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Value of Serum Kidney Injury Molecule-1 in Early Prediction of Kidney Injury in Patient with Ascites and Spontaneous Bacterial Peritonitis

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ABSTRACT

Background: Ascites is a main complication of cirrhosis that can be complicated by spontaneous bacterial peritonitis (SBP). A major predictor for mortality in this condition includes renal failure.

Objective: The current study aimed to evaluate the value of serum kidney injury molecule-1 (KIM-1) in the early prediction of kidney injury in cases with SBP.

Patients and Methods: A prospective cohort study was conducted on admitted patients with decompensated liver disease in Hepatology and Gastroenterology Unit, Specialized Medical Hospital, Mansoura University, Egypt. A total 160 patients were recruited; 120 patients with SBP (cases) and 40 patients without SBP (controls). Serum KIM-1 was measured for all patients. Additionally, serum creatinine (S.cr) was done every 48 hours during admission and every week after discharge.

Results: A statistically significant lower AST, direct bilirubin, and Child-Pugh score was noticed in cases versus controls. Additionally, a significantly higher S.cr (on admission and at follow up), and KIM-1 in AKI vs. non-AKI was noted in cases vs. controls. Moreover, KIM-1, at a cutoff value of >88.6, had a high sensitivity and specificity (95.8% and 93.7%, respectively) in discriminating AKI from non-AKI patients.

Conclusion: KIM-1 as a biomarker may allow evaluation of the functional condition, hepatorenal syndrome and acute tubular necrosis as a result potentially allowing early treatment decisions. In addition, this biomarker plays an essential role in early AKI diagnosis and overall prognostic assessment. This combination of biomarkers may be utilized to plan upcoming interventional researches in order to improve the outcomes of such cases.

Keywords: Kidney Injury Molecule-1, Spontaneous Bacterial Peritonitis, Kidney Injury, Ascites, Cohort study, Mansoura University.

INTRODUCTION

Cirrhosis is the histological development of regenerative nodules surrounded by fibrous bands owing to chronic hepatic injury which has been demonstrated to be accompanied by portal hypertension (PHT) and end stage liver disease (ESLD). Progress in proper identification of the course and pathophysiology of cirrhosis, and management of its adverse events, have been demonstrated to be associated with improvement of therapeutic modalities and quality of life (QoL) **(1).**

The main adverse events of cirrhosis involve varices, ascites, hepatic encephalopathy (HE), hepatopulmonary hypertension, hepatocellular carcinoma (HCC), hepatorenal syndrome (HRS), Spontaneous bacterial peritonitis (SBP), and coagulations disorders. SBP has been considered as a frequent and critical adverse event of decompensated cirrhosis with an incidence of about 20% in hospitalized cases **(2)**. Its association with high frequencies of adverse events and morbimortality is triggered by cardiovascular derangement which ultimately ends in liver failure and renal failure **(3).**

Renal failure has been considered as one of the main predictors of mortality in SBP. Acute kidney injury (AKI) occurs commonly in cases with advanced cirrhosis with ascites **(4)**. Expert committees have suggested the utilization of the AKI Network (AKIN) classification to be utilized in the context of cirrhotic cases, as it appears to predict hospital mortality either in presence or absence of ascites **(5)**.

Even though serum creatinine (S.cr) is the most commonly utilized marker for renal function (RF), its value could be influenced by non-renal factors which include gender, ethnicity, age, body mass index (BMI), and medications. As regards cirrhotic, the diagnostic value could be decreased owing to a reduction hepatic synthesis, reduction in skeletal muscle bulk, low protein intake, increased distribution volume and increased tubular secretion. In brief, the delay between RF reduction and elevation in S.cr has been considered as a main limitation for S.cr to be used as an early marker. Novel biomarkers comprising cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and Kidney Injury Molecule-1 (KIM-1) are suggested to overcome such restriction, and have demonstrated advantages with regard to diagnosis and outcomes in various populations **(6)**.

KIM-1, a transmembrane glycoprotein situated in proximal tubules, is elevated throughout ischaemia, whereas soluble KIM-1 is secreted in urine. In the context of cirrhotic cases, a multi-centric research demonstrated elevated urinary values among cases with acute tubular necrosis (ATN) and its correlation with AKI advancement and death **(7).**

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The current study aimed to evaluate the value of serum kidney injury molecule-1 (KIM-1) in the early prediction of kidney injury in cases with SBP.

