

# The diagnostic accuracy of routine clinical findings for detection of esophageal varices in rural sub-Saharan Africa where schistosomiasis is endemic

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## Abstract

**Background:** Variceal upper gastrointestinal bleeding (UGIB) is common in sub-Saharan Africa (SSA). However, poor access to endoscopy services precludes the diagnosis of varices.

**Objectives:** We determined the diagnostic accuracy of routine clinical findings for detection of esophageal varices among patients with UGIB in rural SSA where schistosomiasis is endemic.

**Methods:** We studied patients with a history of UGIB. The index tests included routine clinical findings and the reference test was diagnostic endoscopy. Multivariable regression with post-estimation provided measures of association and diagnostic accuracy.

**Results:** We studied 107 participants with UGIB and 21% had active bleeding. One hundred and three (96%) had liver disease and 86(80%) varices. Factors associated with varices ( $p$ -value  $<0.05$ ) were  $\geq 4$  lifetime episodes of UGIB, prior blood transfusion, splenomegaly, liver fibrosis, thrombocytopenia, platelet count spleen diameter ratio  $<909$ , and a dilated portal vein. Two models showed an overall diagnostic accuracy of  $> 90\%$  in detection of varices with a number needed to misdiagnose of 13(number of patients who needed to be tested in order for one to be misdiagnosed by the test).

**Conclusion:** Where access to endoscopy is limited, routine clinical findings could improve the diagnosis of patients with UGIB in Africa.

**Keywords:** The diagnostic accuracy of routine clinical findings for detection of esophageal varices in rural sub-Saharan Africa where schistosomiasis is endemic.

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## Introduction

Endoscopy is recommended for anyone with a history of upper gastrointestinal bleeding (vomiting blood or passing black stool or rarely, passing frank blood in one's stool). It is the most accurate and best available diagnostic test for upper gastrointestinal bleeding<sup>1,2</sup>. On the other hand, limited access to endoscopy is associated with poor

disease outcomes<sup>3,4</sup>. In sub-Saharan Africa (SSA), upper gastrointestinal bleeding (UGIB) is a frequent cause of hospitalization and death<sup>5-8</sup>. It is mainly due to bleeding esophageal varices and is a complication of chronic schistosomiasis and/or liver cirrhosis. Diagnosis of varices and UGIB in SSA is challenging because of limited access to endoscopy<sup>9,10</sup>. This has had undesirable effects like increased frequency of death<sup>7,11,12</sup>. Just a few studies have identified potential surrogates to endoscopy for diagnosis of UGIB or varices. These include thrombocytopenia, splenomegaly, an abnormal platelet count/spleen diameter ratio, and ultrasound periportal fibrosis patterns<sup>13-16</sup>. However, none of these parameters have been studied at any primary health care settings in rural SSA where endoscopy services are absent. We studied the

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diagnostic accuracy of routine clinical findings for detection of esophageal varices among patients reporting one or more lifetime episodes of upper gastrointestinal bleeding. Our study was conducted at a primary health facility in rural sub-Saharan Africa where schistosomiasis is endemic and access to endoscopy is limited.

## **Materials and methods**

### **Overview**

Our study was part of one study that profiled upper gastrointestinal bleeding<sup>17</sup>. It was a diagnostic accuracy study at Pakwach Health Centre IV in Northwestern Uganda. We enrolled participant's  $\geq 12$  years of age, with a history of UGIB and/or admitted for acute severe UGIB. For each participant, we obtained consent and administered a questionnaire collecting information on current or past history of UGIB. We then performed a physical examination, laboratory tests, and liver sonography. The above were performed independently of the endoscopy team.

