ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF INTERNAL MEDICINE

Platelet count to spleen diameter ratio for prediction of esophageal varices in liver cirrhosis in Addis Ababa, Ethiopia: a cross sectional institutional multicentered study

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List of acronyms/ Abbreviations

AASLD- American Association for the study of liver disease

AUC -Area under the Curve

APRI - AST to Platelet Ratio Index

CBC- Complete Blood Count

CI -Confidence Interval

CLD – chronic liver disease

EGD - Esophagogastroduodenoscopy

EV/OV-esophageal varices

GI -Gastroenterology

HBN: Hemoglobin

HBV- Hepatitis B virus

HBsAG: Hepatitis B surface Antigen

HCV AB: Hepatitis C Virus Antibody

HCV -Hepatitis C virus

HMIS - Health Management Information Systems

HSROC: Hierarchical Summary Receiver Operating Characteristic

IQR: Interquartile Range

INR: International Normalized Ratio

Kpa -kilopascal

LR+: Likelihood Ratio Positive

LR-: Likelihood Ratio Negative

LS -liver stiffness

LV -large varices

MELD - Model for End-Stage Liver Disease

NAFLD - Nonalcoholic fatty liver disease

NPV: Negative Predictive Value

OR: Odds Ratio

PC -platelet count

PC/SD – platelet count to spleen diameter ratio

PPV: Positive Predictive Value

ROC: Receiver Operating Characteristic

SD -spleen diameter

UGIB -upper gastrointestinal bleeding

WBC: White Blood Cell

Abstract

Background - Liver cirrhosis is the end stage of progressive liver fibrosis as a consequence of chronic liver inflammation wherein the normal hepatic architecture is replaced by regenerative hepatic nodules, which eventually leads to liver failure. Cirrhosis without any symptoms is termed as compensated cirrhosis. Complications such as ascites, variceal bleeding, and hepatic encephalopathy herald the onset of decompensated cirrhosis. Gastroesophageal varices are the hallmark of clinically significant portal hypertension

Objective -the aim of this study is to assess the accuracy of PC/SD ratio as noninvasive predictor of esophageal varices in patients with liver cirrhosis of different etiologies in Ethiopia

Method -cross sectional retrospective analytic study was conducted in patients who visited Tikur Anbesa hospital from January 1, 2019 to December 30, 2023.data was collected by chart review and direct patient interview with structured questioner through Kobo toolbox. The data was exported to SPSS 26 for analysis and data clearance. ROC curve was plotted for SD, PLT count and PC/SD ratio to get the sensitivity, specificity PPV, NPV, LR+ and LR-.

Result: among 140 participants in this study 67% were males. The median age of participants was 40.5(IQR:31-54). HBV (38%) was the commonest cause of cirrhosis followed by cryptogenic cirrhosis and HCV which account for 28% and 16% of the participants respectively. 117(83.6%) of participants have endoscopic evidence of esophageal varices and 72(51.1%) of participants have gastric varices. decompensated cirrhosis and platelet count are associated with presence of EV on multivariate analysis with adjusted OR: 12.63 (95% CI (3.16-67.58, P=0.001) and 0.14 (95% CI (0.037-0.52, P=0.004) respectively. PC/SD ratio less than 1119 has sensitively of 86.32% and specificity of 70% with AUC:0.835 (95% CI (0.736-0.934, p<0.001). platelet count of less than 133000 and SD of more than 160.5mm have sensitivity of 93.68% and 31.62%, specificity of 37.78% and 100% and AUC value of: 0.815 (95% CI (0.718-0.913, P<0.001) and 0.712 (95% CI (0.605-0.82, P=0.001) respectively. PC/SD ratio was superior to platelet count and spleen diameter alone in predicting EV presence.

Recommendation: Prospective, multicenter studies involving larger and more homogeneous patient groups are warranted to validate the efficacy of these non-invasive tests within our population.

1 Introduction

1.1 Statement of the problem

Liver cirrhosis is the end stage of liver fibrosis, resulting in hepatic architecture distortion (1). It is a consequence of a long period of inflammation that results in the replacement of liver parenchyma by diffuse hepatic fibrosis with regenerative nodules, which leads to portal hypertension (2). The presence of complications like ascites, variceal bleeding, or hepatic encephalopathy indicates decompensated cirrhosis. On the other hand, the absence of these symptoms suggests compensated cirrhosis (3). The Child-Pugh score further stratifies patients into three classes. Class A predominantly comprises compensated patients, while Classes B and C encompass a majority of decompensated patients. Gastroesophageal varices, a key indicator of clinically significant portal hypertension, form a compensatory mechanism to alleviate the elevated pressure within the portal venous system and divert blood flow to the systemic circulation (3). The prevalence of gastroesophageal varices among cirrhotic patients ranges from 25–35% and rises to 40% and 85% in compensated and decompensated cirrhotic patients, respectively. Despite standard treatment, variceal bleeding has a high mortality rate, with 10–15% experiencing treatment failure, 21% rebleeding, and 24% mortality within the first 6 weeks (4).

A significant public health challenge looms large on the global stage: liver disease. Estimated to claim the lives of 2 million people annually, it stands as a major contributor to global mortality. Cirrhosis, viral hepatitis, and hepatocellular carcinoma (HCC) each exact a heavy toll, with roughly 1 million deaths attributed to each annually, solidifying their place as leading causes of death. Collectively, these liver-related conditions account for a staggering 3.5% of all deaths worldwide. Several factors fuel this substantial disease burden. High levels of global alcohol consumption, with over 75 million diagnosed with alcohol use disorders, significantly increase the risk of alcohol-associated liver disease. The rising tide of overweight and obesity (affecting 2 billion adults) and diabetes (over 400 million cases) are major contributors to non-alcoholic fatty liver disease and HCC. Despite ongoing efforts, the global persistence of viral hepatitis remains a

cause for concern. Furthermore, drug-induced liver injury is emerging as a growing threat, posing a substantial risk factor for acute hepatitis cases (5).

