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International Normalised Ratio-to-Albumin Ratio as a Prognostic Tool among Patients of Liver Cirrhosis and Sepsis

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Abstract

***Background:** Liver cirrhosis is a chronic condition characterised by progressive liver dysfunction and is a significant cause of morbidity and mortality, globally. Sepsis is a common and severe complication in cirrhotic patients. The Prothrombin time-international normalised ratio (PT-INR) and serum albumin levels are critical indicators of liver function and nutritional status, respectively. This study aims to evaluate the prognostic value of INR to Albumin Ratio (PTAR) in patients of cirrhosis with sepsis.*

***Methods:** This prospective hospital-based observational study included 90 patients aged 18 - 65 years with cirrhosis and sepsis (qSOFA $\geq$2). Patients were excluded if they had bleeding disorders, were on anticoagulants, pregnant, malignancy, or other chronic illnesses. INR to Albumin Ratio was calculated at admission. Patients were categorised into low, intermediate, and high-risk groups based on the score and were followed up to record outcomes.*

***Results:** The study revealed that in low-risk patients (PTAR<0.55), 84% patients survived whereas 16% died. In intermediate risk patients (PTAR 0.55-1), 56.7% survived whereas 43.3% died. In high-risk patients (PTAR >1), 20% survived whereas 80% died. The p value was <0.001.*

***Conclusion:** The PTAR score can be easily calculated at the bedside and correlates significantly with prognosis, with higher scores assosciated with increased mortality. This underscores its utility in clinical settings and supports its use as a valuable marker for assessing prognosis in cirrhotics with sepsis.*

***Key words:** Cirrhosis, sepsis, INR, albumin.*

Introduction

Liver cirrhosis is a chronic and insidious condition marked by the progressive degeneration of liver function caused by tissue fibrosis and conversion of normal liver architecture into structurally abnormal nodules[1]. This complicated ailment, often caused by factors like chronic alcoholism or viral hepatitis, intricately disrupts the liver's structural integrity and undermines its vital functions[2]. A patient with liver cirrhosis is initially asymptomatic or in a phase of "compensated" cirrhosis. With further disease progression, patient develops complications of portal hypertension and liver dysfunction and develops a phase of "decompensated" cirrhosis which is defined by the presence of ascites, variceal bleeding, hepatic encephalopathy, and/or jaundice[3]. Cirrhosis is one of the leading causes of mortality and morbidity all over the world[4]. Around 2 million deaths worldwide per year are due to liver disease, with 1 million deaths due to the complications of cirrhosis and 1 million deaths due to viral hepatitis and hepatocellular carcinoma[5].

The International Normalised Ratio (INR) is a standardised measure of blood coagulation, primarily used to monitor the effectiveness of anticoagulant medications. In cirrhosis, compromised liver function results in decreased synthesis of clotting factors, leading to an elevated INR. As a standardised measure of blood clotting time, INR provides clinicians with profound insights into the liver's synthetic function, acting as a sentinel for the subtle changes and disruptions that characterise the relentless progression of cirrhosis[6].

Albumin, a protein synthesized by the liver, serves as a key component of the body's oncotic pressure, and contributes to maintaining vascular integrity. In cirrhosis, reduced liver function results in decreased albumin production, leading to hypoalbuminaemia. Beyond its role in maintaining osmotic pressure, albumin plays a crucial role in modulating immune response and inflammation.

Cirrhosis, in advanced stages predisposes an individual to various complications, with sepsis being a critical and life-threatening event, the occurrence of which is estimated to be around 30% to 50% of all hospital admissions[7]. The Third International Consensus Definition Task Force defines sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection[8]. Physiologically, sepsis is viewed as a pro-inflammatory and pro-coagulant response to

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invading pathogens with a progressively increased risk of end-organ failure and death[9]. Sepsis in cirrhotic patients leads to further worsening of liver function and development of organ or system failure and hence, emerges as a formidable adversary especially in cirrhotics. In patients with suspected infections, a bedside clinical score-quick Sequential Organ Failure Assessment Score (q SOFA) can predict poor outcomes typical of sepsis[8].

