

Factors of Development of Hepatorenal Syndrome in Patients with Liver Cirrhosis of Viral Etiology

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Abstract: Hepatorenal syndrome (HRS) is a type of acute kidney injury (AKI), occurring in patients with decompensated liver cirrhosis and is associated with high mortality. We aim to describe the predictors associated with the development of HRS in cirrhotic patients with AKI. We retrospectively analyzed 125 cirrhotic patient encounters with AKI across all Health institutions between 1 January 2019 and 31 December 2022. We performed multivariate analyses to determine independent predictors of development of HRS. Alcoholic cirrhosis was the most common identified etiology of cirrhosis. The mean Model for End-Stage Liver Disease Score was 18 (± 7). Ascites was the most commonly identified clinical feature of portal hypertension. Infection was identified in 38.4% of patients with urinary tract infection/pyelonephritis being the most common. Spontaneous bacterial peritonitis occurred in 5.9% of patients. The most common cause of AKI was pre-renal. Hepatorenal syndrome was identified in 9.8% of patient encounters. Predictors of HRS were history of ascites, serum creatinine >2.5 mg/dL, albumin <3 g/dL, bilirubin >2 mg/dL and spontaneous bacterial peritonitis. We demonstrate strong predictors for the development of HRS which can aid clinicians to attain an early diagnosis of HRS, leading to prompt and targeted management and improving outcomes.

Keywords: predictors, hepatorenal syndrome, cirrhosis, mortality, acute kidney injury

Introduction

Acute kidney injury (AKI) is a common complication in patients with decompensated liver cirrhosis with the most common cause being dehydration and volume depletion [1,2]. AKI in cirrhotic patients is associated with high morbidity and mortality [3], with an estimated median survival of less than 50% at 3 months [4,5,6].

Mechanisms of development of AKI in cirrhotic patients are variable. Cirrhotic patients are at risk of decreased effective arterial blood volume secondary to splanchnic vasodilatation, resulting in decreased renal perfusion. Cirrhotic patients are also at increased risk of acute or chronic gastrointestinal bleeding, as well as volume depletion due to medications such as lactulose and diuretics, which can result in further reduction of their effective arterial volume.

Hepatorenal syndrome (HRS) is a form of AKI, occurring in patients with decompensated liver cirrhosis. The definition of HRS has evolved over the past several years. The updated definition of HRS by the International Club of Ascites (ICA) in 2015 [7] renamed the previously known HRS-type 1 as HRS-AKI, and abandoned the previously required doubling of serum creatinine to >2.5 mg/dL within 2 weeks, to replace it with the definition of AKI based on the updated KDIGO guidelines which is an increase in serum creatinine by 0.3 mg/dL within 48 h, or 1.5 times increase in baseline creatinine which is known or presumed to have occurred within the prior 7 days [8].

The pathophysiology of HRS-AKI is multifactorial and mostly attributed to an uncompensated hyperdynamic circulatory system, renal vasoconstriction and systematic inflammation [9,10,11]. The diagnosis of HRS-AKI is often demanding and complex due to the clinical challenge of differentiating between HRS-AKI and other causes of AKI (such as pre-renal azotemia and acute tubular necrosis (ATN)). In addition, it is required to exclude structural kidney and bladder diseases which in turn often results in delaying timely management.

Early diagnosis and treatment of hepatorenal syndrome is important as better prognosis substantially depends on timely management in this group of patients [12,13]. Treatment with albumin and terlipressin or vasopressors has clearly been shown to improve mortality [14,15,16]. In our study herein, we hypothesize

that the risk of development of HRS-AKI can be predicted based on patient baseline clinical characteristics and laboratory values at the time of development of acute kidney injury. We therefore aimed to describe the variables associated with the development of HRS-AKI in cirrhotic patients with acute kidney injury to guide clinicians in determining the risk of development of HRS-AKI which would help attaining an early diagnosis by increasing clinical awareness specifically in this group of patients.