### **Diagnostic endoscopy**

All participants were eligible for a diagnostic endoscopy and underwent diagnostic upper digestive endoscopy. No participant was excluded for any reason. Endoscopy was performed in the unit's operating theatre by a trained gastroenterologist and his team using a Pentax EPKi digital video processor and Pentax 9.8mm video gastroscope<sup>18</sup>. The esophagus, stomach, and duodenum were examined for evidence of UGIB or cause of UGIB with emphasis on varices, esophageal or gastric/duodenal erosions or ulcers<sup>18</sup>. Endoscopic findings were reported as recommended by the Japanese research for Portal Hypertension, and/or the modified Forrest classification for upper gastrointestinal bleeding<sup>19,20</sup>. The report was written and pictures saved. Results were communicated to each participant; appropriate treatment given (propranolol for varices or triple therapy for peptic ulcer disease or hematinics for anemia), and linkage to care ensured.

Ethical approval was obtained from the School of Medicine Research and Ethics Committee of Makerere Uni-

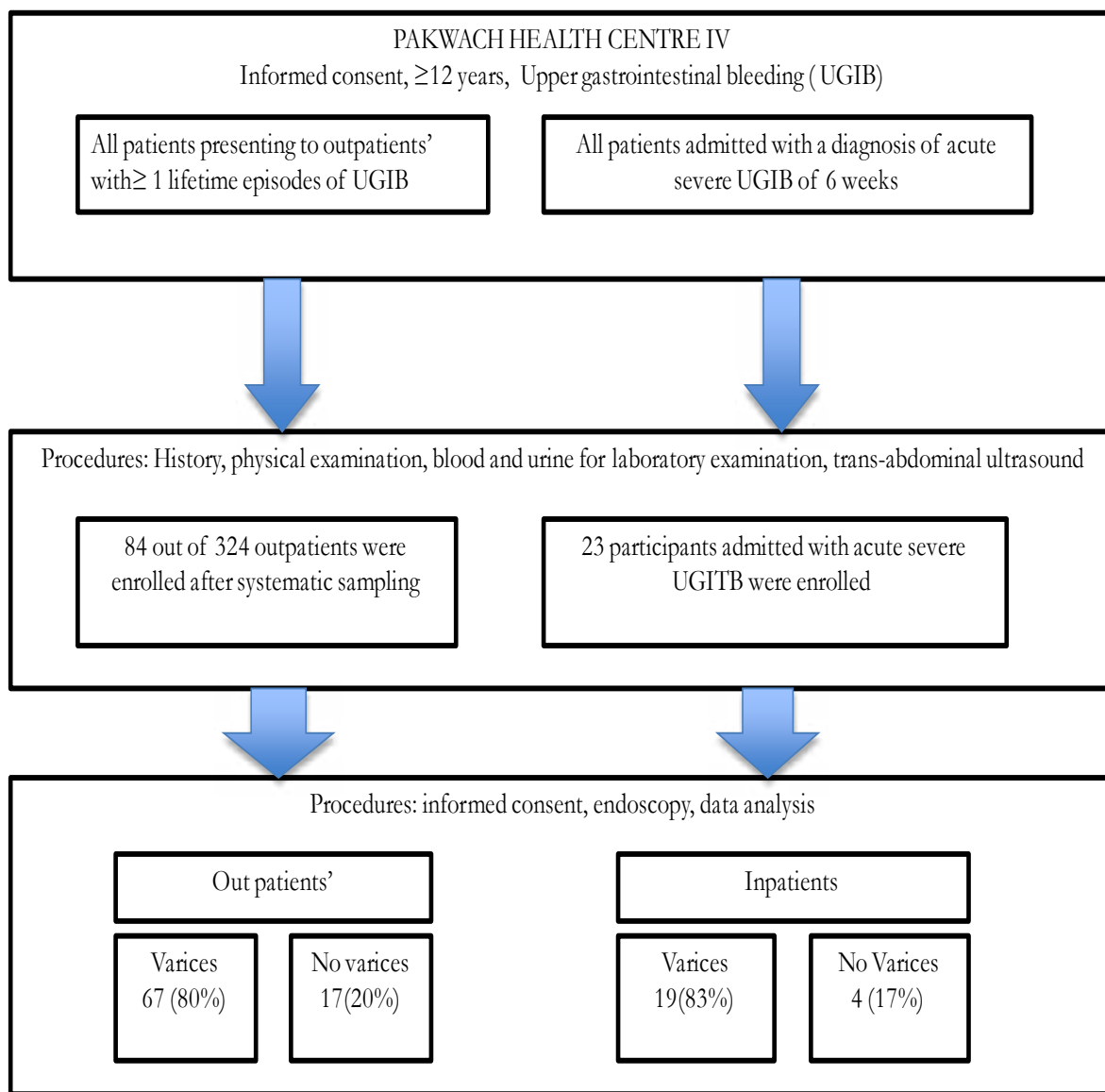
versity College of Health Sciences, and the Uganda National Council for Science and Technology. Our study was carried out in accordance with the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from all participants.