Prothrombin time-international normalised ratio (PT-INR) to Albumin Ratio (PTAR) is a novel, objective score developed by Haruki *et al* to assess liver functional reserves in patients with hepatocellular cancer following hepatic resection[10]. They showed that in a retrospective analysis involving 199 patients, the PTAR score was effective in forecasting both the short- and long-term results. Patients with cirrhosis experience abnormalities in liver function and decreased reserves, just like those who have undergone hepatocellular carcinoma resection.

The promise held within the integration of these two metrics lies in their collective ability to function as a prognostic tool. The PTAR score could be a reliable metric for evaluating patients of liver cirrhosis with sepsis. Consequently, we decided to conduct a study on patients suffering from cirrhosis of the liver with sepsis to evaluate the PTAR score and its prognostic value.

Aim

The study was conducted with the aim to study the combined prognostic value of INR to albumin ratio amongst patients of liver cirrhosis who have sepsis.

Material and Methods

The study was conducted in the Department of Medicine at Gandhi Medical College, Bhopal after approval from Institutional Ethics Committee. This was a prospective hospital based observational study. The inclusion criteria consisted of:

1. Age 18 - 65 years
2. Patients of cirrhosis of liver with sepsis (with history/ clinical examination/investigations supportive of infection)
3. qSOFA score ≥ 2

The exclusion criteria consisted of patients aged <18 years and >65 years, qSOFA score <2, individuals with other known bleeding disorders, those on anticoagulant or drugs affecting PT/INR (Table I), pregnancy, patients with malignancy, and, patients with any other chronic systemic illness.

Table I: Drugs affecting PT/INR.

Vitamin K antagonists	Warfarin, Acenocoumarin
Direct Factor Xa Inhibitors	Apixaban, Rivaroxaban, Edoxaban
Direct Thrombin Inhibitors	Argatroban, Dabigatran
Antibiotics	Cotrimoxazole, Macrolides, Fluoroquinolones
Antifungals	Azoles (Fluconazole)

After a detailed clinical history, examination and investigations, the data was collected in a proforma which was pre-designed and included lab parameters such as CBC, LFT, RFT, PT-INR, blood and urine cultures, serology (HBsAg, anti-HCV and HIV), and ultrasound of abdomen. Even though biopsy is the gold standard for diagnosing cirrhosis, patients of cirrhosis were identified using clinical, laboratory and radiology as biopsy is not always required[11]. The qSOFA score was calculated for all patients at the time of admission. The score consists of three components with 1 point to each component - respiratory rate >22/min, Change in mental status (GCS <15) and systolic blood pressure <100 mm of Hg. A score of two or more points in patients with presumed infection defines sepsis. Patients of cirrhosis of liver with presumed infection based on history and clinical examination along with qSOFA score ≥2 were recruited for the study on fulfillment of inclusion and exclusion criteria. The PTAR score on the day of admission was calculated by using a simple formula, INR divided by albumin (g/dL). Based on this score, patients were classified as low-risk (PTAR score <0.55), intermediate-risk (PTAR score 0.55 - 1.00), or high-risk (PTAR score >1.00). These patients were then followed up and the outcome was recorded (discharged/expired) at the end of the hospital stay.

Results

The study revealed a predominant middle-aged demographic (Fig. 1) with most participants, 44.4% in the age group 41 - 50 years, followed by 25.6% in the 51 - 60 years group, 24.4% in the 31 - 40 years group, 5.6% in 61 - 65 years group and none in 18 - 30 years group. Additionally, 88.9% of participants were males.

Aetiological work-up (Fig. 2) of the participants revealed that the probable cause of cirrhosis was alcohol in 75.6%, viral (Hepatitis B and C) in 22.2% and 2.2% could be attributed to other causes like NAFLD.

