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The Role of Bilirubin - Albumin Ratio Versus Platelet - Albumin Ratio as a Predictor of Mortality in Critically Ill Patients Without Pre-Existing Liver or Biliary Tract Disease – A Prospective Study

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Abstract:_**Objective:** - To compare the bilirubin - albumin ratio versus platelet - albumin ratio as a better indicator for predicting mortality in critically ill patients without existing liver or biliary tract disorders. **Methods:** - A prospective study was conducted among adults (>18 years) admitted to the ICU at a tertiary care centre in India among 196 patients. Platelet albumin ratio (PAR) and Bilirubin - Albumin Ratio (B/A ratio) were obtained from patients' records on the day of admission. **Results:** - The mean age of the participants was 53.8 years (SD 16.8 years). Twenty-one (10.7%) deaths were reported in the hospital during the period of study. The mean Bilirubin-Albumin Ratio (B/A ratio) was significantly higher among those who died (2.8; SD 1.7) compared to those who survived (0.6; SD 0.96; mean difference 2.2; 95% CI: 1.6 to 2.8; p<0.001). B/A ratio on admission had a good predictability (AUC 0.87, p<0.001)) of mortality, but the predictability of PAR was quite low (AUC 0.48). The cut-off for the B/A ratio for predicting mortality is 0.4 with a sensitivity of 87% and specificity of 74%. **Conclusion:** - The B/A ratio is a reliable predictor of mortality in critically ill patients who do not have pre-existing liver or biliary tract disorders.

Keywords: Albumin, Bilirubin, critically ill, Mortality, Prognosis

Background (Introduction)

Critically ill patients, admitted to intensive care units (ICUs) due to life-threatening conditions, face a significant risk of mortality. Early and accurate identification of patients at high risk of death is crucial for optimizing treatment strategies, allocating resources effectively, and improving patient outcomes. Liver dysfunction, a frequent complication

arising during critical illness, is a well-established predictor of poor prognosis. The breakdown of red blood cells produces bilirubin. The liver normally conjugates and excretes bilirubin. In critically ill patients, however, various factors can impair bilirubin metabolism, leading to elevated bilirubin levels (hyperbilirubinemia). It is well-established that an increased level of serum bilirubin indicates liver dysfunction and also contributes to an imbalanced immune response, renal or cardiac dysfunction; and aggravated bacterial infections. Furthermore, the increased bilirubin levels are closely associated with increased mortality

Albumin, a major liver protein synthesized by the liver, is a carrier for various substances, including bilirubin. Albumin reflects the nutritional status of the patient and low albumin predicts a poor prognosis in acutely ill patients [1] Hypoalbuminemia has been proven to be related to increased mortality, prolonged hospital stays, and increased duration of invasive mechanical ventilation. In critical illness, decreased albumin production (hypoalbuminemia) can further reduce the liver's capacity to eliminate bilirubin.

Platelets are blood cells essential for clotting. A growing body of research suggests that a complex interplay exists between inflammation, liver function, and platelet count. Platelets can trigger and elevate the risk of inflammation through interaction with a variety of immune cells and secretion of pro-inflammatory cytokines and inflammation drives the development of malnutrition, which may in turn amplify systemic inflammatory responses, leading to a vicious cycle.[2] In critical illness, systemic inflammation can activate platelets and contribute to their consumption. Additionally, liver dysfunction can impair platelet production.

