Gastroenterología y Hepatología 45 (2022) 25–39

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ORIGINAL ARTICLE

Evidence-based protocol for diagnosis and treatment of hepatorenal syndrome is independently associated with lower mortality☆

Alana Zulian Terres[a,b], Rafael Sartori Balbinot[c,d], Ana Laura Facco Muscope[d], Morgana Luisa Longen[d], Bruna Schena[d], Bruna Teston Cini[d], Gilberto Luis Rost Jr.[d], Juline Isabel Leichtweis Balensiefer[d], Louise Zanotto Eberhardt[d], Raul Angelo Balbinot[e,f], Silvana Sartori Balbinot[e,f], Jonathan Soldera[e,g,*]

[a] *Internal Medicine, Hospital Pompeia, Caxias do Sul, RS, Brazil*
[b] *Gastroenterology, Hospital Geral de Caxias do Sul (RS), Brazil*
[c] *Residency in Internal Medicine, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil*
[d] *Faculty of Medicine, Universidade de Caxias do Sul, Caxias do Sul, RS, Brazil*
[e] *Clinical Gastroenterology, Universidade de Caxias do Sul (UCS), Caxias do Sul, RS, Brazil*
[f] *Department of Gastroenterology, Universidade de São Paulo (USP), São Paulo, SP, Brazil*
[g] *Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil*

Received 23 October 2020; accepted 5 February 2021
Available online 18 March 2021

KEYWORDS
Hepatorenal syndrome;
End stage liver disease;
Clinical protocol;
Prognosis;
Terlipressin;
Liver cirrhosis

Abstract
Background: Hepatorenal syndrome (HRS) is the deadliest complication of cirrhosis. The purpose of this study is to analyze if the use of a protocol for HRS is associated with higher survival in these patients.
Methods: An evidence-based protocol for the diagnosis and treatment of HRS was instituted in 2013. Data from medical records from 2010 to 2016 were obtained by searching the hospital database for patients who received terlipressin, in the three years before and after the institution of the protocol. Data were reviewed to confirm the diagnosis of HRS and multiple variables were collected. Liver-specific scores were calculated and a stepwise Cox regression approach was used for univariate and multivariate analysis.

Abbreviations: HRS, hepatorenal syndrome; ESLD, end-stage liver disease; LT, liver transplantation; AKI, acute kidney injury; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease-sodium; CLIF-SOFA, chronic Liver-Failure – Sequential Organ Failure Assessment; EASL-CLIF, European Society for the Study of the Liver – Chronic Liver Failure; ACLF, acute-on-chronic liver failure; DC, decompensated cirrhosis; RRT, renal replacement therapy.

☆ Previous presentation: Residency conclusion thesis for Alana Zulian Terres in 2018. Partial data presented as an oral presentation in Semana Brasileira do Aparelho Digestivo, November-2018. Complete data presented as poster in UEG Week, 2019.

* Corresponding author.
E-mail address: jonathansoldera@gmail.com (J. Soldera).

https://doi.org/10.1016/j.gastrohep.2021.02.007

Results: The study included 46 patients, 20 from the pre-protocol period and 26 from the post-protocol period. Respectively, mortality at 30 days, 90 days and 365 days was 75%, 75% and 90% for the pre-protocol period, and 61%, 69% and 80% for the post-protocol period. In the multivariate analysis, an aspartate aminotransferase (AST) of <40 U/L, the pre-protocol period and higher Child-Turcotte-Pugh scores were associated with higher 30-day and 90-day mortality. The total mean dose of terlipressin and human albumin used per patient was reduced from 27 mg to 22 mg and from 236 g to 144 g, respectively, after the institution of the protocol. This was not associated with higher mortality.
Conclusion: The use of an evidence-based protocol for the treatment of HRS translated into a higher survival. The authors suggest that the use of evidence-based protocols for the diagnosis and treatment of HRS could reduce cost and mortality in tertiary hospitals.

PALABRAS CLAVE
Síndrome hepatorrenal;
Enfermedad hepática en etapa terminal;
Protocolo clínico;
Pronóstico;
Terlipresina;
Cirrosis hepática

El protocolo basado en la evidencia para el diagnóstico y tratamiento del síndrome hepatorrenal se asocia de forma independiente con una menor mortalidad

Resumen
Antecedentes: El síndrome hepatorrenal (SHR) es la complicación más mortal de la cirrosis. El objetivo de este estudio es analizar si el uso de un protocolo para el SHR se asocia a una mayor supervivencia en estos pacientes.
Métodos: En 2013 se instituyó un protocolo basado en la evidencia para el diagnóstico y tratamiento del SHR. Los datos de los registros médicos del 2010 al 2016 se obtuvieron mediante la búsqueda en la base de datos del hospital de pacientes que recibieron terlipresina, 3 años antes y después de la institución del protocolo. Se revisaron los datos para confirmar el diagnóstico de SHR y se recopilaron múltiples variables. Se calcularon las puntuaciones específicas del hígado y se utilizó un enfoque gradual de la regresión de Cox para el análisis univariado y multivariado.
Resultados: Se incluyó a 46 pacientes, 20 del período preprotocolo y 26 posprotocolo. Respectivamente, la mortalidad a los 30, 90 y 365 días fue del 75, el 75 y el 90%, respectivamente, para el período previo al protocolo y del61, el 69 y el 80%, respectivamente, para el posterior al protocolo. En el análisis multivariado, aspartato aminotransferasa (AST) < 40 U/l, el período preprotocolo y las puntuaciones más altas de Child-Turcotte-Pugh se asociaron con una mayor mortalidad a los 30 y 90 días. Las dosis media total de terlipresina y albúmina humana utilizada por paciente se redujo de 27 a 22 mg de terlipresina y de 236 a 144 g de albúmina humana después de la institución del protocolo. Esto no se asoció con una mayor mortalidad.
Conclusión: El uso de un protocolo basado en la evidencia para el tratamiento del SHR se tradujo en una mayor supervivencia. Los autores sugieren que el uso de protocolos basados en la evidencia para el diagnóstico y tratamiento del SHR podría reducir el costo y la mortalidad en los hospitales de tercer nivel.

Introduction

Hepatorenal syndrome (HRS) is a severe complication of end-stage liver disease (ESLD), which occurs in cirrhotic patients with ascites.[1] These patients generally have a marked circulatory dysfunction: the activation of cytokines and vasoactive hormones and the alteration in circulatory function in advanced cirrhosis and ascites without overt sepsis are similar to that seen in sepsis and septic shock without cirrhosis, which might cause renal hypoperfusion.[2] Such circulatory dysfunction can also occur in patients with acute and acute-on-chronic liver failure (ACLF).[3,4] This does not explain alone the multiorgan failure that is associated with ESLD: severe decompensation results from systemic spread of bacterial products, which cause activation of host innate immune triggers and leads to arterial vasodilatation, causing organ dysfunction through a storm of pro-inflammatory cytokines and reactive oxygen and nitrogen species – ESLD might be result of an inflammatory syndrome and not solely an hemodynamic process.[5]

Even though HRS is a functional syndrome, it carries a poor prognosis[6] and liver transplantation (LT) is the only available definitive treatment in the long term.[7] HRS is divided in two types: HRS type 1, rapidly progressive; and HRS type 2, slowly progressive; the first carrying a worse prognosis.[1,8]

Nevertheless, some studies have shown efficacy over placebo of diverse treatment strategies for HRS – generally the association of human albumin with a vasopressor drug,[8] such as norepinephrine[9,10] and terlipressin.[11–14] Even though both have not been compared in a definitive head-to-head randomized clinical trial, terlipressin has been shown to reduce cost in a systematic review and meta-analysis.[15] Terlipressin is, nevertheless, an expensive drug and norepinephrine, although inexpensive, requires monitoring in an intensive care unit, making both treatments costly. Also, the pharmacological treatment of HRS does not seem to increase survival in the long run except in a few patients – LT is still the choice of treatment for this severe complication of ESLD.[16] Terlipressin has been shown to be superior to an association commonly used in the United States: midodrine and octreotide plus human albumin.[17]

The diagnosis of HRS is one of exclusion, using criteria established by the International Ascites Club. The first set of criteria were published in 1994 [18] and later reviewed in 2007.[19] These criteria defined in 2007 have been updated to include the concept of Acute Kidney Injury (AKI) in 2015.[20] This modification, nevertheless, has not been shown to be superior in predicting adverse events when compared to the cutoff previously used of a serum creatinine above 1.5 mg/dL.[21]

The concept of ACLF has been used as a step between decompensated cirrhosis (DC) and death, defined by the failure of multiple organic systems.[22] Such concept lacked a definition when Intensive Care and Hepatology began to discuss it,[23–29] but the multi-centric prospective study CANONIC published in 2013 has developed criteria based in the CLIF-SOFA score, which were shown to predict mortality.[22] Hence HRS defines kidney failure, its presence already defines a patient as having ACLF.

The purpose of this study is to analyze if the use of an evidence-based protocol for diagnosis and treatment of HRS is associated with higher survival in these patients.

Methods

Study population

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval on June 2017 by the human research committee of the University, under protocol no. 66646617.3.0000.5341. Informed consent was waived by the human research ethics committee; since this study analyzed only medical records. An evidence-based protocol for diagnosis and treatment of HRS was developed by the Clinical Hepatology team of the University, based in the diagnostic criteria published in 2007,[19,30] and instituted as standard-of-care in 12/23/2013 in the Hospital (Fig. 1). Afterwards, this protocol was used as guidance for diagnosis and treatment of HRS type 1 by every attending physician and medical resident of the team.

