemodynamic triggers and could be affected by various factors. Also, patients with decreased muscle mass may not have a vigorous rise in SCr despite a substantial kidney injury [4].

Over the past decade there has been a massive expansion in discovery and validation of specific biomarkers of kidney disease. The ideal biomarker is one that can predict and detect AKI, identify the site of injury, the type and cause of

injury, predict outcomes and enable the starting and monitoring of therapeutic interventions. Biomarkers involve kidney function (glomerular filtration), tubule function (reabsorption of filtered molecules) or damage/injury. Multiple molecules have been identified that represent non-renal molecules filtered, secreted or reabsorbed, molecules that are constitutive or up regulated or molecules secreted by infiltrating immune cells. These biomarkers are proteins or molecules that exist in urinary exosomes and free filtered urine [5]. These biomarkers encompass neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, liver-type fatty acid binding protein, interleukin 18, insulin-like growth factor binding protein 7, tissue inhibitor of metalloproteinase 2, calprotectin, urine angiotensinogen and urine micro- RNA [6]. Recently, a novel biomarker, urinary chitinase3 like protein 1(UCHI3L1) can detect acute kidney injury stage 2 or more within 12 or 24hr and their results were compared to the performance of UNGAL [7]. CHI3L1 protein was recognized as a minor 39 kD whey glycoprotein detected in secretions of bovine mammary glands during non lactating periods and was established to be CHI3L1 almost a decade later. The protein was later recognized as a secreted product of human synovial cells and MG-63 osteosarcoma cells, the latter statement naming the protein YKL-40 for the one-letter symbols for the first three N terminal amino acids Tyrosine (Y), Lysine (K), and Leucine (L) and the molecular weight. CHI3L1 secreted by articular chondrocytes and synovial cells was recognized as a member of the chitinase family in 1993, and the porcine protein was sequenced in 1995 [8]. CHI3L1 has no catalytic activity and has been found to connect with strong affinity to chitin and with lower affinity to heparin and type I collagen. For a limited number of cell types in vitro, CHI3L1 has been revealed to act as a mitogen, chemotactic factor, and adhesion factor [8]. This work aimed to assess the role of urinary chitinase 3 like protein 1 (CHI3L1) as an early biomarker for detection of acute kidney injury in adult critically ill patients.

PATIENTS and METHODS

This study was observational cohort study and it was conducted in Ain Shams University Hospital. The study included **30** adult critically ill patients and they were observed for 48 hours.

The development of acute Kidney Injury will be based on serum creatinine and urine output criteria according to Kidney Disease Improving Global Outcomes (KDIGO).

An informed consent were obtained from all patients.

Inclusion criteria:
- Age 18 years or more
- Expected ICU admission 48 hours or more.
- Respiratory SOFA score (Sequential Organ Failure Assessment Score) 2 or more (pao2/fio2 <300)
  PaO2 refers to partial pressure of O2, Fio2 refers to fraction of inspired oxygen **OR**
- Cardiovascular SOFA score 1 or more (MAP <70 mmHg or patient is on vasopressor) .

Exclusion criteria:
- AKI according to KDIGO at time of enrolment
- Chronic kidney disease: by the estimated GFR using Cockcroft-Gault Equation: (140-age)*weight*.85(if female)/(serum creatinine*72)
- Recent Renal transplantation

After obtaining an informed written consent all patients were subjected to the following data:

1. **Full History and clinical Examination:**

All enrolled subjects underwent full history taking including history of co-morbidities (Hypertension, diabetes mellitus and Ischemic heart disease) and current medications. Full clinical examination with assessment of vital signs emphasis on blood pressure, urine output, cardiac and respiratory SOFA scores evaluation.

1. **Laboratory Investigations:**
❖ **Blood sample:**

Samples of venous blood were collected under complete aseptic precautions. Samples for were put in plain test tubes without anticoagulant, and the remaining were put in a test tube with ethylene diamine tetra-acetate (EDTA) (1.2mg/ml) as an anticoagulant, to be used for performing complete blood picture. After clotting, samples were centrifuged at 1500 x g for 15 minutes. Part of the separated serum was used to perform serum urea, creatinine and c- reactive protein (CRP). Serum creatinine samples were collected 4 times, first at enrollment, 2nd after 12 hours, 3rd after 24 hrs and 4th after 48 hours.

