Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i18.3377

HEPATORENAL SYNDROME: UPDATE

Katherine Lucía Gordón Reyes[1*], Manuel Rafael Aldás Erazo[2]

[1]*Estudiante de la carrera de Medicina de la Universidad Católica de Cuenca
Email: rkgordon22@est.ucacue.edu.ec, Orcid: https://orcid.org/0000-0001-6905-5876
[2]Docente Universidad Católica de Cuenca, Email: manuel.aldas@ucacue.edu.ec, Orcid: 0000-0003-1229-490X

***Corresponding Author:** Katherine Lucía Gordón Reyes
*Estudiante de la carrera de Medicina de la Universidad Católica de Cuenca
rkgordon22@est.ucacue.edu.ec, Orcid: https://orcid.org/0000-0001-6905-5876

Abstract
Hepatorenal syndrome is kidney dysfunction due to a decrease in renal flow secondary to chronic liver disease such as liver cirrhosis or acute liver disease. Causing a decrease in the glomerular filtration. In the classification there are two types recognized, AKI, which is characterized by a rapid and progressive deterioration of kidney function, and Non-AKI, by a slow deterioration, but with a better prognosis. This pathology represents a high mortality rate, so timely diagnosis will be key to successful treatment.
General objective: To describe the updates in the diagnostic criteria and treatments of hepatorenal syndrome.
Methods: A narrative literature review was conducted using Science direct, Pubmed, Springer, Scielo/Redalyc and Scopus databases. Scientific articles published during the period 2018-2023 in Spanish and English were included. Likewise, articles that are in indexed journals and ranked in quartiles according to the SJR (Scimago Institutions Rankins) were selected.
Results: After the results obtained from the literature reviews, there are no specific clinical findings, however, clinical manifestations reflect an underlying advanced liver disease, acute renal injury and circulatory abnormalities.
Conclusions: it is essential to add Doppler ultrasound studies to the clinical manifestations for the diagnosis, for a comprehensive management in the patient, the optimal treatment is liver transplantation, but it is not always viable, therefore, the pharmacological treatment of vasoconstrictors and albumin is used.

Key words: Hepatorenal syndrome; liver cirrhosis, acute kidney injury; diagnosis; treatment

INTRODUCTION

Hepatorenal Syndrome (HRS) is defined as renal dysfunction resulting from a reduction in renal blood flow caused by portal hypertension or underlying cirrhosis. This pathology is a serious complication of liver cirrhosis, characterized by an increase in splenic blood flow, a hyperdynamic state, a decrease in blood flow, activation of vasoconstrictor systems and renal vasoconstriction, as a subsequent decrease in the glomerular filtration rate (GFR) (1,2).
Serum creatinine is used in renal function control, GFR, and the diagnosis of AKI and HRS. An increase of 0.3 mg/dL or 50% from baseline in patients with cirrhosis is associated with significant morbidity for the patient. Currently, the ICA has updated the definitions and classifications of AKI in

patients with cirrhosis, which are aligned with the Kidney Disease Improving Global Outcomes (KDIGO) classification (2).
Therefore, the old term SHR type 1 is replaced by SHR-AKI. Functional renal injury in patients with liver cirrhosis who do not meet the criteria for SHR-AKI will be referred to as SHR-NAKI (SHR-Non-AKI) based on the estimated glomerular filtration rate and not on serum creatinine. SHR-NAKI has two subtypes: SHR-AKD and SHR-CKD (2).
For the diagnosis of Hepatorenal Syndrome we have certain criteria: 1. Cirrhosis and ascites 2. Diagnosis of ARF according to your criteria ICA-AKI 3. Absence of shock 4. No response to diuretic withdrawal and plasma volume expansion 5. No recent use of nephrotoxic drugs 6. No Macroscopic Signs of Structural Kidney Injury (3,4).
As there is no precision with the current criteria, biomarkers such as interleukin-18, the marker of kidney injury, the protein binding to fatty acids of the liver type and lipocalin associated with neutrophil gelatinase, better known as NGAL, are also used, which are the most common. NGAL and Interleukin-18 are important for the differential diagnosis between acute kidney injury-acute tubular necrosis and SHR-AKI (5,6).
Detection and intervention in an AKI lesion in patients with cirrhosis should be prompt, starting with the discontinuation of unnecessary nephrotoxic drugs and non-steroidal anti-inflammatory drugs, beta-blockers as prophylaxis for varicose veins and other complications, and the risk-benefit should be evaluated. Diuretics and laxatives should be monitored for possible excessive diuresis or dehydration, and volume expanders should be evaluated if necessary (7,8).
In the absence of improvement in creatinine values, treatment of vasoconstrictor drugs with albumin supplements should be initiated to prevent loss of cardiac output and loss of effective circulating volume. The drugs used are terlipressin, noradrenaline, octreotide and midodrine (8). Terlipressin has been the most studied, is more effective and has fewer adverse effects, and several studies have shown its better function accompanied by albumin compared to other vasoconstrictors (9).
Renal replacement therapy (RRT) is not a treatment for SHR-AKI, it would help the patient in improving liver function (7). Jugular intrahepatic portosystemic shunt (TIPS) is the treatment for SHR-AKI, improving portal hypertension and consequently renal function. The only definitive treatment for RHS refractory to drug therapy is liver transplantation, although it is still being studied (10,11).
Hepatorenal Syndrome represents a high mortality, so its timely diagnosis and correct classification will help us differentiate between SHR-AKI and SHR-NKI, since their treatments vary and early intervention could improve the patient's prognosis. That is why the understanding of pathophysiology is fundamental to the understanding of the diagnosis and the certainty of the treatment (9).

