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Metabolic Acidosis in Patients With Chronic Liver Disease And Predict Severity Using Child-Pugh Score.

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ABSTRACT

Metabolic acidosis is a common reason for intensive care unit (ICU) admission and is a cause for increased ICU deaths. The liver is an important acid-base regulatory organ that plays an important role in lactate metabolism, ketone production, synthesis of albumin and urea production and severe liver damage results in metabolic acidosis. Liver cirrhosis is considered the irreversible end result of chronic liver inflammation and fibrosis. The Information for the study was collected from Chronic Liver Disease patients, including OPD and IPD in BLDE(DU) Shri B M. Patil Medical College, Hospital and Research Centre, Vijayapura-583106, Karnataka from September 2022-March 2024 and sample size being 96. A complete blood gas analysis (ABG) includes pH, partial pressure of arterial oxygen (PaO2), partial pressure of carbon dioxide (PCO2), sodium (Na+), potassium (K+), ionized calcium (Ca2+), magnesium, chloride (Cl−), inorganic phosphate, bicarbonate (HCO3−), BE, and lactate were taken. The levels of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), activated partial thromboplastin time (aPTT), blood urea nitrogen (BUN), creatinine, glucose, haemoglobin, haematocrit, international normalized ratio (INR), platelet count, prothrombin time and USG Abdomen and pelvis were done. The Aim of the study is to correlate the severity of Metabolic acidosis/ Lactic acidosis with severity of chronic liver disease (Child Pugh A/B/C) and to correlate between severity of Metabolic acidosis with MELD-Na Score. The average age group of patients predominantly being between 31 to 40 years of age and the youngest being 25 and oldest being 84 years. The study population predominantly consisted of male patients (96.8%). Among the risk factors, the most common being Alcohol (94.7%) and 13 patients in this study had either Diabetes or HTN (13.5%). Majority of patients showed Metabolic Acidosis (46.8 %) and Respiratory Alkalosis (12.5%) and the rest being within normal limits. This study thus explains that there is correlation between Cirrhosis and Metabolic Acidosis and sepsis causes increase in Lactate levels and formation of Lactic Acidosis and formation of Metabolic Acidosis. There is also a correlation between cirrhosis and respiratory alkalosis which is caused due to breathlessness and co2 washout.

Keywords: Metabolic Acidosis, Chronic Liver Disease, predict severity, Child-Pugh Score.

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INTRODUCTION

Cirrhosis is a major cause of morbidity and mortality in people with chronic liver disease worldwide. In 2019, cirrhosis accounted for 2.4% of global deaths [1]. Owing to the rising prevalence of obesity and increased alcohol consumption on one hand, and improvements in the management of hepatitis B virus and hepatitis C virus infections on the other, the epidemiology and burden of cirrhosis are changing [1]. Cirrhosis and other chronic liver diseases are the 14th leading cause of death worldwide, contributing significantly to the mortality and disability-adjusted life years (DALYs) [2]. It represents an advanced stage of various liver diseases such as hepatitis B and C infections, non-alcoholic fatty liver disease, alcohol consumption, autoimmune disorders, and so on [2]. Liver cirrhosis (LC) is still a major problem as it has many consequences due to long clinical course, and it is the final stage of the diffuse progressive liver fibrosis process characterized by distortion of the liver architecture and the formation of degenerative nodules [3]. Abnormalities of acid-base balance are commonly seen in critical patients in the intensive care unit (ICU) [4]. Severe acid-base disorders, especially metabolic acidosis have been associated with increased mortality [4].

Patients with advanced cirrhosis are often complicated by many serious consequences which include portal hypertension with its consequences (eg. Gastroesophageal varices and splenomegaly), ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome and hepatocellular carcinoma [5]. Micro-nodular cirrhosis progresses to macro-nodular cirrhosis in the absence of hepatic inflammation and necrosis [6]. Liver injury activates stellate cells in the dissection space and Stellate cells activate cytokines generated by hepatocytes, tissue macrophages (Kupfer cells), and lymphocytes. Monocytes are the key cells in the body's immune system and play a major role in the pathogenesis of liver fibrosis [7]. Monocytes get activated by endotoxins and result in the release of large number of cytokines. These cytokines result in the recruitment of other blood cells. All these cells release further cytokines, which can result in circulatory changes and fibrosis in liver disease [7]. Alcohol stimulates metabolism on its own. Cytochrome P4502E1-based Microsomal Ethanol Oxidizing System is an alternative mechanism for the metabolism of alcohol. Alcohol causes CYP2E1, which makes other medications hepatotoxic such as Paracetamol.