PATIENTS AND METHODS

Study design: A prospective cohort study was conducted on admitted patients with decompensated liver disease in Hepatology and Gastroenterology Unit, Specialized Medical Hospital, Mansoura University, Egypt.

Patients: A total 160 patients were recruited between May 2020 and February 2022. This included 120 patients with SBP (**Group A**) and 40 cases without SBP (**Group B**). SBP diagnosis was established when ascitic fluid (AF) PMN count is more than 250/mm^3. Cases with SBP, compensated liver cirrhosis (Child Pugh A), history of preceding episodes of SBP, antibiotics usage in the preceding 14 days, history upper gastrointestinal bleeding (UGIB) in the preceding 30 days, cases with previous renal dysfunction (S.cr > 1.2mg/dl) or HCC were excluded from the study. Patients with cirrhosis divided into two groups:

Group A: SBP group. N =120. This group was further subdivided into two subgroups according to AKI development:

- Subgroup A1: SBP cases who developed AKI. N = 22 cases (18.3%).
- Subgroup A2: SBP cases who didn't developed AKI. N = 98 cases (81.7%).

Group B: Control group (No SBP). N = 40

Patient assessment:

Clinical assessment: Entire cases were subjected to complete history taking with special focus on history of preceding occasions of UGIB, SBP or HE. Complete physical examination with special focus on manifestations of hepatic decompensation was performed for all cases.

Laboratory investigations: CBC, S.cr, liver function tests, HCV antibodies, HBV surface antigen, serum, and complete AF analysis were done for all patients.

Serum KIM-1 was done for all patients as well. Three mL of blood were in dry tube and centrifuged at 3000 r.p.m speed. After that, the serum was preserved at 80^{o}C until examined by KIM-1 kit (USA).

***Radiological investigations*:**

Abdominal US was performed to entire cases to prove or disprove the existence of ascites, exclusion of secondary reasons of peritonitis and aspiration of AF specimen.

The cases were followed up during the period of admission and up to 5 days. S.cr was done every 48 hours during admission and every one week after discharge.

Severity of liver disease was done based on CHILD PUGH system and MELD Score (as demonstrated in Table 3).

Ethical Consideration:

This study was ethically approved by the Institutional Review Board (IRB number MS.19.12.981) of the Faculty of Medicine, Mansoura University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test, Fisher's exact test and Monte Carlo test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data) while Mann-Whitney U test was used for non-normally distributed Data (non-parametric data). Spearman's correlation was used to test the correlation between two variables with non-parametric quantitative data. Logistic regression analysis was used to test for risk factors for categorical outcomes. P-value $\leq$0.05 was considered significant.

RESULTS

Table 1 demonstrates the demographic characteristics of cases vs. control where there is a statistically significant higher age in case vs. control group. Also, there is higher male predominance in the cases group as in comparison with the control group.

Table (1): Comparisons of the demographic data in cases vs. control.

Characteristic	Case (SBP)	Control (No SBP)	Test of significance	
	N=120	N=40	Z/ χ^2	p-value
Age (years)	63.5 (54.5-68.7)	57.5 (54-64)	2.549	**0.011**
Sex				
Male	74 (61.7%)	16 (40%)		
Female	46 (38.3%)	24 (60%)	5.723	**0.017**

Data is N (%). Test of significance is Chi-square test or Fisher's exact test (FET).

Tables 2 and 3 show the clinical and laboratory characteristics in the cases and controls respectively.

Table (2): Comparisons of the clinical characteristics in cases vs. control.

