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Interleukin-18 as a urinary Biomarker for Diagnosis of Hepatorenal Syndrome in Patients with Decompensated Liver Cirrhosis

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ABSTRACT

Background: Hepatorenal syndrome [HRS] is a common complication that occurs in people with decompensated cirrhosis and may result in a higher chance of death if not addressed. HRS is a prevalent complication observed in individuals with decompensated cirrhosis which leads to an elevated risk of mortality if left untreated.

The aim of the work: To assess the ability of urinary interleukin-18 [IL-18] to be used as potential biomarker for HRS in patients with decompensated liver cirrhosis.

Patients and Methods: 120 hospitalized patients with decompensated liver cirrhosis, either with or without HRS were participated in the study. Two groups of patients were identified: 60 patients who had HRS and 60 patients who did not have HRS.

Results: Group I exhibited a considerably elevated IL-18 level compared to Group II [57.7±19.7 vs. 19.1±7.93 ng/ mL] [P = 0.001]. At the cutoff point of IL-18, more than 30.1[ng/ mL], it had 96% sensitivity and 90% specificity in detecting HRS patients.

Conclusion: Urinary IL-18 may prove to be a valuable biomarker for identifying HRS in patients with decompensated liver cirrhosis, providing valuable insights for diagnosis and management in this clinical setting.

Keywords: Child Pugh score; Decompensated liver cirrhosis; Hepatorenal syndrome; Interleukin-18.

INTRODUCTION

Renal failure affects over half of patients hospitalized with acute liver decompensation, especially those with ascites. This can develop gradually over weeks to months or suddenly within days. Type 1 hepatorenal syndrome [HRS] is a severe form of acute kidney failure with a poor prognosis if not managed effectively and is a key example of severe kidney failure in cirrhosis patients [1].

Recently, it's been recognized that even mild episodes of acute kidney failure [AKF] can worsen the prognosis for cirrhosis patients. The hepatology and nephrology communities, led by the International Club of Ascites [ICA], have redefined AKF, establishing new diagnostic criteria and measures to assess the severity of renal failure [2]. The term "acute kidney injury" [AKI] has replaced "acute renal failure" to standardize terminology across patient categories. In Egypt, where hepatitis C virus [HCV] is prevalent and leads to liver cirrhosis, hepatorenal syndrome [HRS] is common. AKI occurs in about 20% of hospitalized cirrhosis patients, and after AKI develops, the risk of mortality increases fourfold [3].

Individuals with decompensated liver cirrhosis often experience circulatory dysfunction, including vasodilation, decreased peripheral resistance, and renal artery vasoconstriction. This can lead to pre-renal azotemia [68% prevalence], hepatorenal syndrome [25%], and acute tubular necrosis [33%]. However, serum creatinine [sCr], the current standard for assessing kidney function, is not very effective in distinguishing between these types of acute kidney injury [AKI] in cirrhosis. Urinary albumin and fractional sodium excretion are used but are not very precise alone. New biomarkers are emerging that could improve the differentiation of AKI causes in cirrhosis patients [4, 5]. Biomarkers indicating kidney damage help pointing the exact location of renal injury. In cirrhosis, key biomarkers include liver fatty acid binding protein [L-FABP], kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin, interleukin-18 [IL-18], and cystatin C [6].

IL-18, a cytokine released by macrophages, promotes inflammation and is found in kidney tubule cells, appearing in urine following kidney damage. It helps predict AKI progression and mortality. A recent meta-analysis by **Yerramilli *et al.*** [7] involving 8 trials and 1,129 patients, found that both NGAL and IL-18 effectively differentiate acute tubular necrosis [ATN] from other types of kidney damage in AKI cases.

Urine IL-18 has been proven to be a dependable biomarker for differentiating ATN from other causes of renal illness. Urine IL-18 has demonstrated predictive usefulness for overall patient populations admitted to intensive care units [6].

The main purpose of this study was to assess urinary IL-18 as a biomarker for HRS in Egyptian patients with decompensated liver cirrhosis.

