Correlation of Serum Lactate with Short Term Outcome in Critically Ill Patient with Liver Cirrhosis

Monkez Motieh Yousif ; Osama Abdel Aziz ; Ghada Mohammed Samir; Hend Monsour Mohammed; Essam Adel Abdelrahman

Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: **Hend Monsour Mohammed,**
hendmonsour749@gmail.com

Abstract

Background: Acute decompensation of liver cirrhosis result in progressive organ failure where the mortality rates may range between 40-60%, so patients admission into ICU is a need for better outcomes.

Objective: This current study aimed to evaluate the better management and improving outcome of patient admitted to MICU with complicated liver cirrhosis.

Patients and methods: This observational cohort study was included 151 critically ill patients with decompensated liver cirrhosis of both sexes and age above 18 years. Full history and thorough clinical examination, routine laboratory investigations, and radiological investigations as abdominal and pelvic ultrasonography, upper endoscopy CT were done. After 24h of admission another sample was taken to measure serum lactate level. The disease severity is assessed using APACHE II, child pugh, MELD, MELD-Na, MELD- Lactate scores.

Results: Serum lactate level on admission was correlated positively with APACHE II and CTP and negatively with GCS scores. Serum lactate measured after 24h of admission was correlated positively with APACHE II, MELD, MELD Na and CTP and negatively with GCS. MELD lactate score measured on admission was correlated positively with APACHE II and CTP and negatively with GCS. By Multivariate regression analysis high lactate level measured after 24h of admission had an impact on mortality among study populations. High lactate level measured after24h of a dmission and low GCS, high CTP, high APACHE II were independent predictory of mortality while blood urea, haemoglobin, platelets, albumin, and serum Na were not. APACHE II ≥24.5and serum lactate measured after 24h of admission ≥ l3 were predictors of mortality(AUC 0.877 & 0.809, respectively).

Conclusion: APACHE II score and serum lactate values 24 h after admission considered the highest predictors of ICU mortality among patients with liver cirrhosis.

Keywords: Liver Cirrhosis; Serum Lactate; APACHE II score

DOI: 10.48047/ecb/2023.12.8.720

INTRODUCTION

Liver cirrhosis is a progressive disease that may occur along weeks or even years. For example, hepatitis c as a chronic hepatitis may last many years before progressing to cirrhosis **(1)**. Liver injury that leads to necro inflammation and fibrogenesis causes

Cirrhosis. This disease is characterized by diffuse nodular regeneration surrounded by dense fibro tic septae, so parenchymal extinction and collapse of liver structure occur together causing pronounced distortion of hepatic vascular architecture (**2)**.

Despite all of available predictors and guidelines,complicated liver cirrhosis in medical ICU continues to be inadequately managed **(3)**.

Serum lactate levels is elevated as a consequence of complicated liver cirrhosis , may be measured on admission of patient to medical ICU and follow up for 24 h to predict better assessment of outcome of patients **(4)**.

The prognostic value of measurement of serum lactate level and serial measurement has been investigated in various settings **(5,6)**.

Therefore, this study aimed to correlate those variables with the outcome in complicated liver cirrhosis.

PATIENTS AND METHODS

This observational cohort study was included 151 critically ill patients with decompensated liver cirrhosis of both sexes and age above 18 years. Full history and thorough clinical examination, routine laboratory investigations, and radiological investigations as abdominal and pelvic ultrasonography, upper endoscopy CT were done. After 24h of admission another sample was taken to measure serum lactate level. The disease severity is assessed using APACHE II, child pugh, MELD, MELD-Na, MELD- Lactate scores.

Ethical Consideration:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (ZU-IRB#5498). Written informed consent of all the participants was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

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.

