

Outcomes of cirrhotic patients admitted to the intensive care unit after a successful cardiac arrest resuscitation

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ABSTRACT

الأهداف: لتقييم نتائج مرضى التليف الكبدي الذين ادخلوا إلى وحدة العناية المركزة (ICU) بعد السكتة القلبية.

المنهجية: أجريت هذه الدراسة الاسترجاعية في مركز واحد على جميع مرضى التليف الكبدي، الذين تم قبولهم في وحدة العناية المركزة، مدينة الملك عبد العزيز الطبية، الرياض، المملكة العربية السعودية، بعد إجراء إنعاش القلب الناجح، خلال الفترة من عام 1999 إلى عام 2017م. قمنا بمقارنة خصائص الناجين وغير الناجين من المستشفى.

النتائج: ادخلنا 76 مريضاً إلى وحدة العناية المركزة خلال فترة الدراسة، بمتوسط عمر 64 عاماً. بالإضافة إلى تليف الكبد، كان لدى المرضى أمراض مزمنة أخرى مصاحبة، بما في ذلك أمراض الكلية المزمنة (32.9%)، السكري (47%) وأمراض مصاحبة أخرى (46%). من هذه المجموعة، توفي 67 في المستشفى، وتوفي 54 (71%) أثناء وجودهم في وحدة العناية المركزة ICU والمقارنة بالمجموعة التي نجت، احتاج غير الناجين إلى تهوية ميكانيكية (p=0.771)، وكان متوسط درجة APACHE II أعلى من 38 (p=0.006)، ومتوسط مقاييس غالاسكو للغيبوبة (GCS) أقل من 3 (p=0.032)، ومتوسط حمض اللاكتيك أعلى من 6.4 (p=0.0003). من خلال التحليل متعدد المتغيرات، كانت المؤشرات المهمة لوفيات المستشفى في مرضى التليف الكبدي الذين تم إدخالهم إلى وحدة العناية المركزة، بعد الإنعاش الناجح للسكتة القلبية هي APACHE II القيمة الإحصائية (p=0.006) ومستوى البيليروبين (p=0.008).

الخلاصة: اظهرت الدراسة أن مرضى التليف الكبدي الذين ادخلوا إلى وحدة العناية المركزة بعد توقف القلب لديهم معدل وفيات مرتفعه. كما أن المرضى الذين لديهم ارتفاع درجات APACHE II، وارتفاع مستوى البيليروبين وانخفاض GCS لديهم مخاطر أعلى لوفيات داخل المستشفى.

Objectives: To evaluate the outcomes of cirrhotic patients admitted to the intensive care unit (ICU) following cardiac arrest.

Methods: This was a single centre retrospective study of all the cirrhotic patients, admitted to the ICU at King Abdulaziz Medical City, Riyadh, Saudi Arabia, after a successful cardiac arrest resuscitation, from 1999 to 2017. The characteristics of the hospital survivors and non-survivors were compared.

Results: A total of 76 patients were admitted to the ICU during the study period, with a median age of

64 years. In addition to cirrhosis, the patients had other chronic comorbidities, including chronic renal disease (32.9%) and diabetes (47%). Of this group, 67 (88.2%) died in the hospital, and 54 (71%) died while in ICU. Compared to the group who survived, all non-survivors required mechanical ventilation and had a higher median APACHE II score of 38 ($p=0.006$), a lower median Glasgow coma score (GCS) of 3 ($p=0.0003$), and a higher median lactic acid of 6.4 mmol/L ($p=0.032$). On multivariable logistic regression analysis, the important predictors of hospital mortality were APACHE II score ($p=0.006$), bilirubin level ($p=0.008$) and GCS ($p=0.005$).

Conclusion: Cirrhotic patients admitted to the ICU following cardiac arrest have high mortality. Patients with higher APACHE II scores, higher bilirubin and lower GCS have higher risk of in-hospital mortality.