PATIENTS AND METHODS

The case control study was carried out at the National Liver Institute [hepatology and gastro-enterology department], El-Menoufia University, Egypt from March 2022 to March 2023. This study was taken out on 120 hospitalized patients with decompensated liver cirrhosis with or without HRS according to the following inclusion criteria aged 18-75 years diagnosed with hepato-renal syndrome according to ICA 2015 criteria, including cirrhosis, ascites, AKI, no shock, no nephrotoxic drugs, and no structural kidney injury. Exclusion criteria were acute cardiovascular events, cerebrovascular ischemia diseases, severe infection, malignant tumours, hepatocellular carcinoma or cholangiocarcinoma, liver or kidney transplant, multinodular hepatocellular carcinoma, portal vein thrombosis, bleeding, coronary or peripheral artery disease, arterial hypertension, outpatient kidney injury management, renal replacement therapy, obstructive uropathy, or parenchymal renal disease.

From all patients, written consent was acquired after being informed. Our study was checked and accepted by the ethical committee at the National Liver Institute with institutional review board [IRB: 00607/2024] of the National Liver Institute. Patients aged from 18 to 75 years who met the criteria for the diagnosis of HRS per the ICA 2015 diagnostic requirements were included [8].

- Diagnosis of cirrhosis and ascites;
- Diagnosis of AKI according to ICA-AKI criteria [an increase in Scr ≥ 50% of baseline and >1.5 mg/dl [133 μmol/l].
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin [1 g/kg of body weight].

- Absence of shock.
- No current or recent use of nephrotoxic drugs [non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.].
- No macroscopic signs of structural kidney injury, defined as absence of proteinuria [> 500 mg/d], absence of microhematuria [> 50 red blood cells per high power field] and normal findings on renal ultrasound.

The following patients were not included in the ICA 2015 diagnostic criteria: patients aged under 18 years; those suffering from acute cardiovascular events; patients with cerebrovascular ischemic diseases; individuals with severe infections; patients diagnosed with cholangiocarcinoma or hepatocellular carcinoma; chronic kidney disease patients who were maintained on regular hemodialysis before admission; liver transplant patients; kidney transplant patients; individuals with ongoing or recent (within the last week) bleeding; patients receiving renal replacement therapy (renal/hemodialysis transplantation); those with obstructive uropathy; and patients currently taking nephrotoxic drugs. Additionally, patients were excluded if they had no evidence of granular casts in their urinalysis or any ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

All studied patients were divided into two groups: Group I, which included sixty patients with HRS [n=60], and Group II, which included sixty patients without HRS [n=60]. Every individual who took part in the study was exposed to:

I. Full history taking included demographic and clinical data were collected: gender, age and medical history.

II. Thorough clinical examination: General examination [diastolic blood pressure [DBP], systolic blood pressure [SBP], body mass index, heart rate, vital signs, urinary output, presence of hepatic encephalopathy]. The abdominal examination [with careful examination of the liver, kidney, and spleen].

III. Laboratory investigations

Patients' results were recorded from the patients' sheets. Blood samples were collected from the veins after the participants had fasted overnight. The serum samples were collected after being centrifuged and then stored at -80 °C. Blood samples were used to measure laboratory data, including complete blood counts [CBC], liver and renal function tests, low-density lipoprotein cholesterol [LDL-c], high-sensitivity C-reactive protein [hs-CRP], triglycerides, total cholesterol [TC], random blood glucose, and serum alpha-fetoprotein [AFP] ng/ml.

The calculated glomerular filtration rate [eGFR] was counted employing the CKD-EPI Creatinine 2009 equation according to serum creatinine [Scr] levels along with race, sex, and age according to the following equation. GFR = 141 x min [S.cr/ 1] x max [S.cr/ 1]-1.209 x 0.993 Age x 1.018 [if female] _ 1.159 [if male] [9].

All patients underwent 2D Doppler echocardiography. Specific parameters measured included left ventricular posterior wall depth [LVPWd], left ventricular diastolic dimension [LVDd], Left atrium [LA] size, left ventricular ejection fraction [LVEF]. Also, Child-Pugh, MELD scores, and ascites [abdominal fluid accumulation] presence and severity were computed.

Child-Pugh score: The Child-Pugh score is a scoring system employed to evaluate the severity of chronic liver disease and classify patients into different classes [A, B, or C] based on the severity. It considers three parameters:

MELD score [Model for End-Stage Liver Disease]: Another scoring method for determining the severity of liver disease and forecasting patient outcomes, especially survival, is the MELD score. It utilizes three laboratory parameters; Serum bilirubin concentration, Scr concentration, INR.