The hepatic response is crucial in host defense mechanisms in patients with sepsis or other critical illnesses. [3-5] Hepatic dysfunction is indicative of poor outcomes in critically ill patients, and abnormal liver function tests, including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin, are commonly observed in these patients [6,7]. Hepatic dysfunction, especially hyperbilirubinemia, is associated with poor outcomes [8,9] . Bilirubin level is widely used scoring systems for sepsis, such as the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score and the Simplified Acute Physiology Score (SAPS) [10,11]. Additionally, low albumin levels are useful for predicting poor prognosis in acutely ill patients [6,1] . Due to its significance in predicting outcomes in ICU patients, serum albumin levels are included in the Acute Physiology and Chronic Health Evaluation (APACHE) III score. [12]

Several studies have investigated the relationship between the serum bilirubin to albumin ratio (B/A ratio) and patient prognosis. [13,14] In neonates, the B/A ratio can be used to predict acute bilirubin-induced neurologic dysfunction.[13,14]. In addition, recent studies

have indicated that the platelet-to-albumin ratio (PAR), an indicator of the inflammatory response, may serve as a predictive marker or progression factor for various types of critically ill conditions including cancers.[15–17] .

The B/A ratio combines these two markers, potentially providing a more comprehensive picture of liver dysfunction in critically ill patients. A higher B/A ratio may indicate both impaired bilirubin clearance and decreased protein synthesis, potentially signifying a more severe illness and higher mortality risk.

The Platelet-Albumin Ratio (PAR) takes these factors into account. A high PAR may indicate increased inflammation, platelet activation, and potential impairment in platelet production by the liver, all of which could contribute to adverse outcomes in critically ill patients
This study delves into the potential of two readily available biomarkers, the bilirubin-to-albumin ratio (B/A) and the platelet-to-albumin ratio (PAR), as mortality predictors in critically ill patients.

By specifically focusing on patients without pre-existing liver or biliary tract diseases, we aim to isolate the effects of critical illness on liver function and subsequent mortality. This targeted approach allows us to investigate the specific impact of critical illness-induced liver dysfunction on patient outcomes, independent of confounding factors caused by underlying liver pathology.

By directly comparing the effectiveness of B/A and PAR in predicting mortality, this study seeks to definitively identify the most informative and readily available biomarker for risk stratification in this vulnerable patient population.

Ultimately, this research has the potential to improve clinical decision-making in the ICU setting, leading to more personalized and optimized care for critically ill patients

Lacuna in Knowledge
There is only limited evidence examining the role of B/A ratio versus PAR in predicting the prognosis of critically ill patients.Hence, we intended to conduct this study.

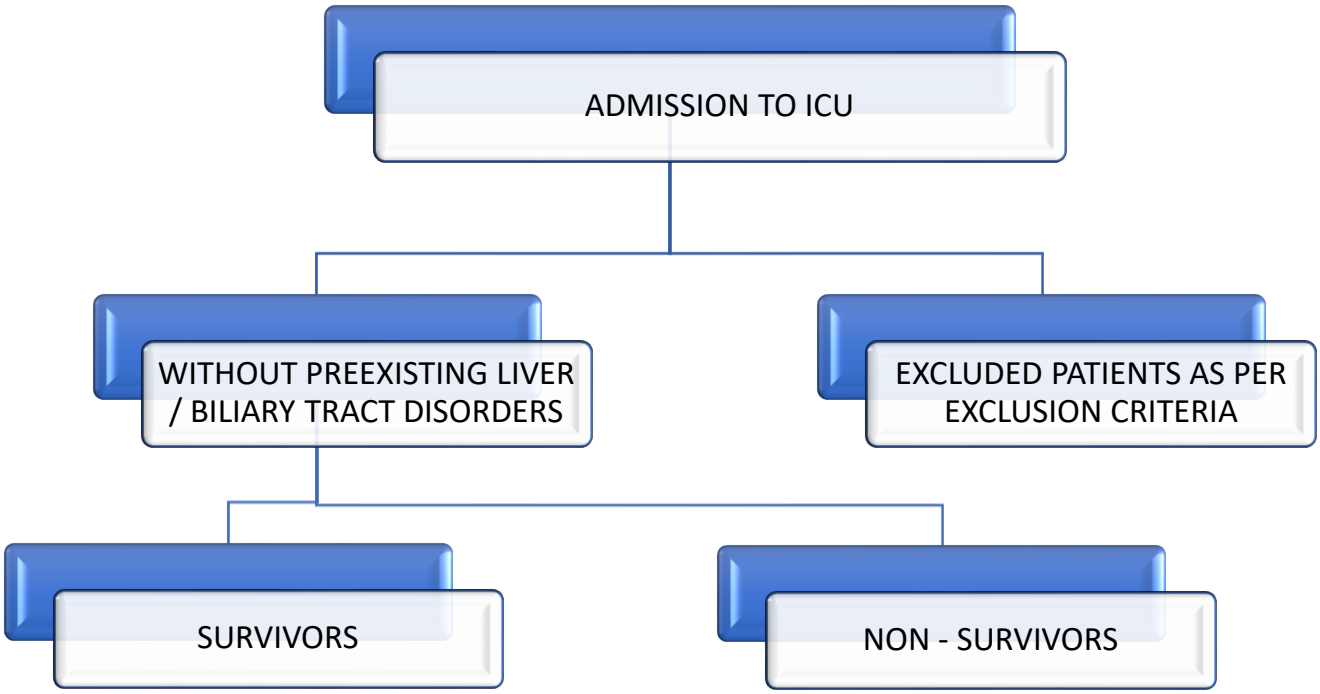
Objectives
The primary objective of the study is to compare the bilirubin - albumin ratio versus platelet - albumin ratio as a better indicator for predicting mortality in critically ill patients without existing liver or biliary tract disorders in a tertiary care set-up in India