Data from medical records from 2010 to 2016 was obtained by searching the hospital electronic database for every patient who received terlipressin, ranging from three years prior to three years after the institution of the protocol. Electronic and physical medical records were analyzed and a data collection form was filled for each patient. Patients over 18 years old with the diagnosis of cirrhosis, ascites and AKI supported by laboratory and imaging data were included. The diagnosis of HRS type 1 was defined using the criteria published in 2007:[19]

- Cirrhosis with ascites.
- Serum creatinine >1.5 mg/dL.
- No improvement of serum creatinine (decrease to a level of 1.5 mg/dL or lower) after at least 2 days with diuretic withdrawal and volume expansion with human albumin. The recommended dose of human albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

Patients were excluded if they did not have a diagnosis of cirrhosis, had incomplete medical records or the absence of ascites and kidney failure, or if they used terlipressin because of acute variceal bleeding. Data regarding clinical and laboratory variables were gathered in order to calculate liver-specific scores. The patients were stratified as pre-protocol and post-protocol, according to the date of the diagnosis of HRS and the adherence of the attending physician to the protocol, which was 96% in the post-protocol period – only one patient admitted to the Nephrology ward before the Clinical Gastroenterology Team was called had a substantial delay to start the protocol. HRS resolution was defined as a discharge creatinine of less than 1.5 mg/dL, for patients who survived the hospital stay.

Variables

Data was gathered through the analysis of electronic and physical medical records. Clinical data was obtained and each case was individually assessed. Standardized imaging criteria were used for the diagnosis of hepatocellular carcinoma.[31,32] Hepatic encephalopathy was defined and stratified according to West-Haven criteria.[33] Laboratory data is expressed in units commonly used in the hospital. Days to be started on human albumin or terlipressin was defined as the days it took after the result of the first creatinine equal or higher than 1.5 mg/dL during that hospital stay for the patient to receive the first dose of human albumin and terlipressin.

Liver-specific scores

Commonly used liver-specific scores were calculated to analyze their accuracy into predicting mortality. Child-Turcotte-Pugh (CTP) is a score used in the clinical care for cirrhotic patients that aims to predict 1-year mortality for compensated and decompensated cirrhosis.[34,35] CTP was calculated through an online calculator.

Model for End-Stage Liver Disease (MELD)[36] and Model for End-Stage Liver Disease – Sodium (MELD-Na)[37] are scores currently used for organ allocation in liver transplantation,

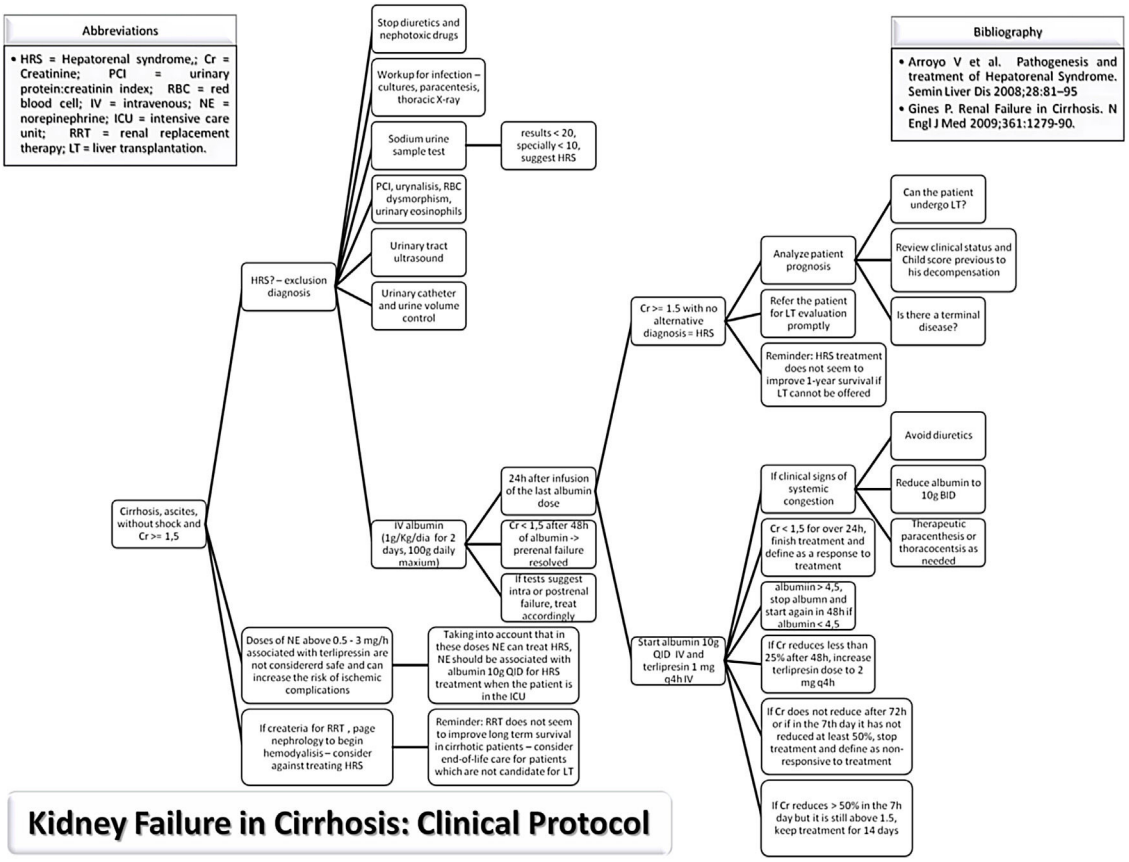

Figure 1 Evidence-based protocol for diagnosis and treatment of hepatorenal syndrome (December, 2013).

developed to predict 90-day mortality for cirrhotic patients. Both were calculated using online calculators.

Chronic Liver-Failure – Sequential Organ Failure Assessment (CLIF-SOFA) is a score developed by the European Society for the Study of the Liver – Chronic Liver Failure (EASL-CLIF) group, adapted from the Sequential Organ Failure Assessment (SOFA) score used in intensive care (Supplementary Table 1). It aims to define ACLF and divides it in three grades.[22] Both CLIF-SOFA and ACLF grade were calculated using an online calculator developed by the CLIF Research Group (https://www.clifresearch.com/ToolsCalculators.aspx). These criteria already define HRS as ACLF. Therefore, ACLF was stratified in grade 1, 2 and 3 for this study:

- ACLF grade 1: isolated kidney failure.
- ACLF grade 2: two organ failures.
- ACLF grade 3: three organ failures.

Another scores developed by the EASL-CLIF group, CLIF Consortium Acute Decompensation (CLIF-C AD) score and CLIF-C ACLF, were developed with the purpose of predicting expected mortality for 30-day, 90-day, 180-day and 365-day for DC and ACLF patients.[38] CLIF-C ACLF was calculated using the online calculator developed by the EASL-CLIF Group.

Outcome

Death from all causes was used as main outcome. Data was gathered using medical records and searching through national death databases (https://www.falecidosnobrasil.org.br/). If the patient was admitted to the hospital more than once for HRS, data regarding only the first admission was collected.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 15.0. Categorical variables are described using frequency and corresponding percentage and continuous variables by mean and standard deviation. Cox regression was used for univarate analysis and a multivariate analysis was performed using a stepwise progression to the Cox regression. All statistical tests performed for the analysis of variables excluded missing data. Kaplan–Meier curves were used for the graphical description of survival.

Results

Medical record analysis retrieved 177 hospital admissions of patients who received terlipressin. Of these, 46 admissions were diagnosed as HRS type 1 and included in the study – 20 patients from the pre-protocol and 26 from the post-protocol period (Fig. 2). The remaining 131 patients

Table 1 Demographic, clinical and laboratory findings of the study population and for each protocol period.

