BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057214
Article Type:	Original research
Date Submitted by the Author:	08-Sep-2021
Complete List of Authors:	Abd El-Wahab, Ekram; Alexandria University High Institute of Public Health, Tropical Health Youssef , Ebtessam; Alexandria University High Institute of Public Health, Tropical Health Hassouna, Ehab; Alexandria Medical School, Internal Medicine
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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The relationship between *Helicobacter pylori* infection and inflammatory bowel diseases: A real-life observation

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Running title: Inflammatory bowel diseases and *Helicobacter pylori* infection

- **word count**: 4052

- **number of references**: 52

- **number of tables**: 5

- **number of figures** : 2

Abstract

Background: Numerous epidemiological studies have investigated the association between *Helicobacter pylori* (*H. pylori)* infection and inflammatory bowel disease (IBD) with various conflicting results.

Objective(s): To further explore the possible association between *H. pylori* infection and IBD and its impact on disease course.

Methods: We conducted a prospective observational study and enrolled a total of 182 IBD patients who were screened for *H. pylori* infection. All the participants were clinically evaluated at the initial visit and bimonthly for 3 months.

Results: Overall, 49.5% of IBD patients had evidence of *H. pylori* infection. The course did not differ significantly in relation to *H. pylori* infection or the IBD treatment option. In Cox regression analysis, adults in age groups 20 – <35 years and 35 – 55 years, high socioeconomic standard, daily intake of food rich in insoluble fibers, occasional intake of snacks between meals and eating four meals per day predicted IBD flare ($p < 0.05$). On the other hand, eating fruits and vegetables was strongly protective.

Conclusions: The association between IBD and the presence of *H. pylori* infection seems to be uncertain and remains to be explored considering specific environmental exposures that impact the development of the disease or its relapse.

Keywords: Inflammatory Bowel Disease; Crohn's disease; Ulcerative colitis; Helicobacter pylori

Article summary

Strengths and limitations of this study

- The relationship between *Helicobacter pylori* infection and inflammatory bowel diseases has been extensively studied
- No consensus on the impact of *H. pylori* infection on the course of inflammatory bowel diseases
- There is still much to be learned about the etiology of IBD and how specific exposures impact its course
- The causal relationship between H. *pylori* infection and IBD cannot be established through a non-controlled study and further large scale prospective clinical trials are needed.

Introduction

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic, disabling, and progressive disorders characterized by lifelong treatment and a significant growing global health burden (Ponder & Long, 2013). In recent decades, many developing countries have seen a dramatic rise in the incidence of IBD [1]. It is speculated that improved access to a cleaner environment and the resulting decreased incidence of common childhood infections may be contributing to this rise by altering susceptibility to certain diseases with an autoimmune component, such as IBD [2,3]. Thus, according to this speculation, microbial infections during childhood may protect from IBD. This rise may partially be accounted for by the implementation of improved diagnostic methods and heightened awareness of IBD.

Although the pathogenesis of IBD is unknown, it is thought to result from complex and unidentified interactions between environmental factors (such as infections, medicines, tobacco, food particles) and genetic factors of the host, resulting in abnormal and/or inappropriate immunological reactions to elements of the intestinal flora [4,5].

Helicobacter pylori (*H. pylori*) is believed to be present in the upper gastrointestinal tract of around 50 percent of the world's population. Of these, over 80 percent of cases are entirely without symptoms [6]. In Egypt, the prevalence mounts to 80% among the general population [7].

H. pylori can elicit a chronic systemic inflammatory response, which under certain conditions may trigger autoimmune reactions and may be implicated in the pathogenesis of autoimmune diseases. The inflammatory response of the gastric mucosa is mainly attributed to the stimulation of the host's immune system caused by the bacterium. This results in cell mediated immune response and elevated levels of cytokines. As a consequence, products of the local immune reactions may migrate to extra-gastric sites and this may explain the link between *H. pylori* infection and a variety of extra-gastric diseases, including autoimmune disorders [8].

Numerous studies have examined the association between *H. pylori* infection and IBD. However, the published literature is diverse [8,9]. Whether the link between *H. pylori* and IBD is coincidental, epiphenomenal or mechanistic remains uncertain. There are contradictory data regarding both the causative and the protective role of *H. pylori* infection against IBD [10-18].

Based on the potential protective role of *H. pylori* infection on IBD, it is suggested that *H. pylori* eradication treatment can impact IBD course and thus should be administered with caution although more prospective studies are needed [15].

IBD was found to be more prevalent in regions with lower rates of *H. pylori* colonization. There is a steady rise in the incidence of IBD in *H. pylori* endemic regions which may reflect the era of initiating anti-*H. pylori* therapy for peptic ulcer disease [12]. Furthermore, meta-analyses of relevant studies have reported that the prevalence of *H. pylori* infection is lower in patients with IBD compared to controls [8,9,12,18,19]. One study suggested that long-term treatment with sulphasalazine leads to eradication of *H. pylori* infection [20]. Although this has not been confirmed by other studies, evidence from most studies points to a protective role for this infection in the development of IBD [8,19].

With the advances in the understanding of the pathological mechanisms involved in IBD, new therapies have been proposed, with the most important development being the introduction of disease response modifiers, also known as biological agents. The latter includes anti-tumor necrosis factor (anti-TNFα), IL-1/IL-6 receptor antagonist and anti-CD20 antibody. They are generally well tolerated, but their use was found to be associated with adverse effects, including risks of infection and malignancies [21].

This prompted us to further analyze the association between *H. pylori* infection and the flare of IBD activity in a longitudinal study and to explore the possible impact of *H. pylori* infection on response to convectional versus biological treatment of IBD.

Methods

Study population and sampling

We conducted a prospective observational study at Alexandria University Student Hospital. This hospital is affiliated with Alexandria University in Egypt and is serving all students, faculty and staff members at Alexandria University. It has a total bed capacity of 1000 beds and comprises outpatient clinics and inpatient and emergency departments. We enrolled in the study adult patients with ages ≥ 18 years that were confirmed to have IBD [triphasic CT abdomen,

endoscopy/colonoscopy and fecal calprotectin] and have started IBD treatment [conventional or biological]. Patients having irritable bowel syndrome were excluded by applying Rome III criteria [22].

The treatment decision (standard vs biological) was made by clinicians at the Internal Medicine department of the University student hospital. The prescribed treatment is the standards of care adopted by the university hospital for treating IBD patients. Details of the treatment regimens and the parameters used for standard vs biological decision are described in File S1.

The percentage of *H. pylori* infection among IBD patients can reach 10.0% [19]. Since Egypt is endemic for *H. pylori* infection [7]. We assumed that this percentage could be higher. Using a using an alpha error of 0.05, a 95% confidence level, and a study power of 80%; the minimum required sample size was found to be 138 patients. However, we ultimately enrolled a total of 182 IBD patients. The sample size was calculated using Epi info 7 software. Confirmed IBD cases who accepted to participate in the study were consecutively enrolled until the required sample size was fulfilled. According to patient disposition depicted in Figure 1, the patients were assigned into two groups according to the prescribed treatment regimen (File S1): Group 1 comprised patients on conventional IBD treatment, whereas Group 2 included patients on biological IBD treatment.

To screen for *H. pylori* infection, all enrolled IBD patients were subjected to stool analysis to detect *H. pylori* antigen in stool using a commercially available enzyme immunoassay (EIA) kit [Foresight EIA test kit for qualitative and quantitative detection of *H. pylori* in the stool (ACON® laboratories, Inc. San Diego, USA)]. Accordingly, each of the assigned groups included IBD patients infected or not with *H. pylori*. IBD patients found positive for *H. pylori* were informed about their lab results. We did not start *H. pylori* eradication therapy during the study period. Instead, after the three months of follow up, IBD patients found positive for *H. pylori* were referred to a specialist for further evaluation and management of their case according to the adopted standard of care.

Patient and Public Involvement

We informed the patients about the aims and concerns of the study and how it will add to better understanding of the disease etiology and triggering factors, which was highly appreciated by the patients, and the patients were motivated to be a part of the cohort

intended for the long term follow-up by the clinicians. However, It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research. All the laboratory and clinical data were reported to the participants and we discussed the study findings in a simple language.

Assessments

Baseline evaluation included thorough history taking, full clinical examination and laboratory testing. A structured data collection form (File S2) was designed and used to collect the baseline data [sociodemograpgics, personal habits, lifestyle, physical activity and exercise, dietary habits and restrictions, family history, medical history, co-morbidities, medications] as well as clinical data [Disease onset, history of the present complaints, frequency and duration of the attacks, past and current IBD medications, history of switching therapeutic regimens, surgical interventions, complications] from each patient at the initial visit. History of *H. pylori* infection and receiving *H. pylori* eradication therapy during the past 12 months was also recorded. at each follow-up visit. All patients were followed bimonthly for three months (6 visits) during the period of IBD treatment. Patients were called weekly through their telephone numbers and were asked about the frequency, and severity of motions and if any side effects for the assigned treatment occurred during the previous week.

All the participants were clinically checked. Trained investigators assessed for blood pressure (BP) and performed the anthropometric measurements according to standard techniques [23-25]. Body mass index (BMI) was calculated according to the Quetelet's index: BMI = [weight (kg)/height^2 (m^2)]. At each follow-up visit all enrolled IBD patients were subjected to laboratory measurement of complete blood count (CBC), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), fasting blood glucose (FBG), and fecal calprotectin [26]. Imaging techniques including Triphasic CT and endoscopy/colonoscopy were done when indicated and their findings were recorded. Full length colonoscopy was performed for all patients, using Pentax colonoscopies. Colonoscopic biopsies were obtained from the rectal, sigmoid, descending, transverse, ascending colonic, and cecal mucosa of

each patient. Histological assessment of the degree of inflammation in CD and UC was evaluated according to the European consensus on the histopathology of inflammatory bowel disease [27].

The socioeconomic status of the enrolled IBD patients was calculated and categorized as high, middle, low and very low according to the modified social scoring of Fahmy and El-Sherbini [28].

Outcomes

The enrolled patients in each group were evaluated clinically every two weeks for a total period of 3 months to record potential improvement/flare of the IBD condition. The primary outcome of the study is the number of patients with IBD who achieved remission at the end of the follow-up period.

Statistical analysis

The collected data were reviewed for accuracy and integrity and fed into computer software. Data were analyzed using a statistical software package (IBM SPSS statistics for windows, version 21.0, Armonk, NY: IBM Corp., Released 2011). Continuous variables were presented as the mean ± standard deviation (SD). Categorical variables were expressed as numbers with proportions, n (%). Variables relevant to laboratory data were dichotomized according to prefixed cutoffs, taking into consideration the normal reference values. Student's *t*-test was performed to compare quantitative variables between two groups of normally distributed data. Chi Square (χ^2) test was performed to examine the association between qualitative variables. Fischer's Exact test with Yates Correction was used when cells were fewer than five. Repeated measures ANOVA was used to test the differences in means of quantitative variables measured at different time points. Multiple logistic regression analyses were conducted to identify independent risk factors of *H. Pylori* infection among IBD patients. Cox regression analysis (or proportional hazards regression) was used to investigating the effect of several variables upon the time a specified event takes to happen; thus to determine the factors associated with IBD flare/remission when testing variables that had statistically significant differences at significance levels <0.05 in the simple logistic regression analyses. Kaplan Meier analysis was used to determine the probability of recovery (improvement in IBD condition as the event-of-interest) considering the *H. pylori* infection status and treatment option given. Recovery

defined improvement in IBD status based on clinical and laboratory data, whereas censored defined lack of improvement or flare of the inflammatory condition. All the statistical analyses were conducted with two-tailed tests and statistically significant levels were determined as being <0.05.

Results

Sociodemographics and clinical characteristics of the study cohort

A total of 182 IBD patients [96 (52.7%) UC and 86 (47.3%) CD] were enrolled in the study, being more frequently male (51.7%), married (58.2%), urban residents (51.6%), possessing high literacy levels (76.9%), and non-smokers (82.4%). The average age was 27.0 ± 7.3 years with the majority being in the age group 20 – 35 years. Overall, normal BMI was a predominant feature among the study population (59.3%) while 31.9% were overweight. Other sociodemographic characteristics of the study participants are shown in (Table 1).

The study participants did not differ significantly in relation to their total physical activity score. However, IBD patients found free of *H. pylori* infection deemed to have a more favorable food habit score compared to IBD patients with *H. pylori* infection (12.2 ± 5.0 *vs* 10.7 ± 3.8 , $p = 0.018$) (Table S1)

Baseline clinical and laboratory findings of all IBD patients are demonstrated in Table S2. IBD patients with *H. pylori* infection had higher rates of abdominal pain, abdominal cramps, bloating, indigestion, flatulence, diarrhea, bleeding per rectum, fever, chills, infection, fatigue/lack of energy, sick leaves/absenteeism as well as higher mean CRP and ESR levels than those found free of *H. pylori* infection although the differences were not statistically significant. GIT endoscopy and colonoscopy for the enrolled patients proved to have features of CD and UC in the form of superficial ulcerations and mild infiltration.

H. pylori infection among IBD patients

We detected *H. pylori* infection in almost half (49.5%) of the enrolled IBD patients, being almost equally presented among UD [48 (50.0%)] and CD [42 (48.8%)] patients [OR (95% CI)= 1.05 (0.59 – 1.88)], although most of them (82.8%) admitted receiving *H. pylori* eradication therapy during

the past 12 months. The infection rate was highest (82.2%) among age group 20 – < 35 years (Table 1). In our logistic regression model, conventional treatment of IBD [OR 95% CI= 1.99 (1.03 – 3.85)], adults in age groups 20 – <35 years [OR 95% CI= 6.20 (1.74 – 22.12)] and 35 – 55 years [OR 95% CI= 11.1 (1.18 – 104.64)], and mixed food source [OR 95% CI= 3.12 (1.60 – 6.06)] predicted *H. pylori* infection in IBD patients (p <0.05) (Table 2).

Assessment of IBD improvement/flare in relation to *H. pylori* infection

The total symptom score as well as the levels of ESR, CRP, Hb and fecal calprotectin showed significant linear decline throughout the follow-up period in all IBD patients regardless of the status of *H. pylori infection* ($p < 0.05$). The other tested parameters (body weight, pulse, pulse pressure, WBCs, platelet count, and FBG) tended to fluctuate in values in a non-linear pattern although the levels were still within the normal ranges. Overall, the changes (effect size) were attributable to the effect of the time course since the pattern did not differ significantly in relation to *H. pylori* infection (Table 3 and Figure S1). Similar results were obtained in subgroup analysis considering the type of treatment given [conventional (Table S3 and Figure S1) or biological (Table S4 and Figure S1)].

Factors associated with improvement in IBD condition

In Cox regression analysis, adults in age groups 20 – <35 years [OR 95% CI= 6.20 (1.74 – 22.12)] and 35 – 55 years [OR 95% CI= 557.9 (17.4 – 17922.8)], high socioeconomic standard [OR 95% CI= 2.9 (1.11 – 7.8)], daily intake of food rich in fibres [OR 95% CI= 5.1 (1.32 – 19.5)], occasional intake of snacks between meals [OR 95% CI= 2.8 (2.5 – 70.5)], and eating four meals per day [OR 95% CI= 13.3 (1.03 – 7.7)] were significantly associated with IBD flare ($p < 0.05$). On the other hand, eating fruits and vegetables was protective against IBD flare (Table 4 and Table S5).

Probability of improvement in IBD condition in relation to *H. pylori* infection and IBD treatment option

Kaplan Meier analysis revealed that the probabilities of recovery among the IBD patients at 12 weeks of follow up were comparable when considering *H. pylori* infection status (0.793 in *H. pylori* negative *vs* 0.778 in *H. pylori* positive) or the IBD treatment option (0.811 conventional

therapy *vs* 0.750 in biological therapy). The number of people who recovered among *H. pylori* negative patients was almost equal to that in *H. pylori* positive patients. On the other hand, the proportion of recovered IBD patients under conventional therapy was relatively higher than those receiving biological therapy although the difference was not statistically significant. In total, 39 subjects did not recover until the end of the study. The Log Rank, Breslow and Tarone-Ware tests of equality of recovery did not differ significantly among the enrolled IBD patients in relation *H. pylori* infection status or the IBD treatment option ($p > 0.05$) (Table 5 and Figure 2).

Discussion

In recent decades, improving hygienic conditions and socioeconomic status have reduced *H. pylori* infection rates and this trend has concurrently been accompanied by an increased IBD incidence in most countries. However, the role of *H. pylori* in IBD remains unresolved yet [1,15,29]. Numerous studies have reported a lower *H. pylori* infection rate in patients with CD and/or UC than in non-IBD control individuals, although a small number of studies showed no significant association [8,9,12,19,29]. Recently, emerging epidemiologic studies and animal experiments revealed an inverse correlation between *H. pylori* infection and IBD onset, suggesting that *H. pylori* colonization exerts a special protective effect on autoimmune diseases [12,21].

In attempting to further explain the negative association between *H. pylori* infection and IBD, we enrolled in a longitudinal study IBD patients having or not *H. pylori* infection and observed the possible impact of *H. pylori* infection on response to convectional versus biological treatment of IBD.

In our IBD cohort, *H. pylori* was detected in almost half of the patients. These numbers are relatively low compared to the prevalence among the general population in Egypt where the disease tends to be endemic [30-33]. This supports previous reports of lower rates *H. pylori* of in IBD patients and suggests a possible link between *H. pylori* and IBD [8,19]. The rate *H. pylori* infection was significantly higher among IBD patients on conventional treatment which disagrees with studies suggesting that 5-aminosalicylates or sulphasalazine interfere with the adhesion of *H. pylori* to the mucosa and block its replication [20,34-36]. In fact, several studies did not support the aspect that as treatment with sulfasalazine or any other medical therapy such as 5-aminosalicylic acid (5-ASA),

thiopurines steroids, antibiotics had an influence on *H. pylori* colonization rate [12,37-39]. The same holds for novel therapeutic modalities, such as anti-tumor necrosis factor alpha (TNF-α) treatment [40].

In the present study, the majority of *H. pylori* positive IBD patients admitted receiving *H. pylori* eradication therapy in the past 2 months which brings into question the effectiveness of the eradication therapy in treated cases or highlights the occurrence of reinfection among this group of patients. It is noteworthy that most of the previous studies did not inquire into the participants' past history of treatment for *H. pylori* infection [12]. It is therefore possible that their IBD patients had been treated for *H. pylori* prior to enrollment in the study, thereby producing a falsely low *H. pylori* infection rate.

Accumulating evidence suggests that *H. pylori* through its immune regulation capacity protects human from various diseases with an auto-immune nature including IBD [41]. Such speculation has been explored in various studies and the results are controversial. Certainly, the heterogeneity among studies accounted for by methods of IBD and *H. pylori* diagnosis, study location, or study population and the possibility of publication bias limit the certainty of this conclusion and bring into question the robustness of their findings. We extended previous work by investigating the association between *H. pylori* infection and IBD disease from a different angle in a prospective study. A potential avenue for extending our study involved broadening the inclusion criteria to gain further insight into the local variation of the protective effects of *H. pylori* on IBD. Differing from previous studies, we added subgroup analysis on *H. pylori* infection and the type of IBD treatment. However, we did not observe a significant relationship between the existence of the two conditions. For instance, the course of the disease was similar in all IBD patients regardless of their *H. pylori* infection status or when considering the type of treatment given (conventional or biological). There also seemed a trend that the extent and severity of IBD increased with *H. pylori* infection decreasing. Intriguingly, the proportion of recovered IBD patients under conventional therapy was relatively higher than those receiving biological therapy. This might be ascribed to the higher *H. pylori* infection among IBD patients under conventional therapy or that patients receiving biological therapy are those who were refractory to previous conventional therapy, thus having a more severe disease activity. Although our

findings do not support the inverse association between *H. pylori* infection and IBD disease, they increase in some part the credibility of previous studies.