Decompensated liver cirrhosis: Patients with liver cirrhosis are considered to have decompensated liver cirrhosis if they develop significant complications like hepatic encephalopathy, gastroesophageal variceal bleeding, or ascites [9]. The majority of its liver function falls into the Child-Pugh B or C category.

Urinary IL-18: Urinary IL-18 was calculated utilizing commercial Human Interleukin 18 [IL-18] ELISA Kit Catalogue No.201-12-0148 sandwich enzyme-linked immunoassay kits with a detection threshold of 7.8 ng/L. The device used was Biotech Version in National Liver Institute

Statistical Analysis: Data were analyzed using IBM SPSS [versions 19 and 22]. Descriptive statistics included mean ± SD, median, range, frequencies, and percentages. Statistical significance was set at $p < 0.05$. Analyses included: Chi-

square test for associations between qualitative variables; Mann-Whitney test for comparing non-normally distributed quantitative variables; Spearman's correlation for associations between quantitative variables; ROC Curve to evaluate diagnostic test accuracy, identifying optimal cutoff points based on sensitivity and specificity.

RESULTS

There was no significant difference among the studied groups concerning their demographic data [P value >0.05]. Group II had significantly higher systolic and diastolic blood pressure compared to Group I. No significant difference among the studied groups regarding their heart rate [P value > 0.05]. Severe and moderate ascites were significantly higher in patients with HRS [P value 0.003]. Moderate encephalopathy was higher in patients with HRS [P value <0.001] [Table 1].

The ALT level was substantially greater in group I compared with group II [P value 0.001]. The AST level was considerably higher in group I than group II [P worth 0.006]. The INR level was considerably higher in group I than group II [P worth 0.001]. Group I had considerably higher levels of both total and direct bilirubin contrasted to Group II [P worth <0.001]. Group II had much more serum albumin than group [P worth 0.002]. Regarding CRP was largely higher in group [mg/dl] [P worth <0.001] [Table 2].

Group I had significantly more White Blood Cells than Group II [P worth <0.001]. Group I had considerably less platelets than group II [P worth <0.001]. The Scr level was drastically greater in group I than group II [P worth <0.001]. Mean GFR was significantly lower in group I than group II [P worth <0.001]. Additionally, group I had a considerably higher level of alpha fetoprotein than group II [P worth <0.001]. Group I had an extensively higher Child-Paugh score than Group II [P worth <0.001]. Group I's MELD score was considerably higher than Group II's [P worth <0.001]. Group I had significantly more IL-18 [ng/mL] than Group II [P worth <0.001] [Table 2]. At cutoff point more than 30.1 of IL 18 it had 96% sensitivity and 90% specificity in detection of HRS patients [Table 3, Figure 1].

There was positive correlation between IL-18 [ng/ mL] and CHILD score in patients with HRS [P value <0.001]. No significant correlation between IL-18 [ng/ mL] and AFP, CHILD and MELD scores among patients without HRS [P value >0.05] [Table 4].

Table [1]: Demographic and clinical data of the studied groups.

	Studied variables	Group I with HRS [N=60]	Group II without HRS [N=60]	Test	P value
Age [years]	Mean ±SD	59.1±5.38	57.1±6.56	1.74	0.080
Gender [n, %]	Male Female	42 [70.0] 18 [30.0]	33 [55.0] 27 [45.0]	2.88	0.090
Blood pressure [mmHg]	Systolic blood pressure	99.8±12.4	112.9±9.42	6.59	**<0.001****
	Diastolic blood pressure	65.5±10.4	71.5±6.30	3.66	**<0.001****
Heart rate [beat/min]	Mean ±SD	76.6±9.04	73.8±7.26	1.60	0.108
Ascites [n, %]	No Mild Moderate Severe	0 [0.00] 17 [28.3] 30 [50.0] 13 [21.7]	4 [6.70] 25 [41.7] 29 [48.3] 2 [3.30]	13.6	**0.003****
Encephalopathy [n, %]	No Minimal Overt	14 [23.3] 18 [30.0] 28 [46.7]	33 [55.0] 25 [41.7] 2 [3.30]	31.3	**<0.001****
Diabetes Mellitus	Yes No	22 [36.7] 38 [63.3]	19 [31.7] 41 [68.3]	0.33	0.564

Data are presented as mean ± SD or frequency and percentage. HRS: hepatorenal syndrome, SD: standard deviation, Sig: significant, U: Mann-Whitney, X^2: Chi-Square.

