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Full title of the research	Rate and predictors of endoscopic mucosal healing among IBD patients on medical therapy at Tikur Anbessa Specialized Hospital: Institution Based Prospective Cross-sectional study
Duration of the project	January-September 2023
Study area	Addis Ababa, Ethiopia
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We the undersigned are the principal investigator and the advisors for this study. We declare that this thesis is our original work.

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List of acronyms

ADA Adalimumab

AZA Azathioprine

BUN Blood urea nitrogen

CBC Complete blood count

CD Crohn's disease

CDAI Crohn's disease activity index

CDEIS Crohn's disease endoscopic index of severity (CDEIS)

CRP C- reactive protein

EMR Electronic medical record

ESR Erythrocyte sedimentation rate

HBI Harvey Bradshow Index

IBD Inflammatory bowel disease

IFX Infliximab

MES The Mayo endoscopic sub-score for UC

MH Mucosal healing

MRI Magnetic resonance imaging

MTX Methotrexate

SES-CD Simple endoscopic score for CD

STRIDE Selecting therapeutic target in inflammatory bowel disease

TASH Tikur Anbesa Specialized Hospital

T2T Treat to target

UC Ulcerative colitis

UCIES Ulcerative Colitis Endoscopic Index of Severity

WBC White blood cell count

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Summary

Introduction

Inflammatory bowel diseases (IBD) are characterized by chronic inflammation of the intestinal mucosa resulting from strong interaction between genetic, environmental, immunologic and intestinal microbial factors. Medical treatment for inflammatory bowel disease (IBD) has undergone a complete transformation over the last several decades due to the advent of different drugs. Clinical remission and endoscopic healing are integral components of the treat to target strategy in IBD therapy. Endoscopic healing is associated with significant reduction in complications of IBD and/or need for surgery.

Objective

The objectives of this study are to determine the rates of clinical remission and endoscopic mucosal healing among IBD patients on treatment and to sort out predictors of endoscopic healing.

Methodology

A prospective cross-sectional study was conducted at Tikur Anbesa Specialized Hospital from January, 2023 to October 2023. The study included all consecutive IBD patients on treatment for six months or more who showed up for a regular follow up at TASH GI clinic in the study period and who were willing to consent and undergo follow up colonoscopy.

Results

Overall Clinical remission rate from this Cross-sectional study is 69 /106, including 62/87, (71.3%) of CD, 7/17 (41.2%) of UC and 0 /2 Unclassified. Thirty-five (33%) of IBD patients in the study achieved endoscopic healing. Twenty-six of the 87 (29%) patients with CD, 8 of the 17(47%) UC, and one of the two with indeterminate colitis achieved endoscopic mucosal healing. Only 10 of the 32 CD patients with previous history of bowel resection achieved endoscopic healing. Higher ESR value (P = 0.040, AOR 0.946 with 95% CI 0.898-0.997) and younger age at diagnosis (P = 0.046, AOR 1.322 with 95% CI 1.005-1.739) predicted absence of endoscopic healing.

Conclusion

Sixty-nine of the one hundred six IBD patients (65.1%, 70% for CD, 41.2% for UC) were in clinical remission. The overall endoscopic mucosal healing rate from this study is 33% (29.1% CD, 47.1% UC). Elevated ESR and younger age at the diagnosis predicted absence of endoscopic healing within the study period.

Introduction

Statement of the problem

Inflammatory bowel diseases (IBD) are characterized by chronic inflammation of the intestinal mucosa resulting from strong interaction between genetic, environmental, immunologic and intestinal microbial factors. (1) The term 'IBD' is most often used to describe two separate conditions: ulcerative colitis (UC) and Crohn's disease (CD). (2) Available evidence suggests that the incidence of IBD is increasing globally in general and in Africa particularly. Switch from an agriculture based lifestyle towards an industrial and postindustrial mode and changing fiber based diets for industrial fast food are believed to be among the environmental factors contributing to the increasing burden of IBD worldwide.(3)

The increment in the incidence of IBD has different pattern in different geographic regions. If Africa follows the same epidemiological trends as in the West and Asia, IBD is likely to represent a significant public health challenge in the near future. A recent modeling study has shown an increase in age-standardized prevalence rate of IBD in regions that formerly had low prevalence, including east and south Asia, Oceania, and sub- Saharan Africa. With the changing in living standard and urbanization, increasing of IBD cases is expected in Ethiopia too. A case control study has shown that Ethiopian Jews migrating to Israel are at risk of developing IBD, corroborating the strong link of genetic predisposition and role of environmental factors in IBD development.(4-6)

Medical treatment for inflammatory bowel disease (IBD) has undergone a complete transformation over the last several decades due to the advent of different drugs. Historically, the standard of care for IBD patients has focused on managing the patient's IBD symptoms; however, this symptom driven approach does not significantly alter the disease course and patients' need for surgery. This approach can lead to long delays in achieving remission, and subsequent poor quality of life or even development of IBD related complications and surgery. Using a conventional treatment approach, almost 50% of patients with CD and 16% of patients with UC will require intestinal surgery within 10 years of diagnosis. Traditionally the mainstay of therapy was to achieve clinical remission, or absence of symptoms. However, a substantial proportion of patients in clinical remission have evidence of ongoing inflammation. Studies have shown that patients with severe ulcerations have a worse clinical course and disease related complications, including flares, hospitalization and the need for surgery, while those achieving mucosal healing or endoscopic healing are at a much-reduced risk of complications. Endoscopic healing or Mucosal healing assessment is an integral component of a treat-to-target (T2T) approach, which involves close monitoring of specific and objective measures of inflammation. Endoscopic healing or Mucosal healing has been advocated for IBD in an attempt to improve long term patient outcomes and reduce need for surgeries.

The goal of T2T in IBD is to achieve disease remission by periodically measuring the treatment response against predefined targets and adjusting treatment as required to meet this goal. Evidence based treatment targets for IBD patients were identified by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) panel of international experts. These include clinical, patient reported outcome, and endoscopic outcome. STRIDE recommended that the assessment of remission requires considering both clinical symptoms and endoscopic outcomes. In addition to predicting a better clinical course, use of endoscopic healing or mucosal healing as clinical endpoint helps clinicians to distinguish symptoms due to underlying inflammation from other etiologies such as irritable bowel syndrome, hence avoiding unnecessary treatment escalations. According to STRIDE, the agreed target for UC is clinical / patient reported outcome (PRO) remission (defined as resolution of rectal bleeding and diarrhea / altered bowel habit) and endoscopic remission (defined as a Mayo endoscopic sub-score of 0 or 1). Target for CD was defined as resolution of abdominal pain and diarrhea / altered bowel habit and endoscopic remission, defined as resolution of ulceration at ileo-colonoscopy, or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be assessed with ileo-colonoscopy.(7-15)

Even though endoscopic healing or mucosal healing (MH) is the best-established therapeutic end point both in UC and CD, there is currently no single universally accepted definition. Definitions have been different among diverse clinical trials. Some studies define mucosal healing as a normal appearing mucosa devoid of any inflammatory changes, or absence of ulceration while others define it as significant improvement in the appearance of the mucosa during follow up. Each definitions have their own advantages and limitations. The Crohn's Disease Endoscopic Activity Index (CDEIS) and the Simple Endoscopic Score for Crohn's disease (SES-CD) are the most commonly used tools for assessing endoscopic healing or mucosal healing in non-post operative CD patients. The Rutgeert's score of endoscopic recurrence is utilized in the postoperative setting. CDEIS and SES-CD < 3 are used as cut off point for defining mucosal healing in most studies. Rutgeerts score of i0 or i1 are considered as marker of endoscopic remission in post operative CD. The Mayo endoscopic sub-score and Ulcerative Colitis Endoscopy Index of Severity (UCEIS) are the most commonly utilized endoscopic score for MH assessment in ulcerative colitis. UCEIS and Mayo endoscopic sub score of 0 and1 are used as a definition for endoscopic or mucosal healing in ulcerative colitis.(16-19)
Different studies have shown poor correlation between clinical remission and mucosal healing / endoscopic healing. Significant proportion of patients with IBD may have clinical improvement following a course of treatment but only smaller proportion achieve mucosal healing which is usually delayed in time. One of the evidence for this came from the evaluation of post-surgical recurrence of CD which revealed,73% of patients displaying endoscopic lesions, but only 20% with symptoms after one year of surgery.(20, 21) A retrospective descriptive study (unpublished) by Neway et al. at TASH GI clinic has shown a onetime visit clinical remission rate of 79% among IBD patients but the study did not look in to endoscopic / mucosal healing rate.(22)

Recently, different treatment approaches have been proposed. One of these is a top-down approaches using combination therapy of immunomodulator and anti-TNF early in the disease course to avoid long-term complications. In 'treat to target' approach instead of aiming for clinical remission, a treatment target such as mucosal healing has been proposed as a new standard of care. Regular disease assessment is mandatory to ensure proper escalation of treatment until clinical remission and mucosal healing is achieved. Two clinical trials have shown that a treat to target approach leads to better medium-term outcomes in CD.(13, 23, 24)

Literature review

After the introduction of biologic treatment in IBD, endoscopic / mucosal healing has been proposed to be an important measure of treatment efficacy.(25)

The first phase III study with biologic treatment in CD, the ACCENT I trial, (A Crohn's disease Clinical study Evaluating infliximab in a new long term Treatment regimen), patients with MH showed less demands for hospitalization and surgery after treatment with infliximab.(26)

From a recent revision of ASCEND I AND II trials, comparing two different doses of 5- ASA for inducing remission in three hundred ninety-one patients with mild to moderate active UC, it emerged that after six weeks of treatment, mucosal healing defined by Mayo sub score 0 or 1 was achieved in 80 % of patients receiving ASA 4.8g/day and in 68% of patients receiving 5-ASA 2.4g/day (P=0.012). When MH was defined more strictly as a Mayo sub-score equal to 0, the rates dropped to 32% and 24%, respectively, with no statistical difference between the two groups.(27) It has been known for a long that steroids, despite their excellent capacity to induce clinical remission, are not powerful in inducing MH in CD. A historical trial evaluated the endoscopic status of one hundred thirty-one patients with ileocolonic CD and steroid induced clinical remission. Endoscopic examination revealed that only 29% of patients' in clinical remission were also in endoscopic remission, while the remaining 71% had persistence of endoscopic activity.(28)