IBD is thought to be triggered by a complex interplay of environmental and genetic factors. The growing burden of IBD could be a proxy of the hygiene hypothesis and improved sanitary living conditions, lifestyle and dietary changes, more frequent antibiotic use, enhanced diagnostic methods and heightened awareness of IBD [42-44]. In this regard, we examined in addition to *H. pylori* infection the role of some host and environmental cofactors that have been reported as either alleviating or inciting factors for IBD flare. These included diet, smoking, physical activity, breastfeeding, socioeconomic standard, education, occupation, urban versus rural lifestyle, and exposure to medication [44]. In this context, we were guided by existing studies that recognized differences in potential risk factors or unique features to certain populations, such as the Mediterranean diet. Indeed, dietary factors play a crucial role in disease initiation or relapse [45], although certain diets, such as the Mediterranean diet, are purported to be protective of IBD [46-48]. The Mediterranean diet, plant-based diet and semi-vegetarian diet have been shown by some studies to alleviate symptoms of IBD and keep patients in remission potentially through reducing inflammation and improving microbiota [49,50]. In the present cohort, IBD patients negative for *H. pylori* infection and those experiencing less flare had a more favorable overall dietary habit score. In line with Kakodkar's recommendations [49], which encourage the consumption of all vegetables and fruits in an IBD diet, we observed a strong protective role for the daily as well as 2-3 times per week intake of vegetables and fruits on IBD flare. In a recent meta-analysis, the beneficial effect of *H. pylori* against IBD in Mediterranean populations was lower compared to East Asian and European regions [18]. Nevertheless, the included studies did not explicitly incorporate dietary information or study the putative beneficial effect of diet as a confounder in their analyses. Moreover, this positive effect could be attributed to the relative abundance of CagA *H. pylori* in these populations, a strain with specific constituents that modulate host immune defenses[51].

Fiber has a potential anti-inflammatory role in IBD, although a converse effect can occur [44]. Our cox regression model revealed that consumption of food rich in insoluble fibers such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs and

spices, on daily basis significantly increased the risk of IBD flare particularly in patients consuming four meals per day with occasional snacks between meals.

In agreement with Gentschew et al., [52] trans fat intake was also associated with higher odds of IBD flare although this did not appear in our final model. Although our findings might suggest a role for diet in IBD flare, the effect of diet is questionable due to limitations in terms of recall bias and multifactorial exposures. Moreover, IBD patients may alter their dietary habits based on the symptoms that vary with disease activity. This raises the need for further explicit research into the role of diet in IBD.

Variation in the protective effect of *H. pylori* on IBD could also be ascribed to socioeconomic factors. In the present study, IBD patients with higher socioeconomic standards who were mostly urban residents had a higher chance of disease flares. Importantly, *H. pylori* infection did not significantly vary in relation to the socioeconomic standard in our IBD cohort. These findings lend support to those factors associated with an urban lifestyle and industrialization can influence one's risk of IBD.

Furthermore, the rate of *H. pylori* gastric colonization was significantly higher in adults older than 20 years although there was no significant difference in the IBD average age of onset between positive and negative *H. pylori* groups. This age group has also higher disease flares. These findings are probably due to their co-morbid history or other aspects of their lifestyle or which affects IBD occurrence. Apart from the age, other demographic variables did not show any effects on our results.

Collectively, the association between IBD and the presence of *H. pylori* infection seems to be uncertain and remains to be explored. Looking forward, there is still much to be learned about the etiology of IBD and how specific environmental exposures intimately impact the development of disease and also the potential for relapse.

Study limitations

Several limitations of the current work should be listed. First, we did not test *H. pylori* in colon biopsy, which may decrease the disease prevalence rate. However, this would cause additional burdens of an invasive procedure to the patients which is against medical ethics. A urea breath test

would have been a better alternative, but we did not have access to it in our centers. Second, the small sample size was a major limitation and might have impacted the estimation of the effect size. Third, the trend of decreased *H. pylori* infection in patients under biological therapy thus paralleling with increased severity of IBD should be investigated in a larger randomized controlled trial for statistical significance. Also, our results merit reassessment in a cohort of patients from a background population with a low prevalence of *H pylori* and with explicit information about eradication treatment and exposure to other antibiotics. Finally, the causal relationship between *H. pylori* infection and IBD cannot be established through a non-controlled study and further large scale prospective clinical trials are needed. Towards this, studies investigating the effect of eradication of *H. pylori* on the development of IBD and considering environmental exposures, hygiene diet, physical activity and intestinal microbiota as strong confounders are warranted. An ideal study would be conducted at the time of IBD diagnosis and proceed prospectively.

Ethical consideration

The study was approved by the institutional review board and the ethics committee of the High Institute of Public Health affiliated with Alexandria University, Egypt [Ref no. 603 - 2019]. The study was conducted in accordance with the international ethical guidelines and that of the Declaration of Helsinki. Informed written consent was obtained from each participant after explaining the aim and concerns of the study. The datasheets were coded by number to ensure anonymity and confidentiality of the participants' data.

No field research was done, and this article does not contain any studies with animals performed by any of the authors.

Conflict of Interest

All authors declare no conflict of interest.

Data sharing statement

All data are fully available without restriction by the corresponding author at ekram.wassim@alexu.edu.eg

Funding: Authors' own work

Acknowledgements

We would like to acknowledge the study participants for accepting to participate in the study.

Author contribution

EWAW: Conceptualization, developed the theoretical framework and study design, took the lead for overall direction and planning of the study implementation, data curation, statistical analysis and interpretation of data, major contribution to writing, revised and approved final version of the manuscript

EIY: Study implementation and recruitment of the study participants, data collection, clinical evaluation and follow up, analysis and interpretation of data, contributed to the writing of the manuscript, revised and approved final version of the of the manuscript.

EMH: Supervised the study implementation and data collection, facilitated the recruitment of the study participants, clinical evaluation and follow up, data curation, contributed to the writing of the manuscript, revised and approved final version of the manuscript.

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Figure legend

Figure 1: Patients' disposition throughout the study

Figure 2: The equality of recovery (improvement in IBD condition) over the follow-up periods in relation to *H. pylori* infection status and the IBD treatment option

Figure S1: clinical and laboratory findings of IBD patients over the follow-up periods in relation to *H. pylori infection* status and the IBD treatment option

List of Tables

Table 1: Characteristic of the study population

		IBD patients		H pylori infection in IBD patients				*p*~
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.	%	
Type of IBD diagnosed	Crohn's disease	86	47.3	44	47.8	42	46.7	0.876
	Ulcerative colitis	96	52.7	48	52.2	48	53.3	
Onset of *H. pylori* infection	NA	92	50.5	92	100.0	0	0.0	<0.001
	Few weeks ago	7	3.8	0	0.0	7	7.8	
	3 – 6 months	10	5.5	0	0.0	10	11.1	
	6 months – 1 year	35	19.2	0	0.0	35	38.9	
	> 1 year	38	20.9	0	0.0	38	42.2	
History of receiving *H. pylori* eradication therapy during the past 12 months	No	92	50.5	92	100.0	0	0.0	0.000
	Yes	90	49.5	0	0.0	90	100.0	
Treatment option given	Conventional	106	58.2	47	51.1	59	65.6	0.048
	Biological	76	41.8	45	48.9	31	34.4	
Sex	Male	94	51.6	46	50.0	48	53.3	0.653
	Female	88	48.4	46	50.0	42	46.7	
Age (Years)	16 – <20 Years	20	11.0	15	16.3	5	5.6	0.036
	20 – <35 Years	136	74.7	62	67.4	74	82.2	
	35 – 55 Years	26	14.3	15	16.3	11	12.2	
Mean ± SD		27.0 ± 7.3		27.6 ± 8.0		26.3 ± 6.5		*t*=1.3, *p*= 0.204
Age at IBD diagnosis	10 – >19	69	37.9	35	38.0	34	37.8	0.211
	20 – <30	83	45.6	46	50.0	37	41.1	
	30 – 45	30	16.5	11	12.0	19	21.1	
Mean ± SD		21.6 ± 6.4		21.4 ± 6.3		22.0 ± 6.5		*t*= -0.583, *p*= 0.560

Residence	Rural	88	48.4	51	55.4	37	41.1	.053
	Urban	94	51.6	41	44.6	53	58.9	
Education	Illiterate	2	1.1	0	0.0	2	2.2	0.096
	Read and Write	23	12.6	12	13.0	11	12.2	
	Primary	4	2.2	4	4.3	0	0.0	
	Preparatory	13	7.1	9	9.8	4	4.4	
	Secondary	44	24.2	24	26.1	20	22.2	
	University education	96	52.7	43	46.7	53	58.9	
Working status	No	88	48.4	39	42.4	49	54.4	0.104
	Yes	94	51.6	53	57.6	41	45.6	
Occupation	Unemployed	37	20.3	21	22.8	16	17.8	0.012
	Student	45	24.7	16	17.4	29	32.2	
	Clerical	2	1.1	2	2.2	0	0.0	
	Professional	39	21.4	17	18.5	22	24.4	
	Housewife	21	11.5	10	10.9	11	12.2	
	Auxiliary worker	22	12.1	12	13.0	10	11.1	
	Farmer	16	8.8	14	15.2	2	2.2	
Marital status	Single	73	40.1	37	40.2	36	40.0	0.37
	Married	106	58.2	55	59.8	51	56.7	
	Widowed	2	1.1	0	0.0	2	2.2	
	Divorced	1	0.5	0	0.0	1	1.1	
Socioeconomic standard	High	58	31.9	24	26.1	34	37.8	0.206
	Middle	52	28.6	30	32.6	22	24.4	
	Low	72	39.6	38	41.3	34	37.8	
Consanguinity	No	144	79.1	70	76.1	74	82.2	0.309
	Yes	38	20.9	22	23.9	16	17.8	
History of being breastfed	No	26	14.3	14	15.2	12	13.3	0.716
	Yes	156	85.7	78	84.8	78	86.7	

Smoking	Never	150	82.4	75	81.5	75	83.3	0.724
	Current smoker	26	14.3	13	14.1	13	14.4	
	Ex-Smoker	6	3.3	4	4.3	2	2.2	
Age of starting Smoking	NA	153	84.1	77	83.7	76	84.4	0.655
	< 20 Years	17	9.3	10	10.9	7	7.8	
	20-30 Years	12	6.6	5	5.4	7	7.8	
	>30 Years	0	0.0	0	0.0	0	0.0	
Smoking other than cigarette	Never	180	98.9	90	97.8	90	100.0	0.160
	Shisha	2	1.1	2	2.2	0	0.0	
BMI categories	< 18.5 (underweight)	3	1.6	2	2.2	1	1.1	0.345
	18.5-24.99 (Normal weight)	108	59.3	58	63.0	50	55.6	
	25-29.99 (Overweight)	58	31.9	24	26.1	34	37.8	
	30-39.99 (Obese)	13	7.1	8	8.7	5	5.6	
Co-morbidities	No	82	45.1	43	46.7	39	43.3	0.644
	Yes	100	54.9	49	53.3	51	56.7	
	Diabetes Mellitus	10	5.5	4	4.3	6	6.7	
	Hypertension	30	16.5	15	16.3	15	16.7	
	Bronchial Asthma/COPD	15	8.2	11	12.0	4	4.4	
	Heart disease	1	0.5	0	0.0	1	1.1	
	Renal disease	1	0.5	1	1.1	0	0.0	
	Liver disease	1	0.5	0	0.0	1	1.1	
	Skin allergy	18	9.9	11	12.0	7	7.8	
	Hyperthyroidism	4	2.2	1	1.1	3	3.3	
	Hypothyroidism	8	4.4	0	0.0	8	8.9	
	Other autoimmune diseases	1	0.5	0	0.0	1	1.1	
	Others (Chronic sinusitis, vertigo, lumbar disc prolapse, familial dyslipidemia, hemorrhoids, scleritis, HCV, anemia, fatty liver, steatosis, psoriasis, peripheral neuropathy, chronic cholecystitis)	27	14.8	8	8.7	19	21.1	

Autoimmune diseases	No	163	89.6	85	92.4	78	86.7	0.207
	Yes	19	10.4	7	7.6	12	13.3	
Medications	None	13	7.1	12	13.0	1	1.1	0.002
	Analgesic (NSAIDs)	12	6.6	3	3.3	9	10.0	
	Antidiabetics	6	3.3	3	3.3	3	3.3	
	Antihypertensives	32	17.6	16	17.4	16	17.8	
	Corticosteroids	10	5.5	4	4.3	6	6.7	
	IBD therapy	151	83.0	70	76.1	81	90.0	
	Hormonal contraceptives	2	1.1	0	0.0	2	2.2	
	Thyroxin	9	4.9	2	2.2	7	7.8	
	Others	37	20.3	15	16.3	22	24.4	

~ *p value* for Chi Square test.
Significant at <0.05
IBD; inflammatory bowel disease
No history of alcohol or drug abuse was reported

Table 2: predictors of *H. pylori* infection in IBD patients

Backward Stepwise (Wald) Logistic Regression		B	S.E.	Wald	df	Sig. (*p* value)	Exp(B)	95.0% C.I. for EXP(B)	
								Lower Limit	Upper Limit
Step 5	Treatment of IBD								
	Biological treatment	-0.686	0.337	4.14	1	**0.042**	**0.50**	**0.26**	**0.98**
	Conventional treatment	0.686	0.337	4.14	1	**0.042**	**1.99**	**1.03**	**3.85**
	Age group (Years)								
	16 - <20			7.93	2	0.019			
	20 - <35	1.825	0.649	7.92	1	**0.005**	**6.20**	**1.74**	**22.12**
	35 - 55	2.408	1.144	4.43	1	**0.035**	**11.11**	**1.18**	**104.64**
	Food source								
	Homemade			11.48	2	0.003			
	Restaurant	-0.024	0.915	0.00	1	0.979	0.98	0.16	5.87
	Mixed	1.137	0.339	11.25	1	**0.001**	**3.12**	**1.60**	**6.06**
	Constant	0.108	1.015	0.01	1	0.915	1.11		

p value significate at <0.05
IBD; inflammatory bowel disease

Parameter	*H. pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA												
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects						Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12														
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	34.6 ± 13.2	30.5 ± 10.9	27.0 ± 10.3	24.2 ± 8.9	20.6 ± 27.3	17.3 ± 6.9	14.0 ± 5.3	T	96.93	<0.001	0.769	1.000	T	350.0	<0.001	0.660	570.0	<0.001	1.75	0.188	0.010
	Negative	33.6 ± 14.1	29.1 ± 11.3	25.2 ± 9.4	21.4 ± 8.6	19.2 ± 6.9	15.9 ± 5.3	13.0 ± 4.9	T × S	1.156	0.322	0.038	0.448	T × S	0.666	0.538	0.004	0.001	0.974			
CRP	Positive	33.0 ± 23.0	26.4 ± 18.4	22.8 ± 16.1	18.9 ± 13.0	15.1 ± 9.7	12.5 ± 6.9	10.1 ± 7.2	T	31.74	<0.001	0.521	1.000	T	152.0	<0.001	0.458	181.4	<0.001	2.59	0.109	0.014
	Negative	28.2 ± 23.9	22.9 ± 19.5	19.0 ± 15.4	15.9 ± 12.7	13.0 ± 9.4	10.6 ± 6.8	8.2 ± 4.5	T × S	0.708	0.644	0.024	0.276	T × S	0.788	0.418	0.004	0.848	0.358			
FBG	Positive	94.9 ± 11.1	93.0 ± 10.6	91.6 ± 9.8	94.4 ± 11.5	92.1 ± 9.5	94.5 ± 14.1	93.7 ± 9.0	T	3.52	0.003	0.108	0.945	T	2.77	0.016	0.015	2.753	0.11	0.974	0.325	0.005
	Negative	96.1 ± 11.6	93.0 ± 10.6	95.1 ± 9.3	96.0 ± 13.1	93.7 ± 9.7	92.9 ± 10.4	95.1 ± 8.4	T × S	1.48	0.187	0.048	0.565	T × S	1.56	0.168	0.009	0.443	0.507			
Calprotectin	Positive	515.0 ± 206.7		314.5 ± 166.3		157.4 ± 82.2		74.5 ± 29.3	T	253.0	<0.001	0.810	1.000	T	569.4	<0.001	0.760	753.5	<0.001	0.424	0.516	0.002
	Negative	517.4 ± 214.4		326.3 ± 139.4		172.0 ± 88.1		85.5 ± 66.9	T × S	0.157	0.925	0.003	0.078	T × S	0.108	0.854	0.001	0.073	0.787			
Hb	Positive	11.0 ± 1.4	11.1 ± 1.3	11.2 ± 1.2	11.5 ± 1.1	11.6 ± 1.0	11.7 ± 0.9	12.0 ± 0.9	T	49.7	<0.001	0.63	1	T	151.0	<0.001	0.456	279.2	<0.001	0.042	0.837	0.00024
	Negative	10.8 ± 1.4	11.0 ± 1.6	11.3 ± 1.1	1.5 ± 1.0	11.7 ± 1.0	12.0 ± 0.81	12.2 ± 0.75	T × S	3.1	0.007	0.096	0.91	T × S	3.75	0.012	0.02	5.61	0.019			
WBCs	Positive	6821.1 ± 1506.9	6701.1 ± 1349.8	6511.8 ± 1161.0	6597.6 ± 1271.7	6625.4 ± 1057.3	6497.2 ± 1025.5	6369.2 ± 1131.6	T	4.21	0.001	0.126	0.977	T	7.26	<0.001	0.039	2.44	0.120	14.7	<0.001	0.076
	Negative	6420.8 ± 1530.5	6249.0 ± 1385.3	8170.1 ± 1195.3	5890.8 ± 1066.8	5985.9 ± 1022.0	5873.3 ± 1033.1	5895.6 ± 979.3	T × S	1.05	0.394	0.035	0.409	T × S	1.18	0.318	0.007	1.65	0.200			
Platelets	Positive	296.2 ± 67.4	292.3 ± 66.3	287.0 ± 65.7	282.1 ± 57.9	282.5 ± 51.1	281.8 ± 50.2	284.2 ± 54.0	T	3.23	0.005	0.100	0.922	T	5.12	0.003	0.028	7.37	0.007	0.015	0.904	0.0001
	Negative	304.8 ± 61.7	283.0 ± 50.4	279.2 ± 44.3	282.0 ± 48.5	288.1 ± 46.5	280.0 ± 39.4	284.1 ± 44.2	T × S	1.02	0.415	0.034	0.396	T × S	1.22	0.302	0.007	0.559	0.456			
Total symptom score	Positive	20.9 ± 3.2	20.3 ± 3.4	14.2 ± 4.2	5.8 ± 3.1	2.9 ± 3.3	2.9 ± 3.0	0.7 ± 2.1	T	754.9	<0.001	0.964	1.000	T	1371.1	<0.001	0.890	432	<0.001	0.007	0.932	0.00004
	Negative	20.6 ± 3.1	20.4 ± 3.7	13.8 ± 4.6	5.4 ± 2.7	3.4 ± 3.0	3.3 ± 2.9	0.8 ± 1.6	T × S	0.901	0.496	0.031	0.35	T × S	0.728	0.502	0.004	0.003	0.955			
Body weight	Positive	68.3 ± 11.7	68.3 ± 11.8	69.1 ± 11.7	69.4 ± 11.5	69.4 ± 11.4	69.6 ± 11.1	69.3 ± 11.9	T	20.34	<0.001	0.411	1.000	T	16.67	<0.001	0.085	0.061	0.805	0.067	0.797	0.0004
	Negative	67.6 ± 12.2	67.6 ± 12.1	68.3 ± 12.1	68.0 ± 13.8	68.9 ± 12.1	69.6 ± 12.2	70.2 ± 12.0	T × S	2.08	0.058	0.067	0.740	T × S	3.95	0.013	0.021	7.73	0.006			
Pulse	Positive	80.8 ± 5.0	79.9 ± 4.3	78.3 ± 4.0	77.2 ± 4.8	78.3 ± 4.1	77.4 ± 4.1	78.5 ± 2.8	T	5.36	<0.001	0.155	0.995	T	8.24	<0.001	0.044	6.93	0.009	3.13	0.079	0.017

