ACCURACY OF REVISED IBD-REFER CRITERIA FOR EVALUATION OF PATIENTS WITH SUSPECTED INFLAMMATORY BOWEL DISEASE IN LOW RESOURCE SETTING: A DIAGNOSTIC PROSPECTIVE COHORT STUDY

GASTROENTEROLOGY & HEPATOLOGY DIVISION

DEPARTMENT OF INTERNAL MEDICINE, COLLEGE OF HEALTH SCIENCE

ADDIS ABABA UNIVERSITY

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SUMMARY

Background: Diagnosis of inflammatory bowel disease (IBD) often faces significant delays. Early recognition tools offer the best chance for timely treatment and positive outcomes.

Objective: To prospectively validate the original IBD REFER criteria and Assess the diagnostic accuracy of revised IBD-REFER criteria for clinical use in screening at-risk patients and determine the diagnostic delay in three Ethiopian gastroenterology centers in 2024.

Method: A multi-center prospective diagnostic cohort study of 272 undiagnosed GI clinic patients was employed. A modified Delphi method with three steps was used to establish consensus among 10 expert gastroenterologists. Both revised and original IBD-REFER criteria were scored for each patient. Data was presented as means [± standard deviation], or medians (interquartile range [IQR]). A point estimate (e.g., odds ratio, sensitivity, specificity) was accompanied by 95% confidence intervals [CI]. All comparisons were made with two-sided significance levels of $p < 0.05$ and analyzed with SPSS V20.0.

Result: This study involved 272 participants from three medical centers in Addis Ababa, Ethiopia. Gastrointestinal symptoms were prevalent, with 23.6% experiencing watery diarrhea for at least one month and 11.8% having recurrent diarrhea for at least two weeks. Elevated ESR or CRP was noted in 34.7% of participants, and 28.0% experienced involuntary weight loss. The original IBD REFER criteria showed a sensitivity of 97.8% and specificity of 58.4%, while the revised criteria had the same sensitivity but a slightly lower specificity of 52.7%. The positive predictive value (PPV) and negative predictive value (NPV) for the original IBD REFER criteria were 31.9% and 99.2%, respectively, while the revised criteria had a PPV of 29.1% and an NPV of 99.2%. The area under the ROC curve (AUC) for the original IBD REFER criteria was 0.65, compared to 0.64 for the revised criteria. Multivariable logistic regression identified watery diarrhea lasting for at least one month (AOR: 14.8 (95%CI: 4.1, 54.3)), recurrent bloody diarrhea for at least two weeks (AOR: 88.6 (95% CI: 15.7, 499.9)) Eelevated ESR or CRP, weight loss, and a history of unexplained bowel obstruction to be associated with IBD diagnosis. The mean time to diagnosis for IBD was 26.6 months, with a range of 2 to 186 months, longer for Crohn's disease (27.2 months) compared to ulcerative colitis (25.6 months).

Conclusion: The study highlights the significant challenges in diagnosing IBD in low-resource settings like Ethiopia, emphasizing the need for improved diagnostic pathways and early referral systems. Future research should focus on refining diagnostic criteria to enhance specificity and exploring the integration of advanced diagnostic tools. Addressing these challenges can lead to earlier diagnosis, better patient outcomes, and reduced disease-related complications in resource-limited settings.

Keywords-Inflammatory bowel disease, IBD REFER Criteria, diagnostic delay, screening criteria, Ethiopia

ACKNOWLEDGEMENT

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ACRONYMS

AUC- Area under curve

CD –Crohn’s disease

CI: Confidence interval

IBD- Inflammatory bowel disease

NPV; Negative Predictive Value

PPV; Positive predictive value

ROC: Receiver Operating Curve

OR: Odds ratio

UC- Ulcerative colitis

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1. INTRODUCTION

I. BACKGROUND

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract with repetitive episodes of inflammation of the gastrointestinal tract. (1) It is a chronic immune-mediated inflammation of the gastrointestinal tract with a highly heterogeneous presentation (1)

IBD has two main sub-types that are differentiated by their location and depth of involvement in the bowel wall. Crohn's disease (CD) is one of the subtypes of IBD and can present anywhere in the gastrointestinal tract with transmural inflammation. Crohn's disease most often affects the terminal ileum and colon. It can have inflammatory, structuring, or penetrating phenotype. Ulcerative colitis, another sub-type of IBD, involves diffuse inflammation of the colonic mucosa. Ulcerative colitis most often affects the rectum (proctitis) but it may extend into the sigmoid(proctosigmoiditis), beyond the sigmoid colon(distal/left side UC) or it may include the entire colon up to the cecum (pan colitis)(2)

Historically, inflammatory bowel disease (IBD) was primarily found in North America and Europe, with a higher prevalence in the northern regions. However, over the last 100 years, there has been a significant increase in IBD cases overall, particularly among children. In the past 50 years, IBD has also become more prevalent in developing countries. Although IBD is mainly a disease that affects young adults, it can occur at any age. (3) Few published data describing the natural history of IBD in sub-Saharan Africa, and the true burden of the disease remains largely unknown, although there is some evidence that the incidence of IBD is rising in this region. (4)

Symptoms of inflammatory bowel disease (IBD) differ based on the type. Those with ulcerative colitis often feel pain in the lower left abdomen and have bloody diarrhea, which can lead to weight loss. On the other hand, individuals with Crohn's disease usually experience pain in the lower right abdomen, and rectal bleeding is less common compared to ulcerative colitis. (5)

The manifestations of CD are more varied than those of UC, which reflects the range of sites that can be affected. Patients can present with dysphagia, vomiting, nausea, epigastric pain, abdominal pain, weight loss, diarrhea, anorexia, perianal skin tags, peri-anal fistula & abscess depending on which part of the gastrointestinal tract is involved with CD. Extraintestinal

symptoms are seen in both CD and UC; about 40% of patients with IBD have extra-intestinal features including arthroplasty, eye involvement, erythema nodosum, pyoderma gangrenosum, hepatobiliary involvements, and fever(6)

It has consistently been demonstrated that there are significant delays in presentation, referral, and diagnosis for both UC and CD (7). This is especially true for Crohn's disease (CD), as its early signs and symptoms can be vague and often overlap with those of irritable bowel syndrome (IBS). In a Swiss IBD cohort, delays in diagnosis were more common among CD patients compared to those with ulcerative colitis, with median delays of 9 months versus 4 months, respectively. Seventy-five percent of CD patients were diagnosed within 24 months, while the same percentage for ulcerative colitis was achieved within 12 months. Additionally, delayed diagnosis has been linked to more urgent presentations, which in turn are associated with worse clinical outcomes.

Delayed diagnosis negatively affects disease outcomes. Longitudinal studies indicate that Crohn's disease (CD) progresses over time, and patients who experience a longer diagnostic delay have higher odds of developing complications and intestinal strictures incrementally at diagnosis. Reducing the time to diagnosis enables earlier treatment, potentially leading to better outcomes. Multiple studies have shown that early immunosuppressive therapy is associated with improved treatment response and fewer adverse outcomes. (10)

Given that early treatment of IBD is linked to improved disease outcomes, it is essential to create effective strategies for early referral of individuals with indicative signs and symptoms. (10) Many countries in Sub-Saharan Africa face challenges such as limited endoscopic capacity, insufficient access to diagnostic imaging, and a shortage of histo-pathologists, radiologists, and gastroenterologists. Establishing highly specific referral criteria is crucial to prevent the overuse of scarce resources and to enable timely referrals. (11)

At present, the Red Flag Index, created under the initiative of the International Organization of IBD (IOIBD), is the primary tool used by primary practitioners to identify patients at risk of IBD. However, the Red Flag index has not undergone external validation and is not appropriate for use in children or for diagnosing ulcerative colitis (UC). (12) On the other hand, IBD-REFER

criteria were developed to guide general practitioners and pediatricians in selecting children and adults for early referral to a gastroenterologist for suspected CD and UC. (13)

The IBD-REFER criteria were developed using a combination of clinometric and psychometric methods, incorporating expert clinical judgments from a Delphi group and statistical analyses of retrospective patient and control cohorts. These criteria were validated on separate patient and control cohorts. Although the IBD-REFER criteria appeared to outperform the Red Flag index, the study's retrospective design limits its ability to report predictive values. (13)

II. STATEMENT PROBLEM

Early and accurate identification of patients with inflammatory bowel disease is important, more than ever before. Inflammatory bowel disease incidence is rising including in sub-Saharan Africa and the association of improved outcomes for patients treated early in the course of the disease is proven. (14)

There are tools available to guide primary practitioners in selecting patients who are at risk of having IBD, Including the Red Flag index, developed as part of an International Organization of IBD (IOIBD) initiative and IBD REFER criteria. (12)(13)

The Red Flags Index is an 8-item tool created to identify patients with Crohn's disease. It was developed using a cohort of individuals with either confirmed Crohn's, irritable bowel syndrome, or healthy volunteers. However, the Red Flag Index has certain limitations, including a lack of external validation and reliance on patients' recollections of symptoms, which can introduce bias. Additionally, it is not suitable for pediatric patients or those with ulcerative colitis. (12)

The IBD-REFER criteria were designed and validated to provide a more effective tool for identifying IBD in both adults and children, using both historical and laboratory data. These criteria demonstrated strong internal and external validity, with sensitivity/specificity rates of 98%/96% in adults and 96%/96% in children. When applied to the same external validation cohort of IBD cases and controls, the IBD-REFER criteria outperformed the Red Flags Index. However, a notable limitation is their reliance on historical recall rather than objective findings. Additionally, the validation was performed on individuals with known IBD versus non-IBD diagnoses, which introduces biases that may restrict its applicability in real-world settings. (13)

This study aimed to revise and validate IBD-REFER Criteria in prospective investigation of the undiagnosed GI referral patients, and to see whether or not the high sensitivity and specificity seen in previous IBD cohorts can be replicated in sub-Saharan Africa where IBD-mimickers like Intestinal Tuberculosis are common.

In addition, this study looked into factors associated with IBD diagnosis and among those patients who were diagnosed with IBD, time to diagnosis was studied.

III. SIGNIFICANCE OF THE STUDY

With the increasing incidence of inflammatory bowel disease worldwide and the fact that early diagnosis improves patient outcomes, a clinical tool to facilitate early diagnosis of IBD is very important. IBD REFER criteria have the potential to identify patients who require expedited referral to gastroenterologists. Therefore, this research can contribute to developing revised criteria and prospectively validate IBD REFER criteria that can improve diagnostic delay in IBD diagnosis. This study could also highlight factors associated with IBD diagnosis time to diagnosis of patients with inflammatory bowel disease in the current research setting.

The result of this study will benefit the following.

Patients: It has been consistently shown that there are significant delays in diagnosis and referral of IBD. Delayed diagnosis has been associated with more adverse outcomes including emergency presentation, the need for surgery, and prolonged hospitalization. On the contrary, evidence strongly supports the improved outcome of patients who are diagnosed in the early stage of IBD. Therefore among the solutions to improve early diagnosis and overcome delay is developing clinical tools to identify patients who need timely referrals to gastroenterologists and IBD specialists. This study will help patients to have an early diagnosis of IBD with better outcomes.

Health care setups: In addition, developing and validating improved IBD Refer criteria can help to use scarce resources needed to diagnose IBD like endoscopy appropriately. Since these advanced diagnostic tests are limited in resource-limited setups, they will have a meaningful healthcare cost-related impact. As early diagnosis is associated with fewer emergency visits, surgery, and Hospitalization, it will minimize healthcare-associated costs.

