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FACTORS OF DEVELOPMENT OF HEPATORENAL SYNDROME

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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 Scorewas18 (±7).

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 medial survival of less than 50% at 3 months [4,5,6].

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

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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

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.
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

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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 ± 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

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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.

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.

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