Characteristic	Case (SBP)	Control (No SBP)	Test of significance	
	N=120	N=40	χ^2	P-value
Hematemesis in last 6-months	24 (20%)	10 (25%)	0.448	0.503
History of hepatic encephalopathy	36 (30%)	36 (90%)	43.636	**<0.001**
Previous EGD	76 (63.3%)	30 (75%)	1.826	0.177
Hepatocellular carcinoma	36 (30%)	6 (15%)	3.487	0.062
Positive anti-HCV antibody	88 (73.3%)	36 (90%)	4.779	**0.029**
History of paracentesis	22 (18.3%)	0 (0%)	FET	**0.001**
History of blood transfusion	14 (11.7%)	2 (5%)	FET	0.361
Dilated IHBR	6 (5%)	10 (25%)	FET	**0.001**
Portal vein thrombosis	12 (10%)	4 (10%)	FET	1.000
Calcular cholecystitis	36 (30%)	8 (20%)	1.505	0.220
Presence of splenomegaly	102 (85%)	40 (100%)	FET	**0.007**
Ascites			1.659	0.198
Moderate	64 (53.3%)	26 (65%)		
Marked	56 (46.7%)	14 (35%)		

Data is N (%). Test of significance is Chi-square test or Fisher's exact test (FET). EGD = esophagogastro-duodenoscopy. HCV = hepatitis C virus. IHBR = Intrahepatic biliary radicles.

Table (3): Comparisons of laboratory data in cases vs. control.

Characteristic	Case (SBP)	Control (No SBP)	Test of significance	
	N=120	N=40	Z	P-value
Serum creatinine (mg/dl) on admission	1.05 (0.9-1.2)	0.9 (0.72-1)	3.431	**0.001**
KIM-1 (ng/ml)	20.8 (13.63-88.63)	60.5 (14.8-152.68)	2.041	**0.041**
Hemoglobin (g/dl)	10.3 (8.6-11.8)	11.25 (8.6-12.2)	0.118	0.906
WBCs count	8.45 (5.8-13.7)	8.9 (6.9-9.57)	0.449	0.653
Platelet count	110.5 (61-206.2)	128.5 (43.2-240.5)	0.189	0.850
ALT (IU/L)	31 (20.5-47.5)	40.5 (32.5-49)	2.997	**0.003**
AST (IU/L)	38 (29-54.7)	47 (39.2-52)	2.776	**0.006**
Serum albumin (g/dl)	2.8 (2.3-3.1)	2.8 (2.5-3.05)	0.206	0.837
Serum total bilirubin (mg/dl)	1.1 (0.6-4.2)	0.75 (0.52-2.5)	1.326	0.185
Serum direct bilirubin (mg/dl)	0.7 (0.4-1.9)	1 (0.8-1.4)	0.663	0.507
INR	1.3 (1.1-1.4)	1.3 (1.1-1.5)	1.226	0.220
Serum sodium (mmol/l)	133.5 (130-137.7)	140.5 (135.2-143)	5.141	**<0.001**
Serum potassium (mmol/l)	3.5 (3.1-4.1)	3.2 (3.1-3.8)	0.829	0.407

Median and range: non-parametric test.
Data is Median (Q1-Q3). Test of significance is Mann-Whitney U-test.

Table 4 shows a statistically significantly lower AST, direct bilirubin, and Child-Pugh score. Additionally, it shows a statistically significantly higher S.cr (on admission and at follow up), and KIM-1 in AKI vs. non-AKI.

Table (4): Comparisons of laboratory data in cases with AKI versus cases without AKI.

Characteristic	AKI	Non-AKI	Test of significance	
	N=22	N=98		P-value
Serum creatinine (mg/dl) on admission	1.2 (1.1-1.2)	1.0 (0.9-1.2)	0.783	**<0.001**
Serum creatinine (mg/dl) on follow up	2 (1.7-2.3)	1.0 (0.8-1.1)	0.362	**<0.001**
KIM-1 (ng/ml)	262.8 (155.9-385.5	17.9 (12.3-47.3)	0.480	**<0.001**
Hemoglobin (g/dl)	10.7 (8.5-11.7)	10.2 (8.6-11.8)	0.081	0.935
WBCs count	9.7 (6.1-16.9)	8.3 (5.6-13.1)	0.357	0.175
Platelet count	144 (60-201)	103 (61.8-208.2)	0.800	0.423
ALT (IU/L)	25 (16-45)	32 (21.5-48.3)	0.882	0.378
AST (IU/L)	35 (20-40)	39 (30-62.3)	0.294	**0.022**
Serum albumin (g/dl)	3.0 (2.5-3.1)	2.8 (2.3-3.1)	0.673	0.094
Serum total bilirubin (mg/dl)	0.8 (0.6-1.5)	1.2 (0.68-4.5)	0.412	0.158
Serum direct bilirubin (mg/dl)	0.5 (0.2-0.8)	0.8 (0.4-1.9)	0.203	**0.028**
INR	1.3 (1.0-1.4)	1.3 (1.1-1.4)	0.274	0.203
Serum sodium (mmol/l)	132 (128-140)	134 (130-137)	1.102	0.271
Serum potassium (mmol/l)	3.9 (3.2-4.3)	3.5 (3.1-4.0)	0.332	0.183
Ascitic fluid WBC count	1100 (550-12000)	1200 (600-4800)	0.353	0.724
Child-Pugh score	8 (8-9)	9 (8-10)	2.365	**0.018**
MELD score	12 (8-13)	10 (9-17)	0.872	0.383