For future Researchers: This study will further open doors for future researchers to refine and expand studies on clinical tools for early diagnosis of IBD. As the literature on IBD from Sub-Saharan Africa is limited this may serve as a source of information about how effective clinical tools are in IBD where IBD mimickers like intestinal Tuberculosis are common. The research could lead to the development of more effective clinical tools that improve the time to diagnosis of IBD which leads to a better clinical outcome.

2. LITERATURE REVIEW

Diagnosing inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, relies on clinical, endoscopic, radiologic, and histologic criteria (17). The suspicion of IBD typically arises from the medical interview, physical examination findings characteristic of IBD, and results from endoscopic and other imaging studies. Symptoms such as chronic abdominal pain, diarrhea, bloody stools, weight loss, fever, and anal lesions should particularly prompt suspicion of IBD, especially in younger patients. (18)

Endoscopic examination is a mainstay in the diagnosis of IBD. Often, Ileo-colonoscopy is performed as an initial examination. Initial diagnostic colonoscopy should intubate the terminal ileum and include systematic biopsies from each anatomic segment (rectum; sigmoid, left, transverse, and right colon; and ileum). Endoscopic appearance (distribution and shape of lesions) helps to differentiate CD from UC in most cases. (17)

In active inflammatory bowel disease (IBD) patients, microscopic evaluation shows significant infiltration of the lamina propria by neutrophils, macrophages, dendritic cells, and natural killer T cells. In ulcerative colitis, histopathology reveals involvement limited to the mucosa and submucosa, with the formation of crypt abscesses and mucosal ulcers. Biopsy specimens exhibit neutrophilic infiltration, crypt distortion, and crypt abscesses, but granulomas are absent. The disease is contiguous and typically affects the rectum. In contrast, Crohn's disease involves the entire intestinal wall and may present with granulomas. The inflammation in Crohn's disease is transmural and characterized by lymphocytic infiltration. (19)

Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are utilized in diagnosing IBD and assessing its complications. Trained professionals can use the US to evaluate the right lower quadrant for ileal disease, while MRI is useful for identifying rectal fistulas. CT is commonly employed to detect perforations or bowel obstructions, and CT enterography is particularly helpful for assessing strictures or for surgical planning. Recent advancements in imaging technology have enhanced the ability to noninvasively monitor disease activity and treatment response and to distinguish IBD from other conditions such as intestinal tuberculosis. (20)

There are no specific blood tests available for diagnosis of IBD. Elevated leukocyte and thrombocyte count as well as elevated acute phase reactant proteins (such as C-reactive protein [CRP]) are indicative of extensive, active intestinal inflammation. Patients with long-lasting inflammation in IBD are often anemic, and the degree of anemia relates to the inflammatory load in CD. Therefore, hemoglobin and hematocrit are useful parameters. Low serum protein and albumin suggest severe protein loss or malabsorption. Assessment of vitamin levels or rare elements is only warranted for differential diagnosis of complications (eg, macrocytic anemia owing to decreased ileal absorption of vitamin B12 or orofacial eczema and arthropathy as a sign of zinc deficiency). (17)

Fecal calprotectin testing is useful for differentiating between organic intestinal diseases such as IBD and functional intestinal diseases such as irritable bowel syndrome (IBS). (18) Fecal calprotectin can also be used as a marker for intestinal inflammation. Levels of perinuclear anti-neutrophilic cytoplasmic and anti-saccharomyces cerevisiae antibodies may be elevated in Crohn's disease. Finally, stool studies must be done to rule out ova and parasitic organisms. (18)

The clinical presentation of IBD can resemble other gastrointestinal conditions, such as irritable bowel syndrome (IBS), celiac disease, lactose intolerance, and dyspepsia, or may present with isolated extra-intestinal manifestations. (25)(26) Additionally, in sub-Saharan Africa, several chronic infections, including amoebic colitis, colonic schistosomiasis, and intestinal tuberculosis, can mimic the clinical and endoscopic features of ulcerative colitis (UC) and Crohn's disease (CD). (4)

A single reference standard for the diagnosis of Crohn’s disease [CD] or ulcerative colitis [UC] does not exist. The diagnosis of CD or UC is based on a combination of clinical, biochemical, stool, endoscopic, and histological investigations. When IBD is suspected, infectious colitis, including *Clostridium difficile*, Intestinal tuberculosis, colonic schistosomiasis…etc. Should be excluded. (21)

Reports suggest the average diagnostic delay of IBD can range anywhere from 2 months to 8 years(24)and the delays in the diagnosis of CD are longer than for UC [7,8]. As the manifestations of inflammatory bowel disease (IBD) are nonspecific, the diagnosis is often

established following considerable delay. (7,8)) In a French referral center-based cohort of CD patients, the median diagnostic delay was 5 months (7) From other studies examining median delay in UC, three-quarters (12 of 16) reported a delay between 2 and 6 months. In contrast, three-quarters of the CD studies (17 of 23) reported a delay of between 2 and 12 months. In CD, delayed diagnosis was associated with higher odds of structuring (OR = 1.88; CI: 1.35–2.62), penetrating disease (OR = 1.64; CI: 1.21–2.20), and intestinal surgery (OR = 2.24; CI: 1.57–3.19). In UC, delayed diagnosis was associated with higher odds of colectomy (OR = 4.13; CI: 1.04–16.40). (23)

Despite a significant diagnostic delay in most countries, early treatment of inflammatory bowel disease (IBD) is associated with positive outcomes. (10) There is limited literature on diagnostic delay in IBD in Africa. One of the main challenges in the management of IBD in sub-Saharan Africa is making a timely and accurate diagnosis, as this requires a combination of clinical history, laboratory findings, imaging, endoscopy, and histopathology. Unfortunately, these different investigation modalities are inadequate in SSA, contributing to a delay in the diagnosis of IBD. (4) Often IBD is mistaken for infectious enteritis, given the high burden of infectious mimics in the region. (4) Therefore, Identifying patients who require expedited referral to a gastroenterologist may thus be challenging and lead to a significant diagnostic delay. (27)

Early treatment for IBD is linked to better disease outcomes, highlighting the importance of developing effective strategies for early referral of individuals with signs and symptoms indicative of IBD. (10) Currently, the Red Flag index,(12) created as part of an initiative by the International Organization of IBD (IOIBD), and the IBD-REFER criteria are the primary tools available to guide primary practitioners in identifying patients at risk of IBD.(13)

The Red Flag Index has several limitations, including the lack of external validation and reliance on patients' recollections of symptoms, which introduces bias and makes it unsuitable for pediatric patients and those with ulcerative colitis. (12) Conversely, the IBD-REFER criteria, developed using both the Delphi method and multiple regression with sensitivity analysis, showed excellent performance in both internal and external validation cohorts. Sensitivity and specificity reached 98%/96% in adults and 96%/96% in children. (13) When tested on the same

external validation cohort of IBD cases and controls, the IBD-REFER criteria outperformed the Red Flag Index, with ROC values of 0.97 versus 0.78 ($P < 0.001$). (13)

Although the IBD-REFER criteria demonstrate high sensitivity and specificity, their performance in real-world settings and among GI clinic patients without a known diagnosis remains uncertain. Additionally, the criteria include laboratory parameters such as ASCA/ANCA, which may not be easily accessible or frequently available in resource-limited settings.

To our knowledge, this is the first prospective investigation of the IBD-REFER criteria in undiagnosed GI referral patients, and revised IBD-REFER criteria were developed using a modified Delphi method (28). Validation of both the existing and revised IBD criteria was performed on undiagnosed GI referral patients. In addition, for those who were diagnosed with inflammatory bowel disease, diagnostic delay was studied.

CONCEPTUAL FRAMEWORK

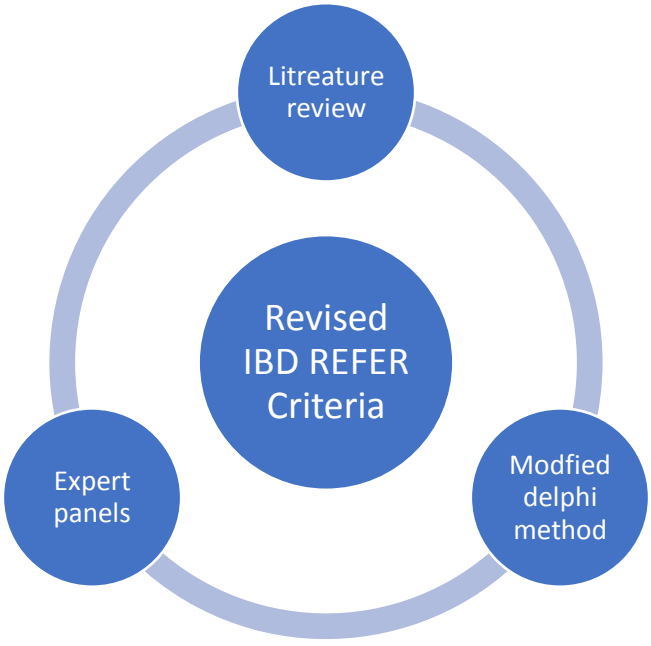


Figure 1-Conceptual Framework for Revised IBD REFER criteria

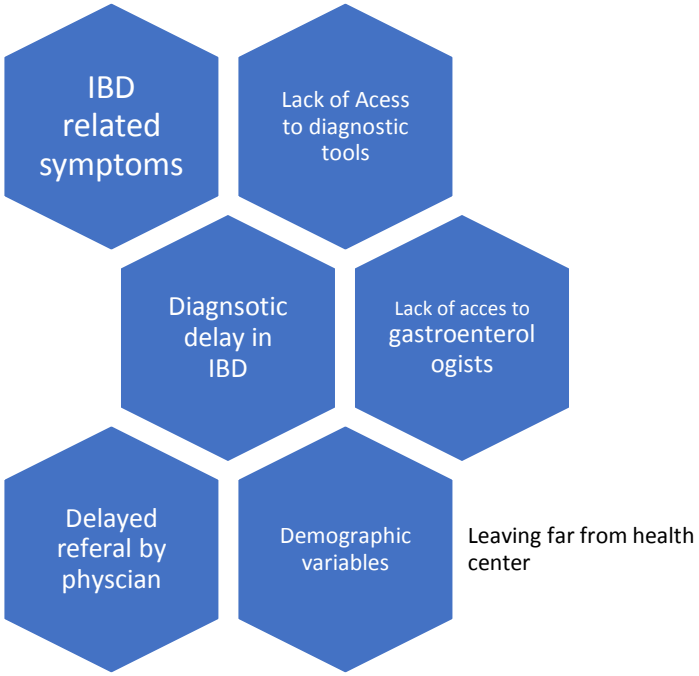


Figure 2- Diagnostic Delay in IBD

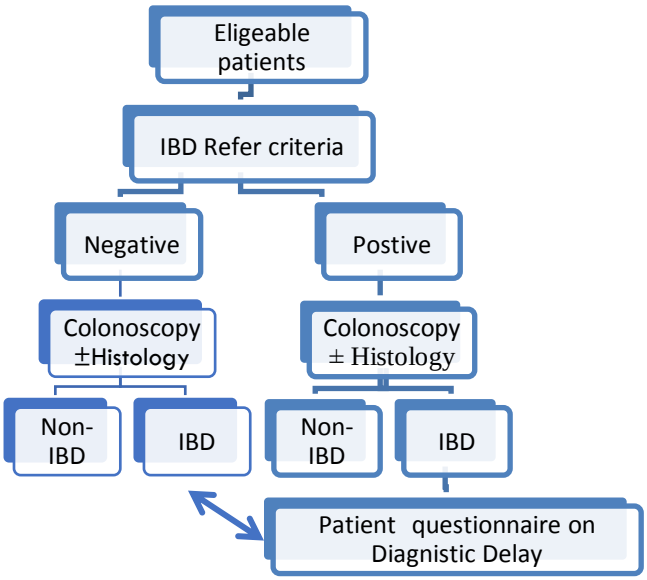


Figure 3- Study design layout (Validation of IBD REFER criteria)

