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Non-invasive predictors of esophageal varices in patients with cirrhosis: a cross-sectional study in Ethiopia

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Abstract

Background: Esophageal varices (EV) with gastrointestinal (GI) bleeding, is one of the major consequences of portal hypertension. It is also a leading cause of death in patients with end-stage liver disease. The only reliable diagnostic evaluation for confirming EV is an Esophagogastroduodenoscopy (EGD). But, EGD is an invasive test and requires an expensive machine, an experienced trained interventional endoscopist, and infrastructure. Such kind of setups are not available in many Low-middle income countries. Hence, a non-invasive predictor for the presence of EV is very important in areas where endoscopy services are not promptly available.

Objective: The study aimed to determine the validity of a platelet count (PLTc), and platelet count/spleen diameter ratio to predict the presence or absence of EV in patients with cirrhosis of any cause with no history of prior upper GI bleeding.

Methods: The study analyzed data from patients with cirrhosis, from February 2017 to December 2018 at St. Paul's Hospital Millennium Medical College (SPHMMC). An Observational, prospective cross-sectional study design was employed in individuals with no prior history of GI bleeding. Relevant clinical parameters, laboratory evaluation, and ultrasound diameter of the spleen were assessed. SPSS version 23 was used for data analysis. Univariate and multivariate analysis were done for predictors of EV, and a p-value <0.05 was considered statistically significant.

Results: Sixty-two (62) patients with cirrhosis were included; 44(71%) were male and the median age was 37 years. Platelet counts less than 150,000 is a good predictor for the presence of esophageal varix, with sensitivity and specificity of 86% and 42% (OR=4.4,95% CI of 1.08-17.76, P=0.029) respectively. Platelet count to Spleen Diameter ratio cut-off at 833 has better sensitivity and specificity of 68% and 83% (OR=10.63 (CI 2.08-54.25; P=0.001)) respectively, for predicting the presence of esophageal varices.

Conclusions: The level of platelet count and platelet count to spleen diameter ratio can be used as non-invasive predictors of esophageal varices. These non-invasive measures can help physicians to implement lifesaving prophylaxis for variceal upper GI bleeding, in areas where endoscopic services are not promptly available. We recommend a platelet count to spleen diameter ratio (n/mm3)/mm) cut-off 833 as a non-invasive predictor of esophageal varices.

Keywords: Esophageal Varices, Cirrhosis, Non-invasive tests, Variceal bleeding, Ethiopia

Background

Esophageal variceal bleeding is one of the major complications of cirrhosis. Patients with cirrhosis develop varices as the disease progresses, usually at the rate of 5% per year, and as the size of the varices increases the risk of bleeding increases. Generally, EGD is the single most important confirmatory means for the diagnosis of esophageal varices to date. Only very few studies have shown non-endoscopic markers to predict the presence and also severity of esophageal varices with a fair degree of sensitivity and specificity but the results have not yet been well standardized (1-3)

Cirrhosis is a common problem in Africa including Ethiopia with higher morbidity, and mortality (4). A major cause of cirrhosis-related morbidity and mortality is the development of variceal hemorrhage, a direct consequence of portal hypertension (1). Each episode of active variceal hemorrhage is associated with up to 30 percent mortality (2,3). In addition, survivors of an episode of active bleeding have a 70 percent risk of recurrent hemorrhage within one year of the bleeding episode (5). The prevalence of esophageal varices in cirrhotic patients ranges between 24% and 69% according to the degree of liver dysfunction, and one-third of all patients with varices will develop variceal hemorrhage (1,6). The risk of hemorrhage has been related to the size and appearance of the varices, as well as the degree of hepatic dysfunction (7,8).

EV appear if the hepatic venous pressure gradient (HVPG) has increased to at least 10 to 12 mm Hg (9,10). In patients with cirrhosis, the incidence of esophageal varices increases by nearly 5% per year, and the rate of progression from small to large varices is approximately 7-8%, yearly increment (11,12). Increasing the size of varices is associated with a significance in variceal-wall tension to a critical level at which varices rupture and cause life-threatening bleeding (8). As stated above, this is associated with a 1/3rd risk of mortality in untreated varices, and there are some factors that could predict this outcome.

