Early Prediction of Acute Kidney Injury in Patients with Acute on Chronic Liver Failure by Measuring Kidney Injury Molecule-1 Level in Urine at Zagazig University Hospitals

Ahmed A. Wahdan[1], Ahmed M. El-Gebaly[2], Khorshed SE[2], Mohamed Emam[2], Heba F Pasha[3], Elkhashab MN[2]

[1]Tropical Medicine Department, Ahrar Teaching Hospital ,Zagazig, Egypt.
[2]Tropical Medicine Department, Faculty of Medicine, Zagazig University, Egypt.
[3]Biochemistry Department ,Faculty of Medicine, Zagazig University, Egypt.

Corresponding Author
Ahmed M. El-Gebaly

Mobile:
+201225540307

E mail:
icegebo2011@yahoo.com

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Background and study aim: Some of patients with decompensated cirrhosis will exhibit newly developed acute liver failure. This condition is called acute-on-chronic liver failure (ACLF). Acute kidney injury (AKI) is common with ACLF. Kidney injury Molecule-1 (KIM-1) is an ideal biomarker of AKI. The aim of this study was to evaluate role of KIM-1 in prediction of AKI in ACLF patients.

Patients and Methods: Eighty four patients were included in this study. They were selected from hospitalized patients with acute decompensated cirrhosis. They were allocated into two groups; group I: patients with no acute-on-chronic liver failure (ACLF), group II: patients with ACLF.

Results: KIM-1 was significantly higher in the ACLF (group II). KLM-1 median was 2.4 in group I vs 7.35 in group II with p value <0.001. We found that at cut off value of ≥0.5 KLM-1 can predict the presence of AKI with sensitivity of 85.7%, specificity 88.1%, positive predictive value 87.8%, negative predictive value 86%, accuracy 86.9% and AUC= 0.867 p <0.001.

Conclusion: KLM-1 rises significantly in patients with ACLF. KLM-1 can be reliable in prediction of the presence of acute kidney injury in decompensated cirrhosis.

INTRODUCTION

Patients with cirrhosis may create intense inconveniences, for example, ascites, hepatic encephalopathy, gastrointestinal bleeding, and bacterial infection necessitate hospitalization **[1]**. On admission, a portion of these patients will have insignificant decompensated cirrhosis, though others will show decompensated cirrhosis related with recently created liver or potentially additional hepatic organ disappointment **[2]**.

Patients with cirrhosis and intense organ disappointment are at high hazard for momentary passing. It has turned out to be standard to allude to these people as patients with intense acute-on-chronic liver failure (ACLF). ACLF scenes are in charge of an enormous extent of the social insurance costs owing to intense decompensation of cirrhosis. Subsequently, the advancement of ACLF is a significant result in clinical preliminaries, and its avoidance is a key segment of cirrhosis **[3, 4]**.

It is suggested that the Sequential Organ Failure Assessment (SOFA) score be used to diagnose failure of organs in patients with cirrhosis referred to hospital **[5].** Like the original score, the Chronic liver failure (CLIF)-SOFA score assessed six organ (circulation, kidneys, liver, lungs, brain and coagulation); function tests of the kidney is deteriorated in ACLF patients **[6]**.

There is some agents for AKI detection, including: kidney injury molecule 1 (KIM-1), interleukin-18 (IL-18) and NGAL (uNGAL) and blood neutrophil gelatinase lipocalin (sNGAL) and cystatin C **[7]**. (KIM-1) has definite properties so it is a perfect reagent of harmness of the kidney **[8]**.

The Aim of This Work

This work aims to investigate non-invasive reagents for speedy detection, prognostic indicators and their association with adverse events, mainly mortality for AKI in ACLF patients.