❖ **Urine sample**

Urine samples, for assessment of urinary CHI3L1, urine creatinine and urine CHI3L1/Cr ratio were collected under aseptic techniques at 3 times intervals. First at time of enrollment, 2nd after 12 hours and 3rd after 24 hours. They were

centrifugated at 2000-3000 rpm for 20 minutes then supernatant was collected into aliquots and stored at -20ºC for CHI3L1 levels estimation by ELISA. Repeated freezing and thawing was avoided. Chitinase 3 like protein 1 concentrations were measured using a commercially available enzyme-linked immuno-sorbent assay (ELISA) kits supplied by Glory Science Co., Ltd. Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were**,** Chi-square test**,** Fisher's Exact or Monte Carlo correction**,** Student t-test, F-test (ANOVA**,** Mann Whitney test**,** Kruskal Wallis test**,** Receiver operating characteristic curve (ROC), Sensitivity, Specificity**,** Positive Predictive value (PPV)**,** Negative Predictive value (NPV).

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

RESULTS

Table 1 showed that 46.7% of patients, were females and 53.3% were males with mean of age 55.53% ±11.08 ranging from 32-72 years old. 15 patients developed acute kidney injury and 15 patients had normal kidney function.

Table 2 showed that there was no statistically significant difference between the studied groups as regards GFR with either Cockroft-Gault or CKD-EPI equations at time of enrollment (P>0.05).

In **table 3,** 12 patients (40%) had diabetes mellitus, of which 8 patients (53.3%) developed AKI. 13 (43.3%) patients had hypertension, of which 8 patients (53.3%) developed AKI. From the 15 septic patients, 10 patients (66.7%) developed AKI.

Table 4 showed that there was a statistically significant difference between the studied groups as regards cardiac SOFA score (P ≤ 0.05), while this no statistically significant difference as regards respiratory SOFA score (P> 0.05).

Table 5 showed that the percentage of patient who developed AKI according to KDIGO, stage I 60.0%, stage II 33.3% and stage III 6.7%. Of these patients 80% developed AKI based on serum creatinine and 20% based on serum creatinine and urine output. This table also showed

the percentage of patient who progressed to worse stage of AKI, 28.6% remained at stage I, stage II became 42.9% and stage III 28.6%. The progress based on serum creatinine 57.1% and serum creatinine with urine output 42.8%. **Table 6 and figure 1** showed that there was a statistically significant difference between AKI group and non-AKI group as regards urine chitinase 3 like protein 1(CHI3L1) at 0, 12 and 24hours (P≤0.05). As the higher level of urine CHI3L1 was found in AKI group which ranges from 35-135ng/ml with mean 94±34.02 at 0 hour, from 70-200ng/ml with mean 126.80±43.77 at 12 hours and from 105-200ng/ml with mean 160.57±28.02 which means that urine CHI3L1 level increases with AKI.

Table 7and figure 2 showed that there was a statistically significant difference between AKI group and non-AKI group as regards urine CHI3L1/Cr. ratio at 0, 12 s and 24hours (P≤0.05). As the higher level of urine CHI3L1/Cr. ratio was found in AKI group which ranges from 61-318ng/mg with mean 163±68.85 at 0 hour, from 151-804ng/mg with mean 316.33±177.48 at 12 hours and from 143-895ng/mg with mean 590±214.23 which means that urine CHI3L/Cr. ratio level increases with AKI.

Table 8 showed that there was a statistically significant difference between AKI and non-AKI group as regards mortality in days (P ≤0.05).

Table 9 and figure 3 showed that sensitivity of urine CHI3L1 as early marker to predict acute kidney injury in AKI group (versus non-AKI) regarding our study was 100 % at 0, 12 and 24hrs, while specificity is 80% at 0hr, 100% at 12hrs and 100% at 24hrs. With a positive predictive value of 88.2 at 0hr,100 at 12hr and 100 at 24hrs and negative predictive value of 100 at 0, 12 and 24hrs (p<0.001).

Table 10 and figure 4 showed that sensitivity of urine CHI3L1/Cr. as early marker to predict acute kidney injury in AKI group (versus non-AKI) regarding our study is 100 % at 0hr, 12hrs and 24hrs ,while specificity is 93.33% at 0hr, 100% at 12hrs and 100% at 24hrs. With a positive predictive value of 93.7 at 0hr,100 at 12hr and 100 at 24hrs and negative predictive value of 100 at 0hr, 12hrs and 24hrs (p<0.001).