However, if appropriate treatment is optimally, and timely provided, the mortality rate from variceal bleeding is less than 20% (13). Primary prophylaxis with nonselective β-blockers or endoscopic utilization of therapeutic management (mainly rubber band ligation) prevents bleeding in more than half of patients with medium or large varices. American Association for the Study of Liver Diseases (AASLD) practical guidelines for the treatment of portal hypertension, and Baveno VII, have recommended endoscopic screening of patients with cirrhosis for varices, and prophylaxis to be provided for patients with medium or large varices to prevent bleeding. It has been suggested that all patients should undergo endoscopic screening for varices at the time, that cirrhosis is diagnosed, and every 2 to 3 years thereafter in those with compensated disease and no varices. The recommended time interval between endoscopies for those with small varices was 1 to 2 years, and 1 year for those with a decompensated disease, with or without varices (11,14). These recommendations imply a considerable burden of endoscopies and related costs. This will prevent the potential occurrence of bleeding from moderate to large, or small varices (with imminent signs of bleeding), yet, with the cost of repeated endoscopy evaluations. In addition to the need for repeated procedures, it is also actually not important in nearly half of the patients, who may not develop esophageal varices 10 years after the diagnosis of cirrhosis (15-17).

To reduce the number of unnecessary endoscopies in patients with cirrhosis but without varices, several studies have evaluated possible noninvasive predictors of esophageal varices in patients with cirrhosis (7, 18-22). However, the predictive accuracy of such noninvasive markers is still considered to be unsatisfactory, and none of them has been widely utilized for use in clinical practice so far (19).

Prevention of bleeding from esophageal varices is further complicated by uncertainty about whether nonselective beta blockers can prevent the development of varices or the progression of small varices to larger varices that may bleed. A large multicenter, placebo-controlled, double-blinded trial failed to show a benefit of nonselective-beta blocker in the prevention of varices in patients with cirrhosis who had portal hypertension at baseline (HVPG 5 mmHg) but had not yet developed varices (20). These results do not support the suggested universal use of B-blockers in cirrhosis (16).

Since the point prevalence of medium/large varices is approximately 15%-25% (20,21), the majority of subjects undergoing screening EGD either do not have varices or have varices that do not require prophylactic therapy. So, there is considerable interest in developing models to predict the presence of high-risk varices by non-endoscopic methods. Some of the non-invasive laboratory tests used as predictors of esophageal varices in patients with cirrhosis, include platelet count, fibro-test, spleen

diameter, portal vein diameter, and transient elastography (7,22). However, the predictive accuracy of such noninvasive markers is not widely studied in LMIC, and until large prospective studies of noninvasive markers are performed, endoscopic screening is still the main means of assessing for the presence of esophageal varices (7).

In general, there is limited information and knowledge about the diagnostic significance of non-endoscopic markers for the presence and severity of esophageal varices secondary to cirrhosis. Thus, both the Baveno VII (23) and AASLD Practical Guideline, recommend searching for more data to determine the significance of noninvasive markers. In Africa, more than in any other part of the world, the information gap about the significance of non-endoscopic predictors of varices is wider regardless of the usefulness of this method for the diagnosis of varices for resource-limited regions. In Ethiopia, there is no study describing the importance of non-invasive markers for the diagnosis of esophageal varices in cirrhotic patients. This study was performed with the aim to find a non-endoscopic way of predicting the presence and severity of esophageal varices in patients with cirrhosis and helping with the decision of provision of primary prophylaxis.

Methods

Study setting, design, period, and population

This study was conducted in Addis Ababa, Saint Paul's Hospital Millennium Medical College (SPHMMC). SPHMMC is a teaching hospital with an estimated 1200 clinical and nonclinical staff providing care to approximately 290,000 patients each year and a catchment population of more than 5 million people. SPHMMC receives referrals from all over the country and is under the guidance of the Ethiopian Ministry of Health (MOH). It is one of the biggest public tertiary hospitals with a bed capacity of more than 700. The hospital has many departments, and the Department of internal medicine shares the major part of the outpatient department care, and currently, it has 60 functional beds. The GI unit has currently six gastroenterologists, one endosurgeon, and four fellows and it provides services to all patients referred from all over the country. It is one of the major centers providing diagnostic and therapeutic endoscopy services for at least 4000 patients each year. The center is the first African site recognized by World Endoscopy Organization as an outreach endoscopy training center.