Materials and Methods

Study Population and Design

This was a retrospective case-control study of cirrhotic inpatients visits admitted across all Bukhara region between 1 January 2019 and 31 December 2022. Patients below the age of 18 and those with outpatient hospital encounters were excluded. We identified cirrhotic patients using our institution's Information Technology data warehouse; to identify patients with cirrhosis, we used the International Classification of Disease, ninth revision clinical modification (ICD-9-CM) codes as previously defined [17]. The corresponding ICD-10 codes (K70.30, K70.31, K74.6, K74.60, K74.5, K74.69) were selected to identify cirrhotic patients with medical encounters occurring after 1 October 2018. We then used the following ICD-9-CM codes to identify patient with AKI on admission: 584.5, 584.6, 584.7, 584.8 or 584.9 as previously defined [18] with the following corresponding ICD-10 codes: N17.0, N17.2, N17.8, N17.9. This study was approved by the Feinstein Institute for Medical Research, Northwell Health institutional review board.

Data Collection and Definitions

Using our data warehouse, clinical variables including patient demographics, medical and surgical history, cirrhosis history (including etiology, history of esophageal varices, ascites, and hepatic encephalopathy), laboratory data, vital signs were abstracted at the time of admission. Ascites on admission was identified by either physical exam documentation or radiologic evidence of ascites. Charlson Comorbidity Index (CCI) score was calculated [19] and adjusted for liver cirrhosis by excluding liver disease as a comorbidity. Additionally, home medications and medications administered during hospital stay, hospital length of stay, and outcomes (such as requirement of intubation, hemodialysis, and hospital mortality) were obtained. Charts and progress notes were then manually reviewed by RS (author) and AAY (author) to determine the presence of HRS, etiology of AKI other than HRS and suspected or confirmed infection.

AKI was defined using the KDIGO criteria as an increase in serum creatinine by 0.3 mg/dL or more within 48 h or by 1.5 times baseline or more within the last 7 days, or a urine output of less than 0.5 mL/kg/h for 6 h [20]. We defined pre-renal AKI to include patients with AKI secondary to hypovolemia, systemic vasodilation, and increased renal vascular resistance (such as compressive ascites). Intrinsic AKI included patients with tubular, glomerular, interstitial, and vascular injury. Postrenal AKI included extrarenal and intrarenal obstruction [21-26]. AKI due to HRS and cardiorenal AKI were separately identified to allow for more detailed analysis for the purpose of this study. The diagnosis of type 1 cardiorenal syndrome phenotype (i.e., AKI resulting from acute coronary syndrome or acute heart failure) was obtained from manual chart review and was as defined by AKI as per the KDIGO criteria resulting due to underlying acute cardiac pathology as previously described [22].

The primary outcome was development and diagnosis of HRS-AKI during hospital stay. Hepatorenal syndrome was diagnosed using the previously defined criteria [8,23]. Secondary outcomes included the following: need for intubation, hemodialysis requirement, hospital length of stay and hospital mortality.

Statistical Analysis

Patient characteristics and outcomes were presented as mean \pm standard deviation for continuous variables, and frequencies and percentages for categorical variables. Variables were compared between the two groups of patients (patients who developed HRS vs. those who did not) using the student's t-test or Mann-Whitney U-test for the continuous variables and the Pearson's chi-square test or Fisher's exact test for the categorical variables as appropriate. To calculate odds ratios, continuous variables were dichotomized and the odds ratios with corresponding 95% confidence intervals were calculated for all statistically

significant variables. A creatinine cutoff value of 2.5 mg/dL was chosen as a reasonable midrange between the mean creatinine value of patients with chronic kidney disease (CKD), and those without CKD to avoid skewing the predictors of progression to HRS based on baseline creatinine value. An albumin cutoff of 2 g/dL was chosen to reflect hypoalbuminemia. A bilirubin cutoff of 2 mg/dL was chosen to reflect significant hyperbilirubinemia. An INR cutoff of 1.5 was chosen to reflect impaired liver synthetic function. A value was considered statistically significant at a two-tailed test p-value less than or equal to 0.05. All statistical analyses were performed using SPSS.