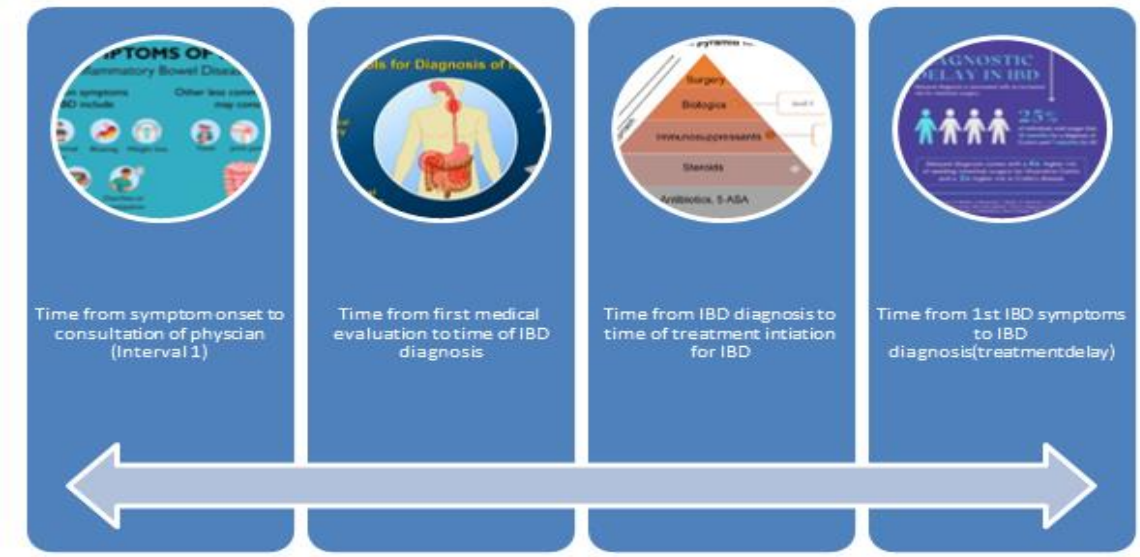


Figure 4-Diagnostic Delay in IBD

Intervals 1–4 in diagnostic delay (adapted from Vavricka et al). Interval 1: time from first IBD symptoms to consultation with a medical professional. Interval 2: time from first medical evaluation to time of time of diagnosis of IBD (by referral to a gastroenterologist, or surgeon…). Interval 3 times from first inflammatory bowel disease (IBD) symptoms to IBD diagnosis (intervals 1+2) is called diagnostic delay.

Table 1- Sensitivity and specificity calculation of Revised IBD Refer criteria

Is IBD REFER criteria sensitive and specific for positive IBD Diagnosis	Patients undergoing colonoscopy for ongoing GI complaints ± Histology			
		IBD	Non-IBD	
IBD refer criteria	Positive	TP	FP	PPV =TP/(TP+FP)
	Negative	FN	TN	NPV = TN/(TN+FN)
		Sensitivity = TP/(TP+FN)	Specificity =TN/(FP +TN)	

(FN, false negative; FP, false positive; GE, gastroenterologist; IBD, inflammatory bowel disease; NPV, Negative Predictive Value; PPV, Positive Predictive Value; TN, true negative; TP, true positive)

3. OBJECTIVE

General objective

- ✓ To develop and assess the diagnostic accuracy of a revised IBD REFER criteria for the evaluation of patients with suspected IBD in low-resource settings.

Specific objective

1. To determine the Sensitivity and specificity of revised IBD REFER and original IBD REFER criteria for a positive IBD diagnosis in low-resource settings.
2. To determine the positive and negative predictive value of revised IBD REFER and original IBD REFER criteria for a positive IBD diagnosis in low-resource settings.
3. To determine significant factors associated with IBD Diagnosis
4. To identify patient-reported diagnostic delay

4. METHODOLOGY

A. Study area and period

Addis Ababa, the capital city of Ethiopia, ranks among the largest urban centers in Sub-Saharan Africa. It is the country's largest city, boasting a population of 4,793,699, with a gender distribution of 52% female and 48% male. The city is divided into 10 sub-cities and spans an area of 527 square kilometers. The estimated population density is approximately 5,165 individuals per square kilometer.

The study was conducted at multiple centers, two government centers (Tikur Anbessa Specialized Hospital (TASH), Saint Paul's Hospital Millennium Medical College), and one Private hospital (Adera Medical and Surgical Centre) which are all located in Addis Ababa, the capital city of Ethiopia. The hospitals have a gastroenterology and Hepatology Division which provides outpatient, inpatient, Endoscopic, and Histopathologic diagnostic services. In addition, the two government hospitals are tertiary care centers that receive referrals from all regions of Ethiopia for gastroenterology consultation. They also provide training for medical residents, GI fellows, and undergraduate students parallel to several clinical services.

B. Study period

Study period- This study was conducted between February 2024 and July 2024

C. Study design

The study is a Multi-centre prospective diagnostic cohort study. It consisted of patients who visited the gastrointestinal outpatient clinic because of ongoing unspecific gastrointestinal symptoms (abdominal pain, bloating, stool irregularities, diarrhea) and undergoing colonoscopy. The study design and procedure are summarized in Figure 1-3

The procedure of the study

A. Development of revised IBD REFER criteria

A three-step modified Delphi method was used to establish the revised IBD REFER criteria. This method included two rounds of email questionnaires followed by a final face-to-face virtual meeting. Initially, a comprehensive list of items was identified through a literature review, incorporating the previous IBD REFER criteria developed by Atia O(12) and the Red Flag criteria from the International Organization for the Study of

IBD(13). Ten expert gastroenterologists, each with over five years of experience in treating IBD patients, were invited to form the expert panel.

In the first round, the tentative items list, determined through a literature search and supplemented by the previous IBD REFER criteria and the Red Flag criteria, was distributed to the panel via email. Panel members were asked to mark each criterion as "agree" or "disagree" and provide comments. The same voting method was used again in the second round. The third round involved a final face-to-face virtual meeting.

First round

The draft document containing the list of criteria was emailed to all expert panel members, along with the study's objectives and specific instructions. Each expert was asked to vote "agree" or "disagree" on each criterion, and to provide comments and suggest additional items that might not have been included in the initial criteria list.

In the first round, the goal was to identify any lack of clarity and repetition among the criteria. Response frequencies for each item were calculated and recorded in a database. Each criterion required 80% agreement from the expert panel (i.e., agreement from 8 out of 10 experts) to be accepted or omitted from the final criteria. If 8 out of 10 experts agreed on a criterion, it was included in the final criteria; if 8 out of 10 disagreed, the item was omitted from the criteria list.

The 80% cut-off was chosen based on Lynn's work, which suggested that at least 80% of experts must agree on an item to achieve content validity when at least 10 experts are participating in consensus development. (15) Criteria that did not meet 80% agreement were modified based on the feedback provided by the expert panel and redistributed to the panelists for the second round.

Second round

The list of criteria that did not meet consensus from round 1 was emailed to all 10 members.

In round 2, the experts used the same voting method as described for round 1. They were aware of the previous group scores and comments. On round 2 expert panels reflected on the round 1 result.

Final responses were analyzed as described in Round 1, and criteria not meeting expert agreement were presented for discussion in Round 3.

Third round

Round 3 comprised a face-to-face virtual meeting. Eighty percent agreement was used to determine acceptance or rejection of a criteria.

Expert Panel members were encouraged to discuss the final criteria until an agreement was reached to retain, modify, or eliminate the Criteria from the final criteria.

Studies have demonstrated that the modified Delphi method can be superior to the original Delphi method and perceived as highly cooperative and effective (16)

The Delphi method produced revised IBD REFER criteria with four major and eight minor Criteria. (Annex, Figure 11)

B. Investigation of the sensitivity and specificity of IBD REFER criteria for positive IBD diagnosis.

- ✓ At baseline T0, Patients seen at the outpatient gastroenterology clinic because of ongoing unspecific gastrointestinal symptoms (abdominal pain, bloating, stool irregularities, diarrhea) and undergoing colonoscopy and fulfilling inclusion criteria were subjected to the Revised & original IBD REFER criteria questionnaire. At T1, endoscopic examination ± histology was performed to obtain a diagnosis. Eventually, patients diagnosed with IBD were asked to complete a questionnaire at T3 investigating the duration of the first onset of symptoms to IBD diagnosis (diagnostic delay).

A. Patient questionnaire on diagnostic delay

Three relevant time intervals of diagnostic delay were assessed in a patient questionnaire. The time intervals are defined as follows (figure 2):

1. Interval 1: Time from first IBD symptoms to consultation with a medical professional. The length of this period is mainly dependent on the patient.
2. Interval 2: Time from first medical evaluation to time of time of diagnosis of IBD (by referral to a gastroenterologist, surgeon, radiologist…). The length of this period is mainly dependent on the treating physician.
3. Interval 3: The time from the first inflammatory bowel disease (IBD) symptoms to IBD diagnosis (intervals 1+2) is called diagnostic delay. This interval is defined as a

diagnostic delay. Diagnostic delay is defined as the period (in weeks) from first symptoms to IBD diagnosis.

The following items in the patient questionnaires are assessed for this study: “Before the IBD diagnosis, how long did you experience symptoms that are now attributed to IBD?”; “How long was the time interval between the first symptoms and the time you decide to see a physician “ “Did you receive any alternative medicine before or after first physician visit”? “How long was the time interval between your decision to visit a physician and the first visit to a physician?”; “How long were you treated by physician/s before referral to a gastroenterologist?” “What kind of treatments did you receive before referral to gastroenterologists “and “What was the period from the first physician visit (due to IBD-related complaints) until IBD diagnosis was established?”

Additionally, patients will answer questions regarding smoking, alcohol habits, intake of non-steroidal anti-inflammatory drugs (NSAIDs) …etc.

D. Study population

4.4.1. Source Population

1. The source population was all patients who will visit the gastroenterology clinic because of ongoing unspecific gastrointestinal symptoms (abdominal pain, bloating, stool irregularities, diarrhea…etc.) and did undergo colonoscopy.

4.4.2. Study Population

- ✓ All patients who fulfilled the inclusion criteria among patients who are seen at the outpatient gastroenterology clinic because of ongoing unspecific gastrointestinal symptoms (abdominal pain, bloating, stool irregularities, diarrhea…etc.)

Inclusion and exclusion criteria

Inclusion criteria

- Age ≥18 years old

- Patients who are referred to a gastroenterologist for endoscopic examination due to ongoing unspecific gastrointestinal symptoms (abdominal pain, bloating, stool Irregularities, diarrhea…etc.)

- Patients who are referred by their primary physician because of ongoing unspecific gastrointestinal symptoms (abdominal pain, bloating, stool Irregularities, diarrhea…etc.)

- Underwent no earlier diagnostic procedures (colonoscopy) for the current complaints within the last year.

Exclusion criteria

- Are younger than 18 years

- Patients who have known/other abdominal pathologies: for example, colonic cancer, radiation proctitis...etc.