Median and range: non-parametric test.
Data is Median (Q1-Q3). Test of significance is Mann-Whitney U-test.

Figure 1 and **Table 5** show that KIM-1 at a cutoff value of > 88.6 has a perfect sensitivity (95.8%) in discriminating AKI from non-AKI. It also has a high specificity (93.7%). The test is statistically significant (P<0.001) with an excellent AUC (0.979).

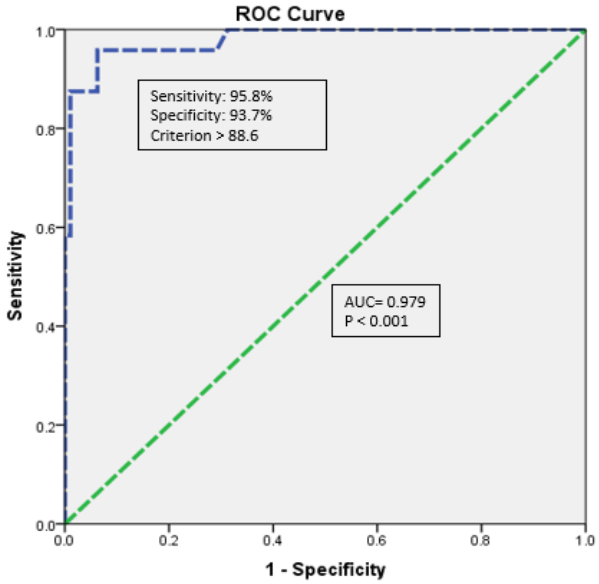

Figure (1): KIM-1 as a predictor of AKI development in SBP cases.

Table (5): Performance of KIM-1 in discriminating AKI from non-AKI.

Measure	Value
Area under the ROC curve (AUC)	0.979
Standard Error (DeLong *et al.* 1988)	0.00618
95% Confidence interval (Binomial exact)	0.952 to 1.000
z statistic	82.25
Significance level P (Area=0.5)	<0.0001
Youden index J	0.9188
Associated criterion (= cutoff value)	>88.6
Sensitivity	95.8
Specificity	93.7

Univariate analysis: Univariate analysis was run first on each of these 5 predictor variables separately. All 5 variables were statistically significant predictors of occurrence of AKI in SBP patients except sex and AST. SBP participants with age >64 years have 7.1 times higher odds to exhibit AKI, SBP participants with initial creatinine > 1 mg/dl have 14.5 times higher odds to exhibit AKI, and SBP participants with direct bilirubin > 0.6 mg/dl have 3.5 times higher odds to exhibit AKI.

Multivariate analysis: A multivariate analysis was then run incorporating all these 5 predictor variables in a model aiming at predicting the occurrence of AKI in SBP patients. Adjusted odds ratios together with their corresponding 95% CIs were presented. The model was significant (χ^2 [5] = 41.081, P<0.001). The model correctly classified 86.7% of cases with 54.5.3% sensitivity, 93.9% specificity, 66.7% PPV and 90.2% NPV (**Figure 2**). Due to its perfect sensitivity in discriminating AKI from non-AKI, KIM-1 was not incorporated in this regression analysis.

Table 6 demonstrates the results of binary logistic regression that was run on all patients with SBP to ascertain the effects of female sex, older age >64 years, initial S.cr >1 mg/dl, AST less than or equal to 36 IU/L, and serum direct bilirubin more than 0.6 mg/dl on the likelihood that SBP patients will exhibit AKI.

Table (6): Predictors of the likelihood of occurrence of AKI in SBP cases.