Measurement of serum lactate levels:

Lactate is oxidized to pyruvate and hydrogen peroxide (H202) by lactate oxidase (LOX). In the presence of peroxidase (POD), hydrogen peroxide reacts with 2,4,6-tribromo-3- hydroxybenzoic acid(THB) and 4- aminoantipyrine (4- AAP) to form a red quinoneimine dye. The color intensity of the former red quinoneimine dye is directly proportional to the lactate concentration. It is determined by measuring the increase in absorbance at 546 nm. Samples were mixed gently and incubated for 5 minutes at 37 °C,

then were measured against the blank at wave length 546 nm. Sample lactate concentration was calculated using the following equation:

$$\text{Lactate concentration (mg/dl):} \quad \frac{\text{Sample absorption}}{\text{Standard absorption}} \times 10$$

Measurement of serum lactate levels were performed on admission to ICU and after 24 h of admission to ICU.

Patients were managed and followed while in MICU according to our unit management protocols. Short-term ICU measures of patient's outcome included

1. Mortality rate
2. Length of ICU stay.

Statistical analysis:

Data analyzed using Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD. Differences between quantitative independent multiple by ANOVA or Kruskal Wallis. Data were presented as odds ratios (ORs) with 95% confidence intervals (95% CI). Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cutoff values of predictors of mortality with maximum sensitivity and specificity for predicting ICU mortality in patients with decompensated liver cirrhosis. P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

The current study included 151 patients with the mean age 57.4 ±14.3 as illustrated in **Figure (1)**.

There was a higher levels of lactate on admission,and after 24 h of admission, higher total bilirubin, higher TLC and lower serum albumin are dependent predictors for mortality **(Table 1).**

Patients who got increasing serum lactate levels 24 h after admission were characterized by having higher mortality while patients who got a decrease in serum lactate had lower mortality **(Table 2)**.

Serum lactate levels (both on admission & 24 h after admission) & MELD lactate score correlated negatively with GCS and positively with APACHE& CTP scores **(Figure 2-7)**.

APACHE II, lactate after 24h of admission, ICU stay, GCS, serum creatinine, blood urea, HB, platelet, serum albumin, serum Na, and CTP score were independent predictors of mortality **(Table 3)**.

APACHE II score ≥24.5 predicts ICU mortality of the study population with a sensitivity of 90.2% & specificity of 83% (AUC=0.877). Lactate 24 h after admission

≥13 mmol/ L predicts ICU mortality with a sensitivity of 82.4% & specificity of 71% (AUC = 0.809) **(Table 4, Figure 8)**.

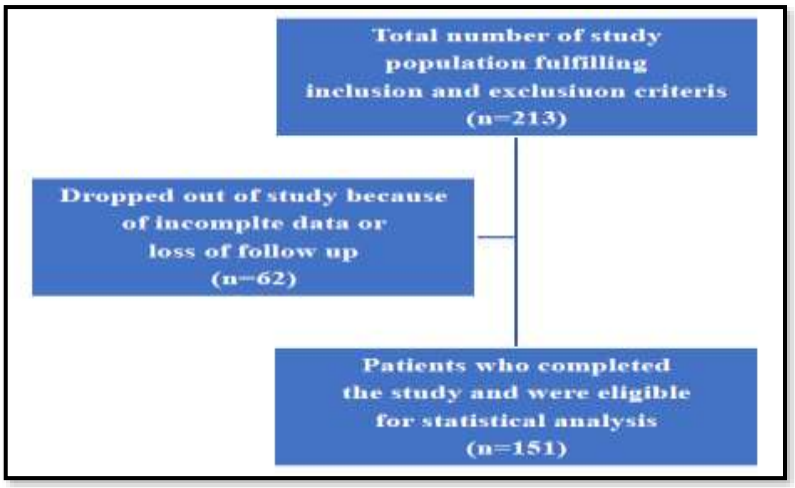

Figure (1): Flowchart of Study Population

Table (1) Comparison between survived (n=100) and deceased (n=51) population of the study regarding biochemical profile