Evidences for AZA induced mucosal healing in CD are limited from retrospective studies and small observational studies. One of the studies which included 15 patients for postoperative recurrence of ileitis being on AZA for more than 6 months, mucosal healing was found only in 40 % after a median follow up of 18 months. In the second study 20 CD patients were treated with AZA for at least 9 months and after a median time of treatment of approximately 2 years, 54% of patients showed healing of the mucosal lesions located in the ileum.(29, 30)

A prospective study published by Mantzaris et al. in 2009, randomized 77 patients with steroid dependent CD who had achieved clinical remission with steroids to receive either budesonide or AZA as maintenance treatment for 1 year and endoscopic and histological activity were assessed at baseline and at end of the study. On intention-to-treat analysis, and considering only complete MH, the percentage of patients with AZA induced MH was 58% compared to 24% of budesonide treated patients (P=0.0001).(31) Another prospective study from the GETAID (Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives), designed to assess the long term outcome after AZA withdrawal in patients with CD in remission, 83 patients in clinical remission under AZA for at least 42 months were randomized to continue AZA or to receive placebo. The primary end point was the relapse rate over 18 months. At baseline, a subgroup of 45 patients underwent endoscopic evaluation. Complete MH, defined as Crohn's disease endoscopic index of severity (CDEIS) = 0, was observed in only 16 of 45 patients (36%). (32)

In the SONIC study which compared AZA, infliximab (IFX), and the combination therapy in moderate to severe CD, MH as secondary end point was assessed in a subset of patients who underwent endoscopy at baseline and at week 26. Only 16% of patients receiving AZA monotherapy achieved complete MH.(33, 34) A randomized controlled trial (RCT) published in 2006 by Ardizzone et al. compared AZA with 5-ASA for the treatment of steroid dependent UC. On intention-to-treat analysis, AZA induced clinical and endoscopic remission in 55% of patients compared to 19% in those using 5-ASA.(35)

Current available evidences show that anti-TNF therapies can induce rapid and sustained MH. In 1999 D'Haens et al. reported the endoscopic and histological response to a single infusion of IFX at a dose of 5, 10, or 20 mg/kg, or placebo, in 30 CD patients. Patients treated with IFX experienced a significant decrease in CDEIS, while patients in the placebo group did not experience any endoscopic improvement.(36) In the ACCENT I endoscopic sub-study, ninety nine patients underwent endoscopic evaluation at baseline and at different time points during the 1-year study period. IFX every 8 weeks induced MH in approximately 50% of patients at week 54, and sustained MH (at both week 10 and week 54) in approximately 30% of patients.(29)

D'Haens et al. also conducted an unblinded trial on newly diagnosed CD patients and compared early combined immunosuppression (IFX and AZA) to conventional management. The primary endpoints were remission off steroids and no bowel resection at weeks 26 and 52. A subset of 49 patients underwent colonoscopy at baseline and after 2 years of therapy. Ulcer regression at 104 weeks occurred in 73.1% of patients receiving combined immunosuppression and in 30.4% of patients receiving conventional approach ($P = 0.002$). (37) In the SONIC study, 508 adult patients with moderate to severe CD were randomized to receive a 30-week treatment course with IFX (5 mg/kg at weeks 0, 2 and 6, and then every 8 weeks), AZA 2.5 mg/kg, or a combination of the two drugs. Overall, 44% of patients receiving the combination therapy achieved MH, compared to 30% of patients receiving IFX monotherapy and 16% of patients receiving AZA alone.(33)

The EXTEND trial assessed the efficacy of ADA in moderate to severe ileo-colonic CD, and was the first trial to assess MH as a primary end-point [30]. One hundred and twenty-nine patients received an induction dose of ADA (160 mg at week 0 and 80 mg at week 2) followed by either scheduled ADA maintenance (40 mg every other week) or placebo. After 12 weeks MH, defined as endoscopic absence of mucosal ulcerations, was observed in 27.4% of patients in the treatment arm and in 13.1% of those receiving placebo ($P = 0.056$). At week 52, MH was observed in 24.2% of patients receiving ADA and none of those receiving placebo ($P < 0.001$).(38)

The ACT 1 and ACT 2 trials investigated the role of IFX (5 and10 mg/kg, induction and scheduled maintenance) vs placebo, in moderate to severe UC. MH was defined as a Mayo endoscopic sub-score ≤ 1 and was a secondary outcome. At week 8, approximately 60% of patients receiving IFX achieved MH compared to approximately 30% of patients receiving placebo. At week 30 the rates of MH were approximately 50% in the treatment arm and 25% in the placebo arm; at week 54 (only in the ACT 1 trial) the MH rates were 46% vs 18%, respectively [31]. Considering a more strict definition of MH (i.e. Mayo sub-score = 0) the percentage of patients achieving MH at weeks 8, 30 and 54 were 25%, 30%, and 33% in the IFX group and 8%, 10%, and 16% in the placebo group.(27)

A Norwegian population based prospective study showed MH after 1 year of treatment to be predictive of reduced subsequent disease activity and decreased need for active treatment. The study also showed health education, extensive disease at diagnosis, fever at a diagnosis and treatment without steroid were predictors of mucosal healing.(25)

Studies have shown different noninvasive markers to predict mucosal healing among IBD patients on treatment. Kiss et al. analyzed 210 Hungarian patients with CD and showed that normalization of CRP at week 12 is one of the strongest predictors of clinical efficacy and MH during the first year of ADA therapy. In a prospective study on 164 CD patients IL-6 (a proinflammatory cytokine that stimulates the liver to produce CRP) and CRP concentrations correlated with endoscopic disease activity. Current available evidences from different perspective trials showed a strong correlation between levels of Fecal calprotectin (FCp) (a neutrophilic, calcium-binding protein that passes through the intestinal mucosa) and mucosal healing. (39-41) With the available limited evidence, there is also a correlation between treatment response, mucosal healing and genetic factors among IBD patients. Arjis and his colleagues were able to identify five differently expressed genes in responders from colonic mucosal biopsies of patients with CD undergoing IFX therapy.(42)

Noninvasive tests have been used to predict mucosal healing among IBD patients on treatment. In a recent study by Pallotta and his colleagues on assessment of severity of post-operative CD by ultrasound, wall thickness of ileo-colonic anastomosis (>3.5 mm) identified 100% of patients with endoscopic lesions six months after surgery and severe Rutgeert's score. Rimola et al in his study on CD aimed at defining and validating a quantitative index of activity and severity based on Magnetic Resonance Index of Activity (MaRIA), twenty-nine patients with clinically active disease and 19 with clinically inactive disease underwent ileocolonoscopy and MRI. Endoscopic activity was evaluated with CDEIS. Wall thickness, relative contrast enhancement, presence of oedema and ulcers on MRI were found as predictors of disease severity.(43, 44)

Justification

Ethiopia, being in a region where there is a rapid shift in disease epidemiology from communicable to non-communicable disease, there are anecdotal evidences for increasing incidence of IBD. Tikur Anbesa Specialized Hospital is one of the centers in the capital city where a significant proportion of IBD patients get their treatment and follow up. With the current available evidence, Endoscopic or mucosal healing is one of the best reliable end points which needs to be achieved in patients with IBD on treatment. Endoscopic healing rate and predictors among cohort of IBD patients at TASH is not known. This study will prospectively look in to clinical remission rate and endoscopic healing rate among IBD patients on treatment and will sort out predictors of endoscopic healing. The generated evidence will help to improve the care of IBD patients.

OBJECTIVE

General objective

- To assess clinical remission and endoscopic mucosal healing rate among IBD patients on medical therapy at TASH during the study period.

Specific objectives

- To determine clinical remission rate among IBD patients at TASH included in the study
- To determine endoscopic mucosal healing rate among IBD patients at TASH included in the study.
- To sort out predictors of endoscopic mucosal healing among IBD patients at TASH included in the study.

Methodology

Study design

Institution based prospective cross-sectional study was conducted at Tikur Anbessa Specialized Hospital from January 2023 to October 2023 GC.

Study setting

The research was conducted at Tikur Anbesa Specialized Hospital. TASH is the oldest and the principal teaching referral Hospital in Ethiopia, located in the capital city, Addis Ababa. TASH Gastroenterology unit is one of the divisions of Internal medicine which provide both out patient service with three times weekly functioning specialized clinic, endoscopy unit and inpatient service for admitted patients. The endoscopy unit is one of the World Gastroenterology organizations (WGO) centers in east Africa. The endoscopy unit is functional seven days a week and twenty-four hours a day for elective and emergency cases. Elective upper GI endoscopy and colonoscopy are done regularly three days in a week using Karl storz silver and Fujifilm gastroscope and colonoscope. TASH GI unit has eight gastroenterologists, seven trained endoscopy nurses and Seven Gastroenterology and Hepatology fellows.

Source population

Inflammatory bowel disease patients coming for follow up at TASH GI clinic during the study period.

Study population

Inflammatory bowel disease patients on medical therapy for more than six months and being followed at TASH GI clinic.

Sample size and Sampling technique

The predicted number of patients attending TASH GI referral clinic during the study period is less than 10,000. From previous study by Neway et al., there were a total of 148 IBD patients at TASH GI clinic during a study period of 6 months and most of the patients were on Azathioprine maintenance therapy. Considering an endoscopic healing rate with Azathioprine (40%) from similar study by D'haens G et al, the required sample size for the study will be 116 by using population proportion formula assuming CI of 95% and degree of freedom of 0.05. and adjusting for estimated 10 % drop out rate.

$n = N*X / (X + N - 1)$, where, $X = Z_{\alpha/2}^2 * p*(1-p) / MOE^2$

P is the is the (estimated) proportion of the population, 40 %
N is population size (148)
Z2* p(1-p)/d2 (Cochran's formula) =0.9604

Subsequent patients fulfilling the inclusion criteria for the study and appearing for regular follow up at TASH GI referral clinic during the study period were given a chance to be included in the study. Those who consented to participate in the study were included. Only one patient had poor preparation on the initial appointment and didn't come back again.