Materials & Methods:

Study Design: A Prospective observational study

Duration of study:4 months, between January 2024 to April 2024.

Study Participants: This study was conducted on patients of age more than 18 years admitted in the ICU at a tertiary care centre in Kolar, Karnataka, India. We excluded patients having diagnosis like acute/alcoholic hepatitis, chronic hepatitis, liver cirrhosis, cholecystitis, cholangitis, hepatic encephalopathy; and patients who have undergone liver, biliary, or pancreatic surgeries.



Sample size: Sample size is estimated based on the online statistical calculator for estimating a single proportion by taking the proportion of the mortality among the ICU patients as 70% as reported in a study done by [18]. We assumed the power to be 80% and type I error as 5% the estimated sample size is 200.

Inclusion criteria:

• Patients more than 18 years of age admitted in the ICU.

Exclusion criteria:

- Patients under 18 years old
- Readmission of patients according to institution protocol
- Patients admitted due to acute/ alcoholic hepatitis, chronic hepatitis, liver cirrhosis, cholecystitis, cholangitis, hepatic encephalopathy
- Patients who have undergone liver, biliary or pancreatic surgeries

Methodology:

Participants were recruited in the study after obtaining written, informed consent from them or from the legal representatives where participants were unable to provide consent due to their medical condition. Patient baseline characteristics, disease severity such as APACHE II score, vitals of the patient such as heart rate (HR), peripheral capillary oxygen saturation (SPO_2), mean arterial pressure (MAP), respiratory rate (RR) were recorded after admission into ICU on the day of admission. Laboratory parameters include haemoglobin, white blood cell count (WBC), platelets, blood urea, serum creatinine, total bilirubin, serum albumin, and lactate were recorded.

The two major predictor variables were platelet albumin ratio (PAR) and bilirubin albumin ratio (B/A ratio). PAR was calculated by total platelets (per µL blood) expressed as a multiplier of 10^5 divided by total albumin. B/A ratio was expressed as a ratio of total bilirubin and total albumin

Statistical analysis:

The data was entered in Microsoft Excel and analysed in Stata version 18.0. Descriptive statistics were used to express the clinical parameters including mean and standard deviation (SD) or median and interquartile range (IQR), depending upon the distribution of the variables. For statistical comparison between the two groups, a t-test was applied. A ROC curve was created to examine the predictability of mortality by the two variables. A p-value <0.05 was considered statistically significant for all statistical tests.