Variable	Study population ($n = 46$)	Pre-protocol period ($n = 20$)	Post-protocol period ($n = 26$)
Age (years)[a]	58 (9)	59 (8)	55 (9)
Male sex[b]	37 (80.4)	16 (80)	21 (80.8)
Period[b]			
Pre-protocol	20 (43.5)	–	–
Post-protocol	26 (56.5)	–	–
Etiology of cirrhosis[b]			
Alcohol	35 (76.1)	16 (80)	19 (73.2)
Hepatitis C	6 (13)	2 (10)	4 (15.4)
Alcohol and hepatitis C	4 (8.7)	1 (5)	3 (11.5)
Other	1 (2.2)	1 (5)	0
Active alcoholism[b]	19 (41.3)	8 (40)	11 (42.3)
Previous use of medications[b]			
PPI	15 (32.6)	5 (25)	10 (38.5)
Spironolactone	22 (47.8)	11 (55)	11 (42.3)
Furosemide	21 (45.7)	9 (45)	12 (46.2)
NSBB	19 (41.3)	8 (40)	11 (42.3)
Renal replacement therapy[b]	4 (8.7)	1 (5)	2 (11.5)
Portal vein thrombosis[b]	1 (2.2)	0	1 (3.8)
Hepatocellular carcinoma[b]	5 (10.9)	2 (10)	3 (11.5)
Hepatic enchephalopathy[b]			
Absent	20 (43.5)	7 (35)	13 (50)
Grade 1	5 (10.9)	2 (10)	3 (11.5)
Grade 2	11 (23.9)	5 (25)	6 (23.1)
Grade 3	4 (8.7)	2 (10)	2 (7.7)
Grade 4	6 (13)	4 (20)	2 (7.7)
Esophageal varices[b]			
Absent	28 (60.9)	12 (60)	16 (61.5)
Small caliber	4 (8.7)	0	4 (15.4)
Medium caliber	10 (21.7)	5 (25)	5 (19.2)
Large caliber	4 (8.7)	3 (15)	3 (3.8)
Infection[b]			
Absent	14 (30.4)	5 (25)	9 (34.6)
SBP	16 (34.8)	7 (35)	9 (34.6)
RTI	3 (6.5)	1 (5)	2 (7.7)
UTI	1 (2.2)	0	1 (3.8)
Sepsis with undefined source of infection	10 (21.7)	7 (35)	3 (11.5)
Other	2 (4.3)	0	2 (7.7)
Laboratory – before terlipressin[a]			
Hemoglobin (g/dL)	9.3 (2)	9.4 (2)	9.3 (2)
Hematocrit (%)	27.5 (5.3)	27.9 (5.1)	27.1 (5.5)
Leukocyte (/mm^3)	9951 (5160)	10,821 (5492)	9281 (4892)
Platelets (10^3/mm^3)	97.2 (51)	96 (51)	97 (51)
Total bilirubin (mg/dL)	6.4 (7.3)	6.8 (7.3)	6.2 (7.5)
INR	2.5 (5.6)	1.7 (0.5)	3.2 (7.6)
AST (U/L)	89.5 (100)	99 (136)	81 (59)
ALT (U/L)	58 (154)	28 (21)	80 (201)
GGT (U/L)	230 (300)	147 (172)	309 (373)
Creatinine (mg/dL)	3.75 (2.27)	4.7 (8.5)	2.9 (1.1)
Sodium (mg/dL)	138 (7)	138 (7)	137 (8)
Potassium (mg/dL)	5.2 (1.5)	6.5 (8.6)	4.2 (0.9)
Albumin (mg/dL)	2.7 (0.6)	2.6 (0.7)	2.7 (0.4)
CRP (mg/L)	74 (64)	68 (72)	82 (58)

Table 1 (*Continued*)

Variable	Study population ($n = 46$)	Pre-protocol period ($n = 20$)	Post-protocol period ($n = 26$)
Laboratory – after terlipressin[a]			
Hemoglobin (g/dL)	8.3 (1.7)	8.3 (1.9)	8.2 (1.6)
Hematocrit (%)	24.7 (5.4)	25.6 (5.7)	24.1 (5.1)
Leukocyte (/mm^3)	11,466 (12,257)	14,197 (17,230)	9304 (5566)
Platelets (10^3/mm^3)	73 (43)	70 (42)	74 (45)
Total bilirubin (mg/dL)	7.8 (7.2)	7.7 (5.4)	8 (8.5)
INR	2 (0.5)	1.9 (0.6)	2 (0.5)
AST (U/L)	237 (353)	150 (187)	395 (532)
ALT (U/L)	68 (124)	39 (28)	122 (205)
GGT (U/L)	142 (186)	119 (156)	175 (237)
Creatinine (mg/dL)	2.65 (1.6)	2.9 (1.6)	2.4 (1.5)
Sodium (mg/dL)	139.4 (22)	144 (7)	135 (28)
Potassium (mg/dL)	4.2 (1.2)	4.5 (1.4)	4 (1.1)
Albumin (mg/dL)	3.4 (0.6)	3.7 (0.4)	3.1 (0.6)
CRP (mg/L)	80 (32)	63 (20)	99 (34)
Terlipressin[a]			
Mean dose (mg/day)	7.1 (2.7)	7.6 (2.9)	6.7 (2.4)
Total dose (mg)	24.2 (13.6)	27.1 (15.5)	22.1 (13.5)
Days used	3.4 (1.7)	3.9 (2.1)	3.1 (1.4)
Time to start (days)	3.8 (3.5)	5.1 (4.4)	2.8 (2.3)
Human albumin[a]			
Mean dose (g/day)	51.2 (20.1)	60.7 (23.9)	43.8 (12.7)
Total dose (g)	184.3 (109.9)	236.5 (113.2)	144.3 (88.2)
Days used	3.5 (1.7)	4.1 (1.97)	3.19 (1.47)
Time to start (days)	1.6 (2.8)	2.7 (3.2)	0.9 (2.2)
Liver-specific scores[a]			
CTP	12 (2)	10 (2)	11 (2)
MELD	27 (7)	27 (7)	27 (7)
MELD-Na	28 (7)	27 (7)	28 (7)
CLIF-SOFA	9.6 (1.6)	9.4 (1.4)	9.8 (1.7)
CLIF-C ACLF	49.5 (11.8)	48.1 (6.8)	50 (14.6)
ACLF[b]			
Grade 1	25 (54.3)	12 (60)	13 (50)
Grade 2	12 (26.1)	5 (35)	7 (26.9)
Grade 3	8 (17.4)	3 (15)	5 (19.2)
Time to death (days)[a]	35 (69)	35 (91)	35 (47)
HRS resolution[a]	12 (26.1)	4 (20)	8 (30.7)
All-cause mortality[b]			
30-day	31 (67.3)	15 (75)	16 (61.5)
90-day	33 (71.7)	15 (75)	18 (69.2)
365-day	38 (82.6)	18 (90)	21 (80.8)

PPI = proton pump inhibitor; NSBB = non-selective beta-blockers; SBP = spontaneous bacterial peritonitis; RTI = respiratory tract infection; UTI = urinary tract infection; INR = international normalized ratio; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein; CTP = Child-Turcotte-Pugh score; MELD = Model for End-Stage Liver Disease; MELD-Na = Modified Model Including Sodium; CLIF-SOFA = Chronic Liver Failure Sequential Organ Failure Assessment; CLIF-C ACLF = CLIF Consortium Acute Decompensation Acute-on-chronic liver failure.

[a] Mean (standard deviation).

[b] Frequency (%).

that received terlipressin was because of suspected or confirmed acute esophageal variceal hemorrhage. Demographic, clinical and laboratorial data are described in Table 1 for the study population. Mean age was 58 years-old and 80% were male. The most common cause of cirrhosis was alcohol abuse (76%).

All-cause mortality for 30-day, 90-day and 365-day was 75%, 75% and 90% for the pre-protocol period and 61%, 69% and 80% for the post-protocol period, respectively (Fig. 3). ACLF grade 1 was present in 25 patients, grade 2 in 12 and grade 3 in 8. All-cause mortality for 30-day, 90-day and 365-day was 60%, 68% and 83.3% for ACLF grade 1 patients,

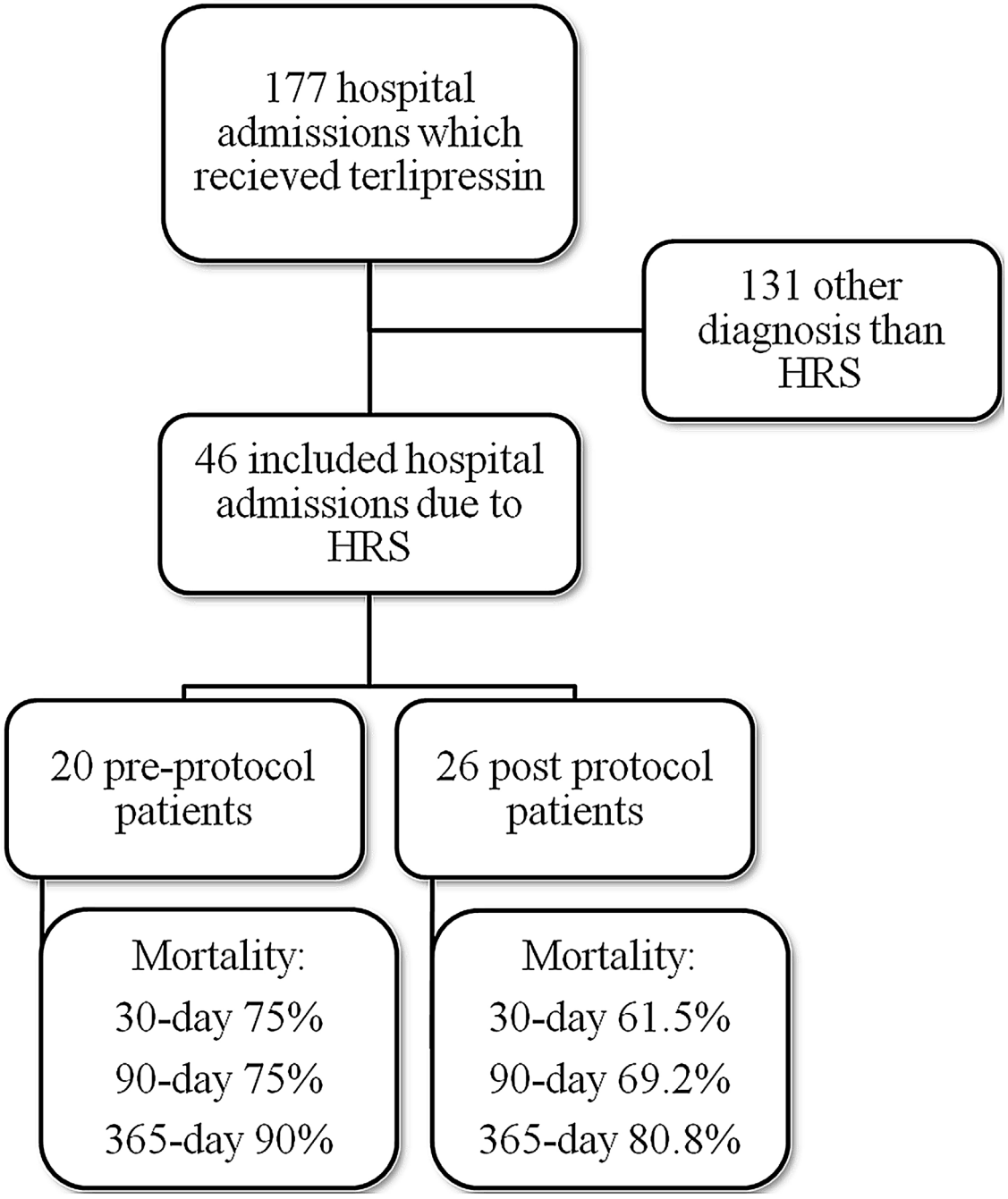

Figure 2 Fluxogram for study population and mortality for hepatorenal syndrome (HRS) patients according to protocol period.

