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Value of Acute Kidney Injury in Predicting Mortality in Vietnamese Patients with Decompensated Cirrhosis

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Abstract: Background: Acute kidney injury remains a common complication with a poor prognosis, and is a significant predictor of mortality in cirrhosis patients. We aimed to determine the percentage of acute kidney injury in decompensated cirrhosis patients and evaluate the treatment results of acute kidney injury as well as several factors related to the mortality of decompensated cirrhosis patients. Methods: A prospective study was conducted on decompensated cirrhosis patients in Can Tho City, Vietnam, from 2019 to 2020. Decompensated cirrhosis patients were found to have acute kidney injury on admission by a blood creatinine test. They were treated according to ICA 2015 standards, after which they were monitored and evaluated for treatment outcomes during hospitalization. Results: Of 250 decompensated cirrhosis patients, 64 (25.6%) had acute kidney injury and 37.5% died. Several factors were associated with mortality in decompensated cirrhosis patients, such as Child–Pugh C ($p = 0.02$; OR = 3, 95% CI 1.5–6.3), acute kidney injury ($p < 0.0001$; OR = 9.5, 95% CI 4.3–21.1), hyponatremia ($p = 0.01$; OR = 2.5, 95% CI 1.2–5.1), elevated total bilirubin > 51 µmol/L ($p = 0.03$; OR = 2.2, 95% CI 1.1–4.6), and prothrombin < 70% ($p = 0.03$; OR = 6.8, 95% CI 1–51.6). Hypoalbuminemia was unrelated to mortality in these patients ($p = 0.8$; OR = 1.2, 95% CI 0.5–2.7), but gastrointestinal bleeding significantly increased mortality in these patients up to 2.3 times ($p = 0.03$; OR = 2.3, 95% CI 1.1–4.9). Three independent factors regarding mortality in decompensated cirrhosis patients included acute kidney injury, hepatic encephalopathy, and gastrointestinal bleeding. The rate of acute kidney injury in patients with decompensated cirrhosis was 25.6%; the mortality rate was 37.5%. Conclusions: Acute kidney injury was a valuable predictor of mortality in Vietnamese patients with decompensated cirrhosis.

Keywords: acute kidney injury; cirrhosis; mortality; hepatic encephalopathy; gastrointestinal bleeding

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1. Introduction

Cirrhosis, a common disease in our country and worldwide, is the 12th leading cause of death globally in 2020, and is the fifth in Southeast Asia [1]. In Vietnam, the incidence of the hepatitis B virus thrived, experiencing an increase from 6.4 million to 8.4 million between 1990 and 2005; this figure is predicted to decline to 8.0 million during the 20 years following 2005 [2]. Hepatitis B represents a major cause of cirrhosis in most Asian countries, particularly Vietnam, while most Europeans contract cirrhosis from alcohol and nonalcoholic fatty liver disease [2,3].

Recent studies have revealed that acute kidney injury becomes more prevalent in cirrhosis patients at nearly 20–50% on admission. In addition, cirrhosis patients have often been more prone to kidney failure than those without liver diseases [4–6]. Acute kidney injury (AKI) is a common complication with a poor prognosis, and is a significant predictor

of mortality in cirrhosis patients [7]. Therefore, patients with decompensated cirrhosis who are diagnosed early through the factors related to the mortality of AKI and are treated timely for their kidney injury have an improved prognosis.

Kidney complications are some of the most troublesome complications when patients with cirrhosis have moved to the decompensated stage, as it is a cause of an increase in death rate. Currently, clinicians have developed a new concept of acute kidney injury to monitor and detect kidney injury early. If intervention and treatment measures are proposed early, this may help with a good prognosis for cirrhosis [8].

In Southern Vietnam, a study by Vo Thi My Dung was carried out and showed the incidence of AKI and several factors related to the increase in its rate in patients with decompensated cirrhosis. However, the role and factors associated with the mortality rate in cirrhosis patients have not yet been clearly elucidated [9]. Furthermore, studies on AKI in decompensated cirrhosis patients have presently been scarce in our country, so we conducted this study to determine the rate of AKI in patients with decompensated cirrhosis. We also evaluated the treatment results of AKI, the role of AKI, and several factors regarding mortality prognosis in these patients.

