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**ORIGINAL ARTICLE**

**The Association between Recurrent Variceal Bleeding and Acute Kidney Injury in Cirrhotic Patients**

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| **\*Corresponding Author:** Ahmed Fathy Gomaa, Assistant Professor of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt.E-mail: dr.afgomaa1980@gmail.com**Submit Date 2022-11-20** **Revise Date 2022-12-16** **Accept Date 2022-12-22** | **ABSTRACT****Background:** Patients with liver cirrhosis who present with bleeding esophageal varices are at a higher risk of developing acute kidney injury (AKI), which, in turn, has negative impacts and a poor prognosis. In our study, we aimed to determine the association between recurrent esophageal variceal bleeding and the presence of AKI in patients with liver cirrhosis.**Methods:** Our study included 203 cirrhotic patients, divided into two groups based on the absence or presence of AKI. All patients underwent a comprehensive medical history evaluation, clinical examination, and laboratory investigations. Treatment for all patients included fluid resuscitation, vasopressor agents, and endoscopic management. Both groups were closely monitored to assess the rate of esophageal variceal re-bleeding.**Results:** Out of the 203 patients, 91 (45%) developed AKI. Several factors, such as low systemic blood pressure, a high volume of blood transfusion, and a high Child-Pugh score, were identified as independent predictors for AKI. Factors such as Child-Pugh scores (*p* = 0.006), active bleeding observed during endoscopy (*p* = 0.04), and the occurrence of AKI (*p* = 0.049) were identified as independent predictors of variceal re-bleeding at both 72 hours and 1 month. Among patients with AKI, the variceal re-bleeding rate was 27.5% at 72 hours, 16.5% at 1 month, and 12.1% at 3 months, compared to 9%, 5.4%, and 4.5%, r espectively, in patients without AKI. Within the first 72 hours, the rate of esophageal variceal re-bleeding was higher in patients with a more advanced stage of AKI.**Conclusions:** The incidence of recurrent esophageal variceal bleeding was significantly higher in patients with liver cirrhosis who developed AKI.***Key******words****:* Ascites, Renal failure, Hematemesis.  |

**INTRODUCTION**

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iver cirrhosis is associated with significant complications, among which variceal bleeding stands out as a primary cause contributing to elevated mortality rates ranging from 15% to 57% in patients with portal hypertension [1] [2]. In Egypt, hepatitis C virus infection has been the predominant underlying cause of liver cirrhosis and the development of varices [3].

Several factors have been identified as increasing the risk of variceal bleeding, including the size of the varices, ascites drainage, the severity of hepatic disease, and the presence of cherry red spots on the variceal wall [4].

Acute Kidney Injury (AKI) is a common and significant complication in patients with liver cirrhosis, with a prevalence ranging from 20% to 50% among hospitalized cirrhotic patients [5]. Various factors contribute to the development of AKI in these patients, including gastrointestinal bleeding, infections, excessive diuretic use, and large volume paracentesis without adequate albumin replacement [6].

The diagnosis of AKI in cirrhotic patients is typically made when there is an acute increase in serum creatinine of >0.3 mg/dL within 48 hours or a ≥50% elevation above the baseline within 3 months [7]. AKI in cirrhosis is associated with a poor prognosis and high mortality rates [8].

Hepatorenal syndrome represents a distinct pattern of renal failure that occurs in advanced liver disease. It is characterized by functional kidney disturbances resulting from renal artery vasoconstriction while maintaining tubular function without significant histologic changes. The primary cause of renal artery vasoconstriction in hepatorenal syndrome is splanchnic artery vasodilation, leading to a reduction in effective arterial pressure [9].

Therefore, the aim of our study is to investigate the association between the incidence of AKI in patients with liver cirrhosis and variceal re-bleeding. We will employ the criteria proposed by the International Club for Ascites for diagnosing AKI in patients with liver cirrhosis.

 **METHODS**

**Study Design:** This study is a prospective cohort investigation. The sample size was determined using the Buderer formula [Buderer, N. M. (1996)] with an expected prevalence of 50% and a sensitivity of 95%, at a 95% confidence interval (CI). Thus, the estimated sample size required was 240 cirrhotic patients. The study was conducted over 8 months, from January 2021 to August 2021, and involved cirrhotic patients admitted to the hepatology unit at Zagazig University Hospitals who presented with upper gastrointestinal bleeding.