Predictor	Univariate			Multivariate		
	COR	95% CI	P-value	AOR	95% CI	P-value
Sex						
Male	r(1)	r(1)	0.449	r(1)	r(1)	0.275
Female	1.4	0.56-3.65		1.99	0.58-6.8	
Age (years)						
≤64	r(1)	r(1)	**0.001**	r(1)	r(1)	**0.004**
>64	7.1	2.2-22.6		6.59	1.8-23.8	
Initial creatinine						
≤1 mg/dl	r(1)	r(1)	**0.001**	r(1)	r(1)	**0.001**
>1 mg/dl	14.5	3.2-65.5		17	3.2-90.6	
AST (IU/L)						
>36	r(1)	r(1)	0.082	r(1)	r(1)	0.404
≤36	2.3	0.98-6.1		1.67	0.5-5.6	
Direct bilirubin						
≤0.6 mg/dl	r(1)	r(1)	**0.015**	r(1)	r(1)	**0.022**
>0.6 mg/dl	3.5	1.3-9.8		4.4	1.2-15.9	

COR = crude odds ratio. AOR = adjusted odds ratio. CI = confidence interval. r(1) = reference category.
Test of significance is binary logistic regression.

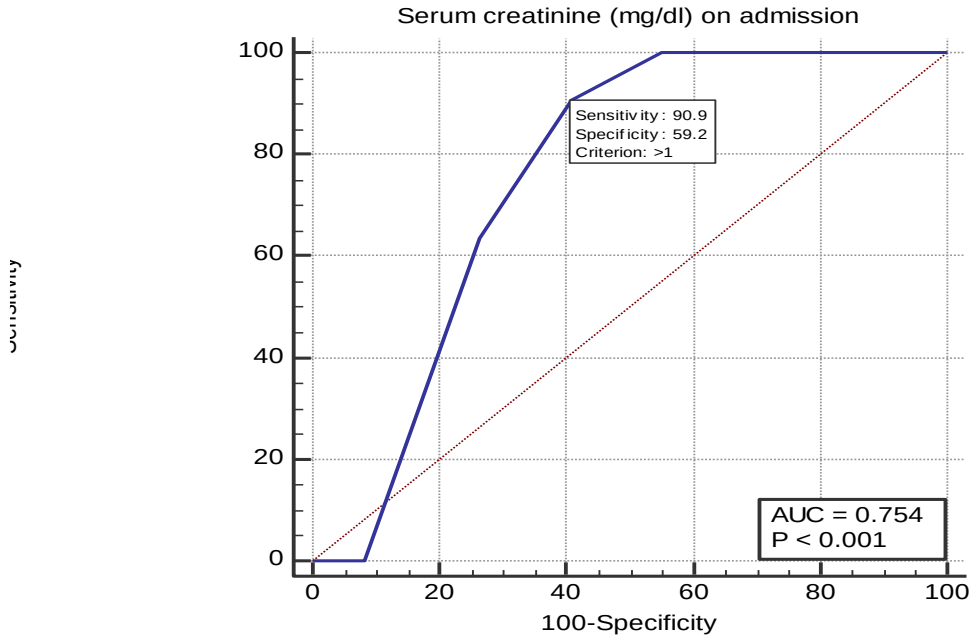

Figure (2): Predictors of the likelihood of occurrence of AKI in SBP cases.

Table 7 shows a statistically significantly negative correlation of medium strength between KIM-1 and AST, serum direct bilirubin, and Child-Pugh score, and a statistically significantly negative correlation of medium strength with serum albumin and of large strength with follow up S.cr. Figure 3 correlate between KIM-1 levels and follow up S.cr level.

Table (7): Correlation between KIM-1 level and clinical / laboratory data in SBP cases (N=120).

Clinical/Llaboratory parameter	r_s	P-value
Age (years)	0.120	0.197
AST (IU/L)	-0.205	**0.025***
ALT (IU/L)	0.002	0.981
Ascitic fluid WBC count	0.175	0.055
Initial serum creatinine (mg/dl)	0.150	0.102
Follow up serum creatinine (mg/dl)	0.841	**<0.001***
Hemoglobin level (g/dl)	-0.030	0.741
WBCs count (mcL)	0.136	0.137
Platelet count (mcL)	0.074	0.422
INR	-0.089	0.331
Serum albumin (mg/dl)	0.294	**0.001***
Serum total bilirubin (mg/dl)	-0.102	0.276
Serum direct bilirubin (mg/dl)	-0.256	**0.005***
Serum potassium (mmol/l)	0.079	0.394
Serum sodium (mmol/l)	-0.098	0.292
Child-Pugh score	-0.304	**0.001***
MELD score	-0.127	0.168

r_s = Spearman's correlation coefficient.