2. Materials and Methods

2.1. Setting and Study Population

A prospective study was conducted at a central hospital in Can Tho City, Vietnam. We enrolled adult patients with decompensated cirrhosis that were admitted to the clinic of gastroenterology of this hospital. In addition, the exclusion criteria in this research were patients (1) with renal failure due to obstruction, diagnosed with renal dysfunction and hydronephrosis on ultrasound; (2) who had received a liver or kidney transplant; (3) were on kidney dialysis; and (4) with comorbid malignancy. The sample size was estimated by using the formula for a single proportion with an estimated proportion of AKI in patients with decompensated cirrhosis, which was 0.191, as reported in a prior study [9], an assumed margin of error of 5%, and a confidence level of 95%, resulting in 237 patients. However, the reality sample size that we obtained was 250 decompensated cirrhotic patients.

2.2. Data Collection and Definitions

Data on eligible decompensated cirrhosis patients treated at the Department of Gastroenterology of Can Tho Central General Hospital between 2019 and 2020 were extracted from medical records. We obtained data according to the convenience sampling technique until 250 patients were reached. The clinical variables were in regard to age, sex, ethnicity, cirrhosis etiology, current complications of cirrhosis, classification of renal dysfunction at admission, infection within the first 48 h of hospitalization, and the regular use of propranolol [6,7]. Outcomes of the laboratory tests, including creatinine, sodium, albumin, international normalized ratio (INR), total bilirubin level, platelet count, and C-reactive protein (CRP), were collected on admission to hospital and 48 h postadmission.

According to the International Association of Ascites (ICA) in 2015, AKI was defined as an increase in serum creatinine $\geq$ 0.3 mg/dL ($\geq$ 26.5 µmol/L) for 48 h or if an increase in serum creatinine $\geq$ 50% over known or presumptive baseline serum creatinine occurred in the previous 7 days. Regarding the creatinine concentration in the serum, patients whose serum creatinine levels had been determined during the previous three months could be used as baseline serum creatinine. In contrast, these patients identified more than three months using the serum creatinine value closest to the time of admission. Moreover, admission serum creatinine was used as baseline creatinine in patients with no prior serum creatinine measurement [8]. Moreover, the AKI stages was defined as follows: stage 1, an increase in sCr $\geq$ 0.3 mg/dL ($\geq$26.5 µmol/L) or an increase in sCr $\geq$ 1.5-fold from baseline; stage 2, an increase in sCr > 2-fold to 3-fold from baseline; and stage 3, an increase in sCr > 3-fold from baseline, sCr $\geq$ 4.0 mg/dL (353.6 µmol/L) with an acute increase $\geq$ 0.3 mg/dL (26.5 µmol/L), or the initiation of renal replacement therapy [8].

2.3. Data Analysis

We used diagnostic criteria and the treatment of acute kidney injury and hepatorenal syndrome (HRS) using terlipressin in treatment, according to the guidelines of ICA 2015. The diagnostic criteria of AKI–HRS included the following: (1) diagnosis of cirrhosis with ascites; (2) diagnosis of AKI according to ICA-AKI criteria; (3) no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg body weight; (4) absence of shock; (5) no current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.); and (6) no macroscopic signs of structural kidney injury. Structural kidney injury is indicated by the absence of proteinuria (>500 mg/day), the absence of microhaematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography [8,10]. We also assessed the effects of several factors, such as Child–Pugh score, AKI, hepatic encephalopathy, gastrointestinal bleeding, ascites, infections, and laboratory outcomes related to cirrhosis (hyponatremia, increased total bilirubin, percentage of prothrombin < 70%, thrombocytopenia, and serum albumin) on the mortality prognosis of patients with decompensated cirrhosis.

2.4. Statistical Analysis

Collected data were statistically analyzed by using SPSS 18. Descriptive statistics related to frequencies and percentages in addition to quantitative analyses related to mean and standard deviation were included in this analysis. *t*-tests and analysis of variance (ANOVA) were statistical methods utilized to compare group means. Univariable and multivariable logistic regression analyses were also conducted to evaluate several factors regarding the prognosis of mortality in patients with decompensated cirrhosis. The variables determined to be significant ($p < 0.05$) in univariable regression analysis were used as independent variables for multivariable regression analyses.