Table 3: Repeated measures ANOVA of clinical and laboratory findings among IBD patient throughout the follow up period

	Negative	80.5 ± 5.6	79.5 ± 5.5	78.9 ± 4.8	80.3 ± 5.0	78.7 ± 5.0	78.2 ± 5.0	78.3 ± 4.7	T × S	2.67	0.017	0.084	0.856	T × S	3.27	0.007	0.018	6.67	0.011			
Pulse pressure	Positive	41.0 ± 5.6	41.3 ± 6.7	39.7 ± 8.9	40.7 ± 8.6	41.1 ± 7.6	39.6 ± 6.9	41.7 ± 9.7	T	0.729	0.627	0.024	0.284	T	0.759	0.593	0.004	1.69	0.195	1.13	0.29	0.006
	Negative	41.5 ± 6.8	40.2 ± 6.8	41.6 ± 7.9	40.9 ± 8.1	41.8 ± 8.5	41.8 ± 8.1	42.0 ± 9.3	T × S	1.28	0.270	0.042	0.493	T × S	1.201	0.305	0.007	0.286	0.593			

$p<0.05$ is significant

[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)

[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant

[c] large effect if the value of partial Eta squared >0.1

T × S; time versus state of H. pylori infection

Table 4: Cox regression analysis for factors associated with IBD flare during the follow up period

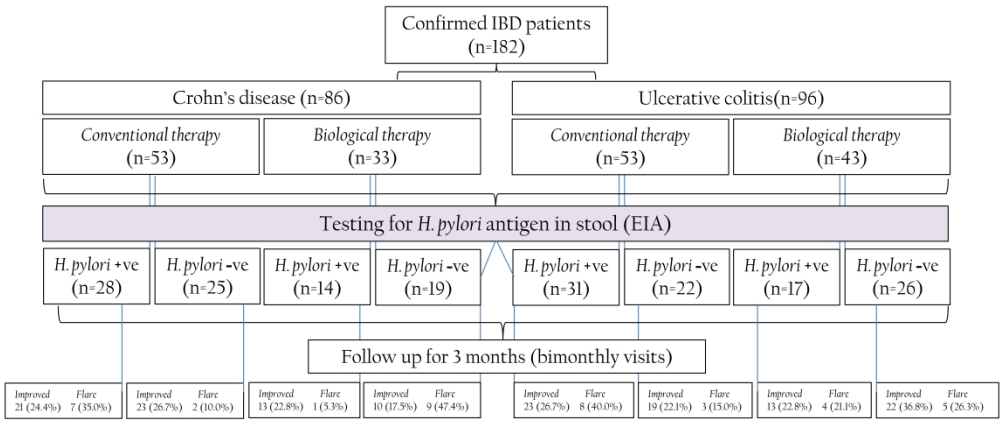
Backward Stepwise (Wald) Logistic Regression		B	SE	Wald	df	Sig. (*p* value)	Exp(B)	95.0% CI for Exp(B)	
								Lower Limit	Upper Limit
Step 6	Age (Years)								
	16 - <20 Years			13.83	2	0.001			
	20 - <35 Years	1.50	0.71	4.41	1	**0.036**	**4.49**	**1.11**	**18.21**
	35 - 55 Years	6.32	1.77	12.76	1	**0.000**	**557.92**	**17.37**	**17922.78**
	Socioeconomic standard								
	High	1.08	0.50	4.71	1	**0.030**	**2.94**	**1.11**	**7.79**
	Middle	0.68	0.48	1.97	1	0.160	1.97	0.76	5.10
	Low			4.71	2	0.095			
	Food rich in insoluble fibers								
	Once per week			8.75	2	0.013			
	2-4 times per week	0.02	0.58	0.00	1	0.973	1.02	0.33	3.18
	Daily	1.62	0.69	5.61	1	**0.018**	**5.08**	**1.32**	**19.49**
	Fruits and Vegetables								
	Never			22.20	3	0.000			
	Once per week	-7.07	1.63	18.74	1	**0.000**	**0.00**	**0.00**	**0.02**
	2-4 times per week	-7.61	1.62	22.06	1	**0.000**	**0.00**	**0.00**	**0.01**
	Daily	-7.47	1.68	19.76	1	**0.000**	**0.00**	**0.00**	**0.02**
	Number of meals per day								
	Two			10.25	2	0.006			
	Three	-0.11	0.38	0.08	1	0.780	0.90	0.43	1.89
	Four	2.59	0.85	9.30	1	**0.002**	**13.33**	**2.52**	**70.46**
	Snacks between meals								
	Never			11.43	2	0.003			
	Occasionally	1.04	0.51	4.07	1	**0.044**	**2.82**	**1.03**	**7.72**
	Daily	-3.89	2.03	3.69	1	0.055	0.02	0.00	1.08

p value significate at <0.05

Table 5: Kaplan Meier analysis of the probability of improvement in IBD condition in relation to *H. pylori* infection and IBD treatment option

Variable	Group	Case summary	No of Events n(%)	Censored n(%)	Event Time (bimonthly visit)	No. of Events (recovery)	No. of relapse	No. at Risk (to recovery)	Probability of recovering	Test of equality of recovery for status of H. pylori infection/treatment option		
										Log Rank (Mantel-Cox)	Breslow (Generalized Wilcoxon)	Tarone-Ware
										p value		
***H. pylori* infection in IBD patients**	Negative	n=92	73 (79.3)	19 (20.7)	1	0	2	92	0.000	0.969	0.708	0.833
					2	1	4	91	0.011			
					3	0	5	91	0.011			
					4	14	3	77	0.163			
					5	17	1	60	0.348			
					6	41	4	19	0.793			
	Positive	n=90	70 (77.8)	20 (22.2)	1	0	0	90	0.000			
					2	0	3	90	0.000			
					3	2	1	88	0.022			
					4	22	6	66	0.267			
					5	8	6	58	0.356			
					6	38	4	20	0.778			
Treatment of IBD	Conventional	n=106	86 (81.1)	20 (18.9)	1	0	0	106	0.000	0.893	0.867	0.880
					2	0	3	106	0.000			
					3	2	1	104	0.019			
					4	21	5	83	0.217			
					5	16	6	67	0.368			
					6	47	5	20	0.811			
	Biological	n=76	57 (75.0)	19 (25.0)	1	0	2	76	0.000			
					2	1	4	75	0.013			
					3	0	5	75	0.013			
					4	15	4	60	0.211			
					5	9	1	51	0.329			
					6	32	3	19	0.750			

p value significate at <0.05
IBD; inflammatory bowel disease



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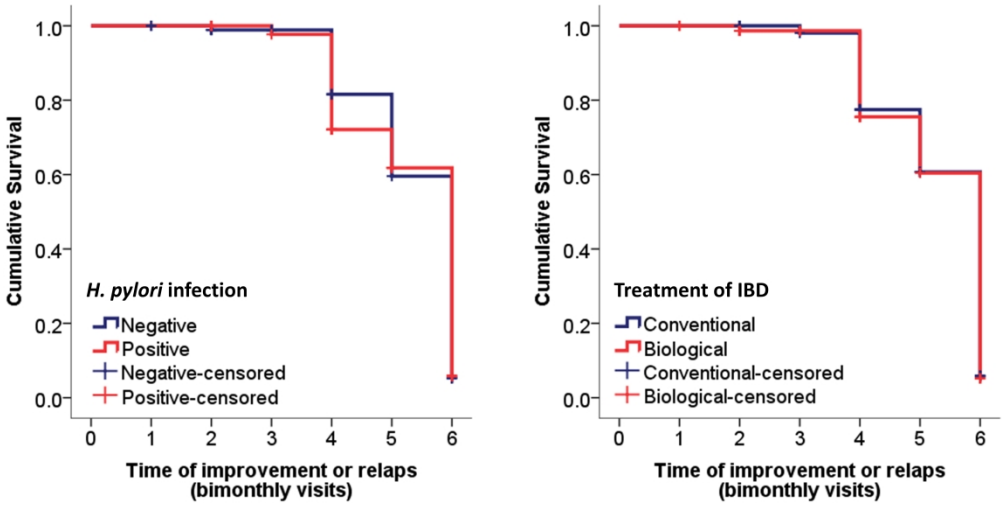

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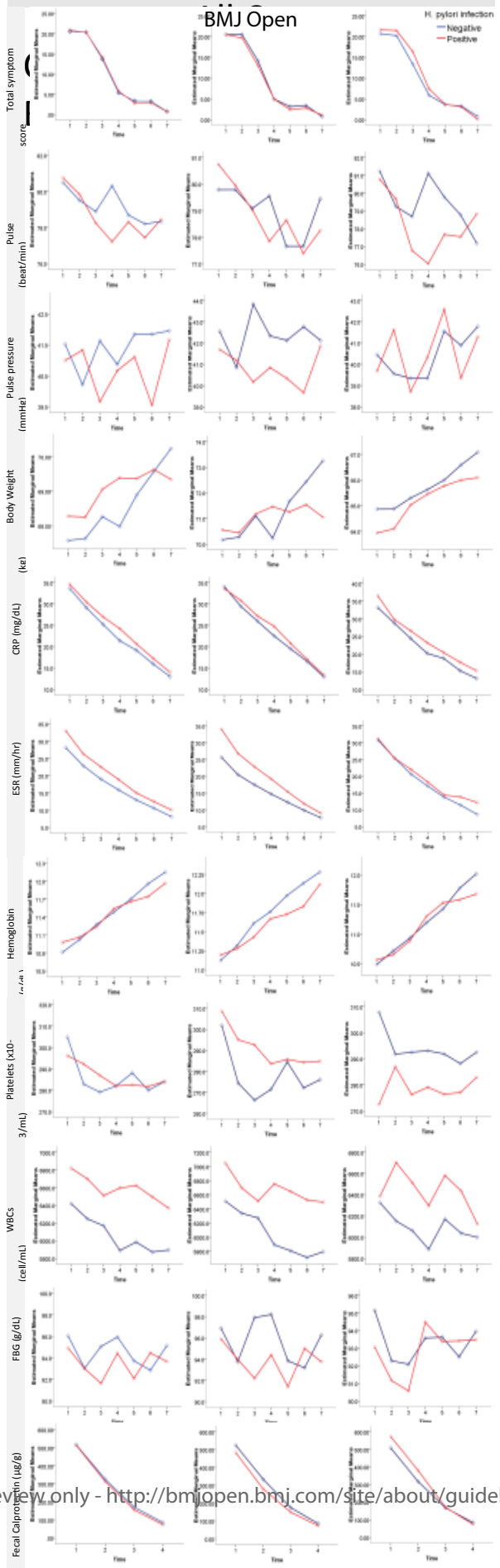
H. pylori infection
Negative
Positive
Total symptom score
Pulse (beat/min)
Pulse pressure (mmHg)
Body Weight (kg)
CRP (mg/dL)
ESR (mm/hr)
Hemoglobin
Platelets (x10^3/mL)
WBCs (cell/mL)
FBG (g/dL)
Fecal Calprotectin (μg/g)
Time

Table S1: Physical activity and dietary habit among the IBD patients

		IBD patients		H pylori infection in IBD patients				*p*~
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.	%	
Physical activity and physical exercise								
Transportation	not working	71	39.0	36	39.1	35	38.9	0.173
	On foot	19	10.4	14	15.2	5	5.6	
	By bicycle	4	2.2	2	2.2	2	2.2	
	Public transport or car	88	48.4	40	43.5	48	53.3	
Working activity	not working	65	35.7	30	32.6	35	38.9	0.001
	minimal	43	23.6	13	14.1	30	33.3	
	moderate	73	40.1	49	53.3	24	26.7	
	high	1	0.5	0	0.0	1	1.1	
Activity outside work	not working	59	32.4	27	29.3	32	35.6	0.451
	minimal	90	49.5	50	54.3	40	44.4	
	moderate	32	17.6	15	16.3	17	18.9	
	high	1	0.5	0	0.0	1	1.1	
Regular exercise	never	136	74.7	76	82.6	60	66.7	0.023
	yes frequent (>3 times/ week)	7	3.8	1	1.1	6	6.7	
	yes infrequent (<3 times/ week)	39	21.4	15	16.3	24	26.7	
Total physical activity score		2.8 ± 2.1		3.01 ± 2.2		2.5 ± 2.1		t=1.6, p= 0.107
Food habits								
Food source	Homemade	97	53.3	61	66.3	36	40.0	0.001
	Restaurant	6	3.3	4	4.3	2	2.2	
	Mixed	79	43.4	27	29.3	52	57.8	
Junk Food, Fast Food	never	50	27.5	25	27.2	25	27.8	0.995
	occasionally	128	70.3	65	70.7	63	70.0	
	daily	4	2.2	2	2.2	2	2.2	
Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	1	1.1	4	4.4	<0.001
	once per week	79	43.4	51	55.4	28	31.1	
	2-4 times per week	85	46.7	39	42.4	46	51.1	
	daily	13	7.1	1	1.1	12	13.3	
Trans fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	never	30	16.5	9	9.8	21	23.3	<0.001
	once per week	91	50.0	61	66.3	30	33.3	
	2-4 times per week	60	33.0	21	22.8	39	43.3	
	daily	1	0.5	1	1.1	0	0.0	
Food rich in insoluble fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs & spices)	never	0	0.0	0	0.0	0	0.0	<0.001
	once per week	39	21.4	28	30.4	11	12.2	
	2-4 times per week	88	48.4	49	53.3	39	43.3	
	daily	55	30.2	15	16.3	40	44.4	

Salty Food (pickled, salty cheese, salted fish, dokka, …)	never	27	14.8	16	17.4	11	12.2	<0.001
	once per week	96	52.7	61	66.3	35	38.9	
	2-4 times per week	54	29.7	12	13.0	42	46.7	
	daily	5	2.7	3	3.3	2	2.2	
Fruits and Vegetables	never	2	1.1	2	2.2	0	0.0	<0.001
	once per week	56	30.8	45	48.9	11	12.2	
	2-4 times per week	81	44.5	37	40.2	44	48.9	
	daily	43	23.6	8	8.7	35	38.9	
Red meat	never	16	8.8	4	4.3	12	13.3	0.013
	once per week	113	62.1	66	71.7	47	52.2	
	2-4 times per week	53	29.1	22	23.9	31	34.4	
	daily	0	0.0	0	0.0	0	0.0	
Under cooked meat	never	157	86.3	80	87.0	77	85.6	0.548
	once per week	24	13.2	11	12.0	13	14.4	
	2-4 times per week	1	0.5	1	1.1	0	0.0	
	daily	0	0.0	0	0.0	0	0.0	
Fish	never	17	9.3	14	15.2	3	3.3	0.007
	once per week	91	50.0	38	41.3	53	58.9	
	2-4 times per week	74	40.7	40	43.5	34	37.8	
	daily	0	0.0	0	0.0	0	0.0	
Consumption of caffeine in diet (tea, coffee)	never	25	13.7	17	18.5	8	8.9	<0.001
	once per week	20	11.0	17	18.5	3	3.3	
	2-4 times per week	61	33.5	30	32.6	31	34.4	
	daily	76	41.8	28	30.4	48	53.3	
Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	never	7	3.8	5	5.4	2	2.2	0.039
	once per week	67	36.8	41	44.6	26	28.9	
	2-4 times per week	91	50.0	41	44.6	50	55.6	
	daily	17	9.3	5	5.4	12	13.3	
Dairy products	never	27	14.8	13	14.1	14	15.6	0.034
	once per week	49	26.9	33	35.9	16	17.8	
	2-4 times per week	78	42.9	36	39.1	42	46.7	
	daily	28	15.4	10	10.9	18	20.0	
Average number of glasses of water consumed per day	one cup	8	4.4	3	3.3	5	6.7	0.102
	2-3 cups	73	40.1	40	43.5	33	36.7	
	at least 4 cups	73	40.1	41	44.6	32	35.6	
	4-8 cups	27	14.8	8	8.7	19	21.1	
Snacks between meals	Never	60	33.0	33	35.9	27	30.0	0.420
	Occasionally	121	66.5	58	63.0	63	70.0	
	Daily	1	0.5	1	1.1	0	0.0	
Number of meals per day	Two	68	37.4	32	34.8	36	40.0	0.092
	Three	109	59.9	55	59.8	54	60.0	
	Four	5	2.7	5	5.4	0	0.0	
Total food score (favorable food habits)		11.4 ± 4.5		12.2 ± 5.0		10.7 ± 3.8		t=2.4 , p= 0.018

Dietary restrictions	No	119	65.4	64	69.6	55	61.1	0.231
	Yes	63	34.6	28	30.4	35	38.9	
	Cereals	0	0.0	0	0.0	0	0.0	
	Brown rice	5	2.7	2	2.2	3	3.3	
	Whole grain bread	2	1.1	2	2.2	0	0.0	
	Seeds (beans, peas)	7	3.8	3	3.3	4	4.4	
	Fruits (apples, plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0	
	High fat or protein food	34	18.7	18	19.6	16	17.8	
	Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	1.1	0	0.0	0.274
	Raw green vegetables	6	3.3	3	3.3	3	3.3	
	Spices	9	4.9	3	3.3	6	6.7	
	Fried food	28	15.4	13	14.1	15	16.7	
	Baked dessert	1	0.5	0	0.0	1	1.1	
	Milk and dairy products	5	2.7	0	0.0	5	5.6	
	Carbonated drinks	14	7.7	4	4.3	10	11.1	
	Tea and coffee	1	0.5	1	1.1	0	0.0	
	Others	5	2.7	2	2.2	3	3.3	
Diet therapy	No	143	78.6	71	77.2	72	80.9	0.538
	Yes	38	20.9	21	22.8	17	19.1	
	Low fiber (bananas, cantaloupe)	7	3.8	2	2.2	5	5.6	
	Refined grains (white pasta, white rice, and oatmeal, potatoes)	13	7.1	3	3.3	10	11.1	
	Omega 3 rich food (fish)	29	15.9	17	18.5	12	13.3	
	Fully cooked, seedless, skinless, non-cruciferous vegetables (squash)	9	4.9	8	8.7	1	1.1	
	Lean sources of protein (poultry, soy, egg)	1	0.5	1	1.1	0	0.0	

