

A Hospital-Based Cross-Sectional Study on Non-Invasive Predictors of esophageal Varices in Patients with Chronic Liver Disease.

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ABSTRACT

Chronic liver disease (CLD) globally affects millions of individuals; the esophageal varices are a major complication of CLD due to portal hypertension. This study evaluates clinical, biochemical, and radiological parameters as non-invasive predictors of esophageal varices in patients with CLD. A hospital-based cross-sectional study was conducted at SRM Medical College Hospital and Research Centre from October 2022 to March 2024, enrolled newly diagnosed CLD patients aged 18–80 years who had not underwent prior treatment for portal hypertension or varices. Thereafter, data on demographics, medical history, laboratory parameters, clinical and imaging findings were collected. The presence and severity of esophageal varices were assessed using endoscopy and correlated with non-invasive predictors. Among 88 participants, 84.1% had esophageal varices, predominantly Grade 1 (58.0%). Significant predictors of varices included low platelet count ($<100,000/\mu\text{L}$), increased spleen size ($>12\text{ cm}$), and platelet-to-spleen ratio (<909) showed correlation with variceal presence. Non-invasive markers, such as serum biomarkers, demonstrated high sensitivity and specificity plays a pivotal role in identifying the early detection of patients at risk of varices. This investigation aids to reduce the reliance on routine endoscopy, improving patient care and resource allocation.

Keywords: Chronic liver disease, esophageal varices, Platelet-spleen ratio, Portal hypertension

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1. INTRODUCTION

Chronic liver disease (CLD) is a persistent inflammatory condition characterized by long-term biochemical and histopathological abnormalities in the liver. It represents a broad range of liver disorders encompassing hepatitis to cirrhosis [1]. CLD affects approximately 300 million individuals globally each year [2]. The principal reasons for CLD are alcohol abuse, chronic viral hepatitis, and metabolic factors such as non-alcoholic steatohepatitis (NASH) [3]. These underlying liver conditions cause chronic liver injury, which leads to the accumulation of extracellular fibrotic tissue in the liver, disrupting normal oxygenation and blood flow within the liver parenchyma [4] [5] [6]

Cirrhosis, the advanced stage of CLD, is generally identified by severe structural and functional modifications in the liver. A significant issue of cirrhosis is portal hypertension, which is determined by an upsurge in hepatic venous pressure gradient to >5 mmHg. Portal hypertension frequently leads to complexities like variceal bleeding and ascites [7, 8]. Esophageal varices, dilated and convoluted veins that predominantly form in the distal esophagus and gastric fundus, are the most clinically significant outcome of portal hypertension [9, 10]. At the time of cirrhosis diagnosis, 60% of patients are decompensated, and 30% of those with compensated cirrhosis already have esophageal varices. The varices produce a substantial hemorrhage risk, with small varices having a 7% chance of bleeding within two years whereas large varices have 30% bleeding for large varices over the same course of time [11, 12, 13, 14]. Acute variceal bleeding is life-threatening, with a mortality rate of 20% from the first haemorrhage [15].

In these aspects, screening for oesophageal varices in cirrhotic patients is crucial for timely intervention. Current guidelines, such as those from the Baveno V Consensus Conference on Portal Hypertension, recommend routine screening endoscopy in all cirrhotic patients [16, 17]. However, the invasive nature, discomfort, and high costs associated with endoscopy make it unsuitable for regular use. The limitations of invasive diagnostic methods have prompted; therefore, this study aims to identify reliable non-invasive predictors of esophageal varices using a combination of clinical, laboratory, and radiological indicators. Validating these predictors can significantly reduce the reliance on endoscopy, decrease healthcare costs, and improve patient comfort. Early identification of high-risk patients will enable timely and appropriate interventions, improving overall outcomes for CLD patients.

2. METHODOLOGY

2.1 Study Design and Setting

This was a hospital-based cross-sectional study conducted at the Department of General Medicine and Medical Gastroenterology, SRM Medical College Hospital and Research Centre, Potheri, Tamil Nadu, India. This study was carried out over a period of 18 months, from October 2022 to March 2024, and included newly diagnosed patients with chronic liver disease (CLD).

2.2 Participants selection

Eligible participants were adults aged between 18 to 80 years who had been newly diagnosed with CLD, irrespective of its etiology. Patients were excluded if they:

Had been previously diagnosed with esophageal varices.

Had receiving prior or current treatment for portal hypertension.

Had undergone procedures for esophageal varices, including banding, sclerotherapy injection, or shunts.