An observational, prospective cross-sectional study was conducted from February 2017 to January 2018. The study enrolled 62 patients with cirrhosis of any etiology, without prior history of upper GI bleeding (GIB) or any history of drugs for primary prophylaxis. The data was collected from cirrhotic patients at SPHMMC, Addis Ababa, including both outpatient and in-patient departments. The patients who are referred for an endoscopy evaluation were assessed for non-invasive tests and their endoscopy results is compared.

The diagnosis of cirrhosis (diagnosed by the treating physician) is made based on clinical (history and physical exam), biochemical, and imaging data (US/CT). The viral etiology of cirrhosis was considered after tests for viral hepatitis B (hepatitis B surface antigen) and/or C (hepatitis C antibody) was positive. Alcoholic etiology was made when the patient's declared alcohol consumption of more than 50 g per day when measurable or local alcohol beverage consumption on most days of the week usually with intoxication and at least for five years, and autoimmune hepatitis diagnosed based on diagnostic criteria after exclusion of other cause. Drug-induced hepatitis is considered when a history of drug exposure followed by hepatitis and other causes are excluded. Treating physicians' (Gastroenterologist) diagnosis of cirrhosis and possible underlying etiology was also considered as an operational definition (e.g., Alcoholic cirrhosis).

Patients were included in the study when they presented with liver cirrhosis diagnosed by clinical, biochemical, and ultrasonographic parameters and aged greater than 14 years. But, patients treated for bleeding of EV (endoscopically-injection sclerotherapy or band ligation or both; TIPS or surgical shunt therapy), and/or patients who received drugs for primary prophylaxis of variceal bleeding (e.g. β-blockers), patients having sonographic evidence of focal hepatic lesion(s) or having either partial or complete portal vein thrombosis, splenic or hepatic veins thrombosis (Budd-Chiari syndrome), and presented diagnosed with Hepatocellular Carcinoma (HCC) were excluded. The severity of cirrhosis was classified based on Child-Pugh criteria (20).

EGD for evaluation of the presence and severity of EV was done by a senior consultant gastroenterologist. EV were graded according to the French classification system derived from the Japan Research Society for Portal Hypertension which comprises 3 stages (24) as follows: Stage 1: Small EV that flatten with insufflations and not confluent. Stage 2: Tortuous EV not confluent and occupying less than one-third of the lumen of the esophagus. Stage 3: Tortuous EV confluent occupying more than one-third of the lumen. The information on each medical record was assessed with a structured validated data collection format. Ethical

clearance was obtained from the Institutional Review Board (IRB) of the SPHMMC. All patients coming to the Endoscopy unit and fulfilling the inclusion criteria were studied. Patients with active gastrointestinal bleeding (or a prior history of bleeding) at the time of admission were excluded. All patients underwent screening EGD.

Data Processing and Analysis

Categorical or ordinal variables were expressed as frequency and percentages and continuous variables as median and interquartile range. Chi-square test was used to compare categorical variables and statistical analysis was carried out with SPSS v23. Categorized platelet count and platelet count to spleen diameter ratio were calculated in order to verify sensitivity, and specificity from 2x2 table; with a confidence interval of 95%. A p value ≤ 0.05 was considered significant.

Results

Socio-demographic characteristics of participants

Sixty-two patients were involved in the study. The basic characteristics of patients are summarized in Table 1. Seventy-one percent (n=44) of the patients are male and the median age is 37 years (Table1). The commonest etiology of cirrhosis is HBV infection 34 (54.8%), followed by alcohol-related 9(14.5%), HCV 8 (12.9%), Drugs and Autoimmune causes in 3 (4.8%) each; 5 individuals have no identified causes of cirrhosis. Considering the clinical profile, most patients had ascites 79 % (n=49), and 80% (n=50) of the patients have esophageal varices. All patients with Child class C stage liver disease have esophageal varices. The mean platelet count was 128,364. The mean spleen diameter was 14.17(±2.25 and, mean platelet count/spleen diameter ratio was 1024 (±8.20). (See Table 1 below).