Non-alcoholic fatty liver disease (NAFLD) is characterized by an accumulation of lipids in the liver of individuals who do not consume significant amounts of alcohol and includes a variety of diseases from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis [8]. The increase in NAFLD is closely connected to contemporary lifestyle issues, such as lack of physical activity, bad eating habits, and the growing occurrence of metabolic syndrome [8]. Mallory Denk bodies are surrounded by a satellite of polymorphs that appears as intracytoplasmic inclusions composed of purple intermediate filaments [9].

MATERIAL AND METHODS

Information collected through prepared proforma from each patient of chronic liver disease admitted in medicine wards and outdoor patient department of Medicine and sample size being 96. The sociodemographic data was obtained using a face-to-face interview technique. A briefing was given to the participants and/or their relatives about the objective of this study and assured confidentiality in collection of personal data. The above-mentioned investigations were done for each patient.

All patients admitted with Liver Cirrhosis diagnosed clinically, laboratorically and radiologically were included and patients with malignancy, acquired immune deficiency syndrome and post organ transplant patients were excluded. It was a Cross-Sectional study and statistical software for the social sciences and the data were analysed statistically after being entered into a Microsoft Excel sheet (Version 20). The results were shown as counts, percentages, graphs, and mean (median) SD. Two groups categorically variables were compared using the Chi square test. The correlation between quantitative variables were determined using the correlation coefficient.

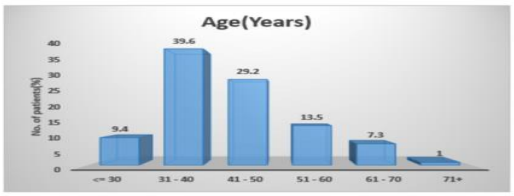
RESULTS

The current study was done on 96 patients diagnosed with Chronic Liver Disease. The average age group of patients predominantly being between 31 to 40 years of age and the youngest being 25 and oldest being 84 years. Among the risk factors, the most common being Alcohol (94.7%) and 13 patients in this

study had either Diabetes or Hypertension (13.5%). Majority of patients showed Metabolic Acidosis (46.8 %) and Respiratory Alkalosis (12.5%) and the rest being within normal limits. The study population predominantly consisted of male patients (96.8%). The severity can be graded using Child Pugh score and majority of patients were under Class C. In the Metabolic Acidosis group, 36 patients were in Class C of Child Pugh score (80%) and the rest 9 in Class B (20%). Majority of patients were in Class C of Child Pugh score (81.25%) and few in Class B (16.6%) and rest in Class A (2.15%). Three year mortality was predicted using MELD-Na score where in the Metabolic Acidosis group, majority were in score of 20- 29 and 30-39 both being 16 patients each (35.5%).

1) AGE

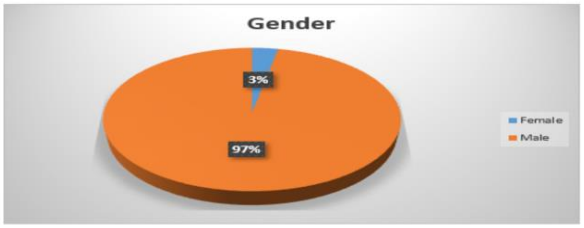
Age(Years)	No. of patients	Frequency
<= 30	9	9.4
31 - 40	38	39.6
41 - 50	28	29.2
51 - 60	13	13.5
61 - 70	7	7.3
71+	1	1.0
Total	96	100.0



- The average age group of patients predominantly being between 31 to 40 years of age and the youngest being 25 and oldest being 84 years.