### **Data management and analysis**

The reference standard test was endoscopy. The dependent variable was esophageal varices and independent variables were routine clinical findings. Data was recorded in forms and transcribed into Microsoft Access database software 2007 (Microsoft Corporation) daily and exported to Stata version 13 (StataCorp, Lakeway, College Station, Texas, USA) for analysis. Descriptive statistics included frequencies and proportions. Inferential statistics involved logistic regression with esophageal varices as the dependent variable. A significance level ( $p$ -value  $< 0.05$ ) was chosen. Odds ratios and confidence intervals were used for inference. Purposeful selection of covariates was performed and models generated. The best-fit model was selected on clinical plausibility, Akaike information criterion, and Bayesian information criterion. The outputs of the 2 best-fit models were represented graphically as nomograms. Post-estimation in Stata generated measures of diagnostic accuracy by a confusion matrix for the best two models and other clinical parameters associated with esophageal varices. Measures of diagnostic accuracy included specificity, sensitivity, positive predictive value, negative predictive value, correct classification rate (overall accuracy), and number needed to misdiagnose-number of patients who needed to be tested in order for one to be misdiagnosed by the test<sup>21-24</sup>. These results are detailed in the subsequent text and tables.

### **Results**

From July to August 2014, one hundred and seven participants underwent endoscopy to determine the possible cause of their UGIB. Eighty-four (78%) were outpatients and 23 (22%) in-patients with severe acute UGIB (Figure 1).



**Figure 1.** Study flowchart describing enrollment and the proportion of participants from outpatients and inpatients with esophageal varices.

The youngest and oldest participants were 25 years and 75 years of age respectively. The median age was 45 years and IQR 13 years. Sixty-four (60%) were females, all participants reported ≥2 contacts with the waters of the Nile every week, 94(88%) reported prior treatment with praziquantel, 103 (96%) reported a past admission for UGIB, and none of the study participants had ever had an endoscopy. Among the 107 participants, 57% (95% CI

47%-66%) experienced two or more episodes of UGIB during their lifetime. At ultrasonography 92% had liver disease with 40% having cirrhosis and 60% had periportal fibrosis. We found esophageal varices in 80% (95% CI, 72%-87%), gastric varices in 17% (95% CI, 11-25%), portal hypertensive gastropathy 78% (95% CI, 69%-84%), and actively bleeding or oozing gastric or duodenal mucosa in 10% (Table 1).