In Ethiopia, cirrhosis constitutes the 7th leading cause of death, accounting for approximately 24 deaths per 100,000 individuals in 2019. A systematic review conducted by Behailu et al. to assess the etiologic spectrum of chronic liver disease shows that hepatitis B virus, alcohol, and hepatitis C virus were the commonest causes, accounting for a pooled estimate of 40.0%, 17.0%, and 15.0%, respectively, and the overall hospital mortality rate of CLD patients was 25.0% (6). Furthermore, a cross-sectional study by YC Mengistie et al. investigating patients with gastrointestinal bleeding found that varices were the most common cause of upper gastrointestinal bleeding (UGIB), accounting for 46.1% (7).

The American Association for the Study of Liver Diseases (AASLD) guidelines recommend esophagogastroduodenoscopy (EGD) for variceal screening in patients with cirrhosis, except those who meet the following criteria: liver stiffness measurement (LSM) less than 20 kPa and platelet count greater than 150,000/mm^3. Additionally, the guidelines advise repeating EGD at 1-2-year intervals based on the variceal grade, stage of cirrhosis, and presence of associated risk factors (8). This strategy creates significant challenges in developing countries, where the prevalence of liver cirrhosis is high and the availability of endoscopy is limited to a few centers due to cost constraints. In the past two decades, we have seen extensive research on the predictive value of various noninvasive markers in detecting esophageal varices (9). Several investigations have revealed that platelet count, splenomegaly, the platelet count-to-spleen diameter ratio, advanced Child-Pugh class, serum albumin level, and a high portal vein diameter are considered to be useful non-invasive predictors of esophageal varices in patients with cirrhosis (10). Due to their simplicity, non-invasiveness, affordability, and ease of use in predicting esophageal varices, with good accuracy in some cases, these markers are particularly valuable in clinical settings (9). Non-invasive prediction of esophageal variceal grade during patient registration has the potential to guide the need for prophylactic beta-blockers or endoscopic variceal ligation in cirrhotic patients with portal hypertension (11). These predictive markers may

exhibit geographical variability due to disparities in the underlying causes and severity of liver disease across different populations (10).

1.2 Significance of the study

Since the availability of EGD is limited to a few centers in Ethiopia, the result of this study will help identify high-risk patients for EGD screening and can decrease the waiting time for screening and starting prophylaxis. It also avoids unnecessary costs and referrals to tertiary care centers.

1.3 Literature review

The use of non-invasive parameters, specifically the platelet count/spleen diameter ratio (PC/SD), for predicting esophageal varices (EV) in cirrhotic patients shows variation across populations. A study by Giannini et al. in Italy reported a 100% negative predictive value (NPV) for identifying EV using a PC/SD cut-off of 909 (9). However, a contrasting retrospective analysis at Beth Israel Medical Center, New York City, found a significantly lower NPV (73%) with the same cut-off, highlighting potential limitations in the generalizability of this non-invasive approach (12). Additionally, a separate study done in Mexico in cirrhotic patients shows that the platelet count/spleen diameter ratio, with a cut-off value of 884.3, had sensitivity, specificity, and positive and negative predictive values of 84%, 70%, 94%, and 40%, respectively, to detect esophageal varices (13).

Several studies conducted in Africa have investigated the accuracy and validity of the platelet count/spleen diameter (PC/SD) ratio for identifying esophageal varices (EV) in patients with liver cirrhosis, aiming to establish it as a non-invasive screening tool. Amoako & Co. A cross-sectional study with patients who had liver cirrhosis conducted in Ghana revealed that a PC/SD cutoff value of ≤833.3 resulted in a sensitivity of 73.5% and a specificity of 64.3%. With a diagnostic accuracy of 72.6%, PPV and NPV were, respectively, 95.2% and 20.1%. for estimating any esophageal varices (14). A similar investigation conducted in Cote d'Ivoire evaluated the predictive power of platelet count (PC), spleen diameter (SD), and PC/SD ratio for the detection of esophageal varices (OV) and large OV in black African patients with cirrhosis. The findings demonstrated that sex, PC, and SD were predictive variables for OV, and the AUROCs (±SE) of PC (cutoff < 110500), SD (cutoff > 140), and PC/SD ratio (cutoff ≤ 868) were 0.879 ± 0.04, 0.768 ± 0.06, 0.679 ± 0.06, and 0.793 ± 0.06, respectively (15). The platelet count/bipolar spleen diameter ratio was evaluated as a noninvasive parameter for the prediction of esophageal varices (EVs) in Egyptian cirrhotic patients in a prospective study. The results showed that the PC/SD ratio was significantly lower in EV-positive patients than in EV-negative patients, with a cutoff value of 939.7. The study also yielded 100% sensitivity and negative predictive values, 86.3% specificity, a 95.6% positive predictive value, and an area under the ROC curve of 0.94 ± 0.02; these findings were extended to a subset analysis of compensated cirrhotic patients (16).