2) GENDER

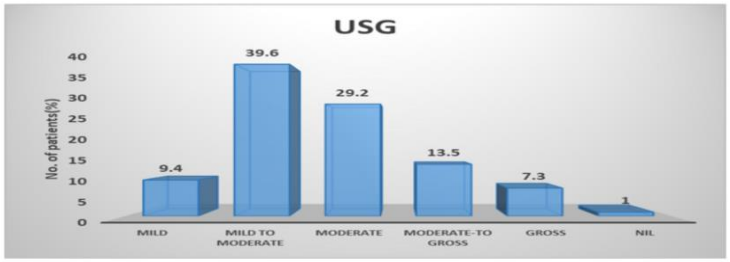
Gender	No. of patients	Frequency
Female	3	3.1
Male	93	96.9
Total	96	100.0



- The study population predominantly consisted of male patients (96.8%).

3) ASCITIS

Ascitis	No. of patients	Frequency
Mild	14	9.4
Mild to Moderate	16	39.6
Moderate	19	29.2
Moderate-to Gross	12	13.5
Gross	28	7.3
Nil	7	1.0
Total	96	100.0



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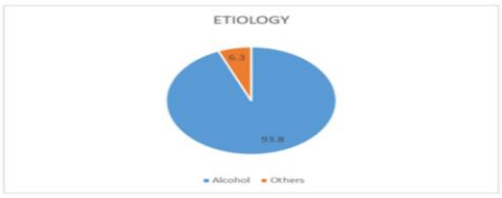
4) ETIOLOGY

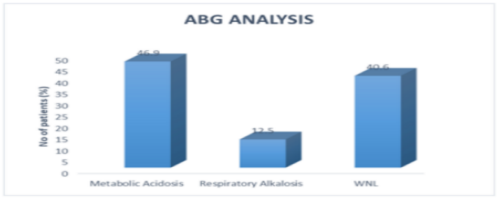
ETIOLOGY			
		Frequency	Percent
	Alcohol	90	93.8
	Others	6	6.3
	Total	96	100.0



- Among the risk factors, the most common being Alcohol (94.7%) and 13 patients in this study had either Diabetes or HTN (13.5%).

5) ABG

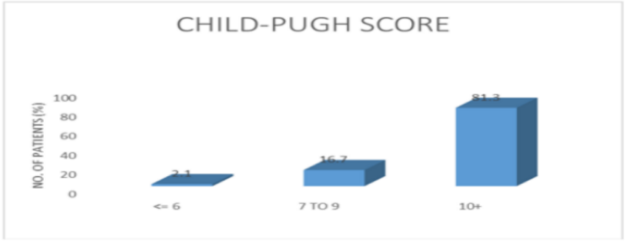
ABG ANALYSIS			
		Frequency	Percent
	Metabolic Acidosis	45	46.9
	Respiratory Alkalosis	12	12.5
	WNL	39	40.6
	Total	96	100.0



- Majority of patients showed Metabolic Acidosis (46.8 %) and Respiratory Alkalosis (12.5%) and the rest being WNL.
- In the Metabolic Acidosis group, 36 patients were in Class C of CHILD PUGH SCORE (80%) and the rest 9 in Class B (20%).

6) CHILD-PUGH SCORE

CHILD PUGH SCORE			
		Frequency	Percent
	<= 6	2	2.1
	7 - 9	16	16.7
	10+	78	81.3
	Total	96	100.0



- Majority of patients were in Class C of CHILD PUGH SCORE (81.25%) and few in Class B (16.6%) and rest in Class A (2.15%).

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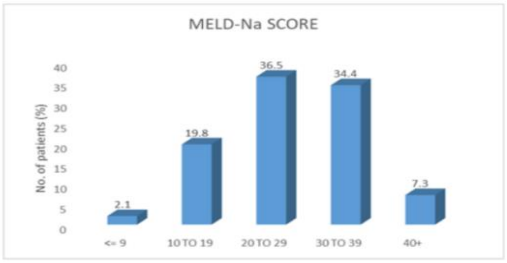
7) **MELD-Na SCORE**

	Frequency	Percent
<= 9	2	2.1
10 - 19	19	19.8
20 - 29	35	36.5
30 - 39	33	34.4
40+	7	7.3
Total	96	100.0



- Majority of patients were in MELD-Na score of 20-29 (36.4%) which has a 3 year mortality of 19.6 % followed by score of 30-39 (34.3%) which has a mortality of 52.6% and in Metabolic Acidosis group, majority were in score of 20-29 and 30-39 both being 16 patients each (35.5%).