**Table 1.** Endoscopy findings, their proportions, and/or 95% confidence intervals for proportions

Endoscopy findings	N (%)	95% CI (%)
Esophageal varices present	86(80%)	(72%-87%)
<b>Grades of varices</b>		
F0: lesions assuming no varicose appearance	21 (19.6%)	
F1: straight small-calibered varices	12 (11.1%)	
F2: moderately enlarged, beady varices	32 (29.9%)	
F3: markedly enlarged, nodular, or tumor-shaped varices	42 (39.4%)	
Red color sign (RC) with esophageal varices		
Red wale marking, cherry Red Spot, hematocytic spot		
RC0: absent	11 (12.8%)	
RC1: small in number and localized	10 (11.6%)	
RC2: intermediate between 1 and 3	27 (31.3%)	
RC3: large in number and circumferential	38 (44.2%)	
Esophageal varices with		
Gushing	0	
Spurting	2 (2%)	
Red plug	13 (12%)	
White plug	8 (8%)	
Gastric varices present	18(17%)	(11%-25%)
Portal hypertensive gastropathy (mosaic pattern)	83 (78%)	(69%-84%)
Abnormal mucosa stomach or duodenal mucosa (erosions or ulcerations) and presence of stigmata of bleeding		
<u>Forrest classification</u>		
I a (spurting hemorrhage)	0	
Ib (oozing hemorrhage)	11 (10%)	
IIa&b (non bleeding visible vessel or adherent clot)	0	
II c (flat pigmented hematin)	1 (1%)	
III (lesions without any signs of recent hemorrhage or fibrin)	17 (16%)	

A number of routine clinical findings were more frequent and more likely to occur among those with varices than those without varices (95% CI for odds ratio >1) at univariable analysis. These included having  $\geq 4$  lifetime

episodes of UGIB, prior history of blood transfusion, palpable spleen, WHO ultrasound periportal fibrosis patterns DEF or X, platelet count  $\leq 140 \times 10^9/L$ , platelet count /spleen diameter ratio  $\leq 909$ , portal vein diameter  $\geq 13$  mm (Table 2).

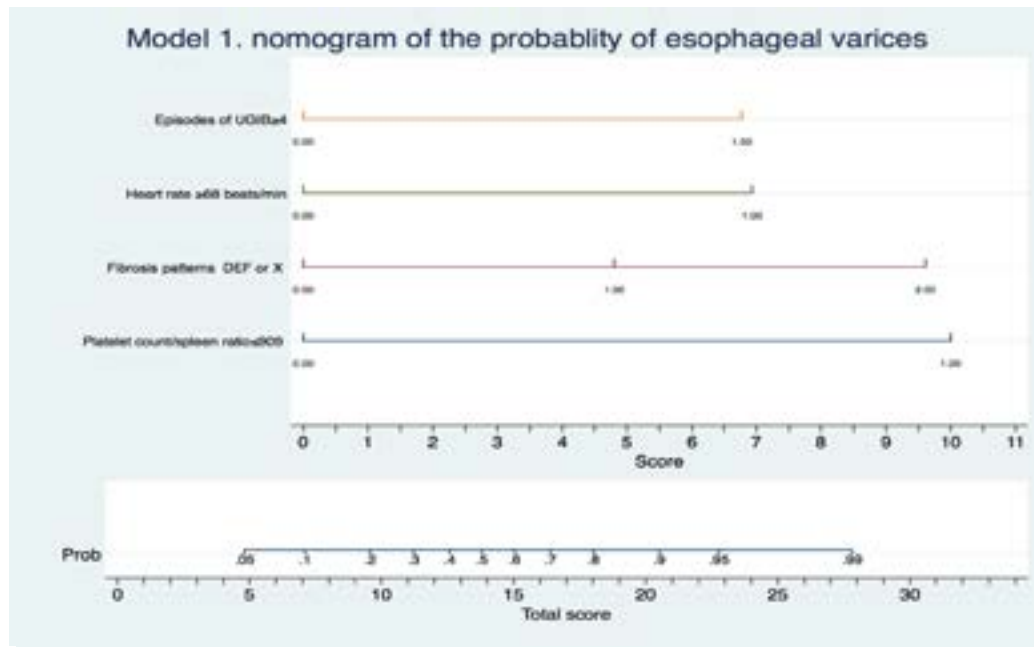
**Table 2.** Routine clinical findings associated with the presence of esophageal varices at endoscopy: proportions, crude odds ratios, and their 95% confidence intervals.