66.6%, 66.6% and 83.3% for ACLF grade 2 patients and 87.5%, 87.5% and 87.5% for ACLF grade 3 patients, respectively (Supplementary Figure 1).

There was a trend toward the reduction of the total mean dose of terlipressin and human albumin used per patient with the institution of the protocol, reducing from 27 to 22 mg of terlipressin and from 236 to 144 g of human albumin per patient. This was not associated with higher mortality and was able to reduce the cost of HRS treatment (Table 2). Also, the patients in the post-protocol group were started earlier on albumin and terlipressin than the patients in the pre-protocol group – such difference was statically significant.

An univariate analysis was performed for 30- and 90-day mortality. Creatinine >2 mg/dL, bilirubin >2 mg/dL, leukocytes >10,000/mm^3, platelets <100 × 10^3/mm^3, AST <40 U/L, pre-protocol period, absence of use of proton pump inhibitors (PPI), presence of infection, upper gastrointestinal bleeding, higher CTP, MELD and MELD-Na were associated to higher 30-day mortality. Also, creatinine >2 mg/dL, bilirubin >2 mg/dL, leukocytes >10,000/mm^3, platelets <10 × 10^3/mm^3, AST <40 U/L, pre-protocol period, absence of use PPI, presence of esophageal varices, presence of infection, upper gastrointestinal bleeding, higher CTP, MELD and MELD-Na were associated to higher 90-day mortality (Table 3). Each one of these variables was used

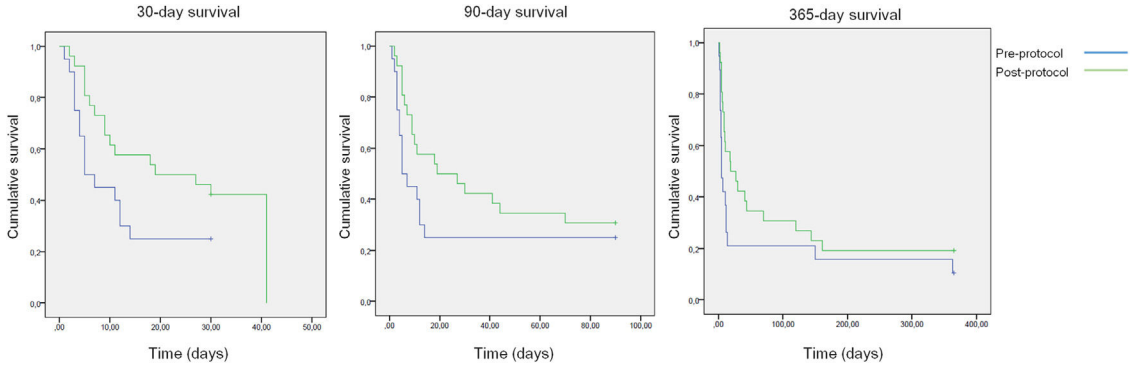

Figure 3 Kaplan–Meier curves for 30-, 90- and 365-day survival for pre and post-protocol periods.

Table 2 Human albumin and terlipressin use for HRS patients.

Variable	Period		
	Pre-protocol	Post-protocol	*p*
Terlipressin[a]			
Mean dose (mg/day)	7.6 (2.9)	6.7 (2.4)	0.07
Total dose (mg)	27.1 (15.5)	22.1 (13.5)	0.83
Days used	3.9 (2.1)	3.1 (1.4)	0.06
Time to start (days)	5.1 (4.4)	2.8 (2.3)	0.007
Human albumin[a]			
Mean dose (g/day)	60.7 (23.9)	43.8 (12.7)	0.09
Total dose (g)	236.5 (113.2)	144.3 (88.2)	0.28
Days used	4.1 (1.97)	3.19 (1.47)	0.23
Time to start (days)	2.7 (3.2)	0.9 (2.2)	0.05

HRS = hepatorenal syndrome.
[a] Mean (standard deviation).

for the multivariate analysis in a stepwise progression to the Cox regression.

In the multivariate analysis, AST <40 U/L, pre-protocol period and higher CTP scores were associated with higher 30-day and 90-day all-cause mortality (Table 4).

Discussion

HRS type 1 is the most severe complication of ESLD, determining an expected 90-day mortality of around 90% if not treated.[1,39] Although treatment has progressed in the last couple of decades, it is yet to show a major impact on survival.[8] The present study has sought to show that the use of an evidence based protocol for treatment and diagnosis of HRS can reduce drug consumption and mortality.

In the present study, 30-day mortality for all ACLF patients was 67.3%. This is higher than the one described in the CANONIC study (33.9%)[22] and other Brazilian studies with mortality rates of 39%.[40–42] This is because the presence of AKI translates into a reduction in survival in ACLF patients – a meta-analysis has described an odds ratio of 3.98 and 4.98 for 30- and 90-day mortality, respectively.[43] Nevertheless, the grade of ACLF did not impact mortality in the present study, probably due to the small number of patients.

Hospital consumption of human albumin and terlipressin for the treatment of HRS decreased with the adoption of the protocol in the present study, reducing total costs for HRS treatment, without impairing outcomes. This is a very important matter, since all treatments for HRS are costly. For example, in France, a previous study has shown a low compliance to current guidelines in human albumin prescription for cirrhotic patients.[44] For HRS, the compliance to current guidelines when prescribing human albumin was higher for senior practitioners in teaching hospitals. On the other hand, an Italian study which took place in a tertiary teaching hospital has shown non-compliance to be under 10%.[45] The adoption of evidence-based local protocols might improve compliance to adequate use of these drugs, mitigating the high cost of HRS treatment. In the present study, there was a high compliance to the studied protocol. This was secondary to the fact that the studied hospital has a small team of registrars and every physician from it agreed on the protocol, and the residents were very aware of its existence and use.

The problem of the cost of terlipressin and human albumin has been studied in two systematic reviews, comparing to the cost of norepinephrine plus human albumin.[15,46] Since norepinephrine requires hospitalization in an intensive care unit, terlipressin was shown to be less costly, hence it can be used in the infirmary. Two studies have addressed the eco-

Table 3 Univariate analysis for 30- and 90-day mortality, comparing pre and post-procotol period.

Variable	Hazard ratio (95% CI)	
	30-day mortality	90-day mortality
Age (years)[a]	0.97 (0.94–1.01) $p = 0.22$	0.98 (0.94–1.01) $p = 0.24$
Male sex	1.16 (0.44–3.05) $p = 0.75$	1.08 (0.44–2.63) $p = 0.85$
Period pre-protocol	1.84 (0.89–3.78) $p = 0.09$	1.54 (0.77–3.07) $p = 0.2$
Etiology of cirrhosis	0.89 (0.31–2.6) $p = 0.84$	0.78 (0.21–2.44) $p = 0.78$
Active alcoholism	1.89 (0.92–3.89) $p = 0.81$	1.86 (0.93–3.71) $p = 0.07$
Previous use of medications		
PPI	0.42 (0.17–1.04) $p = 0.06$	0.41 (0.17–0.95) $p = 0.03$
Spironolactone	1.24 (0.6–2.54) $p = 0.55$	1.16 (0,58–2.3) $p = 0.66$
Furosemide	0.97 (0.47–2.01) $p = 0.94$	1.04 (0,52–2.07) $p = 0.9$
NSBB	1.25 (0.6–2.59) $p = 0.53$	1.22 (0.61–2.44) $p = 0.57$
Renal replacement therapy	0.7 (0.16–2.95) $p = 0.63$	0.94 (0.28–3.09) $p = 0.92$
Portal vein thrombosis	1.88 (0.25–14.11) $p = 0.53$	1.88 (0.25–14.11) $p = 0.53$
Hepatocellular carcinoma	1.41 (0.49–4.05) $p = 0.52$	1.31 (0.45–3.73) $p = 0.61$
Hepatic enchephalopathy	1.58 (0.75–2.34) $p = 0.22$	1.5 (0.74–3.04) $p = 0.25$
Esophageal varices	1.5 (0.71–3.1) $p = 0.27$	1.67 (0.84–3.33) $p = 0.14$
Upper gastrointestinal bleeding	3.6 (1.8–4.9) $p = 0.01$	3.62 (1.76–4.94) $p = 0.01$
Infection		
SBP	0.97 (0.11–8.09) $p = 0.98$	1.1 (0.13–8.95) $p = 0.92$
RTI	2.25 (0.29–17.55) $p = 0.43$	2.71 (0.35–20.8) $p = 0.33$
UTI	0.77 (0.04–12.39) $p = 0.85$	0.72 (0.04–11.56) $p = 0.81$
Sepsis with undefined source of infection	4.55 (0.27–75.33) $p = 0.29$	5.26 (0.31–87.5) $p = 0.24$
Other	4.57 (0.57–36.52) $p = 0.15$	5.29 (0.66–42.48) $p = 0.11$
Laboratory		
Hemoglobin > 9 g/dL	0.76 (0.36–1.56) $p = 0.45$	0.77 (0.38–1.53) $p = 0.46$
Leukocyte (/mm^3)[a]	0.41 (0.19–0.86) $p = 0.019$	0.51 (0.25–1.01) $p = 0.05$
Platelets <100 $\times$ 10^3/mm^3	1.64 (0.36–7.37) $p = 0.51$	2.14 (0.51–8.98) $p = 0.29$
Total bilirubin > 2 mg/dL	0.35 (0.14–0.87) $p = 0.02$	0.43 (0.19–0.98) $p = 0.04$
INR[a]	0.88 (0.33–2.31) $p = 0.79$	0.97 (0.4–2.36) $p = 0.95$
AST > 40 U/L	0.4 (0.13–1.18) $p = 0.09$	0.33 (0.11–0.96) $p = 0.04$