**Inclusion Criteria:** Patients included in the study met the following criteria: they were cirrhotic, presented with upper gastrointestinal bleeding, and were between the ages of 18 and 60 years.

**Exclusion Criteria:** Several exclusion criteria were applied, leading to the exclusion of 37 patients. These criteria included:

1. Inability to provide a 3-month follow-up after variceal bleeding (n=15).
2. Presence of end-stage systemic illnesses (n=10).
3. Chronic renal failure (n=2).
4. Management of variceal bleeding in another medical center (n=10).

**Patient Groups:** After applying the inclusion and exclusion criteria, a total of 203 patients remained in the study. These patients were divided into two groups based on the presence or absence of Acute Kidney Injury (AKI):

* Group I: Cirrhotic patients without AKI.
* Group II: Cirrhotic patients with AKI.

**Additional Exclusion Criteria:** Further exclusion criteria were applied, including patients who:

1. Were terminally ill with major organ afflictions such as severe heart failure, malignancy (except Hepatocellular carcinoma, HCC), and chronic obstructive pulmonary disease.
2. Had undergone organ transplantation.
3. Had chronic renal diseases and were on hemodialysis settings.
4. Had been recently treated for bleeding esophageal varices with fluids, blood transfusion, vasopressor agents, and endoscopy at another medical facility.
5. Had a history of nephrotoxic drug use, including NSAIDs and nephrotoxic antibiotics.
6. Showed a history or evidence of sepsis upon admission.

**Study Objective:** The primary research question addressed in this study was whether AKI could increase the rate of esophageal variceal re-bleeding in patients with liver cirrhosis.

**Study Objective:** The main objective of the study was to elucidate the association between acute kidney injury and the incidence of esophageal re-bleeding in cirrhotic patients.

**Definitions**

 In this study, the diagnosis of Acute Kidney Injury (AKI) and Hepatorenal Syndrome (HRS) followed the criteria established by the International Club of Ascites (ICA) for AKI diagnosis [7]. It's important to note that for the duration of hospitalization, only the first episode of AKI was considered, even if the patient experienced multiple episodes during the same admission.

According to the ICA-AKI criteria, AKI was diagnosed when there was an increase in serum creatinine by >0.3 mg/dL within the first 48 hours of hospitalization or when it exceeded 50% of the last recorded baseline value. The baseline serum creatinine values were determined by considering the most recent values within the preceding three months. If a patient lacked previous admissions, the admission serum creatinine was used as the baseline.

The initial stage of AKI was diagnosed upon admission, following the ICA-AKI criteria, and its progression was assessed during hospitalization using the same criteria with measured serum creatinine levels. AKI was considered at its peak when it reached the highest stage with the highest recorded serum creatinine level during the hospital stay. On the other hand, the recovery of AKI was defined as a reduction in the stages of AKI or when patients' serum creatinine levels returned to within 0.3 mg/dL of the baseline value.

HRS was diagnosed based on specific criteria, including the presence of cirrhosis and ascites, the diagnosis of AKI as previously mentioned, and the absence of a response two days after discontinuation of diuretics and plasma volume expansion with albumin (1 g/kg of body weight). Additionally, other potential causes of kidney injury were ruled out, including the absence of shock, no administration of nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), and no macroscopic signs of structural kidney injury (absence of proteinuria >500 mg/day, absence of micro-hematuria >50 red blood cells per high-power field), and renal ultrasonography showing normal findings.

Liver cirrhosis was diagnosed using a combination of physical examination, laboratory tests, ultrasonography, and endoscopic data, while Hepatocellular carcinoma (HCC) was diagnosed based on characteristic findings from dynamic imaging.

Gastro-esophageal variceal bleeding (GVB) was assessed through emergent endoscopy and according to specific criteria [10], including the presence of hematemesis, melena, or hematochezia, along with endoscopic findings such as active bleeding from esophageal or gastric varices (GVs), white nipple signs, erosions, adherent blood clots, and the presence of distinct red-color signed large varices with the absence of other obvious bleeding sources.

Esophageal varices were classified according to the Westaby grading system as follows:

* Grade 1: Varices slightly protruding above the mucosa and depressible with insufflation.
* Grade 2: Varices occupying less than 50% of the lumen.
* Grade 3: Varices occupying more than 50% of the lumen with a confluent appearance [11].