3. Results

3.1. General Characteristics of Patients

There was a total of 250 patients with decompensated cirrhosis in this study: 167 males, accounting for 66.8% of the total, and 83 females, accounting for 33.2%. The average age was 61.1 ± 12.9 years old, the oldest was 95 years old, and the youngest was 20 years old. Decompensated cirrhosis caused by the hepatitis B virus accounted for the highest rate (37.6%), followed by alcohol (20%). There were 72.4% Child B patients, accounting for a significant proportion in this study, 27.6% Child C patients, and 64 (25.6%) AKI patients. The percentage mortality of the AKI patients in stage one was 20%, reaching 49.9% in stage two and 53.8% in stage three (Table 1).

Table 1. General characteristics of patients.

General Characteristics	Frequency	Percentage (%)
Average age	61.1 ± 12.9 years	
Gender		
Male	167	66.8
Female	83	33.2
Causes of cirrhosis		
Hepatitis B virus	94	37.6
Hepatitis C virus	42	16.8
Alcohol	50	20
Hepatitis B virus + alcohol	11	4.4
Hepatitis C virus + alcohol	1	0.4
Hepatitis B virus + hepatitis C virus	4	1.6

Table 1. *Cont.*

General Characteristics	Frequency	Percentage (%)
Other causes (primary biliary cholangitis, primary sclerosing cholangitis, alpha-1-antitrypsin deficiency, and Wilson's disease)	48	19.2
Child–Pugh Score		
Child–Pugh B	181	72.4
Child–Pugh C	69	27.6
Acute kidney injury		
Yes	64	25.6
No	186	74.4
Acute kidney injury stages		
AKI 1	20	31.3
AKI 2	31	48.4
AKI 3	13	20.3

3.2. Treatment Results for Acute Kidney Injury

The percentage of AKI mortality in decompensated cirrhosis patients reached 37.5%. AKI stage three had the highest mortality rate, with 53.8%, and stage one had the lowest mortality rate, of 20%. The median survival time of decompensated cirrhosis patients with AKI and those without AKI was 10.6 ± 0.7 days and 24 ± 0.5 days, respectively, with a $p < 0.0001$ statistically significant difference (Table 2). AKI significantly increased the mortality of decompensated cirrhosis patients up to 9.5 times, with $p < 0.0001$ (Figure 1).

Table 2. Results of treatment for acute kidney injury.

Results of Treatment	Frequency	Percentage (%)
Overall mortality	35	14
Mortality rate of acute kidney injury	24	37.5
Mortality rate of hepatorenal syndrome	16	84.2
Mortality rate by stage of acute kidney injury		
AKI 1	4	20
AKI 2	13	41.9
AKI 3	7	51.8
Average survival time		
AKI	10.6 ± 0.7 days	
Non-AKI	24 ± 0.5 days	
Mean MELD score (±SD)	21 ± 8.5 scores	