Factor variables	Varices	No varices	Crude odds ratios (95%CI)
	N (%)	N (%)	
Age ≤39 years	25 (29)	4 (19)	1.7 (0.5-6)
Female gender	53 (62)	11 (52)	1.5 (0.6-3.8)
Born in Pakwach	67 (78)	15 (71)	1.4 (0.5-4.1)
Resident in Pakwach > 10 years	77 (90)	17 (81)	2.0 (0.6-7.3)
>2 contacts a week with the waters of the Nile	86 (100)	21 (100)	-
Farmer (occupation)	63 (73)	16 (76)	0.9 (0.3-2.6)
Prior Praziquantel use	75 (87)	18 (85)	1.1 (0.3-4.5)
Previously admitted for upper gastrointestinal bleeding	84 (98)	19 (90)	4.4 (0.6-33.4)
Currently admitted for severe acute variceal bleeding	19 (22)	4 (19)	1.2 (0.4-4)
Number lifetime of episodes of upper gastrointestinal bleeding			
1	33 (39)	13 (62)	
2-3	27 (31)	7 (33)	2.4 (1.2-4.9)*
4 and more	26 (30)	1 (5)	
Previous blood transfusion	64 (72)	9 (43)	3.9 (1.4-10.5)*
Alcohol use	4 (5)	0	-
Jaundice	10 (11)	1 (5)	2.6 (0.3-21.8)
Ascites	17 (20)	1 (5)	4.9 (0.6-39.3)
Liver flap	8 (9)	2 (10)	0.9 (0.2-4.9)
Edema	11 (13)	1 (5)	
#Splenomegaly at palpation	78 (96)	14 (67)	13 (3-56) *
WHO ultrasound patterns			
A+C	1 (1)	8 (38)	4.8 (1.9-12.3)*
D+E+F	51 (59)	8 (38)	
X	34 (40)	5 (24)	
Platelet count spleen diameter ratio ≤909	79 (92)	6 (29)	28 (8-96)*
Portal vein diameter ≥13 mm	69 (80)	10 (48)	4.5 (1.6-12.2)*
Hepatitis B surface antigen positive	5 (6)	2 (9)	0.54 (0.1-3.25)
Hepatitis C-antibody positive	21 (24)	7 (33)	0.65 (0.23-1.81)
Urine circulating cathodic antigen positive	5 (6)	4 (19)	0.26 (0.06-1.07)
Platelet count ≤ 140 x10 <sup>9</sup> /L	82 (95)	12 (43)	27 (7.3-103)*
Hemoglobin level ≤80g/L	26 (30)	6 (29)	1.1 (0.4-3.1)

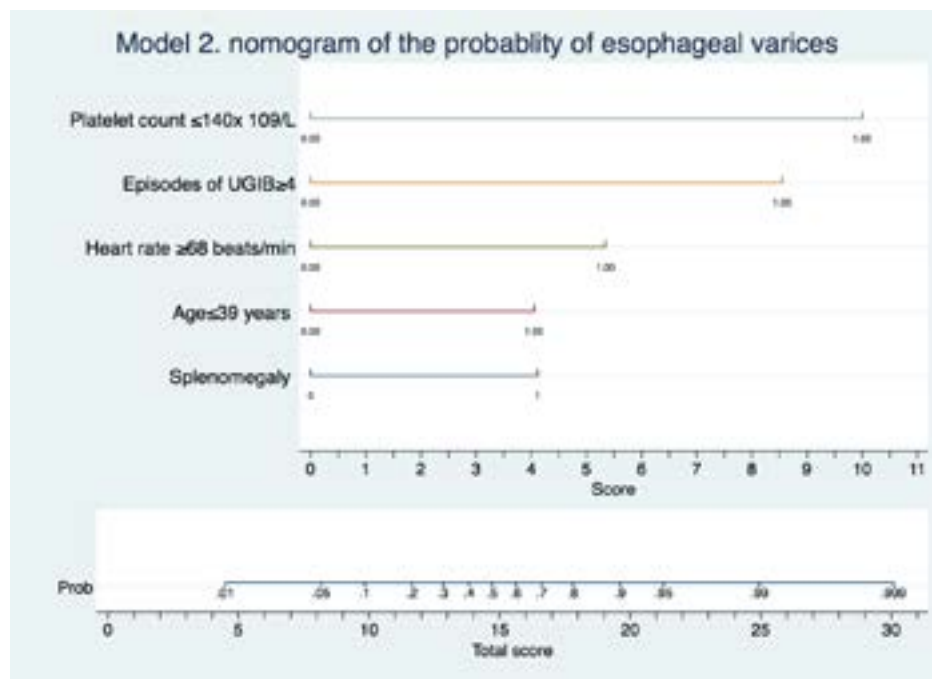
\*P-value <0.05; 95% confidence intervals do not cross 1, #5 missing evaluations due to tense ascites.