Inclusion criteria

Age > 14 years

Idiopathic inflammatory bowel disease (IBD, UC or indeterminate colitis)

IBD patients on treatment for more than six months

Exclusion criteria

Radiation therapy in the past 2 years

Unsettled diagnosis

Patients who are unwilling to consent and /or undergo follow up colonoscopy

Pregnancy

Clinically unstable / Critical patients

Operational definitions

Inflammatory bowel disease: Diagnosis of Ulcerative colitis or Crohn's disease based on combined clinical, laboratory, imaging and endoscopic evidences.

Clinical remission: Resolution of rectal bleeding and diarrhea / altered bowel habit for ulcerative colitis and resolution of abdominal pain and diarrhea / altered bowel habit for Crohn's disease.

CDAI ≤ 150 or HBI ≤ 2 for CD, Partial Mayo score ≤ 2 for ulcerative colitis

Adherence: Adherence to treatment was defined as poor, intermediate and high depending on missed treatment during the previous months.

High adherence: Never or rarely misses treatment

Intermediate: Occasionally misses treatment

Low adherence: Frequently misses treatment.

Dose optimality: Optimal dose of Immuno-suppressive therapy: Decided by the investigator based on the dose of the drug, patient's weight, clinical activity of IBD and drug side effects

Endoscopic mucosal remission: Mayo endoscopic sub-score of 0 or 1 for ulcerative colitis and resolution of ulceration at ileo-colonoscopy for Crohn's disease (CDEIS < 6 or SES-CD <3), Rutgeerts' score i0 or i1 for post-operative patients on treatment.

Lymphopenia: Low lymphocyte counts on the most recent follow up defined as:

Mild Lymphopenia (850-1000/ul), Moderate Lymphopenia (500-850ul), Severe (<500ul)

Variables

Independent variables

- Sociodemographic variables

  Age, Sex, educational level, Income, Marital status, Residency, Health insurance

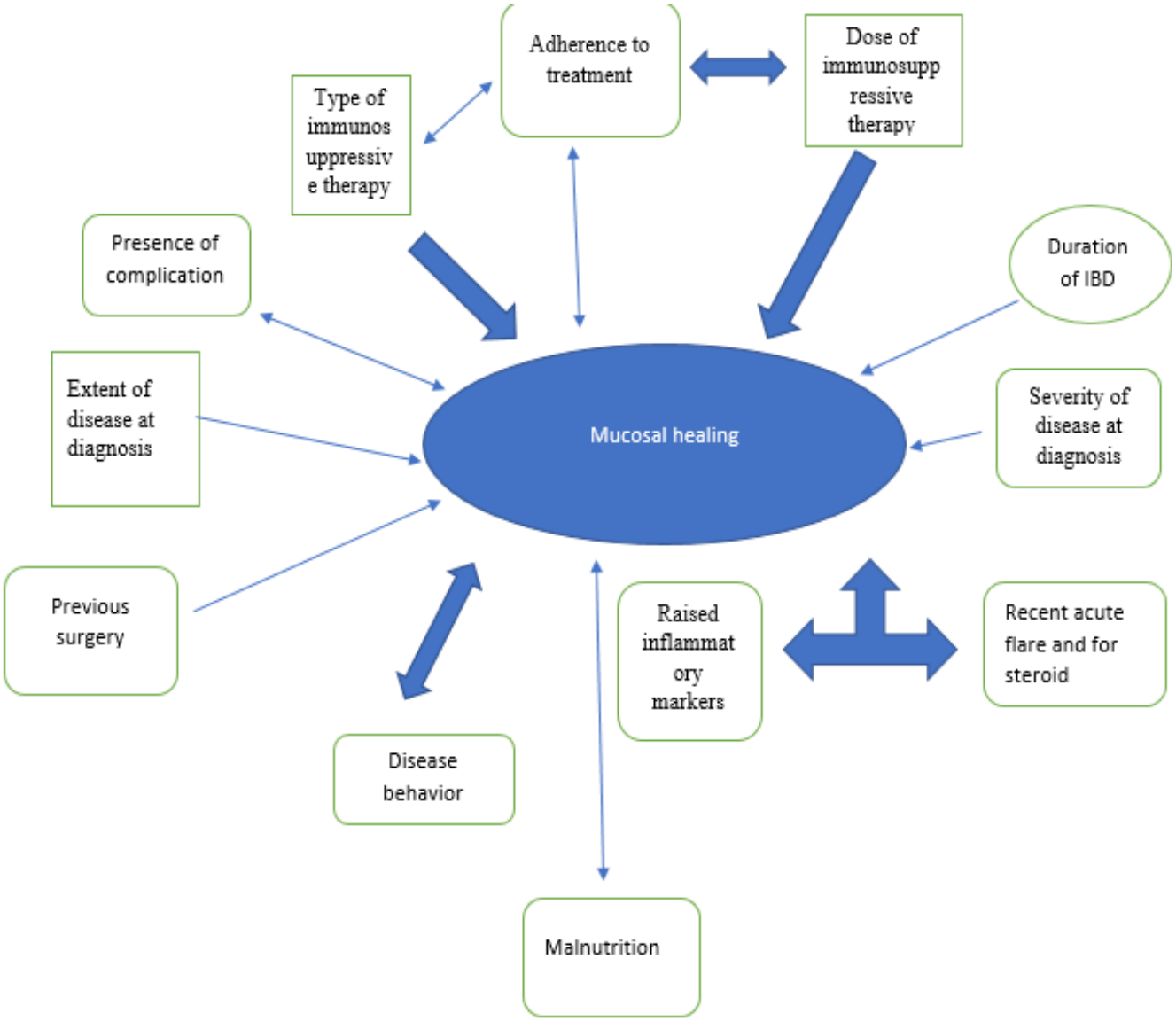
- Clinical variables

  Age at diagnosis
  Delay in diagnosis (duration gap between symptom onset and diagnosis)
  Nutritional status
  Type of IBD
  Extent of the disease at diagnosis
  Current activity of the disease (Clinical remission)
  Disease behavior (Phenotype) for CD (Stricturing, Fistulizing or inflammatory)
  Type of immunosuppressive medication
  Optimality of immunosuppressive therapy
  Adherence to medications
  Previous Intestinal surgery
  Presence of comorbidities
  Previous TB treatment after the onset of IBD symptoms
  Recent flare which needed steroid

Outcome variable

Endoscopic mucosal healing

Conceptual framework



Data collection procedure

Data collection instrument and process

Data was collected using a pretested structured questionnaire. The English version of the questionnaire was translated to Amharic version. The Amharic version was re-translated to the original English version by an independent person for checking uniformity. The Amharic version of the questionnaire was used for data collection from patients. Data collection was done by the principal investigator. Data regarding socio-demographic parameters, clinical parameters (including anthropometry, duration of illness, duration since diagnosis, activity of IBD, recent flares, extra-intestinal manifestations, medication adherence, side effects, comorbidities, previous TB treatment, previous surgery, IBD related complications and habits) were collected directly from the study participants on the date of follow-up colonoscopy. Additional data about the patient including type and classification of IBD, Immuno-suppressive drug type and dose, documented flare, drug side effects, complications related to IBD, extra-intestinal manifestations, previous surgeries related to IBD and laboratory data was retrieved from electronic medical record. Cross checking of data correctness made while interviewing the patient. Data for endoscopic healing was collected on the same day of the procedure.

Data management and analysis

After checking for completeness, data entry and analysis was made using SPSS software version 28. Both descriptive and analytic statistics was performed. After conducting binary logistic regression for each variable, those with significance < 0.2 were selected for multiple logistic regressions. P value less than 0.05 with 95% confidence interval was considered as significant association between the independent variables and the outcome variable (endoscopic healing).

Ethical Consideration

Ethical clearance was obtained from institutional review board of collage of Health sciences, Addis Ababa University, Department of Internal Medicine (Protocol number:50/23). Written informed consent obtained from each patient. All data collected was maintained confidential. Informed consent was obtained from parents or legal guardians for under ages.

Dissemination of results

The findings of this study will be used as an input for improving IBD patients care at the center and beyond. The generated evidence will also serve as an input in the academics to fill the local data gap in the field. The output of the study will be disseminated to Federal Ministry of health of Ethiopia, Teaching / referral Hospitals involved in the care of IBD patients. The findings of this study will be submitted on a peer reviewed journal for publication and will be presented on national and international conferences.

Results

One hundred six IBD patients who have been on treatment at least for six months were included in this study. From this C-sectional study the minimum age of the patient is 14 while the maximum is 60. The mean and median age are 30 and 32 respectively. Females accounted for 68% (n=72), with male to female ratio 1:2.1 with similar pattern between the two disease subtypes. Females predominate across all age category for CD. Eighty nine of the 106 patients (84%) are from urban areas. The Mean and median BMI of the study cohort are 20.65 and 20.20. The mean and median age at the diagnosis of IBD is 27.9 and 25.5 years respectively. The median duration from onset of symptoms to diagnosis is 24 months for UC and 18 months for CD with. (Mean 47 months for UC, and 35 months for CD, minimum 0 and max 300 months). Most patients have health insurance (n=74, 70%) but significant proportion of patients pay out of pocket for medications due to in availability of drugs at the Government centers (n=67, 63.2%). Only six patients (5.7 %, 5 with CD and one with Ulcerative colitis) reported positive family history of IBD (Table 1).