Table 3 (*Continued*)

Variable	Hazard ratio (95% CI)	
	30-day mortality	90-day mortality
ALT > 40 U/L	1.01 (0.42–2.43) $p = 0.97$	0.96 (0.42–2.19) $p = 0.93$
GGT > 60 U/L	1.34 (0.54–3.31) $p = 0.52$	1.28 (0.52–3.13) $p = 0.58$
Creatinine > 2 mg/dL	0.49 (0.01–320) $p = 0.18$	0.41 (0.14–1.19) $p = 0.1$
Sodium > 135 mg/dL	1.18 (0.55–2.53) $p = 0.65$	1.04 (0.51–2.11) $p = 0.91$
Potassium > 3.5 mg/dL	2.52 (0.34–18.55) $p = 0.36$	1.39 (0.33–5.85) $p = 0.64$
Albumin (mg/dL)[a]	0.77 (0.1–5.82) $p = 0.8$	0.64 (0.08–4.84) $p = 0.67$
CRP (mg/L)[a]	1.81 (0.38–8.45) $p = 0.45$	1.98 (0.43–9.12) $p = 0.37$
Terlipressin[a]		
Mean dose (mg/day)	1.01 (0.88–1.14) $p = 0.88$	0.99 (0.87–1.12) $p = 0.91$
Total dose (mg)	0.99 (0.97–1.02) $p = 0.8$	0.99 (0.97–1.02) $p = 0.73$
Days used	0.96 (0.79–1.17) $p = 0.71$	0.97 (0.8–1.17) $p = 0.76$
Human albumin[a]		
Mean dose (g/day)	1.01 (0.99–1.03) $p = 0.16$	1.01 (0.99–1.03) $p = 0.26$
Total dose (g)	1.01 (0.99–1.02) $p = 0.69$	1.01 (0.99–1.02) $p = 0.8$
Days used	0.97 (0.8–1.19) $p = 0.83$	0.98 (0.81–1.18) $p = 0.86$
Liver-specific scores[a]		
CTP	1.3 (1.07–1.57) $p = 0.006$	1.3 (1.08–1.56) $p = 0.004$
MELD	1.04 (0.99–1.09) $p = 0.09$	1.03 (0.99–1.08) $p = 0.11$
MELD-Na	1.03 (0.99–1.09) $p = 0.11$	1.03 (0.99–1.08) $p = 0.12$
CLIF-SOFA	1.09 (0.89–1.32) $p = 0.39$	1.08 (0.9–1.31) $p = 0.38$
CLIF-C ACLF	1.01 (0.97–1.03) $p = 0.97$	0.99 (0.97–1.02) $p = 0.96$
ACLF grade	0.55 (0.22–1.38) $p = 0.2$	0.59 (0.0.24–1.44) $p = 0.24$

CI = confidence interval; PPI = proton pump inhibitor; NSBB = non-selective beta-blockers; SBP = Spontaneous Bacterial Peritonitis; RTI = Respiratory Tract Infection; UTI = Urinary Tract Infection; INR = international normalized ratio; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein; CTP = Child-Turcotte-Pugh score; MELD = Model for End-Stage Liver Disease; MELD-Na = Modified Model Including Sodium; CLIF-SOFA = Chronic Liver Failure Sequential Organ Failure Assessment; CLIF-C ACLF = CLIF Consortium Acute Decompensation Acute-on-chronic liver failure.

[a] Hazard ratio per unit.

nomic burden of HRS treatment in the United States. Both have concluded that, for the private sector and Medicare patients, the burden of the cost of HRS treatment is very high, delivering poor results. Therefore, there is an unmet need of an effective and cheaper treatment,[47,48] which could improve prognosis in a large scale. In the present study, we have demonstrated a lower use of human albumin and terlipressin in patients with HRS after the institution of a protocol – this might translate into reduction of cost for these patients.

LT is the only definitive treatment for HRS, improving mortality and mitigating the risk for the need for long term renal replacement therapy (RRT).[7] Although HRS has been shown to be reversed in around 83% of patients which

Table 4 Multivariate analysis for 30- and 90-day mortality.

Variable	Hazard ratio (95% CI)	
	30-day mortality	90-day mortality
Period pre-protocol	1.84 (1.14–3.9)$p = 0.004$	1.5 (1.05 –3.1)$p = 0.006$
AST > 40 U/L	0.6 (0.1–0.97) $p = 0.01$	0.3 (0.1–0.9) $p = 0.06$
CTP[a]	1.3 (1.07–1.57) $p = 0.01$	1.3 (1.08–1.5) $p = 0.007$

CI = confidence interval; AST = aspartate transaminase; CTP = Child-Turcotte-Pugh score.
[a] Hazard ratio per unit.

undergo LT, it still impacts negatively post-LT survival for up to five years post-LT.[49] Also, the most important risk factor for the need for long-term RRT is actually the need of RRT previously to LT.[7] In the present study, the values of creatinine alone was not an isolated risk factor for mortality.

AKI is a rather common complication of cirrhosis, occurring in 20% of patients admitted to the hospital.[50] The most common causes of AKI for cirrhotic patients are considered bacterial infections, followed by pre-renal kidney failure and HRS.[51,52] The current criteria defined by the International Ascites Club uses the concept of AKI for the diagnosis of HRS.[53] Although, it does not seem to be superior to the previous cut-off used in the criteria published in 2007.[21] In the present study, the cut-off value of serum creatinine for HRS diagnosis used was 1.5 mg/dL.

CTP score has been used for decades to predict mortality for cirrhotic patients. It has been shown to be useful to predict adverse events for patients admitted to the intensive care unit[54] and for HRS.[55,56] In the present study, it was independently associated with mortality. The grade of ACLF has been associated with higher mortality and changed response to HRS treatment in a previous study developed by the EASL-CLIF.[57]

The median for survival for HRS is two weeks if not treated[58] and, therefore, all patients with renal and liver dysfunction should be evaluated for LT, with RRT as a bridge to it.[59] AKI, and therefore HRS, can be triggered by precipitating events: the most important of these are infections (most importantly spontaneous bacterial peritonitis), gastrointestinal bleeding, use of vasodilators (such as angiotensin-converting enzyme inhibitors) and large-volume paracentesis without human albumin administration.[60–65] Because of this high mortality associated with HRS, it is crucial to develop protocols to guide care and improve outcomes. In our study, the institution of the protocol resulted in a shorter time to start human albumin and terlipressin. The smaller delay to receive appropriate care probably caused the higher survival in the post-protocol period.

Since infections are a major concern, they ought to be suspected when AKI occurs, collecting blood, urine and ascites cultures[66]; although, empirical antibiotics should not be used in the absence of infection. Diuretics ought to be discontinued.[66] Non-selective beta-blockers discontinuation is still a controversial subject – initially, it was believed that it might increase the risk for HRS, especially in patients with spontaneous bacterial peritonitis[67]; currently it is not believed to impact mortality.[68–70] Nevertheless, it should be used with extreme caution or discontinued to avoid hypotension – it is well documented that when vasopressors cause an increase in mean arterial blood pressure, the reversal of HRS is more likely.[71,72] Also, in order to avoid hypotension, if RRT is necessary, continuous hemodiafiltration seems to be superior in severe kidney failure for unstable cirrhotic patients.[73] It seems reasonable; therefore, that hypotension needs to be avoided. In the present study, the use of non-selective beta-blockers did not impact mortality.

The use of PPI have been associated with higher mortality and decompensation in previous studies,[74] translating into a higher risk for the development of spontaneous bacterial peritonitis and adverse events.[75–77] Nevertheless, other studies have suggested that this finding only occurred because of the retrospective nature of the previous papers.[78–80] MELD and MELD-Na scores are used to allocate organs for LT and are useful tools to predict 90-day mortality for ESLD, even for HRS patients.[81] In the present study, the absence of use of PPI and higher MELD and MELD-Na scores were associated with higher 30- and 90-day mortality in the univariate analysis, but not in the multivariate analysis.