Methodology

Type of study:
Narrative literature review
Literature Search:
Keywords such as "Hepatorenal Syndrome", "Management of Hepatorenal Syndrome", "Treatment with Terlipressin in Hepatorenal Syndrome", "Diagnostic criteria for the Hepatorenal Syndrome", found in bibliographic descriptors such as DeCs and MeSh, were applied. Thus, the information was also filtered through Boolean Operators such as "NOT", "OR", "NOT".
Data Extraction:
In this review, several articles obtained from digital scientific databases such as: Science direct, Pubmed, Springer, Scielo/Redalyc and Scopus were recognized. The information was also classified using tables with the help of Microsoft Excel. Likewise, articles that are in indexed journals and ranked in quartiles according to the SJR (Scimago Institutions Rankins) were selected. In the PRISMA model, it will be used exclusively for the development of the flow chart of scientific articles identified from the bibliographic search.
Inclusion criteria:

- Articles in Spanish, English and Portuguese

- Articles published between 2018 and 2023
- Systemic Literature Reviews
- Meta-analysis
- Clinical Trials
- Case Reports

Exclusion Criteria:
- Duplicate Items
- Theses published exclusively for university repositories
- Letters to editors

Conflicts of interest:
There are no conflicts of interest on the part of the author.

Financing:
The current work is self-financed by the author.

Definition
Hepatorenal Syndrome (HRS) is defined as renal impairment caused exclusively by liver diseases such as: advanced cirrhosis and associated ascites, acute liver failure and circulatory dysfunction, resulting in a decrease in renal perfusion due to the reduction of effective circulating volume and massive activation of the endogenous vasoactive system, hence renal vasoconstriction (systemic and splanchnic arterial vasodilation) (6,7).
The criteria of Injury, Insufficiency, Risk, Loss of Renal Function, and End-Stage Renal Disease (RIFLE) classify the severity of acute renal dysfunction based on serum creatinine (sCr) or glomerular filtration rate (GFR) or both (4,15). Subsequently, the Acute Kidney Injury Network classification (AKIN, 2005) leads to an additional definition criterion of AKI, in which it describes an increase in sCr 0.3 mg/dL during the 48 hours. Finally, Kidney Disease: Improving Global Outcomes (KDIGO, organization 2012) defines AKI as an increase in sCr 0.3 mg/dl in 48 hours, an increase in sCr by 50% from its baseline value in 7 days, or a decreased urine output of 0.5 ml/kg/hour for 48 hours or more (2,8).
SHR-NAKI is commonly associated with refractory ascites accompanied by gradual declines in renal function, while SHR-AKI is characterized by acute renal failure (16).

Physiopathology
Pathophysiology of SHR-AKI
- Circulatory dysfunction
Peripheral arterial vasodilation results in renal dysfunction which cannot be neutralized by activation of the renin-angiotensin-aldosterone system (RAAS) and other compensatory mechanisms (8). Glomerular pressure may be maintained in equilibrium, but in the course of advanced chronic liver disease (ACLD) and aggravation of hyperdynamic circulation and/or predisposing events may increase systemic vasodilation (8,13).
-Systemic inflammation
Systemic inflammation (SI) is a mark of disease progression and development in extrahepatic organs, primarily renal dysfunction in ACLD (13). There is a high prevalence of Systemic Inflammatory Response Syndrome (SIRS) in renal dysfunction with SI. Observational studies in patients with cirrhosis and AKI have reported that those with spontaneous bacterial peritonitis (SBP) had increased circulating levels of pro-inflammatory cytokines (tumor necrosis factor-α and interleukin 6) compared to those without SBP (12,13).
Cirrhotic cardiomyopathy
Cirrhotic heart disease is caused by systolic dysfunction caused by physical or pharmacological stress, and diastolic dysfunction caused by electromechanical irregularities. Therefore, it will affect renal

function, some studies have shown that in patients with low cardiac output it is characteristic of RHS (4,12).

- Other pathophysiological mechanisms

Abdominal hypertension (HAI) is considered to affect AKI and/or SHR in patients with ascites, in previous studies conducted with patients with tension ascites and SHR, it was shown that large volume paracentesis improved HIA, as well as glomerular filtration rate (GFR) and cardiac output, decreasing systemic vascular resistance and renal resistance index, consequently by the reduction of RAAS activation (8,17).

SHR-NonAKI Pathophysiology

Predominant causes in SHR-NonAKI include parenchymal kidney disease, drug-induced kidney injury and prerenal azothermia (PRA), sepsis, PBS, upper gastrointestinal bleeding, and shock (7,18). Infections and sepsis (pneumonia, skin or urinary tract infections) cause a decrease in blood flow in the renal vasculature, thus causing kidney damage in patients with cirrhosis (19). Hypovolemia is caused by large volume paracentesis, gastrointestinal bleeding, and renal dysfunction. The drugs that commonly trigger AKI are diuretics and laxatives, with lactulose predominantly (7,15).

The mechanisms that contribute to liver inflammation may result from molecular patterns associated with damage including interleukin IL-1, IL-33 and bile acids with involvement in hepatocytes and attenuation of intestinal immunity. In patients with cirrhosis, adrenal insufficiency and hyponatremia are presented as a marker of poor prognosis (5). In viral hepatitis, immune complexes are created with the virus, direct cytopathic impact, or antibodies against infected hepatocytes. Hepatitis C infections are often associated with glomerular disease (7,20).

Etiology and Risk Factors

Cirrhosis is considered to be the most common underlying liver disease, other etiologies such as fulminant liver failure, chronic hepatitis in cirrhotic phase with ascites and other conditions such as alcoholic hepatitis and chronic liver failure are also considered (1,21).