Most patients have Crohn's disease (n=87, 82%), Ulcerated colitis accounted for less than a quarter (n=17, 16%) UC and only two patients with Indeterminate colitis. Most patients with CD (n=75, 86.2%) were diagnosed in the age range 17- 40 Montreal classification A2. The leading phenotype (n=35, 33%) of CD according to this study is Stricturing (Montreal B2) type and ileocolonic disease (Montreal L3) is the commonest location (n=61, 57.5%). Most patients with CD (n=62, 69.7%) were in clinical remission according to HBI or CDAI. Twenty-six of the 32 IBD patients who had bowel resection were in clinical remission (81.2%). Most patients with ulcerative colitis presented in the age category 18-30 years, most (n=9, 52.9%) have extensive colitis and significant proportion were in clinical remission (n=7, 41.2%). Both patients with unclassified IBD (overlapping clinical, endoscopic and histologic features) have colonic disease one with severe disease activity and the other with mild disease activity. Thirteen (12.3%) IBD patients had extra-intestinal manifestations of IBD at some point during the course of the disease. Arthropathy is the commonest extra-intestinal manifestation (n=11, 85%). Fourteen patients with CD (16.1%) have Peri-anal fistula and 3 had upper GI involvement. One of the three CD patients with upper GI involvement had bypass surgery for GOO resulting from a polypoid obstructive mass which revealed CD on histopathology while the other two had H-pylori negative gastro-duodenopathy. Forty-four CD patients (41.5%) had some form of surgery related to IBD, 32 (30%) had bowel resection surgery. Among those who had bowel resection, most were in clinical remission (26/32, 81.25%). Fifty IBD patients (47.2%) had some form of complications related to IBD (history and /or electronic medical record). Fistula and intestinal obstruction are the major type of complications. Thirty-three patients with CD (37.9%) had TB treatment history before the diagnosis of IBD and /or after symptom onset (Table 1).

Most patients (n=95, 89.6%) were taking Azathioprine as maintenance therapy. Most (n = 80 75.5%) were on optimal dose of immunosuppressive therapy. Sixteen patients (15%) were on steroid during the study time, but only 7 of the 16 patients had documented flare in the past 3

months. Significant proportion of patients (n=49 46.2%) had maintenance therapy related side effects (based on history and/or EMR). Only 19% had WBC < 4K (Leukopenia) but significant proportion had some form of lymphopenia (42.5%). Severe Lymphopenia (n=27,55%) is the commonest treatment related side effect followed by GI upset and Hepatotoxicity. Most maintenance related side effects were related with Azathioprine intake except for five patients (one 5- ASA related cytopenia, four MTX related side effects (cytopenia, GI, and alopecia). The shortest duration of maintenance therapy (AZA, S-ASA or MTX) from this study is 3 months (one patient) and the longest 180 months. Mean and median duration of treatment are 29.85 and 24 months respectively. Forty-four patients (41.5%) had maintenance therapy for 24-60 months. Twenty-one patients (19.8%) had poor adherence to adherence to treatment. Financial reason (medication expense) was the commonest cause for low adherence (71%). (Table 1).

Inflammatory markers were normal only in about 30 % of the patients. Among CD patients none with moderate or severe disease activity had normal CRP or ESR. Significant proportion of patients had some form of lymphopenia (n=46, 43.4%). Sixteen patients (15.1%) had anemia according to WHO criteria. In Fifty-four (51.4%) patients, RFT was not determined in the previous 6 months, but was normal in all whose RFT was determined (Table 1).

Thirty-five (33%) of IBD patients in the study achieved endoscopic healing. Twenty-six of the 87 (29.1 %) patients with CD (SES- 0 =14.5%, SES 0 /1= 29.1%), 8 of the 17 (47.1%) UC (Mayo-0 3, 17.6%, Mayo 0/1= 8, 47.1%) and one of the two with indeterminate colitis achieved endoscopic healing. The mean and median SES endoscopic score for those CD patients (n=55) without bowel resection is 5.8 and 5 respectively (Minimum 0 and maximum 35). Only 10 of the 32 CD patients with previous history of bowel resection achieved endoscopic healing. The exact timing of treatment initiation in relation to surgery was not assessed in our study, but some patients reported gap between surgical resection and initiation of medical therapy. Out of the 37 patients who were not in clinical remission, 8 had endoscopic healing (21.6%) and out of the 69 patients who were in clinical remission, 27 showed endoscopic healing (39.1%) (Table 1 and 2).

On bivariate analysis age at the diagnosis, duration between symptom onset and diagnosis, behavior of CD according to Montreal classification, CRP and ESR showed significant association with endoscopic healing. After checking and documenting absence of multicollinearity between ESR and CRP with variance inflation factor (VIF) of 1.18, multiple logistic regression carried out. Age at the diagnosis (P= 0.046, AOR 1.322 with 95% CI 1.005-1.739), and ESR (P=0.040, AOR 0.946 with 95% CI 0.898-0.997) showed significant association with absence of endoscopic healing (Table 3)

Table 1. Socio-demographic, clinical, laboratory and endoscopic profile

Variables	Category	Frequency	Percentage (%)
Residence	AA	80	75.5
	Oromia	16	15.1
	Amhara	6	5.7
	SNNP	3	2.8
Occupation	Private institution	31	29.2
	Government institution	14	13.2
	Student	20	18.9
	Unemployed	20	18.9
	House wife	20	18.9
	Farmer	1	.9
Gender	Female	72	67.9
	Male	34	32.1
Educational status	Unable to read and write	7	6.6
	Able to read and write	8	7.5
	Primary education	16	15.1
	Secondary education	25	23.6
	College level and above	50	47.2
Access to health care	Health insurance	7	6.6
	Out of pocket	32	30.2
	Both	67	63.2
BMI (kg/m2)	Normal (18.5-24.9)	62	58.5
	<18.5 Underweight	31	29.2
	25-30 Over weight	9	8.5
	>30 Obese	1	.9
IBD type	CD	87	82.1
	UC	17	16.0
	Unclassified	2	1.9
Age at Dx (Montreal)	A1 Age < = 16	4	4.6
	A2 Age 17-40	75	86.2
	A3 Age > 40	8	9.2
Location CD (Montreal)	L1 Ileal	23	26.4
	L2 Colonic	3	3.4
	Ileo-colonic	61	70.1
Behavior CD (Montreal)	B1 Non stricturing, non penetrating	30	34.5
	B2 Stricturing	35	40.2
	B3 Penetrating	22	25.3
Activity of CD HBI/CDAI	In remission	62	69.7
	Mild disease	16	18.0
	Moderate disease	8	9.0
	Severe disease	3	3.4
UC age at Dx	Age 18-30	10	58.8
	Age 31-50	7	41.2
UC Disease extent (Mayo)	E1 Proctitis	1	5.9
	E2 Left side colitis	7	41.2

	E3 Extensive colitis	9	52.9
Severity UC (Partial Mayo)	S0 In remission	7	41.2
	S1 Mild UC	5	29.4
	S2 Moderate UC	4	23.5
	Severe UC	1	5.9
Comorbidities	None	93	87.7
	DM	2	1.9
	HTN	4	3.8
	HIV	2	1.9
	Stroke	3	2.8
	Others	2	1.8
Extra- GI manifestation	None	93	87.7
	Arthropathy	12	11.4
	Pyoderma Gangrenosum	1	.9
Current medications	Azathioprine	83	78.3
	Prednsolone plus Azathioprine	12	11.3
	Others*	11	10.4
Dose Optimality	No	26	24.5
	Yes	80	75.5
Side effects	No	57	53.8
	Yes	49	46.2
Side effect types'	Lymphopenia	27	25.5
	Hepatotoxicity	5	4.7
	GI side effect	6	5.7
	Others	8	7.5
	Steroid related ¥	3	2.8
Duration of therapy	<12 months	34	32.1
	12-24 months	15	14.2
	24-60 months	44	41.5
	>60 months	13	12.3
Medication adherence	Low	21	19.8
	Medium	19	17.9
	High	66	62.3
Recent flare	None	90	84.9
	Yes	16	15.1
IBD related surgery	None	62	58.5
	Abscess drainage	4	3.8
	Bowel resection	32	30.2
	Fistula repair	1	.9
	Other / Unknown	7	6.6
IBD complications	None	56	52.8
	Fistula	23	21.6
	Peri-anal	14	13.2
	ECF	9	8.4
	Abscess	4	3.8
	Peritonitis / Perforation	3	2.8
	Intestinal obstruction	11	10.4
	Micronutrient deficiency	5	4.7
	Multiple complications	4	3.8

Previous TB treatment	None	73	68.9
	Yes	33	31.1
ESR	Normal	20	18.9
	Elevated	75	70.8
	Not done	11	10.4
CRP	Normal	28	26.4
	Elevated	34	32.1
	Not done	44	41.5
Lymphopenia	Normal (>1000)	59	55.7
	Mild (850-1000)	9	8.5
	Moderate (500-850)	27	25.5
	Severe (<500)	9	8.5
Anemia (WHO criteria)	No	89	84.0
	Yes	16	15.1
RFT	Normal	52	49.1
	Not done	54	50.9
Liver enzymes	Normal	87	82.1
	Elevated	2	1.9
	Not done	17	16.0
Endoscopic Healing	No	71	67.0
	Yes	35	33.0

*MTX PO 2 (1.9%), MTX SC/IM 2 (1.9%), 5-ASA 2 (1.9%), Pred plus 5-ASA 2 (1.9%), Prednisolone plus MTX (PO/P) 2 (1.9%), AZA + 5 ASA 1 (0.9%)

¥ Steroid use during the study period

'Only 19% had WBC < 4K (Leukopenia) but significant proportion had some form of lymphopenia (42.5%)

Table 2. Crosstabulation for endoscopic mucosal healing

Variables		Endoscopic healing		Total
		No	Yes	
Gender	Female	47	25	72
	Male	24	10	34
Residence	Urban	61	28	89
	Rural	10	7	17
Marital status	Single	41	11	52
	Married	28	22	50
	Divorced / Widowed	2	2	4
Educational status	Unable to read & write	3	4	7
	Able to read & write	2	6	8
	Primary education	13	3	16
	Secondary education	18	7	25
	College level & above	35	15	50
Access to health	Health insurance	3	4	7
	Out of pocket	22	10	32
	Both	46	21	67
BMI (kg/m2)	Normal (18.5-24.9)	35	27	62
	<18.5 Underweight	27	4	31
	25-30 Over weight	5	4	9
	>30 Obese	1	0	1
IBD type	CD	61	26	87
	UC	9	8	17
	Unclassified	1	1	2
CD age @ DX	A1 Age < = 16	4	0	4
	A2 Age 17-40	54	21	75
	A3 Age > 40	3	5	8
CD Location	L1 Ileal	14	9	23
	L2 Colonic	3	0	3
	Ileo-colonic	44	17	61
CD behavior	B1	16	14	30
	B2	30	5	35
	B3	15	7	22
CD activity	In remission	41	21	62
	Mild disease	12	3	15
	Moderate disease	6	2	8
	Severe disease	2	0	2
CD Fistula types	None	46	22	68
	Peri-anal	10	4	14
	ECF	6	3	9
CD with Upper GI	No	61	27	88
	Yes	1	2	3
UC age @ DX	Age 18-30	7	3	10
	Age 31-50	2	5	7
UC disease extent	E1 Proctitis	1	0	1