The largest drawback of the present study is the small sample size. This probably happened because HRS is not a very common complication of cirrhosis. Most studies in this subject are generally multi-centric, which helps to gather more data. Nevertheless, the extensive data accumulated has allowed a deep study of the population, providing an evidence-based protocol which has been shown to improve survival when compared to a historical cohort from the same hospital. Another limitation to the study is the use of the criteria published in 2007 as definition for HRS: the criteria which include AKI definitions were published in 2015, after the protocol was already in place and being used. Nevertheless, AKI criteria has not been shown to be superior to the cutoff previously used of a serum creatinine above 1.5 mg/dL.[21]

Conclusion

In conclusion, the adoption of an evidence-based protocol for the diagnosis and treatment of HRS translated into a higher survival rate. Also, it was associated with lower total drug use. The authors suggest that, taking into account the high mortality and cost of HRS treatment, the use of evidence-based protocols for diagnosis and treatment of HRS could reduce cost and mortality in tertiary hospitals.

Key summary

Hepatorenal syndrome (HRS) is one of the deadliest complications of cirrhosis and carries a high mortality. An evidence-based protocol for diagnosis and treatment of HRS was instituted as standard-of-care in 2013 in the studied hospital. Data from medical records from 2010 to 2016 were

obtained by searching the hospital electronic database for every patient who received terlipressin, ranging from three years prior and after the institution of the protocol. A stepwise approach to the Cox regression was used for univariate and multivariate analysis. It was included 46 patients who were diagnosed with HRS, 20 from pre-protocol and 26 post-protocol period. Respectively, mortality for 30-day, 90-day and 365-day was 75%, 89% and 89% for the pre-protocol period and 61%, 69% and 80% for the post-protocol period. In multivariate analysis, AST <40 U/L, pre-protocol period and higher Child-Pugh-Turcotte scores were associated with higher 30-day and 90-day all-cause mortality. Also, the total mean dose of terlipressin and human albumin used per patient reduced with the institution of the protocol, reducing from 27 to 22 mg of terlipressin and from 236 to 144 g of human albumin per patient. This was not associated with higher mortality. In conclusion, the use of an evidence-based protocol in the treatment of HRS translated in a higher survival. Also, it was associated with lower drug used for treatment of HRS.

Main points

- Hepatorenal syndrome (HRS) is the deadliest complication of cirrhosis, generally treated with the association of terlipressin plus human albumin.
- An evidence-based protocol for diagnosis and treatment of HRS was instituted in 2013 in the studied Hospital and data was gathered from 3 years prior to 3 years after the institution of the protocol.
- In multivariate analysis, AST <40 U/L, pre-protocol period and higher Child scores were associated with higher 30-day and 90-day mortality.
- Total mean dose of terlipressin and human albumin used per patient reduced after the institution of the protocol and such was not associated with higher mortality. Also, time to start human albumin and terlipressin reduced in the post-protocol period.
- The use of evidence-based protocols for diagnosis and treatment of HRS could reduce cost and mortality in tertiary hospitals.

Authors contributions

Terres AZ – Design, data collection, writing and review.
Balbinot RS – Data collection, writing and review.
Muscope ALF – Data collection, writing and review.
Longen ML – Data collection, writing and review.
Schena B – Data collection, writing and review.
Cini BT – Data collection, writing and review.
Rost Jr. GL – Data collection, writing and review.
Balensiefer JIL – Data collection, writing and review.
Eberhardt LZ – Data collection, writing and review.
Balbinot RA – Design, writing and review.
Balbinot SS – Design, writing and review.
Soldera J – Design, statistical analysis, translation, writing and review.

Funding

None.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.gastrohep.2021.02.007.

References

1. Ginès P, Guevara M, Arroyo V, Rodés J. Hepatorenal syndrome. Lancet. 2003;362:1819–27, http://dx.doi.org/10.1016/S0140-6736(03)14903-3 [PMID: 14654322].
2. Krag A, Bendtsen F, Burroughs AK, Moller S. The cardiorenal link in advanced cirrhosis. Med Hypotheses. 2012;79:53–5, http://dx.doi.org/10.1016/j.mehy.2012.03.032 [PMID: 22537409].
3. O'Grady JG. Clinical disorders of renal function in acute liver failure. In: Gines P, Arroyo V, Rodes J, Schrier RW, editors. Ascites and renal dysfunction in liver disease. 2nd edn. Oxford: Blackwell Publishing; 2005. p. 383–93.
4. Jiang QQ, Han MF, Ma K, Chen G, Wan XY, Kilonzo SB, Wu WY, Wang YL, You J, Ning Q. Acute kidney injury in acute-on-chronic liver failure is different from in decompensated cirrhosis. World J Gastroenterol. 2018;24:2300–10, http://dx.doi.org/10.3748/wjg.v24.i21.2300 [PMID: 29881239] [PMCID: PMC5989244].
5. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol. 2015;63:1272–84, http://dx.doi.org/10.1016/j.jhep.2015.07.004 [PMID: 26192220].
6. Ginès A, Escorsell A, Ginès P, Saló J, Jiménez W, Inglada L, Navasa M, Clària J, Rimola A, Arroyo V, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology. 1993;105:229–36, http://dx.doi.org/10.1016/0016-5085(93)90031-7 [PMID: 8514039].
7. Wong F, Leung W, Al Beshir M, Marquez M, Renner EL. Outcomes of patients with cirrhosis and hepatorenal syndrome type 1 treated with liver transplantation. Liver Transpl. 2015;21:300–7, http://dx.doi.org/10.1002/lt.24049 [PMID: 25422261].
8. Thomson MJ, Taylor A, Sharma P, Lok AS, Tapper EB. Limited progress in hepatorenal syndrome (HRS) reversal and survival 2002–2018: a systematic review and meta-analysis. Dig Dis Sci. 2020;65:1539–48, http://dx.doi.org/10.1007/s10620-019-05858-2 [PMID: 31571102] [PMCID: PMC7103565].
9. Nassar Junior AP, Farias AQ, D' Albuquerque LA, Carrilho FJ, Malbouisson LM. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. PLoS ONE. 2014;9:e107466, http://dx.doi.org/10.1371/journal.pone.0107466 [PMID: 25203311] [PMCID: PMC4159336].
10. Sharma P, Kumar A, Shrama BC, Sarin SK. An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response. Am J Gastroenterol. 2008;103:1689–97, http://dx.doi.org/10.1111/j.1572-0241.2008.01828.x [PMID: 18557715].
11. Allegretti AS, Israelsen M, Krag A, Jovani M, Goldin AH, Schulman AR, Winter RW, Gluud LL. Terlipressin versus placebo or no intervention for people with cirrhosis and hepatorenal syndrome. Cochrane Database Syst Rev. 2017;6:CD005162,

