The Egyptian Journal of Hospital Medicine (October 2023) Vol. 93, Page 7207- 7210

Serum Lactate can predict Short-Term Outcome of Critically-Ill Patient with Liver Cirrhosis admitted to Medical Intensive Care Unit

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ABSTRACT

Background: Serum lactate level can be used as an important predictor of short-outcomes in critically ill patients with complicated liver cirrhosis.

Objective: To improve risk prediction and better assessment of short-term outcomes of ill critically cirrhotic, through assessment of serum lactate level on ICU admission and after 24 hours.

Patients and methods: This observational descriptive cohort study included 151 critically ill patients with decompensated liver cirrhosis who were admitted into ICU of Zagazig University Hospitals.

Results: Causes of admission to ICU included hepatic encephalopathy (34.4% of cases), bleeding esophageal varices (33.8%), hepatorenal syndrome (23.2%), SBP (7.3%) and hepatopulmonary syndrome (1.3%). Serum lactate levels were 14.5 ± 8.6 and 14.2 ± 9 mmol/L on admission and 24 h after admission to ICU, respectively. These figures are much higher than figures in a healthy population and in patients with compensated cirrhosis. Serial measurement of serum lactate showed a tendency toward elevation in 43.7% of patients, and a drop in 50.3%, 24 h after admission, with the remaining 6% of cases being unchanged. ICU mortality was encountered in 33.8% of patients.

Conclusion: In critically-ill patients with liver cirrhosis, lactate levels were independently related with short-term mortality and indicate the severity of the illness and organ failure. Measures that decrease serum lactate toward normal as early as possible may help improve the chances of survival of these patients in the ICU.

Keywords: Liver cirrhosis, ICU, Serum lactate, Short-term outcome.

INTRODUCTION

Lactate level is known as an important predictor of outcome in critically ill patient in the medical intensive care unit (MICU) [(1)]. It is essential to determine the prognosis in patients with cirrhosis in the MICU in order to direct treatment measures [(2, 3)]. Normally, glucose is fully oxidized in the cell mitochondria to produce efficient energy [adenosine triphosphate (ATP)] under stress condition, glucose is converted into lactate intracellularly that is secreted as lactic acid resulting in metabolic acidosis [(4)]. Under normal conditions, lactate is cleared rapidly by the liver, with a small amount by the kidney [(5)]. The liver is the organ primarily clear the body from lactate, so lactate clearance may be impaired in the presence of severe liver dysfunction [(6)]. Acute decompensation with increasing organ failure is common in patients with liver cirrhosis. Therefore, they must be hospitalised to the MICU [(7)]. Due to organ failure, acute on-chronic liver failure brought on by abrupt decompensation of cirrhosis has a significant mortality rate [(8)]. The death rates for cirrhotic patients receiving care in the MICU vary from 40 to 60% [(7, 9)].

Therefore, this study aimed to determine the impact of elevated serum lactate level on complicated liver cirrhosis outcome. Also, to evaluate the demographic, clinical and biochemical variable in complicated liver cirrhosis.

PATIENTS AND METHODS

This was a prospective cohort study that included critically-ill patients with decompensated liver cirrhosis admitted to the medical intensive care unit (MICU) of Zagazig University Hospitals.

Inclusion criteria:

Patients with decompensated liver cirrhosis were admitted to MICU in the period from January to December 2020 with complications of hepatic encephalopathy, bleeding varices, spontaneous bacterial peritonitis, hepatorenal syndrome, and other decompensated liver-related complications. Age ≥18 years old and both sexes were included.

Exclusion criteria: Patients with incomplete data during follow-up while in ICU, age below 18 years old and patients' relative refusal to participate.

Methods:

Two hundred thirteen admissions were screened during the study period. Only 151 patients were available for valid analysis. The remaining patients (62) were excluded because of incomplete data and/or loss of follow-up.