~ *p* value for Chi Square test. Significant at <0.05

Table S2: Baseline clinical and laboratory findings among the enrolled IBD patients

		IBD patients		H pylori infection in IBD patients				*p*~
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.	%	
Clinical symptoms	Weight loss	125	68.7	68	73.9	57	63.3	0.124
	Diarrhea	178	97.8	89	96.7	89	98.9	0.323
	Constipation	12	6.6	6	6.5	6	6.7	0.969
	Flatulence	179	98.4	89	96.7	90	100.0	0.084
	Bloating/indigestion	177	97.3	88	95.7	89	98.9	0.182
	Hurt burn	176	96.7	90	97.8	86	95.6	0.391
	Urge incontinence	20	11.0	17	18.5	3	3.3	0.001
	Soiling	7	3.8	6	6.5	1	1.1	0.058
	Tenesmus	176	96.7	89	96.7	87	96.7	0.978
	Frequent bowel movements	166	91.2	85	92.4	81	90.0	0.569
	Abd cramps	160	87.9	78	84.8	82	91.1	0.190
	Epigastric pain	177	97.3	90	97.8	87	96.7	0.632
	Generalized abdominal pain	152	83.5	75	81.5	77	85.6	0.463
	Nausea	175	96.2	89	96.7	86	95.6	0.678
	Vomiting	168	92.3	85	92.4	83	92.2	0.966
	Loss of appetite	161	88.5	81	88.0	80	88.9	0.858
	Frequent bowel movement	171	94.0	89	96.7	82	91.1	0.111
	Blood in stool	155	85.2	75	81.5	80	88.9	0.162
	Bleeding per rectum	126	69.2	60	65.2	66	73.3	0.236
	Back pain	156	85.7	77	83.7	79	87.8	0.431
	Fever	54	29.7	24	26.1	30	33.3	0.285
	Chills	13	7.1	4	4.3	9	10.0	0.139
	Fatigue/lack of energy	143	78.6	63	68.5	80	88.9	0.001
	Headache	166	91.2	87	94.6	79	87.8	0.106
	Dizziness	148	81.3	76	82.6	72	80.0	0.652
	Insomnia/troubled sleep	155	85.2	82	89.1	73	81.1	0.791
	Limited sexual activity	65	35.7	32	34.8	33	36.7	0.128
	Infection	34	18.7	13	14.1	21	23.3	0.111
	Sick leaves/absenteeism	14	7.7	6	6.5	8	8.9	0.549
	Others	3	1.6	1	1.1	2	2.2	0.548
	Eye (stye, conjunctivitis, iridocyclitis)	4	2.2	1	1.1	3	3.3	0.301
	Joints (arthralgia, arthritis)	146	80.2	77	83.7	69	76.7	0.234
	Kidney (renal stones, hematuria)	5	2.7	3	3.3	2	2.2	0.668
	Liver (elevated liver enzymes, hepatitis B, hepatomegaly)	4	2.2	0	0.0	4	4.4	0.041

	Reproductive organs (delayed menstruation, polycystic ovary)	1	0.5	0	0.0	1	1.1	0.311
	Total symptom score	20.7 ± 3.2		20.6 ± 3.1		20.9 ± 3.2		t -0.5 p=0.616
	ESR (males <15 mm/h, females <20 mm/hr)	34.1 ± 13.6		33.6 ± 14.1		34.6 ± 13.2		t -0.49 p= 0.628
	CRP (< 10 mg/L)	30.6 ± 23.5		28.2 ± 23.9		33.0 ± 23.0		t -1.4 p= 0.162
	FBG (70-100 mg/dl)	95.5 ± 11.4		96.1 ± 11.6		94.9 ± 11.1		t 0.7 p= 0.504
	Fecal Calprotectin (<50 µg/g stool)	516.2 ± 210.0		517.4 ± 214.4		515.0 ± 206.7		t -1.8 p= 0.077
Laboratory findings	Hb (men 13.5 to 17.5 g/dl , women 12.0-15.5 g/dl)	10.9 ± 1.4		10.8 ± 1.4		11.0 ± 1.4		t 0.8 p= 0.940
	WBCs (4-11 k/ul)	6618.7 ± 1527.9		6420.8 ± 1530.5		6821.1 ± 1506.9		t -0.8 p= 0.419
	Platelets (150-450 k/ul)	300.6 ± 64.5		304.8 ± 61.7		296.2 ± 67.4		t 0.9 p= 0.372
	Body weight	67.9 ± 11.9		67.6 ± 12.2		68.3 ± 11.7		t -0.4 p= 0.693
	Pulse (60-100 beats per minute)	80.6 ± 5.3		80.5 ± 5.6		80.8 ± 5.0		t -0.3 p= 0.745
	Pulse pressure (40 and 60 mmHg)	41.3 ± 6.2		41.5 ± 6.8		41.0 ± 5.6		t 0.6 p= 0.573
Abdominal ultrasound	Normal abdominal findings	23	12.6	12	13.0	11	12.2	0.987
	Colonic distention	77	42.3	39	42.4	38	42.2	
	Diffuse bright liver	58	31.9	31	33.7	27	30.0	
	Diffuse hepatic fatty infiltration	31	17.0	15	16.3	16	17.8	
	Chronic noncalcular cholecystitis	14	7.7	8	8.7	6	6.7	
	Renal stones	12	6.6	7	7.6	5	5.6	
	Chronic calcular cholecystitis	12	6.6	5	5.4	7	7.8	
	Splenomegaly	1	0.5	0	0.0	1	1.1	
	Cystitis	3	1.6	2	2.2	1	1.1	
	Unremarkable	21	11.5	11	12.0	10	11.1	
Endoscopy	Normal endoscopic findings	27	14.8	14	15.2	13	14.4	0.867
	GERD	75	41.2	35	38.0	40	44.4	
	Antral gastritis	33	18.1	15	16.3	18	20.0	
	Pangastritis	56	30.8	32	34.8	24	26.7	
	Pre-pyloric erosions	17	9.3	10	10.9	7	7.8	
	Superficial duodenal bulb ulcers	28	15.4	15	16.3	13	14.4	
	Incompetent cardia	10	5.5	7	7.6	3	3.3	
	Gastrodudonitis	21	11.5	9	9.8	12	13.3	
	Antral erosions	17	9.3	9	9.8	8	8.9	
	Duodenal inflammatory polyp	7	3.8	4	4.3	3	3.3	
	Erosive gastritis	1	0.5	0	0.0	1	1.1	
	Peptic ulcer	1	0.5	1	1.1	0	0.0	
	Erosive gastrodudonitis	4	2.2	2	2.2	2	2.2	
Colonoscopy	Chronic active colitis	63	34.6	34	37.0	29	32.2	0.087

	Chronic active ileocolitis-Ulcerative Colitis	25	13.7	11	12.0	14	15.6	
	Chronic active colitis with lymphoid hyperplasia	5	2.7	1	1.1	4	4.4	
	Chronic active colitis with multiple superficial ulcers	3	1.6	0	0.0	3	3.3	
	Internal piles	4	2.2	1	1.1	3	3.3	
	ulcerative proctitis	15	8.2	3	3.3	12	13.3	
	Chronic active ulcerative pancolitis	1	0.5	1	1.1	0	0.0	
	multiple superficial aphthoid ulcers - mild ileitis of Crohn's disease	35	19.2	20	21.7	15	16.7	
	Ileocolitis - Crohn's disease	31	17.0	14	15.2	17	18.9	
	Rectal Crohn's	10	5.5	5	5.4	5	5.6	
	Multiple superficial colonic ulcers and skip lesions with eosinophilic infiltration, terminal ileitis - Crohn's disease	13	7.1	9	9.8	4	4.4	
	Chronic active colitis with lymphoid hyperplasia - Crohn's disease	2	1.1	0	0.0	2	2.2	
	perianal fistula	1	0.5	1	1.1	0	0.0	
History of complications	None	137	75.3	77	83.7	60	66.7	0.066
	Fistula	4	2.2	2	2.2	2	2.2	
	Stricture	4	2.2	1	1.1	3	3.3	
	Ulcer	26	14.3	10	10.9	16	17.8	
	Intestinal perforation	0	0.0	0	0.0	0	0.0	
	GIT cancer	2	1.1	1	1.1	1	1.1	
	Abscess formation	5	2.7	0	0.0	5	5.6	
	Others	5	2.7	2	2.2	3	3.3	
Surgical intervention	None	171	94.0	91	98.9	80	88.9	0.061
	Stricturoplasty	3	1.6	1	1.1	2	2.2	
	GIT cancer	1	0.5	0	0.0	1	1.1	
	Abscess intervention	4	2.2	0	0.0	4	4.4	
	Others	3	1.6	0	0.0	3	3.3	

~ *p* value for Chi Square test. Significant at <0.05

Table S3: Repeated measures ANOVA of clinical and laboratory findings among IBD patient on biological treatment throughout the follow up period

Parameter	*H. Pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA											
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects					Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12													
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T × S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	36.5 ± 12.6	29.8 ± 9.0	26.6 ± 8.4	23.2 ± 8.1	20.5 ± 7.3	17.7 ± 7.9	13.3 ± 7.1	T	33.9	<0.001	0.747	1.000	T	128.90	<0.001	0.635	199.6	<0.001	1.78	0.186	0.024
	Negative	33.2 ± 13.7	28.8 ± 10.7	24.4 ± 8.8	20.2 ± 7.8	18.8 ± 7.2	15.3 ± 5.0	13.1 ± 5.4	T × S	0.846	0.540	0.069	0.312	T × S	0.37	0.771	0.005	0.009	0.927			
CRP	Positive	31.2 ± 18.6	25.4 ± 14.7	22.0 ± 12.5	18.3 ± 8.7	14.4 ± 7.5	13.8 ± 7.3	12.2 ± 9.3	T	13.500	<0.001	0.540	1.000	T	60.54	<0.001	0.450	69.79	<0.001	0.225	0.637	0.003
	Negative	30.8 ± 26.2	25.4 ± 21.8	20.6 ± 16.6	17.1 ± 14.0	13.8 ± 10.1	11.4 ± 7.5	8.6 ± 4.5	T × S	0.893	0.505	0.072	0.330	T × S	0.420	0.681	0.006	0.35	0.556			
FBG	Positive	93.1 ± 9.5	91.2 ± 11.6	91.6 ± 9.6	94.5 ± 13.8	93.4 ± 11.8	93.4 ± 10.9	93.5 ± 10.4	T	1.530	0.182	0.117	0.554	T	1.56	0.172	0.021	0.665	0.417	0.136	0.713	0.002
	Negative	95.2 ± 8.8	92.3 ± 6.8	92.1 ± 7.7	93.6 ± 8.6	93.6 ± 8.7	92.5 ± 6.9	94.0 ± 5.9	T × S	0.385	0.886	0.032	0.153	T × S	0.42	0.832	0.006	0.289	0.593			
Calprotectin	Positive	573.8 ± 218.6		380.7 ± 190.6		171.3 ± 96.1		75.2 ± 30.8	T	113.0	<0.001	0.825	1.000	T	250.0	<0.001	0.772	347.5	<0.001	1.39	0.242	0.018
	Negative	508.6 ± 216.3		317.6 ± 153.5		168.3 ± 84.2		84.7 ± 49.8	T × S	1.350	0.266	0.053	0.344	T × S	2.31	0.111	0.030	2.87	0.037			
Hb	Positive	10.6 ± 1.3	10.7 ± 1.3	10.9 ± 1.3	11.3 ± 1.1	11.5 ± 0.9	11.6 ± 0.9	11.7 ± 1.0	T	29.00	<0.001	0.716	1.000	T	89.43	<0.001	0.547	172.7	<0.001	0.047	0.829	0.001
	Negative	10.5 ± 1.1	10.7 ± 1.2	10.9 ± 10.2	110.1 ± 10.1	11.4 ± 1.1	11.8 ± 0.84	1.0 ± 0.81	T × S	2.440	0.034	0.175	0.791	T × S	1.06	0.363	0.032	3.89	0.052			
WBCs	Positive	6385.5 ± 1029.0	6704.8 ± 1023.4	6512.9 ± 1013.5	6298.4 ± 1046.3	6582.3 ± 1075.4	6438.1 ± 1255.8	6125.5 ± 1092.8	T	2.520	0.029	0.180	0.806	T	2.51	0.135	0.033	0.093	0.761	2.85	0.096	0.037
	Negative	6326.7 ± 1479.9	6153.3 ± 1263.2	6062.2 ± 1102.1	5887.8 ± 966.4	6171.1 ± 1030.4	6038.7 ± 1093.6	5999.6 ± 1052.4	T × S	1.324	0.258	0.103	0.486	T × S	1.03	0.399	0.014	3.44	0.068			
Platelets	Positive	272.6 ± 51.0	286.9 ± 44.8	276.3 ± 40.5	279.1 ± 35.1	276.4 ± 31.5	277.1 ± 30.3	282.9 ± 40.5	T	0.738	0.621	0.060	0.273	T	0.41	0.675	0.005	0.605	0.439	5.56	0.021	0.07
	Negative	307.9 ± 69.6	291.8 ± 50.0	292.5 ± 41.8	293.1 ± 42.9	291.9 ± 41.2	288.2 ± 40.7	292.5 ± 44.1	T × S	0.753	0.610	0.061	0.278	T × S	1.18	0.317	0.016	0.527	0.47			
Total symptom score	Positive	21.6 ± 2.3	21.5 ± 2.6	16.4 ± 3.6	7.2 ± 3.0	3.7 ± 3.6	3.1 ± 2.4	0.1 ± 0.4	T	4.150	<0.001	0.973	1.000	T	551.50	<0.001	0.883	98.9	<0.001	4.6	0.035	0.06
	Negative	20.7 ± 3.5	20.2 ± 4.1	13.4 ± 5.6	5.9 ± 3.2	3.6 ± 3.4	3.3 ± 3.1	0.8 ± 1.9	T × S	2.040	0.072	0.153	0.702	T × S	2.85	0.052	0.038	7.61	0.094			
Body weight	Positive	63.9 ± 9.8	64.1 ± 10.1	65.0 ± 10.0	65.5 ± 10.0	65.8 ± 10.0	66.0 ± 10.0	66.1 ± 10.0	T	11.40	<0.001	0.498	1.000	T	33.70	<0.001	0.313	51.8	<0.001	0.055	0.816	0.001
	Negative	64.7 ± 11.0	64.9 ± 10.9	65.3 ± 10.8	65.6 ± 10.7	66.0 ± 10.6	66.6 ± 10.5	67.1 ± 10.4	T × S	2.280	0.046	0.166	0.759	T × S	1.40	0.252	0.018	11.1	0.001			

Pulse	Positive	80.8 ± 2.5	79.7 ± 2.5	76.8 ± 4.5	76.0 ± 4.7	77.7 ± 4.5	77.5 ± 4.4	78.8 ± 2.5	T	3.700	0.003	0.245	0.946	T	4.24	0.001	0.054	4.55	0.036	4.93	0.029	0.062
	Negative	81.2 ± 6.8	79.2 ± 6.7	78.7 ± 5.3	81.1 ± 5.1	79.8 ± 5.1	78.8 ± 5.1	77.2 ± 4.6	T × S	3.010	0.011	0.208	0.882	T × S	3.90	0.003	0.050	12.81	0.001			
Pulse pressure	Positive	39.7 ± 4.1	41.6 ± 5.8	38.7 ± 9.2	40.3 ± 8.3	42.6 ± 6.8	39.4 ± 6.8	41.3 ± 9.6	T	1.350	0.248	0.105	0.493	T	1.57	0.156	0.021	0.537	0.466	0.009	0.924	0.0001
	Negative	40.4 ± 7.4	39.6 ± 7.1	39.3 ± 7.5	39.3 ± 8.1	41.6 ± 8.5	40.9 ± 7.6	41.8 ± 10.1	T × S	0.728	0.628	0.060	0.270	T × S	0.59	0.440	0.008	0.604	0.440			

$p<0.05$ is significant

[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)

[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant

[c] large effect if the value of partial Eta squared >0.1

T × S; time versus state of H. pylori infection

Table S3: Repeated measures ANOVA of clinical and laboratory findings among IBD patient on conventional therapy throughout the follow up period

