Hepatorenal Syndrome: A Way for Early and Accurate Diagnosis

Mohammad A. Aboul-Ezz1, Ali Abdel Rahim1, Ahmed El-Mikkawy1, Mohammad A. Elkady1, Mohamed A. Elrefaiy1, Samia El-Shishtawy2, Osama Mosbah3, Khaled Mabrouk4, Mostafa Elshafie4, Omar M. Sabry5

1Department of Hepato-Gastroenterology, Theodor Bilharz Research Institute, Giza, Egypt; 2Department of Nephrology, Theodor Bilharz Research Institute, Giza, Egypt; 3Department of Clinical Chemistry, Theodor Bilharz Research Institute, Giza, Egypt; 4Department of Radiology, Theodor Bilharz Research Institute, Giza, Egypt; 5Department of Hematology, Theodor Bilharz Research Institute, Giza, Egypt

Abstract

BACKGROUND: Hepatorenal syndrome (HRS) is a devastating consequence of liver cirrhosis that is clinically categorized into two subtypes. Acute malfunction of renal role, as measured by an elevation in blood creatinine, significantly underestimates the loss in renal function in cirrhotic individuals; more accurate biomarkers are desperately required in cirrhotic patients.

AIM: The present study set out to uncover new biomarkers for the early prediction of AKI in cirrhotic cases. A comprehensive panel of biomarkers was investigated to get a clear insight into the pathogenesis of HRS.

PATIENTS AND METHODS: Participants in this study were 70 individuals from the hepatogastroenterology unit of the Theodor Bilharz Research Institute (TBRI). Detailed medical data and a physical examination were recorded. Three groups of patients have been identified; Group 1: 30 cases with compensated liver cirrhosis and normal kidney functions. Group 2: 20 cases with decompensated liver cirrhosis and normal kidney functions. Group 3: 20 cases with decompensated liver cirrhosis proved hepatorenal syndrome Type 2 h. The following biomarkers were detected in serum using the sandwich-ELISA method: Human L-arginine ELISA kit, human neutrophil gelatinase related lipocalin (NGAL), human renin, human nitric oxide (NO), and human renin.

RESULTS: There was a highly significant difference between Groups 1 and 2 in NITRIC and ADMA. Significant differences between Groups 2 and 3 in NGAL, noradrenalin, and SDMA were observed. There was a significant difference (Group 2 vs. Group 3) in renin, NITRIC, ADMA, and L-ARGININE. There was highly significant differentiation (Group 2 vs. Group 3) in NGAL, noradrenalin, and SDMA. There was highly significant variation as per odd ratio and confidence interval between (Group 3 vs. Group 2) in NGAL.

CONCLUSION: Assessment of renal biomarkers in individuals with decompensated cirrhosis gives critical information on the etiology of AKI. Further, it may aid in the diagnosis and prognosis of AKI. Renin, NITRIC, ADMA, and L-ARGININE could be used as biomarkers to indicate HRS in individuals with advanced cirrhosis.

Introduction

HRS is a serious side effect of liver cirrhosis related to a raised risk of death and disease, glomerular filtration rate decreases because of anomalies in the renal circulatory system that exceed compensatory measures. As cirrhosis, alcoholic hepatitis, or metastatic tumors are the most common causes of portal hypertension, people with this condition might suffer from fulminant hepatic failure for any reason [1], [2]. A liver transplant or the utilization of vasoconstrictor medicines can enhance renal function by maintaining enough renal blood flow. The hepatorenal syndrome was categorized into two clinical subtypes: Type 1 is a rapid decline in renal function manifested by a doubling of initial serum creatinine to at least 2.5 mg/dL or a 50% decrease in initial 24-h creatinine clearance to < 20 mL/min at < 2 weeks and Type 2 is as a progressive decline in renal function that did not meet the Type 1 criteria [3].
SBP), resulting from the sepsis-induced exacerbation of circulatory dysfunction [6]. HRS can also develop with large-volume paracentesis (LVP) [7]. Bile cast (or choleric) nephropathy has been found in cirrhosis cases and increased serum bilirubin levels over a long time [8].