	E2 Left side colitis	2	5	7
	E3 Extensive colitis	6	3	9
UC Severity	S0, In remission	1	6	7
	S1 Mild UC	3	2	5
	S2 Moderate UC	4	0	4
	Severe UC	1	0	1
Clinical remission	No	29	8	37
	Yes	42	27	69
Medication	Azathioprine	56	27	83
	Pred + Azathioprine	6	6	12
	Others*	9	2	11
Dose optimality	No	19	7	26
	Yes	52	28	80
Side effect	No	39	18	57
	Yes	32	17	49
Duration of therapy	<12 months	22	12	34
	12-24 months	8	7	15
	24-60 months	33	11	44
	>60 months	8	5	13
Medication adherence	Low	16	5	21
	Medium	12	7	19
	High	43	23	66
Recent flare	None	60	30	90
	Yes	11	5	16
TB treatment	None	49	24	73
	Yes	22	11	33
CRP	Normal	17	11	28
	Elevated	29	5	34
	Not done	25	19	44
ESR	Normal	9	11	20
	Elevated	55	20	75
	Not done	7	4	11
Lymphopenia	None	40	19	59
	Mild Lymphopenia	5	4	9
	Moderate Lymphopenia	20	7	27
	Severe	6	3	9
Anemia	No	56	33	89
	Yes	15	1	16

*MTX PO 2 (1.9%), MTX SC/IM 2 (1.9%), 5-ASA 2 (1.9%), Pred plus 5-ASA 2 (1.9%), Prednisolone plus MTX (PO/P) 2 (1.9%), AZA + 5 ASA 1 (0.9%)

Table 3. Multivariable binary logistic regression for endoscopic mucosal healing

Variable	Category	P- Value	COR (95% CI)	P value	AOR (95% CI)
Residence		0.44			
	Urban		0.66 (0.23-1.9)		
	Rural		1		
Educational status		0.075		0.5	
	Unable to R/W		3 (0.6-15)		
	Able to R/W		7 (1.2-38)		0.331 (0.000-)
	Primary		0.54(0.1-2.1)		0.114 (0 .004-3.718)
	Secondary		0.9 (0.3-2.6)		2.236 (0.122-41.115)
	College		1		
Access to health		0.4			
	Insured		2.9 (0.6-14)		
	Out of pocket		0.9 (0.4-2.4)		
	Both		1		
Age at diagnosis	-	0.01	1.1 (1.01-1.11)	0.046*	1.322 (1.005-1.739)
Gap in diagnosis		0.02	1.01 (1.002-1.0022)	0.567	0.991 (.963-1.021)
IBD type		0.35			
	CD		1		
	UC		0.4 (0.3-7)		
	Unclassified		0.8 (0.4-16)		
Location CD		0.6			
	L1		1.6 (0.6-4)		
	L2		0		
	L3		0		
	L4		1		
Behavior CD		0.02		0.17	
	B1		1		
	B2		1.9 0.6-6)		4.678 (0.176-124)
	B3		0.4 (0.11-1.3)		0.050 (0.01-2.2)
CD activity		0.7			
	Remission		1		
	Mild		1.02 (0.08-11)		
	Moderate		0.4 (0.03-6)		
	Severe		0.6 (0.37-11)		
UC Extent		0.34			
	E1		1		
	E2		0 (0.0-)		
	E3		5 (0.6-42)		
Severity of UC		0.5			
	In remission		1		
	Mild		969284….		
	Moderate		107698…		
	Severe		1		
Dose optimality		0.5			
	No		1		
	Yes		0.7(0.3-1.8)		
Duration of therapy		0.96	1		

Medication adherence		0.6			
	Low		1		
	Medium		0.5 (0.2-1.7)		
	High		1.1 (0.4-3.1)		
Recent flare		0.87			
	No		1		
	Yes		1.1 (0.35-3.4)		
IBD related surgery		0.94			
	No		1		
	Yes		1		
IBD- complications		0.96			
	No		1		
	Yes		1		
TB treatment		0.96			
	No		1		
	Yes		0.98 (0.4-2)		
CRP		0.05	0.72 (0.52-0.999)	0.12	0.346 (0.09-1.354)
ESR		0.009	0.98(0.96-0.99)	0.040*	0.946 (0.898-0.997)

*P < 0.05

Discussion

Similar to previous studies from Ethiopia and current evidences for sub-Saharan Africa, CD predominates the cohort of IBD patients as compared to UC (82% vs 16%). Beside the significant geographic variation, this study is an institution-based C-sectional study, hence might not show the true proportion of IBD types in the community. Even though there is a significant geographic variation in epidemiology, consistent with most evidences from developed nation, Females predominate the IBD-CD patients. Similar trends have recently been seen for CD in developing nations. Most of the patients in this C-sectional study are from Urban setting and only 6% patients had positive family history of IBD. The leading phenotype of CD in this study is Stricturing type (B2 n=35, 33%), with ileocolonic disease (L3, n=61, 57.5%) as the commonest location. This finding is similar to most studies from Indian subcontinent. The higher number of complicated CD (stricturing type) might be related to genetic factors and longer duration of illness before presentation. Similar to the studies from Australia and India, most patients with ulcerative colitis (n=9, 52.9%) have pan-colitis.(45-51)

The median duration between onset of symptoms and diagnosis is 24 months, which is longer than the duration from Multicenter Asian ACCESS study (median 5.5 months) and significant proportion of IBD patients in this cohort (37.9%) received treatment for intestinal TB, reveling the longer duration of illness before the diagnosis and the challenges in IBD diagnosis. This may partly explain the higher proportion of complicated cases among IBD-CD patients in the cohort.(47, 49, 52, 53)

The overall clinical remission rate of IBD patient from this study is 65%, lower than previous study done by Neway et al. who reported overall remission rate of 81.5%. This could be related with the deference in the study design. The clinical remission rate from our study is closer to other retrospective study done in Portugal by Leite S et al, which included 30 IBD patients treated with Azathioprine and reported a clinical remission rate of 75%. Nearly 70 % of CD (n=62,69.7%) and 81.25 % of those who had bowel resection were in clinical remission. A systematic review done by L. Peyrin-Biroulet & M. Le´mann showed maintenance of remission was reported in 71% (range, 56–95%) of CD patients on Azathioprine. This finding is higher than a single center 30-year retrospective study by Fraser et al. at the oxford IBD center, which showed a remission rate of 45% for CD and Single centered Indian study by RV Yewale et al. who found out overall remission rate 49.7%. This study found a lower clinical remission rate among Ulcerative colitis (7/17, 41.2%) as compared to other studies which used similar drug regimen. The relatively higher rate of endoscopic remission among UC patients (10/17, 58.8%) will lead us to the conclusion that some of the patients with UC not in clinical remission but with endoscopic remission may have symptoms not related to the inflammatory process of UC. The lower rate of overall clinical remission rate in this study as compared to recent prospective studies and randomized trials is likely related to the lower efficacy of the drug regimens used in this study.(22, 54-59)

Twenty six of the 87 (29.1 %) patients with CD (SES- 0 =14.5%, SES 0 /1= 29.1) achieved Endoscopic healing. Mantzaris et al randomized steroid dependent CD patients to Azathioprine or Budesonide. Twenty-five of 30 (83%) AZA treated patients achieved complete (n =22) or near-complete (n = 3) endoscopic / mucosal healing at one year. In contrary to other studies, Mantzaris and his colleagues found exceptionally high (83%) endoscopic healing rate but the study excluded patients left-sided colonic CD, fibrostenotic or fistulizing CD, and patients with prior intestinal resection. A prospective study from the GETAID designed to assess the long-term outcome after AZA withdrawal in patients with CD, a subgroup of 45 patients underwent endoscopic evaluation as secondary endpoint. Complete healing (CDEIS) = 0, was observed 16 of 45 patients (36%) which is higher than the finding from our study (14.5%). In the secondary end point of the SONIC trial which included, 508 adult patients with moderate to severe CD, only 16% of those patients receiving AZA alone achieved mucosal healing (the absence of mucosal ulceration at the week 26 ileo-colonoscopy in a patient who had evidence of ulceration at the baseline ileo-colonoscopy). This is comparable to our finding (SES-0, 14.5%). Even though there is variation in the study design and drugs used, endoscopic remission among IBD - CD patients is comparable to the first randomized trial with primary end point of mucosal healing (The EXTEND trial) which assessed the efficacy of ADA in moderate to severe ileo-colonic and found that a MH rate of 24.2% among patients receiving ADA.(31-33, 38)

Only 10 of the 32 CD (31.25%) patients with previous history of bowel resection achieved endoscopic healing (81.25% 26/32 were in clinical remission). The rate of endoscopic healing in this study is lower than older study by D'haens et al,1997. D'haens and his colleagues prospectively studied 19 postoperative severe recurrent CD patients on Azathioprine for more than 6 months and endoscopic healing was assessed using Rutgeerts' score and they found out that 40% (6/15) achieved endoscopic healing. The smaller sample size D'haens et al (n=19) as compared to the subgroup of postoperative CD patients (n=32) in our study may explain the difference in healing rate. Another prospective study by Dome`nech et al showed an endoscopic healing rate similar to our study. Among 56 post-operative CD patients who were initiated on Azathioprine immediately following resection, 29.1% achieved endoscopic healing (absence of endoscopic recurrence) after a median duration of 12 months. Azzam, et al. showed a relatively higher rate of endoscopic remission (76.2%) at 24 months postoperatively among 105 Post operative CD patients (41.9% on biological, and 34.3% were on non-biological therapy, mainly azathioprine) defined by Rutgerts score i 0 or i 1. The retrospective nature of the study by Azzam, et al. limits its generalizability. The exact timing of treatment initiation in relation to surgery was not assessed in our study but some patients reported gap in medical treatment initiation following surgery which limits the efficacy of medical therapy in prevention of post-operative recurrence.(30, 60-62)