Had hepatocellular carcinoma identified by ultrasonography or elevated alpha-fetoprotein levels.

Had primary hematologic disorders.

Patients were enrolled consecutively based on inclusion criteria after obtaining written informed consent.

2.3 Variables

The study's primary outcome was the presence and grading of esophageal varices, determined via endoscopy. Key predictors included:

Clinical parameters: The cause of liver diseases was identified using medical history, laboratory analyses, and imaging examinations. The identification and esophageal varices grading were analysed through endoscopic evaluation.

Radiological parameters: Ultrasonographic findings including liver echotexture, spleen size, portal vein diameter, presence of ascites, and identification of portosystemic collaterals.

The Model for End-Stage Liver Disease (MELD) score was computed using creatinine, International Normalized Ratio (INR) values and serum bilirubin. The Child-Pugh category was employed to evaluate liver or hepatic function.

Esophageal varices were graded using the modified Paquet classification system:

Grade I: Varices extend just above the mucosal level.

Grade II: Varices project to one-third of the luminal diameter and are incompressible with air insufflation.

Grade III: Varices extend up to 50% of the luminal diameter and are in contact with each other.

2.4 Data Sources and Measurement

All data were collected during routine clinical evaluations, which included detailed history-taking, physical examination, laboratory investigations, ultrasonography, and endoscopy. Standardized protocols were followed to ensure uniformity in data collection. Laboratory tests were performed in the hospital's central laboratory, and ultrasonography was conducted by trained radiologists.

2.5 Study Size

The required sample size was calculated using the formula:

$$n = Z^2 * p * \frac{(1 - p)}{d^2} \quad (1)$$

Where:

Z is the standard score for a 95% confidence level (1.96),

p is the estimated prevalence of cirrhosis-related complications (2% worldwide burden),

d is the desired precision (3%).

Using this formula, the required sample size was 88 participants.

2.6 Efforts to Address Bias

To minimize selection bias, all eligible patients who presented to the hospital during the study period were considered for inclusion. Measurement bias was reduced by adhering to standardized diagnostic and grading criteria. All data collection was supervised by trained clinicians and researchers to ensure consistency.

2.7 Statistical Methods

The data obtained were analyzed by SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) with significance set at $p < 0.05$. The continuous variables and categorical variables were analysed using Chi-square and one-way annova respectively.

2.8 Ethical Considerations

The study protocol was approved by the Institutional Human Ethics Committee (SRMIEC-ST0922-241). Written informed consent was obtained from all participants prior to inclusion in this study. All patient data were anonymized, and confidentiality was strictly maintained. Participation was voluntary, with no coercion, and all patients received standard medical care irrespective of their inclusion in the study.

3. Results

3.1 Demographic Variation: Analysis of study participant's Age and Gender

A total of 88 patients were included in the study. Of these, the distribution of age revealed that 13.6% (n=12) were under 40 years, 23.9% (n=21) were aged 41–50 years, 35.2% (n=31) were aged 51–60 years, 13.6% (n=12) were aged 61–70 years, and 13.6% (n=12) were older than 71 years. The peak representation was in the 51–60 years age group (Figure 1). In addition, the gender distribution showed a predominantly male cohort, with 77.3% (n=68) males and 22.7% (n=20) females, highlighting a significant gender disparity (Figure 1).

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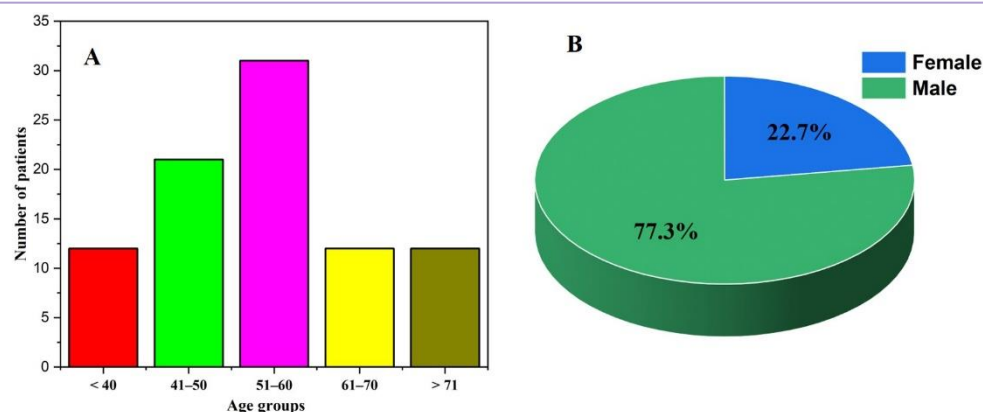