All participants were submitted to the following:

I. **Thorough history taking:** Personal history, presentation problem, past history of the disease, drugs, operation, and present history of current symptomatology as fever, shortness of breath, vomiting, diarrhea, abdominal pain, melena, hematemesis, bleeding tendency, anorexia, oliguria, abdominal distension and altered conscious level.

II. **Full clinical examination including:**

A. **General examination:** Signs of decompensated liver cirrhosis including jaundice, pallor, lower limb edema, ascites, gynecomastia, palmar erythema, spider nevi, leukonychia, parotid

Received: 04/01/2023
Accepted: 03/03/2023

enlargement, and conscious level using Glasgow Coma scale (GCS).

B. Abdominal assessment: Including hepatomegaly, ascites, and splenomegaly. Other recorded complications as variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, infection, hepatorenal, hepatopulmonary syndromes, HCC, hydrothorax, and spontaneous bacterial peritonitis.

III. Investigations:

A. Routine laboratory investigations including: Complete blood count. Kidney function tests (Serum creatinine and blood urea). Liver function tests: serum total proteins, serum albumin, total and direct bilirubin, and liver enzymes (e.g., ALT, AST). Arterial blood gases, serum electrolytes (Na^+ & K^+) and random blood sugar. Coagulation profile (PT & INR. Radiological investigations as necessary. GIT endoscopy, echocardiography and urine analysis when indicated.

B. Special investigations: Including measurement of serum lactate level on admission to ICU and after 24 h of admission to ICU.

Ethical approval: Zagazig Medical Ethics Committee of the Zagazig Faculty of Medicine gave its approval to this study. All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

All data were analyzed using IBM SPSS version 25 for Windows. Continuous variables were expressed as mean ± SD or as median and IQR, while the categorical variables were expressed as a number (percentage). All normally distributed variables were analyzed using the independent student *t*-test. While nonparametric continuous variables were analyzed by the Mann-Whitney *U* test. The percentage of categorical variables was compared using Pearson's chi-square test. Multivariate adjusted logistic regression analyses were performed to identify baseline factors associated with ICU mortality. P value ≤ 0.05 was considered significant.

RESULTS

The present study showed that the mean age was distributed as 57.4 ± 14.3 years, the majority were males (54.7%) and 39.1% were smokers. GCS was distributed as 10.2 ± 3.37, APACHE-II was 23.7 ± 7.37. Meld score was distributed as 26 ± 7.2, Meld Na score was 28.3 ± 6.3, Meld lactate score was 29.4 ± 6.6 and CTP was 10.3 ± 1.6. Child score class B with 35.1% and class C with 64.9% (Table 1). The baseline biochemical data of study population was illustrated in table (2).

Table (1): Baseline demographic and clinical characteristics of the study population (n=151)

Age (years):	
Mean ± SD	**57.4 ± 14.3**
Median (IQR)	**60 (16)**
Gender:	
Male: n (%)	**82 (54.3%)**
Female: n (%)	**69 (45.7%)**
Smoking: n (%)	**63 (41.7%)**
Hypertension: n (%)	**57 (37.7%)**
DM: n (%)	**74 (49%)**
IHD: n (%)	**26 (17.2%)**
Child Class:	
B: n (%)	**53 (35.1%)**
C: n (%)	**98 (64.9%)**
CTP	
Mean ± SD	**10.3 ± 1.6**
Median (IQR)	**10 (2)**
GCS	
Mean ± SD	**10.2 ± 0.3**
Median (IQR)	**10 (6)**
APACHE II	
Mean ± SD	**23.7 ± 7.38**
Median (IQR)	**23 (11)**
MELD	
Mean ± SD	**26 ± 7.2**
Median (IQR)	**25 (11)**
MELD Na	
Mean ± SD	**28.3 ± 6.3**
Median (IQR)	**29 (9)**
MELD-Lactate	
Mean ± SD	**29.4 ± 6.6**
Median (IQR)	**29 (9)**

Table (2): Baseline biochemical data of study population (n=151)

