Utility of Lactate to Bilirubin Index in predicting short-term mortality in Acute on Chronic Liver Failure- a single centered study

Abstract

Introduction

Most of the lactate in the body is cleared in the liver. Tissue hypoxia results in increased production of lactate and decreased utility of it. Hepatic insult results not only an increase in the blood lactate levels but also is an independent prognostic marker in critically ill cirrhotic patients. Alteration of liver function is indicated by rise in serum bilirubin. The aim of this study was to therefore to assess the utility of blood lactate to Bilirubin index (LBi) in predicting mortality in patients with acute on chronic liver failure (ACLF).

Methods:

This prospective observational study was conducted from January 2019 to June 2021 at the Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation. Patients aged > 12 years and presenting ACLF were included and their baseline characteristics were recorded. Primary outcome was observed in terms of 30-days mortality and secondary outcome was six months mortality. These indices were then used to calculate the lactate to bilirubin index (LBi) as [1000 × lactate (mmol/L) × bilirubin (μmol/L)]/2. Area under Receiver operating curves (AUROC) for LBi, Child Turcotte Pugh score(CTP) and Model for End-stage Liver Disease score (MELD) were obtained in predicting both 30 days and six months mortality and at an optimal cutoff sensitivity, specificity and diagnostic accuracy for these scores were calculated.

Results:

A total number 159 patients with ACLF were included in the study. Most of the patients were young with mean age of 35.1 ±16.8 years. Males were 97(61%). Hepatitis C was the most common cause of chronic liver disease followed by hepatitis B and autoimmune hepatitis seen in 41 (25.8%), 39(24.5%) and 36 (22.6%) respectively. Hepatitis E was the most common cause of acute injury noted in 60 (37.7%) patients. The baseline characteristics showed mean serum lactate levels of 0.93±1.33 mmol/L, bilirubin levels of 258.5 ± 155.3 μmol/L, CTP score of 10.7 ± 1.8 and MELD score of 26 ±7.6. Out of 159 patients, 26 (16.4%) patients died within 30 days due to ACLF related complicaitons while 133 (83.6%) were discharged. AUROC obtained for LBi, CTP score and MELD score in predicting 30-day mortality in ACLF was 0.98, 0.79 and 0.78 respectively. A cut off of ≥11.8 for LBi Index, ≥30 for MELD score and ≥13 for CTP score were significantly associated with increased risk of 30-day mortality in ACLF patients in our population. However, the sensitivity, specificity, PPV, NPV and diagnostic accuracy of LBi in predicting 30-day mortality was significantly higher than that of CTP and MELD score. The diagnostic accuracy of LBi in predicting 30 days mortality was 87.5%. Similarly, AUROC obtained for LBi, CTP score and MELD score in predicting 6-month mortality in ACLF was 0.89, 0.72 and 0.66 respectively and the diagnostic accuracy of LBi dropped down to 76.6% with a sensitivity of 49.28%, specificity of 97.28%, PPV of 94.4% and NPV of 71.54%.

Conclusion:

Our results showed that LBi score of ≥11.8 had an excellent sensitivity and specificity in predicting mortality in ACLF with an excellent diagnostic accuracy in predicting one month mortality as compared to the other scores. However, its utility in predicting long term mortality is yet to be proven. Further studies are needed to validate this index.

Keywords: Chronic Liver Failure, lactate, Bilirubin Index, mortality

INTRODUCTION:

Approximately 2 million deaths in the world occur due to the complications related to liver disease making it one of the commonest causes of death.[1]The dismal survival of less than 2 years in patients with acute on chronic liver failure(ACLF) has a huge impact on health care system in terms of health related costs and time, as there is increased rates of multiple hospital admissions.[2] Patients with ACLF have significant morbidity and mortality due to prolonged hospital stay and increased risk of detrimental complications.[3] Saliba *et al*.[4] demonstrated 34 to 86% mortality of patients admitted in ICU with ACLF related complications. Lately, different models and indices have been proposed to assess the severity of liver cirrhosis so that therapeutic regimens can be accurately identified.