Table 11 showed that there was a statistically significant difference as regards urine CHI3L1 between non-AKI group and the 3 stages of AKI in AKI group at 0hr, 12hrs and 24hrs (P≤0.05). Table 12, showed that there was no statistically significant difference as regards urine CHI3L1 level in different stages of AKI in AKI group (P>0.05).

Table 1: comparison between the two studied groups according to demographic data

	Total (n = 30)		AKI (n = 15)		Non-AKI(n = 15)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Gender							$\chi^2=$ 0.000	1.000
Female	14	46.7	7	46.7	7	46.7		
Male	16	53.3	8	53.3	8	53.3		
Age (years)							t = 0.786	0.438
Min. – Max.	32.0 – 72.0		35.0 – 72.0		32.0 – 65.0			
Mean ± SD.	55.53 ± 11.08		57.13 ± 12.53		53.93 ± 9.57			
Median	56.0		60.0		55.0			
BMI (kg/m²)							U = 108.00	0.852
Min. – Max.	17.72 – 51.40		20.20 – 50.60		17.72 – 51.40			
Mean ± SD.	28.44 ± 9.16		28.56 ± 9.10		28.32 ± 9.53			
Median	25.55		25.70		25.39			

Table 2: comparison between the two studied groups according to GFR

GFR	Total (n = 30)	AKI (n = 15)	Non-AKI (n = 15)	t	p
Cockroft				0.956	0.347
Min. – Max.	92.0 – 234.0	92.0 – 234.0	92.0 – 200.0		
Mean ± SD.	137.53 ± 37.38	131.0 ± 35.11	144.07 ± 39.62		
Median	134.0	124.0	143.0		
CKD-EPI				0.849	0.403
Min. – Max.	91.0 – 159.0	95.0 – 159.0	91.0 – 151.0		
Mean ± SD.	114.90 ± 18.61	112.0 ± 17.61	117.80 ± 19.74		
Median	113.50	105.0	118.0		

Table 3: comparison between the two studied groups according to risk factors

Risk factors	Total (n = 30)		AKI (n = 15)		Non-AKI (n = 15)		χ^2	p
	No.	%	No.	%	No.	%		
Diabetes M	12	40.0	8	53.3	4	26.7	2.222	0.136
Hypertension	13	43.3	8	53.3	5	33.3	1.222	0.269
Sepsis	15	50.0	10	66.7	5	33.3	3.333	0.068
HF	5	16.7	1	6.7	4	26.7	2.160	FEp=0.330
IHD	7	23.3	2	13.3	5	33.3	1.677	FEp=0.390
Arrhythmia	8	26.7	3	20.0	5	33.3	0.682	FEp=0.682
Pul. Embolism	2	6.7	0	0.0	2	13.3	2.143	FEp=0.483
Nephrotoxic drugs	9	30.0	4	26.7	5	33.3	0.159	FEp=1.000

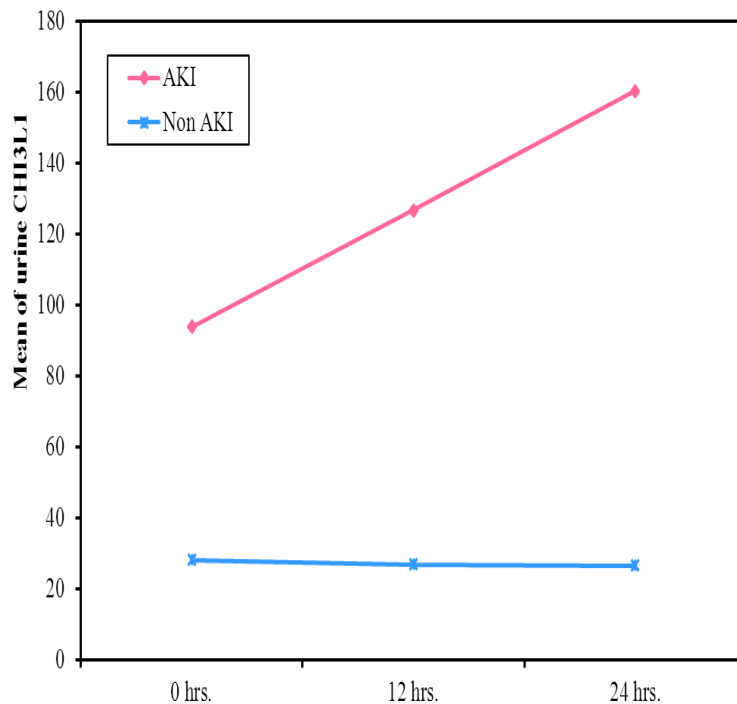**Table 4: comparison between the two studied groups according to SOFA**