Parameter	*H. pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA												
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects						Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12														
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	33.6 ± 13.5	30.8 ± 11.9	27.2 ± 11.1	24.8 ± 9.3	20.7 ± 7.4	17.0 ± 6.4	13.3 ± 3.9	T	64.2	<0.001	0.795	1.000	T	219.50	<0.001	0.679	359.3	<0.001	0.335	0.564	0.003
	Negative	34.1 ± 14.6	29.4 ± 12.0	26.0 ± 10.0	22.5 ± 8.2	19.5 ± 6.7	16.5 ± 5.7	12.9 ± 4.5	T × S	1.18	0.325	0.067	0.444	T × S	0.75	0.492	0.007	0.01	0.921			
CRP	Positive	34.0 ± 25.1	26.8 ± 20.2	22.9 ± 17.9	19.3 ± 14.8	15.4 ± 10.7	11.9 ± 6.7	9.1 ± 5.7	T	17.1	<0.001	0.508	1.000	T	83.80	<0.001	0.446	102.1	<0.001	3026	0.074	0.030
	Negative	25.7 ± 21.4	20.5 ± 16.9	17.5 ± 14.2	14.8 ± 11.4	12.3 ± 8.7	9.9 ± 6.1	7.7 ± 4.5	T × S	0.518	0.794	0.030	0.201	T × S	2.30	0.133	0.022	2.81	0.097			
FBG	Positive	95.9 ± 12.0	94.0 ± 10.1	92.2 ± 9.9	94.4 ± 10.3	91.4 ± 8.0	95.0 ± 15.0	93.8 ± 9.3	T	3.06	0.009	0.156	0.896	T	2.43	0.038	0.023	1.32	0.254	1.41	0.238	0.013
	Negative	96.9 ± 13.7	93.8 ± 13.2	97.9 ± 9.8	98.2 ± 16.1	93.9 ± 10.7	93.2 ± 13.0	96.3 ± 10.2	T × S	2.17	0.053	0.116	0.746	T × S	2.10	0.068	0.020	2.06	0.155			
Calprotectin	Positive	484.1 ± 195.0		279.7 ± 141.7		150.1 ± 73.7		74.1 ± 28.8	T	144.8	<0.001	0.810	1.000	T	325.50	<0.001	0.758	417	<0.001	3.23	0.075	0.030
	Negative	525.7 ± 214.2		334 ± 125.5		175.6 ± 92.5		86.3 ± 80.5	T × S	1.19	0.317	0.034	0.312	T × S	0.82	0.411	0.008	0.718	0.399			
Hb	Positive	11.1 ± 1.1	11.3 ± 1.3	11.4 ± 1.2	11.7 ± 1.1	11.7 ± 1.0	11.8 ± 1.0	12.1 ± 0.8	T	24.18	<0.001	0.594	1.000	T	65.83	<0.001	0.338	118.9	<0.001	0.508	0.477	0.005
	Negative	11.1 ± 1.5	11.3 ± 1.1	11.6 ± 1.0	11.8 ± 0.9	12.0 ± 0.8	12.1 ± 0.8	12.3 ± 0.7	T × S	2.19	0.050	0.117	0.753	T × S	1.90	0.137	0.018	2.12	0.148			
WBCs	Positive	7050.0 ± 1667.9	6699.2 ± 1501.3	6511.1 ± 1239.8	6754.7 ± 1357.3	6648.1 ± 1026.2	6528.3 ± 891.8	6497.3 ± 1138.6	T	3.61	0.003	0.179	0.944	T	6.95	<0.001	0.063	4.57	0.035	11.34	0.001	0.098
	Negative	7968.1 ± 1588.2	6340.4 ± 1500.8	6273.4 ± 1281.5	5893.6 ± 1165.3	5808.5 ± 992.5	5714.9 ± 956.7	5796.0 ± 903.8	T × S	1.67	0.137	0.092	0.612	T × S	1.99	0.118	0.019	0.118	0.732			
Platelets	Positive	308.6 ± 71.9	295.1 ± 75.4	292.6 ± 75.3	283.6 ± 67.1	285.7 ± 58.8	284.3 ± 58.1	284.9 ± 60.1	T	3.59	0.003	0.179	0.943	T	5.89	<0.001	0.054	7.84	0.006	1.99	0.161	0.019
	Negative	301.8 ± 53.6	274.4 ± 49.9	266.4 ± 43.2	271.4 ± 51.5	284.5 ± 51.3	272.2 ± 36.8	276.1 ± 43.2	T × S	1.74	0.120	0.095	0.633	T × S	1.13	0.335	0.011	0.357	0.551			
Total symptom score	Positive	20.5 ± 3.6	19.7 ± 3.6	13.0 ± 4.0	5.0 ± 2.8	2.4 ± 3.1	2.8 ± 3.3	1.1 ± 2.5	T	360.0	<0.001	0.959	1.000	T	834.60	<0.001	0.895	424.6	<0.001	2.42	0.123	0.024
	Negative	20.5 ± 2.8	20.5 ± 3.3	14.2 ± 3.5	5.0 ± 1.9	3.2 ± 2.4	3.4 ± 2.7	0.7 ± 1.3	T × S	2.93	0.011	0.159	0.880	T × S	0.85	0.436	0.009	3.97	0.049			
Body weight	Positive	70.6 ± 12.0	70.4 ± 12.1	71.2 ± 12.1	71.5 ± 11.8	71.3 ± 11.8	71.5 ± 11.5	71.1 ± 12.6	T	11.15	<0.001	0.403	1.000	T	6.05	0.002	0.055	0.196	0.659	0.01	0.922	9.2×10^{-5}
	Negative	70.2 ± 12.8	70.3 ± 12.8	71.1 ± 12.8	70.2 ± 16.1	71.7 ± 12.9	72.4 ± 13.1	73.3 ± 12.8	T × S	2.32	0.039	0.123	0.779	T × S	3.43	0.029	0.032	4.26	0.042			
Pulse	Positive	80.7 ± 5.8	79.9 ± 5.1	79. ± 3.5	77.8 ± 4.7	78.6 ± 3.8	77.4 ± 4.0	78.3 ± 3.0	T	3.01	0.010	0.154	0.891	T	5.31	<0.001	0.049	4.6	0.034	0.141	0.079	0.017

	Negative	79.8 ± 4.1	79.8 ± 4.1	79.1 ± 4.2	79.6 ± 4.7	77.7 ± 4.9	77.7 ± 4.8	79.4 ± 4.6	T × S	1.50	0.189	0.083	0.555	T × S	1.53	0.584	0.015	0.111	0.739			
Pulse pressure	Positive	41.7 ± 6.2	41.2 ± 7.2	40.2 ± 8.8	40.8 ± 8.8	40.3 ± 7.9	39.7 ± 6.9	41.9 ± 9.9	T	0.481	0.821	0.028	0.188	T	0.43	0.544	0.004	0.599	0.441	0.141	0.708	0.001
	Negative	42.6 ± 6.1	40.9 ± 6.5	43.8 ± 7.7	42.3 ± 7.9	42.1 ± 8.6	42.8 ± 8.5	42.1 ± 8.6	T × S	1.026	0.413	0.059	0.388	T × S	1.11	0.349	0.011	2.04	0.156			

$p<0.05$ is significant

[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)

[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant

[c] large effect if the value of partial Eta squared >0.1

T × S; time versus state of H. pylori infection

Table S5: Univariate analysis for factor associated with IBD flare during disease follow up

		IBD patients		Flare during IBD therapy				p~	Exp(B)	95.0% C.I. for EXP(B)	
		Total (n=182)		No (n=143)		Yes (n=39)				Lower Limit	Upper Limit
		No.	%	No.	%	No.	%				
H pylori infection	Negative	92	50.5	73	51.0	19	48.7				
	Positive	90	49.5	70	49.0	20	51.3	0.820	1.08	0.57	2.02
Onset of *H. pylori* infection	NA	92	50.5	73	51	19	48.7	0.837			
	Few weeks ago	7	3.8	6	4.2	1	2.6	0.540	0.53	0.07	3.99
	3-6 months	10	5.5	7	4.9	3	7.7	0.488	1.54	0.45	5.21
	6 months - 1 year	35	19.2	29	20.3	6	15.4	0.789	0.88	0.35	2.21
	> 1 year	38	20.9	28	19.6	10	25.6	0.560	1.26	0.58	2.70
Type of IBD diagnosed	Crohn's disease	86	47.3	67	46.9	19	48.7				
	Ulcerative colitis	96	52.7	76	53.1	20	51.3	0.697	0.88	0.47	1.66
Crohn's disease	*H. pylori* Negative	44	24.2	33	23.1	11	28.2	0.526			
	H. pylori Positive	42	23.1	34	23.8	8	20.5	0.374	0.66	0.27	1.65
Ulcerative colitis	*H. pylori* Negative	48	26.4	40	28.0	8	20.5	0.196	0.55	0.22	1.36
	H. pylori Positive	48	26.4	36	25.2	12	30.8	0.853	0.93	0.41	2.10
Treatment of IBD	Conventional	106	58.2	86	60.1	20	51.3				
	Biological	76	41.8	57	39.9	19	48.7	0.254	1.44	0.77	2.70
Sex	Male	94	51.6	76	53.1	18	46.2				
	Female	88	48.4	67	46.9	21	53.8	0.241	1.46	0.78	2.74
Age	16 – <20 Years	20	11.0	15	10.5	5	12.8	0.708	ref		
	20 – <35 Years	136	74.7	106	74.1	30	76.9	0.814	0.89	0.35	2.30
	35 – 55 Years	26	14.3	22	15.4	4	10.3	0.440	0.60	0.16	2.22
Mean ± SD		27.0 ± 7.3		27.8 ± 7.6		23.8 ± 4.9		t= 4.0, p< 0.001			
								0.008	0.92	0.87	0.98
Age at diagnosis	10 – >19	69	37.9	48	33.6	21	53.8	0.086			
	20 – <30	83	45.6	71	49.7	12	30.8	0.029	0.45	0.22	0.92
	30 – 45	30	16.5	24	16.8	6	15.4	0.341	0.64	0.26	1.60
Mean ± SD		27.0 ± 7.3		22.3 ± 6.5		19.1 ± 4.8		t= 3.4, p= 0.001			
								0.01	0.92	0.87	0.98
Residence	Rural	88	48.4	74	51.7	14	35.9				
	Urban	94	51.6	69	48.3	25	64.1	0.051	1.92	1.00	3.70
Education	Illiterate	2	1.1	2	1.4	0	0.0	0.982	0.00	0.00	
	Read and Write	23	12.6	20	14.0	3	7.7	0.160	0.42	0.13	1.40
	Primary	4	2.2	4	2.8	0	0.0	0.978	0.00	0.00	
	Preparatory	13	7.1	11	7.7	2	5.1	0.309	0.47	0.11	2.00
	Secondary	44	24.2	35	24.5	9	23.1	0.487	0.76	0.36	1.64
	University education	96	52.7	71	49.7	25	64.1	0.715			
Working status	No	88	48.4	63	44.1	25	64.1				
	Yes	94	51.6	80	55.9	14	35.9	0.032	0.49	0.25	0.94
Occupation	Unemployed	37	20.3	31	21.7	6	15.4	0.024			
	Student	45	24.7	26	18.2	19	48.7	0.023	2.89	1.15	7.25
	Clerical	2	1.1	1	0.7	1	2.6	0.353	2.73	0.33	22.67
	Professional	39	21.4	33	23.1	6	15.4	0.962	0.97	0.31	3.02
	Housewife	21	11.5	19	13.3	2	5.1	0.566	0.63	0.13	3.10
	Auxiliary worker	22	12.1	19	13.3	3	7.7	0.701	0.76	0.19	3.05
	Farmer	16	8.8	14	9.8	2	5.1	0.643	0.69	0.14	3.40
Marital status	Married	73	40.1	50	35.0	23	59.0	0.110			
	Not married							0.016	2.20	1.16	4.21
	Single	106	58.2	91	63.6	15	38.5	0.018	2.20	1.15	4.21
	Widowed	2	1.1	1	0.7	1	2.6	0.276	3.08	0.41	23.35
	Divorced	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Socioeconomic standard	High	58	31.9	41	28.7	17	43.6	.015	2.730	1.215	6.14
	Middle	52	28.6	39	27.3	13	33.3	.127	1.938	.828	4.54
	Low	72	39.6	63	44.1	9	23.1	.052			
Consanguinity	No	144	79.1	114	79.7	30	76.9				
	Yes	38	20.9	29	20.3	9	23.1	0.888	0.95	0.45	2.00
Being breastfed	No	26	14.3	22	15.4	4	10.3				
	Yes	156	85.7	121	84.6	35	89.7	0.382	1.59	0.56	4.47
Smoking	Never	150	82.4	119	83.2	31	79.5	0.915			
	Current smoker	26	14.3	19	13.3	7	17.9	0.774	1.128	0.50	2.57
	Ex-Smoker	6	3.3	5	3.5	1	2.6	0.775	0.75	0.10	5.48
Age of starting Smoking	NA	153	84.1	119	83.2	34	87.2	0.679			
	< 20 Years	17	9.3	14	9.8	3	7.7	0.573	0.71	0.22	2.32
	20 – 30 Years	12	6.6	10	7.0	2	5.1	0.475	0.59	0.14	2.48
Smoking other than cigarette	Never	180	98.9	143	100.0	37	94.9				
	Shisha	2	1.1	0	0.0	2	5.1	0.079	3.59	0.86	14.94
Alcohol	No	182	100.0	143	100.0	39	100.0				
	Yes	0	0.0	0	0.0	0	0.0				

Drug Abuse	No	182	100.0	143	100.0	39	100.0				
	Yes	0	0.0	0	0.0	0	0.0				
Chronic diseases	No	82	45.1	64	44.8	18	46.2				
	Yes	100	54.9	79	55.2	21	53.8	0.811	0.93	0.49	1.74
	Diabetes Mellitus	10	5.5	8	5.6	2	5.1				
	Hypertension	30	16.5	25	17.5	5	12.8				
	Bronchial Asthma/COPD	15	8.2	13	9.1	2	5.1				
	Heart disease	1	0.5	1	0.7	0	0.0				
	Renal disease	1	0.5	0	0.0	1	2.6				
	Liver disease	1	0.5	1	0.7	0	0.0				
	SLE	0	0.0	0	0.0	0	0.0				
	rheumatoid arthritis	6	3.3	5	3.5	1	2.6				
	Skin allergy	18	9.9	16	11.2	2	5.1				
	Hyperthyroidism	4	2.2	3	2.1	1	2.6				
	Hypothyroidism	8	4.4	5	3.5	3	7.7				
	Other autoimmune diseases	1	0.5	1	0.7	0	0.0				
	Others (Chronic sinusitis, vertigo, lumbar disc prolapse, familial dyslipidemia, hemorrhoids, scleritis, HCV, anemia, fatty liver, steatosis, psoriasis, peripheral neuropathy, chronic cholecystitis)	27	14.8	21	14.7	6	15.4				
Autoimmune diseases	No	163	89.6	129	90.2	34	87.2				
	Yes	19	10.4	14	9.8	5	12.8	0.555	1.33	0.52	3.39
Medications	None	13	7.1	10	7.0	3	7.7				
	Analgesic (NSAIDs)	12	6.6	7	4.9	5	12.8				
	Antidiabetics	6	3.3	6	4.2	0	0.0				
	Antihypertensives	32	17.6	27	18.9	5	12.8				
	corticosteroids	10	5.5	5	3.5	5	12.8				
	IBD therapy	151	83.0	118	82.5	33	84.6				
	Hormonal contraceptives	2	1.1	0	0.0	2	5.1				
	Thyroxin	9	4.9	6	4.2	3	7.7				
	Others	37	20.3	28	19.6	9	23.1				
Family history of similar condition	No	141	77.5	108	75.5	33	84.6				
	Yes	41	22.5	35	24.5	6	15.4	0.279	0.62	0.26	1.48
	Yes; first degree relatives	40	22.0	34	23.8	6	15.4				
	Yes; other relatives	1	0.5	1	0.7	0	0.0				
	Other autoimmune disease	3	1.6	3	2.1	0	0.0				
Physical activity											
Transportation	not working	71	39.0	60	42.0	11	28.2	0.208			
	On foot	19	10.4	17	11.9	2	5.1	0.503	0.60	0.13	2.70
	By bicycle	4	2.2	3	2.1	1	2.6	0.709	1.48	0.19	11.47
	Public transport or car	88	48.4	63	44.1	25	64.1	0.090	1.85	0.91	3.76
Working activity	not working	65	35.7	53	37.1	12	30.8	0.655			
	minimal	43	23.6	31	21.7	12	30.8	0.249	1.60	0.72	3.57
	moderate	73	40.1	58	40.6	15	38.5	0.882	1.06	0.50	2.26
	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Activity outside work	not working	59	32.4	48	33.6	11	28.2	0.733			
	minimal	90	49.5	71	49.7	19	48.7	0.838	1.08	0.51	2.27
	moderate	32	17.6	23	16.1	9	23.1	0.293	1.60	0.66	3.87
	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Regular exercise	never	136	74.7	109	76.2	27	69.2	0.397			
	yes frequent (>3 times/ week)	7	3.8	5	3.5	2	5.1	0.758	1.25	0.30	5.27
	yes infrequent (<3 times/ week)	39	21.4	29	20.3	10	25.6	0.176	1.66	0.80	3.45
Total physical activity score		2.8 ± 2.1		2.7 ± 2.2		2.9 ± 2.0		t= 0.40, p= 0.695			
								0.855	1.01	0.88	1.17
Dietary habits											
Food source	Homemade	97	53.3	78	54.5	19	48.7	0.858			
	Restaurant	6	3.3	5	3.5	1	2.6	0.829	0.80	0.11	5.99
	Mixed	79	43.4	60	42.0	19	48.7	0.639	1.16	0.62	2.20
Junk Food, Fast Food	never	50	27.5	41	28.7	9	23.1	0.806			
	occasionally	128	70.3	99	69.2	29	74.4	0.535	1.27	0.60	2.68
	daily	4	2.2	3	2.1	1	2.6	0.706	1.49	0.19	11.75
Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	5	3.5	0	0.0	0.399			
	once per week	79	43.4	65	45.5	14	35.9	0.898	2383.0	0.00	1.6×10^{68}
	2-4 times per week	85	46.7	62	43.4	23	59.0	0.891	4190.1	0.00	2.9×10^{68}
	daily	13	7.1	11	7.7	2	5.1	0.898	2475.2	0.00	1.7×10^{68}
Transfat (such as in cake, cookies, pies, dessert,	never	30	16.5	27	18.9	3	7.7	0.017			
	once per week	91	50.0	75	52.4	16	41.0	0.506	1.52	0.44	5.22

cream, mayonnaise,	2-4 times per week	60	33.0	41	28.7	19	48.7	0.061	3.21	0.95	10.85
processed meat as burger & sausage)	daily	1	0.5	0	0.0	2	5.1	0.020	14.82	1.52	144.45
Food rich in insoluble	never	0	0.0	0	0.0	0	0.0				
fibers (such as whole	once per week	39	21.4	31	21.7	8	20.5	0.022			
bread, cereals, beans,	2-4 times per week	88	48.4	76	53.1	12	30.8	0.362	0.66	0.27	1.61
peas, wheat, oat, artichoke, squash, cabbage, cauliflower, broccoli, dried herbs & spices, fruits, vegetables)	daily	55	30.2	36	25.2	19	48.7	0.163	1.80	0.79	4.12
Salty Food (pickled,	never	27	14.8	22	15.4	5	12.8	0.470			
salty cheese, salted fish,	once per week	96	52.7	78	54.5	18	46.2	0.885	0.93	0.34	2.51
dokka)	2-4 times per week	54	29.7	40	28.0	14	35.9	0.516	1.40	0.51	3.90
	daily	5	2.7	3	2.1	2	5.1	0.299	2.38	0.46	12.29
Fruits and Vegetables	never	2	1.1	0	0.0	2	5.1	0.005			
	once per week	56	30.8	44	30.8	12	30.8	0.001	0.07	0.01	0.31
	2-4 times per week	81	44.5	64	44.8	17	43.6	0.000	0.07	0.02	0.31
	daily	43	23.6	35	24.5	8	20.5	0.001	0.07	0.01	0.34
Red meat	never	16	8.8	13	9.1	3	7.7	0.959			
	once per week	113	62.1	88	61.5	25	64.1	0.950	0.96	0.29	3.20
	2-4 times per week	53	29.1	42	29.4	11	28.2	0.835	0.87	0.24	3.14
	daily	0	0.0	0	0.0	0	0.0				
Under cooked meat	never	157	86.3	120	83.9	37	94.9	0.259			
	once per week	24	13.2	22	15.4	2	5.1	0.100	0.30	0.07	1.26
	2-4 times per week	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
	daily	0	0.0	0	0.0	0	0.0				
Fish	never	17	9.3	16	11.2	1	2.6	0.220			
	once per week	91	50.0	67	46.9	24	61.5	0.102	5.30	0.72	39.19
	2-4 times per week	74	40.7	60	42.0	14	35.9	0.176	4.06	0.53	30.95
	daily	0	0.0	0	0.0	0	0.0				
Consumption of caffeine	never	25	13.7	22	15.4	3	7.7	0.027			
in diet (tea, coffee)	once per week	20	11.0	16	11.2	4	10.3	0.571	1.54	0.34	6.89
	2-4 times per week	61	33.5	54	37.8	7	17.9	0.949	0.96	0.25	3.70
	daily	76	41.8	51	35.7	25	64.1	0.078	2.94	0.89	9.74
Soft drinks (carbonated	never	7	3.8	7	4.9	1	2.6	0.181			
drinks, cola, canned and	once per week	67	36.8	56	39.2	11	28.2	0.780	1.34	0.17	10.48
sweetened drinks)	2-4 times per week	91	50.0	70	49.0	21	53.8	0.519	1.93	0.26	14.38
	daily	17	9.3	10	7.0	7	17.9	0.215	3.77	0.46	30.66
Dairy products	never	27	14.8	22	15.4	5	12.8	0.552			
	once per week	49	26.9	41	28.7	8	20.5	0.831	0.89	0.29	2.71
	2-4 times per week	78	42.9	58	40.6	20	51.3	0.409	1.51	0.57	4.03
	daily	28	15.4	22	15.4	6	15.4	0.497	1.51	0.46	4.98
Average number of	one cup	9	4.9	6	4.2	3	7.7	0.346			
glasses of water	2-3 cups	73	40.1	59	41.3	14	35.9	0.367	0.56	0.16	1.96
consumed per day	at least 4 cups	73	40.1	54	37.8	19	48.7	0.734	0.81	0.24	2.74
	4-8 cups	27	14.8	24	16.8	3	7.7	0.156	0.31	0.06	1.56
Snacks between meals	Never	60	33.0	54	37.8	6	15.4	0.009			
	Occasionally	121	66.5	89	62.2	32	82.1	0.014	2.99	1.25	7.14
	Daily	1	0.5	0	0.0	1	2.6	0.009	17.12	2.02	144.86
Number of meals per day	2	68	37.4	55	38.5	13	33.3	0.058			
	3	109	59.9	86	60.1	23	59.0	0.857	1.06	0.54	2.10
	4	5	2.7	2	1.4	3	7.7	0.022	4.37	1.24	15.37
Total food score (favorable food habits)		11.4 ± 4.5		11.9 ± 4.3		9.9 ± 5.0		t=2.2 , p=0.029			
								0.029	0.93	0.86	0.99
	No	119	65.4	95	66.4	24	61.5				
	Yes	63	34.6	48	33.6	15	38.5	0.406	1.32	0.69	2.51
	Cereals	0	0.0	0	0.0	0	0.0				
	Brown rice	5	2.7	4	2.8	1	2.6				
	Whole grain bread	2	1.1	2	1.4	0	0.0				
	Seeds (beans, peas)	7	3.8	3	2.1	4	10.3				
	Fruits (apples; plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0				
Dietary restrictions	High fat or protein food	34	18.7	25	17.5	9	23.1				
	Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	0.7	0	0.0				
	Raw green vegetables	6	3.3	6	4.2	0	0.0				
	Spices	9	4.9	7	4.9	2	5.1				
	Fried food	28	15.4	22	15.4	6	15.4				
	Baked dessert	1	0.5	1	0.7	0	0.0				
	Milk and dairy products	5	2.7	3	2.1	2	5.1				