Prognostic scores help us to estimate the disease severity, complication, expected survival, prognosis and estimate the risk of various medical interventions in the patients with chronic liver disease. These models include Child–Pugh system(CTP), [5] sequential organ failure assessment (SOFA), [6] chronic liver failure-sequential organ failure assessment (CLIF-SOFA), [7] model for end stage liver disease (MELD) score [8] and platelet to White blood cell ratio(PWR)[9]. Although, these models are non-invasive but they have certain deficiencies. One of the major drawbacks associated with Child-Pugh score is that it doesn't include the cause of cirrhosis, the possible confounding factors and is also unable to explain whether the factor causing injury or insult is removed. [10, 11] Model for end stage liver disease (MELD) score does not incorporate complication of end stage liver disease i.e. the severity of hepatic encephalopathy; a prognostic marker in cirrhotic patients.[12] Hence, a simple, non-invasive, bedside comprehensive and

practicable parameter is not only required to predict mortality in this population but also to guide in management such as early referral for liver transplantation.

Lactate to bilirubin index (LBi) is a simple, easily measurable bedside score that can be utilized to predict early mortality in ACLF patients. Liver is primarily responsible for up to 70 percent clearance of the body lactate. [13, 14] In patients with acute liver failure and ACLF, raised level of serum lactate are due its release from the splanchnic circulation due to enhanced glycolysis in the absence of splanchnic hypoxia.[15]

Study by Xiao-Fu Chen et al [16] reported that lactate bilirubin index is a strong predictor of short term mortality (30-day) with sensitivity and specificity of 70% and 79% respectively, Positive Predictive Value (PPV) of 61% and Negative Predictive Value (NPV) of 84%. Varis E et al [17] also reported that lactate monitoring is very important in patients of sepsis in critical care units. J.A Cruse et al documented that raised lactate levels were independently associated with both acute hepatic impairment, and mortality in critically ill cirrhotic patients. [18-21].

Recently, few studies have been conducted regarding the utility of lactate as a marker of severity in chronic liver disease. However, no study has been performed in our population, explaining the role of LBi as prognostic marker in predicting mortality in ACLF patients. Our main purpose was to predict early mortality in ACLF patient by using simple score of lactate bilirubin index. This can help us in stratifying the patients according to the need of urgent and aggressive medical treatment including early listing for liver transplantation.

Therefore, the aim of our study was to determine the utility of the Lactate to bilirubin index (LBi) in predicting short-term mortality (30-days and six months) in patients with acute on chronic liver failure.

Methodology:

Study Population:

This prospective observational study was conducted at the department of Hepato-gastroenterology, Sindh Institute of Transplantation, from January 2019 to June 2021.All patients of either gender and aged between 18 to 70 years having liver cirrhosis and fulfilling the criteria of ACLF as per operational definition were included in the study. While, the patients with history of Hepatocellular Carcinoma, prior liver transplantation, life threatening comorbidities (renal failure, ischemic heart disease),seizures, cardiac arrest, heart failure, mesenteric ischemia ,acute pancreatitis, diabetes ketoacidosis, renal failure and other causes of increased lactate such as sepsis as evident by skin/soft tissue infections, upper and lower respiratory tract infections, CNS infections , CVS infections, intra-abdominal infections , urinary tract infections, bone , joint and systemic infections were excluded from the study.

Data Collection

Clinical data was recorded on the predesigned proforma including baseline laboratory investigations, etiology of liver disease and cause of acute insult. Baseline laboratory investigations included pro thrombin time, serum creatinine, serum Bilirubin, albumin and serum lactate levels. Ultrasound abdomen was performed for ascites. In order to evaluate the chronic liver disease etiology, multiple investigations were performed including viral markers along with other investigations as per requirement including autoimmune serology, metabolic profile, doppler ultrasound and cross-sectional imaging. Similarly, in order to determine the cause of acute insult, the history was obtained regarding the prior use of any herbal or hepatotoxic medications and specific investigations were also performed as required including those for

hepatotropic viruses and cultures including that of blood, urine and ascetic fluid. Predesigned formula was used to calculate CTP and MELD score .[5, 7, 8] Lactate to bilirubin index was calculated using the formula

Lactate Bilirubin Index (LBi):[16]

$$\ln [1000 \times \text{lactate (mmol/L)} \times \text{bilirubin } (\mu\text{mol/L})]/2.$$

The follow up of the patients was for six months and the outcome was recorded in terms of 30-days and six months mortality in ACLF patients.