Keywords: cirrhosis, ICU, outcome, cardiac arrest, successful resuscitation

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Chronic liver disease is prevalent globally. Cirrhosis is its last stage in which patients present with a diversity of clinical manifestations, presentations, and complications. The World Health Organization (WHO) reported that 46% of the diseases globally, and 59% of the global mortality is due to chronic diseases, equating to 35 million deaths.¹ Of the chronic diseases, chronic liver disease constitutes a large proportion, which increases annually. The United Kingdom's National Statistics reported that liver disease is the fifth most prevalent cause of mortality.² In the United States (US), liver diseases was ranked second in the leading causes of fatalities due to gastrointestinal disorders.³ As stated by the WHO in 2018, liver disease in Saudi Arabia was responsible for 3.08% of the total mortality.⁴ The age-adjusted mortality rate per 100,000 was 20.24 in Saudi Arabia, ranking 71 globally.⁴

The number of patients with liver cirrhosis requiring hospital admission is increasing.^{5,6} Admission is due to various medical complications, in addition to the chronic liver disease, causing high rates of morbidity and mortality.^{7,8} Cardiac arrest (CA) is a catastrophic complication in patients with cirrhosis, which frequently requires admission to ICU.⁹ An estimated 375,000-700,000 patients have CA in Europe and USA annually and receive resuscitation (CPR).^{10,11} Despite the advancements in critical and emergency care, the rates of survival after CA, remain very low, ranging from 14%-23% for in-hospital and 8%-16% for out of hospital CA.¹²⁻¹⁵

Literature related to the outcome of patients with liver cirrhosis, with a successful resuscitation after CA, is limited. Roedl et al⁹ investigated the outcome of in- and out-of-hospital CA survivors with liver cirrhosis. The patients with cirrhosis who survived CA had worse outcome compared to the group without cirrhosis.⁹ Although almost 20% of the cirrhotic patients survived more than 28 days after the successful CPR, the patients with Child-Turcotte-Pugh C and advanced acute-on-chronic liver failure did not survive 28 days with good neurological outcome.⁹ The objective of this study was to examine the hospital mortality and other clinical outcomes of cirrhotic patients admitted to the ICU after a successful CA resuscitation.

Methods. This was a retrospective study of all the consecutive cirrhotic patients admitted to the ICU at King Abdulaziz Medical City, Riyadh, Saudi Arabia, from 1999-2017 after a successful CA resuscitation. We excluded patients transferred from other hospitals. For patients admitted to the ICU more than once within the same hospitalization, we included the first admission only. The study protocol was approved by the Institutional Review Board, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia (IRBC/1816/20).

Data were extracted from the ICU database, which has been maintained prospectively from 1999 to 2017. The data included variables collected at baseline and follow-up. The baseline variables included age, gender, chronic diseases as defined by the Acute Physiology And Chronic Health Evaluation II (APACHE II system),¹⁶ mechanical ventilation, vasopressor therapy, bilirubin, Glasgow coma scale (GCS), creatinine, lactic acid, international normalized ratio (INR), and ratio of arterial oxygen partial pressure to fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$ ratio). The primary outcome was hospital mortality, and the secondary outcomes were ICU mortality, ICU and hospital lengths of stay, tracheostomy, and mechanical ventilation duration.

Statistical analysis. The data were analyzed using Statistical Analysis System (SAS), version 9.0 (SAS Institute, CARY, NC, USA). Continuous variables were presented as medians and interquartile ranges and categorical variables as frequencies and percentages. All variables at baseline and follow-up were compared between the group who died or survived at hospital discharge. Categorical variables were compared using Fisher's exact test and continuous variables with Mann-Whitney test. To determine the predictors of hospital mortality for the cirrhotic patients admitted with CA, a multivariable logistic regression analysis was performed adjusting for the following variables, selected on the basis of statistical as well as their clinical significance: age, APACHE II, bilirubin, INR, chronic cardiac disease, vasopressor therapy, mechanical ventilation, lactic acid and $\text{PaO}_2/\text{FiO}_2$ ratio. The results are reported as odds ratios (OR) and 95% confidence intervals (CI). A p -value of <0.05 was considered statistically significant.

Results. A total of 76 cirrhotic patients were admitted to the ICU after a successful CA resuscitation from 1999 to 2017. Of the 76 patients, 67 patients died in hospital (88.2%) and only 9 survived (11.8%). The median age was 64 years (Q1, Q3: 57, 73) and 59% were males. In addition to cirrhosis, patients had other chronic comorbidities, including chronic renal

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disease (32.9%), chronic cardiac disease (22.4%), diabetes (47%), chronic respiratory disease (15%), and immunocompromised state (9%). Forty-seven patients (62%) were receiving vasopressors and 73 (96%) were mechanically ventilated on admission. The median APACHE II score was 37 (Q1 [quartile 1], Q3 28.5, 42.0), bilirubin was 63 µmol/L (Q1, Q3: 21, 162), GCS score was 3 (Q1, Q3: 3, 8), creatinine was 195.5 µmol/L (Q1, Q3: 131, 271), lactic acid was 5.8 mmol/L (Q1, Q3: 2.9, 10.1), INR was 1.7 (Q1, Q3: 1.4, 2.7), and the PaO₂/FiO₂ ratio was 155 (Q1, Q3: 79, 237) (**Table 1**).