	Outcome	Mean	SD	t/MW	p
Lactate on admission (mmol/L)	**Survived**	**12.98**	**7.89**	**-3.101****	**0.002**
	Deceased	**17.33**	**9.2**		
Lactate after 24h of admission (mmol/L)	**Survived**	**11.2**	**6.17**	**-6.202****	**0.000**
	Deceased	**20.1**	**10.59**		
Total Bilirubin (mg/dl)	**Survived**	**6.02**	**2.92**	**-4.897****	**0.000**
	Deceased	**10.05**	**5.52**		
INR	**Survived**	**1.81**	**.636**	**-1.342****	**0.180**
	Deceased	**2**	**.84**		
Serum Creatinine (mg/dl)	**Survived**	**3.2**	**3.456**	**-0.008****	**0.994**
	Deceased	**2.85**	**3.17**		
Blood Urea 9mg/dl)	**Survived**	**101.16**	**75.88**	**-1.279****	**0.201**
	Deceased	**130.54**	**108.54**		
TLC (× 10^3/mm^3)	**Survived**	**11.359**	**7.013**	**-3.951***	**0.000**
	Deceased	**16.416**	**8.217**		
HB (g/dl)	**Survived**	**8.11**	**1.57**	**0.476***	**0.635**
	Deceased	**7.998**	**1.04**		
Platelet Count (× 103/mm^3)	**Survived**	**113.367**	**90.922**	**-1.539****	**0.124**
	Deceased	**92.429**	**54.169**		
Serum Albumin (g/dl)	**Survived**	**2.46**	**.31**	**6.510***	**0.000**
	Deceased	**2.11**	**.32**		
Serum Na (mEq/L)	**Survived**	**136.6**	**8.6**	**0.121***	**0.904**
	Deceased	**136.4**	**12.1**		
Serum K (mmol/L)	**Survived**	**4.6**	**1.07**	**0.032***	**0.974**
	Deceased	**4.6**	**1.25**		

* by t-test ** by Mann-Whitney test

Table (2) Serial Lactate Changes and ICU Mortality

		Serum Lactate			Total	X^2	P
		No change	Increasing	Decreasing			
Outcome	Survived	5	34	61	100		
	Deceased	4	32	15	51	13.6	0.001
Mortality %		44.4%	48.5%	19.7%	33.8%		
Total		9	66	76	151		

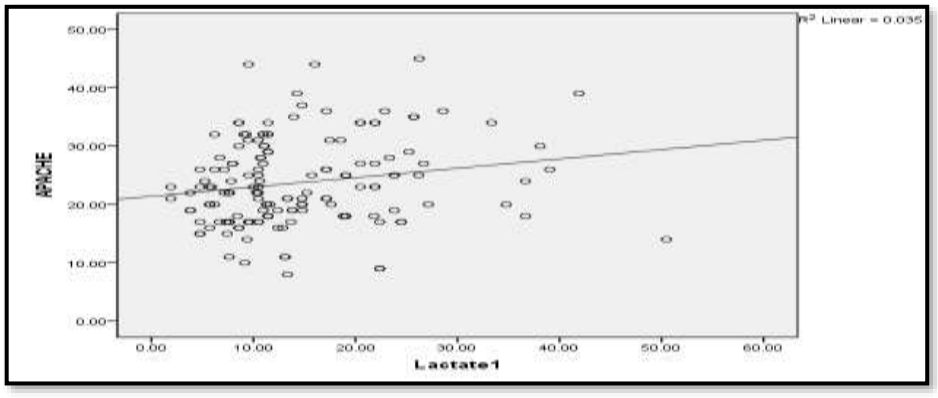

Figure (2) Correlation of serum lactate level on admission and baseline APACHE II score