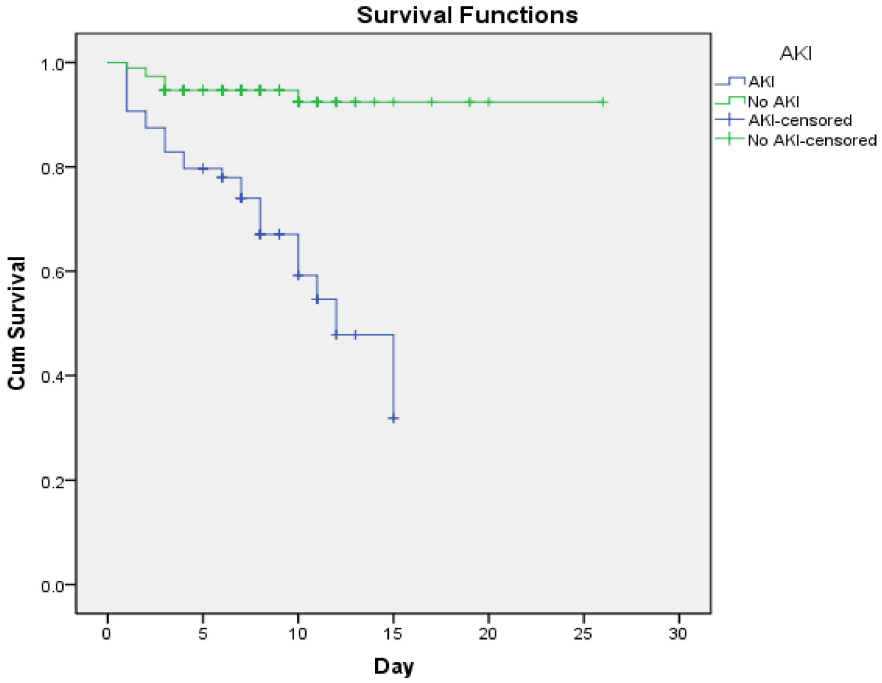

Figure 1. Survival time in hospital.

3.3. Factors Related to Mortality Prognosis in Patients with Decompensated Cirrhosis

Child C increased the rate of acute kidney injury by three times. There was a relationship between the Child–Pugh scale and AKI mortality prognosis in decompensated cirrhotic patients. We found that AKI significantly increased the mortality of decompensated cirrhosis patients up to 9.5 times compared with those without decompensated cirrhosis ($p < 0.0001$). Infectious diseases related to acute kidney injury increased mortality in patients with decompensated cirrhosis by 4.4 times, with $p < 0.0001$. Hyponatremia ($p = 0.01$; OR 2.5, 95% CI 1.2–5.1), increased total bilirubin ($p = 0.03$; OR 2.2, 95% CI 1.1–4.6), and prothrombin < 70% ($p = 0.03$; OR 6.8, 95% CI 1–51.6) were associated with an increase in mortality in patients with decompensated cirrhosis, with a statistically significant difference (Table 3). 95% CI

We included several factors regarding the mortality prognosis of decompensated cirrhosis patients in multivariable logistic regression analyses. We found that AKI, hepatic encephalopathy, and gastrointestinal bleeding were three independent factors associated with mortality in decompensated cirrhosis patients. Of the three factors, AKI was the most independent factor related to mortality in decompensated cirrhosis patients ($p < 0.0001$; OR = 7.7, 95% CI 2.9–20.1) (Table 3).

Table 3. Univariable and multivariable logistic regression analysis for factors related to mortality prognosis in patients with decompensated cirrhosis.

Factors	Dead	Survival	Univariable		Multivariable	
	n (%)	*n* (%)	OR (95% Confidence Interval)	*p*	OR (95% Confidence Interval)	*p*
Child–Pugh						
Child C	17 (25)	51 (75)	3 (1.5–6.3)	0.02	0.8 (0.3–2.4)	0.7
Child B	18 (9.9)	164 (90.1)				

Table 3. *Cont.*

Factors	Dead	Survival	Univariable		Multivariable	
	n (%)	*n* (%)	OR (95% Confidence Interval)	*p*	OR (95% Confidence Interval)	*p*
Acute kidney injury						
Yes	24 (37.5)	40 (62.5)	9.5 (4.3–21.1)	<0.0001	7.7 (2.9–20.1)	< 0.0001
No	11 (5.9)	175 (94.1)				
Hepatic encephalopathy						
Yes	16 (30.8)	36 (69.2)	4.2 (1.9–8.9)	<0.0001	4 (1.5–10.4)	0.005
No	19 (9.6)	179 (90.4)				
Gastrointestinal bleeding						
Yes	14 (22.6)	48 (77.4)	2.3 (1.1–4.9)	0.03	5 (1.8–13.5)	0.002
No	21 (11.2)	167 (88.8)				
Ascites						
Yes	33 (15)	187 (85)	2.5 (0.6–10.9)	0.2	-	-
No	2 (6.7)	28 (93.3)				
Infections						
Yes	18 (30)	42 (70)	4.4 (2.1–9.2)	<0.0001	2.4 (0.9–6.0)	0.07
No	17 (8.9)	173 (91.1)				
Hyponatremia						
Yes	20 (21.1)	75 (78.9)	2.5 (1.2–5.1)	0.01	2.3 (0.9–5.9)	0.09
No	15 (9.7)	140 (90.3)				
Increased total bilirubin						
Yes	22 (19.1)	93 (80.9)	2.2 (1.1–4.6)	0.03	1.2 (0.4–3.2)	0.7
No	13 (9.6)	122 (90.4)				
Prothrombin < 70%						
Yes	34 (16)	179 (84)	6.8 (1–51.6)	0.03	0.9 (0.9–3.3)	0.06
No	1 (2.7)	36 (97.3)				
Thrombocytopenia						
Yes	25 (13.7)	157 (86.3)	0.8 (0.4–2.0)	0.9	-	-
No	10 (14.7)	58 (85.3)				
Serum albumin						
<30 g/L	28 (14.4)	167 (85.6)	1.2 (0.5–2.7)	0.8	-	-
<30 g/L	7 (12.7)	48 (87.3)				