- Patients who have been treated with steroids (topical and/or oral) and/or aminosalicylates within 30 days before inclusion in this study

- Patients who underwent endoscopic examination within 1 year before screening

E. Sample size

The sample size was calculated according to Flahault et al.& Buderer, et al (18). Assuming a 0.1 precision significance level, n=272 would have 90 % power to detect sensitivity and specificity of 90% of revised IBD Refer criteria for a positive IBD diagnosis.

For this calculation, the expected sensitivity and specificity are 90% with a lower acceptable limit of sensitivity of 70%. The assumed prevalence of IBD within the sample is 15% (17). A $p<0.05$ is considered statistically significant. A final sample size of 272 is calculated including a possible 15% dropout.

F. Sampling procedure

Consecutive Sampling was used as a sampling technique._All patients who meet the inclusion criteria and are conveniently available were part of the study.

G. Data collection procedures

Data was collected using an interviewer-administered structured questionnaire. Different questionnaires were used to assess Revised IBD REFER criteria and assessment of diagnostic delay.

H. Study variable

Dependent variable (outcome variables)

- Sensitivity, specificity, PPV, & NPV of original and Revised IBD REFER criteria
- Diagnostic delay

Independent variables (exposure variables)

- Socio-demographic related factors:
  - Sex
  - Age
  - Occupation
  - Marital status
  - Educational level
- Clinical factors
  - Gastrointestinal symptom
  - Duration of IBD-related symptoms before medical consultation
  - Duration between first medical visit and diagnosis of IBD
  - Use of alternative treatment
  - Type of treatment received before IBD diagnosis

I. Operational definitions

1. Sensitivity -Sensitivity denotes the probability of a positive test result when disease is present. It is calculated as the percentage of individuals with a disease who are correctly categorized as having the disease. (17)
2. Specificity-Specificity denotes the probability of a negative test result when the disease is absent. It is calculated as the percentage of individuals without the disease who are correctly categorized as not having the disease. (17)

3. Positive predictive value- Positive predictive value (PPV) denotes the probability of disease being present when the test is positive and is calculated as the percentage of individuals with positive test results who have the disease. (17)
4. Negative predictive value - Negative predictive value (NPV) denotes the probability of disease being absent when the test is negative and is calculated as the percentage of individuals with negative test results who are free from disease. (17)
5. CD- Crohn's disease is an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area
6. Ulcerative colitis - Ulcerative colitis is an idiopathic inflammatory condition of the colon that results in diffuse friability and superficial erosions on the colonic wall and associated bleeding.
7. IBD- Inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract
8. Colonoscopy is a diagnostic as well as a therapeutic procedure performed to evaluate the large intestine (i.e., colon, rectum, and anus) as well as the distal portion of the small intestine (terminal ileum).
9. Colitis_ inflammation of the mucosal lining of the colon which may be acute or chronic.
10. Proctitis _ is inflammation of the lining of the rectum.
11. Diagnostic delay - Diagnostic delay was defined as *the delay between the onset of IBD-related symptoms and IBD diagnosis*.
12. Patient delay: Period from the onset of the first symptom(s) related to IBD such as abdominal pain, and diarrhea… to the first medical consultation.
13. Health system delay: the period from the first medical consultation to the date of diagnosis of IBD.
14. Validation- is a process to compare the accuracy of a measure with a gold standard measure.
15. Modified Delphi method - method is a formal group consensus process that systematically and quantitatively combines expert opinion and evidence by asking panelists to rate, discuss, and then re-rate items.

J. Data processing and analysis

Sensitivity and specificity calculations for the IBD-REFER criteria were provided based on confidence intervals. (Refer to Figure 3 for sensitivity and specificity details). Data were presented as means [± standard deviation], or medians (interquartile range [IQR]), depending on the normality of distribution. Point estimates, such as odds ratios, sensitivity, and specificity, were accompanied by a 95% confidence interval [CI]. Unpaired categorical data were compared using the $\chi 2$ or Fisher's exact test, as appropriate. Continuous data were analyzed using the unpaired Student's t-test, Wilcoxon rank sum test, or Kruskal-Wallis test, depending on the normality of distribution and the number of groups. Time-to-event analysis, including Kaplan-Meier curves and Cox proportional hazards multivariable modeling, was utilized to investigate factors associated with IBD and the time to IBD diagnosis. All comparisons were made using two-sided significance levels of $p < 0.05$ and were conducted with the SPSS V20.0 software.

K. Data quality management

To maintain the quality of data to be collected, proper training of data collectors and regular supervision was conducted. Pre-test was conducted one week before actual data collection and data was checked for consistency, accuracy, and any ambiguity. Problems identified during the pretest were corrected before the commencement of data collection. The collected data was checked for completeness and accuracy on a daily base.

L. Ethical consideration

Ethical approval and clearance were obtained from the AAU ethical review board and all study hospitals. Written informed consent was obtained from the study participants. No personal identification was used on the data collection form. Collected data was accessed only by the investigators and was kept confidential.

M. Dissemination plan

The findings of the study will be disseminated and communicated to responsible bodies for quality improvement projects, guideline preparation, and further research on this topic. The findings from this research will be published in peer-reviewed journals to be accessed by the scientific community.

5. RESULTS

A. Socio-demographic characteristics

In this study, 271(158 from Adera Medical and Surgical Centre (AMSC), 27 from Saint Paul's Hospital Millennium Medical College (SPH), and 86 from Tikur Anbessa Specialized Hospital (TASH)) participated. More than half of the study participants 158(58.3%) were males. More than ninety percent of the participants 250(92.3%) were urban residents. Almost half of the participants 117(43.2%) had an educational level of secondary education. Two-thirds of the participants 177(65.3%) were married. Based on participants' occupational status 63(23.2%) were private workers. The mean (±SD) age of participants was 43.7±17.5 years and half of, 140(51.7%) of the participants ranged from 31 to 60 years old.

Table 2- Sociodemographic characteristics of patients visiting the gastroenterology unit, Addis Ababa, 2024

Variables	Categories	Final Diagnosis		Total (%)
		IBD (%)	Non-IBD (%)	
Data collection site	AMSC	20(44.4)	138(61.1)	158(58.3)
	SPH	4(8.9)	23(10.2)	27(10.0)
	TASH	21(46.7)	65(28.8)	86(31.7)
Sex	Male	21(46.7)	137(60.4)	158(58.3)
	Female	24(53.3)	89(39.4)	113(41.7)
Age	<=30	21(46.7)	59(26.1)	80(29.5)
	31-60	20(44.4)	120(53.1)	140(51.7)
	>60	4(8.9)	47(20.8)	51(18.8)
Marital status	Single	16(35.6)	59(26.1)	75(27.7)

	Married	27(60.0)	150(66.4)	177(65.3)
	Divorced/Widowed	2(4.4)	17(7.5)	19(7.0)
Educational status	No formal education	2(4.4)	5(2.2)	7(2.6)
	Read and write	3(6.7)	9(4.0)	12(4.4)
	Primary education	11(24.4)	42(18.6)	53(19.6)
	Secondary education	17(37.8)	100(44.2)	117(43.2)
	College and above	12(26.7)	70(31.0)	82(30.3)
Residence	Urban	39(86.7)	211(93.4)	250(92.3)
	Rural	6(13.3)	15(6.6)	21(7.7)
Occupational status	Civil servant	15(33.3)	53(23.5)	68(25.1)
	Student	8(17.8)	27(11.9)	35(12.9)
	Private workers	9(20.0)	77(34.1)	86(31.7)
	Farmer	2(4.4)	8(3.5)	10(3.7)
	Others	11(24.4)	61(27.0)	72(26.6)

B. Gastrointestinal symptoms

Among the participants 64(23.6%) have watery diarrhea lasting for at least one month, 32(11.8%) have recurrent diarrhea for at least two weeks associated with tenesmus and urgency, 40(14.8%) have imaging evidence suggestive of IBD (stricture, bowel wall thickening, etc.), 13(4.8%) have recurrent peri-anal, entero-cutaneous, or another fistula or per-anal abscess, 94(34.7%) have elevated ESR or CRP, 76(28.0%) have weight loss (5% of normal body weight over three months, involuntarily), 8(3%) have fever associated with raised ESR or CRP, 4(1.5%) have first-degree relative with confirmed inflammatory bowel disease, 25(9.2%) have night-time

symptom (patient awake from sleep because of abdominal pain or diarrhea), and 8(3.0%) have history of unexplained bowel obstruction, intra-abdominal abscess or inflammatory mass.

Table 3 Gastrointestinal symptoms of patients visiting gastroenterology unit, Addis Ababa, 2024

Symptoms	Categories	Final Diagnosis		Total (%)
		IBD (%)	Non-IBD (%)	
Have watery diarrhea lasting for at least one month	Yes	27(60.0)	37(16.4)	64(23.6)
	No	18(40.0)	189(83.6)	207(76.4)
Have recurrent diarrhea for at least two weeks associated with tenesmus and urgency	Yes	20(44.4)	12(5.3)	32(11.8)
	No	25(55.6)	214(94.7)	239(88.2)
Have imaging evidence suggestive of IBD	Yes	22(48.9)	18(8.0)	40(14.8%)
	No	23(51.1)	208(92.0)	231(85.2)
Have recurrent fistula or per-anal abscess	Yes	6(13.3)	7(3.1)	13(4.8%)
	No	39(86.7)	219(96.9)	258(95.2)
Have elevated ESR or CRP	Yes	34(75.6)	60(26.5)	94(34.7%)
	No	11(24.4)	166(73.5)	177(65.3)
Weight loss	Yes	31(68.9)	45(19.9)	76(28.0%)
	No	14(31.1)	181(80.1)	195(72.0)
Have fever associated with raised ESR or	Yes	3(6.7)	5(2.2)	8(3)

CRP	No	42(93.3)	221(97.8)	263(97.0)
Have a first-degree relative with confirmed IBD	Yes No	2(4.4) 43(95.6)	2(0.9) 224(99.1)	4(1.5) 267(98.5)
Have night-time symptoms	Yes No	5(11.1) 40(88.9)	20(8.8) 206(91.2)	25(9.2) 246(90.8)
Have a history of unexplained bowel obstruction, intra-abdominal abscess, or inflammatory mass.	Yes No	4(8.9) 41(91.1)	4(1.8) 22(98.2)	8(3.0) 263(97.0)

*Weight loss_5% of normal body weight over three months, involuntarily, Imaging evidence of IBD (stricture, bowel wall thickening, etc.), Fistula (Entero-cutaneous, Perianal), IBD(Inflammatory bowel disease)

C. Findings from diagnostic modality

Table 4 Diagnostic modality of patients visiting gastroenterology unit, Addis Ababa, 2024

Diagnostic modalities	**Categories**	**Final Diagnosis**		**Total (%)**
		IBD (%)	**Non-IBD (%)**	
Haemoglobin level(g/dl)	7-9.9 10-11.9 >=12	3(6.7) 6(13.3) 36(80.0)	9(4.0) 19(8.4) 198(87.6)	12(4.4) 25(9.2) 234(86.3)
Colonoscopy Finding	Normal colonoscopy	131(45.5%)		
	Ileocecal Crohn's	36(12.8%)		

	disease	
	Hemorrhoids	27(9.6%)
	Colonic polyp	19(6.76%)
	Colorectal mass and colonic polyps	24(8.5%)
	Infectious colitis	8(2.85%)
	Intestinal Tuberculosis	7(2.5%)
	Ischemic colitis	3(0.1%)
	Ulcerative colitis	16(5.7%)
	Other	10(3.6)
	Total	281(100%)
Final Clinical Diagnosis	Irritable bowel syndrome	122(44.85%)
	IBD	46(16.9%)
	Haemorrhoid	31(11.4%)
	Idiopathic constipation	22(8%)
	Intestinal Tuberculosis	12(4.4%)
	Other	39(14.33%)

D. Diagnostic accuracy of original and revised IBD criteria

The finding from this study for original IBD refer criteria reveals that sensitivity and specificity of 97.8% (95% CI: 97.2, 98.4) and 58.4% (95% CI: 55.2, 61.6) respectively. And revised IBD refer criteria have sensitivity and specificity of 97.8 % (95% CI: 97.2, 98.4) and 52.7% (95% CI: 48.5, 56.9) respectively.