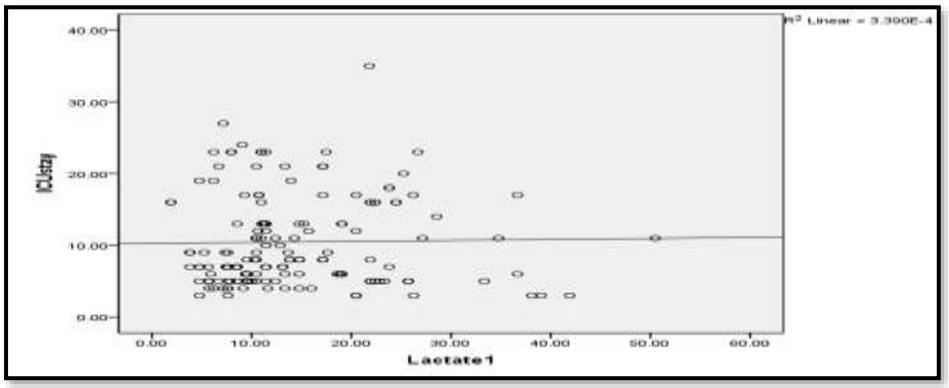

Figure (3) Correlation of serum lactate level on admission and ICU stay

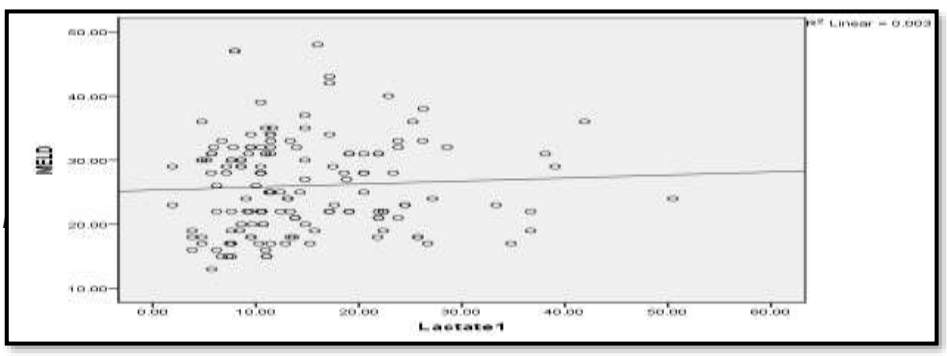

Figure (4) Correlation of serum lactate level on admission and baseline MELD score

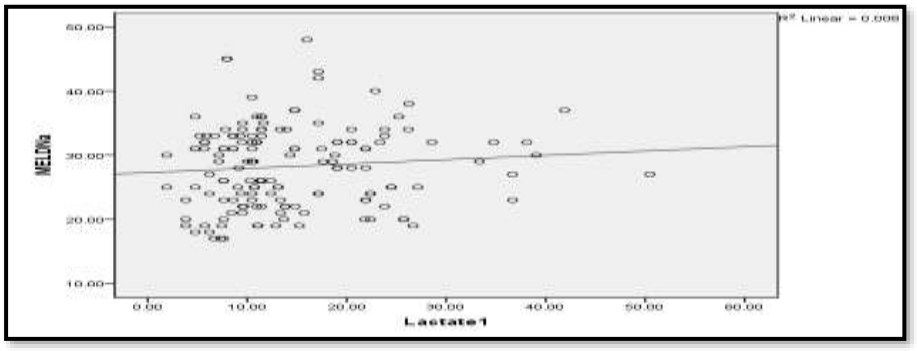

Figure (5) Correlation of serum lactate level on admission and baseline MELD Na score

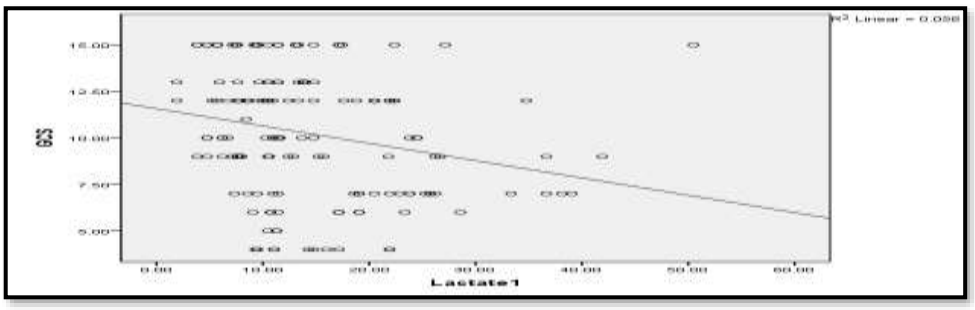

Figure (6) Correlation of serum lactate level on admission and baseline GCS score