Kidney failure is commonly insidious, but it can be caused by a bacterial infection or gastrointestinal bleeding from esophageal varices. There are multiple risk factors that give way to SHR, in order of frequency we have the most common factor with around 30% incidence in SHR-AKI is spontaneous bacterial peritonitis, causing an infection of the ascitic fluid (mainly enteric gram-negative bacteria: Klebsiella pneumoniae, Pseudomonas aureginosas, serratia marcescens), in the absence of a specific intra-abdominal infectious focus for sepsis (1,6,14).

The second factor is large-volume paracentesis without plasma expansion that affects hyperdynamic circulation in cirrhosis, causing progressive systemic vasodilation and insufficient arterial filling. Other factors include the use of diuretics that promote acute kidney injury in cirrhosis with ascites, contrast media, nonsteroidal anti-inflammatory drugs (NSAIDs), nephrotoxic antibiotics and urinary tract infections (1,22).

Classification

In the 1996 breakthroughs of the definition of HRH, the ICA defined it as a functional impairment in renal function due to circulatory dysfunction in patients with advanced chronic liver disease (ACLD) and portal hypertension. Two types are determined: Type 1 is given a 2-fold increase in sCr to at least 2.5 mg/dL or a 50% decrease to less than 20 ml/min within 2 weeks of creatinine clearance. Cases of renal failure with sCr of less than 1.5 mg/dL that did not meet the criteria were referred to as type 2 (4,7).

In 2015, the ICA, together with the subclassification of SHR and the updated definition of AKI, named SHR type 1 as SHR-AKI with the general criteria of: increase in sCr of 0.3 mg/dL in 48 hours or increase in sCr of at least 1.5 times since its onset (evolution of eligible 3-month sCr values) reaching a final sCr of 1.5 mg/dL (AKI 1b) (1,7).

Recalling that the diagnosis of RHS depends solely on the lack of improvement in renal function within 48 hours after withdrawal of diuretics and albumin volume expanders (1g/kg/day up to 100g/day maximum) (6).

Type 2 is referred to as SHR-NAKI (non-AKI), endorsed by the European Association for the Study of the Liver (EASL) in 2018, defined as not meeting the criteria for AKI hepatorenal syndrome with respect to the time dynamics of sCr. It is subclassified by estimated GFR (eGFR) and time of renal dysfunction based on KDIGO criteria: increased sCr >50% or an eGFR of < 60 mL/min per 1.73m2 for less than 3 months, calling it SHR-acute kidney disease (SHR-AKD), and eGFR <60 mL/min at 1.73m2 for more than 3 months, was defined as SHR-chronic kidney disease (CKD-HRS) (2,16).

Clinical manifestations

RHS does not have specific clinical manifestations, but we can see them reflected in advanced chronic liver disease, renal failure, and circulatory abnormalities. The clinical findings of ACLD are: ascites, jaundice, coagulopathy, stigmata of portal hypertension (caput medusae, hepatic encephalopathy, esophageal varices, etc.), palmar erythema, hepatomegaly, gynecomastia, constitutional nevi, drumstick fingers and spider nevus, alterations such as fatigue, poor nutritional status, anorexia and weakness (1,6).

Circulatory disturbances include a reduction in systemic vascular resistance and hyperdynamic circulation, manifesting clinically with low mean arterial pressure, outgoing pulse, low jugular venous pressure, wide pulse pressure, and tachycardia. In patients with RHS who do not have oliguria (at the beginning of the course), serum creatinine may increase to as little as 0.1 mg/dL/day, with sporadic periods of stabilization or improvement. In the urinary sediment we can find anomalies such as granular casts due to hyperbilirubinemia, hematuria due to bladder instrumentation and/or underlying coagulopathy (1).

- SHR-AKI

It is the most severe type and has a rapid and progressive worsening of renal function, with an increase >= 100% of the initial sCr to 2.5 mg/dL in a period of less than 2 weeks. In renal insufficiency, oliguria and sodium retention are observed. At the time of diagnosis, the patient has a urine output <400-500 ml/day. Approximately two-thirds of patients with SHR-AKI have hypervolemic hyponatremia, related to their alteration in solute-free water excretion due to dysfunction in renal capacity(1).

In severe renal failure, there are signs of severe circulatory dysfunction, which is evidenced by hypotension (MAP around 70mmHg), hypotension, vasoconstriction in the extrarenal vascular beds, and systemic vascular resistance. Similarly, patients with ACLD present with coagulopathy, ascites, jaundice, malnutrition, hepatic encephalopathy, and edema. These patients are in poor general condition, with a short average survival (1,23).

- SHR-NonAKI

Patients with SHR-NonAKI have a less marked alteration in renal function (sCr between 1.5 and 2.5 mg/dL) and a better preserved general condition. Without the presence of infections, this state remains stable. Compared to SHR-AKI, these patients have fewer clinical manifestations, and their main clinical difficulty is ascites, which is generally refractory. It should be noted that these patients may develop SHR-AKI spontaneously or due to precipitating factors such as bacterial infections. Patients with SHR-NonAKI have better survival (1).