Conflict Of Interest- Nill

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Results:

We recruited a total number of 196 patients for the study. The mean age of the participants was 53.8 years (SD 16.8 years), and both genders were equally distributed (Table 1). The median APACHE score was 25 (IQR 22 to 27). The majority of the participants (n=134, 68.4%) had at least one comorbidity with them (Table 1).

Table 1: Clinical characteristics of the participants

		Estimates	
Characteristics	**Survived**	**Died**	**p-value**
Mean age, years (SD)	53.5 (16.9)	56.3 (16.2)	0.47
Gender, n (%)			

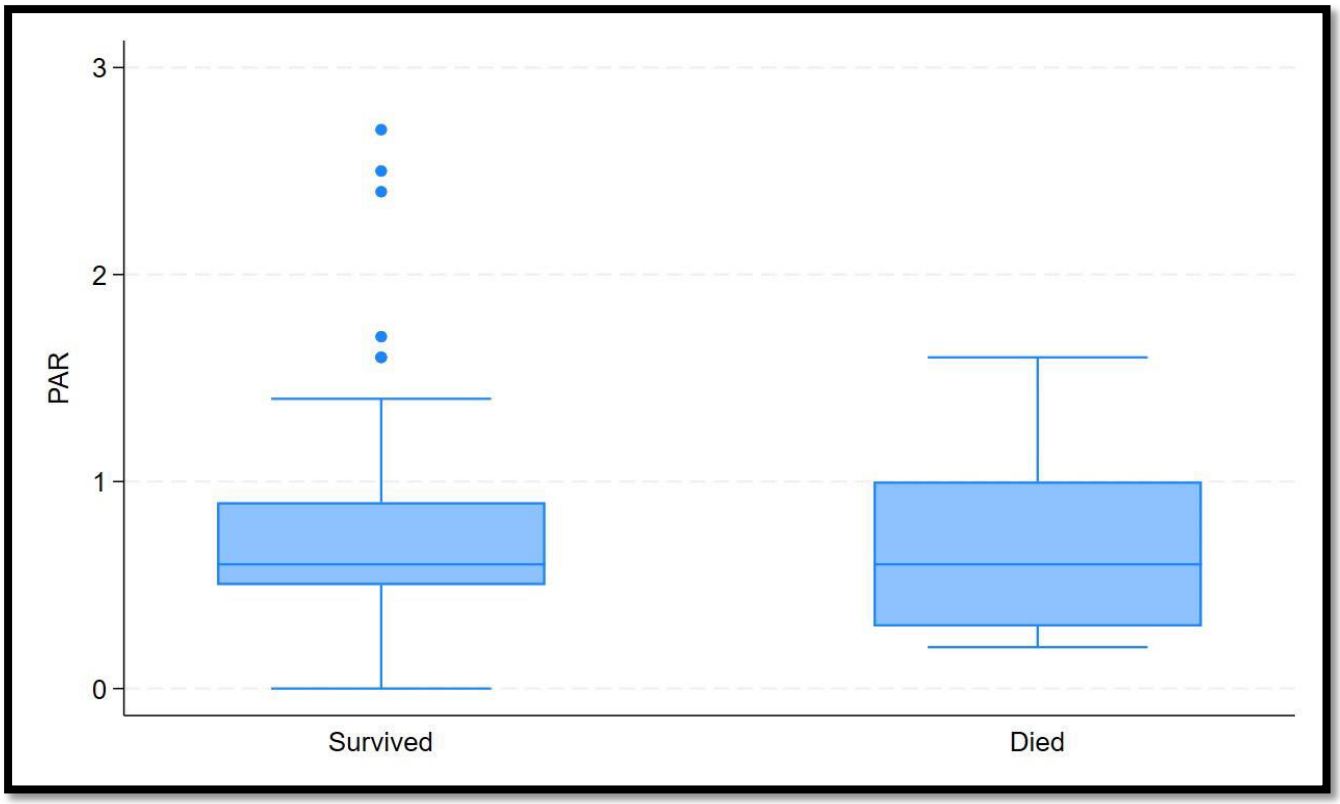
Male	86 (49.1)	10 (47.6)	0.9
Female	89 (50.9)	11 (52.4)	
APACHE2 score, median (IQR)	25 (22 to 27)	26 (23 to 28)	0.15
Presence of at least one comorbidity (%)	53 (30.3)	9 (42.9)	0.24
Mean haemoglobin, gm/dL (SD)	11.6 (3.2)	11.9 (3.5)	0.66
Mean WBC ($\times 10^3$) per µL blood (SD)	15.8 (7.9)	17.5 (7.1)	0.36
Mean platelets ($\times 10^5$) per µL blood (SD)	2.17 (0.88)	1.82 (0.73)	0.08
Median urea (IQR)	68.0 (48.2)	129.2 (67.6)	<0.001*
Median creatinine (IQR)	1.2 (0.8 to 1.9)	1.2 (0.8 to 2.2)	0.002*
Median bilirubin (IQR)	0.85 (0.5 to 1.5)	3.9 (2.7 to 7.3)	<0.001*
Median albumin (IQR)	3.5 (2.7 to 4.2)	2.7 (2.3 to 3.8)	0.09