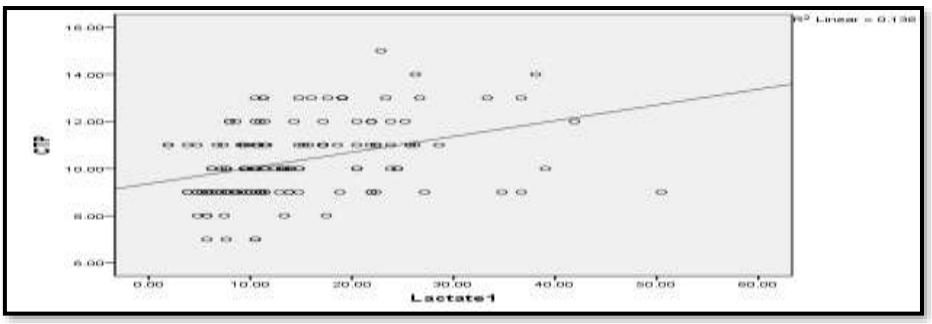

Figure (7) Correlation of serum lactate level on admission and baseline CTP score

Table (3) Multivariate logistic regression analysis for independent predictors of mortality

	Wald	Sig.	Adjusted	95% C.I. for EXP(B)

			OR	Lower	Upper
Age	**3.278**	**.070**	**.846**	**.706**	**1.014**
APACHE II	**4.919**	**.027**	**2.184**	**1.095**	**4.357**
Lactate on admission	**2.984**	**.084**	**.618**	**.357**	**1.067**
Lactate after 24 hours	**4.974**	**.026**	**2.049**	**1.091**	**3.850**
ICU stay	**6.111**	**.013**	**1.728**	**1.120**	**2.666**
Total Bilirubin	**.441**	**.507**	**.870**	**.577**	**1.312**
INR	**1.039**	**.308**	**.040**	**.000**	**19.487**
MELD	**3.703**	**.054**	**6.482**	**.966**	**43.493**
MELD Na	**3.365**	**.067**	**.191**	**.033**	**1.120**
GCS	**7.208**	**.007**	**.138**	**.032**	**.586**
Serum Cr	**4.291**	**.038**	**.487**	**.246**	**.962**
Blood Urea	**6.429**	**.011**	**1.032**	**1.007**	**1.057**
TLC	**1.366**	**.243**	**1.127**	**.922**	**1.378**
HB	**5.125**	**.024**	**.125**	**.021**	**.756**
Platelets	**4.618**	**.032**	**.976**	**.954**	**.998**
Serum Albumin	**4.438**	**.035**	**.000**	**.000**	**.405**
Serum Na	**5.936**	**.015**	**.575**	**.368**	**.897**
Serum K	**.287**	**.592**	**.563**	**.069**	**4.594**
MELD-Lactate	**.257**	**.612**	**1.130**	**.705**	**1.812**
CTP	**5.333**	**.021**	**.035**	**.002**	**.603**
Gender	**.416**	**.519**	**.334**	**.012**	**9.315**
IHD	**.536**	**.464**	**7.997**	**.031**	**2088.217**
DM	**1.756**	**.185**	**.057**	**.001**	**3.932**
HTN	**1.644**	**.200**	**.053**	**.001**	**4.730**
Smoking	**.337**	**.561**	**.318**	**.007**	**15.234**
Child Class	**.987**	**.321**	**82.138**	**.014**	**492436.126**

Table (4) Area under the Curve and Cutoff values of different predictors of mortality in ICU

Test Result Variable(s)	AUC	95% CI	Cutoff value	Sensitivity	Specificity
APACHE II	**0.877**	**0.821-0.933**	**24.5**	**90.2**	**83**
Lactate 24h after admission	**0.809**	**0.741-0.877**	**13**	**82.4**	**71**
CTP	**0.740**	**0.653-0.826**	**10.5**	**68.6**	**72**
MELD Lactate	**0.687**	**0.600-0.774**	**28.5**	**74.5**	**61**
Lactate on admission	**0.655**	**0.565-0.744**	**12**	**54.9**	**58**
MELD Na	**0.622**	**0.526-0.718**	**27.5**	**66.7**	**52**
MELD	**0.611**	**0.513-0.708**	**25**	**54.9**	**55**