4. Discussion

In our study, decompensated cirrhosis caused by the hepatitis B virus accounted for the highest rate (37.6%), followed by alcohol (20%), nonalcoholic fatty liver disease (10%), autoimmune liver disease (3.2%), hemochromatosis (1.6%), and other liver diseases (4.4%), including primary biliary cholangitis, primary sclerosing cholangitis, alpha-1-antitrypsin deficiency, and Wilson's disease. In comparison to other research in the world, such as Yuna Kim's study in 2019 in Korea or Bansho's study in 2018 in Brazil, the leading causes of cirrhosis were alcohol consumption (36.1%) and the hepatitis C virus (HCV) (15.9%) [11,12]. In recent years, cirrhosis was primarily caused by the hepatitis B virus in Asian countries in general, especially in Vietnam. A gradual increase in the prevalence of alcoholic and nonalcoholic fatty liver disease was also witnessed in these countries. In contrast, the epidemiology of cirrhosis has changed in developed countries, reflecting the implementation of hepatitis B vaccination and hepatitis C treatment programs on a large scale.

Our study confirmed that decompensated cirrhosis patients with AKI had a mortality rate of 37.5%. This figure reached 26% in Belcher's study in 2013 and 28.4% in Gessolo's study in 2018 [6,13]. The mortality of AKI in decompensated cirrhosis patients on admission discovered in Shetty's (2018) and Gomes's (2019) studies was 44.7% and 28.6%, respectively [6,14]. A number of factors, be it the severity of underlying decompensated cirrhosis, background diseases, and the healthcare systems in different countries, result in the difference in AKI mortality rates in patients with decompensated cirrhosis between studies. Despite this, it is generally agreed that AKI was a common complication and was present in a rather high rate of patients with decompensated cirrhosis. The more severe the stage of AKI, the higher the mortality rate; in particular, the percentage of mortality in patients with AKI with stage one was 20%, reaching 49.9% with stage two and 53.8% with stage three, as reported in our study. According to research by Vo Thi My Dung in Vietnam, the hospital mortality rate increased significantly in the AKI group from stage one to stage three, by 3.8%, 21.2%, and 39.4%, respectively [9]. This trend could also be observed in a series of recent studies worldwide.

Kaplan–Meier analysis was used to evaluate the difference in survival; the mean survival time of decompensated cirrhosis patients with AKI and without AKI was 10.6 ± 0.7 days and 24 ± 0.4 days, respectively, with a logrank test with $\chi^2 = 33.6$ and $p < 0.0001$. Thus, there was a statistically significant difference in mean hospital survival in patients with AKI and without AKI. We concluded that the death of decompensated cirrhosis patients with AKI accounted for a significantly high proportion.

The findings of this study showed a relationship between the Child–Pugh score and the prognosis of death from AKI in decompensated cirrhosis patients, of which Child–Pugh C patients had a three-fold increase in mortality rate from AKI, with $p = 0.02$. The study by Vicco in 2015 was conducted on patients with decompensated cirrhosis and showed that Child–Pugh C cirrhosis patients had a higher mortality rate, accounting for 75.2% [15]. AKI was a common complication predictor of mortality in decompensated cirrhosis patients. This study demonstrated that AKI significantly increased the mortality of decompensated cirrhosis patients up to 9.5 times compared with those without decompensated cirrhosis ($p < 0.0001$). Therefore, AKI could also be considered to be a factor that predicts the death rate for cirrhotic patients.