Compared to the group who survived, the group who died in hospital was more likely to have required mechanical ventilation ($p=0.003$) and had a higher median APACHE II score of 38 (Q1, Q3: 30, 43, $p=0.006$), a lower median GCS of 3 (Q1, Q3: 3, 7) ($p<0.0003$), and a higher median lactic acid of 6.4 mmol/L (Q1, Q3: 3.7, 11.5, $p=0.032$) (**Table 1**).

Secondary outcomes. Of the cohort, 54 (71%) died while in ICU. The median ICU length of stay was 2.2 days (Q1, Q3: 0.5, 9.3), the hospital length of stay was 10 days (Q1, Q3: 4, 30), and the median mechanical

ventilation duration was 3 days (Q1, Q3: 1, 10). A minority (13%) had a tracheostomy. There were no significant differences in the duration of mechanical ventilation and the length of stay in the ICU and hospital between hospital survivors and nonsurvivors (**Table 2**).

Table 2 - Outcomes of cirrhotic patients admitted to the ICU after successful cardiac arrest resuscitation between non-survivors and survivors.

Variable	All n=76	Died n=67	Survived n=9	P-value
ICU LOS (days), median (Q1, Q3)	2.2 (0.5, 9.3)	1.8 (0.5, 9.2)	3.5 (2.5, 14.3)	0.181
Hospital LOS (days), median (Q1, Q3)	10 (4, 30)	13 (3, 26)	64 (7, 380)	0.136
Mechanical ventilation duration (days), median (Q1, Q3)	3 (1, 10)	3 (1, 9)	2 (0, 17)	0.771
Tracheostomy, n (%)	10 (13)	7 (11)	3 (33)	0.057

The denominator is the total number of subjects in the group. For continuous variables, Mann-Whitney test is used to calculate the p -value. For categorical variables, Fisher's exact test is used to calculate the p -value
ICU: intensive care unit, LOS: length of stay, Q: quartile

Table 1 - Comparison of baseline characteristics of cirrhotic patients admitted to the ICU after successful cardiac arrest resuscitation between non-survivors and survivors.

Variable	All n=76	Died n=67	Survived n=9	P-value
Age (yrs), median (Q1, Q3)	64 (57, 73)	64 (54, 73)	67 (59, 72)	0.625
Male gender, n (%)	45 (59)	39 (58)	6 (67)	0.628
Diabetes, n (%)	36 (47)	32 (48)	4 (44)	0.852
<i>Other chronic Diseases, n (%)</i>				
Chronic respiratory	11(15)	8 (12)	3 (33)	0.087
Chronic renal	25 (32.9)	23 (34.3)	2 (22)	0.468
Immunocompromised	7 (9)	5 (8)	2 (22)	0.151
Chronic cardiac	17 (22.4)	12 (17.9)	5 (55.56)	0.007
GCS on ICU admission, median (Q1, Q3)	3 (3, 8)	3 (3, 7)	10 (9, 15)	0.0003
Mechanical ventilation, n (%)	73 (96)	67 (100)	6 (66.7)	0.003
Vasopressors, n (%)	47 (62)	42 (63)	5 (56)	0.679
APACHE II, median (Q1, Q3)	37 (28.5, 42)	38 (30, 43)	24 (15, 29)	0.006
<i>Laboratory findings in the first 24 hours</i>				
Bilirubin (µmol/L), median (Q1, Q3)	63 (21, 162)	65 (29, 191)	17.5 (10.5, 26.5)	0.008
Creatinine (µmol/L), median (Q1, Q3)	195.5 (131, 271)	199 (141, 283)	167 (74, 215)	0.150
Lactic acid mmol/L, median (Q1, Q3)	5.8 (2.9, 10.1)	6.4 (3.7, 11.5)	2.9 (2, 4.7)	0.032
INR, median (Q1, Q3)	1.7 (1.4, 2.7)	1.75 (1.40, 2.70)	1.5 (1.3, 2.2)	0.715
PaO ₂ /FiO ₂ ratio, median (Q1, Q3)	155 (79, 237)	150 (74, 230)	214 (128, 238)	0.425

For categorical variables, Fisher's exact test is used to calculate the p -value. For continuous variables, Mann-Whitney test is used to calculate the p -value. For all percentages, the denominator is the total number of subjects in the group.