Table1: Socio-demographic characteristics of patients with cirrhosis at SPHMMC, (n=62)

Variable	Number (%)
Age, in yrs. (Median)	37
Sex Male Female	 44(71) 18(29)
Etiology of cirrhosis Alcohol HBV HCV AIH Drugs Unknown	 9(14.5) 33(53.2) 8(12.9) 3(4.8) 3(4.8) 5(8.1)
Ascites (present)	49(79)
Child-Pugh class A B C	 20(32.3) 25(40.3) 17(27.4)
Spleen size, cm (mean ± SD)	14.2 (± 2.25)
PLT to spleen size ratio (mean ± SD)	1024(±8.20) ᵅ
Esophageal varices	50 (80.6)
Grade of varices** 1 2 3	 16(32) 23(46) 11(22)

* AIH-Autoimmune Hepatitis, HBV-Hepatitis B virus, HCV-Hepatitis virus; * α-PLT count x 103 (k) divided by spleen size in centimeter, expressed as a number of cells x k/cm.
** Grade1. small, grade 2 & 3 = large.

Clinical characteristics and relation to varices

Most variables including child class, ascites, INR, splenomegaly, and etiology are associated with the presence of esophageal varices but are not statistically significant. According to the child class, 20 individuals have child A (10 (50%) have varices and all are stage I); 25 have child B (92% have varices; 72% have large varices of stage III); 17 individuals are child C, and all have varices.

Table 2: Clinical characteristics of participants at SPHMMC, (n=62)

Variables	**Mean (±SD)**
WBC Count	36.5(±2687)
Hemoglobin	13.4(±2.42)
Liver Enzymes ALT AST Bil (T)	 68.0 79.0 2.3
Albumin	3.1
INR	1.6
Creatinine	0.8
PLT to spleen size ratio	1024 (±8.20) α

Non-Invasive Tests in relation to the presence of varices

Low platelet count and platelet count to spleen diameter ratio are the two most important predictors of the presence and absence of EV (Table 3) and were analyzed using cross tabs. Platelet count less than 150,000(150k) is a good predictor of the presence of esophageal varix, with sensitivity and specificity of 86% and 42 %, (OR=4.4,95% CI1.08-17.76, p-value=0.029) respectively. Platelet count to spleen diameter (longest diameter) ratio at a cut-off 1250 has a sensitivity of 84% and specificity of 50% (OR=5.25, 95%CI, 1.35-20.47; p=0.006) and platelet count to spleen diameter ratio cut-off 833 has a sensitivity and specificity of 68% and 83 % (OR=10.63 (CI,2.08-54.25; p=0.001)) respectively.

Table 3: Non-Invasive Tests in relation to the presence of varices

Variables	Varices		OR (CI 95%)	p-value
	Present	Absent		
Platelet count ≥150000 <150000	7 43	5 7	4.4(CI,1.08-17.76)	0.029
PLT count to spleen diameter ratio <1250 Vs ≥1250 ≥833 Vs < 833	50 16	12 10	10.63, (CI,2.08-54.25)	0.001
**p-value <0.05, ** Variables statistically significantly associated with poor practice*				