A prospective study originating in India evaluated the diagnostic accuracy of the platelet count-to-spleen diameter ratio (PC/SD) as a non-invasive biomarker for predicting esophageal varices (EV) in a cohort of patients diagnosed with cirrhosis. The study established a PC/SD cutoff of ≤1014, demonstrating significantly improved diagnostic performance compared to using platelet count or spleen diameter alone. This enhanced accuracy is reflected in the high positive predictive value (PPV) of 95.4% and negative predictive value (NPV) of 95.1%, signifying the PC/SD ratio's strong potential to accurately identify both patients with and without esophageal varices (17). An analytical cross-sectional study from Pakistan investigated the diagnostic accuracy of the platelet count-to-spleen diameter ratio (PC/SD) for predicting esophageal varices in patients with liver cirrhosis with an AUC of 0.9 ($p<0.0001$). Additionally, a PC/SD cutoff value of ≤1077.42 exhibited high sensitivity (88.75%) and specificity (81.43%) for the identification of esophageal varices (18).

Manuela and associates evaluated the diagnostic accuracy of the platelet count/spleen diameter ratio for identifying esophageal varices (OV) and/or hypertensive gastropathy in patients with compensated cirrhosis. Their results showed that a ratio below 936.4 offered a sensitivity and specificity of 64.5% and 64.3%, respectively, for diagnosing OV. However, the study concluded that, regardless of the cutoff value, the platelet count/spleen diameter ratio should not be used by patients with compensated cirrhosis to avoid inappropriate upper endoscopy (19).

A retrospective analysis conducted in Turkey investigated the association between the size of gastroesophageal varices and the platelet count/spleen diameter ratio (PC/SD) in patients diagnosed with cirrhosis. The study revealed a statistically significant correlation, with patients harboring large esophageal varices exhibiting a demonstrably lower PC/SD compared to those with small varices. Notably, the PC/SD ratio demonstrated an 82% sensitivity for identifying large varices (20). An analogous investigation in India on liver disease patients identified palpable spleen, low platelet count, spleen size >13.8mm, portal vein >13mm, and splenic vein >11.5mm as independent predictors of large varices (LV), with the PC/SD ratio showing 88.5% sensitivity and 83% specificity for LV detection (21). An Egyptian study investigated the use of

the PC/SD ratio for screening large varices in patients with post-hepatitis C cirrhosis. A PC/SD ratio cutoff of ≤806.93 had a sensitivity of 75% and a specificity of 47.8%. The study found that a lower PC/SD ratio was associated with large esophageal varices (22). A further study in cirrhotic patients assessed the PC/SD ratio for EV screening and severity. A cutoff of 921 yielded a high negative predictive value (93%). The study suggests the PC/SD ratio as an independent predictor of EV presence and potentially its severity (23).

A study by Xu et al. investigated the efficacy of the platelet count-to-spleen diameter ratio (PC/SD) in predicting esophageal varices (EV) among patients with hepatosplenic schistosomiasis. The study demonstrated that PC/SD offered superior diagnostic accuracy for EV compared to spleen diameter (SD) alone. The optimal PC/SD cutoff value was established at 1004, yielding a positive predictive value (PPV) of 77.1% and a negative predictive value (NPV) of 89.3%. However, a lower cutoff of 909, while achieving a higher PPV of 79.5% and NPV of 83.1%, would also lead to a miss rate of 25.3% for existing varices, potentially delaying crucial screening endoscopy. Consequently, the study suggests that the PC/SD ratio presents as a promising non-invasive marker for predicting EV in patients with schistosomiasis-induced liver cirrhosis, but with limitations requiring further consideration (24).

A Brazilian study on cirrhotic patients investigated the use of platelet count, spleen diameter, ascites presence, Child and MELD scores, and the platelet count/spleen diameter ratio (PC/SD) to non-invasively predict esophageal varices. However, the study found the PC/SD ratio to be insufficient for this purpose, with a sensitivity of 77.5%, a specificity of 45.5%, a positive predictive value of 79.5%, a negative predictive value of 42.6%, and an accuracy of 68.9% (25). A prospective cross-sectional study, involving 62 patients with cirrhosis of any cause, was conducted at St. Paul's Hospital Millennium Medical College to assess the validity of platelet count and the platelet count/spleen diameter ratio (PC/SD) in predicting the presence of esophageal varices (EV). The study found that a PC/SD ratio cutoff of 833 demonstrated a sensitivity of 68% and a specificity of 83% for predicting esophageal varices (26).

2 Objective

2.1 General objective –

- To evaluate the diagnostic accuracy PC/SD ratio for prediction of esophageal varices in liver cirrhosis Ethiopian patients

2.2 Specific objective

1. To assess the sensitivity and specificity of PC/SD compared with endoscopy for detection of esophageal varices
2. To assess the sensitivity and specificity of PC/SD for prediction of large varices
3. To assess the effect of etiology and stage of cirrhosis on the value of PC/SD in relation to the presence of EV

3 Methods and materials

3.1 Study setting

This study was conducted at Tikur Anbessa Specialized Hospital and Adera Medical Center. Tikur Anbesa Specialized Hospital is the largest referral and teaching hospital in Addis Ababa, Ethiopia. It provides different specialty and subspecialty training and clinical services. It is one of the referral sites for endoscopy for cirrhotic patients and has a particular GI clinic that works three times per week and sees more than 600 patients per month. The study was conducted from May 2023 to January 2024.

3.2 Study design

Hospital based retrospective cross sectional analytical study was done.

3.3 Source population

The source population was all cirrhotic patients who visited GI clinic in Tikur Ambesa hospital and Adera medical center from January 2019 to February 2024.

3.4 Study population

All eligible patients who fulfill the inclusion criteria and willing to take part in the study were included.