Acute renal impairment, as defined by an elevated in serum creatinine, underestimates the decrease in renal function observed in cirrhotic individuals because of impaired hepatic generation of creatine (creatinine precursor), inaccurate measurement of creatinine by calorimetric techniques in elevated serum bilirubin, and decreased muscle mass, and creatinine tubular secretion. Consequently, more precise indicators are required in persons with cirrhosis [9]. Tubular proteins upregulated in response to injury (neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid-binding protein, and kidney injury molecule-1), tubular proteins secreted throughout cellular damage (N-acetyl-β-D-glucosaminidase, α-glutathione S-transferase), inflammation markers (interleukin-18), and plasma proteins with diminished tubular reabsorption (retinol-binding protein, α-1-microglobulin, and β-2-microglobulin) [10]. Individuals with cirrhosis have the most investigated biomarker, NGAL, differentiating ATN from AKI-HRS with the maximum diagnostic accuracy. In addition, urine NGAL levels are a powerful predictor of sudden death in the short-term. Nonetheless, the findings are encouraging and need additional investigation [11].

**Aim of the work**

This study targeted identifying novel biomarkers for the diagnosis of HRS in cirrhotic individuals. A comprehensive panel of biomarkers was investigated to get a clear insight into the pathogenesis of HRS.

**Patients and Methods**

**Study population and demographic information**

This work was conducted at Hepato-Gastroenterology Department, Theodor Bilharz Research Institute, Egypt, and all subjects signed a written informed permission form under the 1975 declaration of Helsinki’s ethical standards. This work was approved by the ethics committee at TBRI.

Between January 2019 and March 2022, this trial enrolled a total of 70 individuals. All individuals involved in this study underwent a full thorough history and clinical examination. All individuals were hospitalized in the clinic for gastroenterology in TBRI. All subjects had liver cirrhosis. HRS was diagnosed in 20 patients with cirrhosis, while 50 patients did not have HRS. The hepatorenal syndrome was diagnosed by the latest criteria suggested by the International Ascites Club. The criteria included: Cirrhosis with ascites, low glomerular filtration, serum creatinine over 133 μmol/L (over 1.5 mg/dL), proteinuria < 500 mg/day, absence of shock, absence of bacterial infection, loss of fluid, impaired kidney function after cessation of diuretic treatment (serum creatinine value which remains at the level of ≥ 133 μmol/L for at least 48 h, after administration of albumin dose 1–100 gr/kg a day), treatment without nephrotoxic drugs, and absence of parenchymal renal disease (patient does not have proteinuria > 500 mg/day, no microhematuria >50 erythrocytes, and no pathological findings of ultrasound examination of the kidneys).

Individuals were categorized into three groups: Group 1: 30 cases with compensated liver cirrhosis and normal kidney functions. Group 2: 20 cases with decompensated liver cirrhosis and normal kidney functions. Group 3: 20 cases with Type 2 h.

**Sample collection and storage**

About two vacutainer tubes were used to withdraw venous blood samples through a single aseptic venipuncture from patients. 2 ml were collected into EDTA vacutainer for CBC. 2 ml were collected into a serum separator vacutainer tube for blood chemistry and special investigations. Blood was permitted to clot by keeping it undisturbed for 10–20 min at room temperature. Centrifugation at 2000–3000 rpm for 20 min was used to dislodge the clot. The supernatant was carefully collected and stored at −20°C until used for viral marker assays.

**Laboratory investigations involving**

Qantas, an automated cell counter made by Boule Diagnostics in Sweden, was used to get a complete blood picture. Blood chemistry such as (serum albumin, aspartate aminotransferase (AST), urea, alanine aminotransferase (ALT), and creatinine) was conducted on Olympus AU480 Chemistry Analyzer, Beckman Coulter, USA. The viral markers such as hepatitis B surface antigen (HBsAg), and HCV immunoglobulin G (HCV IgG) were carried out on ADVIA Centaur CP Immunoassay System, Siemens, Germany.