In our study, eight of the seventeen ulcerative colitis patients (47.1%) achieved endoscopic mucosal healing using a Mayo endoscopic score of ≤1 which is in line with most available evidences. Complete healing, Mayo= 0 was achieved in only 3 patients (17.6%,) which is lower than the report in other studies. Basaranoglu et al retrospectively analyzed endoscopic mucosal healing rate of 120 IBD patients (45 with chronic ulcerative colitis) from Turkey treated with Azathioprine (EMH defined as the absence of ulceration and active inflammation by visual assessment). Minimum duration of Azathioprine treatment in the study was 4 months. Basaranoglu and his colleagues reported an endoscopic mucosal healing rate of 42% among UC patients which is closer to the healing rate from our study. The ACT 1 and ACT 2 trials investigated the role of IFX in achieving mucosal healing as a secondary outcome in patients with moderate to severe UC. MH was defined as a Mayo endoscopic sub-score ≤ 1. At week 30 the rates of MH were approximately 50% in the treatment arm; at week 54 (ACT 1 trial) the MH rates were in the treatment arm was 46% respectively. Considering a stricter definition of MH (Mayo sub-score = 0) the percentage of patients achieving MH in the IFX group at weeks 30 and 54 were 30%, and 33%. A recent Korean multicenter prospective study among moderate to severe ulcerative colitis patient treated with Adalimumab (Seung Yong Shin, et al) reported a lower mucosal healing rate of 30.1 % but unlike our study the Korean multicenter study excluded patients with mild ulcerative colitis.(27, 63, 64)

In line with the current available evidence our study revealed that clinical remission doesn't predict endoscopic healing (P=0.7 for CD and 0.5 for UC). In this study younger age at diagnosis (P=0.046, AOR =1.322, CI 1.005-1.739) and elevated ESR (P=0.040, AOR 0.946, CI 0.898-0.997) predicted absence of endoscopic healing among IBD patients on treatment for more than six months. In our study ESR is correlated with endoscopic healing but not CRP, this could be due to the fact that 44(41.5%) patients didn't have CRP determined during the study but most 95(89.6%) patients have ESR value determined. Similar to the finding from our study Basaranoglu et al found young age at diagnosis as a poor predicter of mucosal healing. A prospective multicenter study from Asia by C. M. Leung et al among 433 ulcerative colitis found that elevated ESR predicted less likelihood of mucosal healing at one year.(20, 21, 63, 65, 66)

Conclusion

Among 106 IBD patients on treatment for at least 6 months in our center 65% (70% for CD and 41.2% for UC) achieved clinical remission and 33% (29.1% for CD and 47.1% for UC) achieved endoscopic features of mucosal healing during the study period. Clinical remission did not match with endoscopic mucosal healing, as only 39% of those in clinical remission had demonstrated mucosal healing, while 21.6% among those in clinical remissions had active mucosal lesions on colonoscopy. Elevated ESR and younger age at the diagnosis predicted absence of endoscopic healing.

Recommendation

To clinicians:

1. There is a poor correlation between clinical remission and endoscopic healing among IBD patients, hence colonoscopy should be included in the routine care of IBD patients follow up.
2. Elevated ESR and young age at the diagnosis predicted absence of endoscopic healing, hence a due attention and treatment adjustment is required for such group of IBD patients.
3. Sixteen patients (15%) were on steroid during the study time, but only 7 of the 16 patients had documented flare in the previous 3 months. Hence continuation of steroid in the absence of acute flare beyond the induction period should be discouraged.
4. Even though most IBD patients were on Azathioprine as maintenance therapy (78.3%), RFT was determined in less than half of the patients and Liver enzymes were not followed in 17% of patients in the prior six months before the C-sectional study. As per the recommendation from most guidelines RFT and LFT should be determined at least every 3 months.
5. Significant proportion of patients with normal WBC count (31.6%) has some form of lymphopenia, in addition to total WBC count, absolute lymphocyte count should be taken in to account in adjusting doses of thiopurines

To Federal Ministry of health, Ethiopia:

1. The median duration of illness before diagnosis from this study is 24 months, this probably has contributed for higher proportion of complicated CD patient (65.5%) in the study cohort. MoH should work in creating public awareness about IBD using different mass media platforms and training of low-level health professionals about IBD.
2. MoH should work in collaboration with other partners to avail drugs for IBD therapy at affordable cost. Twenty percent of patients in the study had poor adherence to treatment and most mentioned drug cost and non-availability as a reason for poor adherence. Even though significant proportion of patients have health insurance (70%), most pay out of pocket for drugs due to unavailability of the drugs in the Hospital / Government owned pharmacies.

To researchers:

As this study is a single center (referral center) study with possible socio-referral bias, a multi-center study with larger sample size recommended to see the true proportion of patients in clinical remission, endoscopic healing and predictors. Inclusion of histology for deep remission and assessing the role of imaging studies as a predictor of endoscopic healing would be of a paramount advantage.

Strength and limitations of the study

To the best of our knowledge, this is the first C- sectional study at TASH specifically and in the whole country at large, involving a relatively large cohort of IBD patients. Moreover, this study prospectively looked in to clinical remission and endoscopic healing rates. Our study is a reflection of real-world clinical practice without Intervention but we acknowledge that it has the following limitations:

1. IBD has a variable clinical course, hence a one-time clinical remission by C- sectional study may not truly show the real picture of disease activity.
2. The scoring systems validated for IBD clinical activity including the ones used in this study might miss a significant proportion of patients who have true disease activity. In our study most of the CD patients have structuring type disease (40.2%), in the presence of moderate severity of abdominal pain, they may be mislabeled as being in remission while abdominal pain being the sole (predominant) manifestation of disease.
3. The follow up colonoscopies for mucosal healing assessment were done by different physicians and there was no independent reviewer. Though less likely to affect the overall endoscopic healing rate, there could be an interobserver difference scoring.