At multivariable logistic regression we identified two of the best-fit models 1 and 2. These are summarized visually as two nomograms, Figure 2 and Figure 3. These represent an approximate graphical computation of a mathematical function of each model. The sums of the scores of all factors in the graphs indicate the predicted

probability of having varices. This is obtained by linking the total scores with the corresponding probability. The diagnostic accuracy of these clinical factors and statistical models are summarized in Table 3. All factors were found to have very good sensitivity (>90%) while model 1 and 2 had the best specificity. Model 1 and 2 had the best number needed to misdiagnose esophageal varices of 13.



**Figure 2.** A nomogram of model 1 consisting of platelet count spleen diameter ratio  $\leq 909$ , WHO peri-portal fibrosis patterns EF or X, number lifetime of episodes of UGIB  $\geq 4$ , heart rate  $\geq 68$  beats/minute. This enables one to calculate output probabilities for predictive models with a visual approach. Estimate the probability of having varices through 3 steps. Step 1 -establish scores for all variable values, step 2-obtain the total score adding up all the scores obtained in the previous step, step 3-obtain the probability of the event (total Score -> Probability of event).



**Figure 3.** A nomogram of model 2 consisting of includes age  $\leq 39$  years, heart rate  $\geq 68$  beats/minute, palpable spleen,  $\geq 4$  Number lifetime of episodes of UGIB, platelet count  $< 140 \times 10^9/L$ . This enables one to calculate output probabilities for predictive models with a visual approach. Estimate the probability of having varices through 3 steps. Step 1 -establish scores for all variable values, step 2-obtain the total score adding up all the scores obtained in the previous step, step 3-obtain the probability of the event (total Score -> Probability of event).

**Table 3.** The diagnostic accuracy of routine clinical findings or their combinations for detection of esophageal varices in rural Africa where schistosomiasis is endemic: diagnostic tests, study size, and measures of diagnostic accuracy.

Diagnostic tests	N	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Accuracy (95%CI)	NNM (95%CI)
Model 1 (involves ultrasonography)	107	97% (90-99%)	71% (48-89%)	93% (88-97%)	83% (61-94%)	92% (85-96%)	13 (7-25)
Model 2 (no ultrasonography)	102	96% (90-99%)	76% (53-92%)	94% (89-97%)	84% (63-94%)	92% (85-97%)	13 (7-25)
Platelet count spleen diameter ratio <909	107	92% (84-97%)	71% (48-89%)	93% (87-96%)	68% (50-82%)	88% (80-93%)	8 (5-14)
≥4 Number lifetime of episodes of upper gastrointestinal bleeding (UGIB)	107	100% (96-100%)	0 (0-16%)	83% -	- -	80% (72-87%)	5 (4-8)
Fibrosis patterns EF or X*	107	99% (94-100%)	38% (18-62%)	87% (82-90%)	89% (51-98%)	87% (79-93%)	8 (5-14)
Palpable spleen	102	96% (90-99%)	33% (15-57%)	85% (80-88%)	70% 40-89%	83% (79-90%)	6 (5-10)
Platelet count ≤140 x10 <sup>9</sup> /L	107	95% (89-99%)	57% (34-79%)	90% (85-94%)	75% (56-89%)	88% (80-93%)	8 (5-14)
Heart rate ≥68beats/min	107	100% (96-100%)	0 (0-16%)	80% -	- -	80% (72-87%)	5 (4-8)
Age ≤39 years	107	100% (96-100%)	0 (0-16%)	80% -	- -	80% (72-87%)	5 (4-8)