Figure 1 (A) Distribution of Age Among Study Participants (B) Gender distribution Among Study Participants

3.2 Prevalence of Esophageal Varices and Etiology in Individuals with Hepatic Disease

This study evaluated the etiology of disease across patients, indicating that ethanol-induced liver disease was the predominant cause, resulting in 56 patients (63.6%). Subsequently, NAFLD impacted 13 patients (14.8%). Additional etiologies comprised cryptogenic causes in 9 patients (10.2%), Hepatitis B virus (HBV) exist in 3 patients (3.4%), Portal vein thrombosis (PVT) occurred in 3 patients (3.4%), Hepatitis C virus (HCV) present in 2 patients (2.3%), Wilson's disease in 2 patients (2.3%), Budd-Chiari syndrome, nonspecific Hepatitis C, and Non-alcoholic steatohepatitis (NASH) each account for 1 patient (1.1%). These data underscore that consumption of alcohol is the primary cause of liver disease, accompanied by metabolic-related factors like NAFLD. In addition, among participants, 39 patients (44.3%) presented with jaundice, while 49 patients (55.7%) did not have jaundice (Figure 2).

Our study categorizes patients according to the existence and ascites in the following order: Absence of Ascites: 38.60% (34 patients), Mild Ascites: 26.10% (23 patients), Moderate Ascites: 35.20% (31 patients) (Figure 2). A large number of patients displayed varying degrees of ascites, with moderate instances becoming the most common. This range underscores the differing severity of ascites throughout the analyzed patient cohort.

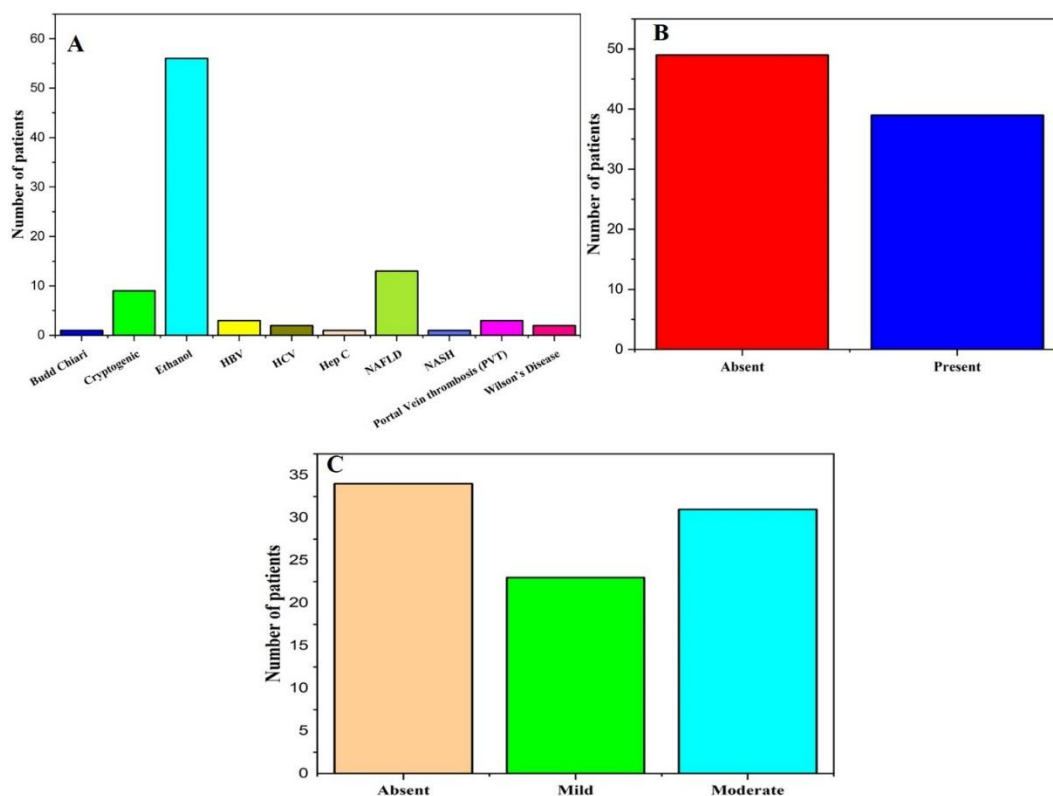


Figure 2 (A) Aetiology of Chronic Liver Disease Among Study Participants, (B) Presence of Jaundice Among Study Participants and (C) Presence and Severity of Ascites Among Study Participants