PATIENTS AND METHODS

Our study was case control study. It included 84 patients with liver cirrhosis diagnosed by combination of clinical, radiological and laboratory evidence. They were selected from patients who have sudden decompensated liver cirrhosis hospitalized between 2014 to 2018 in Tropical Medicine Department, Hospital of Zagazig University and in Tropical Medicine Department, Al ahrar Teaching Hospital, Zagazig, Egypt who did not require hospital entry within the last three months of screening for a complication of cirrhosis and admitted to the medical center for further than 24 hours for the cure of sudden decay of liver function. ACLF patients can have other organ failure, assessed by The EASL CLIF-SOFA which assesses six organ systems (brain, coagulation, circulation, lungs, liver and kidneys). Liver failure was outlined as a blood level of bilirubin 12.0 mg/dl or higher. Failure of the kidney was outlined as a level of serum creatinine 2.0 mg/dl or higher. The following patients were prohibited from the study; patients <18 years old, patients who didn't give consent to partake in the study, patients with history of one or more attack of decompensation before last admission, patients with severe long standing extra-hepatic diseases, patients with long standing kidney failure and patients with intra or extra hepatic malignancy. On admission, patient underwent basic evaluation including thorough history taking and clinical examination. Patients also conducted ultrasonic examination of the abdomen. Patients were exposed to routine laboratory investigations including; complete blood picture and ESR, liver function tests namely serum albumin, bilirubin and serum transaminases, coagulation profile, HCV Ab and HBVs Ag and kidney function tests namely estimated Glomerular Filtration Rate (eGFR), urea and creatinine. The severity of liver disease was classified according to Child-Pugh classification. EASL CLIF SOFA score was done. Urine KIM1was done by Human KIM-1 ELISA Test KIT for the detection of KIM-1 in Human Urine.

Patients were dispensed into 2 groups according to existence or nonappearance of ACLF. Group I included patients without acute on top of chronic liver failure (no=42) 29 males and 13 females. Group II included patients with ACLF (no=42) 27 males and 29 females.

Statistical methods

All data were gathered, systematized and analyzed statistically utilizing SPSS model 20. Continuous numerical factors were demonstrated as the mean ± SD & median (range), and categorical qualitative factors were demonstrated as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Independent samples Student's t-test was utilized to differentiate two classes of normally distributed data. One way ANOVA (F test) was utilized to differentiate further than two classes of normally distributed data. Smallest remarkable variation (Tukey LSD) was utilized to differentiate between each two independent groups. Categorical data were differentiated using Chi-square test. Pearson correlation test was utilized to decide correlation of different quantitative variables. Spearman's correlation was performed for qualitative or nonparametric data. Linear regression was performed for quantitative continuous data. Every analysis were two sided. P-value <0.05 was reviewed statistically remarkable (S), p-value <0.001 was considered extremely statistically remarkable (HS), and p-value ≥0.05 was performed statistically unremarkable (NS).

RESULTS

Table 1 exhibits a differentiation uniting the examined gatherings as regards to the data related to stricture of population. It exhibits that there is no remarkable differentiation between the two examined gatherings as regards to sex and age.

Table 2 exhibits a differentiation between the examined groups as regards to routine laboratory parameters, It exhibits that there is remarkable differentiation between the two examined groups as regards to ALT and AST, while no remarkable differentiation as regards to creatinine, INR, platelets and total bilirubin levels. Also no remarkable differentiation between the two examined groups as regards to albumin, total protein and WBCs.

Table 3 exhibits that there is remarkable differentiation between the two examined groups as regards to ascites and Glasgow coma scale. But there is no remarkable differentiation between the examined groups as regards to GI bleeding, encephalopathy and jaundice.

Table 4 exhibits there is remarkable differentiation between the examined groups as regards to kidney affection by ultrasonography but no remarkable differentiation between the examined groups as regards to liver enlargement, and splenic enlargement.

Table 5 exhibits that there is high remarkable differentiation between the examined groups as regards to Child Pugh classification.

Table 6 exhibits that there is high remarkable differentiation between the examined groups as regards to Clif sofa score.

Table 7 exhibits that there is high remarkable differentiation between the two examined groups as regards to KIM-1.

ROC curve

On blotting ROC curve to test diagnostic performance of KIM-1 in detecting the AKI. It shows that at cut off value of ≥0.5 KIM-1 can predict the presence of AKI with sensitivity of 85.7%, specificity 88.1%, positive predictive value 87.8%, negative predictive value 86%, accuracy 86.9% and AUC= 0.867 p<0.001 (Table 8).

Table 9 exhibits that there is high rejection remarkable interdependence between KIM-1 and Glasgow coma scale. The lower the level of KIM-1 the higher the Glasgow coma scale. Also there is a positive significant correlation between KIM -1 and kidney affection by ultrasonography.

Table 10 exhibits that KIM -1 level can predict Glasgow coma scale by 21.4%.

Table 11 exhibits that KIM -1 is remarkable predictor for acute kidney injury as it is 11-12 times alike to be higher in AKI patients.