The study revealed that the possible source of sepsis (Fig. 3) was pneumonia in 28.9%, urinary tract infection in 26.7%, spontaneous bacterial peritonitis in 13.3%, skin and soft tissue infections in another 13.3% and gastrointestinal tract infections in 6.7%. A positive blood culture indicating septicaemia was found in 5.6% cases. No cause could be

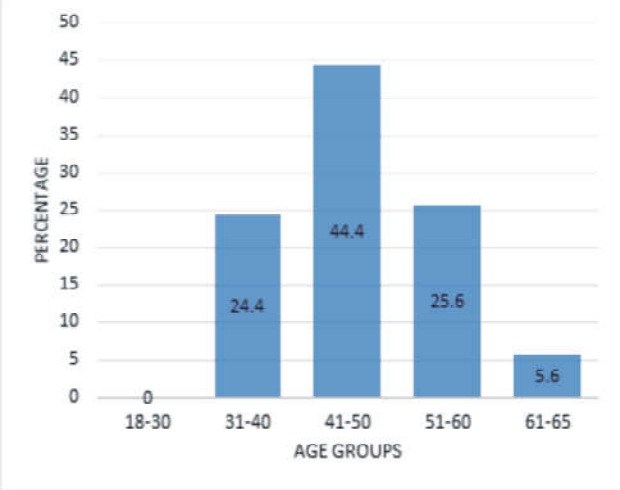

Fig. 1: *Age-wise distribution of cases*

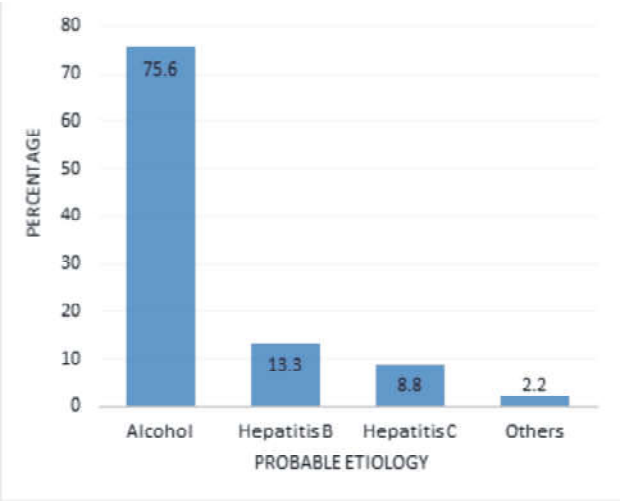

Fig. 2: *Probable aetiology of cirrhosis*

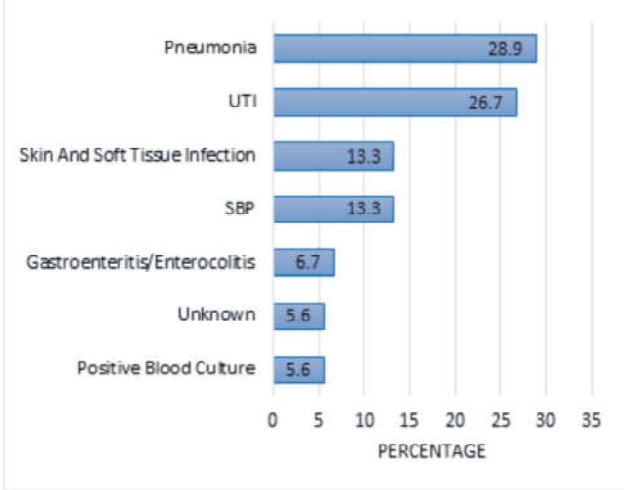

Fig. 3: *Possible source of sepsis in cases*

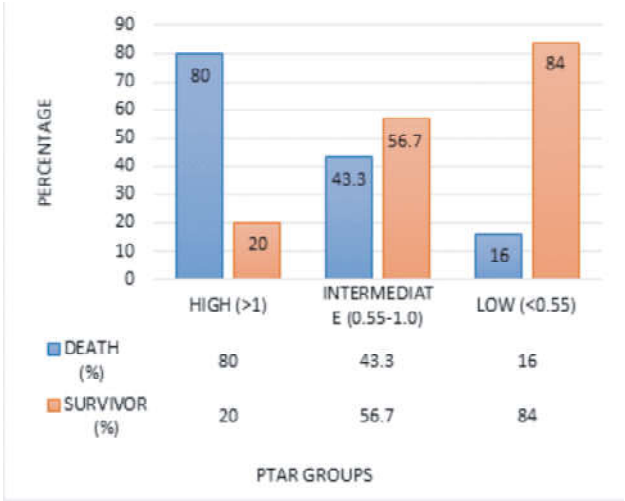

Fig. 4: *Outcome of cases according to PTAR scores (in percentage)*

identified in another 5.6% patients.

Blood cultures yielded a growth in 57.8% of cases, the most common organism being *Enterococcus*. Additionally, 42.2% of cases were negative for any growth. Urine cultures revealed a growth in 26.7% of cases and the most common organism isolated was *Escherichia coli*. Additionally, 73.3% of urine cultures were negative. The percentage distribution of the sample with cirrhosis of the liver with sepsis in various PTAR scores shows that 38.9% had a high score (>1), 33.3% had an intermediate score (0.55 - 1.00), and 27.8% had a low score (<0.55). The association between PTAR score and outcome (Fig. 4) revealed that:

- Out of 25 (27.7%) low risk patients, 21 (84%) patients survived (discharged) whereas 4 (16%) died.
- Out of 30 (33.3%) intermediate risk patients, 17 (56.7%) survived (discharged) whereas 13 (43.3%) died.
- Out of 35 (38.8%) high-risk patients, 7 (20%) survived (discharged) whereas 28 (80%) died.