SOFA	Total (n = 30)	AKI (n = 15)	Non-AKI (n = 15)	Test f Sig.	p
Cardiac				U = 67.50*	0.041*
Min. – Max.	0.0 – 4.0	0.0 – 4.0	0.0 – 4.0		
Mean ± SD.	1.77 ± 1.89	2.40 ± 2.03	1.13 ± 1.55		
Median	0.50	4.0	0.0		
Resp.				t = 1.570	0.128
Min. – Max.	1.0 – 3.0	2.0 – 3.0	1.0 – 3.0		
Mean ± SD.	2.30 ± 0.60	2.47 ± 0.52	2.13 ± 0.64		
Median	2.0	2.0	2.0		

Table 5: distribution of the studied cases according to stage and progress in AKI group

	No.	%
Stage (n = 15)		
I	9	60.0
II	5	33.3
III	1	6.7
Cr. Criteria	12	80.0
Cr. Criteria& UOP	3	20.0
Progress (n = 14)		
Stage I	4	28.6
Stage II	6	42.9
Stage III	4	28.6
Cr. Criteria	8	57.1
Cr. Criteria& UOP	6	42.8

Table 6: comparison between the two studied groups according to urine CHI3L1 (ng/ml)

Urine CHI3L1	Total	AKI	Non-AKI	t	p
0 hrs.	**(n = 30)**	**(n = 15)**	**(n = 15)**		
Min. – Max.	20.0 – 135.0	35.0 – 135.0	20.0 – 45.0		
Mean ± SD.	61.10 ± 41.28	94.0 ± 34.02	28.20 ± 7.25	7.327[*]	<0.001[*]
Median	40.0	103.0	26.0		
12 hrs.	**(n = 30)**	**(n = 15)**	**(n = 15)**		
Min. – Max.	21.0 – 200.0	70.0 – 200.0	21.0 – 38.0		
Mean ± SD.	76.87 ± 59.27	126.80 ± 43.77	26.93 ± 4.35	8.794[*]	<0.001[*]
Median	54.0	120.0	25.0		
24 hrs.	**(n = 29)**	**(n = 14)**	**(n = 15)**		
Min. – Max.	20.0 – 200.0	105.0 – 200.0	20.0 – 38.0		
Mean ± SD.	91.24 ± 70.89	160.57 ± 28.02	26.53 ± 5.34	17.600[*]	<0.001[*]
Median	38.0	156.0	27.0		

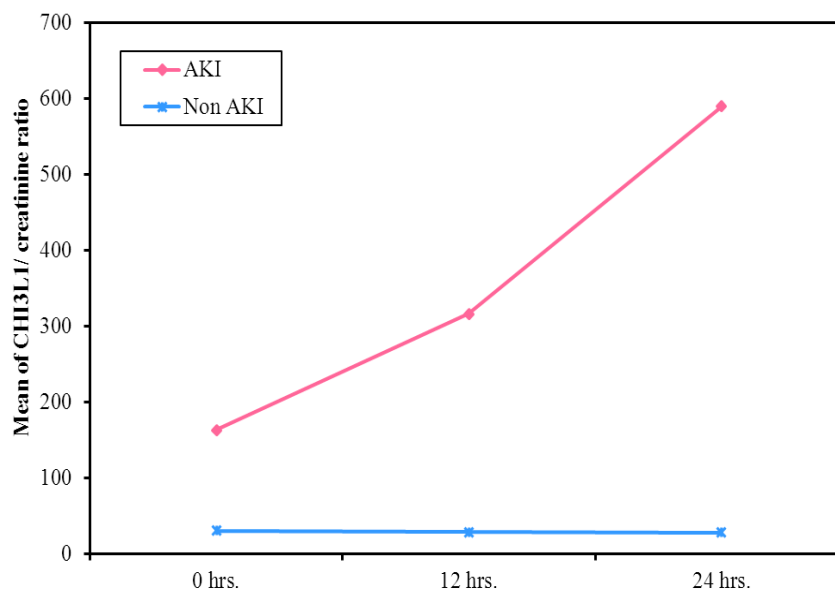**Figure 1: comparison between the two studied groups according to urine CHI3L1**