ABG * CHILD PUGH SCORE (Binned) Crosstabulation

			CHILD PUGH SCORE (Binned)			Total
			<= 6	7 - 9	10+	
ABG	Metabolic Acidosis		0	9	36	45
			0.0%	56.3%	46.2%	46.9%
	Respiratory Alkalosis		0	0	12	12
			0.0%	0.0%	15.4%	12.5%
	WNL		2	7	30	39
			100.0%	43.8%	38.5%	40.6%
Total			2	16	78	96
			100.0%	100.0%	100.0%	100.0%

Lactate (Binned)

		Frequency	Percent
Valid	<= 1.50	13	13.5
	1.51+	83	86.5
	Total	96	100.0

ABG * Lactate (Binned) Crosstabulation

			Lactate (Binned)		Total
			<= 1.50	1.51+	
ABG	Metabolic Acidosis		3	42	45
			23.1%	50.6%	46.9%
	Respiratory Alkalosis		1	11	12
			7.7%	13.3%	12.5%
	WNL		9	30	39
			69.2%	36.1%	40.6%
Total			13	83	96
			100.0%	100.0%	100.0%

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Chi-Square Tests		
	Value	Asymptotic Significance (2-sided)
Pearson Chi-Square	5.123	.077

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	96	25	84	43.45	10.862
Ph	96	6.890	7.580	7.33759	.133630
HCO3	96	5.9	29.3	16.460	5.5094
Lactate	96	.80	16.40	3.6147	3.16626
MELD-NA	96	7	40	26.79	8.716
CHILD PUGH SCORE (Binned)	96	1	3	2.79	.457
Valid N (listwise)	96				

DISCUSSION

Liver biopsy is the gold standard test for diagnosing liver fibrosis and cirrhosis. Referral for liver biopsy should be considered if a thorough serologic and radiographic evaluation fails to confirm a diagnosis of fibrosis or cirrhosis [10]. Patients may come with cirrhosis issues for the first time or may be asymptomatic and discovered after a routine examination for unrelated reasons or abnormal liver tests. Cirrhosis is divided clinically into two forms: compensated and decompensated. Heavy drinkers, with or without liver disease (ALD), may have elevated γ-GT levels without biochemical evidence of liver damage. However, biochemical abnormalities can also be present in well-compensated cirrhosis, heart failure and fever, suggesting difficulty in assessing the severity of liver disease [9]. Hyponatremia results from increased renal absorption of H2O (as seen in hepatorenal syndrome), stimulating the renin-angiotensin system, and stimulation of antidiuretic hormone due to reduced effective circulating blood volume [11]. The replacement of HCO3 by Cl leads to the appearance of hyperchloremic Metabolic Acidosis, another acidifying factor observed in patients with liver cirrhosis and ascites [11]. Hyponatremia parallels ascites formation and is a well-known trigger of hepatic encephalopathy; its management in this particular population poses a risky challenge due to the high susceptibility of cirrhotic patients to osmotic demyelination [12].

In patients with stable cirrhosis, studies have found that hypoalbuminemic alkalosis, dilutional acidosis and hyperchloremic acidosis work together to achieve a compensatory effect, in which alkalizing and acidifying acid-base disturbances can achieve an equilibrium that eventually results in a stable metabolic acid-base state [13]. Hepatorenal syndrome (HRS) is a severe form of renal failure in patients with cirrhosis and ascites. Renal failure is the most common complication in patients with cirrhosis and ascites, occurring in 20-49% of patients [14]. For a long time, renal dysfunction in cirrhosis was synonymous with type 1 hepatorenal syndrome (HRS1), a condition associated with a fatal outcome in days to weeks if left untreated [14]. Spontaneous bacterial peritonitis is diagnosed after paracentesis when neutrophil ascites concentration is greater than 250/μl. Up to a third of patients with spontaneous bacterial peritonitis do not have fever or pain. Therefore, diagnostic paracentesis is recommended for all hospitalized patients with cirrhosis and ascites [15].