*Statistically significant

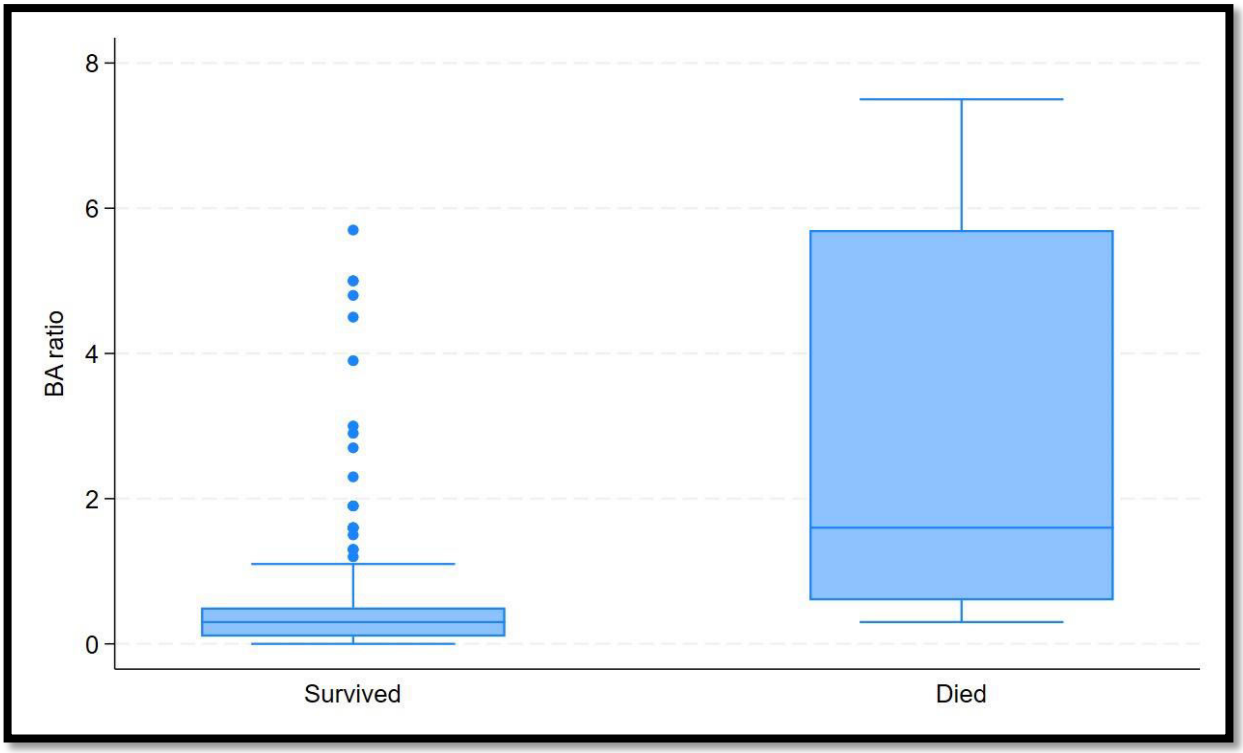
Mortality: A total number of 21 (10.7%) deaths happened in the hospital among the study participants.