Figure 2: comparison between the two studied groups according to CHI3L1/ Creatinine ratio

Table (7): Comparison between the two studied groups according to urine CHI3L1/ Creatinine ratio (ng/mg)

L1/ Creatinine ratio	Total	AKI	Non-AKI	U	p
0 hrs.	**(n = 30)**	**(n = 15)**	**(n = 15)**		
Min. − Max.	16.0 − 318.0	61.0 − 318.0	16.0 − 94.95		
Mean ± SD.	96.81 ± 83.77	163.13 ± 68.85	30.49 ± 19.29	3.000[*]	<0.001[*]
Median	73.0	144.0	24.87		
12 hrs.	**(n = 30)**	**(n = 15)**	**(n = 15)**		
Min. − Max.	20.58 − 804.0	151.0 − 804.0	20.58 − 55.46		
Mean ± SD.	172.58 ± 191.37	316.33 ± 177.48	28.83 ± 9.10	0.000	<0.001[*]
Median	103.23	239.0	24.52		
24 hrs.	**(n = 29)**	**(n = 14)**	**(n = 15)**		
Min. − Max.	18.0 − 895.0	143.0 − 895.0	18.0 − 71.0		
Mean ± SD.	299.45 ± 320.92	590.0 ± 214.23	28.28 ± 12.77	0.000	<0.001[*]
Median	71.00	653.0	25.92		

Table (8): Comparison between the two studied groups according to mortality (days)

	Total (n = 30)		AKI (n = 15)		Non-AKI (n = 15)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Mortality (days)								
Survived	6	20.0	0	0.0	6	40.0	$\chi^2=$	[FE]p=
Died	**24**	**80.0**	**15**	**100.0**	**9**	**60.0**	7.500[*]	0.017[*]
Min. − Max.	1.0 − 120.0		1.0 − 15.0		10.0 − 120.0		U =	<0.001[*]
Mean ± SD.	32.21 ± 40.28		6.87 ± 3.85		74.44 ± 37.79		2.500[*]	
Median	9.50		7.0		60.0			

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Table 9: agreement (sensitivity, specificity) for urine CHI3L1 to predict AKI vs non-AKI

Urine CHI3L1	AUC	P	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
0 hrs.	0.979*	<0.001*	0.94 – 1.02	>30	100.0	80.0	88.2	100.0
12 hrs.	1.000*	<0.001*	1.0 – 1.0	>38	100.0	100.0	100.0	100.0
24 hrs.	1.000	<0.001*	1.0 – 1.0	>38	100.0	100.0	100.0	100.0

Figure 3: ROC curve for Urine CHI3L1 to predict AKI vs non- AKI

Table 10: agreement (sensitivity, specificity) for CHI3L1/ Creatinine ratio to predict AKI vs non-AKI

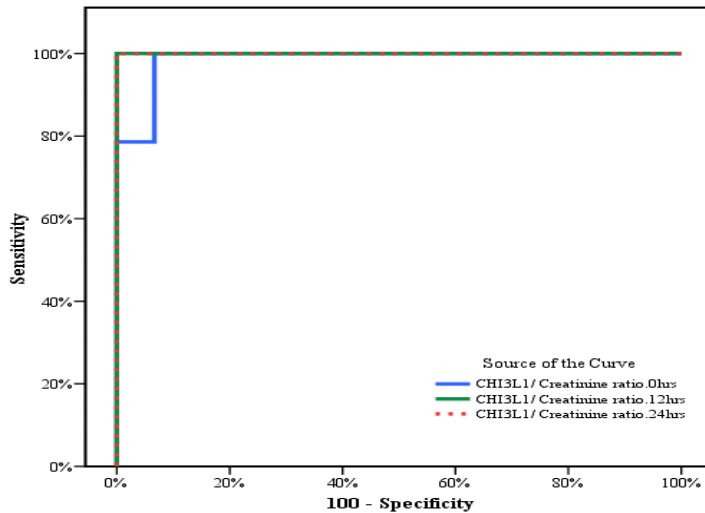| CHI3L1/ Creatinine ratio	AUC	P	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
0 hrs.	0.986*	<0.001*	0.95 – 1.02	>46	100.0	93.33	93.7	100.0
12 hrs.	1.000*	<0.001*	1.0 – 1.0	>55.46	100.0	100.0	100.0	100.0
24 hrs.	1.000*	<0.001*	1.0 – 1.0	>71	100.0	100.0	100.0	100.0