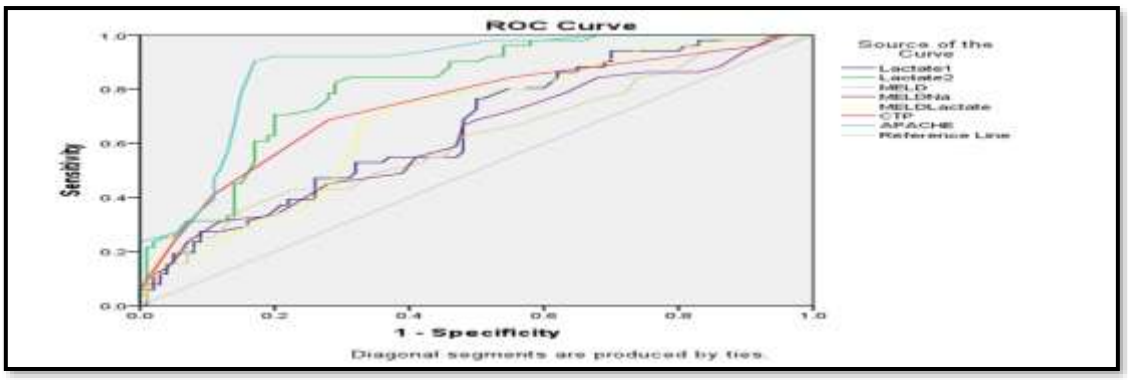

Figure (8) ROC Curve for the validity of significant ICU mortality predictors.

DISCUSSION:

Patients with liver cirrhosis require admission into medical intensive care unit ICU if acute decompensation occurred. Diagnosis of acaute-on-chronic liver cirrhosis is done if there is combination of decompensated cirrhosis, organ failure, and high mortality rate **(7)**.

About one-third of patients admitted to the medical ICU of Zagazig University Hospital with decompensated liver cirrhosis due to variable-related complications die while in the ICU.

Nafeh et al. (8) revealed that a higher mortality rate (57.5 %), among 120 Patients, with liver cirrhosis admitted to ICU in Egypt. Simillary, **Saliba et al. (9)** suggested ICU mortality rate among patients with liver cirrhosis ranges from 34 to 69%.

Regarding the analysis of data for predictors of mortality, Hb% blood urea, serum Na and platelet count had no impact on mortality of the study population in MICU as Hb % of deceased patients is 7.998 ± 1.04 g/dI while in survived ones is 8.11 ± 1.57 g/dl with significant p value=0.635, mean blood urea in deceased and survived are 130.54 ±108.54 and 101.16 ±75.88 mg/dl, respectively with P=0.201, mean serum Na in deceased and survived are 136.4±12.1 and 136.6±8.6 mEq/L, respectively with P= 0.904, and mean platelet count in deceased and survived are 92.429 ±54.169 and 113.367 ±90.922*10^3/ mm3, respectively with P=0.124. While serum lactate after 24 h of admission may predict mortality of the study population in MICU as its level in survived and deceased was 11.2±6.17 and 20.1 ± 10.59 mmol/L, respectively with P value=0.000. Also, high CTP, high APACHE II, lower GCS, and low albumin were significant predictors of mortality in univariate analysis, mean CTP of deceased and survived are 11.2±1.6 and 9.87 ± 1.32, respectively with significant P=0.000, APACHE II score of deceased and in survived are 29.9 ±6.04 and20.56 ± 5.86, respectively with significant P =0.000 and mean GCS of deceased and survived ones are 7.43±2.36 and11.65±2.89, respectively with significant P value= 0.000, And mean serum albumin levels in deceased and survived ones are 2.11±0.32 and 2.46±0.31, respectively with significant P= 0.000. These results in our current study agree with **Khalil et al. (10)**,

Zakareya et al. (11), and **Zhang et al. (12)** showed higher lactate, APACHE II, MELD, CTP, and lower GCS in the deceased than in survived patients .