3.4.1 Inclusion and exclusion criteria

3.4.1.1 Inclusion criteria

- ✓ Patients diagnosed with liver cirrhosis and had measurement of platelet count, ultrasonography examination and EGD within 3 months
- ✓ Age >18 years
- ✓ Not on chemotropic or other medication which can affect platelet count

3.4.1.2 Exclusion criteria

- ✓ Patient diagnosed with hepatocellular carcinoma,
- ✓ use of medications for the primary prophylaxis of variceal bleeding,
- ✓ history of esophageal variceal bleeding,
- ✓ alcohol consumption within the admission

- ✓ history of variceal ligation, sclerotherapy, and/or portal hypertension surgery
- ✓ Patients with chronic malaria, liver abscess, abdominal tuberculosis, hematologic malignancies, and sickle cell anemia
- ✓ Patients who have comorbidity which affect spleen size or platelet count like lymphoproliferative disorders, metastatic malignancies, visceral leishmaniasis.
- ✓ Patients who were hemodynamically unstable

3.5 Sample size determination

Sample size is determined based on the following assumptions; the confidence level to be 95%, margin of error <0.05 to be significant.

$n=(z^2p(1-p))/d^2$ where n= number of samples, z= standard score at 95% CI which is 1.96, P - 0.5 since there is no similar study done previously 'd' is margin of error. n=384

Since, the number of sources of population is 200 (which is less than 10,000). Therefore, sample size is Sample size = n/(1+n/N) = 384/ (1+384/200) =131, the non-respondent rate will be 10%. This makes the sample size of 144.

3.6 Sampling procedure

The participants were selected using non probability convenience sampling method. Individuals who met the inclusion criteria were chosen from the endoscopy registry and HMIS monthly audit report. Those who had any of the exclusion criteria were excluded from the study. Their charts and I care data were reviewed, and follow-up interviews with participants were conducted using a structured questionnaire at the follow-up clinic.

3.7 Variables

3.7.1 Dependent variables

diagnostic accuracy of PC/SD

3.7.2 Independent variables

- Age
- PT/INR

- Child-Pugh score
- MELD score
- Platelet count
- Spleen diameter
- PC/SD

3.8 Operational definition

- Diagnosis of liver cirrhosis will be based on the presence of two or all three of the following;
    - Clinical signs of chronic liver disease (clubbing, palmar erythema, spider naevi, gynecomastia, distended abdominal veins, female pubic hair pattern, encephalopathy, splenomegaly or ascites)
    - Impaired liver function test consistent with cirrhosis (elevated INR, and low serum albumin)
    - Ultrasound diagnosis of cirrhosis (Shrunken or enlarged nodular liver with increased echotexture, a blunt edge, and distorted architecture, with or without a dilated portal vein, thickened gallbladder wall, splenomegaly or ascites
- According to the grade of esophageal varices:
    - Grade I: varicose veins disappear on insufflations;
    - Grade II: varicose veins that do not disappear on insufflation but not confluent;
    - Grade III: varicose veins that do not disappear on insufflation and confluent.
- Grade III was considered to be large OV and grades I and II were considered to be small varicose veins.
- Thrombocytopenia was defined as a platelet count < 150,000/mm3. It was said to be severe when it was <100,000/mm3.
- Hepatitis B Virus (HBV) defined by the positivity of HBsAg
- Hepatitis C Virus (HCV) defined by positive anti-HCV Ab and RNA HCV
- International ascites club grading system for ascites
    - Grade I Mild ascites only detectable by ultrasound

- Grade II Moderate ascites evident by moderate symmetrical distension of abdomen
- Grade III-Large or gross ascites with marked abdominal distension

3.9 Data collection and materials

Data was collected from study population by trained medical students using structured questionnaire and chart review through kobo toolbox. The questioner has four sections which includes socio demographic factor, physical finding laboratory results, clinical condition and other factors. Abdominal ultrasound done by senior resident/senior radiologist had documentation of the longest bipolar dimeter of the spleen was taken. Screening EGD done by senior gastroenterologist and had documentation of presence and grading of esophageal varices and gastric varices was taken.

3.10 Data quality assurance and analysis

Data were collected using a structured questionnaire administered through the Kobo Toolbox. Following data export to SPSS, the data were cleaned and analyzed. Continuous variables were summarized using medians with interquartile ranges (IQRs), while categorical variables were summarized using frequencies and percentages. Receiver operating characteristic (ROC) curves were plotted for spleen diameter (SD), platelet count (PC), and the PC/SD ratio. Cut-off values were determined using the Youden Index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were calculated using MedCalc statistical software.

4 Ethical consideration

Ethical approval was granted by Addis Ababa University, college of health sciences, school of medicine Institutional Review Board and the research proposal passes ethical clearance. A letter to go ahead and support the study was obtained from the university. A written consent was taken from each selected participant to confirm their willingness. Privacy and confidentiality of collected information was ensured throughout the process.

5 Result

Among the 140 cirrhotic patients who underwent esophagogastroduodenoscopy, 67% were male and 33% were female. The median age was 40.5 years with an interquartile range (IQR) of 31-54 years. The etiology of cirrhosis was; Hepatitis B virus (HBV) for 37.9% of patients, Hepatitis C virus (HCV) for 16% of patients, Alcohol for 12% of patients, Non-alcoholic fatty liver disease (NAFLD) for 4% of patients and cause Unknown for 29% of patients.