Table 5 Diagnostic accuracy of original and revised IBD criteria of patients visiting gastroenterology unit, Addis Ababa, 2024

Diagnostic criteria	Finding	Final Diagnosis		Total (%)
		IBD (%)	Non-IBD (%)	
Original IBD REFER criteria	Positive	**44(97.8)**	94(41.6)	138(50.9)
	Negative	1(2.2)	**132(58.4)**	133(49.1)
Revised IBD REFER criteria.	Positive	**44(97.8)**	107(47.3)	151(55.7)
	Negative	1(2.2)	**119(52.7)**	120(44.3)

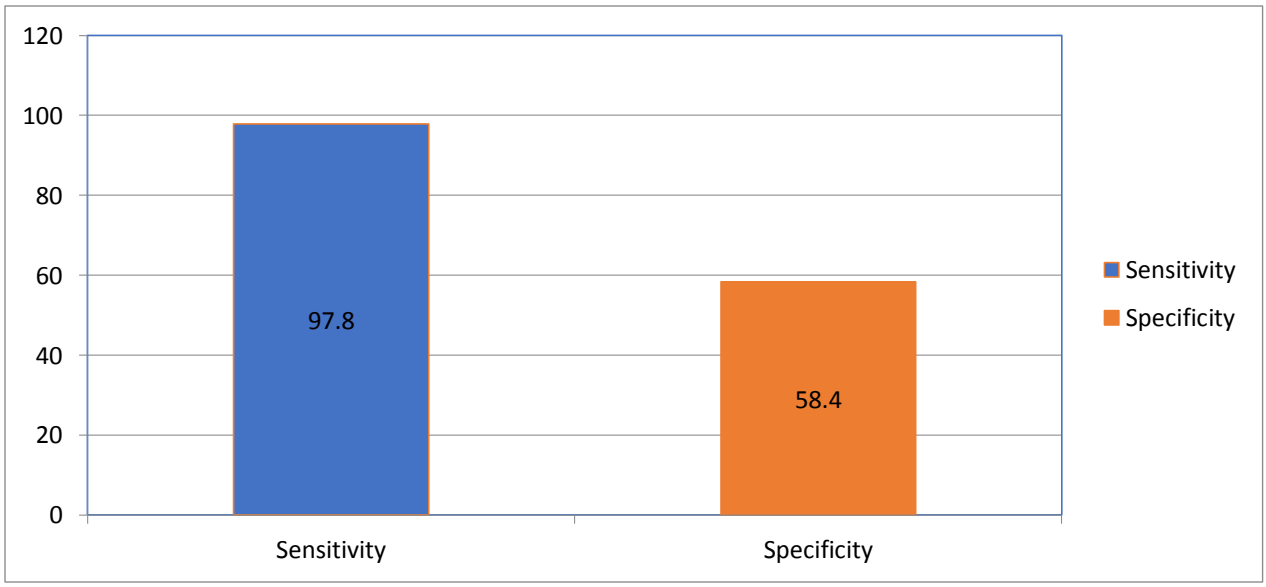


Figure 5 Sensitivity and specificity of original IBD diagnostic criteria

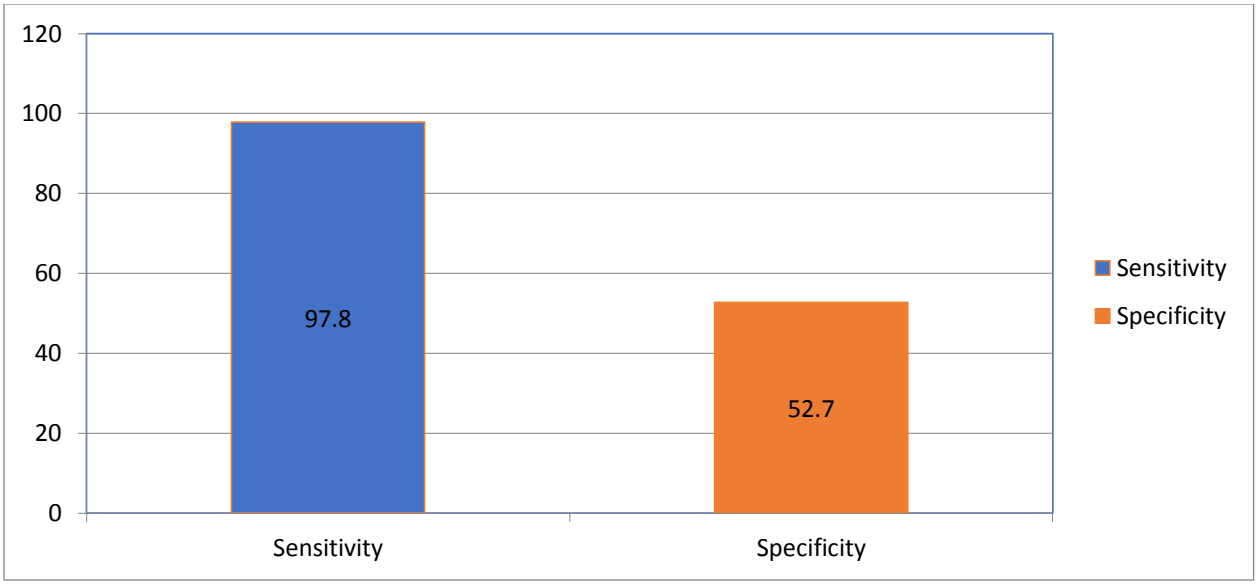


Figure 6: Sensitivity and specificity of Revised IBD diagnostic criteria

According to this study, positive predictive value and negative predictive value were calculated and found to be 31.9% (95% CI: 26.5, 37.3) and 99.2% (95% CI: 98.8, 99.6) respectively for original IBD refer criteria. For revised IBD REFER criteria 29.1% (95% CI: 25.5, 32.7) and 99.2% (95% CI: 98.8, 99.6) positive predictive value and negative predictive value respectively.

Table 6: Diagnostic accuracy of original and revised IBD criteria of patients visiting gastroenterology unit, Addis Ababa, 2024

Diagnostic criteria	**Finding**	**Final Diagnosis**		**Total (%)**
		IBD (%)	**Non-IBD (%)**	
Original IBD REFER criteria	Positive	**44(31.9)**	94(68.1)	138(100)
	Negative	1(0.8)	**132(99.2)**	133(100)
Revised IBD REFER criteria.	Positive	**44(29.1)**	107(70.9)	151(100)
	Negative	1(0.8)	**119(99.2)**	120(100)

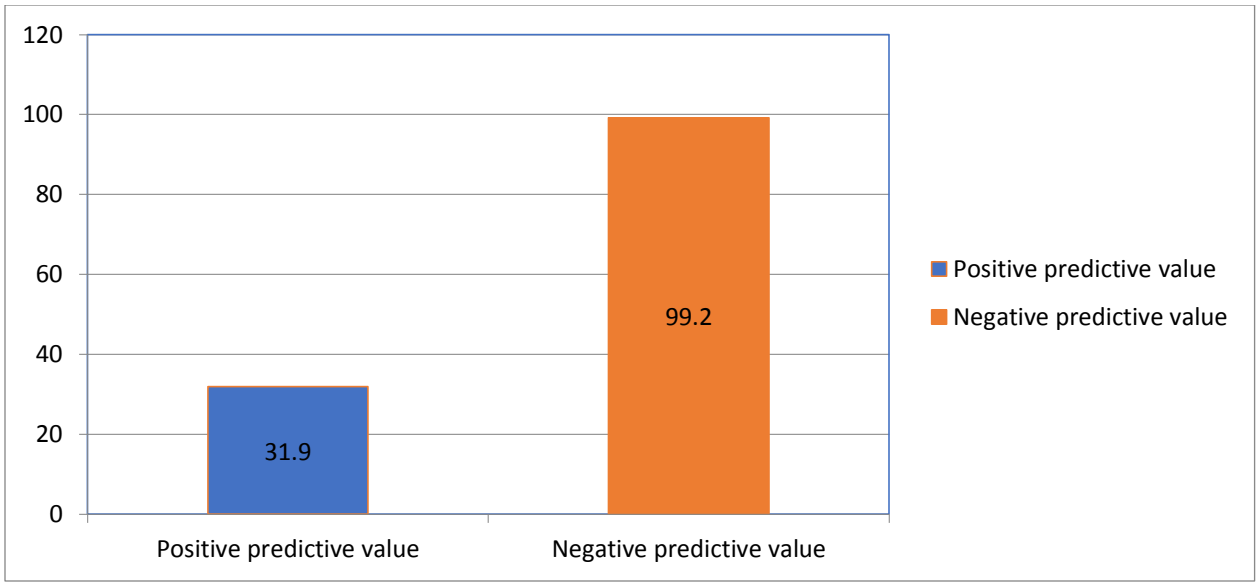


Figure 7 Positive predictive value and negative predictive value of original IBD REFER criteria