Statistical Analysis:

SPSS software version 22.0 was utilized for data analysis. Baseline characteristics of the patients with ACLF was recorded along with 30-days and six months mortality. Mean and standard deviation were used for expression of continuous variables like age, weight, height, white blood cell count, platelet count, International Normalized Ratio (INR), arterial lactate levels, bilirubin, Child Pugh score and MELD score while frequency and percentages were acquired for categorical variables including gender, cause of liver disease and acute insult. Student t-test was used to analyze continuous variables while categorical variables were evaluated using Chi square test with a p-value of < 0.05 considered statistically significant.

Area under the receiver operating curve (AUROC) was obtained for LBi, CTP and MELD score for predicting 30-days and six months mortality in ACLF patients. A cut off was taken using AUROC, at which the sensitivity, specificity, PPV, NPV and diagnostic accuracy

was calculated for LBi, MELD and CTP score for predicting 30-days and six months mortality in ACLF patients.

Results:

A total of 159 patients with ACLF were enrolled in the study. The baseline characteristics of the patients included in the study are expressed in **Table 1**. Mean age of the patients were 35.1 ±16.8 years. Among them, 97 (61%) were males and 62 (39%) were females. The most common cause of chronic liver disease(CLD) was hepatitis C followed by hepatitis B and autoimmune hepatitis seen in 41 (25.8%), 39(24.5%) and 36 (22.6%) respectively. Alcohol accounted for 9.4% and Wilson disease accounted for 6.3 % of the causes CLD. Acute insult was most commonly caused by Hepatitis E, noted in 60 (37.7%) patients followed by drug induced liver injury (DILI) in 40 (25.2%) patients. On admission, ascites was observed in 126 (79.2%) while hepatic encephalopathy (HE) was seen in 49 (39.8%) patients respectively. At baseline, Renal failure was present in 34 (21.4%) and hepatorenal syndrome (HRS) was noted in 8(5%) patients respectively with 13 (8.2%) patients requiring either single or multiple sessions of hemodialysis during admission. Spontaneous Bacterial Peritonitis (SBP) was seen in 19 (11.95) patients. Thirty two (20.1%) patients had more than 3 organ failure at the time of admission. On admission, mean serum lactate levels were of 0.93±1.33 mmol/L, bilirubin levels of 258.5 ± 155.3 µmol/L, CTP score of 10.7 ± 1.8 and MELD score of 26 ±7.6. Out of 159 patients, 26 (16.4%) patients died within 30 days due to complications of ACLF while 133 (83.6%) were discharged. Six months mortality was noted in 69(43.4%) patients. Increased age at baseline, raised serum creatinine, serum total bilirubin, serum lactate, CTP and MELD score and decreased Total Leucocyte count(TLC) were significantly associated with increased risk of mortality (**Table 2 and 3**)

AUROC obtained for LBi, CTP score and MELD score in predicting 30-day mortality in ACLF was 0.98, 0.79 and 0.78 respectively.(**Figure 1**). A cut off of ≥11.8 for LBi, ≥30 for MELD score and ≥13 for CTP score were significantly associated with increased risk of 30-day mortality in ACLF patients in our population. However, the sensitivity, specificity, PPV, NPV and diagnostic accuracy of LBi in predicting 30-day mortality was significantly higher than that of CTP and MELD score.

At a cutoff of ≥11.8, the sensitivity, specificity, NPV and PPV were 92.3%, 84.2%, 80% and 94.12% respectively for LBi in predicting the risk of 30 days mortality among ACLF patients with an excellent diagnostic accuracy of 87.5% .

Similarly, AUROC obtained for LBi, CTP score and MELD score in predicting 6-month mortality in ACLF was 0.89, 0.72 and 0.66 respectively and the diagnostic accuracy of LBi dropped down to 76.6% with a sensitivity of 49.28%, specificity of 97.28%, PPV of 94.4% and NPV of 71.54%.(**Figure 2**,**Table 4**)

Discussion:

Lactate to Bilirubin index(LBi) have been used previously in a Chinese population to estimate prognosis in patients with ACLF.[16] However, in our region, we are the first one to validate this score and its diagnostic accuracy and also compared this index with the other already established predictors of mortality i.e. MELD and CTP score.