**Study Process**

During patient admission, various laboratory and physical findings were recorded. The Child Score plus Model for End-Stage Liver Disease (MELD) score were calculated upon admission [12][13]. The estimated glomerular filtration rate (GFR) was determined using the Modification of Diet and Renal Disease (MDRD) equation [16].

All patient data, including vital signs, laboratory results, transfused blood, and endoscopic findings were collected, and endoscopic variceal management was performed for all patients within 24 hours of admission.

Upon patient arrival, Somatostatin with or without Terlipressin was administered as vasoactive agents for a period of 3 days, and prophylactic antibiotics were given for 5 days. Packed red blood cells (PRBC) were transfused as needed to maintain hemoglobin levels at 8 mg/dL. All patients underwent endoscopic procedures within 24 hours, using an OLYMOUS EVIS EXERAIII CLV-190 and a 22-gauge injection needle for gastric varices. Each injection consisted of 0.5 ml n-butyl-2-cyanoacrylate (Glustitch Inc., Delta, BC, Canada) and 0.5 ml Lipiodol (Guerbet Laboratory, Anulnay-Sous-Bris, France), with a maximum of six injections per session [11][12]. Esophageal varices were eradicated using band ligation.

Patients were prospectively followed until hospital discharge and for an additional 6 months post-discharge. Renal functions and the incidence of esophageal re-bleeding were documented during this follow-up period.

Follow-up of patients adhered to the following guidelines: initially, endoscopic treatment was conducted every 4 weeks until complete eradication of gastro-esophageal varices was achieved. Subsequently, follow-up endoscopy was performed every 12 weeks until complete eradication. In cases where signs of bleeding were observed during surveillance, an emergent upper gastrointestinal endoscopy was conducted to identify the source of bleeding. If new bleeding occurred, treatment options were considered, including conservative management or endoscopic intervention.

**Ethical Approvals**

The study received approval from the Institutional Review Board (IRB) committee at the Faculty of Medicine, Zagazig University, with the reference number IRP No. 10050. Prior to their participation in the study, written informed consent was obtained from all subjects as an essential ethical consideration. This study adhered to The Code of Ethics of the World Medical Association, specifically the Declaration of Helsinki, governing research involving human subjects.

**STATISTICAL ANALYSIS**

All statistical analyses were conducted using SPSS for Windows, version 19.0, developed by SPSS Inc. based in Chicago, IL, USA.

The data were presented as means ± SD for continuous quantitative variables and as numbers and percentages for categorical variables. To compare the means of continuous, normally distributed data between the two groups, an unpaired t-test was employed. For qualitative variables, the Chi-square test was utilized.

In cases involving multiple dependent and independent variables, multivariate analysis was performed. Statistical significance was defined as a *p*-value of less than 0.05.

**RESULTS**

The clinical and demographic characteristics of the patients are summarized in Table 1. The mean age of the patients was 59 ± 12.5 years. Viral hepatitis was the most common cause of liver cirrhosis (86.6%). During the initial endoscopic examination, active gastro-esophageal variceal bleeding (GVB) was observed in 82 cases (40.4%).

Of the patients, 163 (80.3%) had preadmission serum creatinine values available, while 40 patients (19.7%) lacked previous data, so their admission levels were considered as baseline. According to the ICA-AKI criteria, 91 patients (44.8%) were diagnosed with AKI (group II), with the distribution as follows: 69 cases had grade 1 AKI (75.8%), 15 had grade 2 (16.4%), and 7 presented with grade 3 (7.8%). The causes of AKI were diverse, with approximately 50 patients (54.9%) experiencing pre-renal AKI, 30 patients (33%) having parenchymal renal diseases, and 11 patients (12.1%) diagnosed with Hepatorenal Syndrome (HRS).

Patients in group II (with acute kidney injury) exhibited lower blood pressure upon admission (*p* < 0.001), a higher rate of active bleeding during endoscopic examination (*p* < 0.001), and a higher volume of transfused blood prior to endoscopic management (*p* < 0.001) in comparison to group I. Additionally, group II patients had higher Child scores (*p* < 0.028), lower sodium levels (*p* < 0.001), and elevated C-reactive protein (CRP) levels (*p* < 0.001) compared to group I (see Table 1).

Multivariate analysis revealed that the independent variables predicting the occurrence of acute kidney injury were Child scores, systolic pressure at presentation, and the number of units of red blood cells (RBC) transfused before endoscopy.