APACHEII: Acute Physiology And Chronic Health Evaluation II, GCS: Glasgow coma score, INR: internal normalized ratio, PaO₂/FiO₂ ratio: the ratio of the partial pressure of oxygen to the fraction of inspired oxygen, Q1: first quartile, Q3: third quartile

Table 3 - Logistic regression analysis to identify independent predictors of in-hospital mortality among cirrhotic patients admitted to the intensive care unit after successful cardiac arrest resuscitation.

Variables	OR	95% CI	P-value
Age (per 1-year increase)	0.99	0.93-1.06	0.830
APACHE II (per 1-unit increase)	1.21	1.06-1.38	0.005
Bilirubin (per 1-unit increase)	1.04	1.01-1.07	0.022
Vasopressor	13.69	0.62-301.91	0.097
GCS	0.66	0.50-0.88	0.005

GSC: Glasgow coma scale, OR: odds ratio, CI: confidence interval

Multivariate analysis to determine the predictors of hospital mortality. The multivariable logistic regression analysis demonstrated that the important predictors of hospital mortality for the cirrhotic patients admitted to the ICU after a successful CA resuscitation were APACHE II score (OR 1.21, 95% CI 1.06 to 1.38, $p=0.005$), the level of bilirubin (OR 1.02, 95% CI 1.00 to 1.05, $p=0.02$) and GCS (OR 0.66, 95% CI 0.50 to 0.88, $p=0.005$) (Table 3).

Discussion. In this study, we analyzed 76 cirrhotic patients admitted to ICU following a successful CA resuscitation. We found that these patients had high mortality. Patients with higher APACHE II scores, higher bilirubin and lower GCS had higher risk of in-hospital mortality.

The prevalence of cirrhosis in the ICU ranges from 4% to 7% of critically ill patients.^{17,18} We report a hospital mortality of 88.2% for patients with cirrhosis who had a CA. Another study reported a similar mortality rate of 79% in cirrhotic patients, compared to 50% in non-cirrhotic patients, admitted to ICU after CA.⁹ In addition, they reported that the group with liver cirrhosis who survived had poor neurological outcomes. This high mortality rate could be explained by high rates of non-cardiac causes of CA, the prevalent comorbidities and high rate of non-shockable rhythms in the group with cirrhosis. There is a slight difference in the mortality rates between the current study and that of Roedl et al⁹. The factors that may have resulted in this difference include risk factors of liver cirrhosis in Saudi Arabia. Most of the patients with liver cirrhosis in Saudi Arabia are due to a complication of hepatitis C and hepatitis B, which have poorer prognosis.¹⁹ In contrast, alcoholic liver disease is more common than viral hepatitis as a cause of liver cirrhosis in Western countries, which have a relatively better prognosis compared to viral hepatitis.²⁰ Cirrhotic patients with

cardiac diseases can be successfully resuscitated after CA, however, they have a significant decrease in the functional outcome and a significant chance of dying after the resuscitation. The current study and literature support this statement.^{7,21} The high APACHE II scores indicate severe liver disease; hence, the significant association with an increased mortality rate. The median score for the group with the worst outcome was 38, compared to 24 in the group who survived. Several studies reported a similar negative outcome for patients with severe liver disease, indicated in the current study by the high APACHE II scores.^{7,22} Roedl et al⁹ described several possible predictors, including witnessing of the CA and the period of ischemia. They attributed the worse outcomes following CA to the severity of the liver disease. Literature highlights post-CA syndrome, in which an exacerbation of liver disease is expected, and as a consequence, an increased mortality rate.^{22,23}

Our study indicated that the use of mechanical ventilation, low GCS score and high levels of lactic acid were associated with increased mortality. Of the 73 patients who were mechanically ventilated, 67 died and 6 survived. The group with worse outcomes had a median GCS of 3, compared to the group who survived with a median of 10. Similarly, patients with higher lactate levels had worse outcomes (median lactate of those who died was 6.4 mmol/L compared to 2.9 mmol/l for the group who survived).

Study limitations. Although the sample size of the current study was 76, which is relatively high, a larger sample size will result in more precise data and better interpretation of findings. Prospective multicentric studies and data containing more details and clinical scores such as the Child-Pugh score are required.

In conclusion, cirrhotic patients with CA have poor outcomes. Patients with higher APACHE II scores, higher bilirubin and lower GCS have higher risk of in-hospital mortality.

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