3.3 Association of Right Liver Lobe/Albumin Ratio with Esophageal Varices

The Right Liver Lobe/Albumin Ratio was evaluated in connection to the existence and severity of esophageal varices. Figure 3 , the study showed that

participants without varices had the greatest Right Liver Lobe/Albumin Ratio, while those without varices had a comparable value. Lesser ratio were the exhibiting the Grade 2 varices. The Right Liver Lobe/Albumin Ratios for the various varices' grades indicates are not statistically significant, according to the P-values.

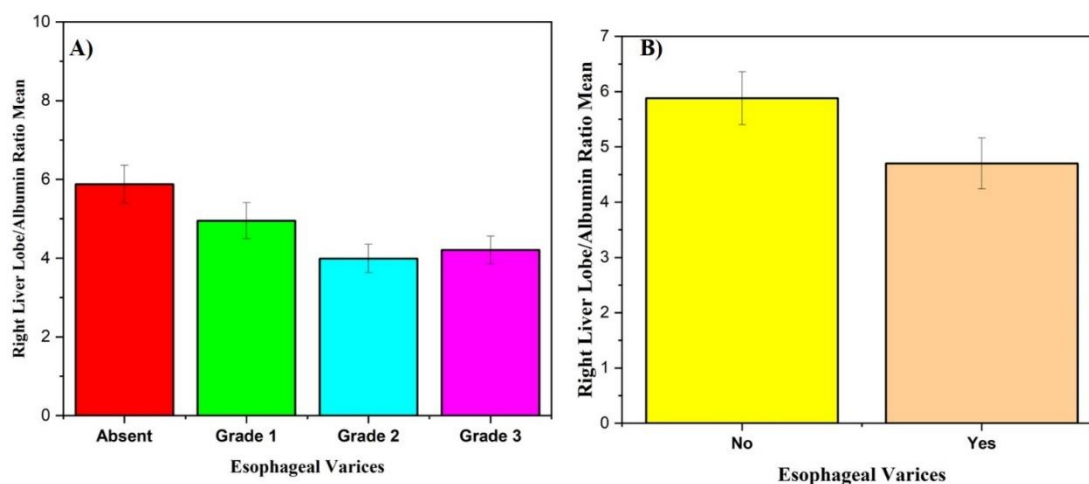


Figure 3 A) Right Liver Lobe/Albumin Ratio mean among various esophageal varices grades, B) Comparative analysis of the Right Liver Lobe to Albumin Level among patients without and with esophageal varices.

3.4 Correlation of Spleen size, Platelet Ratio, and Esophageal Varices in Individuals with Portal Hypertension

The following parameters were used to characterize the participants' spleen size distribution: Spleen size < 12 cm: 39.8% (35 patients) and Spleen size > 12 cm: 60.2% (53 patients). The spleen enlargement (>12 cm) was indicated by the majority of patients (53). On the other hand, the spleen size < 12 cm was 35 patients, indicating a smaller or normal spleen (Figure 4 A). The spleen enlargement is frequently linked to diseases like portal hypertension or cirrhosis.

The data demonstrate that probability of esophageal varices presence and absence among the Portal Hypertension Grades (PHTG) severity levels. Of the patients with Absence PHTG, 12 (absence of esophageal varices) and 6 patients (presence of esophageal varices) lacked esophageal varices. Mild PHTG: 2 and 41 patients exhibited the absence and presence of esophageal varices respectively, demonstrating a significant incidence of varices within this cohort. None of the populations moderate and Severe PHTG, exhibited no sign of esophageal varices. Whereas, 14 (PHTG-moderate) and 13 (PHTG-severe) patients showed esophageal varices. Figure 4 B, demonstrate that as the severity of PHTG escalates, the probability of the lack of esophageal varices diminishes, with acute PHTG being positively linked to their occurrence of esophageal varices. The results revealed that PHTG and esophageal varices are statistically significant.

The Spleen Platelet Ratio (SPR) was determined across the study participant via severity and existence of esophageal varices (Figure 4 C & D). Participants with Grade 1 varices had a mean SPR of 1439.43, whereas those with no esophageal varices had a SPR of 1060.39. The mean SPR for individuals exhibiting Grade 2 varices was 1286.53, while the mean SPR for individuals having Grade 3 varices was 1015.19. The mean SPR was 1060.39 for the group no varices and 1329.57 for the group having varices. The data indicate that although there are variations in the SPR among the groups, signifying no statistically significant correlation ($P = 0.153$) across the various esophageal varices grades and presence or absence of esophageal varices. This indicates that accurate marker to evaluate the severity or existence of esophageal varices in this investigation.