The p value was <0.001, indicating a significant association between PTAR score and outcome.

Discussion

Our study revealed male predominant demographics with majority of participants in the age group of 41 - 50 years of age. Comparatively, Bhattacharya *et al*[12] study reported a higher mean age of 58.87 years with a male preponderance of 69.8%. A study by Karvellas *et al*[13] found a mean age of 55 years and a male percentage of 60%. However, in other studies carried out by Acharya *et al*[96] and Wang *et al*[14], 83.62% and 83.16% of study participants were males. Lucidi *et al*[15] included patients with a mean age of 49.7 years and 75.7% of participants were males. Thulstrup *et al*[16]

population-based study reported a mean age of 58.1 years and a male percentage of 59%. Our younger age group and higher male percentage highlight potential regional variations in alcohol consumptions, lifestyle, healthcare access and epidemiology of cirrhosis.

Worldwide, hepatotropic viruses are the most common causes of cirrhosis of liver. However, our study shows that 75.6% of cirrhosis cases were due to alcohol, 22.2% were viral, and 2.2% were attributed to other causes. This is consistent with findings from several other studies on the aetiology of cirrhosis carried out in India. Alcohol could be attributed as the aetiology of cirrhosis of liver in 72.2% in the study by Bhattacharyya *et al*[17], 62.9% by Sharma *et al*[18], 63.3% by Mishra *et al*[19] and 69% by Ahmed *et al*[20]. The increasing prevalence of alcohol consumption in the country is increasing the burden of alcohol-induced liver cirrhosis and mortality, particularly in the productive age group. Alcohol in itself is an independent risk factor for sepsis and mortality.