During hospitalization, AKI progressed to higher stages in 25 patients (27.4% of group II patients), with renal replacement therapy administered to 7 patients. The overall variceal re-bleeding rate was 17.2% (n = 35) at 72 hours, 10.3% (n = 21) at 4 weeks, and 7.8% (n = 16) at 3 months (see Table 2). Univariate analysis indicated that a higher grade of hepatic illness, lower serum sodium values, active variceal bleeding during endoscopic examination, higher CRP values, and the occurrence of AKI were associated with 72-hour and 1-month variceal re-bleeding.

The rate of variceal re-bleeding among AKI patients was 27.5%, 16.5%, and 12.1% at 72 hours, 1 month, and 3 months, respectively, compared to 9%, 5.4%, and 4.5% in patients without AKI (see Table 2 and Figure 1). Multivariate analysis revealed that higher Child-Pugh scores (*p* = 0.006), active variceal bleeding during endoscopic examination (*p* = 0.04), and the incidence of AKI (*p* = 0.049) were significant predictors of 72-hour and 1-month variceal re-bleeding.

Moreover, it was observed that patients with stage 3 AKI had the highest re-bleeding rates (57%) among patients with the same AKI stage, compared to 46.6% in cases with stage 2 and 20.2% in patients with stage 1 AKI who experienced variceal re-bleeding (see Table 3). Additionally, a higher re-bleeding rate was noted in cases with progressive AKI (68%) compared to patients without progression (12%) (see Table 3).

**Table 1** Demographic and clinical characteristics of all patients on admission in both AKI and non AKI groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** **(No. 203)** | **Group I without AKI (No. 112)** | **Group II with AKI (No. 91)** | ***p*-value** |
| **Age** | 59±12.5 | 60±11.2 | 57±10.5 | 0.526 |
| **Sex , male (n)** | 118 | 72 | 46 | 0.04 |
| **viral hepatitis (HCV, HBV) (n)** | 176 | 97 | 79 | 0.9 |
| **Alcohol (n)** | 5 | 3 | 2 | 0.82 |
| **Other etiology (n)** | 18 | 10 | 8 | 0.9 |
| **Baseline Creatinine (mg/dl)** | 0.9±0.16 | 0.9±0.15 | 0.9±0.17 | 0.21 |
| **SBP (mmHg)** | 116±10.6 | 120±13.5 | 110±9.5 | <0.001 |
| **Shock (n)** | 45 | 13 | 32 | <0.001 |
| **Hematemesis (n)** | 120 | 62 | 58 | 0.22 |
| **Melena (n)** | 100 | 67 | 33 | <0.001 |
| **Ascites (n)** | 88 | 40 | 48 | 0.014 |
| **Diabetes (n)** | 50 | 24 | 26 | 0.24 |
| **CKD (n)** | 30 | 14 | 16 | 0.31 |
| **Blood transfusion (units)** | 53 | 21 | 32 | <0.001 |
| **Encephalopathy (n)** | 30 | 14 | 16 | 0.31 |
| **Hb (g/dl)** | 11±0.5 | 11.5±0.4 | 10±0.2 | <0.001 |
| **Albumin (g/dl)** | 2.8±0.4 | 3.1±0.3 | 2.6±0.2 | <0.001 |
| **Bilirubin (mg/dl)** | 1.6±0.6 | 1.4±0.5 | 1.8±0.7 | <0.001 |
| **INR** | 1.2±0.2 | 1.2±0.1 | 1.3±0.2 | <0.001 |
| **S. Sodium (mmol/l)** | 137±7 | 138±2 | 134±5 | <0.001 |
| **CRP** | 1±0.3 | 0.9±0.2 | 1.1±0.3 | <0.001 |
| **Child score** | 8±1.2 | 7±0.5 | 9±0.4 | 0.028 |
| **Hospital stay (days)** | 5±1.2 | 4±0.8 | 6±1.1 | 0.001 |
| **Active bleeding on endoscopy, n (%)** | 82 | 28 | 54 | <0.001 |
| **Re-bleeding after 72h (n)** | 35 | 10 | 25 | 0.001 |
| **Re-bleeding at 1 month (n)** | 21 | 6 | 15 | 0.01 |
| **Re-bleeding at 3 months (n)** | 16 | 5 | 11 | 0.04 |

SBP: Systolic blood pressure; CKD: Chronic Kidney disease; Hb: Hemoglobin; INR: International normalized ratio; CRP: C-reactive protein.