Variable	Mean ± SD
Hb (g/dl)	**8.1 ± 1.4**
Plt (× 10^3/mm^3)	**106.295 ± 25.826**
TLC (× 10^3/mm^3)	**13.067 ± 3.2**
Serum albumin (g/dl)	**2.34 ± 0.36**
Total bilirubin (mg/dl)	**7.4 ± 1.7**
INR	**1.9 ± 0.38**
Serum creatinine (mg/dl)	**3.1 ± 0.71**
Blood urea (mg/dl)	**111 ± 26.7**
Serum Na (mEq/L)	**136.5 ± 9.9**

Causes of admission to ICU included hepatic encephalopathy (34.4% of cases), bleeding esophageal varices (33.8%), hepatorenal syndrome (23.2%), SBP (7.3%) and hepatopulmonary syndrome (1.3%) (Table 3).

Table (3): Causes of admission to the medical intensive care unit.

Preliminary diagnosis	n (%)
Bleeding esophageal varices (BEV)	**51 (33.8)**
Hepatic encephalopathy (HE)	**52 (34.4)**
Spontaneous bacterial peritonitis (SBP)	**11 (7.3)**
Hepatorenal syndrome (HRS)	**35 (23.2)**
Hepatopulmonary syndrome (HPS)	**2 (1.3)**

Serum lactate on admission was distributed as 14.5 ± 8.6 with a median of 11.4 and serum lactate after 24 h after admission 14.2 ± 9 with a median of 12.9. Also, serum lactate increased in 66 patients (43.7%), decreased in 76 patients (50.3 %), and had no change in 9 patients (6%) (Table 4).

Table (4): Serum lactate level (mmol/L) of the Study population (n=151)

Variable	Mean ± SD	
Serum Lactate on admission (mmol/L)	**14.5 ± 3.51**	
Serum Lactate 24h after admission (mmol/L)	**14.2 ± 3.42**	
Serial Lactate change status	**n**	**%**
- **Increasing**	**66**	**43.7**
- **Decreasing**	**76**	**50.3**
- **No change**	**9**	**6**

ICU outcome of the study population showed that ICU stay (days) was distributed as 10.5 ± 6.3 with a median of 8 days and a mortality rate of 33.8 % (Table 5).

Table (5): ICU outcome of the study population (n=151)

ICU Stay (days)	Mean ± SD	Median (IQR)
	10.5 ± 6.3	**8 (11)**
ICU Mortality	**n**	**%**
	51	**33.8**

DISCUSSION

Serum lactate level can improve the prediction of outcomes of critically-ill patients in the ICU [(1)]. A study found that high serum lactate level is associated with higher hospital mortality and longer hospital stay more than patients with normal lactate levels [(2)]. Normally, glucose is oxidized in mitochondria into adenosine triphosphate (ATP) producing energy. Glucose is converted into lactate under stress conditions intracellularly to generate energy [(4)].

The normal liver primarily clears the lactate rapidly. So, liver cirrhosis impairs this function resulting in hyperlactatemia. So, acute decompensation on top of chronic liver impairment results in high serum lactate levels. But under stable conditions even with severe liver cirrhosis, rarely lactate is relevantly [(10)].

Our study analysis included one hundred fifty one patients with decompensated liver cirrhosis who were treated at the medical ICU of Zagazig University Hospitals. The average age of patients was 57.4 ± 14.3 years, with 54.3% being males, 35% being Child B and 65% being child C.

The most common causes of admission were hepatic encephalopathy (34.4 %), followed by bleeding oesophageal varices (33.8%), hepatorenal syndrome (23.2 %), spontaneous bacterial peritonitis (7.3%), and then hepato-pulmonary syndrome (1.3%). These results don't agree with that of **Vaz *et al.*** [(11)], which announced that the most common causes of admission were sepsis (26.7%), surgical (23.4%), hepatic encephalopathy (16.7%), and gastrointestinal bleeding (16.7%).