**Special investigations**

The biomarkers of interest were detected in serum using the sandwich-ELISA method. Human L-arginine ELISA kit (Cat No In-Hu4073), Human Neutrophil Gelatinase Associated Lipocalin (NGAL) ELISA kit (Cat No In-Hu3931), Human Noradrenalin (NA)
Table 1: Demographic data and laboratory investigations

| Parameters          | Group 1 N = 30 | Group 2 N = 20 | Group 3 N = 20 | p-value     |
|---------------------|----------------|---------------|---------------|-------------|
| Demographic data    |                |               |               |             |
| Age                 | 40.2 ± 14.1    | 43.6 ± 13.5   | 53.3 ± 12.7   | 0.4         |
| Sex                 | 0.04*          | 0.01**        | 0.02*         |             |
| Age                 | 40.2 ± 14.1    | 43.6 ± 13.5   | 53.3 ± 12.7   | 0.4         |
| Sex                 | 0.04*          | 0.01**        | 0.02*         |             |
| Sex                 | 0.04*          | 0.01**        | 0.02*         |             |
| Laboratory investigations |          |               |               |             |
| Hgb                 | 12.1 ± 2.0     | 10.8 ± 1.7    | 9.3 ± 2.3     | 0.04*       |
| RBCs                | 4.9 ± 0.5      | 3.5 ± 0.7     | 3.2 ± 1.0     | 0.001**     |
| Hct                 | 37.8 ± 5.9     | 32.0 ± 4.5    | 26.1 ± 8.6    | 0.001**     |
| TLC                 | 7.4 ± 1.8      | 8.2 ± 4.7     | 7.2 ± 3.3     | 0.001**     |
| Neutrophil          | 57.4 ± 12.1    | 68.0 ± 12.2   | 70.3 ± 15.3   | 0.001         |
| Lymph               | 36.9 ± 11.3    | 26.0 ± 12.1   | 22.6 ± 11.9   | 0.001**     |
| Monocyte            | 3.7 ± 1.1      | 4.9 ± 1.9     | 3.2 ± 1.2     | 0.001**     |
| Eosin               | 2.2 ± 0.6      | 2.3 ± 0.9     | 1.9 ± 0.6     | 0.8         |
| Platelets           | 274.5 ± 63.0   | 163.8 ± 49.3  | 76.3 ± 20.5   | 0.001**     |
| AST                 | 19.8 ± 7.4     | 77.4 ± 58.6   | 65.6 ± 14.2   | 0.001**     |
| ALT                 | 17.6 ± 11.2    | 55.7 ± 38.9   | 52.0 ± 30.2   | 0.001**     |
| S. albumin          | 4.1 ± 0.4      | 3.0 ± 0.7     | 2.2 ± 0.6     | 0.001**     |
| Creatinine          | 0.8 ± 0.2      | 1.2 ± 0.2     | 5.7 ± 1.3     | 0.001**     |
| Urea                | 26.8 ± 9.0     | 39.7 ± 9.2    | 181.8 ± 55.1  | 0.001**     |
| INR                 | 1.1 ± 0.1      | 1.7 ± 0.3     | 2.7 ± 0.5     | 0.001**     |
| BIL                 | 0.4 ± 0.2      | 3.5 ± 0.5     | 7.8 ± 11.4    | 0.001**     |

