Original Article JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

Impact of Acute Kidney Injury on Mortality of Patients Hospitalized for Complications of Cirrhosis

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Background/aims: **The mortality of hospitalized patients for complications of cirrhosis is very high. We examined the independent predictors of mortality, particularly the impact of increments in creatinine, in 339 consecutive patients (636 admissions) who were admitted for complications of cirrhosis.** ***Methods:*** **Clinical characteristics, biochemical parameters including serum creatinine levels at various time intervals, and mortality data were recorded for all admissions. Data were analyzed for initial as well for all repeated admissions to identify independent predictors of mortality.** ***Results:*** **The in-hospital mortality, 30-day, 90-day, 180 days, and 365 days mortality were 6%, 15%, 23%, 30%, and 41% respectively. Those admitted with spontaneous bacterial peritonitis had the worst survival. Increase in creatinine was noted in 29% of patients and they had lower 30-day (78% vs.91%) and 90-day (73% vs. 82%) survival than those without increase in creatinine. Any increment in serum creatinine (≥0.1 mg/dL) within 48 h after admission (peak 48 h – admission) was associated with a step-wise increase in mortality, but only if peak creatinine reached above 1.2 mg/dl. If peak creatinine levels were below 1.2 mg/dl, increases in serum creatinine had no impact on survival. Cox regression analysis showed that increments in serum creatinine of 0.3 mg/dl or higher had the worst outcome (HR 2.51, CI 1.65–3.81). Etiology of cirrhosis or the use of PPI, beta blockers or rifaxamin did not predict mortality. Other independent predictors of mortality were age, reason for admission, hyponatremia, and INR.** ***Conclusion:*** **In patients with cirrhosis, any increment in serum creatinine within 48 h from hospitalization is associated with a higher mortality provided the peak serum creatinine within 48 h is above 1.2 mg/dl. (J Clin Exp Hepatol 2017;xx:1–10)**

Cirrhosis is a major cause of morbidity and mortality worldwide, and as per Healthcare Cost and Utilization Project (HCUP), the number of people hospitalized with cirrhosis in the US hospitals increased steadily (6.2% increase per year) from 403,665 in 2004 to 578,573 in 2011. It has been estimated that 25.7 per 100,000 people died from liver related disease in the US in 2008.[1] The above estimates suggest that the management of people with end-stage liver disease will continue to cause significant financial burden on the entire health care system.[2]

The transition from a compensated cirrhosis to a decompensated (ascites, encephalopathy, variceal bleeding) state occurs at an annual rate of five to seven percent, and this reduces the median survival time from twelve to two years.[3] It has been estimated that about 58% of patients with cirrhosis will decompensate within 10 years from the time of diagnosis of cirrhosis and the 10-year survival of people with cirrhosis is only 47%.[4] To reduce short-term and long-term mortality of people with cirrhosis, it is important to identify important negative risk factors and optimize their care. Previous studies showed that people hospitalized with complications of cirrhosis have a very high mortality[5,6] but reliable prognostic indicators and risk factors for worse outcomes are currently unavailable. Although the MELD or Child–Pugh score scores could predict short term mortality, it is important to identify modifiable risk factors in hospitalized cirrhotic patients to improve the outcomes.[7–15]

Recently, development of acute kidney injury (AKI) has shown to be an independent negative predictor of mortality in people with cirrhosis, and it is possible that this is a modifiable risk factor. The Acute Kidney Injury Network (AKIN)[16] defined AKI as an abrupt (within 48 h) increase in the serum creatinine level by at least 0.3 mg/dL or the equivalent to a percentage increase of 50% (1.5 fold)

Keywords: acute kidney injury, hospitalized patients, cirrhosis, liver failure, complications of cirrhosis
Received: 2.11.2016; *Accepted:* 2.05.2017; *Available online:* xxx
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Abbreviations: ADQI: Acute Dialysis Quality Initiative (ADQI); AKI: acute kidney injury; AKIN: acute kidney injury network; HRS: hepatorenal syndrome; INR: international normalized ratio; MELD: model for end-stage liver disease; PPI: proton pump inhibitor; SBP: spontaneous bacterial peritonitis
http://dx.doi.org/10.1016/j.jceh.2017.05.004