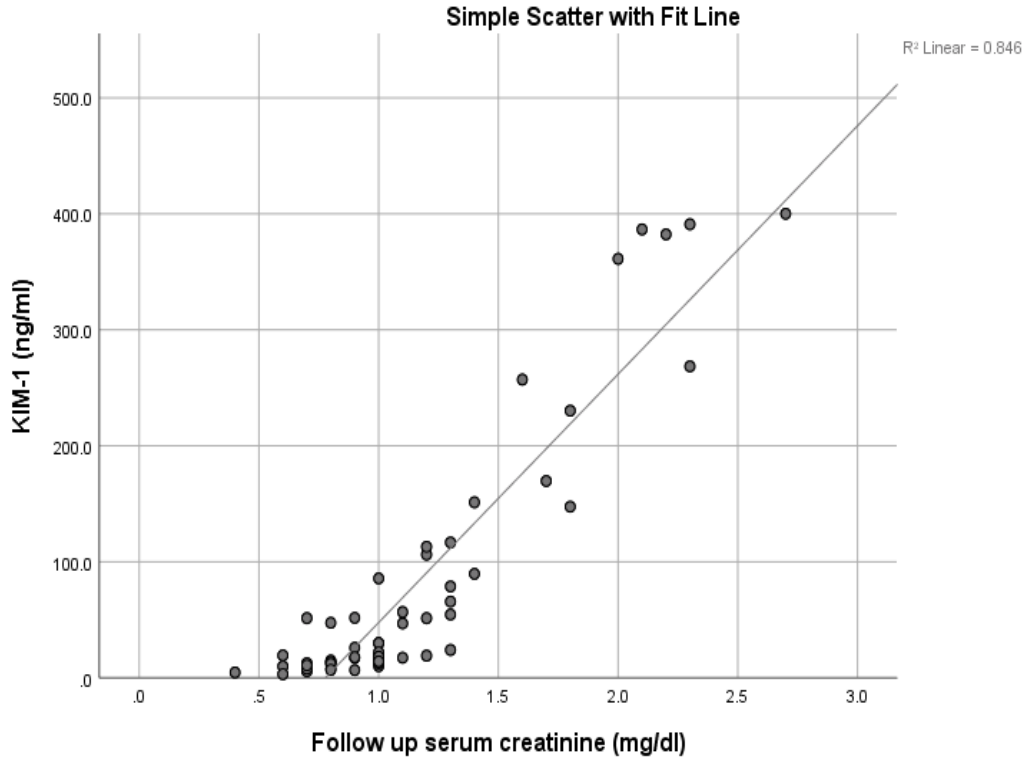

Figure (3): Correlation between KIM-1 level and follow up S.Cr level.

DISCUSSION

Spontaneous bacterial peritonitis (SBP) is a common and fatal adverse event in patients with cirrhosis, accompanied by significant morbimortality. The average hospital mortality among cirrhotic cases with SBP is about 30% [8].

In addition, AKI is common in cirrhotic cases with SBP and is believed to be correlated with hospital mortality. Furthermore, a systematic review comprising eighteen researches displayed that kidney impairment is the most essential predictor of mortality in cirrhotic patients with SBP [9].

S.cr is the most commonly utilized marker for RF. Of note, its value could be influenced also by non-renal factors which include gender, ethnicity, age, BMI, and medications. In the context of cirrhotic cases, the diagnostic value could be reduced owing to the reduction in hepatic synthesis, diminished muscle bulk, reduction in protein intake and increase in both distribution volume and tubular secretion [10].

New biomarkers, including KIM-1, have been proposed to overcome these limitations and have demonstrated benefits with regard to diagnosis and outcomes in various populations [11].