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Annex

Figures

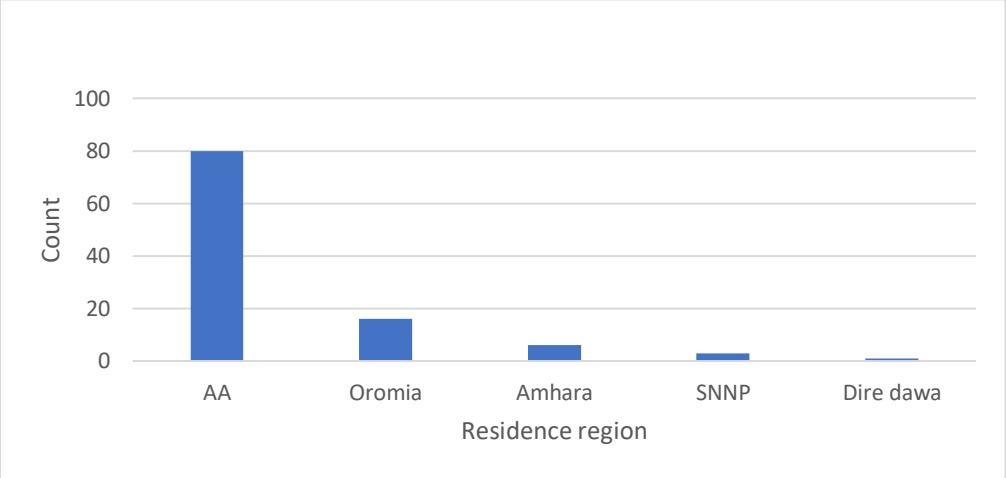

Figure 1: Residence of patients

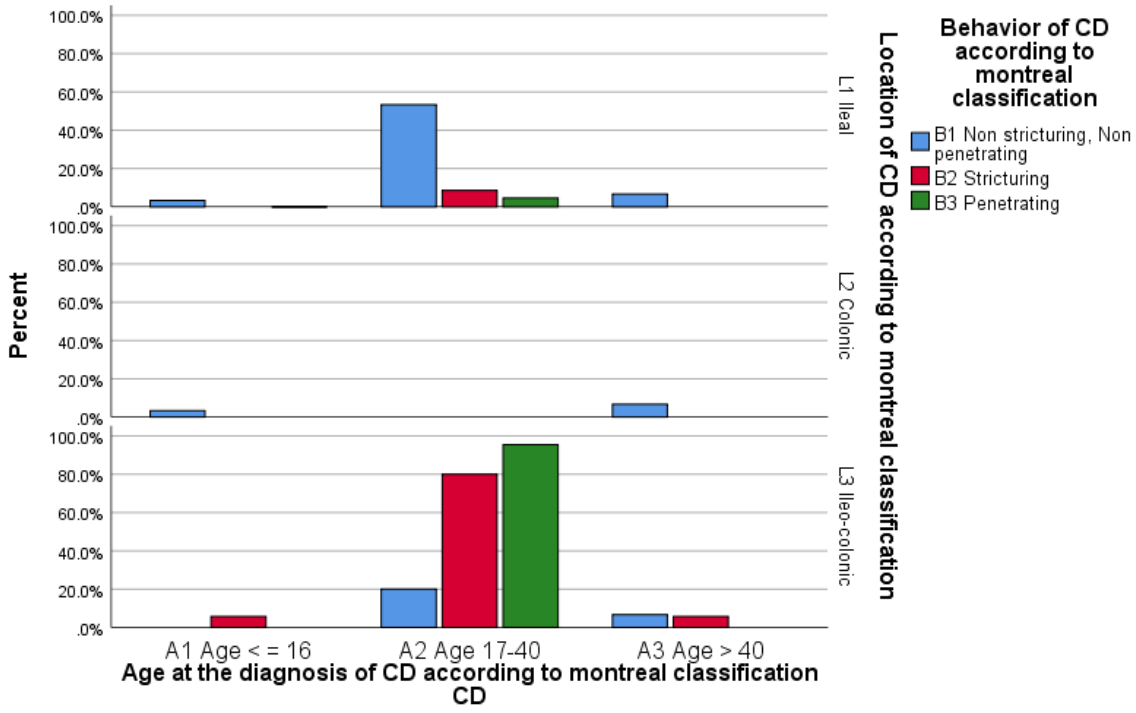

Figure 2: Montreal classification of CD

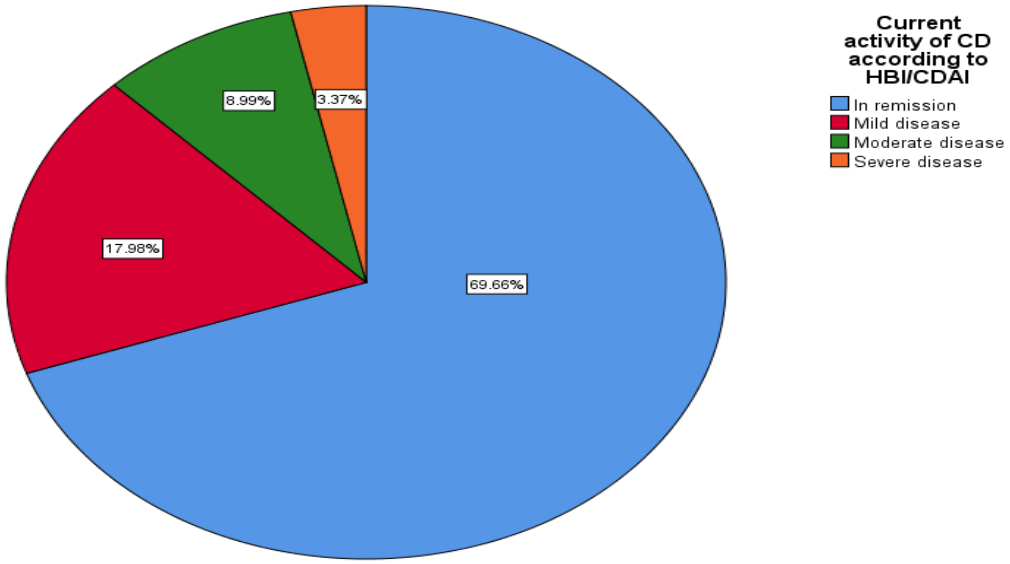

Figure 3: Activity of CD according to HBI/CDAI

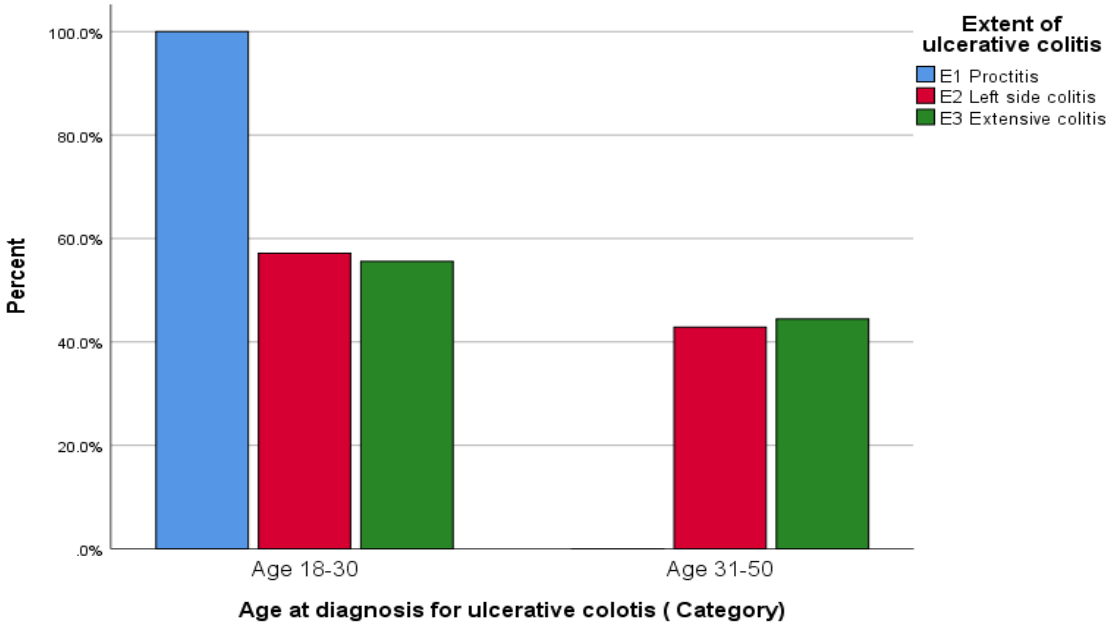

Figure 4: Extent of Ulcerative colitis in the age category

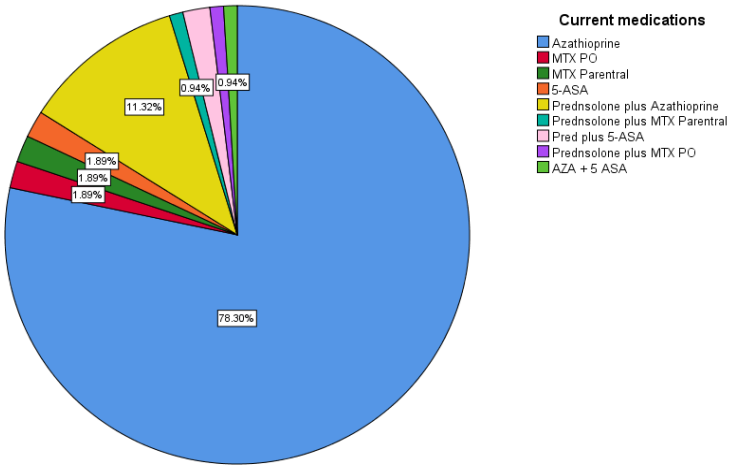

Figure 5: Medications used for IBD maintenance therapy

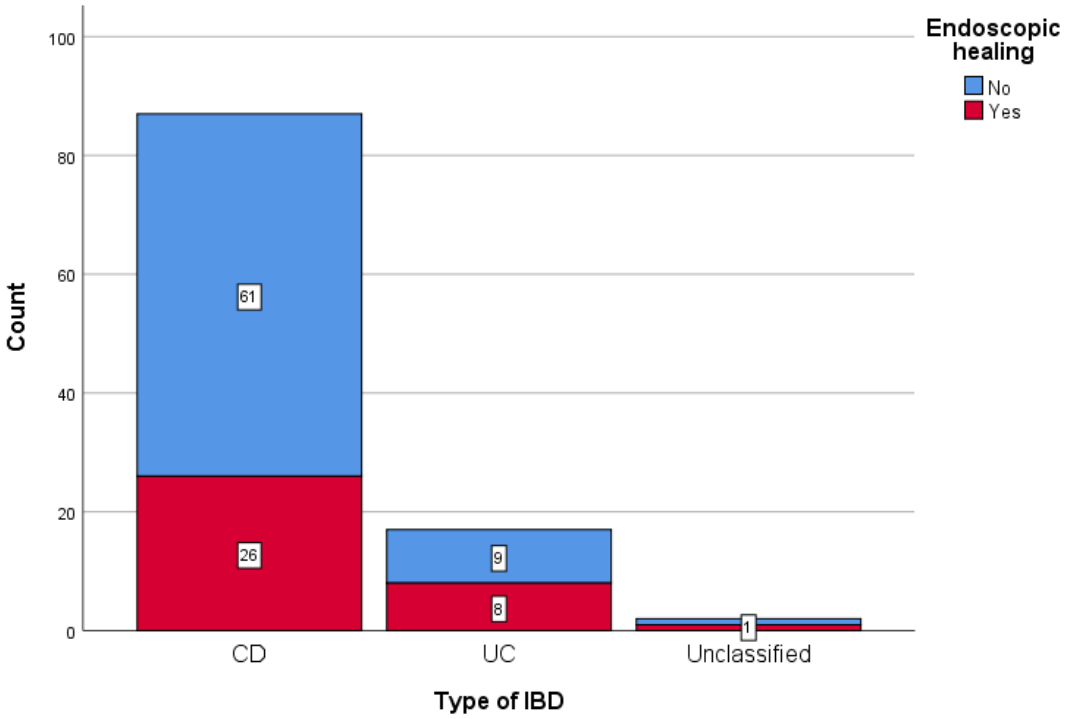

Figure 6: IBD subtypes and Endoscopic healing

Consent (English version)

I am Dr. Habtewold Shibru, Gastroenterology and Hepatology fellow at Addis Ababa University, college of health sciences. I am doing research on Inflammatory bowel disease titled rate and predictors of mucosal healing among IBD patients. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

This consent form may contain words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask f me.

This research is being done to fill the gap in knowledge about mucosal healing IBD patients in Ethiopia and improve patient care subsequently based on the findings of the research.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. If you choose not to participate all the services you receive at this Centre will continue and nothing will change.
We are inviting you to take part in this research project. If you accept, you will be asked few questions related to your disease and your clinical, laboratory, imaging and endoscopic data's will be used for the research.
All the investigations you undergo (including the colonoscopy) are part of the routine standard of care for IBD patient. There will not be any diagnostic investigation or additional cost to be incurred on you for the study purpose.
There will be no direct benefit to you, but your participation in this research is likely improve the care of IBD patients in our country and adds significant knowledge.
I will not be sharing information about you to anyone outside of the research team. The information that we collect from this research project will be kept private. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study

Name and Signature of the participant ----------

Date ----------

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

Name and Signature of the researcher----------
Date ----------

Questionnaire (English version)

Questionnaire to assess rate and predictors of endoscopic mucosal healing among IBD patients at Tikur Anbessa Specialized Hospital: Institution based Prospective Cross-sectional study

Code _____

MRN_____

Study site_____

Part I: Sociodemographic parameters

1. Age in years /Sex ----------
2. Residency (please specify)
   A- Urban_____ B- Rural _____
3. Marital status
   A- Single B- Married C- Divorced / Separated
4. Educational Status
   A. No formal education B. Primary C. Secondary D. College and above
5. Occupation
   A- Student B- Unemployed C- Government employed C- Private institution D. Marchant
6. Average monthly income (birr) ----------
7. How do you access health service including costs for laboratory investigations and drug?
   A- Health insurance B- Out of pocket C. Both