Discussion

Esophageal varices-related upper GI bleeding is a major cause of cirrhosis-related morbidity and mortality and increased Heath care costs (4). Because primary prophylaxis with nonselective β-blockers or rubber band ligation prevents bleeding in more than half of patients with medium or large varices, international guidelines have recommended endoscopic screening of patients with cirrhosis for varices, thereby treatment and prophylaxis of patients with medium or large varices will be provided to prevent bleeding (11,14). These recommendations impose LMICs a considerable burden of endoscopies and related costs; which is only available in tertiary care centers. In this study, we utilized only simple, commonly available, reproducible parameters, which have less inter-observer variability like platelet count, spleen diameter, severity of liver disease based on Child class, INR, albumin, and presence of ascites. In the univariate analysis, the patient's platelet count and platelet count/spleen diameter ratio, mean spleen diameter, presence of ascites, Child-Pugh classification, INR, and etiology of cirrhosis are associated with the presence of EV. Based on our analytical result, only platelet count and platelet count to spleen diameter ratio showed statistical significance. Categorized platelet count and platelet count to spleen diameter ratio were analyzed. Platelet count categorized as : greater or equal to 150, 000 (normal range), less than 150, 000;and platelet count greater or equal to 100,000, and platelet count less than 100,000 (moderate to severe). As only one patient was having a low platelet count of <100 000 and absent varices, we couldn't't compute this association. A platelet count of < 150 000 gave an OR of 4.4 with a P-value of 0.029. A platelet to spleen diameter of 1250 has an OR of 5.3 at a P value of 0.011, which is statistically significant. A platelet level of less than 150,000 has good sensitivity but poor specificity to predict the presence of esophageal varices whereas, a platelet count of less than 100,000 has good specificity but less sensitivity. Similarly, a platelet count to spleen ratio of less than 1250 has good sensitivity but is nonspecific, and a platelet count to spleen diameter ratio of less than 833 has good specificity with better sensitivity.

In this study platelet count of less than 150,000 and platelet count to spleen diameter ratio at a cut-off 833 have good sensitivity, and may be considered as a screening method if there is no access to upper GI endoscopy. Previous studies have shown varices needing treatment (VNT), a sensitivity of 85% was achieved using a cut-off of 909. Other non-invasive methods include liver stiffness and platelet count, and the EVENDO score (based on INR, AST, BUN, Platelet, and Hemoglobin).

Limitations of the study

Such non-invasive tests generally do not replace the utilization EGD, but can be used in areas where an EGD service is not emergently available. In patients with cirrhosis thrombocytopenia and/ or splenomegaly can be caused by other etiology other than portal hypertension secondary to cirrhosis, such as infections, alcohol, autoimmune disease, or hematologic malignancies, thus these should be considered as limitations when we consider platelet count and spleen size as predictive parameter. Additional limitation of this study is the small sample size and that the study was at a single center which could limit generalizability

Conclusion

In conclusion, Low platelet count and/ or platelet to spleen diameter ratio can be used as a predictor of esophageal varices in resource-limited settings. This study was done in a single center and in a relatively small number of patients, thus multi-centered and large sample size including other noninvasive parameters will have paramount importance to recommend unequivocally the predictive value of non-endoscopic methods. Based on this study, we recommend a cut-off of 833 for PLT count to spleen diameter ratio as a noninvasive prediction of esophageal varices.

Abbreviations

AASLD-American Association for the Study of Liver Disease, AAU-CHS-Addis Ababa University College of Health Science, ALT(SGPT)-Alanine aminotransferase (formerly called SGPT), AST(SGOT)-

Aspartate aminotransferase (formerly called SGOT), CBC-Complete blood count, EASL-European Association for the Study of Liver Disease, EGD-Esophagogastroduodenoscopy, EV-Esophageal varices, LFT-Liver function test, OPD - Outpatient Department, PLT-Platelet, RFT-Renal function test, SPHMMC- St. Paul's Hospital Millennium Medical Collage, TIPS Trans jugular intrahepatic portosystemic shunt, UGIB – Upper GI Bleeding, US-Ultra sound, WBC-White blood cell

Declarations

Consent for publication

Not applicable.

Ethical declaration

The study was approved by SPHMMC's Institutional Review Board (IRB). Informed written consent was obtained from the participants. The study was conducted based on the approved protocol following the Helsinki Declaration principles.

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Authors' contributions

GL conceptualized the research problem, designed the study, conducted data collection, collected and data analyzed, and drafted the manuscript. HD conceptualized the research problem, designed the study, data analyzed, and drafted the manuscript, responsible for submission, and do the final correction with the journal managers, MC, HC were involved in revising the final manuscript. All authors of the manuscript have read and agreed to its content.

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Competing interest

All authors read and approved the final manuscript. The authors declare that they have no competing interests.

Availability of data and materials

The datasets used in the current study or data collection tool are available from the corresponding author with a reasonable request.

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