Please cite this article in press as: Nuthalapati A, et al. Impact of Acute Kidney Injury on Mortality of Patients Hospitalized for Complications of Cirrhosis. *J Clin Exp Hepatol.* (2017), http://dx.doi.org/10.1016/j.jceh.2017.05.004

from baseline, irrespective of final serum creatinine. The International Ascites Club (IAC) and the Acute Dialysis Quality Initiative (ADQI) group[17] proposed a modified definition for AKI in people with cirrhosis by removing the staging aspect of AKI (Stage 1–3) proposed by AKIN. People with cirrhosis are susceptible to AKI because of a progressive vasodilatory state, reduced effective circulating blood volume, and subsequent compensatory stimulation of vasoconstrictor hormones.[18,19] It has been estimated that approximately 20% of people admitted to hospitals with a complication of cirrhosis will have AKI and the mortality is higher in those with AKI when compared to those who do not develop AKI.[20–22] However, the reported studies of mortality using the AKI criteria in patients with cirrhosis have mostly focused on specific groups (i.e. intensive care, outpatients and decompensated patients with ascites or infections), which may limit the generalization of these results.[23–26] In this study, our objective was to identify the risk factors, including AKI, of mortality in unselected and consecutive patients admitted to a hospital for complications of cirrhosis, and to critically evaluate the utility of existing diagnostic criteria for AKI in cirrhotic patients.

SUBJECTS AND METHODS

After obtaining institutional review board approval, all adult patients (age 18 and above) admitted to the Mercy Medical Centre in Baltimore, MD from January 2009 to December 2013 were screened for inclusion in the study. To be eligible for inclusion, patients must have been admitted for complications resulting from underlying cirrhosis. Patients admitted for elective procedures (i.e. transarterial chemoembolization or percutaneous tumor ablation, transjugular portosystemic shunt, large-volume paracentesis or surgical procedures) and patients admitted for observations were excluded. For eligible patients admitted to our hospital between January 2009 and December 2012, data were collected in a retrospective fashion using a comprehensive, electronic patient record database. For eligible patients admitted between January 2013 and December 2013, data were prospectively collected after obtaining informed consent.

During the study period, there were no changes in the management of complications of cirrhosis at the hospital. All patients were managed by experienced hepatologists. All patients with ascites had diagnostic paracentesis on admission, received albumin infusion if there was presence of spontaneous bacterial peritonitis (SBP), received prophylactic antibiotics for 5 days if admitted with gastrointestinal bleeding, and had appropriate secondary prophylaxis after discharge. Prophylactic antibiotics (primary prophylaxis) were not given for patients with ascites without a history of SBP. Patients with MELD score above 14 were considered for liver transplant evaluation unless there were obvious contraindications. Terlipressin was not given to any patients during the study period.

Cirrhosis was diagnosed with a combination of clinical, biochemical, radiological, and endoscopic findings in the absence of a liver biopsy confirmation. The collected data included age, race, sex, employment status, etiology of cirrhosis, medication use prior to admission (particularly rifaximin, beta-blockers and acid suppressive agents), admission vital signs, complete blood counts, basic metabolic panel, liver function tests, coagulation panel, severity of liver dysfunction (as determined by Child–Pugh and MELD calculations), and reason for admission. Data regarding the overall length of hospital stay in days and number of days in ICU, data regarding clinical outcomes (i.e. liver transplantation, discharge to home/nursing home/rehab/hospice) and readmission rates at 3, 6, 12 and 24 months were also collected. Mortality data of patients who were discharged alive from the hospital were obtained from the social security database.

For this study, AKI is defined according to the clinically validated AKIN criteria.[16] To analyze the impact of AKI on outcomes, pre-admission serum creatinine values were obtained from a combination of outpatient and emergency department visit records. Pre-admission creatinine is defined as the average of all available serum creatinine measurements within 90 days prior to admission. Serum creatinine on admission, peak creatinine within 48 h, peak creatinine values during the entire length of stay, and creatinine at discharge were recorded. The duration of AKI was also recorded. The differences between peak serum creatinine during the first 48 h admission and admission serum creatinine (peak serum creatinine within 48 h—admission serum creatinine) were calculated in all patients. On admission, peak within 48 h—pre-admission creatinine was also obtained whenever reliable pre-admission creatinine was available. The impact of serum creatinine changes on outcomes when serum creatinine increase was within normal ranges (normal ranges for our laboratory—serum creatinine 0.7 mg/dL to 1.2 mg/dL) and outside the normal ranges (peak serum creatinine more than 1.2 mg/dL) was assessed. We also sought to find the optimal cut-off point at which sharp increases in creatinine related to a meaningful difference in survival. Additionally, we examined the survival based on conventional definition of type 2 hepatorenal syndrome (HRS, peak serum creatinine 1.5 mg/dL or higher). The effect of diuretic use (either before or during admission) or beta blockers, and the mean arterial pressure on the development of AKI were assessed.

STATISTICAL METHODS

The primary outcomes of the analysis were 30-day survival, 90-day survival, and survival time. The 30-day and 90-day survival outcomes were dichotomous, and characteristics of patients who did and did not have these outcomes were

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