Previously, studies have shown an increased risk of mortality in ACLF patients. [4, 22-24] Our study also validated this fact as most of our patients with more than three organ failure died within 30 days. This can directly be related to the poor outcome of the patients with ACLF and cirrhosis related complications admitted in intensive care unit(ICU). Therefore, timely diagnosis

of underlying acute insult, managing the complications of cirrhosis and referring these patients to liver transplant unit can decrease mortality in these patients along with the treatment of the primary cause of chronic liver disease before the development of hepatic decompensation cannot only reduce the burden of hospitalization of these patients with ACLF but can also result in decreasing the mortality and improving the quality of life in this population.

Initially, the utility of CTP score was limited to the evaluation of the hepatic decompensation risk in cirrhotic patients undergoing surgery. However, it was then also utilized to assess prognosis in cirrhotic patients.[5] MELD score is also utilized to predict survival in patients with decompensated chronic liver disease, prioritizing the need of liver transplantation in these patients.[8] However, it is less convenient for bedside usage as compared to CTP and LBi score and also it utilizes more variables as compared to LBi.

Previously, the utility of serum lactate levels has been in the critically ill patients to assess disease severity.[25-27] However, in cirrhotic patients, lactate follows a different metabolic pathway as compared to normal subjects and leads to their increase levels in this population.[13, 28]Previously, studies have shown that cirrhotic patients admitted in intensive unit with increased lactate levels had poor outcome. [18,29,30] This fact was also noted in our population, as high lactate levels were associated with high risk of mortality in our population. Raised serum bilirubin levels also indicates liver dysfunction. Most of the scores assessing disease severity and prognosis in cirrhotic patients include serum bilirubin.

Considering its non-invasiveness, LBi is a novel score was recently utilized in a Chinese population to predict prognosis and mortality in critically-ill cirrhotic patients. Despite being simple it had a good diagnostic accuracy in predicting short term (30-day) mortality with a

sensitivity of 51%, specificity of 82%, PPV of 79% and NPV of 55%. However, on contrary to the MELD score, LBi lacked accuracy in predicting long term mortality (3-year). [16] In our study, LBi showed an excellent diagnostic accuracy of 91.19% in predicting short term mortality 30-days in ACLF with a sensitivity of 92.31%, specificity of 90.98%, PPV of 66.67% and NPV of 98.37%. However, while predicting six months mortality, the diagnostic accuracy of LBi decreased to 76.6% with a sensitivity of 49.28%, specificity of 97.28%, PPV of 94.4% and NPV of 71.54% with a better performance than CTP and MELD score at six months. Lactate can be utilized as an excellent predictor of one month mortality although its use as a long term mortality predictor is yet to be proven. On contrary to research by Chen XF *et al.*[16]; our study showed an excellent accuracy of MELD score in predicting short term mortality while it was a not a good predictor of long term (6-month) mortality. The performance of CTP score was superior than MELD score in prediction both one month and six months mortality in our population.

Our study had certain limitations. First and foremost, it was a single centered study. Secondly, the sample size was small and this might be the reason that LBi failed in predicting six months mortality. Third, the long term mortality was not checked (1 year and 3 year). Lastly, LBi was not compared with other bedside available scores such as SOFA, CLIFF-SOFA etc. that are utilized in the intensive care unit to predict prognosis and mortality.

However, the strength of our study was that it was a cross-sectional study and also was the first study from this part of the world showing the utility of LBi in predicting mortality in ACLF patients.

Conclusion:

LBi score of >11.8 had an excellent sensitivity and specificity in predicting mortality in ACLF patients along with an excellent diagnostic accuracy in predicting one month mortality as compared to the other scores. However, its utility in predicting long term mortality is yet to be proven. Further studies are needed to validate this index.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

Informed consent was taken from either the patients or their first degree relatives in case of altered mental status of the patient.