Endoscopic evidence of esophageal varices was present in 117 patients (83.6%) and gastric varices were present in 72 patients (51.1%). Among patients with esophageal varices, the distribution was as follows; Grade I for 32 patients (27.4%), Grade II for47 patients (40.2%) and Grade III for 38 patients (32.5%)

Additionally, 36.7% of patients with esophageal varices had stigmata of bleeding. Approximately 50% of patients had decompensated cirrhosis, while the remaining patients had compensated cirrhosis

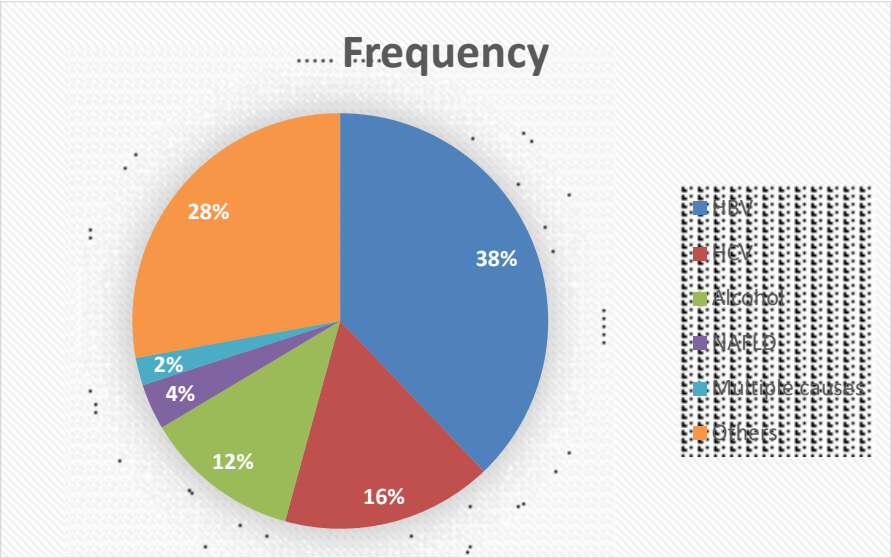


Figure 1 Etiology of cirrhosis

Table 1 basic sociodemographic and clinical characteristics of the patients

Variable		Frequency	Percentage	Median with IQR
Age				40.5(31-54)
sex	Male	95	67.9%	
	Female	45	32.1%	
Hx of jaundice	Yes	47	33.6%	
	No	93	66.2%	
Hx of alcohol use	Yes	21	15%	
	No	119	85%	
ascites	Yes	53	37.9%	
	No	87	62.1	
Cirrhosis classification	compensated	70	50%	
	decompensated	70	50%	
HBsAG	Reactive	56	40%	
	Nonreactive	84	60%	
HCV AB	Reactive	23	16.4%	
	Nonreactive	117	83.6%	
Ascites on ultrasounds	Yes	60/139	42.9%	
	No	79/139	56.4%	
EV on endoscopy	Yes	117	83.6%	
	No	23	16.4%	
Grade of varices	Grade I	32	27.4%	
	Grade II	47	40.2%	
	Grade III	38	32.5%	
Stigmata of Bleeding	Yes	43/124	34.7%	
	No	81/124	65.3%	
Gastric varices	Yes	72	57.1%	
	No	54	42.9%	
AST			Iu (136) *	66(41-119)
ALT			Iu (136) *	48.5(32-79.9
Total Bilirubin			mg/dl (121) *	1.5(0.89-2.62)
ALB			g/dl (85) *	3.78(3-4.15)
INR			(53) *	1.45(1.25-1.81)
Crt			mg/dl (126) *	0.8(0.6-0.92)
HBN			g/dl	13.65(11.6-15.57)
WBC			$\times 10^3$/ml	5.0(3.8-6.575)
PLT			$\times 10^3$/ml	104(73-139
SD			mm	140(123-161.75)
Liver size			cm	14(13-14.8)
Portal vein diameter			mm (53) *	12(10-14.9)
PC/SD				750.88(452.2-1099)

NB; * indicates total number of participants who have the indicated result

Table 2 shows clinical biochemical and ultrasonographic features of patients according to presence of esophageal varices. There is no difference in gender or median age of the patients between the two groups. platelet count and PC/SD is lower in patients with esophageal varices compared with patients without varices. the Midian spleen diameter is higher in patients with varices compared with patients without varices.

Table 2 comparation of clinical, biochemical and ultrasonographic features based on presence of EV

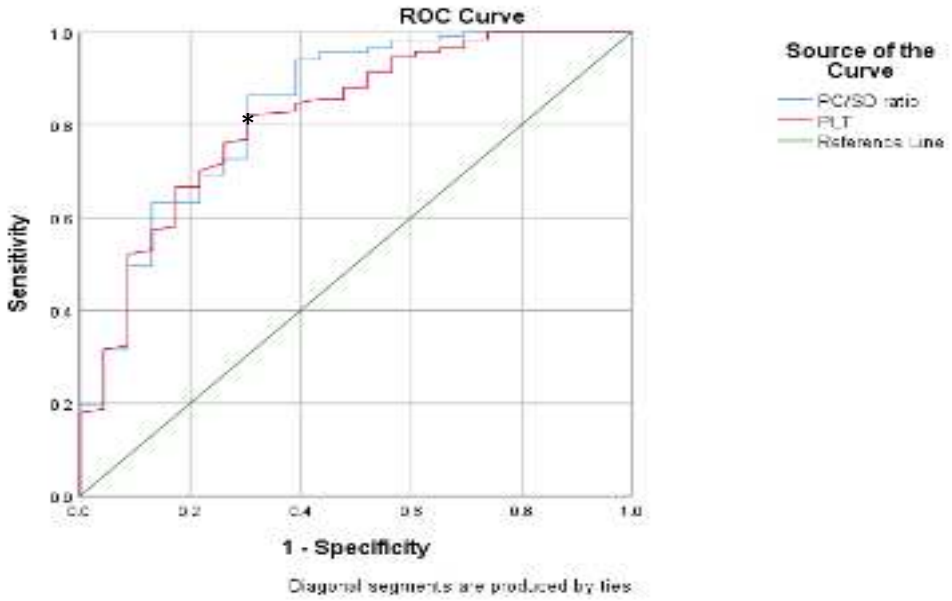
variable	unit	With varices	With out varices	P value
sex	Male	65.8%	78.3%	0.243*
Age		41(31-53)	39(30-55)	0.889
AST	iu	67(43.7-121.5)	41.5(31-85.25)	0.035
ALT	iu	47(32-79.8)	51(27.5-83)	0.96
WBC	$\times 10^3$/ml	5(3.7-6.55)	5.6(4.5-6.8)	0.386
HBN	g/dl	13.3(11.25-15.1)	15.9(14-16.4)	<0.001
PLT	$\times 10^3$/ml	94(68-132)	159(128-207)	<0.001
SD	mm	141(124-168)	125(115-141)	0.001
Liver size	cm	14.1(13-14.8)	14(13-14.7)	0.832
PC/SD		693.8(423.6-1053.2)	1360(920-1886.9)	<0.001