Patients with decompensated cirrhosis often had complex complications that affected their quality of life and increased their risk of death. It was clear that there was an association between hepatic encephalopathy and gastrointestinal bleeding, with a significant increase in mortality rate in patients with decompensated cirrhosis. In contrast, ascites was not discovered in a similar manner in this study. Bjerring's study, performed on 84,947 cirrhotic patients with hepatic encephalopathy, found that the mortality rate in patients with hepatic encephalopathy was 24%, compared with patients without hepatic encephalopathy of 4% ($p < 0.0001$) [16]. Furthermore, 19.87% of patients with decompensated cirrhosis died and had the comorbidity of gastrointestinal bleeding in the research of Kumar [17]. In summary, hepatic encephalopathy and gastrointestinal bleeding were associated with mortality in patients with decompensated cirrhosis. Patients with decompensated cirrhosis had concomitant infections, including primary peritonitis, pneumonia, urinary tract infections, and sepsis, which significantly increased mortality. If infectious diseases were effectively uncontrolled, patients were subjected to more severe kidney failure; in addition, the prescription of antibiotics in patients with severe infections, such as sepsis, accelerated the risk of affecting kidney function. In our study, infection was related to an increased mortality of AKI in decompensated cirrhosis patients by 4.4 times, with $p < 0.0001$. Additionally, several recent studies have found that AKI patients with sepsis had the highest mortality rate on admission, accounting for 35.4–74% [17,18]. Although the death rate in our study was relatively distinct from others, infectious diseases, in general, had a significant impact on the number of patients with decompensated cirrhosis who died.

Other factors, such as hyponatremia, increased total bilirubin, and prothrombin < 70%, substantially expanded the mortality percentage in patients with decompensated cirrho-

sis. According to Vicco's study, serum prothrombin was linearly related to mortality in patients with decompensated cirrhosis (p = 2.0; OR 2.0, 95% CI 1.03–2.31); in particular, every day that 1 g/dL decreased in serum albumin was reported to increase mortality by 137% [15]. There was also an association between high serum bilirubin and mortality rate in decompensated cirrhosis patients in Kumar's study in 2015 [17]. However, in our study thrombocytopenia and hypoalbuminemia were considered unrelated to mortality, possibly since modern-day clinicians have been more interested in serum albumin compensation in decompensated cirrhosis patients, especially those patients with cirrhosis ascites or hepatic encephalopathy.

Using multivariable logistic regression analysis, we found that AKI, hepatic encephalopathy, and gastrointestinal bleeding were three independent factors associated with mortality in patients with decompensated cirrhosis. Of the three factors, AKI was the most independent factor associated with mortality in patients with decompensated cirrhosis ($p < 0.0001$; OR 7.7, 95% CI 2.9–20.1). There were interstudy differences in mortality predictors, possibly due to different study ages, underlying medical conditions, and disease severity.

There are currently few studies on AKI in patients with decompensated cirrhosis in Vietnam, so our study was conducted to provide more data on the rate of acute kidney injury in these patients. Additionally, this study analyzed multivariate logistic regression and found a relationship between acute kidney injury, gastrointestinal bleeding, and hepatic encephalopathy with the death of patients with decompensated cirrhosis.

The limitation of our study is that we only monitored and evaluated patients during hospitalization but did not assess the impact of acute kidney injury on mortality in patients with decompensated cirrhosis after being discharged from hospital. Based on the above limitations, we suggest that future studies could accurately examine the important role of acute kidney injury in predicting mortality in discharged patients after 1 month as well as after 3 months.

5. Conclusions

Acute kidney injury is a common complication associated with mortality in patients with decompensated cirrhosis. Currently, under the difficulty of the healthcare system in Vietnam, the early detection of the complications of diseases (acute kidney injury, gastrointestinal bleeding, and hepatic encephalopathy) in addition to timely treatment not only help to improve quality of life and enhance survival ability but also reduce the burden on the healthcare system.

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