The hepatic encephalopathy (HE) prevalence (34.4 %) of our study population is near that (34.0%) reported by **Maldonado-Garja *et al.*** [(12)] study, which enrolled 104 patients and reported 32.7% as a percentage of HE prevalence among hospitalized cirrhotic patients. But our result of HE prevalence percentage is lower than that (43.8%) reported by **Bamidele *et al.*** [(13)] in Ghana. The different HE prevalence percentages may be attributed to the degree of the disease severity, probable geographical differences and the time of the study conduction.

Among the studied populations, the prevalence of bleeding oesophageal varices (BEV) was 33.8%, and this complication, in this current study, was the second cause of admission of patients into the ICU in our study. This is partially consistent with **Sarangapani *et al.*** [(14)] who reported that the percentage of varices in patients with cirrhosis was about 60-80 % but the risk of bleeding was 25-35%. Their study included 106 cirrhotic patients and showed that the incidence of large varices was 41% and severe upper gastrointestinal hemorrhage due to liver cirrhosis may have an incidence of 30-40 %. Significant mortality and morbidity with health care costs owing to variceal bleeding are burdens on world health. Also, **Zein *et al.*** [(15)] revealed that 36% of 283 patients with primary sclerosing cholangitis & cirrhosis had esophageal varices. **Poynard *et al.*** [(16)] showed that the risk of hemorrhage of oesophageal varices is about 25-35 % of cirrhotic patients with known varices.

Our study revealed that the percentage of hepatorenal syndrome (HRS) was 23.2% among the studied population. Also, a retrospective cohort study that was conducted in Colombia, by **Rey *et al.*** [(17)] revealed the prevalence of HRS was 23.9%, which included 117 patients with liver cirrhosis. **Fida *et al.*** [(18)] announced that the frequency of hepatorenal syndrome was 10.3% among136 patients with liver cirrhosis.

Populations in this current study were characterized by high lactate levels as the serum lactate levels were distributed as 14.5 ± 8.6 with a median level of 11.4 and IQR of 10.5 ($P<0.002$) on admission, and 14.2 ± 9 with a median level of 12.9 and IQR of 9.3 ($p < 0.000$), after 24h of admission. These figures are much higher than figures in a healthy ones and in patients with compensated cirrhosis as reported in the literature. **Jespersen *et al.*** [(19)] study included 142

patients with chronic liver disease and 14 healthy controls who underwent a liver vein catheterization. Fasting lactate levels were estimated using blood samples drawn from hepatic, renal veins, and femoral artery at the same time. Serum lactate levels were higher in cirrhotic patients than others (P < 0.001) and there was a correlation between serum lactate level and portal pressure. Disturbed excretory liver function and high portal pressure in patients with chronic liver disease led to increased serum lactate levels that were higher in the Child class C group than in other child classes. **Sterling *et al.*** [(20)] found an initial lactate > 2 mmol/ L and subsequent measurements of serum lactate levels within 6 hours were done. The study found that lactate normalization is achieved in169/373 patients with no liver disease, 67% (6/9) with mild liver disease, and 8% (1/12) with liver cirrhosis (p<0.03). Lactate clearance was relatively lower in patients with liver cirrhosis (37.7 vs. 40.4 vs. 21.8, P=0.07).

The mortality rate among our study population in the medical ICU was 33.8 % (n: 51/151 and P<0. 001). This result is nearly in accordance with **Khalil *et al.*** [(21)] who found that the mortality rate was 35.71% (n: 25/70). Also, **Vaz *et al.*** [(11)] announced that the mortality rate among 30 cirrhotic patients admitted to ICU was 43.3%. But other studies showed higher mortality rates such as **Drolz *et al.*** [(22)] study, which included 234 cases and revealed that the mortality rate was 41.34%.

CONCLUSION

In critically-ill patients with liver cirrhosis, lactate levels were independently related with short-term mortality and indicated the severity of the illness and organ failure. Measures that decrease of serum lactate toward normal as early as possible may help improve the chances of survival of these patients in the ICU.

Sponsoring financially: Nil.
Competing interests: Nil.

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