Figure 4: ROC curve for CHI3L1/ Creatinine ratio to predict AKI vs non-AKI

Table 11: relation between AKI stage and urine CHI3L1in total sample

Urine CHI3L1	AKI stage			F	p
	0	**I**	**II+III**		
0 hrs.	**(n= 15)**	**(n= 9)**	**(n= 6)**		
Min. – Max.	20.0 – 45.0	45.0 – 133.0	35.0 – 135.0	28.019*	<0.001*
Mean ± SD.	28.20 ± 7.25	100.22 ± 28.27	84.67 ± 42.27		
Median	26.0	103.0	87.50		
Sig. bet. Grps	$p_1<0.001^*,p_2<0.001^*,p_3=0.237$				
12 hrs.	**(n= 15)**	**(n= 9)**	**(n= 6)**		
Min. – Max.	21.0 – 38.0	70.0 – 200.0	70.0 – 160.0	42.805*	<0.001*
Mean ± SD.	26.93 ± 4.35	137.67 ± 47.19	110.50 ± 35.63		
Median	25.0	120.0	107.50		
Sig. bet. Grps	$p_1<0.001^*,p_2<0.001^*,p_3=0.098$				
24 hrs.	**(n= 15)**	**(n= 9)**	**(n= 5)**		
Min. – Max.	20.0 – 38.0	105.0 – 200.0	134.0 – 160.0	208.399*	<0.001*
Mean ± SD.	26.53 ± 5.34	170.22 ± 30.56	143.20 ± 9.86		
Median	27.0	180.0	140.0		
Sig. bet. Grps	$p_1<0.001^*,p_2<0.001^*,p_3=0.012^*$				

Table 12: relation between AKI stage and urine CHI3L1in AKI group

Urine CHI3L1	AKI stage			t	p
	I	**II**	**III**		
0 hrs.	**(n= 9)**	**(n= 5)**	**(n= 1[#])**		
Min. – Max.	45.0 – 133.0	35.0 – 135.0		0.734	0.477
Mean ± SD.	100.22 ± 28.27	85.60 ± 47.19	80.0		
Median	103.0	95.0			
12 hrs.	**(n= 9)**	**(n= 5)**	**(n= 1[#])**		
Min. – Max.	70.0 – 200.0	70.0 – 140.0		1.580	0.140
Mean ± SD.	137.67 ± 47.19	100.60 ± 29.19	160.0		
Median	120.0	95.0			
24 hrs.	**(n= 9)**	**(n= 4)**	**(n= 1[#])**		
Min. – Max.	105.0 – 200.0	134.0 – 160.0		1.634	0.131
Mean ± SD.	170.22 ± 30.56	144.0 ± 11.20	140.0		
Median	180.0	141.0			

DISCUSSION

Acute kidney injury (AKI) occurs in about half of adult critically ill patients. Besides its known adverse effects on individual patient outcomes, both in the short and long-term, AKI leads to an important socioeconomic burden resulting from its relationship with the development of CKD and end stage renal disease demanding renal replacement therapy [7]. Biomarkers, or 'measurable and quantifiable biological parameters, that respond to acute kidney stress (AKS) expose new horizons regarding the prediction and early discovery of emerging AKI. These biomarkers serve as substitute measurements, estimating renal cell perfusion, function or metabolism [9].

The current study aimed to assess the role of urinary chitinase 3 like protein 1 (CHI3L1) using (YKL-40, CHI3L1 ELISA kit) as an early biomarker for detection of acute kidney injury in adult critically ill patients. This study was conducted over 30 adult critically ill patients collected from Ain Shams University Hospital, all with normal kidney function at time of enrollment. Following 48hrs of observation, 15 patients developed AKI according to KDIGO criteria and 15 patients had normal kidney function. Of total patients, 46.7% were females and 53.3% were males with mean of age 55.53% ±11.08 ranged from 32-72 years old, with mean GFR was 137.53±37.38 using cockroft-gault equation and 114.90±18.61 using CKD-EPI.