Hepatic encephalopathy (HE) is defined as altered brain functioning caused by liver damage or portosystemic hypertension, according to the 2014 AASLD/EASL recommendations. The second alteration was to classify HE into four primary elements or axes. Varices are a significant source of upper gastrointestinal haemorrhage. Varices indicate the existence of portal hypertension and portal hypertension is described as an increased hepatic venous portal gradient (HVPG) of more than 5 mmHg [9]. There are several risk factors for variceal haemorrhage, including large variceal size (> 5 mm), higher HVPG, red color signs (RCS), active alcohol consumption and sepsis [16]. There are also certain high-risk factors for re-bleeding, including a pressure gradient measured within 24 h of bleeding more than 20 mmHg, presence of large varices, age ≥ 60 years, renal failure, and severe initial bleeding (on admission, haemoglobin < 8 g/dL) [16]. Causes of Portal Hypertension can be divided into three – Pre hepatic, Hepatic and Post hepatic. Increased levels of factor VIII (procoagulant driver) and decreased levels of protein C

(anticoagulant driver), combined with reduced portal vein flow velocity and endothelial injury, increase the risk of portal vein thrombosis (PVT) [17].

Lactic acidosis occurs when more lactic acid accumulates in the bloodstream than the body can release. The liver and kidneys play an important role in metabolism and in removing excess lactic acid from the body. However, if the production of lactic acid is too high, or if the liver or kidneys are weakened and cannot sufficiently process and clear the lactate, this can lead to a build-up of lactic acid in the blood [9]. A moderate increase in blood lactate is called hyperlactatemia, which may or may not cause significant pH changes [9]. However, when the accumulation of lactic acid reaches a point where it disrupts the body's acid-base balance and causes a decrease in blood pH (acidosis), it is then termed lactic acidosis [9].

Lactate is metabolized mainly in the liver (60%) and kidney (30%), and in a normal liver, lactate removal exceeds lactate production in other tissues. Signs of liver failure, such as bleeding or sepsis disrupts the metabolic acid-base balance in cirrhotic patients. Patients with chronic liver disease have higher fasting lactate levels due to changes in the excretory function of the liver and changes in portal pressure [18]. Moreover higher circulating lactate levels are observed in Child class C patients compared to the other Child classes, suggesting that the lactate level increases with the degree of cirrhosis [18].

Sepsis is the most common cause of lactic acidosis, and septic patients with lactic acidosis have a higher mortality rate. The etiology of lactic acidosis in sepsis is complex [19]. This may be due to either decreased lactate clearance or increased lactate production. Therefore, elevated lactate levels indicate severe sepsis or septic shock. In addition, several laboratory tests can be used to assess the severity or prognosis of sepsis [19]. Leucocytosis, elevated C-reactive protein (CRP), and increased procalcitonin are known as traditional markers for sepsis [19]. Based on the biochemistry of lactate formation, lactic acidosis can be classified into two subtypes: type A is associated with hypoperfusion or tissue hypoxia associated with an imbalance of oxygen delivery and consumption, while type B involves conditions that affect lactate production and elimination, which is not related to the oxygen debt [20]. A blood lactate concentration in excess of 5 mmol/L on ICU admission is associated with a 3 and 30 day mortality rate of 59% and 83%, respectively [20]. When patients with liver cirrhosis become critically ill (e.g., because of sepsis or bleeding), this fragile equilibrium often tilts towards metabolic acidosis, which is attributed to lactic acidosis and acidosis due to a rise in unmeasured anions [21].

Limitations

The sample size is relatively small, Hepatic Encephalopathy grading can be inaccurate / subjective and Hepato-Renal Syndrome patients are also included in the samples which predominantly show Metabolic Acidosis.

CONCLUSION

In our study of 96 samples, major cause of Cirrhosis was Alcohol with majority being Males and around 13 patients had comorbidities in the form of hypertension or diabetes. Majority of patients showed Metabolic Acidosis and also came under Child-Pugh class C and also the three year mortality was predicted using MELD-Na score and majority were under the score of 20-29 followed by 30-39. This study thus explains that there is correlation between Cirrhosis and Metabolic Acidosis.

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