Table [2]: Biochemical parameters of the studied groups.

	Studied variables	Group I with HRS [N=60]	Group II without HRS [N=60]	Test	P value
ALT[IU/ml]	Median Range	66.0 30.0 – 201.0	45.5 24.0 – 60.0	5.71	<0.001**
AST [IU/ml]	Median Range	46.0 18.0 – 180.0	40.0 21.0 – 60.0	2.76	0.006**
INR	Mean ±SD	2.20±0.38	1.44±0.25	8.64	<0.001**
Total bilirubin [mg/dl]	Median Range	2.30 0.40 – 3.80	0.90 0.52 – 2.10	8.27	<0.001**
Direct bilirubin[mg/dl]	Median Range	1.08 0.30 – 2.50	0.40 0.02 – 1.60	6.86	<0.001**
Serum albumin [g/dl]	Mean ±SD	2.42±0.51	2.68±0.46	3.04	0.01**
C. Reactive Protein [mg/dl]	Median Range	15.0 2.40 – 70.3	6.00 2.00 – 17.0	7.62	<0.001**
Hemoglobin[gm/dl]	Mean ±SD	10.8±2.29	9.92±0.92	1.72	0.085
[White Blood Cells] [10^3 /ul]	Median Range	9.75 2.60 – 36.0	6.71 2.83 – 11.1	4.27	**<0.001****
[Platelets Count] [10^3 /ul]	Median Range	105.0 28.0 – 271.0	157.0 78.0 – 249.0	4.90	**<0.001****
Scr [mg/dl]	Mean ±SD	3.04±0.83	0.65±0.20	9.45	**<0.001****
GFR [ML/Min/1.73 M^2]	Mean ±SD	24.4±8.95	105.4±21.0	9.44	**<0.001****
[AFP] [ng/ml]	Median Range	6.00 0.50 – 53.0	3.00 0.50 – 5.60	4.78	**<0.001****
Child-Paugh score	Mean ±SD	10.7±1.59	8.00±1.02	8.06	**<0.001****
MELD score	Mean ±SD	28.9±3.18	10.8±2.26	9.45	**<0.001****
IL-18 [ng/ mL]	Mean ±SD	57.7±19.7	19.1±7.93	9.13	**<0.001****

** Significant. Data are presented as mean ± SD or median [range]. HRS: hepatorenal syndrome, ALT: Alanine transaminase, AST: Aspartate transaminase, INR: international normalized ratio, GFR: glomerular filtration Rate, AFP: alpha-fetoprotein, MELD: Model for End-Stage Liver Disease, IL-18: interleukin-18.

Table [3]: ROC curve for the urine biomarker IL18's sensitivity and specificity in diagnosing HRS in individuals with decompensated liver cirrhosis

IL18	AUC	Cutoff point	Sensitivity [%]	Specificity [%]	NPV [%]	PPV [%]	Accuracy [%]
	1.00	> 30.1	96%	90%	96.4%	90.6%	93.3%

PPV: Positive predictive value - NPV: Negative predictive value - AUC: Area under the curve

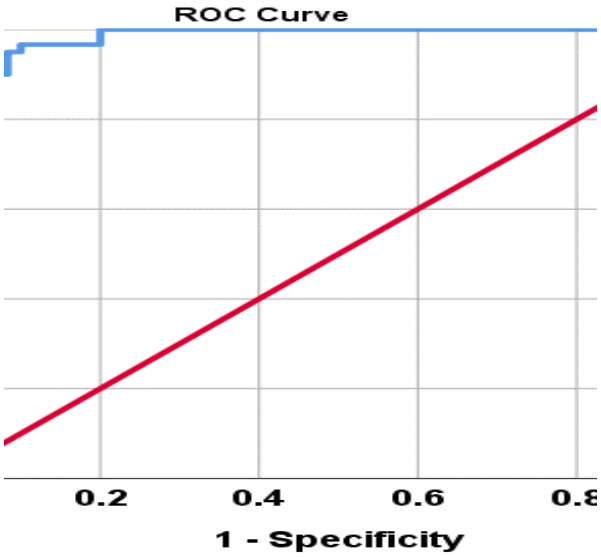

Figure [1]: ROC curve for IL18 as a urine biomarker for HRS diagnosis in individuals with decompensated liver cirrhosis with respect to sensitivity and specificity