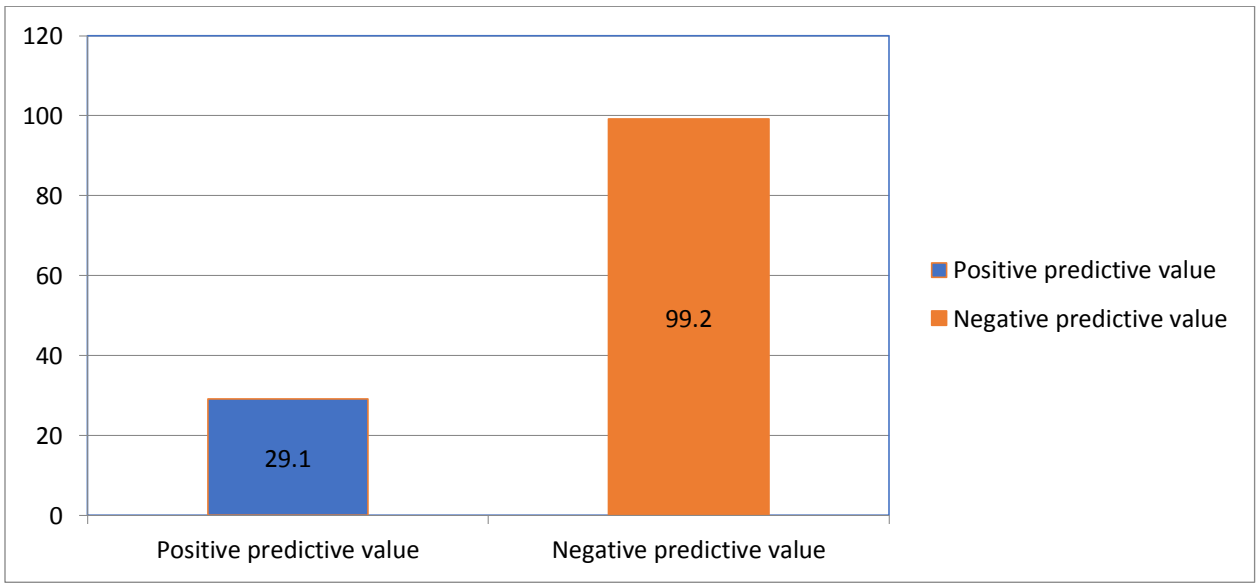
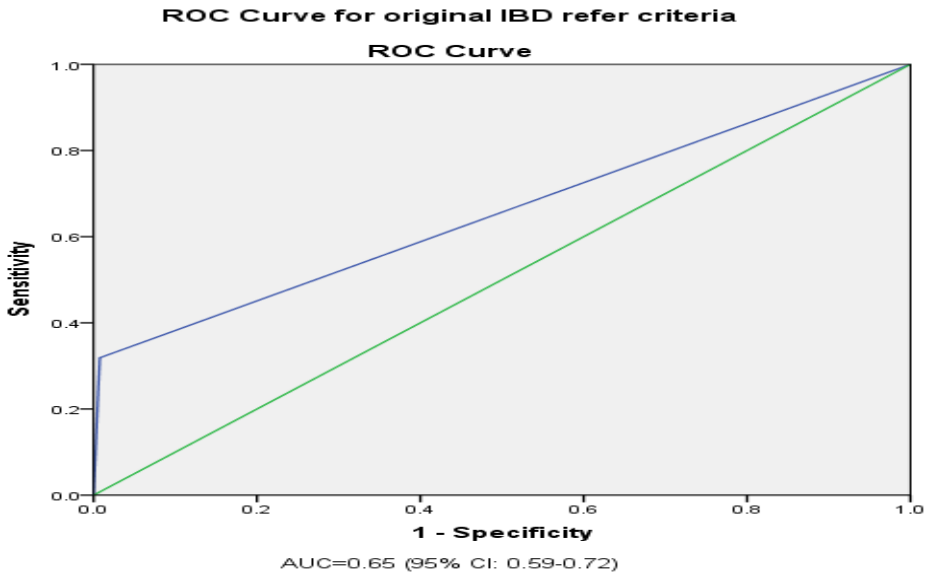


Figure 8 Positive predictive value and negative predictive value of revised IBD refer criteria.

The area under the ROC curve was higher for the original IBD refer criteria (AUC=0.65 (95% CI: 0.59-0.72)) compared with the revised IBD refer criteria (AUC=0.64 (95% CI: 0.57-0.70)).



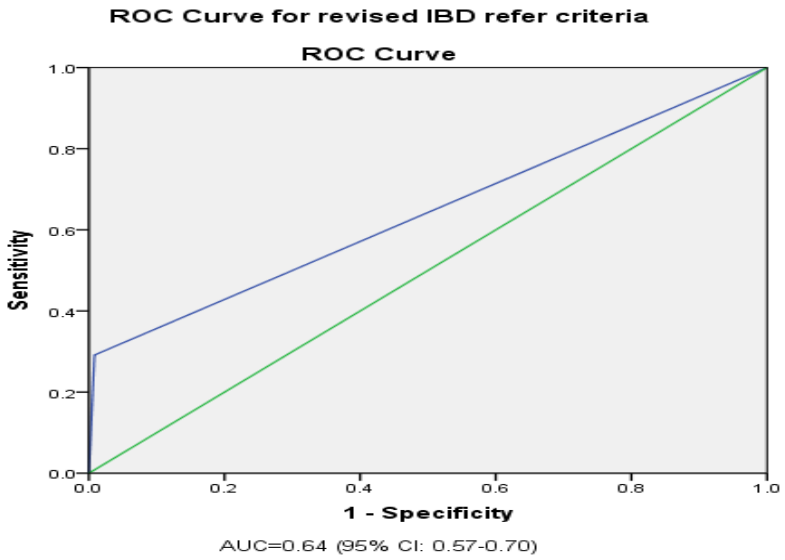


Figure 9 ROC Curve for original and revised IBD refer criteria of patients visiting gastroenterology unit, Addis Ababa, 2024

E. Patient status by standard diagnostic criteria (Final diagnosis)

Out of 271 participants, 45 (16.6%) of the patients were diagnosed with inflammatory bowel disease out of which 29(64.4%) had Crohn's disease 16(35.6%) had Ulcerative colitis, and 226(83.4%) were diagnosed with non-inflammatory bowel disease.

The mean time to diagnosis was 26.6 months with a 95% CI of 14.6 months and 38.6 months with a minimum of 2 months and a maximum of 186 months for all inflammatory bowel disease diagnoses. The mean time to diagnosis was 27.2 months for Crohn's disease and 25.6 months for ulcerative colitis.

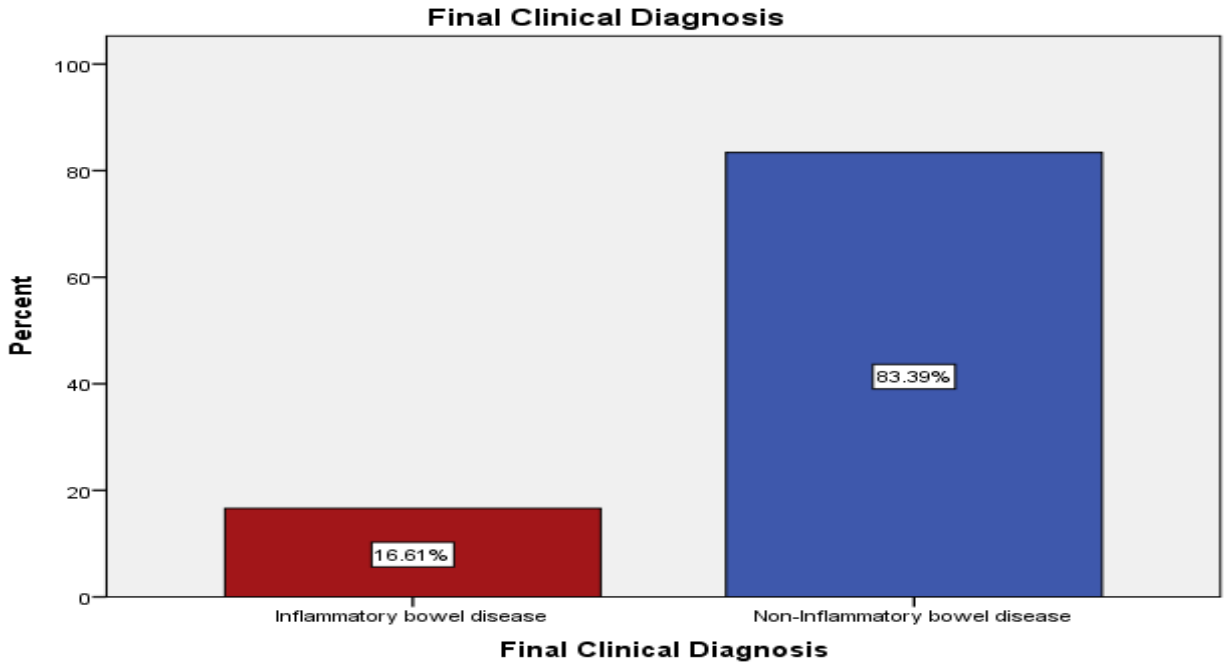


Figure 10; Final clinical diagnosis of patients visiting the gastroenterology unit, Addis Ababa, 2024

Kaplan-Meier test and log-rank test were done for all covariates to look for any significant difference between categories of variables (categorical variables). Having weight loss of 5% of normal body weight over 3 months involuntarily (x^2=8.514, p-value=0.004), and a first-degree relative with confirmed inflammatory bowel disease (x^2=3.9, p-value=0.048) were found to be a significant difference between categories.

F. Factors associated with inflammatory bowel disease (IBD)

"Bi-variable logistic regression was conducted for each independent variable. Variables with a p-value less than 0.25 were included in the multivariable logistic regression. Factors with p-values below 0.05 were considered significantly associated with inflammatory bowel disease. The results of the multivariable logistic regression, using the backward method and verified by the Hosmer and Lemeshow model fitness test (x2=1.92, p-value=0.964), which was non-significant,

indicated the model was a good fit. Multi-collinearity was assessed using a standard error greater than two, confirming that there was no multi-collinearity.

Patients having watery diarrhea lasting for at least one month were 14.8 times more likely to have inflammatory bowel disease than patients not having watery diarrhea (AOR: 14.8 (95%CI: 4.1, 54.3)). Patients having recurrent bloody diarrhea for at least two weeks were 88.6 times more likely to have inflammatory bowel disease than those without bloody diarrhea (AOR: 88.6 (95% CI: 15.7, 499.9)). Having imaging evidence suggestive of IBD were 8.6 times more likely to develop inflammatory bowel disease than those with no evidence of IBD (AOR: 8.6 (95% CI: 2.16, 34.34)). Patients who have elevated ESR or CRP were 30.7 times more likely to have inflammatory bowel disease than their counterparts (AOR: 30.7 (95% CI: 7.5, 125.2)). Patients with weight loss (5% of normal body weight over three months, involuntarily) were 4.87 times more likely to develop inflammatory bowel disease than those without weight loss (AOR: 4.87 (95% CI: 1.36, 17.37)) and patients having history of unexplained bowel obstruction, intra-abdominal abscess or inflammatory were 15.3 times more likely to have inflammatory bowel disease than those without history of unexplained bowel obstruction (AOR: 15.3 (95% CI: 1.55, 151)).

Table 7 Bi-variable and multivariable logistic regression for inflammatory bowel disease of patients visiting gastroenterology unit, Addis Ababa, 2024

Variables	Category	Final Diagnosis		COR(95%CI)	AOR(95%CI)	P-value
		IBD	Non-IBD			
Residence	Rural	6(13.3)	15(6.6)	2.16(0.79, 5.92)	7.5(1.02, 55.6)	0.047
	Urban	39(86.7)	211(93.4)	1	1	
Watery diarrhea lasting for at least one month	No	18(40)	189(83.6)	1	1	
	Yes	27(60)	37(16.4)	0.13(0.06, 0.26)	14.8(4.1, 54.3)	**0.001**
Having recurrent bloody diarrhea for	No	25(55.6)	214(94.7)	1	1	
	Yes	20(44.4)	12(5.3)	0.07(0.03, 0.16)	88.6(15.7,	**0.001**

at least two weeks				499.9)	
Having imaging evidence suggestive of IBD	No Yes	23(51.1) 208(92) 22(48.9) 18(8)	1 0.09(0.04, 0.19)	1 8.6(2.16, 34.34)	**0.002**
Having recurrent fistula or per-anal abscess	No Yes	39(86.7) 219(96.9) 6(13.3) 7(3.1)	1 0.20(0.06, 0.65)	1 8.78(1.15, 66.76)	0.036
Having elevated ESR or CRP	No Yes	11(24.4) 166(73.5) 34(75.6) 60(26.5)	1 0.12(0.05, 0.25)	1 30.7(7.5, 125.2)	**0.001**
Weight loss	No Yes	14(31.1) 181(80.1) 31(68.9) 45(19.9)	1 0.11(0.05, 0.22)	1 4.87(1.36, 17.37)	**0.015**
Having a history of unexplained bowel obstruction, intra-abdominal abscess, or inflammatory mass	No Yes	41(91.1) 22(98.2) 4(8.9) 4(1.8)	1 0.18(0.04, 0.77)	1 15.3(1.55, 151)	**0.02**

*Weight loss_5% of normal body weight over three months, involuntarily, Imaging evidence of IBD (stricture, bowel wall thickening, etc.), Fistula (Entero-cutaneous, Perianal), IBD (Inflammatory bowel disease)

Below are variables with their respective odds of developing inflammatory bowel disease from multiple logistic regression models from the higher coefficient of regression to the lowest coefficient of regression. Recurrent bloody diarrhea for at least two weeks has higher odds of developing inflammatory bowel disease and marital status is the protective factor for the odds of developing inflammatory bowel disease.