KIM-1, a trans-membrane glycoprotein situated in proximal tubules, is elevated in cases with ischaemia, whereas soluble KIM-1 is secreted in urine. In the context of cirrhotic cases, a multi-centric research demonstrated greater urinary values in cases with ATN and its correlation with AKI advancement and death [12].

The current study demonstrated a statistically significantly higher age in cases vs. control group. Also, there was higher male predominance in the cases group in comparison with the control group (61.7% vs 40% respectively). Similar data has been reported by [13] in which age was reported to be an independent predictor to development of SBP. Furthermore, elderly people are more susceptible to development of infection as a result of weak immune system [14,15]. Additionally, aging is in most liver diseases is accompanied by increased morbimortality compared to young patients. [16, 17]. In fact, age has been incorporated in simple scoring system to predict SBP in cirrhotic ascites [18].

The current study showed a statistically significantly lower HE, positive anti-HCV, dilated IHBR, and splenomegaly, and a statistically significantly higher history of paracentesis in cases vs. control group. Moreover, the current study showed statistically significant lower serum sodium and a statistically significantly higher S.cr on admission in cases vs. control group. Several factors can contribute to this observation in cases with hepatic cirrhosis including vasodilation, secondary to increased synthesis of circulating vasodilators, which results in reduction in systemic vascular resistance and reduced mean arterial pressure leading to hyperdynamic circulation which in turn causes an increase in the cardiac output (COP) [19].

Additionally, the resultant portal systemic shunting and defective reticuloendothelial cell functions among cirrhotic patients is a main contributor to NO synthase stimulation in the endothelial cells that occur via different mechanisms including mechanical triggers owing to 'shear stress', VEGF, TNF-alpha, and more essentially endotoxins or bacterial DNA which are of minimal efficiency cleared from the GIT [20].

Owing to several changes that occur to the gut microbiota as well as the gastric permeability, several has suggested that endotoxins and microbial metabolites may translocate to the systemic circulation resulting in increased systemic prostacyclin synthesis which further aggravates the condition [21].

The compensatory mechanisms that aim to correct this status have been reported to contribute to the hyponatremia observed in cirrhotic patients. For example, increased production of anti-diuretic hormone (ADH) occurs in cirrhotic patient due to the reduction of the effective circulating volume in response to splanchnic arterial vasodilatation which has been demonstrated to be associated with hypervolemic hyponatremia. Additionally, reduction of the efficient circulating volume may also contribute to the increased S.cr levels observed in these patients. In fact, studies have shown that both hyponatremia and increased S.cr are accompanied by an increase in the possibility of SBP which in turn increase the risk for development of renal injury, on the other hand, limited data are available in the context of the fundamental mechanism that explain this association [22].

In disagreement with our results, **Yap *et al.*** [23] have demonstrated non- significant difference between HRS cases and patients without HRS as regard age, sex, ALT, AST, positive anti-HCV and S.cr (P values 0.06, 0.5, 0.83, 0.29, 0.82 and 0.06, respectively). However, this study differs from our study in the presence of SBP, a factor that should be excluded to diagnose HRS.

Additionally, the current study showed a statistically significantly lower AST, direct bilirubin, and Child-Pugh score and a statistically significantly higher S.cr (on admission and at follow up), and KIM-1 in AKI vs. non-AKI.

In the same line, **Jaques *et al.*** [7] have demonstrated that patients with AKI had statistically significantly older age, higher S.cr, lower mean blood pressure, lower urinary sodium, higher volumes of ascites evacuated and higher MELD score, as compared with those without AKI (P values 0.004, <0.001, 0.005, 0.009, 0.028 and 0.002, respectively). However, there was no difference in urinary KIM-1 levels.

Duah *et al.* [24] performed a study to detect the prevalence, precipitating factors, predictors, and in-hospital mortality of AKI in cases with hepatic cirrhosis. Patients who developed AKI had higher bilirubin and INR and lower albumin and sodium values. Consequently, Child score and MELDNa were increased in cases with AKI in comparison with AKI free ones.

Cases with AKI had infections and encephalopathy more than those without.

Several researches have evaluated the underlying mechanism for AKI development in patient with liver cirrhosis. The systemic vasodilation, increased production of vasodilators, reduced effective circulatory volume, and high COP are all contributors to the development of kidney injury [4,25]. Furthermore, the systemic inflammatory condition that occur as a result of increased incidence of infections, such as SBP, further reduce the effective circulatory volume aggravating the renal damage [26]. For this reason, scientists have suggested using prophylactic antimicrobials in patient with liver cirrhosis to reduce the risk for development of infection, thus, protect against renal damage [27].