Acknowledgement: None

Conflict of Interest: None

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Study population(n=159)	n (%)

"Acid?base disturbances in critically ill patients with cirrhosis," Liver International,vol. 27, no. 7, pp. 901–909, 2007

Table 1: Baseline characteristics of the population included in the study (n=159)

Mean age(years±S.D)		35.1±16.8
Gender	**Male**	97(61)
	Female	62(39)
Etiology of chronic liver disease	**HCV**	41(25.8)
	HBV	39(24.5)
	Alcohol	36(22.6)
	Autoimmune	15(9.4)
	Wilson disease	10(6.3)
Cause of acute liver injury	**HEV**	60(37.7)
	DILI	40(25.2)
	AIH flare	11(6.9)
	Alcoholic Hepatitis	9(5.7)
Ascites	**Present**	126(79.2)
	Absent	33(20.8)
Hepatic Encephalopathy	**Present**	49(39.8)
	Absent	110(40.2)
Hemoglobin(g/dL)		9.9±2.1
Total Leucocyte Count(x10^9/L)		11.7±8.4
Platelet Count(x10^9/L)		141±101
Total Bilirubin(µmol/L)		15.2±9.1
Alkaline Phosphatase(IU/L)		250.1±450.3
Aspartate Transaminase(AST)(IU/L)		327±605
Alanine Transaminase(ALT)(IU/L)		215±402
Albumin(g/dl)		2.3±0.7
Serum Lactate(mmol/L)		0.9±1.3
LBi Index		10.8±1.4
Child Turcotte Pugh Score		10.7±1.8
MELD score		26±7.6
≥3 Organ failure	**Present**	32(20.1)
	Absent	127(79.9)
Renal Failure	**Present**	34(21.4)
	Absent	125(78.6)
SBP	**Present**	19(11.9)
	Absent	140(88.1)
30 days mortality	**Present**	26(16.4)
	Absent	133(83.6)

6 months mortality	**Present**	69(43.4)
	Absent	90(56.6)

Table 2- Comparison of continuous variables in terms of over all mortality

Variable	Non Survivors (n-69) Mean ± SD	Survivors (n-90) Mean ± SD	p-value
Age	36± 18.4	34 ± 15.4	0.521
Hemoglobin(g/dL)	9.62 ±2.1	10.2 ± 2.1	0.101
Total Leucocyte Count(x10^9/L)	13.9± 10.7	10.1 ±5.43	**0.004**
Platelet Count(x10^9/L)	114 ± 113	138 ± 91	0.739
Total Bilirubin(µmol/L)	323.1± 161.8	208.8 ±130.7	**≤0.001**
Aspartate Transaminase(AST)(IU/L)	362±702	299±517	0.521
Alanine Transaminase(ALT)(IU/L)	176±276	246±479	0.285
Serum Albumin(g/dL)	2.3±0.75	2.41±0.7	0.263
Serum Creatinine	1.6±1.5	1.6±2.26	0.974
Serum Lactate levels(mmol/L)	1.67±1.76	0.37±0.25	**≤0.001**
International normalized ratio(INR)	2.5±0.81	1.2±0.24	≤0.001
LBi Index	11.9± 1.1	10.1± 0.96	**≤0.001**
CTP score	11.5 ± 1.8	10.1± 1.6	**≤0.001**
MELD Score	28.6±7.9	24.1 ±6.7	**≤0.001**

***LBi-**Lactate to Bilirubin**;**CTP-**Child Turcotte Pugh**; ***MELD-**Model for End Stage Liver Disease

Table 3-Comparison of categorical variables in terms of mortality in studied population

Variable		Non-survivors (n-69) n(%)	Survivors (n-90) n(%)	p-value
Gender	**Male**	26(37.7)	36(40)	0.766
	Female	43(62.3)	54(60)	
SBP	**Yes**	10(14.5)	9(10)	0.387
	No	59(85.5)	81(90)	
International Normalized Ratio(INR)	**≥2**	56(81.1)	4(4.5)	**≤0.001**
	<2	13(18.9)	86(95.5)	
HRS	**Yes**	19(27.5)	2(2.2)	**0.021**
	No	50(72.5)	88(97.8)	
Organ Failure	**<3**	46(66.7)	81(90)	**≤0.001**
	>3	23(33.3)	9(10)	
Ascites	**Yes**	59(85.5)	67(74.4)	0.375
	No	10(14.5)	23(25.6)	
CTP score	**<13**	24(34.8)	12(13.3)	**0.001**
	>13	45(65.2)	78(86.7)	
MELD score	**<30**	33(47.8)	17(18.9)	**≤0.001**
	>30	36(52.2)	73(81.1)	
LBi Index	**≥11.8**	34(49.1)	2(2.2)	**≤0.001**