Table 8 Odds of developing inflammatory bowel disease (coefficient of regression)

Variables	**β coefficient**
Recurrent Bloody diarrhoea	4.48
Elevated ESR or CRP	3.43
Unexplained bowel obstruction	2.73
Watery diarrhoea for 1 month	2.69
Imaging evidence suggestive of IBD	2.15
Recurrent perianal entero-cutaneous or another fistula	2.17
Place of residence	2.02
Weight loss	1.58
Marital status	-1.69

6. DISCUSSION

This study involved 271 participants from three medical centers in Addis Ababa. The majority were male (58.3%) and urban residents (92.3%). The mean age of participants was 43.7 years, with a significant portion (51.7%) aged between 31 and 60 years, reflecting the typical age range for IBD diagnosis. Most participants were married (65.3%) and had secondary education (43.2%). These findings are consistent with other studies, such as the one conducted at Saint Paul Hospital Millennium Medical College, which also reported a high prevalence of urban residents and a similar age distribution [29].

A significant portion of participants reported gastrointestinal symptoms, with 23.6% experiencing watery diarrhea lasting for at least one month and 11.8% having recurrent diarrhea for at least two weeks. Elevated ESR or CRP was noted in 34.7% of participants, which is a common inflammatory marker in IBD, and 28.0% experienced involuntary weight loss. These symptoms align with common gastrointestinal issues reported in other studies (30).

This study assessed the diagnostic accuracy of original and revised IBD criteria. The original criteria showed a sensitivity of 97.8% and specificity of 58.4%, while the revised criteria had the same sensitivity but a slightly lower specificity of 52.7%. These findings are comparable to the validation study of the IBD-REFER criteria, which reported a sensitivity of 98% and specificity of 96% in adults [12, 13]. The reduction in specificity in the current study could be attributed to the high prevalence of IBD mimickers like intestinal tuberculosis in low-resource settings including Ethiopia. (32) Low specificity may lead to unnecessary referral of patients with gastrointestinal symptoms but who are at lower risk of IBD. In contrast, patients who had positive original and revised IBD refer criteria but who were not eventually diagnosed with IBD were observed to have alternative diagnoses like intestinal tuberculosis and they still benefit from referral to gastroenterologists.

The positive predictive value (PPV) and negative predictive value (NPV) for the original IBD REFER criteria were 31.9% and 99.2%, respectively, while the revised criteria had a PPV of 29.1% and an NPV of 99.2%. These values indicate that while both criteria are highly effective in ruling out non-IBD cases (high NPV), their ability to confirm IBD cases (PPV) is moderate. This is consistent with other studies that highlight the challenge of achieving high PPV in IBD diagnosis due to overlapping symptoms with other gastrointestinal disorders. (31)

The area under the ROC curve (AUC) for the original IBD-REFER criteria was 0.65 (95% CI: 0.59-0.72), compared to 0.64 (95% CI: 0.57-0.70) for the revised criteria. The AUC values indicate that both criteria have moderate diagnostic accuracy. The slight difference in AUC between the original and revised criteria suggests that the revisions did not significantly impact the overall diagnostic performance. This finding shows the same criteria perform relatively lower in resource-limited settings emphasizing the need for further refinement to improve diagnostic accuracy in low-resource settings. (12, 13)

Multivariable logistic regression identified several factors significantly associated with IBD. Patients with watery diarrhea lasting for at least one month were 14.8 times more likely to have IBD. Recurrent bloody diarrhea for at least two weeks increased the likelihood of IBD by 88.6 times. Elevated ESR or CRP, weight loss, and a history of unexplained bowel obstruction were also significant factors. These associations are consistent with other studies that have identified similar risk factors and clinical features for IBD [13] [33].

The high odds ratios for recurrent bloody diarrhea and elevated ESR or CRP highlight their critical role in the early identification of IBD. The Kaplan-Meier curve and log-rank test revealed significant differences in survival times between categories of variables. Specifically, weight loss of 5% of normal body weight over three months ($x2=8.514$, p-value=0.004) and having a first-degree relative with confirmed IBD ($x2=3.9$, p-value=0.048) were significant. These findings suggest that these factors are important in predicting the diagnosis of IBD. Previous studies also showed that first-degree relatives of CD-affected individuals are enriched with IBD risk alleles compared with the health cohort. (34)

The mean time to diagnosis for IBD was 26.6 months, with a range of 2 to 186 months. This prolonged diagnostic delay is a common issue in low-resource settings, where access to specialized care and advanced diagnostic tools is limited. The mean time to diagnosis was slightly longer for Crohn's disease (27.2 months) compared to ulcerative colitis (25.6 months). This delay in diagnosis can lead to prolonged patient suffering and increased risk of complications. The diagnostic delay noted in this study is longer than the one reported from Western studies which showed a median time to diagnosis of 4-9 months and up to 18 months in Asian studies (7, 8). Limited studies are reporting diagnostic delays in low-resource settings, highlighting the need for improved diagnostic pathways and early referral systems.

The revised IBD-REFER criteria maintain high sensitivity but show a slight reduction in specificity compared to the original criteria. The study underscores the importance of clinical features and basic laboratory tests in the diagnosis of IBD in low-resource settings. Future research should focus on improving the specificity of diagnostic criteria and exploring the integration of advanced diagnostic tools in these settings.

We have prospectively validated the original IBD REFER criteria developed by Atia et.al and developed a revised IBD REFER criteria based on the modified Delphi method, and literature search. We have compared both Criteria. Our objective was to develop a simple screening tool that helps to identify patients who need early referral to gastroenterologists. We hypothesized that simple screening tools allow physicians in resource-limited settings to identify suspected IBD Patients and prioritize those who need early referral thereby allowing early diagnosis of IBD, reducing the time to diagnosis of IBD, and reducing the risk of disease-related complications.

7. CONCLUSION

This study assessed the diagnostic accuracy of original and revised IBD criteria. The original criteria showed a sensitivity of 97.8% and specificity of 58.4%, while the revised criteria had the same sensitivity but a slightly lower specificity of 52.7%. The positive predictive value (PPV) and negative predictive value (NPV) for the original IBD REFER criteria were 31.9% and 99.2%, respectively, while the revised criteria had a PPV of 29.1% and an NPV of 99.2%.

Watery diarrhea lasting for at least one month, recurrent bloody diarrhea for at least two weeks, Elevated ESR or CRP, weight loss, and a history of unexplained bowel obstruction were shown to be significant factors associated with IBD.

The mean time to diagnosis for IBD was 26.6 months, with a range of 2 to 186 months. The mean time to diagnosis was slightly longer for Crohn's disease (27.2 months) compared to ulcerative colitis (25.6 months).

This study highlights the significant challenges and opportunities in diagnosing Inflammatory Bowel Disease (IBD) in low-resource settings like Ethiopia. The demographic profile of the participants, risk factors for IBD, and time to diagnosis of IBD align with other regional studies, reinforcing the relevance of the findings.

The validation and comparison of the original and revised IBD-REFER criteria revealed that while both criteria maintain high sensitivity, their specificity is moderate. This reflects the complexity of diagnosing IBD amidst other prevalent gastrointestinal disorders in the region. The study's findings on the positive and negative predictive values further emphasize the criteria's effectiveness in ruling out non-IBD cases, though confirming IBD remains challenging.

The prolonged diagnostic delay for IBD, averaging over two years, is a critical issue, leading to extended patient suffering and increased risk of complications. This delay is notably longer than in Western and some Asian studies, pointing to the urgent need for improved diagnostic pathways and early referral systems in low-resource settings.

Future research should focus on refining diagnostic criteria to enhance specificity and exploring the integration of advanced diagnostic tools. Addressing these challenges can lead to earlier diagnosis, better patient outcomes, and reduced disease-related complications in resource-limited settings.

8. RECOMMENDATIONS

1. **For Researchers**:
    - Conduct further studies to refine and validate diagnostic criteria with a focus on improving specificity.
    - Explore the integration of advanced diagnostic tools and technologies in low-resource settings.
    - Investigate the impact of early referral systems on patient outcomes and healthcare costs.
2. **For Policy Makers**:
    - Develop and implement policies that support the establishment of early referral systems for IBD.
    - Allocate resources to improve access to specialized care and advanced diagnostic tools in low-resource settings.
    - Promote awareness campaigns to educate healthcare providers and the public about the importance of early diagnosis and treatment of IBD.
3. **For Clinicians**:
    - Utilize the revised IBD-REFER criteria to identify and prioritize patients for early referral to gastroenterologists.
    - Monitor patients with significant gastrointestinal symptoms and inflammatory markers closely for early signs of IBD.
    - Advocate for and participate in training programs to stay updated on the latest diagnostic and treatment protocols for IBD.

9. STRENGTH AND LIMITATION OF THE STUDY

The strength of our study is it has prospectively validated the original IBD REFER criteria and developed simple revised IBD REFER criteria. This study also identified factors associated with IBD diagnosis and time to diagnosis of IBD in resource-limited settings. To our knowledge, this is the first study to prospectively validate the original IBD REFER criteria developed by Atia et.al and to develop revised IBD REFER criteria in a resource-limited setting.

This study is limited by the lack of fecal calprotectin determination in the majority of the study patients. Despite Faecal calprotectin becoming an important screening test for IBD, this is not commonly available in resource-limited setups. Additionally, the patient was enrolled in three referral hospitals and was not from the primary care setup.