Diagnosis

- Diagnostic criteria

In order to determine a diagnosis of hepatorenal syndrome, the following criteria must be met:
1. Cirrhosis and ascites 2. Diagnosis of Acute Renal Failure According to ICA-AKI Criteria 3. No shock 4. No response to diuretic discontinuation and plasma volume expansion 5. Recent non-use of nephrotoxic drugs 6. No signs of gross structural kidney injury
In reference to "no signs of gross structural kidney injury":
1. No proteinuria (>500 mg/dL) 2. No microhematuria (>50 red blood cells x high-power field)

3.	Normal renal ultrasound

Board 1 Diagnostic Criteria
Source: Angeli P, Garcia-Tsap G, Nadim M, Parikh C. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. J Hepatol

Currently, the diagnostic criteria are not very precise for the exclusion of parenchymal kidney injury in patients with cirrhosis. There are several markers for the evaluation of kidney damage in AKI, such as: the marker of kidney injury, IL-18, kidney injury molecule 1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), albumin, neutrophil-gelatinase-associated lipocalin (NGAL), and liver-type fatty acid-binding protein (4,8). IL-18 and NGAL are the markers with the highest sensitivity to make the differential diagnosis between SHR-AKI and acute kidney injury-acute tubular necrosis. As mentioned by Ojeda et. to which the NGAL marker may also function as a predictor of mortality (4,24).
Due to the pathophysiological complexity of SHR-AKI, it becomes a challenge to diagnose or to use the correct strategy for accurate treatment. Several types of AKI should be estimated as part of its evaluation: prerenal AKI, postrenal AKI and acute tubular necrosis (ATN) AKI in patients with advanced chronic liver disease (4,8).
Prerenal AKI should have a favorable response to decreased diuretic therapy, albumin therapy, and fluid replacement, postrenal AKI should be evaluated by ultrasound. While AKI-ATN cannot be differentiated with routine tests, fractional urinary sodium excretion (FeNa) was considered for differential diagnosis according to Simbrunner et. to the (8).
Mogawer et. A study called "Role of renal duplex ultrasonography in evaluation of hepatorenalsyndrome" was carried out with a study duration of one year, with 48 patients, Child's score from 10 to 14, MELD score between 11 and 38. Of these, 17 patients were diagnosed with HRHS according to the ICA-AKI criteria. Revealing portal vein thrombosis in 6 patients (12%) and ascites in 46 patients (92%). There was no significant difference in renal ultrasonographic data (diameter, volume, and echogenicity). This study demonstrated a statistically significant positive correlation between MELD and the Kidney Hilum Resistance Index (25).
Therefore, the IR is related to the progression of liver disease, being a predictor of SHR with a specificity of 66.7% and a sensitivity of 100% (25).
According to Kaptein et. al, in their study that included 20 patients with cirrhosis and ascites, meeting the criteria for a clinical diagnosis of SHR-AKI after discontinuation of diuretics and administration of albumin, with ultrasound follow-up of the inferior vena cava, in this study it was shown that the patients had hypovolemia or intravascular hypervolemia and with IVC ultrasound it was evaluated before, during and after administration of standardized volume or discontinuation of diuretics, thus helping to avoid prolongation of hypovolemia or induction of hypervolemia, thus improving clinical outcomes (26).

Treatment
- Elimination of risk factors and removal of fluids
After the diagnosis of AKI, initial measures include the elimination of risk factors that may be triggering renal dysfunction, we have the suspension of nephrotoxic medications (angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs), diuretics, antibiotics and fluid therapy according to the degree of AKI. It is important to analyze the risk-benefit with the treatment of non-selective beta blockers (NSBB), certain studies mention that they generate a greater risk in patients with AKI or SHR in circulatory stress, relating it to an impact on cardiac output (6,8).
-Albumin
The degree of AKI will determine the need for treatment with albumin plasma volume expanders. Patients with AKI 1b or higher receive albumin for two consecutive days (1g/kg up to maximum 100g/day). Patients with AKI 1a will be monitored for 48 hours after the elimination of risk factors, if there is persistence, individualized treatment should be provided, and if it progresses to AKI 1b or