NB * shows p value was taken from chi square and the rest p value was taken from man Withey test

In multivariant logistic regression both decompensated cirrhosis and platelet count are associated with the presence of esophageal varices with adjusted odd ratio=12.623(95%CI (3.164-67.586), P value=0.001 and o.14(95%CI (0.037-0.526), p value =0.004 respectively.

Table 3 the crude and adjusted OR of variables in univariant and multivariate logistic regression

Variable	Crude OR (95%CI)	P value	AOR (95%CI)	P value
PC/SD	0.069(0.025-0.195%	<0.001	-	-
HBN	0.695(0.551-0.875)	0.002	-	-
PLT	o.129(0.036-0.56)	0.002	0.140(0.037-0.526)	0.004
SD	1.037(10.13-1.061)	0.002	-	--
Ascites on ultrasound	0.044(0.006-0.337	0.003	-	-
stage of cirrhosis	14.571(3.264-65.055	<0.001	12.623(3.164-67-586)	0.001



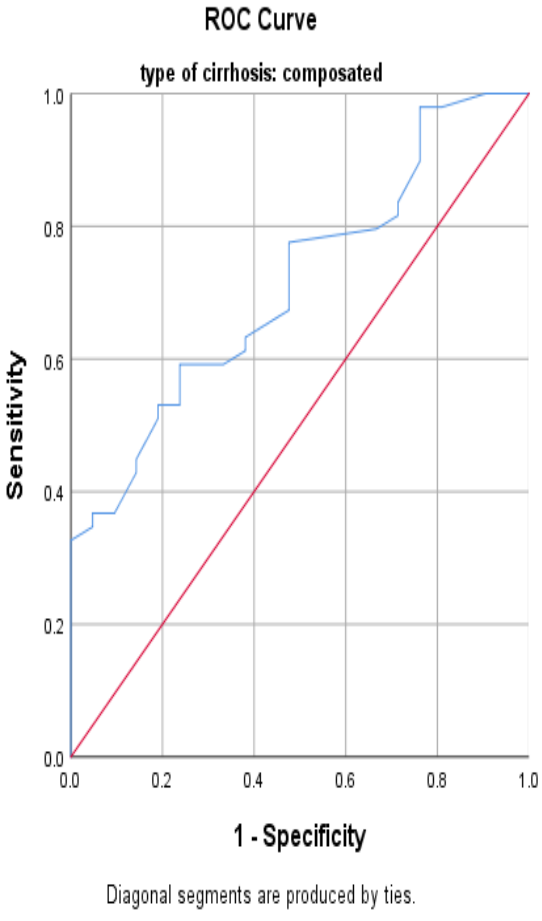


Figure 2: ROC curve for PC/SD and PLT count and SD for presence of EV

ROC curve was constructed to find the best sensitive and specific cutoff values for platelet count and platelet count to spleen diameter ratio which are associated with the presence of esophageal varices in the multivariant analysis. PC/SD<1118.74 has sensitivity of 86.32% and specificity of 69.57% with AUC=0.835(CI (0.736-0.934)) P value<0.001 and platelet count<133000 has sensitivity of 93.68%and specificity of 37.78% with AUC=0.815(CI (0.718-0.913) P value<0.001. PC /SD has better predictive value compared with platelet count and spleen diameter.

Table 4 sensitivity specificity and AUC values of PLT, SD and PC/SD for prediction of EV

Non-invasive marker	Cut-off value	sensitivity	specificity	AUC (95%CI)	P value	PPV	NPV	Accuracy	LR+	LR-
Platelet count	133000	93.68%	37.78%	0.815(0.718-0.913)	<0.001	76.07%	73.91%	75.71%	1.51	0.17
Spleen diameter	160.5	31.62%	100%	0.712(0.605-0.820)	0.001	100%	22.33%	42.86	-	0.68
PC/SD	1118.74	86.32%	69.57%	0.835(0.736-0.934	<0.001	93.52%	50%	83.57%	2.84	0.2

Among patients with compensated cirrhosis, the PC/SD ratio, platelet count, and spleen diameter demonstrated good accuracy in predicting esophageal varices (EV), with AUC values of 0.889, 0.872, and 0.713, respectively. Notably, the cut-off values for these parameters were lower compared to those identified in the entire cirrhotic patient population. While the sensitivity of all three variables was lower in the compensated cirrhosis group compared to the whole cirrhotic cohort, they exhibited improved positive predictive values. However, none of these parameters demonstrated good predictive value in patients with decompensated cirrhosis.