http://dx.doi.org/10.1002/14651858.CD005162.pub4 [PMID: 29943803] [PMCID: PMC6481608].
12. 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). 2018;97:e0431, http://dx.doi.org/10.1097/MD.0000000000010431 [PMID: 29668606] [PMCID: PMC5916651].
13. Wong F, Pappas SC, Boyer TD, Sanyal AJ, Bajaj JS, Escalante S, Jamil K, REVERSE Investigators. Terlipressin improves renal function and reverses hepatorenal syndrome in patients with systemic inflammatory response syndrome. Clin Gastroenterol Hepatol. 2017;15:266–72, http://dx.doi.org/10.1016/j.cgh.2016.07.016 [PMID: 27464593].
14. Boyer TD, Sanyal AJ, Wong F, Frederick RT, Lake JR, O'Leary JG, Ganger D, Jamil K, Pappas SC, REVERSE Study Investigators. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. Gastroenterology. 2016;150:1579–89, http://dx.doi.org/10.1053/j.gastro.2016.02.026 [PMID: 26896734].
15. Mattos ÂZ, Mattos AA, Ribeiro RA. Terlipressin versus noradrenaline in the treatment of hepatorenal syndrome: systematic review with meta-analysis and full economic evaluation. Eur J Gastroenterol Hepatol. 2016;28:345–51, http://dx.doi.org/10.1097/MEG.0000000000000537 [PMID: 26649801].
16. Allegretti AS, Parada XV, Eneanya ND, Gilligan H, Xu D, Zhao S, Dienstag JL, Chung RT, Thadhani RI. Prognosis of patients with cirrhosis and AKI who initiate RRT. Clin J Am Soc Nephrol. 2018;13:16–25, http://dx.doi.org/10.2215/CJN. 03610417 [PMID: 29122911] [PMCID: PMC5753306].
17. Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F, Bernardi M, Romanelli RG, Colletta C, Salinas F, Di Giacomo A, Ridola L, Fornasiere E, Caraceni P, Morando F, Piano S, Gatta A, Angeli P, Italian Association for the Study of the Liver Study Group on Hepatorenal Syndrome. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome. A randomized trial. Hepatology. 2015;62:567–74, http://dx.doi.org/10.1002/hep.27709 [PMID: 25644760].
18. Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Int Ascites Club Hepatol. 1996;23:164–76, http://dx.doi.org/10.1002/hep.510230122 [PMID: 8550036].
19. Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut. 2007;56:1310–8, http://dx.doi.org/10.1136/gut.2006.107789 [PMID: 17389705] [PMCID: PMC1954971].
20. Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, Garcia-Tsao G. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol. 2015;62:968–74, http://dx.doi.org/10.1016/j.jhep.2014.12.029 [PMID: 25638527].
21. Piano S, Rosi S, Maresio G, Fasolato S, Cavallin M, Romano A, Morando F, Gola E, Frigo AC, Gatta A, Angeli P. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol. 2013;59:482–9, http://dx.doi.org/10.1016/j.jhep.2013.03.039 [PMID: 23665185].
22. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V, CANONIC Study Investigators of the EASL-CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–37, http://dx.doi.org/10.1053/j.gastro.2013.02.042 [PMID: 23474284].
23. Jalan R. Acute-on-chronic liver failure: from concept to a new syndrome. Curr Opin Crit Care. 2011;17:152, http://dx.doi.org/10.1097/MCC.0b013e3283455c57 [PMID: 21358404].
24. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. Curr Opin Crit Care. 2011;17:165–9, http://dx.doi.org/10.1097/MCC.0b013e328344b42d [PMID: 21326095].
25. Mookerjee RP. Acute-on-chronic liver failure: the liver and portal haemodynamics. Curr Opin Crit Care. 2011;17:170–6, http://dx.doi.org/10.1097/MCC.0b013e328344a076 [PMID: 21346568].
26. García-Martínez R, Cordoba J. Acute-on-chronic liver failure: the brain. Curr Opin Crit Care. 2011;17:177–83, http://dx.doi.org/10.1097/MCC.0b013e328344b37e [PMID: 21346567].
27. Cárdenas A, Ginès P. Acute-on-chronic liver failure: the kidneys. Curr Opin Crit Care. 2011;17:184–9, http://dx.doi.org/10.1097/MCC.0b013e328344b3da [PMID: 21311322].
28. Liu H, Lee SS. Acute-on-chronic liver failure: the heart and systemic hemodynamics. Curr Opin Crit Care. 2011;17:190–4, http://dx.doi.org/10.1097/MCC.0b013e328344b397 [PMID: 21326096].
29. Hassanein TI, Schade RR, Hepburn IS. Acute-on-chronic liver failure: extracorporeal liver assist devices. Curr Opin Crit Care. 2011;17:195–203, http://dx.doi.org/10.1097/MCC.0b013e328344b3aa [PMID: 21346566].
30. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med. 2009;361:1279–90, http://dx.doi.org/10.1056/NEJMra0809139 [PMID: 19776409].
31. Soldera J, Balbinot SS, Balbinot RA, Cavalcanti AG. Diagnostic and therapeutic approaches to hepatocellular carcinoma: understanding the Barcelona Clínic Liver Cancer Protocol. Clin Med Insights Gastroenterol. 2016;9:67–71, http://dx.doi.org/10.4137/CGast.S30190 [PMID: 27812296].
32. Chagas AL, Mattos AA, Carrilho FJ, Bittencourt PL, Members of the Panel of the 2nd Consensus of the Brazilian Society of Hepatology on the Diagnosis and Management of Hepatocellular Carcinoma, Vezozzo DCP, Horvat N, Rocha MS. Brazilian Society of Hepatology updated recommendations for diagnosis and treatment of hepatocellular carcinoma. Arq Gastroenterol. 2020;57 Suppl 1:1–20, http://dx.doi.org/10.1590/S0004-2803.202000000-20 [PMID: 32294682].
33. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715–35, http://dx.doi.org/10.1002/hep.27210 [PMID: 25042402].
34. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646–9 [PMID: 4541913].
35. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1–85 [PMID: 4950264].
36. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–70, http://dx.doi.org/10.1053/jhep.2001.22172 [PMID: 11172350].

37. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359:1018–26, http://dx.doi.org/10.1056/NEJMoa0801209 [PMID: 18768945].
38. Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut. 2017;66:541–53, http://dx.doi.org/10.1136/gutjnl-2016-312670 [PMID: 28053053].
39. Ginès P. Diagnosis and treatment of hepatorenal syndrome. Baillieres Best Pract Res Clin Gastroenterol. 2000;14:945–57, http://dx.doi.org/10.1053/bega.2000.0140 [PMID: 11139348].
40. Silva PE, Fayad L, Lazzarotto C, Ronsoni MF, Bazzo ML, Colombo BS, Dantas-Correa EB, Narciso-Schiavon JL, Schiavon LL. Single-centre validation of the EASL-CLIF consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. Liver Int. 2015;35:1516–23, http://dx.doi.org/10.1111/liv.12597 [PMID: 24840673].
41. Grochot RM, Luz LB, Garcia R, Balbinot RA, Balbinot SS, Soldera J. CLIF-SOFA is superior to other liver-specific scores for predicting mortality in acute-on-chronic liver failure and decompensated cirrhosis. Austin J Gastroenterol. 2019;6:1105. Available on: https://austinpublishinggroup.com/gastroenterology/fulltext/ajg-v6-id1105.php
42. Grochot RM, Luz LB, Garcia R, Balbinot RA, Balbinot SS, Soldera J. Acute-on-chronic liver failure data from a teaching hospital in Brazil. A historical cohort. Int J Scientific Res. 2020;9:1–6.
43. Jiang W, Hu Y, Sun Y, Shen Y, Xun Y. Prevalence and short-term outcome of acute kidney injury in patients with acute-on-chronic liver failure: a meta-analysis. J Viral Hepat. 2020, http://dx.doi.org/10.1111/jvh.13287 [PMID: 32141141].
44. Garioud A, Cadranel JF, Pauwels A, Nousbaum JB, Thévenot T, Dao T, Louvet A, Sogni P, Talbodec N, Antonini TM, Bureau C, Thabut D, Elkrief L, Jouannaud V, Macaigne G, Bernard-Chabert B, Lison H, Alric L, Carbonell N, Labadie H, Amiot X, Abergel A, Hanslik B, Leroy V, De Lédinghen V, Denis J, Association Nationale des Hépato-gastroentérologues des Hôpitaux Généraux de France, Association Française pour l'Etude du Foie, Club de Réflexion des Cabinets et Groupes d'Hépato-Gastroentérologie. Albumin use in patients with cirrhosis in France: results of the ''ALBULIVE'' survey: a case for better EASL guidelines diffusion and/or revision. J Clin Gastroenterol. 2017;51:831–8, http://dx.doi.org/10.1097/MCG. 0000000000000735 [PMID: 28787354].
45. Mirici-Cappa F, Caraceni P, Domenicali M, Gelonesi E, Benazzi B, Zaccherini G, Trevisani F, Puggioli C, Bernardi M. How albumin administration for cirrhosis impacts on hospital albumin consumption and expenditure. World J Gastroenterol. 2011;17:3479–86, http://dx.doi.org/10.3748/wjg.v17.i30.3479 [PMID: 21941414] [PMCID: PMC3163245].
46. Mattos ÂZ, Mattos AA, Ribeiro RA. Terlipressin versus noradrenaline for hepatorenal syndrome. Economic evaluation under the perspective of the Brazilian Public Health System. Arq Gastroenterol. 2016;53:123–6, http://dx.doi.org/10.1590/S0004-28032016000200014 [PMID: 27305421].
47. Jamil K, Huang X, Lovelace B, Pham AT, Lodaya K, Wan G. The burden of illness of hepatorenal syndrome (HRS) in the United States: a retrospective analysis of electronic health records. J Med Econ. 2019;22:421–9, http://dx.doi.org/10.1080/13696998.2019.1580201 [PMID: 30724682].
48. Rice JB, White AG, Galebach P, Korenblat KM, Wagh A, Lovelace B, Wan GJ, Jamil K. The burden of hepatorenal syndrome among commercially insured and Medicare patients in the United States. Curr Med Res Opin. 2017;33:1473–80, http://dx.doi.org/10.1080/03007995.2017.1331211 [PMID: 28509578].
49. Utako P, Emyoo T, Anothaisintawee T, Yamashiki N, Thakkinstian A, Sobhonslidsuk A. Clinical outcomes after liver transplantation for hepatorenal syndrome: a systematic review and meta-analysis. Biomed Res Int. 2018;2018:5362810, http://dx.doi.org/10.1155/2018/5362810 [PMID: 29992152] [PMCID: PMC5994306].
50. Fede G, D'Amico G, Arvaniti V, Tsochatzis E, Germani G, Georgiadis D, Morabito A, Burroughs AK. Renal failure and cirrhosis: a systematic review of mortality and prognosis. J Hepatol. 2012;56:810–8, http://dx.doi.org/10.1016/j.jhep.2011.10.016 [PMID: 22173162].
51. Martín-Llahí M, Guevara M, Torre A, Fagundes C, Restuccia T, Gilabert R, Solá E, Pereira G, Marinelli M, Pavesi M, Fernández J, Rodés J, Arroyo V, Ginès P. Prognostic importance of the cause of renal failure in patients with cirrhosis. Gastroenterology. 2011;140:488–96, http://dx.doi.org/10.1053/j.gastro.2010.07.043 [PMID: 20682324].
52. Bittencourt PL, Farias AQ, Terra C. Renal failure in cirrhosis: emerging concepts. World J Hepatol. 2015;7:2336–43, http://dx.doi.org/10.4254/wjh.v7.i21.2336 [PMID: 26413223] [PMCID: PMC4577641].
53. Grupo de Interesse em Lesão Renal Aguda, Relatores da Reunião Monotemática de Fígado e Rim, Membros da Sociedade Brasileira de Hepatologia; 2018. Available at: http://sbhepatologia.org.br/wp-content/uploads/2018/03/Recomenda%C3%A7%C3%B5es-LRA-030318.pdf [accessed in 05.12.20].
54. Weil D, Levesque E, McPhail M, Cavallazzi R, Theocharidou E, Cholongitas E, Galbois A, Pan HC, Karvellas CJ, Sauneuf B, Robert R, Fichet J, Piton G, Thevenot T, Capellier G, Di Martino V, METAREACIR Group. Prognosis of cirrhotic patients admitted to intensive care unit: a meta-analysis. Ann Intensive Care. 2017;7:33, http://dx.doi.org/10.1186/s13613-017-0249-6 [PMID: 28321803] [PMCID: PMC5359266].
55. Licata A, Maida M, Bonaccorso A, Macaluso FS, Cappello M, Craxì A, Almasio PL. Clinical course and prognostic factors of hepatorenal syndrome: a retrospective single-center cohort study. World J Hepatol. 2013;5:685–91, http://dx.doi.org/10.4254/wjh.v5.i12.685 [PMID: 24432185] [PMCID: PMC3879690].
56. Terres AZ, Balbinot RS, Muscope ALF, Longen ML, Schena B, Cini BT, Rost GL Jr, Balensiefer JIL, Eberhardt LZ, Balbinot RA, Balbinot SS, Soldera J. Predicting mortality for Hepatorenal Syndrome with liver-specific scores. GastroHep. 2020, http://dx.doi.org/10.1002/ygh2.429. Epub ahead of print.
57. Piano S, Schmidt HH, Ariza X, Amoros A, Romano A, Hüsing-Kabar A, Solà E, Gerbes A, Bernardi M, Alessandria C, Scheiner B, Tonon M, Maschmeier M, Solè C, Trebicka J, Gustot T, Nevens F, Arroyo V, Gines P, Angeli P, EASL CLIF Consortium, European Foundation for the Study of Chronic Liver Failure (EF Clif). Association between grade of acute on chronic liver failure and response to terlipressin and albumin in patients with hepatorenal syndrome. Clin Gastroenterol Hepatol. 2018;16:1792–800, http://dx.doi.org/10.1016/j.cgh.2018.01.035 [PMID: 29391267].
58. Arroyo V, Terra C, Ginès P. Advances in the pathogenesis and treatment of type-1 and type-2 hepatorenal syndrome. J Hepatol. 2007;46:935–46, http://dx.doi.org/10.1016/j.jhep.2007.02.001 [PMID: 17391801].
59. Jagarlamudi N, Wong F. Acute kidney injury: prediction, prognostication and optimisation for liver transplant. Hepatol Int. 2020;14:167–79,