The possible sources of sepsis among participants in our study showed that 28.9% were due to pneumonia, 26.7% from UTIs, 13.3% from skin and soft tissue infections and 13.3% from SBP. Bhattacharya *et al*[12] found that sepsis was a significant predictor of mortality, present in 47.31% of survivors and 100% of non-survivors. Their study highlighted the prevalence of healthcare-associated infections, which aligns with our finding of pneumonia and urinary tract infections as major sources of sepsis. Karvellas *et al*[13] specifically focused on SBP, identifying it as the most frequent infection in cirrhotic patients. They demonstrated that delays and inappropriate antimicrobial therapy were associated with adverse outcomes in SBP cases. In a study by Fernandez *et al*[21], out of 572 patients with cirrhosis of liver with sepsis, the most common infection was SBP (25%), followed by urinary tract infection (20%), pneumonia (15%) and cellulitis (6%). In another study carried by Borzio *et al*[22], out of 150 (34%) bacterial infections (89 community- and 61 hospital-acquired) involving urinary tract (41%), ascites (23%), blood (21%) and respiratory tract (17%) were diagnosed. The prevalence of bacterial peritonitis was 12%. Our study's 13.3% incidence of SBP as a source of sepsis corroborates their findings and underscores the importance of prompt diagnosis and effective antimicrobial treatment. Cholongitas *et al*[23] and Haruki *et al*[10] noted the prevalence of severe infections, including SBP and other bacterial infections, in cirrhotic patients, reinforcing the importance of managing these infection sources to improve outcomes.

In the study by Haruki *et al*[10], the prothrombin time-international normalised ratio to albumin ratio (PTAR) was found to be a predictor of cancer recurrence and poor overall survival in hepatocellular carcinoma patients. The prognostic value of the INR-to-albumin ratio in cirrhotic patients is strongly supported by existing literature. Gao *et al*[24] validated the PTAR score as an effective tool for predicting 90-day mortality in critically-ill cirrhotic patients, demonstrating a significant association with increased mortality rates and good discrimination ability (AUC of 0.72). Their research validates our focus on the INR-to-albumin ratio as a critical metric in liver disease prognosis.

The percentage distribution of our sample with cirrhosis of the liver and sepsis according to PTAR scores shows that 38.9% had a high score (>1), 33.3% had an intermediate score (0.55 - 1.00), and 27.8% had a low score (<0.55). This distribution highlights the varying degrees of risk and severity among the study participants. Our study revealed that among low-risk patients (PTAR <0.55), 84% patients survived whereas 16% died. Among intermediate risk patients (PTAR 0.55 - 1), 56.7% survived whereas 43.3% died. Among high-risk patients (PTAR >1), 20% survived whereas 80% died. The association between PTAR score and outcomes shows a significant correlation, with higher PTAR scores (>1) associated with increased mortality ($p < 0.001$). These findings align with the study by Gao *et al*[24] who validated the prognostic value of the PTAR score in predicting 90-day mortality among critically-ill cirrhotic patients and found out that higher PTAR scores were significantly associated with increased mortality rates (13%, 30% and 58.5% among low risk, intermediate risk and high-risk patients respectively.) Haruki *et al*[10] also found that a higher PTAR score predicted poor overall survival and increased recurrence rates among hepatocellular carcinoma patients, further supporting the utility of PTAR in predicting adverse outcomes. The significant association between PTAR score and outcomes in our study underlines the importance of this ratio as a prognostic tool in clinical practice, helping to identify patients at higher risk and guiding appropriate treatment strategies.

The relatively small sample size may affect the generalisability of the findings. Additionally, the study was conducted at a single centre, potentially introducing selection bias. The observational nature of the study also limits the ability to establish causal relationships. Furthermore, variations in the management and treatment protocols for cirrhosis and sepsis across different institutions could impact the applicability of our results.

Conclusion

Our study highlights the prognostic value of the INR-to-albumin ratio in predicting outcomes during hospital stays for patients with cirrhosis of the liver and sepsis. Our study demonstrated that patients with sepsis and cirrhosis of the liver experienced high mortality rates. Both INR and serum albumin levels are widely available, even in a low resource

setting and inexpensive. The PTAR score can be easily calculated at the bedside and correlates significantly with the prognosis of the patient, with higher scores correlating significantly with increased mortality. This underscores its utility in clinical settings and supports the use of the INR-to-albumin ratio as a valuable marker for assessing prognosis and guiding treatment strategies in cirrhotic patients with sepsis.

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