Of total 15 septic patients, 10 patients were developed AKI (66.7%) and 5 patients had normal kidney function. These results go in agreement with results of **Alobaidi *et al.*** [10] which stated that sepsis associated AKI(SA-AKI) has a high incidence rate in critically ill patients (47.5%). Other common risk factors included diabetes mellitus which was present in 12 patients (40% of total patients, with 53.3% of them developed AKI) and hypertension which was present in 13 patients (43.3% of total patients, with 53.3% of them developed AKI). These results go in agreement with results of **Cartin-Ceba *et al.*** [11] ,they stated that there was a significant increased risk of AKI in critically ill patients with older age, diabetes, hypertension.

The results of our study showed that patients who developed AKI had a higher mean cardiac SOFA score which ranged from 0.0-4 with mean 2.40±2.03 in comparison with non-AKI group which ranged from 0.0-4 with mean 1.13±1.55 which was statistically significant (P≤

0.05). These results go in agreement with those of **Hoste *et al.*** [12]. They stated that greater proportion of AKI had hypovolemic or septic shock and treated with vasopressor at time of ICU admission.

Our results showed that 12 (80%) of AKI patients were diagnosed based on serum creatinine criteria of KDIGO classification and these results go in agreement with those of **De Loor *et al.*** [7] , they demonstrated better AUC-ROCs when considering SCr alone for diagnosis. Out of 12 patients, 60% were stage I, 33.3% were stage II, 6.7% were stage III. This go in agreement with results of **Luo *et al.*** [13] that showed when using KDIGO criteria, stage I predominate followed by stage II then stage III. However, the results didn`t agree with results of **Hoste *et al.*** [12], they reported that 30% of AKI in ICU were stage III, 18.4% were stage I and 8.9% stage II.

The results of our study showed that with progression to more severs stages of AKI, 42.8% of patients were diagnosed depending on both serum creatinine and urine output criteria of KDIGO compared to 20% first diagnosed with AKI depending on both criteria. This goes in agreement with results of **Kellum *et al.*** [14], they demonstrated that patients meeting both UO and SC criteria for AKI have intensely worse outcomes compared with patients who have AKI only or mainly by one criterion.

We measured CHI3L1 concentration in urine using YKL-40 (CHI3L1) ELISA (enzyme-linked immune-sorbent assay) kits. Results of our study demonstrated that the mean of urine CHI3L1 level in AKI group at 0hr (time of enrollment), 12hrs and 24hrs were 94.0±34.02, 126±43.77 and 160.57±28.02 respectively which is significantly higher compared to non-AKI group with mean of 28.20±7.25, 26.93±4.35 and 26.53±5.34 respectively (P< 0.001). This goes with the hypothesis that BRP- 39/YKL-40 is an important mediator of the reparative response after ischemic kidney injury, in both AKI and renal transplantation [15].

Our results go in agreement with other studies as study of **De Loor *et al.*** [7] . They demonstrated that UCHI3L1 measured in critically ill patients admitted to an ICU, predicted the occurrence of AKI stage ≥2 within a 12-h or 24-h observation period. Another study demonstrated that urinary CHI3L1 was increased in human septic patients with AKI and not without AKI [16]. Also, **Mosa *et al.*** [17] stated that,

taken together, YKL-40 with the best renal troponins (NGAL) might improve conformity of the risk of AKI between patients without any indications of primary renal damage and strengthen early prediction of sepsis-induced AKI. Another study of **Hall et al.** [18] demonstrated that YKL-40 is a repair-phase protein that is measurable in urine on the first day of clinically apparent AKI and offers only modest prognostic potential on its own.

Our results didn`t go in agreement with **results of De Loor et al.** [9], they found that in adult patients who had elective cardiac surgery, UCHI3L1 had insufficient predictive value for CSA-AKI. This was also true for the recognized tubular damage biomarker UNGAL. This may be due to the cases of AKI was mainly without acute tubular damage and that subclinical AKI was uncommon in this cohort.