higher, the treatment indicated above should be followed. The difference between AKI 1a and 1b is because AKI 1a is a prerenal cause in 50% of patients and resolves in 90% of cases, while AKI 1b is a cause in 25-30% and resolves in 50%, and occasionally progresses to SHR-AKI (4,8,13).
Currently, albumin therapy is indicated as a prevention of circulatory dysfunction after large volume paracentesis and in the prevention of RHS with spontaneous bacterial peritonitis. Albumin shows a superior effect compared to other plasma expanders, aiding in circulatory dysfunction, however, there are studies that show that albumin helps in the modulation of systemic inflammation (SI) by binding. Therefore, it removes and inactivates pro-inflammatory molecules. Also, albumin helps in the self-regulation of renal perfusion, reducing SI, endothelial activation and oxidative stress (18).
- Vasoactive drugs
Vasoactive drugs effectively increase circulating blood volume and decrease splanchnic accumulation, thereby improving renal perfusion (with albumin, plasma expansion). The EASL recommends terlipressin as first-line treatment. Norepinephrine, as well as midodrine in combination with octreotide, have shown good efficacy for therapy in RHS (7).
Terlipressin is a similar of vasopressin and acts in splanchnic and systemic vasoconstriction, by activating the 1A receptor of vasopressin, while the agonist of vasopressin 1B receptors activates the adrenocorticotropic-cortisol axis, improving acute renal failure and being beneficial for SHR. Therefore, terlipressin decreases the hepatic venous pressure gradient (HVPG) and increases mean arterial pressure (MAP). Midodrine and norepinephrine improve vascular tone. Octreotide is similar to somatostatin, thus promoting splanchnic vasoconstriction. However, while midodrine achieves relative increases in MAP, terlipressin and norepinephrine are potent vasopressors (27–29).
With regard to the means of administration, terlipressin is preferred by continuous infusion (2mg/day up to a maximum of 12mg/day, through a peripheral or central catheter), octreotide by continuous infusion or subcutaneously every 8 hours, midodrine orally and norepinephrine by continuous infusion with the requirement that a central venous catheter be used (29).
-Antibiotics
The impact of systemic inflammation on renal dysfunction in advanced chronic liver disease (ACLD) and association in SBP and AKI, shows beneficial effects on SHR antibiotic prophylaxis. The study conducted by Fernandez et al. shows that by giving primary prophylaxis treatment with norfloxacin in patients with ascites and high risk of EBP, it reduced the risk of RHS by 28% vs 41% in the placebo group (30).
- Transjugular intrahepatic portosystemic shunt
Patients with ascites have a high chance of developing spontaneous bacterial peritonitis or SHR-NonAKI or both, so managing ascites would improve subsequent complications. The lower the portal pressure from medical treatments, the lower the risk of developing SHR-refractory ascites. Transjugular intrahepatic portosystemic shunt (TIPS) may help prevent SHR-NonAKI (31).
TIPS help in the prevention of mortality in patients with recurrent ascites (tension ascites, on three occasions in 12 months despite therapeutic measures) and not necessarily refractory as mentioned in the ICA criteria, in hepatic encephalopathy and prevention of variceal bleeding (32,33).
- Renal replacement therapy, liver transplant, and combined liver-kidney transplant
A study by Allegreti et al. shows that renal replacement therapy (RRT) is a bridge to liver transplantation (HT). SDB did not improve prognosis in patients with SHR-AKI and patients with renal insufficiency and/or renal replacement therapy that were not considered or transplanted had high mortality rates in the short and medium term. In addition, a high percentage of patients in the SDB study at six months required dialysis (34). Also, Piano et al. state that patients who were treated with terlipressin and albumin had a lower risk of needing SDB AND developing CKD after HT (35).
Liver transplantation (HT) is the only definitive treatment for drug-refractory RHS. It is important to use the sCr on the MELD scale for patients with SHR-AKI or SHR-CKD to undergo HT (7). In a study by Wong et. to 325 patients in the group of living donors (LDLT) and those of deceased donors (DDLT) of liver. The risk of death was better in the LDLT group at 43.4% and the DDLT at 19.8%, just as the transplant rate was higher in the LDLT group than at DDLT (78.3% versus 52.2% respectively), the highest mortality was in patients on the post-inclusion waiting list. The LDLT group

had the highest rate of renal recovery at one month (77.4% versus 59.1%) at 3 months (86.1% versus 74.5%), but long-term eGFR was similar in all 2 groups (36).

- Absorbent Recirculating Molecular System (MARS)

It is an extracorporeal dialysis system with albumin that is recycled and perfused through carbon chains and anion exchangers, thereby improving kidney function and survival. In some non-randomized studies the objective is 30-day survival in patients with AKI-SHR and severe hepatic impairment, in several the percentage was favorable in survival and a small percentage had a mortality at 7 days. In the case of the control groups, most had a total mortality at 7 days (37–39).

Results

Hepatorenal syndrome continues to be a challenge in the health area, so its diagnosis is based on a clinical detection that meets diagnostic criteria, on markers of detection of kidney injury such as: KIM-1, albumin, IL-18, NGAL, hepatic fatty acid binding protein and L-FABP, abdominal and renal color Doppler ultrasound with 100% sensitivity, as well as the measurement of the inferior vena cava in order to detect hypervolemia or hypovolemia, this being not only a diagnostic method but also a control and follow-up method in patients.

In terms of treatment, first-line vasopressors, primarily terlipressin plus albumin, but also the combination of norepinephrine plus albumin, dopamine plus furosemide plus albumin would also be options to consider. The definitive treatment for drug-refractory RHS is liver transplantation, kidney transplantation improves liver function, and jugular intrahepatic portosystemic shunt improves portal hypertension, hence renal function as well. The above is detailed in Tables 1, 2 and 3.

Discussion

In a disease with high mortality, markers for early diagnosis and identification in high-risk patients are still lacking, so Sherif et al. (25) A univariate regression analysis was performed, which included 50 patients who underwent abdominal and renal color duplex ultrasound, where they defined as an independent predictor of RHS the resistivity of the renal hilum of the renal artery with a sensitivity of 100% and a specificity of 66.7% (25). Similarly, ultrasound of the inferior vena cava is an evaluation method for intravascular hypervolemia or hypovolemia after diuretic removal or volume administration, it is recommended that it be before, during and after in order to improve clinical outcomes according to Kaptein et al (40).

In a review by Wang et al.(41) shows that terlipressin plus albumin is the first-line treatment for SHR-AKI, but due to its cost it is difficult to use for a long period of time and terlipressin alone has decreased efficacy by one-third to one-half of patients. It is mentioned that norepinephrine plus albumin and terlipressin plus albumin do not show a major difference in efficacy, therefore, norepinephrine plus albumin would be an option to consider. For the reversal of sCr in hepatorenal syndrome, terlipressin plus albumin and dopamine plus albumin plus furosemide should be given priority, and for the increase in sodium, the association of octreotide plus albumin plus midodrin should be taken as a priority.

Pharmacological treatment prior to liver transplantation is important as a lower mortality risk rate has been demonstrated (41). A multicenter medical record review study conducted in the United Kingdom showed that treatment with terlipressin alone had a 73% improvement in sCr, and the response was greater in patients with mild acute kidney injury than in moderate or severe kidney injury (11). According to Vélez et al., their study included 77 patients diagnosed with HRS-type 1 with 2-10 days of treatment with norepinephrine or midodrine/octreotide, where they concluded that the increase in MAP (≥15 mm Hg) with vasoconstrictor therapy improves sCr values where norepinephrine prevails over midodrine/octreotide (42). Therefore, a treatment with terlipressin alone is also possible, with a study that demonstrates its efficacy and that could be carried out in the absence of economic resources or the necessary equipment.