Table (1): Studying of demographic data in between the studied groups

Variable	Non ACLF group (n=42)		ACLF group (n=42)		t-test	P value
Age: (years):						
Mean ± SD Range	47.4±14.4 (19-71)		51.45±14.9 (19-72)		1.26	0.208 (NS)
	No.	**%**	**No.**	**%**	χ^2	**P value**
Sex:						
Female Male	13 29	31.0 69.0	15 27	35.7 64.3	0.214	0.643 (NS)

X2 for Chi square test P value is significant if <0.05

Table (2): Laboratory data in between the studied groups

Variable	Non ACLF (n=42)	ACLF (n=42)	t-test	P value
Total protein:				
Mean ± SD Range	7.82±0.69 6.6-9	7.7±0.74 5.9-9	0.804	0.423 (NS)
Albumin :				
Mean ± SD Range	3.82±0.75 1.8-4.8	3.73±0.68 1.9-4.8	0.578	0.567 (NS)
ALT :				
Median Range	48 17-651	68.5 18-651	652.5*	0.04 (S)
AST:				
Median Range	40 17-263	67 18-569	654*	0.041 (S)
Total bilirubin:				
Median Range	4.5 3.7-24.9	5.15 3.4-24.9	714	0.132 (NS)
INR:				
Mean ± SD Range	2.62±0.66 1.6-3.9	2.64±0.62 1.6-3.9	0.135	0.893 (NS)
Creatinine:				
Mean ± SD Range	2.9±0.39 2.1-3.4	2.91±0.35 2.2-3.4	0.117	0.907 (NS)
Urine analysis for proteinuria				
	20% +ve	-ve		
Hemoglobin:				
Mean ± SD Range	9.87±2.51 4.1-13.2	9.87±2.51 4.1-13.2	0.0	1 (NS)
Platelets *10^3:				
Median Range	16.5 7-317	16 7-210	760*	0.273 (NS)
WBCs *10^3:				
Mean ± SD Range	6.84±1.55 4.1-9.7	6.84±1.55 4.1-9.7	0.0	1 (NS)

* = for Mann Whitney test

Table (3): Basic clinical Data of the studied groups

Variable	Non ACLF (n=42)		ACLF (n=42)		χ^2	p-value
	No.	%	No.	%		
Ascites:						
No: Yes:	16 26	38.1 61.9	5 37	11.9 88.1	7.68	0.006 (S)
GI Bleeding :						
No: Yes:	0 42	0.0 60.0	0 42	0 100.0	Fisher test	1 (NS)
Encephalopathy:						
No: Yes:	0 42	0.0 100.0	0 42	0 100.0	Fisher test	1 (NS)
Jaundice :						
No: Yes:	0 42	0.0 100.0	0 42	0 100.0	Fisher test	1 (NS)
Glasgow coma scale:						
3-8 9-12 ≥13	16 18 8	38.1 42.9 19.0	36 5 1	85.7 11.9 2.4	20.48	<0.001 (HS)

Table (4): Ultrasonography manifestation of the studied group

Variable	Non ACLF (n=42)		ACLF (n=42)		χ^2	p-value
	No.	%	No.	%		
Kidney affection:						
No: Yes:	39 3	92.9 7.1	12 30	28.6 71.4	36.38	<0.001 (HS)
Liver enlargement:						
No: Yes:	39 3	92.9 7.1	40 2	95.2 4.8	0.213	0.645 (NS)
Splenic enlargement:						
No: Yes:	2 40	4.8 95.2	1 41	2.4 97.6	0.346	0.557 (NS)

Table (5): Child Pugh classification of the studied groups

Variable	Non ACLF (n=42)		ACLF (n=42)		χ^2	P value
Child Pugh classification						
A	**10**	**23.8%**	-		**15.86**	**<0.001 (HS)**
B	**17**	**40.4%**	**12**	**28.5%**		
C	**15**	**35.7%**	**30**	**71.4%**		

Table (6): Clif sofa score of the studied groups

Variable	Non ACLF (n=42)	ACLF (n=42)	t-test	P value
Clif sofa score				
No OF*	**35 83.3%**	-	**64.17**	**<0.001 (HS)**
One OF	**7 16.6%**	**17 40.4%**		
Two or more OF	-	**25 59.5%**		

*OF: organ failure

Table (7): Kidney injury molecule-1 in between the studied groups

Variable	Non ACLF group (n=42)	ACLF group (n=42)	Mann Whitney test	P value
kidney injury molecule-1: cut off				
Median Range	2.4 1.6-7.1	7.35 2.5-9.9	74	**<0.001 (HS)**

Table (8): Diagnostic performance of kidney injury molecule-1 in detecting the acute kidney injury

Cut off value	Sensitivity %	Specificity %	PPV %	NPV %	AUC	P
≥0.5 When median 4.9	85.7%	88.1%	87.8%	86%	0.867	<0.001 **(HS)**

Table (9): The correlation between kidney injury molecule-1 and different parameters among the studied group