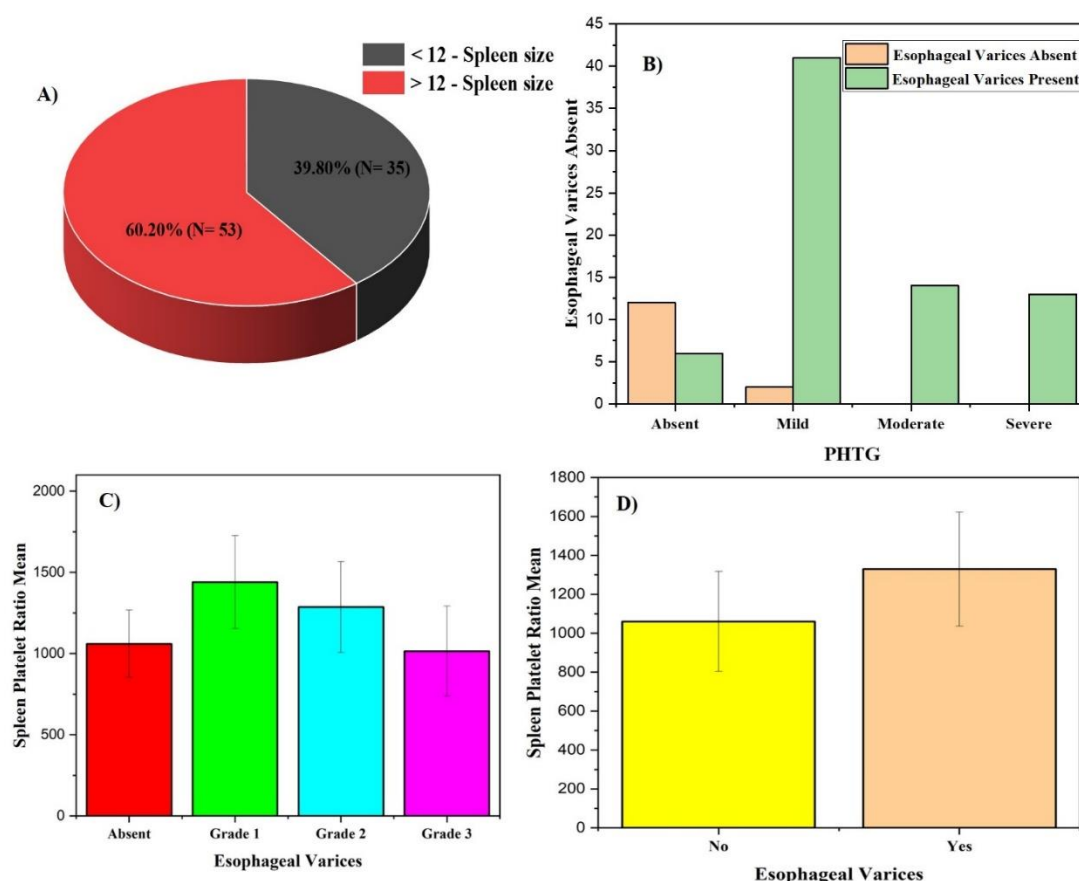


Figure 4 A) Distribution of Spleen Size Among Participants B) Distribution of esophageal Varices Among Participants by Portal Hypertension Grades, C) Distribution of Spleen Platelet Ratio Among Participants by esophageal Varices Grades and D) Distribution of Spleen Platelet Ratio Among Participants with and without esophageal Varices

3.5.1 Distribution of esophageal Varices Among Participants by Child-Pugh Class

Among the participants, the distribution of Child-Pugh classes showed that 17.0% were classified as Class A, 56.8% as Class B, and 26.1% as Class C, illustrated in Figure 5 A. This classification system assesses the severity of cirrhosis based on several clinical parameters, with a notable representation of Class B among the study population.

The distribution of esophageal varices among participants was analysed based on the Child-Pugh class given in Figure 5.B. Participants classified as Child-Pugh class A showed 20.0% with no varices and 80.0% with varices. In Class B, 14.0% had no varices and 86.0% had varices. For Class C, 17.4% had no varices and 82.6% had varices. The P-value for the Child-Pugh class was 0.0015 between yes and no varices, indicating statistically significant association with the presence of esophageal varices. However, with in the yes and no varices group indicates $P > 0.05$, underscoring no statistically significant correlation with the esophageal varices existence.