In a study by Kaewput et al. (14) with a participation of 4938 hospitalized patients from 2005 to 2014, with a mortality initiation rate of 44% and decreasing to 24%. Due to the increase in liver transplantation, renal replacement therapy. Within this study, variables such as: advanced age, alcohol

consumption, mechanical ventilation needs, neurological disorders and coagulopathies were analyzed, which were predictors of a higher percentage of mortality, liver transplantation, abdominal paracentesis and TIPS were associated with a lower percentage of in-hospital mortality (14).
Among other treatments we have kidney transplantation that in a study carried out by Allegretti et al. in the United States where the prognosis is analyzed with a study of 472 patients, who were divided into two groups, those who required liver transplantation (131 participants) and those who did not (341). 15% of those who did not require it had 6 months of life after the start of kidney transplantation, the mean was 21 days for those diagnosed with RHS and 12 days for those diagnosed with acute tubular necrosis. 48% of those requiring liver transplantation obtained it and the median life was 15 days for patients with RHS and 14 days for those with acute tubular necrosis (34).
In a retrospective study conducted in Taiwan, where they compared long-term renal outcomes in patients with CKD and SHR after a living-donor liver transplant, in which both mortality and postoperative complications during the 30 days were comparable in CKD, SHR1M SHR2 and normal renal function. A 5-year survival rate of >90% was obtained, eGFR improved, which progressively improved and peaked within 4 weeks after transplantation. However, renal function in patients with SHR1 deteriorated and gave way to stage ≥ III CKD in 72.7% and in SHR2 in 78.9%. The incidence of the development of end-stage renal disease and chronic kidney disease was similar between CKD, SHR1 and SHR2, but more common in the group with normal renal function. In conclusion, living-donor liver transplantation provided a benefit in patients with RHS, but the risk of developing CKD was similar in the other study groups (43).

Conclusion

- RHS is a renal impairment due to liver diseases, mainly in cirrhosis, therefore, having an impaired renal perfusion due to renal vasoconstriction. Over the years the classification changed, at first it was classified as type I and type II, currently SHR-AKI and SHR-NonAKI respectively, the latter classification has been based on the ICA in conjunction with the subclassification of SHR since 2015.
- Currently, the diagnostic criteria do not have a precision for the exclusion of parenchymal kidney injury in patients with cirrhosis, so we currently have markers for detecting kidney injury such as: IL-18, KIM-1, L-FABP, albumin, NGAL and hepatic fatty acid binding protein. IL-18 and NGAL aid in the differential diagnosis between SHR-AKI and acute kidney injury-acute tubular necrosis. In addition, the NGAL serves as a predictor of mortality. Ultrasound should also be an assessment tool for prerenal AKI, hypervolemia, and hypovolemia.
- With a better knowledge about pathophysiology, it has been possible to have better therapeutic strategies. When considering a pharmacological treatment vasoconstrictors with the most efficacious are norepinephrine and terlipressin infusion, the combination of midodrine with octreotide could be considered as an alternative. Intravenous albumin, when combined with vasoconstrictors, is more effective. Antibiotic prophylaxis has shown benefits in HRS in association with SBP and AKI.
- In patients with ascites, it should be controlled as they have a high probability of developing PBS, with transjugular intrahepatic portosystemic shunt, which also helps in the prevention of mortality. The MARS system improves kidney function and patient survival through albumin extracorporeal dialysis, compared to control groups had better survival at 7 days.
- Liver transplantation is the only definitive treatment for hepatorenal syndrome when it has failed in pharmacological treatment, kidney transplantation is also performed, but it is recognized that it is added to a subsequent liver transplant. Donation by living donors was more popular than by deceased donors. Simultaneous donation (liver-kidney) has been given due to the poor prediction of recovery of kidney function after a liver transplant.

Recommendations

- There is limited information and studies at the national level -Ecuador-, so laboratories, public hospitals, universities and research institutes should be included in order to expand the results of our patients regarding the application of medication from the guidelines, diagnostic methods according

to our resources and viable treatments with better efficacy. Thus contributing to academia, the Ecuadorian scientific community and society.
- A unified diagnostic and treatment protocol for Hepatorenal Syndrome has yet to be established, as research follows several theories of pathophysiology that have been previously demonstrated in this research, therefore, it is recommended to carry out clinical studies regarding this syndrome or a better follow-up in patients.
- Expand studies based on the octreotide drug since it is a drug with better economic access than those recommended in the guidelines, thus allowing countries to provide a long-term and more sustainable treatment to their patients.

Financing:
- This literature review was self-funded by the authors.