	Carbonated drinks	14	7.7	11	7.7	3	7.7			
	Tea and coffee	1	0.5	1	0.7	0	0.0			
	Others	5	2.7	4	2.8	1	2.6			
Diet therapy	No	143	78.6	113	79.0	31	79.5			
	Yes	38	20.9	30	21.0	8	20.5	0.982	0.99	0.46	2.16
	Low fiber (bananas, cantaloupe)			5	3.5	2	5.1				
	Refined grains (white pasta, white rice, and oatmeal, potatoes)			10	7	3	7.7				
	Omega 3 rich food (fish)			24	16.8	5	12.8				
	Fully cooked, seedless, skinless, non-cruciferous vegetables (squash)			6	4.2	3	7.7				
	Lean sources of protein (poultry, soy, egg)			1	0.7	0	0.0				
	Others			0	0.0	0	0.0				
History of complications	None	137	75.3	109	76.2	28	71.8	0.689			
	Yes	41	22.5	31	21.7	10	25.6	0.818	1.09	0.53	2.23
	Fistula	4	2.2	3	2.1	1	2.6	0.949	1.07	0.15	7.86
	Stricture	4	2.2	3	2.1	1	2.6	0.964	1.05	0.14	7.70
	Ulcer	26	14.3	21	14.7	4	10.3	0.546	0.72	0.25	2.07
	Intestinal perforation	0	0.0	0	0.0	0	0.0				
	GIT cancer	2	1.1	2	1.4	0	0.0	0.974	0.00	0.00	1.3×10^{250}
	Abscess formation	5	2.7	3	2.1	2	5.1	0.304	2.12	0.50	8.94
	Others	5	2.7	2	1.4	3	7.7	0.126	2.54	0.77	8.35
Surgical intervention	None	171	94.0	136	95.1	35	89.7	0.711			
	Yes							0.297	1.73	0.62	4.88
	Stricturoplasty	3	1.6	2	1.4	1	2.6	0.657	1.57	0.21	11.47
	Endoscopic balloon dilatation	0	0.0	0	0.0	0	0.0				
	Surgical resection	0	0.0	0	0.0	0	0.0				
	Intestinal perforation	0	0.0	0	0.0	0	0.0				
	GIT cancer	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
	Abscess formation	4	2.2	3	2.1	1	2.6	0.668	1.55	0.21	11.37
	Others (appendectomy, cholecystectomy	3	1.6	1	0.7	2	5.1	0.175	2.68	0.64	11.17
BMI categories	< 18.5 (underweight)	3	1.6	2	1.4	1	2.6	0.687			
	18.5-24.99 (Normal weight)	108	59.3	85	59.4	23	59.0	0.297	0.34	0.05	2.56
	25-29.99 (Overweight)	58	31.9	47	32.9	11	28.2	0.268	0.31	0.04	2.44
	30-39.99 (Obese)	13	7.1	9	6.3	4	10.3	0.474	0.45	0.05	4.04
Colonoscopy	Chronic active colitis	63	34.6	49	34.3	14	35.9				
	Chronic active ileocolitis-UC	25	13.7	20	14	5	12.8				
	Chronic active colitis with lymphoid hyperplasia	5	2.7	4	2.8	1	2.6				
	Chronic active colitis with multiple superficial ulcers	3	1.6	2	1.4	1	2.6				
	Internal piles	4	2.2	3	2.1	1	2.6				
	ulcerative proctitis	15	8.2	13	9.1	2	5.1				
	Chronic active ulcerative pancolitis	1	0.5	0	0	1	2.6				
	multiple superficial aphthoid ulcers - mild ileitis of Crohn's disease	35	19.2	26	18.2	9	23.1				
	Ileocolitis - Crohn's disease	31	17.0	27	18.9	4	10.3				
	Rectal Crohn's	10	5.5	7	4.9	3	7.7				
	Multiple superficial colonic ulcers and skip lesions with eosinophilic infiltration, terminal ileiltis - Crohn's disease	13	7.1	11	7.7	2	5.1				
	Chronic active colitis with lymphoid hyperplasia - CD	2	1.1	2	1.4	0	0				
	perianal fistula	1	0.5	0	0	1	2.6				
Endoscopy	Normal endoscopic findings	27	14.8	19	13.3	8	20.5				
	GERD	75	41.2	61	42.7	14	35.9				
	Antral gastritis	33	18.1	27	18.9	6	15.4				
	Pangastritis	56	30.8	45	31.5	11	28.2				
	Pre-pyloric erosions	17	9.3	13	9.1	4	10.3				
	Superficial duodenal bulb ulcers	28	15.4	21	14.7	7	17.9				

	Incompetent cardia	10	5.5	10	7.0	0	0.0	
	Gastrodudonitis	21	11.5	18	12.6	3	7.7	
	Antral erosions	17	9.3	13	9.1	4	10.3	
	Duodenal inflammatory polyp	7	3.8	5	3.5	2	5.1	
	Erosive gastritis	1	0.5	1	0.7	0	0.0	
	Peptic ulcer	1	0.5	0	0.0	1	2.6	
	Erosive gastrodudonitis	4	2.2	2	1.4	2	5.1	
Abdominal Ultrasound	Normal abdominal findings	23	12.6	19	13.3	4	10.3	
	Colonic distention	77	42.3	60	42.0	17	43.6	
	Diffuse bright liver	58	31.9	46	32.2	12	30.8	
	Diffuse hepatic fatty infiltration	31	17.0	0	0.0	0	0.0	
	Chronic noncalcular cholecystitis	14	7.7	10	7.0	4	10.3	
	Renal stones	12	6.6	9	6.3	3	7.7	
	Chronic calcular cholecystitis	12	6.6	10	7.0	2	5.1	
	Splenomegaly	1	0.5	1	0.7	0	0.0	
	Cystitis	3	1.6	3	2.1	0	0.0	
	Unremarkable	21	11.5	16	11.1	5	12.8	

~ *p* value for Chi Square test. Significant at <0.05
IBD; inflammatory bowel disease

Protocol for treating inflammatory bowel diseases

A. Treatment of ulcerative colitis

Depend on

1- Disease activity (clinical and endoscopic)
2- Extend (distal, left sided, extensive)

I- Mild, moderate + distal extend (proctosigmoiditis)
Topical methotrexate 4g/day
+ oral mesalazine (2-4 g/day)
+ steroid (oral prednisolone 40-60 mg/day with dose tapering over 8 weeks
If no remission (or unstable remission) occurs
The patient is treated as sever disease

If stable remission occurs
So stop steroids and maintain on mesalazine + AZA or 6-mp (for lifelong or 2 years then ….)

II- Mild, moderate + left sided extend (proctosigmoiditis)
5 ASA
+ oral mesalazine (2-4 g/day)
+ topical
If unsatisfactory response occurs
+ steroid (oral prednisolone 40-60 mg/day with dose tapering over 8 weeks
If no remission (or unstable remission or unsatisfactory response) occurs

The patient is treated as sever disease

If stable remission occurs
maintain lifelong on 5 ASA (1-2 g/day)+ AZA (2-2.5 mg/kg for 3-4 years)
sever disease (need hospitalization)
vital signs/ 6 hrs, CBC, ESR, CRP, electrolytes, stool chart, Abd US
antidiarrheal, anticholinergic, antibiotics, nutrition, blood transfusion, fluids
I.V steroids (hydrocortisone 400 mg/day pr methylprednisolone 60 mg/day
If stable remission occurs
Maintain lifelong on 5 ASA 1-2 g/day
+AZA 2-2.5 mg/kg

If unstable remission
Add AZA or methotrexate if still unstable remission occurs shift to biological

If no remission occurs shift to biological

If no response or complication (surgery)

B. Treatment of Crohn's Disease

According to disease severity

a- Mild to moderate
Treatment of active symptoms (antidiarrheal, nutrition, careful observation)
Ileocaecal (budesonide 3-4 mg/day)
Clonic sulfasalazine 2-4 g/day

b- Moderate to severe
Induction therapy (oral corticosteroids 40-60 mg / day with dose tapering over 8 weeks + AZA 2-2.5 mg/kg)

1- Response (maintain on
AZA 1.5-2.5 mg/kg/day
Methotrexate 2.5 mg/kg S.C or IM
Refractory cases will shift to biologicals (Ustekinumab)

2- Steroid resistant
Give anti INF (biological)
+AZA (2-2.5 g/kg)
Maintenance like induction therapy

3- Steroid dependent
Methotrexate 25 mg/kg S.C or IM +/- biologicals

c- Severe/fulminate disease
I.V steroids (hydrocortisone 400 mg/day pr methylprednisolone 60 mg/day
+ Anti INF

d- Perianal / fistula disease
Antibiotics
Drainage of abcess
+ biologics (infliximab, adalimumab)

List of Biologics used

- Infliximab (Remicode)
  IV 5 mg/kg or 10 mg/kg if sever
  Induction : 0, 2, 6 weeks
  Maintained : 8 weeks (4-12 week)

- Adalimumab (Humira)
  S.C 40 mg 80 mg 160 mg
  Induction : week 0; 160 mg
  Week 2; 80 mg
  Maintenance : 2 weeks 40 mg
  1 week 40 mg

- Golimumab (Simponi)
  S.C 50 mg 100 mg 200 mg
  Induction: Week 0; 200 mg
  Week 2; 100 mg
  Week 6; 50 mg (if weight < 70 kg) and 100 mg if weight > 70 kg

- Ustekinumab (Stelara)
  S.C or I.V
  260 mg or 390 mg or 520 mg
  Induction: week 0 I.V
  Week 8 S.C
  Maintenance: 8 – 12 weeks S.C

- Vedolizumab (Entyvio)
  IV
  300 mg
  Induction: 0, 2, 6 weeks
  Maintenance: week 8
  For 4 weeks if sever

- Certolizumab (Cimzia)
  S.C
  400 mg
  Induction : week 0; 400 mg
  Week 2; 400 mg
  Week 4; 400 mg
  Maintenance: 4 weeks 400 mg

Questionnaire: The Relationship between Helicobacter Pylori Infection and Inflammatory Bowel Disease

Pt no:	Name:	tel:

Group no:		H. Pylori (0) -ve (1) +ve	Treatment: (0) Conventional (1) Biologic

I- Sociodemographic Data		Code
1. Gender	(0) Male (1) Female	
2. Age in years	……	
3. Residence	(0) Rural (1) Urban	
4. Education	(0) Illiterate (1) Read and Write (2) Primary (3) Preparatory (4) Secondary (5) University Education	
5. Occupation	(0) Not working (1) Student (2) Clerical (3) Professional (4) HCW (5) House wife (6) Craft (7) Auxiliary worker (8) Farmer (9) Retired (10) Other……	
6. Marital status	(0) Single (1) Married (2) Widowed (3) Divorced	
7. Parent Consanguinity	(0) No (1) Yes	
8. Had been breast fed	(0) No (1) Yes	
9. Smoking	(0) Never (1) Current smoker (2) Ex-smoker	
10. Smoking index	no. of smoked cigarettes per day…… x no. of smoking years …… x 365	
11. Age of starting Smoking	(0) N/A (1) <20 years old (2) 20-30 years old (3) > 30 years old	
12. Smoking other than cigarette	(0) Never (1) Shisha (2) Snuff	
13. Alcohol Intake	(0) NA (1) Occasional (2) <3 cups/ day (3) >3 cups/ day (4) ex-drinker	
14. Drug Abuse	(0) NA (1) Never (2) Cannabis (3) Opium (4) tablets "tamols" (5) powder(heroin, cocaine) (6) IV drugs (7) others: ----------	
15. Chronic diseases	(00) No (01) DM (02) Hypertension (03) Bronchial Asthma/COPD (04) Heart disease (05) Renal Disease (06) liver disease (07) SLE (08) rheumatoid arthritis (09) skin allergy (10) hyperthyroidism (11) hypothyroidism (12) other autoimmune …… (13) others……	
16. Family history of similar condition	(0) No (1) Yes; first degree relatives (2) Yes; other relatives (3) Other autoimmune disease……	
17. Medications	(0) None (1) Analgesic (NSAIDs) (2) anti DM (3) anti HTN (4) corticosteroids (5) IBD therapy (6) hormonal/oral contraceptives (7)thyroxin (8)others ……	
18. Transportation	(-1) not working (1) on foot (2) by bicycle (3) public transport/car	
19. Working activity	(-1) not working (1) Minimal (2) Moderate (3) High	
20. Activity outside work	(-1) not working (1) Minimal (2) Moderate (3) High	
21. Regular exercise	(0) Never (1) Yes Frequent (>3 times/week) (2) Yes Infrequent (<3 times/week)	
22. If yes, mention time spent in min/day	…… (-1) N/A	
23. Food source	(0) Homemade (1) restaurants (2) Mixed	
24. Junk Food, Fast Food	(0) Never (1) occasionally (2) daily If **daily**, mention the number of servings per day ……	
25. Saturated Fat (butter, ghee, cream, ..etc)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
26. trans Fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
27. Food rich in fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, squash, cabbage, cauliflower,	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	

	broccoli, dried herbs & spices, fruits, vegetables)	
28.	**Salty Food (pickled, salty cheese, salted fish, dokka, ...**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
29.	**Fruits & Vegetables**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
30.	**Red meat**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
31.	**Under cooked meat**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
32.	**Fish**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
33.	**Consumption of caffeine in diet (tea, coffee)**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
34.	**Soft drinks (carbonated drinks, cola, canned and sweetened drinks)**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
35.	**Dairy products**	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……
36.	**On average, how many glasses of water consumed per day?**	(1) one cup (2) 2-3 cups (3) at least 4 cups (4) 4 to 8 cups
37.	**Dietary restrictions**	(00) none (01) cereals (02) brown rice (03) whole grain bread (04) seeds (beans, peas) (05) fruits (apples, plums, peaches, skin removed) (06) high fat or protein food (07) vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper) (08) raw green vegetables (09) spices (10) fried food (11)baked dessert (12) milk and dairy products (13) carbonated drinks (14) tea and coffee (15) others ……
38.	**Diet therapy**	(0) none (1) low fiber (bananas, cantaloupe) (2) refined grains (white pasta, white rice, and oatmeal, potatoes) (3) Omega 3 rich food (fish) (4) Fully cooked, seedless, skinless, non-cruciferous vegetables (squash) (5) Lean sources of protein (poultry, soy, egg) (6) others……
39.	**Food preparation method**	(0) No preference (1) boiling (2) grilling (3) steaming (4) frying
40.	**Number of meals per day**	……
41.	**Snackes between meals**	(0) Never (1) occasionally (2) daily; …… per day
II-	**Clinical data**	
42.	**Type of IBD diagnosed**	(0) Crohn's disease (1) ulcerative colitis
43.	**Age at diagnosis**	**……..years old**
44.	**History of H. pylori infection**	
45.	**If yes mention the onset**	(-1) NA (1) few weeks (2) 3-6 months (3) 6 months- 1 year (4)≥ 1 year
46.	**History of receiving H. pylori eradication therapy during the past 12 months**	(0) No (1) Yes; ……
47.	**History of complications**	(0) None (1) fistula (2) stricture (3) ulcers (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others……
48.	**Surgical intervention**	(0) None (1) stricturoplasty (2) Endoscopic balloon dilatation (3) surgical resection (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others
49.	**Current medications used to control IBD**	(00) None (01) 5-ASA "Pentasa (Mesalamine)" (02) 6-mercaptopurine "Purinethol" (03) Methotrexate "Trexall, Rasuvo, Otrexup" (04) Cyclosporine "Sandimmune, Neoral" (05) Corticosteroids "Prednisone" (06) Sulfasalazine (07) Azathiopurines "Imuran" (08) Librax (09) Imodium (10) Azithromycin "Zithromax" (11) Ciprofloxacin (12) Rifabutin (13) Clarithromycin "Biaxin" (14) Flagyl (15) probiotics (16) multivitamin supplements (17) Infliximab (18)PPI (19) Moltilium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others……

50. Medications used in the past to control IBD	(00) None (01) 5-ASA "Pentasa (Mesalamine)" (02) 6-mercaptopurine "Purinethol" (03) Methotrexate "Trexall, Rasuvo, Otrexup" (04) Cyclosporine "Sandimmune, Neoral" (05) Corticosteroids "Prednisone" (06) Sulfasalazine (07) Azathiopurines "Imuran" (08) Librax (09) Imodium (10) Azithromycin "Zithromax" (11) Ciprofloxacin (12) Rifabutin (13) Clarithromycin "Biaxin" (14) Flagyl (15) probiotics (16) multivitamin supplements (17) Infliximab (18)PPI (19) Moltilium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others……	
51. How do you describe the effectiveness of the prescribed medications	(0) no difference (1) slight improved (2) dramatic improvement (3) slightly worsened condition (4) dramatic deterioration	
52. How do you describe the side effects of the prescribed medications	(0) none (1) few and tolerable (2) many but tolerable (3) difficult to tolerate and interfere with daily life	