The grading of varices in the esophagus has been further investigated based on the Child-Pugh categories, given in Figure 5.C. The most prevalent among all categories is Grade 1 varices, with a significant occurrence in Class C and Class B was 69.6% and 54.0% respectively. Whereas, Grade 3 esophageal varices were more prevalent in Class B (24.0%), although Grade 2 esophageal varices were few, however it was absent in Class C. The $P = 0.00015$ signifies the statistically significant correlation between the severity of esophageal varices and Child-Pugh class.

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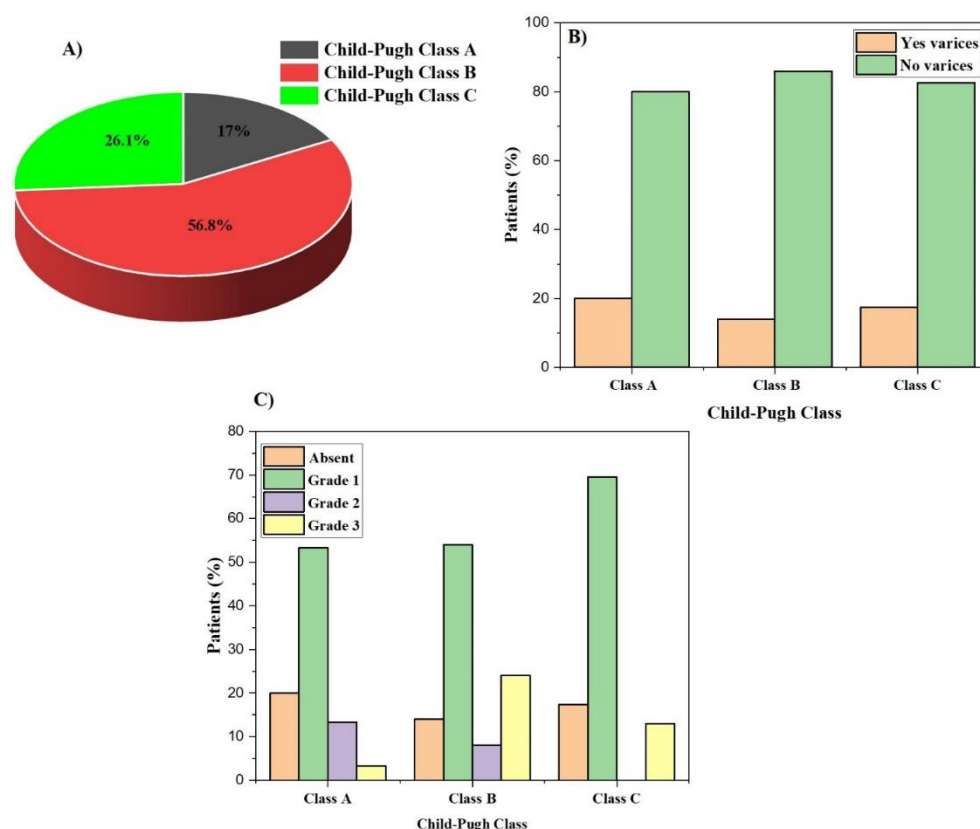


Figure 5 A) Distribution of Child-Pugh Classes Among Participants, B) Distribution of esophageal Varices Among Participants by Child-Pugh Class and C) Distribution of esophageal Varices Among Participants by Child-Pugh Class

3.5.2 Evaluation of MELD Scores in Relation to the Presence and Grading of Esophageal Varices

Our study assessed the association between MELD scores and the existence and severity of esophageal varices. Patients with no esophageal varices had an average MELD score of 9.17. The median MELD scores among individuals having esophageal varices were 8.68 and 9.80 for Grade 3 and Grade 2 varices respectively. Furthermore, individuals who had esophageal varices showed a marginally higher MELD score (9.65) than those with no varices.

The cohort without and with esophageal varices did not significantly differ in their MELD scores, according to statistical analysis ($P = 0.15$). Additionally, there were no statistically significant variations in the MELD ratings between the grades of esophageal varices ($P = 0.21$).