The current study evaluated KIM-1 as a predictor of AKI development in SBP cases. It was showed that KIM-1 (at a cutoff value of >88.6) had a perfect sensitivity (95.8%) in discriminating AKI from non-AKI. It also had a high specificity (93.7%). The test was statistically significant (P<0.001) with an excellent AUC (0.979).

In harmony with our results, **Yap *et al.*** [23] suggested that urinary KIM-1 (at a cut-off value of 1.499 ng/mL) had a perfect PPV (75%) and NPV (84%). The test was significant (P=0.008) with an excellent AUC (0.78).

Additionally, **Yap *et al.*** [23] concluded that KIM-1 is a potential biomarker for prediction of HRS in advanced cirrhotic cases with normal S.Cr. Their values were increased at basal value in cases with HRS and both demonstrated good correlation with HRS development.

Also, **Wahdan *et al.*** [28] performed a study was to assess role of KIM-1 in prediction of AKI in ACLF cases. 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 could predict AKI existence with sensitivity of 85.7%, specificity 88.1%, accuracy 86.9% and AUC 0.867 (P<0.001).

The current study evaluated the predictors of the likelihood of development of AKI in SBP cases with univariate and multivariate analysis (Female sex, age >64 yrs, initial s.cr. >1 mg/dl, AST ≤36 IU/L and serum direct bilirubin >0.6 mg/dl). All 5 variables were statistically significant predictors of occurrence of AKI in SBP patients except sex and AST. SBP participants with age >64 years had 7.1 times higher odds to exhibit AKI. This is not surprising giving the fact that older individual tend to have weaker immune response which makes them more susceptible to infections [29]. Furthermore, not only the immune system activity changes with aging but also the composition of the gut microbiota which affect the gut epithelial barrier integrity and, consequently, facilitate microbial translocation and increase the risk of infection [30].

Another observation in the present study is that SBP participants with initial creatinine >1 mg/dl had 14.5 times higher odds to exhibit AKI, and SBP participants with direct bilirubin >0.6 mg/dl had 3.5 times higher odds to exhibit AKI. Recent studies have linked the effect of elevated bilirubin to increased incidence of AKI [31,32]. The exact underlying mechanism is still not completely understood; however, it has been suggested that hyperbilirubinemia induces perturbations to renal and systemic hemodynamics several mechanisms including negative ionotropic and chronotropic cardiac effects [33].

The present study demonstrated a significant negative correlation of medium strength between KIM-1 and (AST, serum direct bilirubin, and Child-Pugh score), and a statistically significantly positive correlation of medium strength with (serum albumin) and of large strength with follow up (S.cr).

Similarly, **Tariq *et al.*** [34] reported MELD, Child stage C, presence of ascites, and existence of sepsis/septic shock as predictors accompanied by AKI in cirrhotic patients.

In addition, different researches have recorded Child score, INR, total bilirubin, serum albumin, platelet count, MELD, total leucocyte count, SBP, and shock as predisposing factors for AKI development among cirrhotic cases [35].

However, **Duah *et al.*** reported that high BUN, high MELDNa, high INR, and ALP were clinical parameters and scores that were independent predictors of AKI in cirrhotic patients [24].

The difference in the above studies may be is thereby the demographic features of the cases and the degree and cause of hepatic disease, predisposing factors for AKI, and changes of a lot of thresholds for S.cr utilized to define AKI.

One caveat for the present study is small sample size which could not reflect the general population. Thus, additional studies with larger number of patients are warranted.

CONCLUSIONS

This study added evidence that patients with cirrhotic cases with ascites are at very high risk of AKI development. A key factor to reduce morbimortality in cirrhotic cases complicated with SBP is through rapid diagnosis by exclusion of SBP and abrupt treatment. KIM-1 as a biomarker may allow assessment of the functional condition, HRS and ATN thereby potentially allowing early therapeutic decisions. This biomarker might also have a role in early detection of AKI as well as overall prognostic assessment. This combination of biomarkers may be utilized to design future interventional researches in order to improve the outcomes of such cases.

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