III- Examination		
53. Baseline Body Weight	**…….. kg**	
54. Height	**……..cm**	

55. Fahmy and El Sherbini Socioeconomic standard scoring

1- Education		**Score**
	1.Father	**2.Mother**
Read and write or illiterate non working	1	1
Read and write or illiterate working	2	2
Primary education non working	3	3
Primary education working	4	4
Preparatory education non working	5	5
Preparatory education working	6	6
Secondary education non working	7	7
Secondary education working	8	8
University higher non working	9	9
University higher working	10	10
3- Family income		
Satisfactory and saving		8
Satisfactory		6
Satisfactory and debt		4
Unsatisfactory		2
6- Family size		
3-4 members		4
5 members		3
6 members		2
7 or more members		1
4- Crowding index		
5 or more/ room		0
4-		1
2-		2
<2		3
5- Sanitation		
According to the presence of pure water supply all through the day, electricity and special water closets inside the house:		
All the three present		3
2 out of three		2
One out of three		1
1- Total Score		
1- High (≥31.5)		
2- Middle (21 - <31.5)		
3- Low (<21)		

Follow-up sheet

	Pre treatment	Follow Up					
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
	0	week 2	Week 4	week 6	Week 8	Week 10	week 12
Body weight							
Blood pressure							
Pulse							
CRP							
ESR							
Hb							
Plts							
WBCs							
FBS							
Abd US							
CT							
MRI							
GIT Endoscopy							
Colonoscopy							
Others							
Symptoms (frequency per day)							
Weight loss							
Diarrhea							
Constipation							
Flatulence							
Bloating/indigestion							
Hurt burn							
Urge incontinence							
Soiling							
Tenesmus							
Frequent bowel movements							
Abd cramps							
Epigastric pain							
Generalized abdominal pain							
Nausea							
Vomiting							
Loss of appetite							
Bowel movement interfere with ability to eat							
Blood in stool							
Bleeding per rectum							

	Pre treatment	Follow Up					
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
	0	week 2	Week 4	week 6	Week 8	Week 10	week 12
Back pain							
Fever							
Chills							
Night sweating							
Fatigue/lack of energy							
Headache							
Dizziness							
Insomnia/troubled sleep							
Limited sexual activity							
Infection							
Sick leaves/absenteeism							
Others							
Signs of other system affection							
Eye							
Joints							
Kidney							
Skin							
Liver							
Reproductive organs							

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057214.R1
Article Type:	Original research
Date Submitted by the Author:	24-Jan-2022
Complete List of Authors:	Abd El-Wahab, Ekram; Alexandria University High Institute of Public Health, Tropical Health Youssef, Ebtessam; Alexandria University High Institute of Public Health, Tropical Health Hassouna, Ehab; Alexandria Medical School, Internal Medicine
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Epidemiology
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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Helicobacter pylori infection in patients with inflammatory bowel diseases: a single-centre, prospective, observational study in Egypt

Running title: Inflammatory bowel disease and *Helicobacter pylori* infection

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- **word count**: 3983

- **number of references**: 53

- **number of tables**: 5

- **number of figures** : 2

Abstract

Objective: Conflicting results have been reported by numerous epidemiological studies investigating the association between *Helicobacter pylori* infection and inflammatory bowel disease (IBD). We aimed in this study to assess the possible association between *H. pylori* infection and IBD and its effects on disease progression.

Design: Prospective observational study

Setting: Specialized IBD care clinics at Alexandria University Student Hospital in northern Egypt, between March and June 2019.

Participants: Patients with IBD.

Analysis and outcome measures: IBD participants were screened for *H. pylori* infection and clinically evaluated at the initial visit and bimonthly for 3 months to record any potential improvement/flare of the IBD condition.

Results: Overall, 49.5% of patients with IBD had evidence of *H. pylori* infection. The course of IBD did not significantly differ in association with *H. pylori* infection or IBD treatment strategy. Cox regression analysis revealed that patients aged 20–35 years (OR, 95% CI= 6.20 [1.74–22.12]) and 35–55 years (OR, 95% CI = 557.9, [17.4–17922.8]), high socioeconomic status (OR 95% CI = 2.9 [1.11–7.8]), daily consumption of fiber-rich food (OR, 95% CI = 5.1 [1.32–19.5]), occasional consumption of snacks between meals (OR, 95% CI = 2.8 [2.5–70.5]), and eating four meals per day (OR, 95% CI = 13.3 (1.0–7.7]) predicted IBD flare. In contrast, eating fruits and vegetables was strongly protective. the probabilities of improvement of IBD symptoms after 12 weeks of follow-up were comparable, considering *H. pylori* infection status (0.793, *H. pylori*-negative *vs*. 0.778, *H. pylori*-positive) or IBD treatment option (0.811, conventional therapy *vs*. 0.750, biological therapy).

Conclusion: The association between IBD and *H. pylori* infection is unresolved and must be further evaluated in the context of specific environmental exposures that influence the development or relapse of IBD.

Keywords: Inflammatory Bowel Disease; Crohn's disease; Ulcerative colitis; *Helicobacter pylori*

Article summary

Strengths and limitations of this study

- The relatively small sample size may affect the generalizability of the results.
- The study lacks a lack of a non-IBD healthy control group, and the causal relationship between *H. pylori* infection and IBD cannot be established.
- The need of reliable diagnostic tests for *H. pylori* infection to better estimate the disease prevalence.
- We report the effect of *H. pylori* infection on the response to conventional *versus* biological treatment of IBD.

Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), comprises chronic, disabling, and progressive disorders characterized by lifelong treatment that impose a significant globally increasing threat to human health [1]. Numerous economically low-income countries have experienced a dramatic increase in the incidence of IBD [2]. Improved access to a more hygienic environment and the resulting decreased incidence of common childhood infections may represent a contributing factor through altering susceptibility to diseases with an autoimmune component, such as IBD [3 4]. Accordingly, microbial infections during childhood may protect against IBD. This rise may partially be accounted for by, the implementation of improved diagnostic methods and heightened awareness of IBD.

Although the pathogenesis of IBD is unknown, evidence indicates that it involves complex and unidentified interactions between environmental factors (such as infections, medicines, tobacco, food components) as well as host genetic factors that induce abnormal or inappropriate immunological reactions, or both, to components of the intestinal flora [5 6].

Evidence indicates that *Helicobacter pylori* resides in the upper gastrointestinal tract of approximately 50% of the world's population, among which >80% of people lack symptoms [7]. In Egypt, the prevalence is approximately 80% [8]. *H. pylori* can elicit a chronic systemic inflammatory response, which may trigger autoimmune reactions that may contribute to the pathogenesis of autoimmune diseases. The inflammatory response of the gastric mucosa mainly involves stimulation of the host's immune system in response to *H. pylori*, which induces a cell-mediated immune response characterized by elevated levels of cytokines. Consequently, products of local immune reactions may migrate to extra-gastric sites, which may account for the association between *H. pylori* infection and extra-gastric diseases, including autoimmune disorders [9].

Although numerous, diverse studies analyzed the association between *H. pylori* infection and IBD [9 10], a causal association between *H. pylori* and IBD remains to be established; and the are contradictory data related to the potential causative and the protective roles of *H. pylori* infection associated with IBD [11-19].

Assuming a potential protective role of *H. pylori* infection against IBD, *H. pylori* eradication treatment may influence the progression of IBD course and thus should be carefully administered, considering the findings of future prospective studies [16 20].

IBD occurs more frequently in regions with lower rates of *H. pylori* colonization. The steady increase in the incidence of IBD in *H. pylori*-endemic regions may reflect the advent of initiating anti-*H. pylori* therapy to treat peptic ulcers [13]. Furthermore, meta-analyses show that the prevalence of *H. pylori* infection is lower in patients with IBD compared with controls [9 10 13 19 21]. For example, long-term treatment with sulphasalazine contributes to the eradication of *H. pylori* infection [22]. Although unconfirmed, most studies indicate a protective role for *H. pylori* infection against the development of IBD [9 21].

With advances in identifying the pathological mechanisms underlying IBD, new therapies have been proposed, particularly those involving biological response modifiers. These include anti-tumor necrosis factor antibodies (anti-TNFα), IL-1/IL-6 receptor antagonists, and an anti-CD20 antibody. These therapies are generally well tolerated, although they may be associated with adverse effects, including increased susceptibility to infection and increased risk of malignancies [23].

These considerations inspired us to conduct a longitudinal study to further analyze the association between *H. pylori* infection and the flare of IBD and to investigate possible effects of *H. pylori* infection on the response to conventional *versus* biological treatment of IBD.

Methods

Study population and sampling

We conducted a prospective observational study at Alexandria University Student Hospital (AUSH) that is affiliated with Alexandria University, Egypt and serves students, faculty, and staff members. AUSH comprises outpatient clinics and inpatient and emergency departments with a bed capacity of 1000. We enrolled patients aged ≥18 years with confirmed IBD (triphasic CT abdomen, endoscopy/colonoscopy, and fecal calprotectin) and commenced IBD treatment (conventional or biological). Patients with irritable bowel syndrome were excluded according to the Rome III criteria [24].

Clinicians on the staff of the Internal Medicine Department of the AUSH selected the treatment (standard vs. biological). The prescribed treatment is the standard of care adopted by the AUSH for treating patients with IBD. Details of the treatment regimens and the parameters employed to select standard or biological treatment are described in File S1.

The frequency of *H. pylori* infection among patients with IBD is as high as 10.0% [21]. Using an alpha error = 0.05 and a 95% confidence level, the minimum required sample size was 138 patients. However, we ultimately enrolled 182 patients with IBD, because we predicted that the prevalence of *H. pylori* infection might be higher because of the endemicity of *H. pylori* infection in Egypt [8], and to compensate for possible dropouts during the follow-up. The sample size was calculated using Epi info 7 software. Patients with confirmed IBD who agreed to participate in the study were consecutively enrolled. According to their characteristics (Figure 1), the patients were assigned into groups according to the prescribed treatment regimen (File S1) as follows: Group 1 comprised patients administered conventional IBD treatment, and Group 2 included patients undergoing biological IBD treatment.

Stool samples was used to detect *H. pylori* antigen using a commercially available enzyme immunoassay (EIA) kit (Foresight EIA test kit for qualitative and quantitative detection of *H. pylori* in the stool; ACON Laboratories, Inc. San Diego, CA, USA). Each assigned group included patients with IBD with or without *H. pylori* infection, and *H. pylori*-positive patients were shown their laboratory findings. We did not commence *H. pylori* eradication therapy during the study period. After a 3-month follow-up, *H. pylori*-positive patients were referred to a specialist for further evaluation and case management according to the adopted standard of care.

Patient and Public Involvement

We informed the patients about the aims and concerns of the study and how it will add to better understanding of their disease etiology and triggering factors, which was highly appreciated by the patients, and motivated them to be a part of the cohort intended for the long term follow-up by the clinicians. However, It was not appropriate or possible to involve patients or the public in the design,

conduct, reporting, or dissemination plans of our research. All the laboratory and clinical data were reported to the study participants, where we discussed the study findings in a simple language.

Assessments

Baseline evaluation included the patient's history, full clinical examination, and laboratory tests. A data collection form (File S2) was used to collect baseline data as follows: sociodemographics, personal habits, lifestyle, physical activity and exercise, dietary habits and restrictions, family history, medical history, comorbidities, and medications. Clinical data collected were from each patient during the initial visit were as follows: Disease onset, history of present complaints, frequency and duration of IBD attacks, past and current IBD medications, history of changing therapy, surgical intervention, and complications. History of *H. pylori* infection and undergoing *H. pylori* eradication therapy during the past 12 months were recorded during each follow-up visit. All patients were followed bimonthly for three months (6 visits) during IBD treatment. Patients were contacted weekly via telephone and asked about the frequency and severity of symptoms and if adverse effects associated with treatment occurred during the previous week.

Blood pressure (BP) and anthropometric measurements were measured according to standard techniques [25-27]. Body mass index (BMI) was calculated according to the Quetelet's index: BMI = (weight [kg]/height^2 [m^2]). At each follow-up visit, laboratory tests were performed as follows: complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting blood glucose (FBG), and fecal calprotectin [28]. Imaging techniques included triphasic CT and endoscopy/colonoscopy when indicated. All patients underwent full-length colonoscopy (Pentax colonoscopies). Colonoscopic biopsies acquired from the rectum and sigmoid; descending, transverse, ascending colon; as well as the cecal mucosa. Histological analyses of the degree of inflammation associated with CD and UC were evaluated according to the European consensus on the histopathology of IBD [29].

The socioeconomic status of the enrolled patients with IBD was calculated and categorized as high, middle, low, and very low, according to a modified social scoring system [30].

Outcomes

Patients in each group were clinically evaluated every two weeks for 3 months to record potential improvement/flare of IBD. The primary outcome of the study was the number of patients with IBD who achieved remission at the end of the follow-up period.

Statistical analysis

Data were reviewed for accuracy and integrity and analyzed using SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Continuous variables are presented as the mean ± standard deviation, and categorical variables are expressed as numbers with proportion, n (%). Variables relevant to laboratory data were dichotomized according to prefixed cutoffs, considering the normal reference values. The Student *t* test was performed to compare quantitative variables between two groups of normally distributed data. The chi squared (χ^2) test was performed to evaluate the association between qualitative variables. Fisher's exact test with Yates correction was used when cell count was < 5. Reponses that have non-applicable (NA) values were coded with "-1" and we use the SPSS program strategy for handling missing values in the analysis. Repeated-measures ANOVA was used to test the significance of differences in the means of quantitative variables measured at different times. Multivariate logistic regression analyses were conducted to identify independent risk factors for *H. pylori* infection among patients with IBD. Cox regression analysis (or proportional hazards regression) was used to evaluate the effects of several variables at the time of occurrence of a specified event. Factors associated with IBD flare/remission were thus identified when testing variables with significant differences (significance levels <0.05) in the simple logistic regression analyses. Kaplan–Meier analysis was used to estimate the probability of recovery (remission of IBD as the event-of-interest) considering *H. pylori* infection status and treatment option. Recovery-defined remission/improvement in IBD status was based on clinical and laboratory data, whereas censored data defined lack of improvement or flare of the inflammatory condition. Statistical analyses were conducted using two-tailed tests (level of significance <0.05).

Results

Patients' sociodemographics and clinical characteristics

Patients with IBD (n = 182) (n = 96 [52.7%] UC and n = 86 [47.3%] CD) included 51.7% males, 58.2% married, 51.6% resided in urban areas, 76.9% highly literate, and 82.4% nonsmokers. The average age was 27.0 ± 7.3 years, with the majority ranging from 20 to 35 years. Normal BMI was a predominant feature (59.3%), and 31.9% were overweight. Patients' other sociodemographic characteristics are shown in (Table 1).

Patients did not significantly differ according to their physical activity scores. However, those without *H. pylori* infection were judged to have a favorable food-habit score compared with those with *H. pylori* infection (12.2 ± 5.0 vs. 10.7 ± 3.8, $p = 0.018$) (Table S1).

Patients' baseline clinical and laboratory findings are presented in Table S2. Compared with patients without *H. pylori* infection, infected patients had higher rates of abdominal cramps (91.1% *vs*. 84.8%), abdominal pain (85.6% *vs*. 81.5%), bloating/indigestion (98.9% *vs*. 95.7%), flatulence (100.0% *vs*. 96.7%), diarrhea (98.9% *vs*. 96.7%), rectal bleeding (73.3% *vs*. 65.2%), fever (33.3% *vs*. 26.1%), chills (10.0% *vs*. 4.3%), infection (23.3% *vs*. 14.1%), fatigue/lack of energy (88.9% *vs*. 68.5%), sick leave/absenteeism (8.9% *vs*. 6.5%), and higher mean CRP (33.0 ± 23.0 *vs*. 28.2 ± 23.9) and ESR (34.6 ± 13.2 *vs*. 33.6 ± 14.1) levels. However, the differences were not statistically significant. GIT endoscopy and colonoscopy revealed features of CD and UC, indicated by superficial ulcerations and mild infiltration.

H. pylori infection among patients with IBD

We detected *H. pylori* infection in 49.5% of patients, including those with UD (48, 50.0%) and CD (42, 48.8%) (OR, 95% CI = 1.05, 0.59–1.88), although 85.6% reported undergoing *H. pylori* eradication therapy during the past 12 months. The infection rate was highest (82.2%) among the age group 20 to <35 years (Table 1). Regression analysis revealed that conventional treatment of IBD (OR, 95% CI = 1.99 [1.03–3.85]), adults aged 20 or <35 years (OR, 95% CI = 6.20 [1.74–22.12]) and 35–55 years (OR, 95% CI = 11.1 [1.18–104.64]), and mixed food source (OR, 95% CI = 3.12 [1.60–6.06]) predicted *H. pylori* infection ($p < 0.05$) (Table 2).

Assessment of IBD improvement/flare in relation to *H. pylori* infection

The total symptom scores of all patients, as well as the levels of ESR, CRP, Hb, and fecal calprotectin, significantly and linearly declined throughout the follow-up of all patients, independent of the status of *H. pylori* infection ($p < 0.05$). The values of other parameters (body weight, pulse, BP, WBCs, platelet count, and FBG) fluctuated in a nonlinear pattern, although the levels were within normal range. Overall, the changes (effect size) varied with time, because the pattern did not significantly differ relative to *H. pylori* infection (Table 3 and Figure S1). Subgroup analysis yielded similar results associated with the type of treatment (conventional, Table S3 and Figure S1 or biological, Table S4 and Figure S1).

Factors associated with improvement in IBD symptoms

Cox regression analysis revealed that subjects aged 20–35 years (OR, 95% CI= 6.20 [1.74–22.12]) and 35–55 years (OR, 95% CI = 557.9, [17.4–17922.8]), high socioeconomic status (OR, 95% CI = 2.9 [1.11–7.8]), daily consumption of fiber-rich food (OR, 95% CI = 5.1 [1.32–19.5]), occasional consumption of snacks between meals (OR, 95% CI = 2.8 [2.5–70.5]), and eating four meals per day (OR, 95% CI = 13.3 (1.0–7.7]) were significantly associated with IBD flare ($p < 0.05$). In contrast, eating fruits and vegetables protected against IBD flare (Tables 4 and Table S5).

Probability of improvement of IBD symptoms in relation to *H. pylori* infection and IBD treatment strategy

Kaplan–Meier analysis revealed that the probabilities of recovery (remission) among the patients after 12 weeks of follow-up were comparable, considering *H. pylori* infection status (0.793, *H. pylori*-negative vs. 0.778, *H. pylori*-positive) or IBD treatment option (0.811, conventional therapy vs. 0.750, biological therapy). The number of patients who recovered from IBD among *H. pylori*-negative patients was similar to that of *H. pylori*-positive patients. In contrast, the proportion of recovered patients with IBD who underwent conventional therapy was higher compared with those administered biological therapy, although the difference was not significant. Thirty-nine subjects did not recover until the end of the study. The results of log-rank, Breslow, and Tarone-Ware tests of

equality of recovery (remission) did not significantly differ in relation to *H. pylori* infection status or IBD treatment strategy ($p > 0.05$) (Table 5 and Figure 2).