Table 5 sensitivity, specificity and AUC values of SD, PLT and PC/SD in patients with compensated cirrhosis

Variable	Cut off value	sensitivity	specificity	AUCROC (95% CI)	P value	PPV	NPV	Accuracy	LR+	NLR
PLT	119500	73.47%	90.48	0.872(0.785-0.959)	<0.001	94.74%	59.38%	78.57%	7.71	0.29
SD	133.5	59.18%	76.19%	0.713(0.591-0.836)	0.005	85.29%	44.44%	64.29%	2.49	0.54
PC/SD	830.3	69.39%	95.24%	0.889(0.805-0.973)	<0.001	97.14%	57.14%	77.14%	14.57	0.32

For prediction of large EV

Univariate analysis revealed associations between platelet count to spleen diameter ratio, spleen diameter, and hemoglobin level with the presence of large esophageal varices (EV). However, only SD and hemoglobin level remained significantly associated in multivariable analysis, with adjusted odds ratios of 1.022 (95% CI: 1.008-1.037, *P = 0.003*) and 0.845 (95% CI: 0.716-0.998, *P = 0.048*), respectively.

The PC/SD ratio with a cut-off value of less than 696.5 exhibited a sensitivity of 63.16% and a specificity of 55.7%, with an area under the curve (AUC) of 0.655 (CI: 0.543-0.767) and a P value of 0.095, indicating statistical insignificance. Similarly, SD also lacked sufficient predictive power, with an AUC of 0.695, falling below the threshold of 0.7 typically considered indicative of good discrimination.

Table 6 sensitivity, specificity and cutoff values of SD and PC/SD for large EV

Variable	Cutoff value	sensitivity	specificity	AUC (95% CI	P value	PPV	NPV	accuracy
PC/SD	696.5	63.16%	55.7%	0.595(0.488-0.702)	0.095	40.68%	75.86%	58.12%
SD	140.5	78.95%	60.76%	0.695(0.595-0.795)	0.001	49.18%	85.71%	66.67%

6 Discussion

Gastroesophageal variceal bleeding (EV) is a potential complication seen in 25%-35% of patients with cirrhosis. It carries a significant mortality risk, with a six-week mortality rate of 15% to 25% (27). To address this, several society guidelines, including the Baveno VII consensus and the American Association for the Study of Liver Diseases (AASLD), recommend esophagogastroduodenoscopy (EGD) for diagnosis and risk stratification of EV (28, 29). However, a limited number of non-invasive tests are available to predict EV. Among these, PC/SD ratio stands out as a promising option. It offers several advantages: ease of use, wide availability, and good predictive value in identifying high-risk patients

Several studies have suggested that a platelet count to spleen diameter (PC/SD) ratio greater than 909 offers high reliability in predicting esophageal varices (EV)(9, 12, 30, 31). A meta-analysis of 20 studies demonstrated that a PC/SD ratio cutoff of 909 exhibits a sensitivity of 92%, specificity of 87%, and a Hierarchical summary receiver operating characteristic (HSROC) of 0.95 for EV prediction(32).Our study identified a higher cut-off value of 1119, with a sensitivity of 86% and specificity of 70%. This finding aligns with observations from Z. Jamil et al., who reported a cut-off value of 1077 (sensitivity: 89%, specificity: 81%) in their study(33). Similarly, Patil et al. proposed a PC/SD ratio less than 1400 (sensitivity: 90%, specificity: 82%) for predicting esophageal varices in an Indian population(34). A meta-analysis by Chawla et al. encompassing eight studies further emphasized the concept of population-specific PC/SD cut-offs for optimal prediction(35). Studies conducted in Africa have also yielded comparable results(36).

Our study found that a spleen diameter (SD) level exceeding 160.5 mm has a good positive predictive value but a low sensitivity for the presence of esophageal varices (EV). This cut-off value is higher compared to a study by J.B. Okon et al., where a spleen diameter greater than 102 mm predicted 75% of EV cases with an accuracy of 85%(36).Studies have indicated that splenomegaly can be a good indicator of EV. D.G. Ashraf et al. reported that a spleen size exceeding 130 mm yielded a sensitivity of 87.7% and a specificity of 83.3% for EV prediction(37). However, in our study, the higher cut-off value for spleen diameter in our study diverges from observations in other studies(13).

Furthermore, a platelet counts of less than 133,000 displayed a higher sensitivity (93%) but a lower specificity (38%) with a better AUC for EV detection.

This study revealed an association between SD and the presence of large esophageal varices (EV). A SD exceeding 142.5 mm demonstrated a sensitivity of 61% and a specificity of 81%, with acceptable accuracy (area under the curve [AUC] = 0.763). In contrast, the PC/SD ratio failed to achieve similar performance for predicting large EV. These findings align with observations by Amoako et al., who reported no significant association between the PC/SD ratio and large EV prediction(14). However, a study by Barrera F. et al. showed contrasting results. A PC/SD ratio less than 830.8 yielded a sensitivity of 76.9% and a specificity of 74.2% (ROC curve area: 0.78), demonstrating better accuracy compared to our study, despite similar sensitivity(38, 39).