Results

A total of 125 cirrhotic patient encounters were identified between 1 January 2019 and 31 December 2022. Of these patient encounters, 28 met our inclusion criteria. The mean age of our study population was 65 years (± 12 years), and the majority of patients were male (n = 33, 26.4%) and women (n = 92, 75%). The most commonly identified etiology of cirrhosis was alcoholic cirrhosis (n = 12, 9.6%) followed by non-alcoholic steatohepatitis (NASH) cirrhosis (3, 2.4%). Only 17.9% of the patients had baseline chronic kidney disease and the mean adjusted CCI score was 3 (± 2). Ascites was the most commonly identified clinical feature of portal hypertension (n = 207, 39.1%) followed by hepatic encephalopathy, with 66.7% of the patients having clinical signs of portal hypertension. A total of 10 patients were identified to have alcoholic hepatitis.

The most common cause of AKI was pre-renal in nature (35.7%) followed by intrinsic AKI (10.4%). HRS-AKI was identified in 9.8% of patient encounters. A total of 77 (14.6%) and 17 (3.2%) patients required mechanical ventilation and hemodialysis, respectively. Mean hospital length of stay was 10 (± 9) days and 11.2% of the patients had in hospital mortality.

Odds for Development of Hepatorenal-AKI

All variables that were statistically significantly different in the previous correlative analysis were used to calculate odds ratios for the development of HRS-AKI. The bivariate analysis demonstrated that bilirubin > 2 mg/dL was the strongest predictor for development of HRS (OR: 9.5, SD: 5.1–17.7), followed by a history of ascites (OR: 5.7, SD: 2.9–10.9). Interestingly, all degrees of ascites on admission were predictors of development of HRS-AKI, however ascites grade 3 was the strongest predictor. To establish independent predictors and adjusted odds ratios (aOR) for diagnosis of HRS-AKI, we conducted a multivariate analysis which showed that only a history of ascites, baseline serum creatinine > 2.5 mg/dL on admission, albumin < 2 g/dL, bilirubin > 2 mg/dL and spontaneous bacterial peritonitis were statistically significant predictors for development of HRS (Table 1). After stratifying patients based on the presence of chronic kidney disease (CKD) at baseline, a creatinine > 2.5 mg/dL was only a predictor of progression to HRS in those without CKD.

Table 1
 Odds of development of HRS in a bivariate and multivariate analysis.

Variable	Bivariate Analysis		Multivariate Analysis	
	Crude OR (CI)	p-Value	Adjusted OR (CI)	p-Value
Alcoholic cirrhosis	2.0 (1.1–3.6)	< 0.05	1.2 (0.5–2.4)	0.678
History of ascites	5.7 (2.9–10.9)	< 0.05	5.8 (2.6–13.0)	< 0.05
History of hepatic encephalopathy	3.3 (1.8–6.0)	< 0.05	1.5 (0.7–3.1)	0.256
Hb < 11 g/dL	2.6 (1.4–5.0)	< 0.05	1.7 (0.8–3.7)	0.160
Platelets < 150 ($\times 10^3$)	2.4 (1.3–4.4)	< 0.05	1.5 (0.7–3.2)	0.308
Sodium < 135 meq/L	3.1 (1.7–5.8)	< 0.05	2.2 (0.9–4.7)	0.053
Cr > 2.5 mg/dL	3.0 (1.7–5.6)	< 0.05	2.5 (1.2–5.5)	< 0.05
Albumin < 2 g/dL	3.8 (1.5–9.5–8.0)	< 0.05	3.9 (1.1–13.5)	< 0.05

Variable	Bivariate Analysis		Multivariate Analysis	
	Crude OR (CI)	p-Value	Adjusted OR (CI)	p-Value
Bilirubin > 2 mg/dL	9.5 (5.1–17.7)	<0.05	7.9 (3.7–17.0)	<0.05
INR > 1.5	5.6 (2.9–11.1)	<0.05	1.4 (0.3–5.8)	0.630
Spontaneous bacterial peritonitis	4.9 (1.9–12.7)	<0.05	5.5 (1.4–12.2)	<0.05

Conclusions

In this study, we demonstrate that a history of ascites, serum creatinine >2.5 mg/dL, albumin <2 g/dL, bilirubin >2 mg/dL, and spontaneous bacterial peritonitis are predictors for the development of HRS. Establishing potential predictors can aid clinicians to classify patients as high risk or low risk for the development of hepatorenal syndrome and may have a key role in expediting the diagnosis which in turn will lead to earlier targeted management and improved survival. Further studies are needed to verify our established predictors of HRS as well as prospective studies that will aid in providing better evidence on the relevance and clinical benefit of these established predictors.