http://dx.doi.org/10.1007/s12072-020-10018-0 [PMID: 32128705].
60. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodés J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology. 1994;20:1495–501, http://dx.doi.org/10.1002/hep.1840200619 [PMID: 7982650].
61. Terra C, Guevara M, Torre A, Gilabert R, Fernández J, Martín-Llahí M, Baccaro ME, Navasa M, Bru C, Arroyo V, Rodés J, Ginès P. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology. 2005;129:1944–53, http://dx.doi.org/10.1053/j.gastro.2005.09.024 [PMID: 16344063].
62. Cárdenas A, Ginès P, Uriz J, Bessa X, Salmerón JM, Mas A, Ortega R, Calahorra B, De Las Heras D, Bosch J, Arroyo V, Rodés J. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. Hepatology. 2001;34 Pt 1:671–6, http://dx.doi.org/10.1053/jhep.2001.27830 [PMID: 11584362].
63. Salerno F, Badalamenti S. Drug-induced renal failure in cirrhosis. In: Gines P, Arroyo V, Rodes J, Schrier RW, editors. Ascites and renal dysfunction in liver disease. 2nd edn. Oxford: Blackwell Publishing; 2005. p. 372–82.
64. Hsu WF, Yu SH, Lin JT, Wu JC, Hou MC, Huang YH, Wu CY, Peng CY. Renal effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with liver cirrhosis: a nationwide cohort study. Gastroenterol Res Pract. 2019;2019:1743290, http://dx.doi.org/10.1155/2019/1743290 [PMID: 31687012] [PMCID: PMC6811787].
65. Gentilini P, Romanelli RG, La Villa G, Maggiore Q, Pesciullesi E, Cappelli G, Casini Raggi V, Foschi M, Marra F, Pinzani M, et al. Effects of low-dose captopril on renal hemodynamics and function in patients with cirrhosis of the liver. Gastroenterology. 1993;104:588–94, http://dx.doi.org/10.1016/0016-5085(93)90431-b [PMID: 8425702].
66. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, hepatorenal syndrome in cirrhosis. J Hepatol. 2010;53:397–417, http://dx.doi.org/10.1016/j.jhep.2010.05.004 [PMID: 20633946].
67. Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, Hagmann M, Blacky A, Ferlitsch A, Sieghart W, Trauner M, Peck-Radosavljevic M, Reiberger T. Nonselective β blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 2014;146:1680–90, http://dx.doi.org/10.1053/j.gastro.2014.03.005, e1. [PMID: 24631577].
68. La Mura V, Tosetti G, Primignani M, Salerno F. Use of nonselective beta blockers in cirrhosis: the evidence we need before closing (or not) the window. World J Gastroenterol. 2015;21:2265–8, http://dx.doi.org/10.3748/wjg.v21.i8.2265 [PMID: 25741132] [PMCID: PMC4342901].
69. Facciorusso A, Roy S, Livadas S, Fevrier-Paul A, Wekesa C, Kilic ID, Chaurasia AK, Sadeq M, Muscatiello N. Nonselective beta-blockers do not affect survival in cirrhotic patients with ascites. Dig Dis Sci. 2018;63:1737–46, http://dx.doi.org/10.1007/s10620-018-5092-6 [PMID: 29725793].
70. Chirapongsathorn S, Valentin N, Alahdab F, Krittanawong C, Erwin PJ, Murad MH, Kamath PS. Nonselective β-blockers and survival in patients with cirrhosis and ascites: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14:1096–104, http://dx.doi.org/10.1016/j.cgh.2016.01.012, e9. [PMID: 26829026].
71. Velez JC, Nietert PJ. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. Am J Kidney Dis. 2011;58:928–38, http://dx.doi.org/10.1053/j.ajkd.2011.07.017 [PMID: 21962618] [PMCID: PMC3251915].
72. Velez JC, Kadian M, Taburyanskaya M, Bohm NM, Delay TA, Karakala N, Rockey DC, Nietert PJ, Goodwin AJ, Whelan TP. Hepatorenal acute kidney injury and the importance of raising mean arterial pressure. Nephron. 2015;131:191–201, http://dx.doi.org/10.1159/000441151 [PMID: 26485256] [PMCID: PMC4655825].
73. Nand N, Verma P, Jain D. Comparative evaluation of continuous veno-venous hemodiafiltration and continuous arterio-venous hemodiafiltration in patients of hepatic failure and/or hepatorenal syndrome. J Assoc Physicians India. 2019;67:39–42 [PMID: 31562715].
74. De Roza MA, Kai L, Kam JW, Chan YH, Kwek A, Ang TL, Hsiang JC. Proton pump inhibitor use increases mortality and hepatic decompensation in liver cirrhosis. World J Gastroenterol. 2019;25:4933–44, http://dx.doi.org/10.3748/wjg.v25.i33.4933 [PMID: 31543684] [PMCID: PMC6737311].
75. Tergast TL, Wranke A, Laser H, Gerbel S, Manns MP, Cornberg M, Maasoumy B. Dose-dependent impact of proton pump inhibitors on the clinical course of spontaneous bacterial peritonitis. Liver Int. 2018;38:1602–2113, http://dx.doi.org/10.1111/liv.13862 [PMID: 29675988].
76. Min YW, Lim KS, Min BH, Gwak GY, Paik YH, Choi MS, Lee JH, Kim JJ, Koh KC, Paik SW, Yoo BC, Rhee PL. Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites: a propensity score matched cohort study. Aliment Pharmacol Ther. 2014;40:695–704, http://dx.doi.org/10.1111/apt.12875 [PMID: 25078671].
77. Lin L, Hou L, Deng Y, Zhao T, Wang B, Sun C. Acid suppression therapy and its association with spontaneous bacterial peritonitis incidence: a systemic review and meta-analysis. Hepatol Res. 2020;50:233–45, http://dx.doi.org/10.1111/hepr.13447 [PMID: 31667938].
78. Miozzo SA, Tovo CV, John JA, de Mattos AA. Proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhosis: an undesirable association? J Hepatol. 2015;63:529–30, http://dx.doi.org/10.1016/j.jhep.2015.03.041 [PMID: 26015369].
79. Wang J, Wu Y, Bi Q, Zheng X, Zhang J, Huang W. Adverse outcomes of proton pump inhibitors in chronic liver disease: a systematic review and meta-analysis. Hepatol Int. 2020, http://dx.doi.org/10.1007/s12072-019-10010-3 [PMID: 31912308].
80. Miozzo SAS, John JA, Appel-da-Silva MC, Dossin IA, Tovo CV, Mattos AA. Influence of proton pump inhibitors in the development of spontaneous bacterial peritonitis. World J Hepatol. 2017;9:1278–85, http://dx.doi.org/10.4254/wjh.v9.i35.1278 [PMID: 29290909] [PMCID: PMC5740091].
81. Al Sibae MR, Cappell MS. Accuracy of MELD scores in predicting mortality in decompensated cirrhosis from variceal bleeding, hepatorenal syndrome, alcoholic hepatitis, or acute liver failure as well as mortality after non-transplant surgery or TIPS. Dig Dis Sci. 2011;56:977–87, http://dx.doi.org/10.1007/s10620-010-1390-3 [PMID: 20844956].