This study aimed to evaluate the sensitivity and specificity of the PC/SD ratio in identifying EV among cirrhotic patients in Ethiopia. Our findings suggest that the PC/SD ratio offers superior accuracy compared to platelet count and spleen diameter for this purpose. The cut-off value identified in our study diverges from a similar study conducted by HT Gebregziabiher et al. in Gondar, Ethiopia(38). Their study reported lower cut-off values; 818 for PC/SD ratio, 121,000 for platelet count, and 145 mm for spleen diameter. While the sensitivity, specificity, and AUC values of platelet count and PC/SD in our study are comparable to their findings, the sensitivity of spleen diameter in our results is lower. Interestingly, our analysis revealed that these non-invasive parameters exhibited better predictive value in patients with compensated cirrhosis compared to decompensated cirrhosis. This observation contradicts the findings of the aforementioned study by Gebregziabiher et al.(38).

6.1 Limitation of the study

Since we did a retrospective study, we can't control confounding variables that can be identified with appropriate patient selection and proper randomization. The other limitation of the study is the clinical characteristics of selected patients is heterogenous. There is inter observer variability in abdominal ultrasound and EGD result. CBC and other laboratory parameters were done at different laboratory. We didn't get enough number of patients without esophageal varices for head-to-head comparation.

7 Conclusion and recommendation

The PC/SD ratio is a promising non-invasive tool for identifying EV in cirrhotic patients, especially those with compensated cirrhosis. However, further multicentered study with a prospective design and larger sample size is warranted to confirm these findings.

7.1 Recommendation

Prospective, multicenter studies involving larger and more homogeneous patient groups are warranted to validate the efficacy of these non-invasive tests within our population. Such validation is crucial before recommending their utilization in settings lacking EGD for diagnosing and managing esophageal varices.

Future prospective studies should employ standardized laboratory measurements using similar CBC and chemistry machines for all participants. This will help to minimize confounding variables and enhance the overall study design.

To minimize the effects of inter-observer variability in future prospective studies, both EGD and abdominal ultrasound examinations should be performed by the most senior available physician, ideally the same individual for all participants.

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9 Annex

Structured questioner

Participant identification NO: _____

I. Sociodemographic characteristics				
1.	Age(yrs.)		Hospital No	
2	Sex	1.M		2.F

II. History				
No		1.Yes	2.No	remark
1	History of Jaundice			
2	History of body swelling			
3	Have you taken alcohol			
If yes, how much(gm): _____ For how long(years): _____				
4	Do you smoke cigarette			
If yes, pack years: _____				
5	Other: _____			

III. EXAMINATIONS				
No		Yes	No	remark
1	Jaundice			
2	Pallor			
3	Scanty axillary hair			
4	Leukonychia			
5	Digital clubbing			
6	Gynecomastia /breast atrophy			
7				

8				
9				
10	Splenomegaly			
11	Ascites			
12	Others			

IV.		
No	Parameters	Result
1	PT (sec)	
2	INR	
3	Serum Albumin(mg/dl)	
4	Total protein (mg/dl)	
5	HBsAg	
6	Anti HCV Antibody	
7	Creatinine(mg/dl)	
8	Bilirubin total(mg/dl)	
9	AST	
10	ALT	
11	ALP	
12	Platelet count	
13	WBC	
14	Hgn	
15	PC/SD	

V. Imaging, abdominal ultrasound				
No	Parameters	result		
1	Liver size (cm):			
2	Spleen bipolar diameter(cm)			
3	Portal vein diameter(mm)			
		1.Yes	2.No	
4	Ascites			
5	If yes, to the above question grade of ascites	1.Grade I	2.Grade II	3.Grade III
6	others			
Endoscopy				
No		1. yes	2. NO	
1	Presence of Varices			
2	If yes, to the above question grade of varices	1.Grade I	2.Grade II	3.Grade III
		1.yes	2.NO	
3	Stigmata of bleeding			
4	Gastric varices			

VI. Etiology of cirrhosis		
1	alcohol	
2	HCV	
3	HBV	
4	NAFLD	
5	Mixed cause	
6	other	

VII. Child Pugh score	
A	
B	
C	

Informed consent

Hello my name is Dr. Getnet yigzaw, a final year internal medicine resident at Addis Ababa university school of medicine. I'm conducting research on platelet count to spleen diameter ratio for prediction of esophageal varices in cirrhosis patients, in Addis Ababa, Ethiopia.

The aim of the study is to assess the accuracy of platelet count to spleen diameter ration for prediction of esophageal varices in liver cirrhosis patients. data will be collected by chart review and interviewing patients using structured questioner.

Your participation is very important for the success of this study and will entirely be only based on your willingness. You have the right to choose not to take it or withdraw at any time without giving any reason. There will be no direct benefit by participating in this study but the study help policy makers, programmers and researchers to give appropriate attention on the issue and design specific intervention options accordingly, and the finding of the study will serve as the foundation for future studies in the field. The information that you provide will be kept confidential at all times and the data will not be used for purposes other than the study. Your willingness and participation. In case you have any queries or issues regarding the study please feel free to contact the research team anytime.

Investigator's address:

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Yig2008gondar@gmail.com

Consent form

I have read and understood the provided information and I consent to take part in the research: Platelet count to spleen diameter ratio for prediction of esophageal varices in liver cirrhosis in Addis Ababa Ethiopia.

Participants signature……

Declaration

I, Getnet yigzaw, declare that this thesis is my original work and has not been submitted elsewhere. I also declare that a complete list of references is provided indicating all the sources of information quoted or cited.

Signature _____ Date _____

Advisor: Dr. Abdulsemed Mohammed (Consultant Internist, Gastroenterologist and Hepatologist, Interventional Endoscopist)

Signature _____ Date _____

Department head: Dr. Amsalu Bitaw (Consultant Internist, pulmonologist and critical care sub specialist)

Signature _____ Date _____