Platelet albumin ratio (PAR) and bilirubin albumin ratio (B/A ratio):

The mean PAR was 0.77 (SD 0.7), while the mean B/A ratio among the study participants was 0.8 (D 1.4). The mean PAR was slightly higher among those who died (0.77; SD 0.7) compared to those who survived (0.7; SD 0.4); thus, the mean difference was 0.07 (95% CI: -0.23 to 0.4; p=0.62) which was statistically not significant.

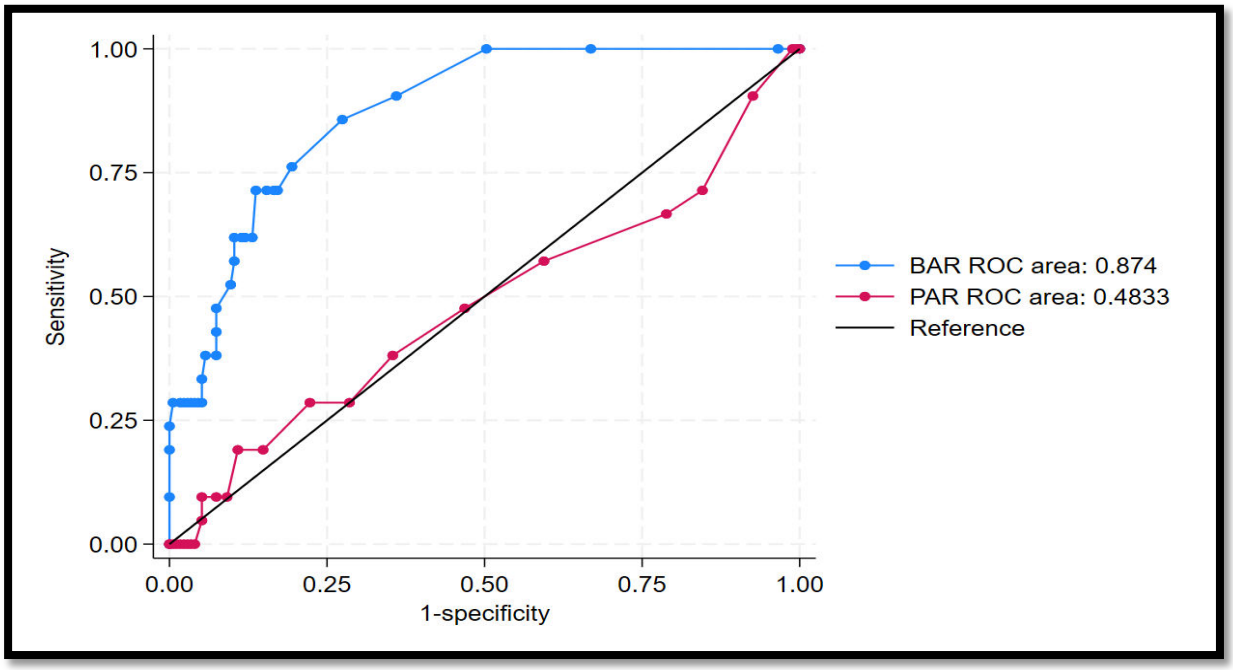


On the other hand, the mean B/A ratio was significantly higher among those who died (2.8; SD 1.7) compared to those who survived (0.6; SD 0.96); thus, the mean difference was 2.2 (95% CI: 1.6 to 2.8; p<0.001).