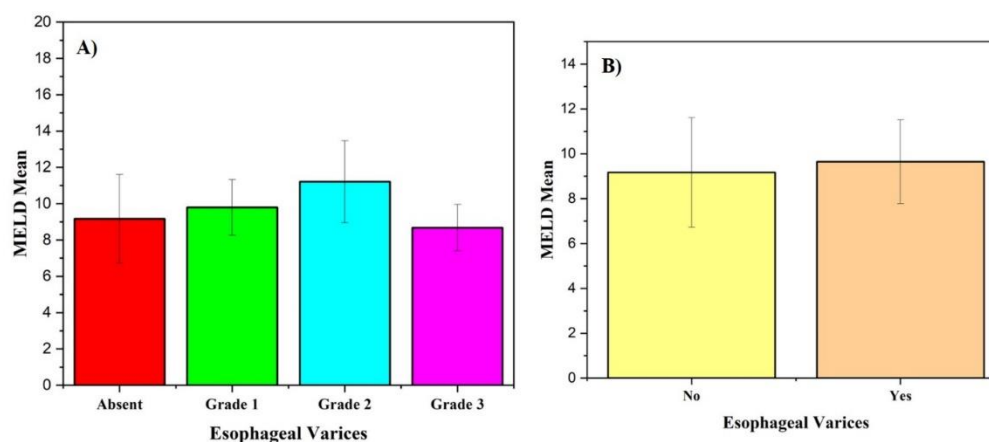


Figure 5.1 Distribution of MELD Scores Among Participants A) esophageal varices grades B) with and without esophageal varices

3. DISCUSSION

The current study indicates that most patients were in the 51–60 years age category, accompanied by the age group of 41–50 years. This pattern aligns with prior research indicating a higher incidence of liver illness, specifically esophageal varices and cirrhosis, among elderly and middle-aged populations. A study by Asrani. A. K et. al (2019) [18] indicated that liver illness was most common among 50–60 years aged patients, corroborating our findings. The reduced occurrence in younger demographics (<40 years) indicates that hepatic problems arise gradually over the period, frequently impacted by chronic liver ailments like metabolic disorders alcoholic liver disease, and viral hepatitis [19, 20, 21].

This study examined the occurrence of esophageal varices and its correlation with various causes of liver disease.

In our investigation, the predominant etiology of liver disease was ALD, preceded by NAFLD and PVT. This trend corresponds with earlier research, including Liu et al. (2021) [22] Jaurigue M.M et al. (2014) [23] and O'Shea S. R (2010) [24], which similarly recognized alcohol as a primary element for variceal development and liver cirrhosis. Hepatitis B and C exhibited lower prevalence in our sample, potentially attributable to regional variations in viral hepatitis as well as enhanced antiviral therapy might mitigating disease progression, as noted by Cox. L. A et al. (2020) [25] and Almeida H. P (2021) [26]. Also, in our investigation, esophageal varices were observed in a considerable percentage of patients, but marginally less than the findings of higher multicenter investigations. A study by O'Brien Jet al. (2013) [27] indicated that around 60% of cirrhotic individuals developed varices, while our sample exhibited a lesser prevalence. This discrepancy may be ascribed to disparities in patient demographics [28, 29, 30, 31]. In addition to this, in this study the majority of newly detected varices are minor upon initial identification. The comparatively low incidence of grade 3 cases in our investigation could result from early detection and endoscopic monitoring measures.

This study survey showed males higher incidence of liver diseases than females and this gender imbalance aligns with several studies [32, 33]. The rise in frequency in males could be ascribed to lifestyle variables, including elevated alcohol use, a greater frequency of viral hepatitis infections and more exposure to hepatotoxic substances [34]. On the other hand, certain studies indicate that estrogen could have an inhibitory effect against the advancement of liver fibrosis in females [32], which might contribute the noted gender discrepancy. Additional research with greater sample size and multi-center datasets is required to validate these tendencies across diverse populations.

This study examined the correlation among the Right Liver Lobe/Albumin Ratio and the occurrence and severity of esophageal varices. The results demonstrate that the average Right Liver Lobe/Albumin Ratio values were diminished among those patients having esophageal varices relative to those population without esophageal varices, indicating a possible correlation. Moreover, esophageal varices severity escalated from Grade 1 to 3, a progressive decrease in Right Liver Lobe/Albumin Ratio was noted. Nonetheless, this variation lacked statistical significance, suggesting a noticeable trend, it could not be sufficiently robust to confirm Right Liver Lobe/Albumin Ratio as a dependable indicator of esophageal varices in this current study cohort.