Age, Hgb, RBCs, Hct, TLC, Neutrophil, Lymph, Monocyte, Eosin, Platelets, AST, ALT, S. albumin, Creatinine, Urea, INR, and BIL are expressed as Mean ± SD. While sex is expressed as frequency and percent. *p < 0.05 is significant. **p < 0.01 is highly significant. *p = 0.01 is greatly significant.
Table 2: Studied biomarkers

| Group 1 N = 30 | Group 2 N = 20 | Group 3 N = 20 | p-value | OR (95% CI) |
|----------------|----------------|----------------|---------|-------------|
| **Studied biomarkers** |                 |                |         |             |
| **Nitric** |                 |                |         |             |
| Nitric | >2.3 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |
| Nitric | >1.5 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |
| Nitric | >1.0 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |
| Nitric | >0.5 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |
| **Nitric** |                 |                |         |             |
| Nitric | >2.3 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |
| Nitric | >1.5 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |
| Nitric | >1.0 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |
| Nitric | >0.5 | 100.0 | 66.7 | 100.0 | 6.67 | 100.0 | 66.7 | 100.0 | 6.67 | 0.01* | 0.01** |

RBCs, neutrophils, lymphocytes, TLC, eosinophil, AST, and ALT.

The results indicated a significant difference between (Group 2 vs. Group 1) (p < 0.05) regarding renin (cutoff >1.3, sensitivity 71%, specificity 66%) and in noradrenalin (cutoff >21.2, sensitivity 100%, specificity 36%) (Table 3, Figures 1 and 2). Our findings demonstrated a highly significant variation between (Group 2 vs. Group 1) (p < 0.01) in NITRIC (cutoff >4.2, sensitivity 100%, specificity 46%), and ADMA (cutoff >99, sensitivity 100%, specificity 63%) (Table 3, Figures 1 and 2). As shown in (Table 3, Figures 1 and 2), there was no considerable difference between (Group 2 vs. Group 1) in the remaining markers.

Discussion

Hepatorenal syndrome (HRS) is a disorder in which persons with severe liver disease have reduced kidney function. People with hepatorenal syndrome do not have a known cause of kidney impairment, and their kidneys are structurally normal [2], [3]. This distinguishes HRS as a distinct pathophysiologic condition that enables the study of the interaction of vasoconstrictor and vasodilator systems in renal circulation [4], [8], [12]. The present study enrolled
90 individuals with liver cirrhosis at the TBRI's Hepatogastroenterology Department. They were divided into three groups: Group 1 comprised 30 individuals with compensated liver cirrhosis and normal kidney function; Group 2 comprised 20 individuals with decompensated liver cirrhosis and normal kidney function; and Group 3 comprised 20 cases with decompensated liver cirrhosis and renal impairment.

We investigated many biomarkers and their relationship with HRS in this study. Regarding NGAL, our result showed a significant difference between Group 3 and Group 1 ($p = 0.001$), and Group 2 ($p = 0.001$). This result is similar to other findings, which indicated another result by Yap and his colleagues, who found that the baseline urinary NGAL was significantly associated with HRS development [13]. Further study showed that urine NGAL is highly effective at identifying ATN from other forms of AKIs in cirrhosis [14].

Nitric oxide (NO) is a vasodilator that is thought to be involved in renal perfusion. Preliminary
evidence, primarily from animal tests, indicates that persons with cirrhosis produce more nitric oxide, even though NO suppression has no finding in renal vasoconstriction due to changes implemented in PG synthesis. When both NO and PG generations are suppressed, a significant vasoconstriction of the kidney occurs. Vasoconstrictor action may well be the dominant system in HRS, although it is not clear whether this is due to decreased vasodilatory activity, or the other way around. Our results showed a substantial difference between Groups 3 and 1 (p = 0.001), and 2 (0.02). In several individuals with decompensated cirrhosis, systemic endotoxemia is hypothesized to boost NO production in cirrhosis. Increased plasma nitrite/nitrate levels in individuals with decompensated cirrhosis are symptomatic of increased NO generation [15]. Cirrhosis cases and ascites had higher plasma RAAS activity and antidiuretic hormone levels, and a high serum NO level is related to reduced urine salt excretion as well as elevated plasma RAAS activity and antidiuretic hormone concentrations [15], [16].