ROC plot shows that B/A ratio on admission has a good predictability (AUC 0.87) of mortality, but predictability of PAR is quite low (AUC 0.48), the difference being statistically significant (p<0.001) (Figure 1) The cut-off for B/A ratio for predicting mortality is 0.4 with a sensitivity of 87% and specificity of 74%.

Figure 1: ROC curve of B/A ratio and PAR for predicting mortality



BAR: bilirubin albumin ratio, PAR: Platelet albumin ratio

Discussion:

This prospective observational study explores the mortality predictability of the B/A ratio and PAR on admission during a hospital stay in an ICU setting in an Indian context. We estimated that the predictability is quite high for the B/A ratio. However, PAR didn't show any relationship with mortality in our setting.

Numerous prior studies have explored the mechanisms behind liver dysfunction and jaundice in critical illnesses. The liver plays a crucial role in host defense and tissue repair, which is mediated by interactions among hepatic cells such as hepatocytes, Kupffer cells, and sinusoidal endothelial cells in patients with sepsis and other critical conditions [4] Hepatic dysfunction, evidenced by abnormal liver tests, has been reported in 10-30% of ICU patients.[7,8,19] Serum bilirubin concentration is typically measured to aid in the initial diagnosis and evaluate the prognosis as a part of the liver function in ICU patients. Bilirubin levels are incorporated into commonly used organ dysfunction scoring systems. [10,20,21]

As a marker of liver dysfunction, elevated bilirubin levels are considered to be directly related to the prognosis of critically ill patients. Brienza et al. found that the prevalence of

hyperbilirubinemia, defined as levels above 2 mg/dL, was 30% among critically ill patients. Their study identified sepsis, severe septic shock, mechanical ventilation with Positive End Expiratory Pressure, and major surgery as risk factors for hyperbilirubinemia. [7] Recently, Pierrakos et al. reported that hyperbilirubinemia without a primary cause could be an independent risk factor for mortality in ICU patients. [9] Their study demonstrated a linear correlation between bilirubin levels and mortality, ranging from 1 to 6 mg/dL. In our study, serum bilirubin levels at ICU admission predicted hospital mortality, aligning with previous reports. In this study, we found that the B/A ratio could be a reliable predictor of mortality. Earlier reports have suggested that the serum B/A ratio could predict bilirubin encephalopathy and neurological dysfunction in neonates. [13,14,22] and in critically ill adults in ICU set-up. [18]
In this study, the AUC of the B/A ratio was significantly higher than that of the P/A ratio. A higher B/A ratio at ICU admission was associated with unfavourable outcomes in critically ill patients.

Platelet-to-albumin ratio (PAR) has recently been proposed as an excellent and reliable index for systemic inflammation and immune nutrition status. [15] This is primarily because the PAR remains more stable across various physiological conditions and diseases than the individual components of platelets and serum albumin. It has been proposed that PAR, which combines platelet and serum albumin levels, more accurately reflects the state of inflammation and nutrition in specific conditions like acute kidney injury (AKI). [16] However, our study found no relationship between PAR and hospital mortality.

Conclusion:
This prospective observational study conducted in a tertiary care setting in India demonstrates that the bilirubin-albumin ratio (B/A ratio) is a reliable predictor of mortality in critically ill patients who do not have pre-existing liver or biliary tract disorders. Conversely, the platelet-albumin ratio (PAR) did not demonstrate a significant relationship with mortality in our cohort. These findings underscore the potential utility of the B/A ratio as a simple and effective tool for early risk stratification in critically ill patients in ICU settings. However, additional evidence in this setting is warranted before incorporating it as a marker in the clinical practice guidelines.

Limitations:
The study has a few limitations. First, its single-centre prospective observational design may limit the generalizability of the results. Secondly, only on-admission bilirubin, platelets, and albumin values were included, and subsequent assessments of these parameters were done as per the needs of the patients, and therefore we could not examine the serial changes. Additionally, interactions with various inflammatory indicators were not included in the database, preventing an assessment of the association between PAR and these inflammatory indicators