Abbreviations
ACLD: Advanced Chronic Liver Disease
sCr: serum creatinine
AKIN: Acute Kidney Injury Network
KDIGO: Kidney Disease: Improving Global Outcomes
ICA: International Ascites Club
GFR: glomerular filtration rate
Estimated TFG: TFGe
EASL: European Association for the Study of the Liver
RAAS: Renin-Angiotensin-Aldosterone System
SI: Systemic inflammation
SIRS: Systemic Inflammatory Response Syndrome
SBP: Spontaneous bacterial peritonitis
AKI: Acute Kidney Injury
PRA: Prerenal azothermia
NGAL: Neutrophil Gelatinase-Associated Licolaline
ATN: acute tubular necrosis
KIM-1: Kidney Injury Molecule
L-FABP: hepatic-type fatty acid-binding protein
HVPG: Hepatic Venous Pressure Gradient
MAP: Mean Arterial Pressure
PFTE: polytetrafluoroethylene
TRS: Renal Replacement Therapy
HT: Liver transplant
ITT: Intent to Treat
LDLT: living-donor liver transplant
DDLT: Deceased Donor Liver Transplant
MELD: A Model for End-Stage Liver Disease
SLK: simultaneous liver and kidney transplantation

REFERENCES:
1. Amador AC, Rodríguez LJV, Hernández G, Aguilar DPS, Córdoba PAB, Muñoz JLR, et al. Hepatorenal syndrome: a review of the literature. Rev Colomb Nefrol. February 21, 2022; 9(1):E539-E539.
2. Subedi A, Kumar VCS, Subedi AS, Sapkota B, Subedi A, Kumar V, et al. A Review of Hepatorenal Syndrome. Cureus [Internet]. July 1, 2021; 13(7). Available in: https://www.cureus.com/articles/63880-a-review-of-hepatorenal-syndrome
3. Nassar M, Nso N, Medina L, Ghernautan V, Novikov A, El-Ijla A, et al. Liver kidney crosstalk: Hepatorenal syndrome. World J Hepatol. September 27, 2021; 13(9):1058-68.

4. Ojeda-Yuren AS, Cerda-Reyes E, Herrero-Maceda MR, Castro-Narro G, Piano S. An Integrated Review of the Hepatorenal Syndrome. Ann Hepatol. 2021 May 1;10:100236 PM.
5. Ospina LLG, Laverde JLG, Tapia JAA, Cahuasquí JPO. Hyponatremia and hepatorenal syndrome. RECIMUNDO. July 11, 2020; 4(3):102-17.
6. Chaney A. A Review for the Practicing Clinician: Hepatorenal Syndrome, a Form of Acute Kidney Injury, in Patients with Cirrhosis. Clin Exp Gastroenterol. 2021 Oct 5;14:385-96.
7. Gupta K, Bhurwal A, Law C, Ventre S, Minacapelli CD, Kabaria S, et al. Acute kidney injury and hepatorenal syndrome in cirrhosis. World J Gastroenterol. July 14, 2021; 27(26):3984-4003.
8. Simbrunner B, Trauner M, Reiberger T, Mandorfer M. Recent advances in the understanding and management of hepatorenal syndrome. Fac Rev. 2021 May 21;10:48 AM.
9. Saner FH, Canbay A, Gerken G, Broelsch CE. Pharmacology, clinical efficacy and safety of terlipressin in esophageal varicose veins bleeding, septic shock and hepatorenal syndrome. Expert Rev Gastroenterol Hepatol. December 2007; 1(2):207-17.
10. Flamm SL, Brown K, Wadei HM, Brown RS, Kugelmas M, Samaniego-Picota M, et al. The Current Management of Hepatorenal Syndrome–Acute Kidney Injury in the United States and the Potential of Terlipressin. Liver Transpl. August 2021; 27(8):1191-202.
11. Moore K, Jamil K, Verleger K, Luo L, Kebede N, Heisen M, et al. Real-world treatment patterns and outcomes using terlipressin in 203 patients with the hepatorenal syndrome. Aliment Pharmacol Ther. July 2020; 52(2):351-8.
12. Habas E, Ibrahim AR, Moursi MO, Shraim BA, Elgamal ME, Elzouki AN. Update on hepatorenal Syndrome: Definition, Pathogenesis, and management. Arab J Gastroenterol. May 1, 2022; 23(2):125-33.
13. Amin AA, Alabsawy EI, Jalan R, Davenport A. Epidemiology, Pathophysiology, and Management of Hepatorenal Syndrome. Semin Nephrol. January 1, 2019; 39(1):17-30.
14. Kaewput W, Thongprayoon C, Dumancas CY, Kanduri SR, Kovvuru K, Kaewput C, et al. In-hospital mortality of hepatorenal syndrome in the United States: Nationwide inpatient sample. World J Gastroenterol. December 7, 2021; 27(45):7831-43.
15. Francoz C, Durand F, Kahn JA, Genyk YS, Nadim MK. Hepatorenal Syndrome. Clin J Am Soc Nephrol. May 2019; 14(5):774.
16. Tangpanithandee S, Thongprayoon C, Krisanapan P, Mao MA, Kaewput W, Pattharanitima P, et al. Distinct Subtypes of Hepatorenal Syndrome and Associated Outcomes as Identified by Machine Learning Consensus Clustering. Diseases. March 2023; 11(1):18.
17. Tariq R, Singal AK. Management of Hepatorenal Syndrome: A Review. J Clin Transl Hepatol. June 28, 2020; 8(2):192-9.
18. Facciorusso A. Hepatorenal Syndrome Type 1: Current Challenges And Future Prospects. Ther Clin Risk Manag. 2019 Nov 27;15:1383-91.
19. Hasan I, Rashid T, Chirila RM, Ghali P, Wadei HM. Hepatorenal syndrome: pathophysiology and evidence-based management update. Rom J Intern Med. Aug. 31, 2021; 59(3):227-61.
20. Sheng XY, Lin FY, Wu J, Cao HC. Development and validation of a prognostic model for patients with hepatorenal syndrome: A retrospective cohort study. World J Gastroenterol. May 28, 2021; 27(20):2615-29.
21. Fida S, Khurshid SMS, Mansoor H, Fida S, Khurshid SMS, Mansoor H. Frequency of Hepatorenal Syndrome Among Patients With Cirrhosis and Outcome After Treatment. Cureus. August 25, 2020; 12(8). Available in: https://www.cureus.com/articles/39160-frequency-of-hepatorenal-syndrome-among-patients-with-cirrhosis-and-outcome-after-treatment
22. Wang S, Zhou Z, Xu C, Chen H, Ren W, Yang X, et al. Establishment and evaluation of an early prediction model of hepatorenal syndrome in patients with decompensated hepatitis B cirrhosis. BMC Gastroenterol. January 2, 2023; 23(1):1.
23. Giraldo C, Jiménez M, Torres J. Hepatorenal syndrome in acute on chronic liver failure. Rev. Colom. Nefrol. 2022; 8(2). Available in: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S2500-50062021000200704&lang=es