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11. ANNEXES

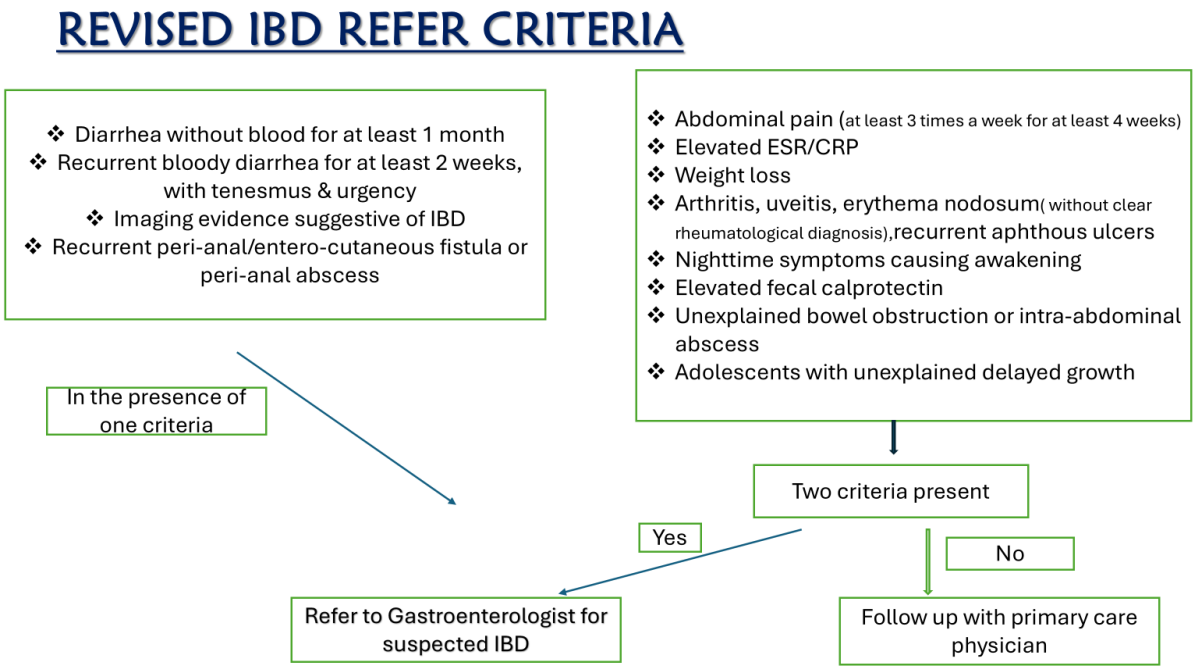

Figure 11- Revised IBD REFER CRITERIA

I. QUESTIONER

DIAGNOSTIC ACCURACY OF REVISED IBD-REFER CRITERIA AMONG ADULT PATIENTS WITH SUSPECTED INFLAMMATORY BOWEL DISEASE, ADDIS ABABA, ETHIOPIA

QUESTIONNAIRE

Part I Socio-Demographic Character

1. Data collection ----------
2. Date of data collection----------
3. Medical record number----------
4. Age----------
5. Place of residence? 1. Urban 2. Rural
6. Sex? 1. Male 2. Female
7. Level of education
    A. No Formal education
    B. Read & write
    C. Only Primary education
    D. Secondary education
    E. College & above
8. Marital status
    A. Married
    B. Single
    C. Divorced /Widowed
9. Occupation
    A. Civil servant
    B. Private Workers
    C. Unemployed
    D. Retired
    E. Student

F. Farmer
G. Merchant
H. Other:

PART II- CLINICAL RELATED QUESTIONS

10. Does the patient have Diarrhea without blood lasting for at least 1 month (Major Criteria?)

A. Yes
B. No

11. Does the patient have recurrent bloody Diarrhea for at least 2 weeks associated with tenesmus & urgency (Major criteria?)

A. Yes
B. No

12. Does the patient have Imaging evidence suggestive of IBD (stricture, bowel wall thickening, etc.) (Major criteria?)

A. Yes
B. No

13. Does the patient have recurrent peri-anal, entero-cutaneous, or another Fistula or Per-anal abscess (Major criteria?)

A. Yes
B. No

14. Does the patient have abdominal pain for at least 3 months (abdominal pain at least 3 times a week for at least 4 weeks (Minor)?

A. Yes
B. No

15. Does the patient have Elevated ESR or CRP (Minor criteria?)?

A. Yes
B. No

16. Does the patient have weight loss -(5% of normal body weight over 3 months, involuntarily(Minor criteria?))?

A. Yes

B. No

17. Does the patient have a fever (>4 weeks not otherwise explained and associated with raised ESR or CRP)? (Minor criteria?)

A. Yes

B. No

18. Does the patient have a First-degree relative with confirmed inflammatory bowel disease? (Minor)

A. Yes

B. No

19. Does the patient have patient Arthritis, uveitis, erythema nodosum, not meeting a clear rheumatological diagnosis? (Minor criteria?)

A. Yes

B. No

20. Does the patient have Recurrent oral aphthous ulcerations? (Minor criteria?)

A. Yes

B. No

21. Does the patient have Nighttime symptoms (patient awake from sleep because of abdominal pain or diarrhea)? (Minor)

A. Yes

B. No

22. Does the patient have elevated fecal calprotectin? (Minor)

A. Yes

B. No

C. Not done

23. Does the patient have a history of unexplained bowel obstruction, Intra-abdominal abscess, or inflammatory mass? (Minor)

A. Yes

B. No

C.

24. Does the patient have a history of unexplained delayed growth or failure to thrive (In children and adolescents)? (Minor)
    A. Yes
    B. No
25. Comorbidity
    A. DM
    B. Hypertension
    C. Chronic Liver disease
    D. Chronic kidney disease
    E. Retroviral infection
    F. CVD Related
    G. NAFLD
    H. None
    I. Other:

PART III- INVESTIGATION

26. Colonoscopy Diagnosis----------
27. Histology Finding…….
28. ESR----------
29. CRP ----------
30. Hemoglobin /MCV----------
31. Albumin----------
32. Abdomino-pelvic ultrasound/CT scan finding ……

PART IV DIAGNOSTIC CRITERIA

33. Revised IBD Refer Criteria (Positive- If one major criterion/two minor criteria are yes on the clinical questionnaire part)
    A. Positive
    B. Negative
34. Final Clinical Diagnosis
    A. Inflammatory bowel disease
    B. Non-Inflammatory bowel disease
35. The final Clinical diagnosis is other than IBD Irritable bowel syndrome

A. Hemorrhoid
B. Infectious colitis
C. Nonspecific colitis
D. Idiopathic Constipation
E. Celiac disease
F. Colonic Diverticula
G. Colonic polyp
H. Normal
I. Intestinal TB
J. Malabsorption syndrome
K. Other:

PART V DIAGNOSTIC DELAY QUESTIONER (To be filled only for patients with a diagnosis of IBD)

36. What is the patient's clinical diagnosis?
    A. Crohn's disease
    B. Ulcerative colitis
37. Which doctor did you see first when you noticed the symptoms?
38. After you noticed the first discomfort and symptoms, how long did you wait to see a physician? (In days, weeks, months/years)?
39. After your initial visit to a Health professional, how long did it take to know/Confirm your current illness (In days, weeks, months/years)?
40. How long did you suffer from your current illness before the disease was diagnosed? (In days, weeks, months/years)10 months
41. How long have you been examined and/or treated by your nearby physician before being referred to a gastroenterologist? (In days, weeks, months/years)
42. Did you smoke at the time of diagnosis?
    A. Yes
    B. No
43. If yes, how much pack year (Write below)
44. Did you take one of the following medicines at the time of diagnosis?

A. Oral contraceptive
B. NSAID
C. Antibiotics
D. Isotretinoin
E. Rituximab
F. Anti-TB
G. I had surgery related to my current complaint before the diagnosis Other:

II. CONSENT FORM

III. የስምምነት ቅፅ (አማርኛ ትርጉም)

የስምምነት ቅፅ

ይህ የስምምነት ቅፅ በኢትዮጵያ “ACCURACY OF REVISED IBD-REFER CRITERIA FOR EVALUATION OF PATIENTS WITH SUSPECTED INFLAMMATORY BOWEL DISEASE IN LOW RESOURCE SETTING: A DIAGNOSTIC PROSPECTIVE COHORT STUDY”በሚል ጥናት እንዲሳተፉ ለተጋበዙ ግለሰቦች የተዘጋጀ ነዉ፡

የዋና ተመርማሪ ስም(ሞች) እና ተቋም/ተቋማቸዉ

ይህ ጥናት የምካሄደው በዶክተር ሮዳስ ተመስገን (MD, MPH, GI Fellow) ፡ በProfessor Abate Bane (Consultant internist, Gastrointerologist, hepatologist) በDr Yohannes Berhanu (Consultant internist, Gastrointerologist, hepatologist)አማካሪነት/ ክትትል ስር ተመርማሪዎች /መርማሪዎች ነዉ።።

የጥናቱ ስፖንሰርዎች፦ ጥናቱ በAdiss Abeba Univeristy ,College of Health science የተደፈ

የሚጠበቀው የጥናት ቆይታ እና የተሳታፊ(ዎች) ተሳትፎ ፡ ይህ ጥናት 5 ደቂቃ አካባቢ ይወስድል.።።

በጥናቱን ለመሳተፍ የምያስወጣ ወጪዎች፡ በዚህ ጥናት ውስጥ ተሳትፎ ምንም ዋጋ አያስከፍልዎትም.

ምስጢራዊነት፡- ከዚህ ጥናት የምንሰበስበው መረጃ በጥቂቱ የጥናት ተመርማሪዎች መካከል በሚስጥር እና በሚስጥር ይጠበቃል። ስለእርስዎ ያለ ማንኛውም መረጃ በስምዎ ምትክ በእሱ ላይ ባለው ቁጥር ይታወቃል። ከዋናው ተመርማሪ እና ከለሎች ተመራማሪዎች በስተቀር ለማንም አይጋራም ወይም አይሰጥም።

በጎ ፈቃደኝነት ፡ በዚህ ጥናት ውስጥ ያለዎት ተሳትፎ ሙሉ በሙሉ በፈቃደኝነት ላይ የተመሰረተ ነው። መሳተፍ አለመሳተፍ የእርስዎ ምርጫ ነው። ለመሳተፍ ከመረጡ፣ ሃሳብዎን በኋላ መቀየር እና ቀደም ብለው የተስማሙ ቢሆንም መሳተፍዎን ሊያቆሙ ይችላሉ።

በጥናቱ ውስጥ መሳተፍ ምን ጥቅሞች አሉት? በጥናቱ ላይ ለመሳተፍ ምንም አይነት ክፍያ አይሰጥዎትም። ውጤታማ የቁጥጥር እና የእንክብካቤ ስልቶችን ለማቀድ የእርስዎ ተሳትፎ ስለ Inflammatory bowel disease ሁኔታ የበለጠ እንድናዉቅ ይረዳናል።

ወደፊት ያልተገለጸ የአጠቃቀም ጥናት ፡-

ጥናቱ ሲያልቅ በምርምር ተሳታፊዎች እና ማህበረሰቦች ፡ ተሳታፊዎች የምርምር ውጤቱን በተለያዩ ሳይንሳዊ ህተመቶች ይነገራቸዋል።

የፈቃድ ወሳጅ መግለጫ/ ማብራሪያ

ይህንን ጥናት ለ_____ ሙሉ ለሙሉ አብራርቼዋለሁ እና በመረጃ ላይ የተመሰረተ ውሳኔ ለማድረግ እንድቻለ ስለ አደጋዎች እና ጥቅሞችን ጨምሮ በቂ መረጃ ሰጥቸዋለሁ፡፡
ቀን፡ _____ ፊርማ፡ _____
ስም፡ _____

የፈቃድ ሰጭ መግለጫ/ ማብራሪያ
የጥናቱን መግለጫ አንብቤያለሁ ወይም በምረዳው ቋንቋ ተብራርቷልኛል፡፡ከሐኪሙ ጋር አጥጋብ በሆነ መልኩ ተነጋግሬያለሁ። ተሳትፎዬ በፈቃደኝነት እንደሆነ ተረድቻለሁ። በማንኛውም ጊዜ የዚህ ጥናት አካል መሆኔን በነፃነት ማቆም እንደምችል ተረድቻለሁ። የዚህ ፈቃድ ቅጽ እና ተጨማሪ የመረጃ ወረቀት ቅጂ ተቀብያለሁ።

ቀን፡- _____ ፊርማ/የአውራ ጣት አሻራ/ ፡ _____
ስም፡ _____
የምሥክር ስም (የአውራ ጣት አሻራ (አሻራ) ከሆነ _____

የምሥክር ፊርማ (የአውራ ጣት አሻራ (አሻራ) ከሆነ _____

IV. ASSURANCE OF PRINCIPAL INVESTIGATOR

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific ethical and technical conduct of these research projects and for the provision of required progress reports as per the terms and conditions of the faculty of medicine. We also provide our assurance on the originality of this work.

Name of the PI: Rodas Temesgen Annose (MD, MPH)

Date. October 20/2024 Signature _____