		<11.8	35(50.9)	88(97.8)

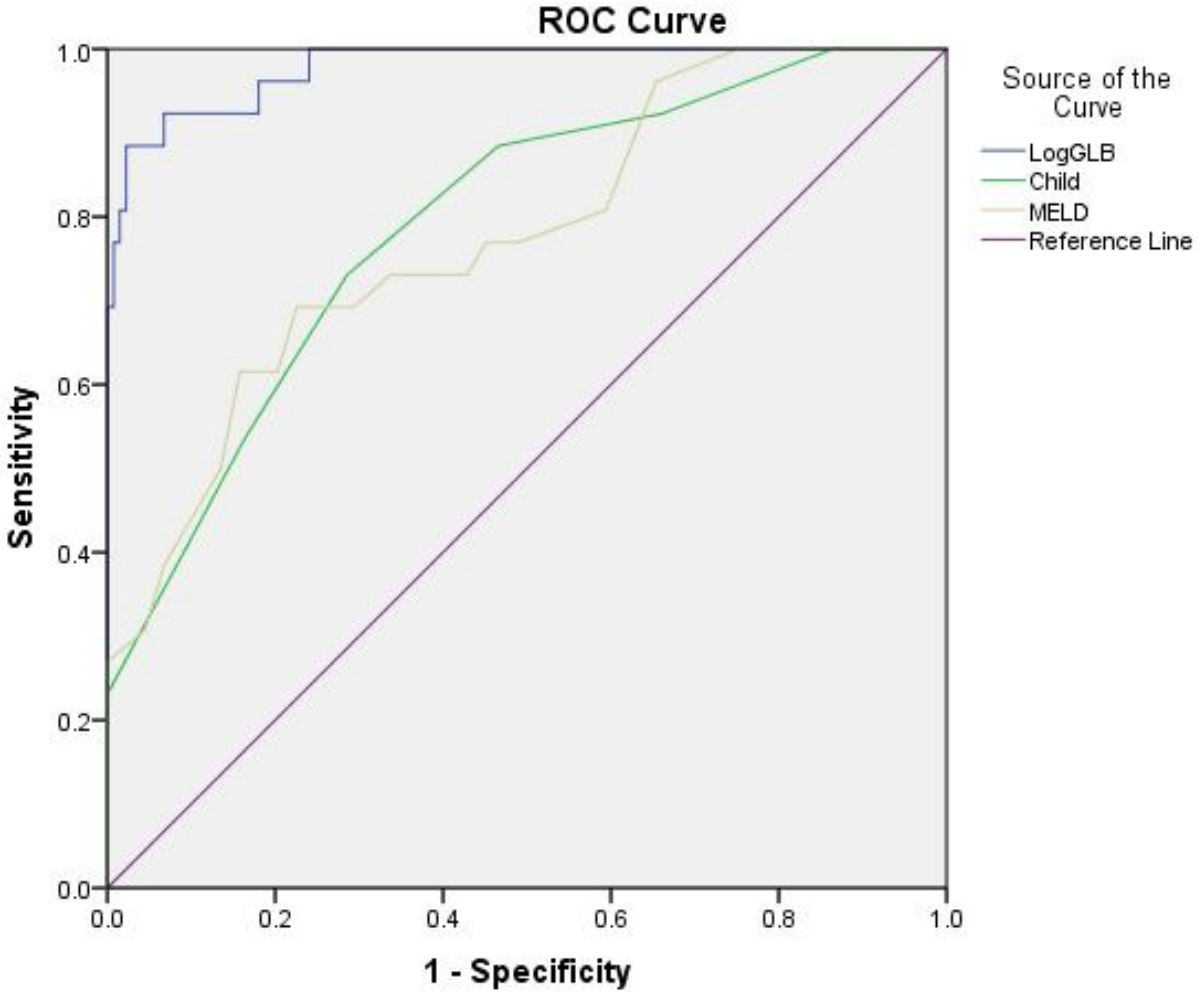

Figure 1-AUROC for LBi Index in predicting one month mortality was 0.98(p-value<0.001)