Variable	kidney injury molecule-1:	
	r	P
Glasgow coma scale:	-0.463	<0.001 HS)
Kidney affection by ultrasonography :	0.556*	<0.001 HS)

r is the correlation coefficient of Pearson's correlation
*= spearman's correlation

Table (10): Linear regression analysis for kidney injury molecule -1 as a predictor for Glasgow coma scale

Variable	B	S.E.	Beta	P
Glasgow coma scale:				
	-0.486	0 .103	-0.463	**0. 000**

R^2 =0.214

Table (11): Logistic regression analysis for kidney injury molecule -1 as a predictor for acute kidney injury

Variable	B	S.E.	Wald	P	OR	95.0% C.I
acute kidney injury::						
	2.476	0 .550	20.28	0.001 HS)	11.893	4.04-34.92

S.E. = standard error
OR = odds ratio
C.I= confidence interval

DISCUSSION

Renal affection in cirrhotic patients is a major problem and occurs in one of each five hepatic patients. It might be in the form of long standing kidney disease or worse in the form of sudden kidney injury. Unfortunately AKI is accompanied by big death rate ; that necessitates development of early noninvasive and simple marker for speedy determination of AKI. Many markers had been discovered recently like Neutrophil gelatinase-related lipocalin (NGAL), IL-18, Liver sort unsaturated fat restricting protein (L-FABP) and Kidney damage particle 1 (KIM-1) **[9]**.

Our experiment included 84 patients, allocated into two groups each including 42 patients. First group included non ACLF patients. The second group incorporate patients who met the criteria of ACLF as indicated by CLIF-SOFA scoring framework. Patients were entered to Zagazig University and Al Ahrar Hospitals in the range of 2015 and 2018. The point of this investigation was to test the job of one of the new biomarkers, KIM-1, for early discovery, common course and prognostic contrasts of AKI between patients with and without ACLF.

KIM-1 is a trans-layer protein with clear favorable circumstances as another marker for the early conclusion of AKI. In ordinary kidney tissue, it is for every targets and justifications not communicated yet it is communicated at moderate to abnormal states in the endothelial cells of the proximal tangled tubules during the beginning times of renal ischemic or nephrotoxic damage **[10]**.

Heterogeneity of definitions ACLF is a disorder described by intense and serious hepatic variations from the norm coming about because of various sorts of abuse, in patients with hidden endless liver malady or cirrhosis at the same time, rather than decompensated cirrhosis, has a high transient mortality, copying the forecast of extreme liver disappointment. By and by, the key terms of the definition 'intense', 'interminable liver' and 'disappointment' have a few varieties and an ongoing methodical audit announced up to 13 meanings of ACLF **[11]**. Given this heterogeneity and the significance of recognizing ACLF patients for a more assisted triage and stir up, four noteworthy social orders/associations have given working definitions that, despite the fact that not steady, lay the preparation for subsequent experimentation **[12]**. The Current examination is the first to research contrasts in AKI among ACLF and cirrhotic patients in our territory by assessing of the degrees of novel rounded harm biomarkers KIM-1 in various gatherings.

The present study showed that KIM-1 was significantly higher in ACLF (7.35) than non ACLF (2.4), p<0.01. That was in concur with that done by Belcher, et al, who concentrated five biomarkers (NGAL, IL-18, L-FABP, KIM-1 and albumin) in their exploration and reasoned that KIM-1 was a decent marker for early identification of renal debilitation in those patients **[13]**. This finding was not in concur with that of Fagundes, et al, who recently indicated KIM-1 were discovered less valuable while other parameter in his work principally NGAL levels in urine was more valuable, this in fact may be due to that most patients in his study were ACLF due to alcoholic hepatitis while our patients were mostly due to HCV infection **[14]**.

We found that at cut off value of ≥0.5 KLM-1 can predict the presence of AKI with sensitivity 85.7%, specificity of 88.1%, positive predictive value 87.8%, negative predictive value 86%, accuracy 86.9% and AUC= 0.867 p <0.001 Our outcomes was in concurrence with Zwiers et al. **[15]**.

Our investigation demonstrated that Urinary KIM-1 expanded fundamentally and GFR diminished as Child-Pugh class of decompensated cirrhosis altogether expanded ($p<0.05$). Serum creatinine levels were fundamentally expanded in Child-Pugh class C patients ($p<0.05$). Urinary KIM-1 was a decent recognition factor, as screening records, could help in the early determination of AKI auxiliary to ACLF. What's more, this was in concur with other study done by Lei, et al, who concentrated the estimation of urinary KIM-1 and NGAL joined with serum Cys C for foreseeing intense kidney damage auxiliary to decompensated cirrhosis, and reasoned that equivalent outcomes to our investigation as respect of urinary KIM-1 alone or in mix with other parameter in discovery of AKI in cirrhotic patients, yet other study included cirrhotic and ACLF patients **[16]**.