References

- Choi Y.J., Kim J.H., Koo J.K., Lee C.I., Lee J.Y., Yang J.H., Ko S.Y., Choe W.H., Kwon S.Y., Lee C.H. Prevalence of renal dysfunction in patients with cirrhosis according to ADQI-IAC working party proposal. *Clin. Mol. Hepatol.* 2014;20:185–191. doi: 10.3350/cmh.2014.20.2.185. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- Wu C.C., Yeung L.K., Tsai W.S., Tseng C.F., Chu P., Huang T.Y., Lin Y.F., Lu K.C. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. *Clin. Nephrol.* 2006;65:28–33. doi: 10.5414/CNP65028. [PubMed] [CrossRef] [Google Scholar]
- Russ K.B., Stevens T.M., Singal A.K. Acute Kidney Injury in Patients with Cirrhosis. *J. Clin. Transl. Hepatol.* 2015;3:195–204. [PMC free article] [PubMed] [Google Scholar]
- Allegretti A.S., Ortiz G., Wenger J., Deferio J.J., Wibecan J., Kalim S., Tamez H., Chung R.T., Karumanchi S.A., Thadhani R.I. Prognosis of Acute Kidney Injury and Hepatorenal Syndrome in Patients with Cirrhosis: A Prospective Cohort Study. *Int. J. Nephrol.* 2015;2015:108139. doi: 10.1155/2015/108139. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
- Cholongitas E., Senzolo M., Patch D., Shaw S., O’Beirne J., Burroughs A.K. Cirrhotics admitted to intensive care unit: The impact of acute renal failure on mortality. *Eur. J. Gastroenterol. Hepatol.* 2009;21:744–750. doi: 10.1097/MEG.0b013e328308bb9c. [PubMed] [CrossRef] [Google Scholar]
- Mukhammadieva M.I. (2022). Modern Clinical and Biochemical Characteristics of Liver Cirrhosis Patients of Viral Etiology with Spontaneous Bacterial Peritonitis //Texas Journal of Medical Science. – 2022.- P. 86-90.
- Oblokulov. A.R., M.I. Mukhammadieva.(2022). Clinical and biochemical characteristics of liver cirrhosis patients of viral etiology with spontaneous bacterial peritonitis//ACADEMICIA GLOBE: INDERSCIENCE RESEARCH.-2022.- P. 210-216
- Simonetto D.A., Gines P., Kamath P.S. Hepatorenal syndrome: Pathophysiology, diagnosis, and management. *BMJ.* 2020;370:m2687. doi: 10.1136/bmj.m2687. [PubMed] [CrossRef] [Google Scholar]
- Thabut D., Massard J., Gangloff A., Carbonell N., Francoz C., Nguyen-Khac E., Duhamel C., Lebre C., Poynard T., Moreau R. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology.* 2007;46:1872–1882. doi: 10.1002/hep.21920. [PubMed] [CrossRef] [Google Scholar]
- Mirzoeva M.R., Sanokulova S.A. Features of the course o contagious giardiasis associated with giardiasis (2022) *Miasto Przyszlosci № 25.* P.186-189