Prior research indicates that alterations in hypoalbuminemia and liver morphology play a role in development of varices and portal hypertension [35]. A diminished Right Liver Lobe/Albumin Ratio correlates with increased severity of disease and hepatic dysfunction, as the levels of albumin decrease with the progression of liver impairment [36, 37]. While our study results align with this hypothesis, the absence of statistical significance suggests that other parameters, like platelet count, spleen size, and acute portal pressure assessments, could be more pivotal in the esophageal varices progression and formation.

This research investigated the correlation among esophageal varices, spleen size, and platelet ratio, in patients with portal hypertension. The results demonstrate that a size of spleen exceeding 12 cm was prevalent (60.2%) among individuals, corroborating other studies that associate splenomegaly with portal hypertension [38, 39]. A pattern was noted indicating that esophageal varices were more prevalent in persons with elevated PHTG, implying a possible correlation with enhanced spleen size and the prevalence of varices. Also, the spleen-platelet ratio was assessed as a non-interventional biomarker, revealing a decreasing pattern in the ratio corresponding to the increasing esophageal varices severity. Participants with esophageal varices exhibited a lesser spleen-platelet ratio compared to individuals with no varices; nevertheless, the variations noted in the current investigation were statistically insignificant. This indicates that although spleen size and platelet count could provide some understanding of variceal development, additional hemodynamic and biochemical variables probably play a role in the pathogenesis of varices. This finding is consistent with other investigations, indicating that a diminished spleen-platelet ratio is associated with the varices occurrence and varices severity [40, 41]. Furthermore, other studies have demonstrated that a spleen-platelet ratio values could efficiently stratify individuals for endoscopic assessment [42, 43]. Although prior research has emphasized the spleen-platelet ratio as a valuable indicator of varices, our results indicate that it could not be used as an independent marker across all populations. Subsequent investigations with larger cohorts and further non-invasive measures may elucidate its potential prognostic usefulness in clinical practice.

The Child-Pugh categorization is a recognized method for evaluating the severity of liver disease and forecasting complications of esophageal varices. Figure 5 illustrates that the predominant proportion of patients are classified as Child-Pugh Class B, accompanied by Class C and Class A. This distribution aligns with research indicating that the majority of

cirrhotic individuals are categorized as Class B, signifying moderate liver impairment [44, 45]. The results confirm the established correlation between the severity of liver disease and the occurrence of varices, validating the Child-Pugh score is a major assessment method. However, further indicators, like spleen-platelet ratio ought to be taken into account. Subsequent research with larger groups and long-term follow-ups will elucidate these variations.

The MELD score is commonly utilized to evaluate the liver disease severity and forecast the risk of mortality in individuals with cirrhosis. This study examines the MELD scores distribution across individuals with various stages of esophageal varices and compares participants without and with varices, elucidating the correlation between progression of variceal and severity of liver disease. In the present investigation, Grade 2 varices patients exhibited a higher mean MELD score. Nonetheless, Grade 3 varices demonstrated a somewhat reduced MELD score, potentially attributable to certain demographic differences. MELD Score and esophageal varices existence indicates that the average MELD score exhibit slight differences among patients with varices and those without. The results indicate that in clinical practice, those who have moderate MELD scores, in addition to individuals with high MELD scores, should be evaluated for variceal screening, especially if they exhibit risk markers like splenomegaly [46, 47].

4. CONCLUSION

This study emphasizes the importance of non-invasive indicators in assessing esophageal varices among individuals with chronic liver disease. The results indicate that elevated MELD scores and Child-Pugh categories correlate with a greater prevalence and esophageal varices severity. Furthermore, spleen platelet ratio, spleen size, and grades of portal hypertension have been identified as vital markers for variceal development. Also, right liver lobe-to-albumin ratio demonstrated potential indicator to, distinguish the patients with and without esophageal varices. The study underscores the clinical efficacy of these non-invasive indicators as assessment for early identification of liver disease, hence diminishing the necessity for regular endoscopy in patients with low risk. Incorporating such indicators into the clinical setting may facilitate rapid diagnosis, early intervention and disease progression monitoring, hence mitigating problems related to portal hypertension. Subsequent research ought to concentrate on confirming these results in larger cohorts

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

Arunkumar K and Abhirami Etican: Conceptualization, data collection, statistical analysis, manuscript writing, and revision. **Vishanthika R:** Study design, manuscript drafting, and methodology development, **Jayakumar K T:** Supervision, validation of results, analysis of findings. **Janardhanan Subramonia Kumar:** Validation and formal analysis, overall study supervision, and final manuscript review.

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