In our study, the serum lactate on admission was correlated positively with APACHE II (r: 0.186; P= 0.011) and CTP (r: 0.369;P=0.000), and it was negatively correlated with GCS(r: - 0.237; P= 0.002). **Khalil et al. (10)** agreed with this study. But serum lactate measured 24h after admission was positively correlated with ICU baseline severity scores; APACHE II (r: 0.360; P= 0.000), MELD (r: 0.206;P=0.006), MELD Na(r:0.225; P=0.003), and CTP (r: 0.480; P=0.000) and negatively correlated with GCS(r: -0.347; P= 0.000). So measurement of lactate 24 h after admission was better predictor than the measured lactate on admission. **Drolz et al. (13)** agreed partially with this option, measured lactate after 24 h of admission significantly facilitates sufficient discrimination between survived and no survived.

Also MELD Lactate score measured on admission was positively correlated with APACHE II (r: 0.357 and P=0.000), CTP score (r: 0.117 and P=0.000), and negatively correlated with GCS (-0.222 and P=0.003). Recent studies, such as **Sarmast et al. (14)** showed that MELD lactate is an early and objective predictor of mortality and may serve as a guide to therapeutic options. **Sarmast et al. (14)** found that an increase in Serum lactate level is associated, significantly (P<0.01) with a linear increase in MELD Lactate and increasing deterioration of organs with an increase in lactate level. Also, it revealed that MELD-Lactate improved risk prediction in 23.5% of the patients.

The area under the ROC curves (95% confidence intervals (CI) of APACHE II, serum lactate24h after admission,CTP, MELD- Lactate, serum lactate on admission, MELD Na, and MELD for ICU mortality prediction were 0.877 (0.821-0.933), 0.809 (0.741-0.877), 0.740 (0.653-0.826),0.687 (0.600-0.774), 0.655 (0.565-0.744),0.622 (0.526-0.718), and 0.611 (0.513-0.708), respectively. APACHE II and serum lactate 24h after admission scored the highest AUROC, significantly superior to that of CTP, MELD lactate, serum lactate on admission, MELD- Na and MELD scores.

Our data found that serum lactate equal to or more than 13, after 24 hours of ICU admission and APACHE II score with cutoff of equal to or more than 24.5 within 24h of ICU admission was associated with poor outcomes with AUC 0.877& 0.809, respectively, and may be good predictors of mortality of URD critically ill patients with cirrhosis. **Lee et al. (15)** revealed that APACHE II is equal to or more than18 associated with 19-31-fold increased risk (with a sensitivity of 75% and specificity of 84 %, P<0.0001). Also **Ahmed et al. (16)** study showed APACHE II with a cutoff greater than20 can predict the outcomes of critically ill patients.

CONCLUSION:

Serum lactate levels are elevated in patients liver cirrhosis on admission and are correlated with other ICU severity scores (positively correlated with baseline APACHE II and CTP scores and negatively correlated with baseline GCS).

Deceased patients are characterized by having significantly higher lactate values on admission to ICU and a higher incidence of increasing values 24 h after admission,

while patient survival is associated with a higher incidence of drop in serum lactate values 24 h after admission.

Analysis of the ROC curves identified APACHE II score and serum lactate values 24 h after admission as the highest predictors of ICU mortality of these patients. Measures that decrease serum lactate toward normal as early as possible may help improve the chances of survival of these patients in the ICU.

We recommend further studies to assess the value of serial measurement of serum lactate levels in patients with critically ill liver decompensation as a marker of treatment success. The impact of serum lactate measurement in patients with decompensated liver cirrhosis on long-term survival and readmission to critical care units because of the recurrence of the critical illness warrants further research.

No Conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies, or not-for-profit sectors.

References:

1- Pinzani, M., Rosselli, M., & Zuckermann, M. (2011). Liver cirrhosis. *Best practice & research Clinical gastroenterology*, *25*(2), 281-290.

2- Edmark, C., McPhail, M. J., Bell, M., Whitehouse, T., Wendon, J., & Christopher, K. B. (2016). LiFe: a liver injury score to predict outcome in critically ill patients. *Intensive care medicine*, *42*, 361-369.