Table [4]: Correlation between IL-18 [ng/ mL] and AFP, CHILD and MELD scores among the studied groups

Studied variables	Group I with HRS [N=60]		Group II without HRS[N=60]	
	IL-18 [ng/ mL]		IL-18 [ng/ mL]	
	R	P value	R	P value
AFP [ng/ ml]	-0.020	0.882	0.014	0.914
Child-paugh score	0.694	**<0.001****	0.041	0.754
MELD score	0.226	0.082	-0.148	0.259

r: Spearman's correlation** Significant. HRS: hepatorenal syndrome, AFP: alpha-fetoprotein, MELD: Model for End-Stage Liver Disease, IL-18: interleukin-18.

DISCUSSION

Hepatorenal syndrome [HRS] represents a condition that involves significant impairment of kidney functioning that can occur during the course of severe chronic liver disease, particularly advanced cirrhosis, although it can also occur following acute liver failure. A meaningful decrease in GFR is observed in HRS [10]. There are no particular diagnostic indicators for HRS, making diagnosis difficult. Furthermore, factors further than HRS, including volume depletion, glomerulo-interstitial disorders, ATN and medication toxicity and, might result in kidney impairment in individuals with liver illness [11].

The case control study was conducted in a single tertiary center from March 2022 to March 2023, National Liver Institute, Menoufia University, Egypt. The study was carried out on 120 hospitalized patients who have decompensated liver cirrhosis who were hospitalized with or without HRS. In the recent study our Patients aged from 18-75 years who met the criteria for diagnosis of HRS based on ICA 2015. Our study was aimed to evaluate the ability of urinary IL-18 to be used as a potential biomarker HRS is seen in people with decompensated liver cirrhosis.

In the present study we found that patients suffering from HRS had worse renal function tests in comparison to those without. Serum urea levels in group I were significantly greater than in group II and Mean GFR was substantially inferior in group I than group II. This result was similar to the result conducted by many other studies [12-14].

There is no specific test to diagnose HRS-AKI. However, one test that can indicate that HRS may be occurring is a lab test for Scr. Scr is a test that measures how well the kidneys are working. It is normal to have Scr in the blood [15].

Creatinine clearance is the main diagnostic tool for HRS. Before diagnosing HRS, other causes of renal failure [e.g., shock, hypovolemia, nephrotoxins, renal disorders] must be ruled out. For severe proteinuria, hematuria, and enlarged kidneys seen on ultrasound sonography, consider renal parenchymal disease and potentially perform a renal biopsy to evaluate the need for a combined liver and kidney transplant. Urine analysis is also important to assess sodium content and differentiate between organic and non-organic causes of renal insufficiency

Our results demonstrated that the Child-Paugh score seemed considerably higher in group I than in group II which goes with the finding of **Ariza *et al*.** [12] who stated that patients with HRS had a higher score [9.9 ± 1.9 vs 8.6 ± 1.5] but was not statistically significant. But the result of **Qasem *et al*.** [13] goes in line with ours which was highly statistically significant [10 ± 2].

Two easily accessible variables that can be used to predict a patient's prognosis with cirrhosis and HRS are the MELD score and HRS type. The managing of patients with HRS may benefit from these data, especially those who may be candidates for liver transplantation [16].

This explains our result which showed that MELD score was substantially higher in patients with HRS disease, and many previous studies give similar results. **Ariza et al.** [12] gave highly significant MELD score result 29 ± 5.

As regarding IL-18 in our recent study was significantly higher in group I suffering from HRS which is similar to the result of other researches [3, 10, 13]. On the other hand, **Hirooka and Nozaki** [17] examined urinary IL-18 serves as a biomarker for AKI and has a modest level of diagnostic accuracy. While urine IL-18 is not consistently accurate in predicting the occurrence of AKI, it has been shown to be helpful in predicting clinical outcomes such as death and

the need for dialysis in a diverse population in the ICU.