NO is more concentrated in portal venous plasma than peripheral venous plasma, implying enhanced splanchnic NO generation [17]. While there is widespread agreement that NO plays a role in peripheral vasodilation, there is still debate on whether an important factor in hyperdynamic circulation’s emergence and maintenance is NO [18]. Even though the vasodilating effect of NO would be expected to offset renal vasoconstriction, this is not the case in HRS, despite increasing levels of NO. To date, no one knows why this is happening, but one theory put up by Lluch et al. [19] is that the high levels of asymmetric dimethylarginine in terminal liver failure act as an

![Figure 2: (a and b) ROC Curve analysis of the studied biomarkers in the studied groups](image)

![Figure 3: Protein-protein interaction network of the studied biomarkers](image)
antagonist to the high levels of NO in the blood, causing renal vasoconstriction in HRS.

In cases with HRS, the sympathetic nervous system is hyperactive, culminating with renal vasoconstriction and increased salt retention [20]. Our findings indicated a significant difference in noradrenaline levels between Groups 3 and 1 (p = 0.001) and 2 (p = 0.001). Numerous investigations have demonstrated increased catecholamine release in the renal and splanchnic vascular beds [21]. Since the 1980s, the relevance of hepatorenal innervation has been recognized. The increased intrahepatic pressure enhanced the function of the efferent renal sympathoadrenergic system [22]. Vasoconstriction of the kidney’s afferent arterioles decreased renal plasma flow and GFR while increasing sodium and water reabsorption through the tubules. More than half of individuals with decompensated liver disease have activated the renin-angiotensin-aldosterone system (RAAS), which is heightened in those with HRS [23], [24]. Our findings indicated that Group 3 had a significantly greater renin level than Group 2 (p = 0.02), Group 1 (p = 0.001), as well as Group 2, had a significantly higher renin level than Group 1 (p = 0.03). Increased angiotensin II levels protect the kidneys by selectively constricting the efferent glomerular arterioles.

Increased plasma renin release followed by an increase in angiotensin II formation was found in refractory ascites and HRS, indicating a role of RAAS in the development of HRS. Angiotensin II helps to maintain vascular tone in patients with advanced liver disease, but has no role in healthy controls or patients with compensated cirrhosis, suggesting that this mediator contributes to vascular dysfunction in cirrhosis [25].

ADMA is an endogenous direct inhibitor of the enzyme nitric oxide (NO) synthase, which participates in NO synthesis. NO participates in the maintenance of vascular tonus. Increased concentration of ADMA in the blood of patients with decompensated liver cirrhosis reduces the synthesis of NO, whereby intrahepatic vascular resistance is increased [26]. ADMA is hydrolyzed by the action of the enzyme dimethylarginine dimethylaminohydrolase (DDAH). Compared to ADMA, SDMA has indirect inhibitory effect on NO synthase. SDMA can disturb the synthesis by competing in the transport against L-arginine on the level of cell membrane [27], [28].

Our study shows an increased level of ADMA and SDMA in Group 3, compared to Group 2 and Group 1. Some studies [29] have demonstrated that increased ADMA level in blood of patients with decompensated liver cirrhosis is probably the result of DDAH enzyme activity exhaustion. Increased level of ADMA has a causative role in the development of HRS. Accumulation of ADMA in patients with liver cirrhosis causes liver damage. Accumulation of ADMA inhibits NO synthase thereby causing vasoconstriction of the kidney blood vessels. Thus, blood flow through the kidney is interrupted, in other words, glomerular filtration is reduced and SDMA is retained in the kidney. Compared to ADMA, SDMA is not broken down by the action of DDAH enzyme but is excreted as such through the kidneys [30], [31].

Conclusion

Renin, Nitric Oxide, ADMA, SDMA, and L-arginine may act as biomarkers for advanced cirrhotic patients to indicate HRS. Integrating biomarkers into clinical decision-making can enhance therapy accuracy by identifying patients who have structural injury underlying their AKI. Additional study is required to characterize biomarkers unique to HRS.

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