Model 1 includes following factor variables platelet count spleen diameter ratio <909, WHO periportal fibrosis patterns EF or X, number lifetime of episodes of UGIB ≥4, heart rate ≥68beats/minute. Model 2 includes age ≤39 years, heart rate ≥68 beats/minute, palpable spleen, ≥4 Number lifetime of episodes of UGIB, platelet count ≤140 x 10<sup>9</sup> /L. PPV- positive predictive value, NPV-negative predictive value, NNM– number needed to misdiagnose.

## Discussion

These results showed our two models of different routine clinical findings demonstrated good diagnostic accuracy in detecting esophageal varices. To our knowledge, this is the first study from a primary health facility in rural SSA that has studied detection of varices using clinical findings. We chose participants with UGIB because UGIB is a well-defined indication<sup>4,20</sup>. Most participants had recurrent UGIB (≥2 episodes of UGIB). Recurrent UGIB is with associated varices, further re-bleeding, and greatest risk of death<sup>25</sup>. Like most studies from SSA, we found esophageal varices were the most common endoscopic finding in UGIB<sup>6-8,26</sup>. This contrasts with other parts of the world where peptic ulcer disease is the most frequent endoscopic finding<sup>27,28</sup>.

As other researchers, we identified clinical findings that were associated with varices<sup>7,29-32</sup>. However, our models 1 and 2 have not been described elsewhere. These two models showed the highest accuracy and best diagnostic test effectiveness than any other routine clinical finding. Model 1 is distinct in that requires ultrasonography unlike model 2 that involves only a medical history, a physical examination, and platelet count. A manual platelet count is possible in every rural health facility laboratory<sup>33</sup>. Abdominal ultrasonography has the advantage of simplifying diagnosis of periportal fibrosis, to a lesser extent liver cirrhosis, and other hepatobiliary diseases such as hepatocellular cancer, gallstones, portal vein thrombosis, and others<sup>34,35</sup>. Our nomograms have potential advantages for rural health facilities. They permit straightforward

estimation of each individual patient's test probability, are simple to understand, can be mass-produced at low cost, and can be easily validated<sup>23</sup>. We acknowledge that these models cannot replace endoscopy as the diagnostic test of choice for detection of varices. However, nomograms have the potential to strengthen clinical decision making in settings where endoscopy is poorly accessible. Specifically, these nomograms could assist in prioritizing referral of patients for endoscopy; justifying the use of emergency medications like terlipressin in acute variceal bleeding and/or chronic use of propranolol to prevent recurrent variceal bleeding while awaiting endoscopy<sup>31,36,37</sup>. Using emergency drugs as terlipressin or octreotide controls acute variceal hemorrhage is effective in up to 90% of individuals with bleeding varices<sup>38</sup>. While chronic treatment with propranolol decreases the risk of re-bleeding from 80% to 20% over one year among patients with Schistosomiasis<sup>31</sup>.

#### Study limitations

Our study has limitations. It was a single center study in a distinct rural community. This limits its generalizability. We also concede that having a larger study sample size would decrease the uncertainty of some of our findings.

#### Conclusion

Nomograms consisting of routine clinical findings effectively detect varices in adults with UGIB, schistosomiasis and/or cirrhosis. These nomograms are potential diagnostic triage tests for detection of varices in areas where schistosomiasis is endemic and access to endoscopy is limited.

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#### Conflict of interest

All the authors declare they have no conflict of interest

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