When compared to other kinds of AKI, it is considerably higher in cirrhotic patients with ATN. It was found in macrophages and monocytes. A noteworthy indicator of inflammation. Not confused by UTI, sepsis, or CKD, yet it does have certain limitations, including While PRA and HRS levels are elevated, there is a notable overlap in values that has no clinical significance. Inflammation levels are increased in the kidney other than AKI [18].

A clear and natural relationship exists between ROC analysis and the cost/benefit examination of diagnostic decision getting. As regarding ROC curve in our recent study for sensitivity and specificity of IL18 as a urinary biomarker for analysis of HRS in patients have decompensated liver cirrhosis we found that, at cutoff point more than 30.1 of IL-18 it had 96% sensitivity 90% specificity and 93% accuracy in detection of HRS patients.

On the other hand, **El-Makarem *et al.*** [1]'s ROC curve analysis assessed urinary IL-18 for diagnosing HRS. An IL-18 cutoff of > 34.8 pg/ml showed 51.72% sensitivity, 76% specificity, and 67.09% accuracy, with a 95% confidence interval of 0.52 to 0.74. Positive predictive value was 55.6, and negative predictive value was 73.1. The area under the curve was 0.641. Elevated urine IL-18 levels were observed in HRS-AKI patients compared to cirrhotic patients with normal kidney function.

According to the ROC analysis, when the cutoff point is set at a value greater than 34.8 pg/ml, IL-18 may be used effectively for diagnosing HRS. In a separate investigation of IL-18 in individuals with liver cirrhosis, including those without HRS, researchers discovered notably elevated levels of urine IL-18 in patients clinically diagnosed with ATN compared to those with non-ATN AKI. Another study steered by **Tsai *et al.*** [19], urine IL-18 levels were significantly higher in patients with acute tubular necrosis [ATN] and mixed acute renal failure [ARF] compared to those with functional ARF. An IL-18 cutoff of 708.5 pg/mL showed 89.06% specificity, 86.11% accuracy, and 81.81% sensitivity, with an area under the curve of 0.882. IL-18 is a useful bio-marker for assessing tubular damage in clinical settings.

A study was previously published by **Wang *et al.*** [3]. They found that ROC curve of IL-18 at cutoff worth of 420.10 pg/mL has sensitivity [90.32 %], specificity [71.70%], and area under the curve was 0.825. Additionally, he mentioned research that suggested IL-18 might be crucial in identifying hepatic cirrhosis in persons with hepatitis B. The estimation of this marker may help with the therapy, evaluation and prediction of HRS in patients with persistent HBV infections.

A significant positive association existed between IL-18 [ng/ mL] and CHILD score in patients with HRS similar finding was detected by **Wang *et al.*** [3] who found that IL-18, IL-22, and CD8+ levels were strongly linked with the Child-Pugh score. Another pervious study of **Sharma *et al.*** [16] stated that Serum IL-18 levels were not related to age or ALT levels, nor did they vary significantly with HCV genotypes. However, in 15 cirrhosis patients, IL-18 levels correlated with liver dysfunction severity and disease progression [$r = 0.777$, $P < 0.05$]. IL-18 levels were higher in patients with Child-Pugh Class C [2220.7 ± 852.7 pg/ml] compared to Classes A [798.7 ± 162.9 pg/ml] and B [1142.6 ± 109.2 pg/ml].

The study has limitations: sCr is an imprecise measure of kidney function in cirrhosis, and GFR cannot be reliably quantified. Kidney biopsies are rarely performed due to bleeding risks. While IL-18 levels can be elevated in conditions like acute viral hepatitis and chronic liver disease, the study did not differentiate IL-18 levels in HRS, ATN, or pre-renal azotemia, nor did it assess IL-18 changes before and after HRS treatment.

Recommendations: Additional prospective studies for comparing advanced liver cirrhosis patients with HRS with those with acute and chronic kidney diseases of variable causes and follow-up of serum IL-18 should be performed for better assessment. Further research with larger sample sizes, multi-center settings, and longer-term follow-up is recommended to validate our findings. Additional studies with larger sample size are recommended. Further prospective multi-centric studies are required to assess the role of IL-18 in the treatment of HRS.

Conclusion: Urinary IL-18 has the potential to be an excellent biomarker for detecting a condition called HRS in patients who have decompensated liver cirrhosis, giving useful information for diagnosis and therapy in this clinical situation.

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