Part III – Clinical parameters

8. Anthropometry
   Weight Height BMI MUAC
9. Age at the diagnosis of IBD _____
10. Duration of illness (in months) _____
11. Duration since diagnosis of IBD (in months) _____
12. Family history of IBD
    A. No B. Yes
13. If yes to no 12, degree of relation_____
14. Type of IBD
    A- CD B- UC C- Unclassified
15. If A to no 14, location of disease according to the Montreal classification
    A- L1 ileal B- L2 colonic C- L3 ileocolonic D- L4 Isolated upper

16. If A for no 14, behavior of the disease according to the Montreal classification?
    A- B1 non-stricturing, non-penetrating B - B2 stricturing
    B- B3 penetrating D- p perianal disease
17. If A to no 14, Current activity of the disease according to the Harvey-Bradshaw Index (HBI)/ CDAI
    A- In remission B- Mild disease C- Moderate disease D- Severe disease
18. If B to no 14, extent of ulcerative colitis according to the Montreal classification?
    A- E1 Proctitis B- E2 left side colitis C- E3 Extensive colitis
19. If B to no 14, Severity of Ulcerative colitis according to Partial Mayo Scoring Index?
    A- S0 In remission B- S1 Mild UC C- S2 Moderate UC D- Severe UC
20. Co-morbidities
    A. None
    B. DM
    C. HTN
    D. Inflammatory arthropathy
    E. HIV
    F. Stroke
    G. Cardiac disease
    H. Asthma
    I. COPD
    J. Other (specify) _____
21. Diagnosed extraintestinal manifestation of IBD
    A- None
    B- Iritis
    C- Episcleritis
    D- Keratoconjuctivitis
    E- Arthritis (specify type _____)
    F- Pyoderma gangrenosum
    G- Erythema nodosum
    H- PSC
    I- Other (specify) _____
22. Current medications
    A- Steroid Type_____ Dose/ Route_____ Duration_____
    B- Azathioprine / 5MP Dose _____Duration _____
    C- Methotrexate Dose_____ Route _____Duration _____
    D- 5-ASA Type_____ Dose ---------- Duration_____
    E- Biologic therapy (Specify drug type, dose and frequency and duration)
    F- Others – Specify
23. Is the dose of the immunosuppressive therapy optimal (weight based)
    A. No B. Yes
24. Immunosuppressive drug side effect experienced by the patient in the past 3 months
    A- No B- Yes (Specify)_____
25. Duration on immunosuppressive therapy (months) (excluding steroid) -------

26. Adherence of patient to IBD treatment?

Low adherence B- Medium adherence C- High adherence

27. If low adherence to treatment, reason for low adherence?

A. Drug interruptions due to financial reason
B. Drug side effects
C. Lack of knowledge about importance / benefits of adherence
D. Attitude related
E. Other reason (specify)

28. Does the patient have documented acute flare of disease and need for steroid in the past 3 months?

A- No B. Yes

29. . Does the patient have past surgery related to IBD (multiple selection possible)

A. None
B. Abscess drainage
C. Bowel resection
D. Fistula repair
E. Other (Specify)
F. Unknown Abdominal surgery

30. If previous bowel resection, did the patient receive post operative antibiotics to reduce post op recurrence

A. Yes B. No C. Unknown

31. Previously identified complications associated with IBD (multiple selections possible) ?

A. None B- Fistula -Type _____ C-Abscess
D- Peritonitis / Perforation
E- E. Intestinal obstruction
F- Malabsorption syndrome
G- Micronutrient deficiency (Specify) Other (specify) _____

32. Previous treatment for intestinal TB before the diagnosis of IBD?

A. No B. Yes

Part III. Endoscopic finding

33. According to the endoscopic finding, does the patient fulfil the criteria for mucosal healing?

A- No B- Yes

34. Colonoscopy finding (Major findings and conclusion)----------

Part IV - Miscellaneous

35. Smoking

A. Never B. Former C. Current

36. Alcohol use

A. Never B. Occasional C. Regular

37. Medications for other co-morbid conditions

A. No B. Yes (Please specify)

Part V Laboratory profile

CBC WBC (/ul) PLT (/ul) HGB (/ul)	
CRP (mg /dl)	
ESR (mg /dl)	
BUN (mg /dl)	
Creatinin mg /dl	
AST U/L	
ALT U/L	
Albumin gm/dl	
Fecal calprotectin	

Additional note:

Amharic version of consent and questionnaire

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Partial Mayo Scoring Index for Ulcerative Colitis Activity

1. Stool Frequency (based on the past 3 days)
   Normal number of stools = 0
   1-2 stools more than normal = 1
   3-4 stools more than normal= 2
   5 or more stools more than normal = 3
2. Rectal Bleeding (based on the past 3 days)
   No blood seen = 0
   Streaks of blood with stool less than half the time = 1
   Obvious blood with stool most of the time = 2
   Blood alone passed = 3
3. Physician's Global Assessment
   Normal = 0 Mild disease = 1
   Moderate disease= 2 Severe diseases = 3
   Total Partial Mayo Index Score

Remission = 0-1 Mild Disease = 2-4 Moderate Disease = 5-6 Severe Disease =7-9

Lewis JD et al, Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008 Dec;14(12):1660-6.

Harvey Bradshaw Index Assessment for Crohn's Disease Activity

1. General Well-being

Very well = 0 Slightly below Par = 1 Poor = 2 Very Poor = 3 Terrible = 4

2. Abdominal Pain

None = 0 Mild = 1 Moderate = 2 Severe = 3

3. Number of Liquid or Soft Stools per day
4. Additional Manifestations

None = 0 Arthalgia = 1 Uveitis = 1 Erythema Nodosum = 1 Aphthous ulcer = 1 Pyoderma gangrenosum = 1 Anal Fissure = 1 New Fistula = 1 Abscess = 1

Total Harvey Bradshaw

Remission = <5
Mild Disease = 5-7
Moderate Disease = 8-16
Severe Disease >16

Vermeire et al, Correlation Between the Crohn's Disease Activity and Harvey–Bradshaw Indices in Assessing Crohn's Disease Severity, *Clinical gastroenterology and hepatology* 2010;8:357–363

Simple endoscopic score for CD (SES-CD)

Variable	0	1	2	3
Ulcers	None	Aphthous ulcers (Diameter 0.1-0.5 cm)	Large ulcers (Diameter 0.5-2 cm)	Very large ulcers (Diameter >2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed

MH as the absence of macroscopic inflammation or a simple endoscopic score for CD (SES-CD) < 3 points

Koutroumpakis E, Katsanos KH. Implementation of the simple endoscopic activity score in crohn's disease. Saudi J Gastroenterol. 2016 May-Jun;22(3):183-91

Crohn's disease endoscopic index of severity (CDEIS)

	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	
Deep ulceration If present, score 12, If absent, score 0						**Total 1**
Superficial ulceration If present, score 6, If absent, score 0						**Total 2**
Surface involved by the disease measured in cm*						**Total 3**
Ulcerated surface measured in cm*						**Total 4**

Total 1 + Total 2 + Total 3 + Total 4 =	**A**
Number (n) of segments totally or partially explored (1-5) =	**n**
Total **A** divided by n =	**B**
Ulcerated Stenosis If present anywhere, score 3, If absent, score 0 =	**C**
Non-Ulcerated Stenosis If present anywhere, score 3, If absent, score 0 =	**D**
TOTAL B + C + D =	

Remission <3, Mild endoscopic activity 3-8, moderate endoscopic activity 9-12 Severe endoscopic activity >12, Mucosal healing 0, 1 ,2

Khanna R et al, Endoscopic scoring indices for evaluation of disease activity in Crohn's disease. Cochrane Database Syst Rev. 2016 Aug 8;2016(8)

The Mayo endoscopic sub-score (MES) for UC

Findings on endoscopy
0 = normal or inactive disease
1 = mild disease (erythema, decreased vascular pattern and mild friability)

2 = moderate disease (marked erythema, lack of vascular pattern, friability and erosions)
3 = severe disease (spontaneous bleeding and ulcerations)

MES mucosal healing 0 and 1

Triana Lobatón et al, The Modified Mayo Endoscopic Score (MMES): A New Index for the Assessment of Extension and Severity of Endoscopic Activity in Ulcerative Colitis Patients, *Journal of Crohn's and Colitis*, Volume 9, Issue 10, October 2015,

The ulcerative colitis endoscopic index of severity

Ulcerative Colitis Endoscopic Index of Severity - UCEIS
Vascular pattern
0 = normal - Normal vascular pattern with arborizations of capillaries clearly defined
1 = patchy obliteration - Patchy obliteration of vascular pattern
2 = obliterated - Complete loss of vascular pattern
Bleeding
0 = none - No visible blood
1 = mucosal - Spots or streaks of coagulated blood on the mucosa surface, which can be washed off
2 = luminal mild - Some free liquid blood in the lumen
3 = luminal moderate or severe - Frank blood in the lumen or visible oozing from the mucosa after washing or visible oozing from a hemorrhagic mucosa
Erosions and ulcers
0 = none - Normal mucosa, no visible ulcers or erosions
1 = erosions - small defects in the mucosa (5 mm), white or yellow, flat edge
2 = superficial ulcer - larger defects in the mucosa (>5 mm), discrete fibrin covered, remain superficial
3 = deep ulcer - Deeper excavated defects in the mucosa, with a slightly raised edge

UCEIS score of 0 or 1 for the definition of endoscopic remission, decrease in UCEIS ≥2 was used to define endoscopic response in UC

Travis SPL *et al*, Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) *Gut* 2012;**61:**535-542.

The Rutgeerts score

i0: no lesions;
i1: < 5 aphthous lesions;
i2: >5 aphthous lesions with normal mucosa between the lesions or skip areas of larger lesions;
i3: diffuse aphthous ileitis with diffusely inflamed mucosa;
i4: diffuse inflammation with already larger ulcers, nodules and/or narrowing.

Chongthammakun V, Fialho A, Fialho A, Lopez R, Shen B. Correlation of the Rutgeerts score and recurrence of Crohn's disease in patients with end ileostomy. Gastroenterol Rep (Oxf). 2017 Nov;5(4):271-276.