24. Angeli P, Garcia-Tsap G, Nadim M, Parikh C. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. J Hepatol. October 1, 2019; 71(4):811-22.
25. Sherif M, Rahman S, Abd S, Elkholy S, Abd N, Ak-Jarhi U, Awad A. Role of renal Duplex ultrasonography in evaluation of hepatorenal syndrome | Egyptian Liver Journal. 2023; 11 (34). . Available in: https://eglj.springeropen.com/articles/10.1186/s43066-021-00104-9
26. Facciorusso A. Hepatorenal Syndrome Type 1: Current Challenges And Future Prospects. Therapeutics and Clinical Risk Management. 2023; 15: 1383-1391. Available in: https://www-tandfonline-com.vpn.ucacue.edu.ec/doi/full/10.2147/TCRM.S205328
27. Kulkarni AV, Ravikumar ST, Tevethia H, Premkumar M, Kumar K, Sharma M, et al. Safety and efficacy of terlipressin in acute-on-chronic liver failure with hepatorenal syndrome-acute kidney injury (HRS-AKI): a prospective cohort study. Sci Rep. 2022 Apr 1;12:5503.
28. Wang H, Liu A, Bo W, Feng X, Hu Y. Terlipressin in the treatment of hepatorenal syndrome: A systematic review and meta-analysis. Medicine (Baltimore). April 2018; 97(16):E0431.
29. Nguyen-Tat M, Jäger J, Rey JW, Nagel M, Labenz C, Wörns MA, et al. Terlipressin and albumin combination treatment in patients with hepatorenal syndrome type 2. United Eur Gastroenterol J. May 1, 2019; 7(4):529-37.
30. Fernández J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology. September 2007; 133(3):818-24.
31. Bosch J. Small diameter shunts should lead to safe expansion of the use of TIPS. J Hepatol. January 2021; 74(1):230-4.
32. Garcia-Pagán JC, Saffo S, Mandorfer M, Garcia-Tsao G. Where does TIPS fit in the management of patients with cirrhosis? JHEP Rep. May 23, 2020; 2(4):100122.
33. Praktiknjo M, Abu-Omar J, Chang J, Thomas D, Jansen C, Kupczyk P, et al. Controlled underdilation using novel VIATORR® controlled expansion stents improves survival after transjugular intrahepatic portosystemic shunt implantation. JHEP Rep. March 3, 2021; 3(3):100264.
34. Allegretti AS, Parada XV, Eneanya ND, Gilligan H, Xu D, Zhao S, et al. Prognosis of Patients with Cirrhosis and AKI Who Initiate RRT. Clin J Am Soc Nephrol CJASN. January 6, 2018; 13(1):16-25.
35. Piano S, Gambino C, Vettore E, Calvino V, Tonon M, Boccagni P, et al. Response to Terlipressin and Albumin Is Associated With Improved Liver Transplant Outcomes in Patients With Hepatorenal Syndrome. Hepatol Baltim, Md., May 2021; 73(5):1909-19.
36. Analysis of Survival Benefits of Living Versus Deceased Donor Liver Transplant in High Model for End-Stage Liver Disease and Hepatorenal Syndrome - Wong - 2021 - Hepatology - Wiley Online Library. Available in: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.31584
37. Lavayssière L, Kallab S, Cardeau-Desangles I, Nogier MB, Cointault O, Barange K, et al. Impact of molecular adsorbent recirculating system on renal recovery in type-1 hepatorenal syndrome patients with chronic liver failure. J Gastroenterol Hepatol. June 2013; 28(6):1019-24.
38. Bañares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatol Baltim, Md., March 2013; 57(3):1153-62.
39. Torre A, Martín-Llahí M, Ginès P. Dilutional hyponatremia, refractory ascites and hepatorenal syndrome: current treatment. Gastroenterol Hepatol. 2004 Oct;27:26-39.
40. Kaptein EM, Oo Z, Kaptein MJ. Hepatorenal syndrome misdiagnosis may be reduced using inferior vena cava ultrasound to assess intravascular volume and guide management. Ren Fail. December 31, 2023; 45(1):2185468.
41. Wang L, Long Y, Li KX, Xu GS. Pharmacological treatment of hepatorenal syndrome: a network meta-analysis. Gastroenterol Rep. April 1, 2020; 8(2):111-8.

42. Velez JCQ, Karakala N, Tayebi K, Wickman TJ, Mohamed MMB, Kovacic RA, et al. Responsiveness to Vasoconstrictor Therapy in Hepatorenal Syndrome Type 1. Kidney360. April 2023; 4(4):E448.
43. Tseng HY, Lin YH, Lin CC, Chen CL, Yong CC, Lin LM, et al. Long-term renal outcomes comparison between patients with chronic kidney disease and hepatorenal syndrome after living donor liver transplantation. Front Surg. 2023;10. Available in: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1116728