In the current study there is noteworthy distinction between the two contemplated groups as respect ALT and AST levels, while no critical contrast were found in our work as respect of level of serum albumin, INR, creatinine, protein, bilirubin level and CBC .This finding was steady with Shi Y, et al, who considered group of patients with HBV - ACLF **[17]**.

Our outcomes propose that AKI happening in patients with or without ACLF ought to be overseen in various ways. Huge scale multi-focus studies are required to approve these discoveries, and the distinctions in AKI between patients with or without ACLF brought about by different reasons rather than HCV still should be additionally studied.

CONCLUSION

ACLF is a serious condition that happens on the foundation of interminable liver brokenness and results in the advancement of organ dis-appointment and is related with extremely high mortality especially if accompanied by AKI. KIM-1 is a dependable agent for detection of AKI with ACLF.

Administrative and ethical design:
The study protocol was accepted by the ethical committee of the Faculty of Medicine, Zagazig University and Institutional Review Board under the number of 1541/5-8-2014 prior to the study. Informed consent was taken from all members in this study.

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Conflict of interest: None.

REFERENCES

1- Moreau R, Jalan R, Gines P Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; 144: 1426 37, 1437.e1 –9.

2- Malik R, Mookerjee RP, Jalan R. Infection and inflammation in liver failure: two sides of the same coin. *J Hepatol* 2009; 51: 426-429.

3- Olson JC, Wendon JA, Kramer DJ, Arroyo V, Jalan R, Garcia-Tsao G, et al. Intensive care of the patient with cirrhosis. *Hepatology* 2011; 54: 1864-1872.

4- Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on-chronic liver failure. *J Hepatol* 2012; 57: 1336-1348.

5- Levesque E, Hoti E, Azoulay D, Ichaï P, Habouchi H, Castaing D, et al. Prospective evaluation of the prognostic scores for cirrhotic patients admitted to an intensive care unit. *J Hepatol* 2012; 56: 95-102.

6- Hartleb M, Gutkowski K. Kidneys in chronic liver diseases. *World J Gastroenterol*. 2012; 18: 3035-49

7- Coca SG, Yalavarthy R, Concato J, Parikh CR: Biomarkers for the diagnosis and risk stratification of acute kidney injury: A systematic review. *Kidney Int* 2008, 73:1008-1016.

8- Dieterle F, Perentes E, Cordier A, Roth DR, Verdes P, Grenet O, et al. Qualification of biomarkers for regulatory decision making—a kidney safety biomarker project. *Toxicol. Off. J. Soc. Toxicol*. 2007; 96: 381.

9- Davenport A, Sheikh MF, Lamb E, Agarwal B, Jalan R. Acute kidney injury in acute-on-chronic liver failure: where does hepatorenal syndrome fit? Kidney Int. 2017 Nov; 92(5):1058-1070. doi: 10.1016/j.kint.2017.04.048. *Epub* 2017 Aug 23

10- Wong F. Acute kidney injury in liver cirrhosis: new definition and application. Clin. Mol. Hepatol. 2016; 22:415–422. doi: 10.3350/cmh.2016.0056.

11- Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA.. A systematic review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality. *Liver Int* 2013; 33: 40–52.

12- Sarin SK, Kedarisetty CK, Abbas Z, Amarapurkar D, Bihari C, Chan AC, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. *Hepatol Int* 2014; 8:453–71.

13- Belcher JM, Garcia-Tsao G, Sanyal AJ, Bhogal H, Lim JK, Ansari N, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. *Hepatology*. 2013; 57: 753–762. doi: 10.1002/hep.25735.

14- Fagundes C, Pepin MN, Guevara M, Barreto R, Casals G, Sola E, et al. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol*. 2012; 57(2):267–273.

15- Zwiers AJM, de Wildt SN, van Rosmalen J, de Rijke YB,Buijs EAB, Tibboel D, et al. *Crit Care*. 2015; 19(1): 181.

16- Lei L, Liang Li L Ping, Zeng Z, Mu J Xi, Yang X, Zhou C, et al. Sci Rep. 2018; 8: 7962. Published online 2018 May 21. doi: 10.1038/s41598-018-26226-6.

17- Feishu Hu, Sheng Bi, Huadong Yan, Yu Shi and Jifang Sheng. Virol J. 2015; 12: 87. Published online 2015 Jun 11. doi: 10.1186/s12985-015-0313-5.