3- Warren, A., Soulsby, C. R., Puxty, A., Campbell, J., Shaw, M., Quasim, T., ... & McPeake, J. (2017). Long-term outcome of patients with liver cirrhosis admitted to a general intensive care unit. *Annals of intensive care*, *7*, 1-9.

4- Sun, D. Q., Zheng, C. F., Lu, F. B., Van Poucke, S., Chen, X. M., Chen, Y. P., ... & Zheng, M. H. (2018). Serum lactate level accurately predicts mortality in critically ill patients with cirrhosis with acute kidney injury. *European Journal of Gastroenterology & Hepatology*, *30*(11), 1361-1367.

5- Gao, F., Huang, X. L., Cai, M. X., Lin, M. T., Wang, B. F., Wu, W., & Huang, Z. M. (2019). Prognostic value of serum lactate kinetics in critically ill patients with cirrhosis and acute-on-chronic liver failure: a multicenter study. *Aging (Albany NY)*, *11*(13), 4446.

6- Drolz, A., Horvatits, T., Rutter, K., Landahl, F., Roedl, K., Meersseman, P., ... & Fuhrmann, V. (2019). Lactate improves prediction of short-term mortality in critically Ill patients with cirrhosis: a multinational study. *Hepatology*, *69*(1), 258-269.

7- Fuhrmann, V., Whitehouse, T., & Wendon, J. (2018). The ten tips to manage critically ill patients with acute-on-chronic liver failure. *Intensive care medicine*, *44*, 1932-1935.

8- Nafeh, H. M., Abdelmoneim, S. S., Hassany, S. M., & Swifee, Y. M. (2014). Risk factors and outcome in ICU patients with end-stage liver disease. *Journal of the Arab Society for Medical Research*, *9*(1), 33-39.

9- Saliba, F., Ichaï, P., Levesque, E., & Samuel, D. (2013). Cirrhotic patients in the ICU: prognostic markers and outcome. *Current opinion in critical care*, *19*(2), 154-160.

10- Khalil, F. M., El-Assal, M. A., Dabour, A. M., El-Alfy, A. K., & Idriss, M. D. (2021). Serum Lactate Levels as a Predictor of Short-Term Mortality in Critically Ill Patients with Liver Cirrhosis. *Benha Journal of Applied Sciences*, *6*(1), 97-101.

11- Zakareya, T., Akl, M., Shibl, S., El-Mazaly, M., & Abdel-Razek, W. (2022). Utility of prognostic scores in predicting short-term mortality in patients with acute-on-chronic liver failure. *Egyptian Liver Journal*, *12*(1), 1-10.

12- Zhang, Y., Nie, Y., Liu, L., & Zhu, X. (2020). Assessing the prognostic scores for the prediction of the mortality of patients with acute-on-chronic liver failure: a retrospective study. *PeerJ*, *8*, e9857.

13- Drolz, A., Horvatits, T., Rutter, K., Landahl, F., Roedl, K., Meersseman, P., ... & Fuhrmann, V. (2019). Lactate improves prediction of short-term mortality in critically Ill patients with cirrhosis: a multinational study. *Hepatology*, *69*(1), 258-269.

14- Sarmast, N., Ogola, G. O., Kouznetsova, M., Leise, M. D., Bahirwani, R., Maiwall, R., ... & Asrani, S. K. (2020). Model for end-stage liver disease-lactate and prediction of inpatient mortality in patients with chronic liver disease. *Hepatology*, *72*(5), 1747-1757.

15- Lee, Y. T., Wang, C. C., Li, C. F., Chen, H. Y., Liao, H. H., & Lin, C. C. (2021). Utility of acute physiology and chronic health evaluation (APACHE II) in predicting mortality in patients with pyogenic liver abscess: a retrospective study. *Journal of Clinical Medicine*, *10*(12), 2644.

16- Ahmed, Y., Adam, M., & Bakkar, L. M. (2019). Effectiveness of APACHE II and SAPS II scoring models in foreseeing the outcome of critically ill COPD patients. *Egyptian Journal of Bronchology*, *13*, 654-659.