After correction of urinary CHI3L1 concentrations for urinary dilution by calculating the ratio to urine creatinine (UCr), these results were statistically significant (P<0.001) with the mean of UCHI3L1/Cr ratio at 0, 12 and 24hrs at AKI group were 163.13±68.85, 316.33±177.48 and 590±214.23 respectively versus 30.49±19.29, 28.83±9.10 and 28.28±12.77 respectively in non-AKI group. These results doesn`t go in agreement with those of **De Loor et al.** [7] stated that with calculating the ratio to UCr, decreasing the AUC-ROC for biomarker when diagnosing AKI stage ≥2 based on SCr or UO, while there is no difference observed when diagnosing AKI stage ≥2 based on SCr alone.

YKL-40 (CHI3L1) is a product of the chitinase 3–like 1 gene and upregulated in kidney macrophages after ischemia-reperfusion injury. In addition, in AKI, increased urinary levels of YKL-40 were linked to adverse outcomes, involving renal function worsening and in-hospital death [19].

The results of our study showed increased mortality rate in patients with AKI versus non-AKI patients which is statistically significant (P<0.001). This goes in agreement with results of **Singbartl and Kellum** [20] they reported that there is now strong evidence from clinical studies that both short-term and long-term outcomes are adversely affected by AKI. Hospital mortality increases in association with AKI stage. Furthermore, survival is affected for at least 1 year and maybe longer.

Regarding our study, we found the sensitivity of UCHI3L1and UCHI3L1/Cr. ratio for early detection of AKI at 0, 12 and 24hrs was 100% ,while the specificity at 0hr was 80%, at 12hrs 100% and at 24hrs 100% for UCHI3L1 and 93.33%, 100% and 100% at 0hr, 12hrs and 24hrs respectively for UCHI3L1/Cr. ratio with a positive predictive value of 88.2%, 100% and 100% for UCHI3L1 and 93.7%,100% and 100% for UCHI3L1/Cr. ratio at 0hr, 12hrs and 24hrs respectively and negative predictive value of 100% at 0hr, 12hrs and 24hrs for both UCHI3L1 and UCHI3L1/Cr. ratio (P<0.001) in AKI group vs non-AKI. According to these findings, utilization of urine CHI3L1 as a biomarker of early detection of AKI seems promising; however, thorough clinical studies and larger clinical trials would be needed to strengthen the argument for its clinical usage and give its value true weight.

Our results go in agreement with **those of De Loor et al.** [7] whom demonstrated that samples collected in the 24 h before diagnosis of the first episode of AKI (SCr/UO) stage ≥2 had 2.0 times higher (95 % CI: 1.3–3.1) estimated marginal mean of UCHI3L1 than those not followed by a first episode of AKI (SCr/UO) stage ≥2 within the next 24 h.The results of our study showed there was a significant correlation between UCHI3L1 and AKI stages (I, II and III) when comparing between AKI group and non-AKI group (P<0.001) at different time interval (0hr, 12hrs and 24hrs). These results go in agreement with those of **De Loor et al** [7] , they demonstrated that samples matching AKI (SCr/UO) stage 1 at time of collection had higher UCHI3L1 concentrations than those corresponding with no AKI (SCr/UO) at the time of collection (P <0.001).

When comparing different stages of AKI in the AKI group, our results showed that there was no statistically significant difference between UCHI3L1 concentrations and different AKI stages (P>0.05). These results go in agreement with those of **De Loor et al.** [7] which stated that stage 1 and stage 2 samples had similar UCHI3L1 concentrations. While, the results didn`t agree with the same study when comparing different concentrations of UCHI3L1 between stage II and stage III which had higher concentrations.

CONCLUSION

Urinary chitinase 3 like protein 1 is a highly sensitive early marker in prediction of acute kidney injury in adult critically ill patients.

LIMITATIONS of the STUDY

First: the small number of studied patients; second: according to KDIGO guidelines,

reference SCr was the lowest within the previous 3 months before enrollment. This was exposed to bias as most of measurements are done when the patient is a sick state so it won`t true baseline kidney function.

RECOMMENDATION

- Further large cohort study and different settings for assessment of urinary Chitinase 3 like protein 1 as early biomarker for diagnosis of acute kidney injury.

- Further large cohort study for assessment of the role of urinary Chitinase 3 like protein 1 as a prognostic marker of severity in acute kidney injury.

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