**Table 2** Comparison between both AKI and non AKI groups regarding variceal re-bleeding at 72 hours, 1 month and 3 months

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Group I****(without AKI)** | **Group II****(with AKI)** | ***p*-value** |
| **Baseline creatinine (mg/dl)** | 0.9±0.15 | 0.9±0.17 | 0.21 |
| **Re-bleeding after 72h (n)** | 10 (8.9%) | 25 (27.5%) | 0.001 |
| **Re-bleeding at 1 month (n)** | 6 (5.4%) | 15 (16.5%) | 0.01 |
| **Re-bleeding at 3 month (n)** | 5 (4.5%) | 11 (12.1%) | 0.04 |

AKI: Acute kidney injury

**Table 3** Renal Variables in AKI group and its relation to variceal re-bleeding after 72 hours

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Re-bleeding****(No. 25)** | **No Re-bleeding (No. 66)** | **Total** | ***p*-value** |
| **Initial AKI stage (n)** |  | 0.02 |
| **AKI stages** | **Stage1** | 14 (20.2%) | 55 (79.7%) | 69 (100%) |
| **Stage2** | 7 (46.6%) | 8 (53.4%) | 15 (100%) |
| **Stage 3** | 4 (57%) | 3 (43%) | 7 (100%) |
| **Progression of AKI (n)** |  |  | <0.001 |
|  | **Yes** | 17 (68%) | 8 (32%) | 25 (100%) |
|  | **No** | 8 (12%) | 58 (88%) | 66 (100%) |

AKI: Acute kidney injury

**Fig. 1** Showed percentage of cirrhotic patients with variceal re-bleeding at 72 hours, 1 month and 3 months after the last variceal endoscopy session in both AKI and non AKI groups.

**DISCUSSION**

This study aimed to investigate the occurrence of recurrent esophageal variceal bleeding in cirrhotic patients with Acute Kidney Injury (AKI). Our findings demonstrated that the development of AKI had a detrimental impact on the incidence of variceal rebleeding following endoscopic hemostasis. Consequently, it is imperative to implement preventive measures aimed at reducing the occurrence of AKI after variceal bleeding to improve patient outcomes.

In our study, various factors were identified as predictors of acute kidney injury, including the advanced stage of hepatic illness and the severity of bleeding from esophageal varices, characterized by hypotension upon admission and the need for greater blood transfusion. Multiple factors related to variceal bleeding can negatively affect kidney function in patients with liver cirrhosis. First, the loss of blood leads to decreased intravascular volume, ultimately resulting in renal hypoperfusion, which can lead to pre-renal acute kidney injury and acute tubular necrosis. Second, bacterial infections that develop during gastrointestinal bleeding can lead to arterial vasodilation [17]. Lastly, the reduced effective arterial volume in advanced cirrhosis can impede the ability to maintain adequate renal blood flow through renal autoregulation mechanisms [18][19].

Additionally, our study revealed that factors such as advanced hepatic failure, lower serum sodium levels, elevated serum creatinine levels, increased blood transfusion requirements, and elevated CRP levels were associated with both AKI progression and variceal rebleeding at 72 hours and 1 month.

Furthermore, the progression of acute kidney injury to higher stages was linked to higher mortality rates and an increased likelihood of variceal rebleeding, consistent with prior studies [5][20]. Therefore, patients with these risk factors should undergo aggressive interventions to facilitate effective management and blood volume restoration.

Moreover, our study found that the incidence of acute kidney injury was a predictor of variceal rebleeding, with higher AKI levels being associated with a greater likelihood of recurrent variceal bleeding. These results underscore the need for future research to emphasize preventive and therapeutic measures for AKI in cirrhotic patients, with the aim of achieving more favorable outcomes.

**Limitations of the Study**

This study has several limitations, including its single-center design and relatively small sample size. We recommend that larger-scale multicenter prospective studies be conducted to validate our findings.

**CONCLUSIONS**

In conclusion, patients with liver cirrhosis who present with upper gastrointestinal bleeding and AKI on admission are at a higher risk of recurrent variceal bleeding. Further research is warranted to assess the impact and role of other contributing factors related to recurrent variceal bleeding across a wider range of patients.

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