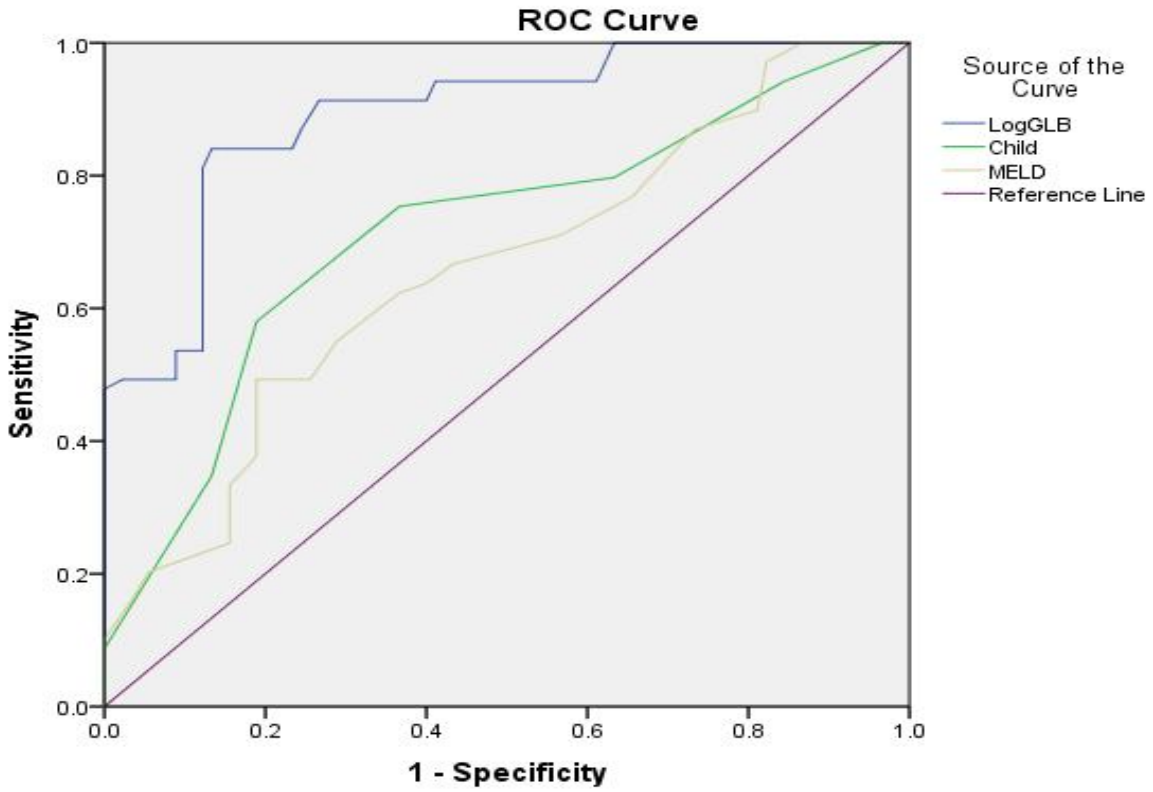

Figure 2- AUROC for LBI Index in predicting six months mortality was 0.90(p-value ≤ 0.001)

Table 4-Diagnostic accuracy of LBi Index, CTP score and MELD in predicting mortality

Predictive model	AUROC	Cutoff	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
One month mortality							
LBi* **Index**	**0.98**	**≥11.8**	**92.3%**	**84%**	**80%**	**91.2%**	**87.5%**
CTP score**	**0.8**	**≥13**	**54%**	**84%**	**39%**	**90%**	**79%**
MELD* score**	**0.77**	**≥30**	**69%**	**76%**	**36%**	**93%**	**75%**
Six months mortality							
LBi **Index**	**0.89**	**≥11.8**	**49%**	**97%**	**94%**	**71%**	**77%**
CTP score	**0.72**	**≥13**	**35%**	**87%**	**67%**	**63%**	**64%**
MELD score	**0.66**	**≥30**	**45%**	**81%**	**66%**	**67%**	**67%**

***LBi-**Lactate to Bilirubin**;**CTP-**Child Turcotte Pugh**; ***MELD-**Model for End Stage Liver Disease