11. Ojeda-Yuren A.S., Cerda-Reyes E., Herrero-Maceda M.R., Castro-Narro G., Piano S. An Integrated Review of the Hepatorenal Syndrome. *Ann. Hepatol.* 2021;22:100236. doi: 10.1016/j.aohep.2020.07.008. [PubMed] [CrossRef] [Google Scholar]
12. Mukhammadieva Musharraf Ibrokhimovna. (2023). IMPROVING THE PREVENTION AND TREATMENT OF COMPLICATIONS OF SPONTANEOUS BACTERIAL PERITONITIS IN PATIENTS WITH LIVER CIRRHOSIS OF VIRAL ETIOLOGY. *Galaxy International Interdisciplinary Research Journal*, 11(4), 388–394. Retrieved from <https://giirj.com/index.php/giirj/article/view/5168>
13. Санокүлова С.А.(2023) Особенности течения контогиозных гельминтов ассоциированного с лямблиозом // *Oriental Renaissance: Innovative, educational, natural and social sciences* -3(2), Feb. -С-910-917
14. Мухаммадиева М.И. (2023). Вирус этиологияли жигар циррози беморларида спонтан бактериал перитонит билан асоратланишнинг профилактикаси ва давосини такомиллаштириш//*Oriental Renaissance: Innovative, educational, natural and social sciences.* - 2023.-P.947-953.
15. Облокулов, А., & Мухаммадиева, М. (2022). КЛИНИКО-ЛАБОРАТОРНАЯ ХАРАКТЕРИСТИКА СПОНТАННОГО БАКТЕРИАЛЬНОГО ПЕРИТОНИТА ПРИ ЦИРРОЗЕ ПЕЧЕНИ ВИРУСНОЙ ЭТИОЛОГИИ. *Журнал вестник врача*, 1(3), 66–69. извлечено от https://inlibrary.uz/index.php/doctors_herald/article/view/2016
16. Flamm S.L., Brown K., Wadei H.M., Brown R.S., Jr., Kugelmas M., Samaniego-Picota M., Burra P., Poordad F., Saab S. The Current Management of Hepatorenal Syndrome-Acute Kidney Injury in the United States and the Potential of Terlipressin. *Liver Transpl.* 2021;27:1191–1202. doi: 10.1002/lt.26072. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Nehra M.S., Ma Y., Clark C., Amarasingham R., Rockey D.C., Singal A.G. Use of administrative claims data for identifying patients with cirrhosis. *J. Clin. Gastroenterol.* 2013;47:e50–e54. doi: 10.1097/MCG.0b013e3182688d2f. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
18. Sanokulova S.A (2023) Clinical and important diagnostic features in the combination of giardiasis with helminthiasis// *European journal of modern medicine and practice.* №01 P-23-26
19. Jepsen P. Comorbidity in cirrhosis. *World J. Gastroenterol.* 2014;20:7223–7230. doi: 10.3748/wjg.v20.i23.7223. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron. Clin. Pract.* 2012;120:c179–c184. doi: 10.1159/000339789. [PubMed] [CrossRef] [Google Scholar]
21. Makris K., Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. *Clin. Biochem. Rev.* 2016;37:85–98. [PMC free article] [PubMed] [Google Scholar]
22. Rangaswami J., Bhalla V., Blair J.E.A., Chang T.I., Costa S., Lentine K.L., Lerma E.V., Mezue K., Molitch M., Mullens W., et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation.* 2019;139:e840–e878. doi: 10.1161/CIR.0000000000000664. [PubMed] [CrossRef] [Google Scholar]
23. Pan H.-C., Chien Y.-S., Jenq C.-C., Tsai M.-H., Fan P.-C., Chang C.-H., Chang M.-Y., Tian Y.-C., Fang J.-T., Yang C.-W., et al. Acute Kidney Injury Classification for Critically Ill Cirrhotic Patients: A Comparison of the KDIGO, AKIN, and RIFLE Classifications. *Sci. Rep.* 2016;6:23022. doi: 10.1038/srep23022. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. 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;105:229–236. doi: 10.1016/0016-5085(93)90031-7. [PubMed] [CrossRef] [Google Scholar]
25. Janicko M., Veseliny E., Senajova G., Jarcuska P. Predictors of hepatorenal syndrome in alcoholic liver cirrhosis. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czechoslov.* 2015;159:661–665. doi: 10.5507/bp.2015.010. [PubMed] [CrossRef] [Google Scholar]
26. Rey R.M., Delgado A.F., De Zubiria A., Pinto R., De la Hoz-Valle J.A., Pérez-Riveros E.D., Ardila G., Sierra-Arango F. Prevalence and short-term outcome of hepatorenal syndrome: A 9-year

experience in a high-complexity hospital in Colombia. PLoS ONE. 2020;15:e0239834.
doi: 10.1371/journal.pone.0239834. [[PMC free article](#)] [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]