Discussion

Recent improvements in hygienic conditions and socioeconomic status have reduced *H. pylori* infection rates, and this trend accompanies increased IBD incidence in most countries. However, the role of *H. pylori* in IBD is unknown [2 16 31]. Numerous studies found lower *H. pylori* infection rates in patients with CD, UC, or both, compared with non-IBD controls, although a few studies did not detect a significant association [9 10 13 21 31]. Recent epidemiological studies, animal experiments, and meta-analyses reveal an inverse correlation between *H. pylori* infection and the onset of IBD onset, suggesting that colonization by *H. pylori* confers a protective effect against autoimmune diseases [13 23 32].

To further explain the negative association between *H. pylori* infection and IBD, we conducted a longitudinal study of patients with IBD, with or without *H. pylori* infection, to determine the influence *H. pylori* infection on patients' responses to conventional vs. biological treatment of IBD.

H. pylori was detected in approximately 50% of the patients, which is low compared with the prevalence among the population of Egypt, where disease is endemic [33-36]. These findings support the results of studies showing that lower rates *H. pylori* infection of patients with IBD, suggesting an association between *H. pylori* and IBD [9 21]. The rate *H. pylori* infection is significantly higher among patients with IBD who undergo conventional treatment, which conflicts with studies suggesting that 5-aminosalicylates or sulphasalazine interfere with the adhesion of *H. pylori* to the mucosa and block its proliferation [22 37-39]. For example, the results of multiple studies do not support the conclusion that treatment with sulfasalazine or other drugs such as 5-aminosalicylic acid (5-ASA), thiopurines, steroids, and antibiotics influence the colonization rate of *H. pylori* [13 40-42]. It is wort noting that although the treatment of IBD patients with anti-TNF-α agents, immunosuppressant and/ or corticosteroid increases the risk of infections, there is no direct evidence that novel therapeutic strategies such as anti-tumor necrosis factor alpha (TNF-α) and immunosuppressants result in

exacerbating or influence the prevalence of H. pylori infection Similar findings were reported by a study of novel therapeutic strategies such as anti-tumor necrosis factor alpha (TNF-α) treatment {Singh, 2011 #145;Triantafillidis, 2014 #29;Zhong, 2021 #144}.

Here we show that the majority of *H. pylori*-positive patients with IBD admitted undergoing *H. pylori* eradication therapy during the previous 12 months, which raises questions about the efficacy of eradication therapy or revels reinfection among this group of patients. Notably, most studies do not report subjects' history of treatment of *H. pylori* infection [13]. It is therefore possible that such patients with IBD were treated for *H. pylori* infection before enrollment, culminating in an incorrectly low rate of *H. pylori* infection.

Accumulating evidence suggests that *H. pylori*, through its ability to regulate the immune response, protects human from diseases with an autoimmune component, including IBD [43]. The results of investigations designed to confirm this possibility are controversial. For example, the heterogeneity among studies accounted for by methods used to diagnose IBD and *H. pylori* infection, study location, study population, and the possibility of publication bias limit the validity of this conclusion and raise questions concerning the robustness of their findings.

Here we conducted a prospective study to extended previous work through investigations of the association between *H. pylori* infection and IBD. A potential avenue for extending our study involved broadening the inclusion criteria to gain further insight into local variations of the protective effects of *H. pylori* against IBD. In contrast to previous studies, we added subgroup analysis of *H. pylori* infection and the type of IBD treatment. However, we did not detect a significant relationship between the two conditions. For example, disease course was similar among all patients with IBD regardless of their *H. pylori* infection status or conventional or biological treatment. Moreover, the extent, and severity of IBD increased with a decrease in *H. pylori* infection. We were intrigued by our findings that that the proportion of patients administered conventional therapy who recovered from IBD was higher than those administered biological therapy. This may be explained by the higher rate of *H. pylori* infection among patients with IBD administered conventional therapy or that patients administered biological therapy were refractory to previous conventional therapy and therefore suffered from increased disease severity.

Evidence indicates that IBD is induced through complex interactions between environmental and genetic factors. The growing burden of IBD may serve as a proxy for the hygiene hypothesis and improvements in the sanitation of living conditions, lifestyle and dietary changes, more frequent antibiotic use, enhanced diagnostic methods, and heightened awareness of IBD [1 44 45]. Accordingly, we further investigated the role of host and environmental cofactors reported to ameliorate or incite factors for IBD flare (e.g., diet, smoking, physical activity, breastfeeding, socioeconomic status, education, occupation, urban versus rural lifestyle, and medication [1]). In this context, we were guided by existing studies that recognized differences in potential risk factors or features unique to certain populations, such as the Mediterranean diet. Indeed, dietary factors play a crucial role in disease initiation or relapse [46], although certain diets such as the Mediterranean diet are purported to protect against IBD [47-49].

The plant-based, semi-vegetarian Mediterranean diet alleviates symptoms of IBD and maintains patients in remission, potentially through reducing inflammation and improving the microbiota [50 51]. In our present cohort, *H. pylori*-negative patients with IBD and those experiencing less flare had a more favorable overall dietary habit score. Consistent with Kakodkar's recommendations [50], which encourage the consumption of all vegetables and fruits in an IBD diet, we observed a strong protective role on IBD flare of daily and 2–3-times weekly consumption of vegetables and fruits. Moreover, a recent meta-analysis shows that the beneficial effect of *H. pylori* experienced by Mediterranean populations with IBD is lower compared with residents of East Asian and European regions [19]. Nevertheless, the analysis did not explicitly incorporate dietary information or study the putative beneficial effect of diet as a confounder. Moreover, this positive effect may be attributed to the relative abundance of CagA *H. pylori* in these populations, a strain that produces specific constituents that modulate host immune defenses [52].

Fiber may serve as an anti-inflammatory component of IBD treatment, although a converse effect can occur [1]. Our Cox regression analysis revealed that daily consumption of foods rich in insoluble fibers, such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs, and spices, significantly increased the risk of IBD flare, particularly in patients who consume four daily meals interspersed with occasional snacks.

In agreement with Gentschew et al., [53] trans-fat consumption was associated with a higher probability of IBD flare, although this was not a variable included in our final model. Although our findings suggest a role for diet in IBD flare, its effect is questionable because of the limitations of recall bias and multifactorial exposures. Moreover, patients with IBD may alter their dietary habits in response to symptoms that vary with disease activity, which requires further direct research into the role of diet in IBD.

Variations in the protective effects of *H. pylori* on IBD may be explained by socioeconomic factors. For example, here we show that patients with IBD with higher socioeconomic status and mainly urban residents had a higher chance of disease flares. Moreover, the frequency of *H. pylori* infection did not significantly vary in association with socioeconomic status. These findings support the argument that factors associated with an urban lifestyle and industrialization influence risk of IBD. Furthermore, the rate of gastric colonization by *H. pylori* was significantly higher in adults aged >20 years, although there was no significant difference in the average age of IBD onset between *H. pylori*-positive and -negative groups. This age group experienced a higher frequency of disease flares. These findings may be explained by patients' histories of comorbidities or lifestyle, which affect the occurrence of IBD. Demographic variables other than age did not exert detectable effects.

The findings of this study must be interpreted in view of its limitations. First, we did not test gastric biopsies for *H. pylori*, which may have decreased the disease prevalence rate. However, this would incur the burdens of an ethically questionable invasive procedure. A urea breath test may serve as a better alternative, although we did not have access to this test in our centers. Second, the small sample size was a major limitation and may have influenced the estimation of effect size. Third, the trend of decreased *H. pylori* infection in patients administered biological therapy coincided with increased severity of IBD, which should be investigated by a larger, statistically robust randomized controlled trial. Moreover, our results merit reassessment in a cohort of patients from a background population with a low prevalence of *H. pylori* that includes detailed information about eradication treatment and administration of other antibiotics. Fourth, a causal relationship between *H. pylori* infection and IBD cannot be established through an uncontrolled study (control group without IBD), and further large scale prospective clinical trials are required. Thus, studies are warranted to

investigate the effects of eradication of *H. pylori* on the development of IBD combined with analyses of environmental exposures, hygiene diet, physical activity, and intestinal microbiota as significant confounders. An ideal study would be prospective and initiated when IBD is diagnosed.

Conclusions

Together, the findings of our present analysis of the association between IBD and *H. pylori* infection are inconclusive, and further studies are required. Thus, much remains to be learned about the causes of IBD and whether specific environmental exposures influence the development of disease and its course.

Ethical considerations

The study was approved by the institutional review board and the ethics committee of the High Institute of Public Health affiliated with Alexandria University, Egypt [Ref no. 603 - 2019]. The study was conducted in accordance with the international ethical guidelines and that of the Declaration of Helsinki. Informed written consent was obtained from each participant after explaining the aim and concerns of the study. The datasheets were coded by number to ensure anonymity and confidentiality of the participants' data.

Conflict of Interest

All authors declare no conflict of interest.

Data availability statement

All data are fully available without restriction by the corresponding author at ekram.wassim@alexu.edu.eg

Funding: None

Acknowledgements

We would like to acknowledge the study participants for accepting to participate in the study.

Author contribution

EWAW: Conceptualization, developed the theoretical framework and study design, took the lead for overall direction and planning of the study implementation, data curation, statistical analysis and interpretation of data, major contribution to writing, revised and approved final version of the manuscript

EIY: Study implementation and recruitment of the study participants, data collection, clinical evaluation and follow up, analysis and interpretation of data, contributed to the writing of the manuscript, revised and approved final version of the of the manuscript.

EMH: Supervised the study implementation and data collection, facilitated the recruitment of the study participants, clinical evaluation and follow up, data curation, contributed to the writing of the manuscript, revised and approved final version of the manuscript.

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Figure legends

Figure 1: Patients' dispositions

Figure 2: The equality of recovery (remission of IBD symptoms) during the follow-up periods associated with *H. pylori* infection status and IBD treatment strategies.

Figure S1: Patients' clinical and laboratory findings during follow-up periods associated with *H. pylori* infection status and the IBD treatment strategy.

List of Tables

Table 1: Characteristic of the study population

		IBD patients		*H. pylori* infection in IBD patients				*p*~
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.	%	
Type of IBD diagnosed	Crohn's disease	86	47.3	44	47.8	42	46.7	0.876
	Ulcerative colitis	96	52.7	48	52.2	48	53.3	
	NA	92	50.5	92	100	0	0	
Onset of *H. pylori* infection	Few weeks ago	7	3.8	0	0	7	7.8	<0.001
	3 – 6 months	10	5.5	0	0	10	11.1	
	6 months – 1 year	35	19.2	0	0	35	38.9	
	> 1 year	38	20.9	0	0	38	42.2	
History of receiving *H. pylori* eradication therapy during the past 12 months	No	92	50.5	76	82.6	13	14.4	<0.001
	Yes	90	49.5	16	17.4	77	85.6	
Treatment option given	Conventional	106	58.2	47	51.1	59	65.6	0.048
	Biological	76	41.8	45	48.9	31	34.4	
Sex	Male	94	51.6	46	50	48	53.3	0.653
	Female	88	48.4	46	50	42	46.7	
Age (Years)	16 – <20 Years	20	11	15	16.3	5	5.6	0.036
	20 – <35 Years	136	74.7	62	67.4	74	82.2	
	35 – 55 Years	26	14.3	15	16.3	11	12.2	
	Mean ± SD	27.0 ± 7.3		27.6 ± 8.0		26.3 ± 6.5		*t*=1.3, *p*= 0.204
Age at IBD diagnosis	10 – >19	69	37.9	35	38	34	37.8	0.211
	20 – <30	83	45.6	46	50	37	41.1	
	30 – 45	30	16.5	11	12	19	21.1	
	Mean ± SD	21.6 ± 6.4		21.4 ± 6.3		22.0 ± 6.5		*t*= -0.583, *p*= 0.560
Residence	Rural	88	48.4	51	55.4	37	41.1	0.053
	Urban	94	51.6	41	44.6	53	58.9	
Education	Illiterate	2	1.1	0	0	2	2.2	0.096
	Read and write	23	12.6	12	13	11	12.2	
	Primary	4	2.2	4	4.3	0	0	
	Preparatory	13	7.1	9	9.8	4	4.4	
	Secondary	44	24.2	24	26.1	20	22.2	
	University education	96	52.7	43	46.7	53	58.9	
Working status	No	88	48.4	39	42.4	49	54.4	0.104
	Yes	94	51.6	53	57.6	41	45.6	
Occupation	Unemployed	37	20.3	21	22.8	16	17.8	0.012
	Student	45	24.7	16	17.4	29	32.2	
	Clerical	2	1.1	2	2.2	0	0	
	Professional	39	21.4	17	18.5	22	24.4	
	Housewife	21	11.5	10	10.9	11	12.2	
	Auxiliary worker	22	12.1	12	13	10	11.1	
	Farmer	16	8.8	14	15.2	2	2.2	
Marital status	Single	73	40.1	37	40.2	36	40	0.370
	Married	106	58.2	55	59.8	51	56.7	
	Widowed	2	1.1	0	0	2	2.2	
	Divorced	1	0.5	0	0	1	1.1	
Socioeconomic standard	High	58	31.9	24	26.1	34	37.8	0.206
	Middle	52	28.6	30	32.6	22	24.4	
	Low	72	39.6	38	41.3	34	37.8	
Consanguinity	No	144	79.1	70	76.1	74	82.2	0.309
	Yes	38	20.9	22	23.9	16	17.8	
History of being breastfed	No	26	14.3	14	15.2	12	13.3	0.716
	Yes	156	85.7	78	84.8	78	86.7	

a; Included chronic sinusitis, vertigo, lumbar disc prolapse, familial dyslipidemia, hemorrhoids, scleritis, HCV, anemia, fatty liver, steatosis, psoriasis, peripheral neuropathy, chronic cholecystitis)

Table 1 continued

		IBD patients		*H. pylori* infection in IBD patients				*p*~
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.	%	
Smoking	Never	150	82.4	75	81.5	75	83.3	0.724
	Current smoker	26	14.3	13	14.1	13	14.4	
	Ex-Smoker	6	3.3	4	4.3	2	2.2	
	NA	153	84.1	77	83.7	76	84.4	
Age of starting Smoking	< 20 Years	17	9.3	10	10.9	7	7.8	0.655
	20-30 Years	12	6.6	5	5.4	7	7.8	
	>30 Years	0	0	0	0	0	0	
Smoking other than cigarette	Never	180	98.9	90	97.8	90	100	0.16
	Shisha	2	1.1	2	2.2	0	0	
BMI categories	< 18.5 (underweight)	3	1.6	2	2.2	1	1.1	0.345
	18.5-24.99 (Normal weight)	108	59.3	58	63	50	55.6	
	25-29.99 (Overweight)	58	31.9	24	26.1	34	37.8	
	30-39.99 (Obese)	13	7.1	8	8.7	5	5.6	
Co-morbidities	No	82	45.1	43	46.7	39	43.3	0.644
	Yes	100	54.9	49	53.3	51	56.7	
	Diabetes Mellitus	10	5.5	4	4.3	6	6.7	
	Hypertension	30	16.5	15	16.3	15	16.7	
	Bronchial Asthma/COPD	15	8.2	11	12	4	4.4	
	Heart disease	1	0.5	0	0	1	1.1	
	Renal disease	1	0.5	1	1.1	0	0	
	Liver disease	1	0.5	0	0	1	1.1	
	Skin allergy	18	9.9	11	12	7	7.8	
	Hyperthyroidism	4	2.2	1	1.1	3	3.3	
	Hypothyroidism	8	4.4	0	0	8	8.9	
	Other autoimmune diseases	1	0.5	0	0	1	1.1	
	Others[a]	27	14.8	8	8.7	19	21.1	
Autoimmune diseases	No	163	89.6	85	92.4	78	86.7	0.207
	Yes	19	10.4	7	7.6	12	13.3	
Medications	None	13	7.1	12	13	1	1.1	0.002
	Analgesic (NSAIDs)	12	6.6	3	3.3	9	10	
	Antidiabetics	6	3.3	3	3.3	3	3.3	
	Antihypertensives	32	17.6	16	17.4	16	17.8	
	Corticosteroids	10	5.5	4	4.3	6	6.7	
	IBD therapy	151	83	70	76.1	81	90	
	Hormonal contraceptives	2	1.1	0	0	2	2.2	
	Thyroxin	9	4.9	2	2.2	7	7.8	
	Others	37	20.3	15	16.3	22	24.4	

~ *p* value for Chi Square test. Significant at <0.05
IBD; inflammatory bowel disease
H. pylori; *Helicobacter pylori*
No history of alcohol or drug abuse was reported
NA; non-applicable

Table 2: Predictors of *H. pylori* infection in patients with IBD

	Backward Stepwise (Wald) Logistic Regression	B	S.E.	Wald	df	Sig. (*p* value)	Exp(B)	95.0% C.I. for EXP(B)	
								Lower Limit	Upper Limit
Step 5	Treatment of IBD								
	Biological treatment	-0.686	0.337	4.14	1	**0.042**	**0.50**	**0.26**	**0.98**
	Conventional treatment	0.686	0.337	4.14	1	**0.042**	**1.99**	**1.03**	**3.85**
	Age group (Years)								
	16 - <20			7.93	2	0.019			
	20 - <35	1.825	0.649	7.92	1	**0.005**	**6.20**	**1.74**	**22.12**
	35 - 55	2.408	1.144	4.43	1	**0.035**	**11.11**	**1.18**	**104.64**
	Food source								
	Homemade			11.48	2	0.003			
	Restaurant	-0.024	0.915	0.00	1	0.979	0.98	0.16	5.87
	Mixed	1.137	0.339	11.25	1	**<0.001**	**3.12**	**1.60**	**6.06**
	Constant	0.108	1.015	0.01	1	0.915	1.11		

p value significate at <0.05
H. pylori; *Helicobacter pylori*
IBD; inflammatory bowel disease

Table 3: Repeated-measures ANOVA of clinical and laboratory findings among patients with IBD during follow-up

Parameter	*H. pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA												
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects					Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12													
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	34.6 ± 13.2	30.5 ± 10.9	27.0 ± 10.3	24.2 ± 8.9	20.6 ± 27.3	17.3 ± 6.9	14.0 ± 5.3	T	96.93	<0.001	0.769	1.000	T	350.0	<0.001	0.660	570.0	<0.001	1.75	0.188	0.010
	Negative	33.6 ± 14.1	29.1 ± 11.3	25.2 ± 9.4	21.4 ± 8.6	19.2 ± 6.9	15.9 ± 5.3	13.0 ± 4.9	T × S	1.156	0.322	0.038	0.448	T × S	0.666	0.538	0.004	0.001	0.974			
CRP	Positive	33.0 ± 23.0	26.4 ± 18.4	22.8 ± 16.1	18.9 ± 13.0	15.1 ± 9.7	12.5 ± 6.9	10.1 ± 7.2	T	31.74	<0.001	0.521	1.000	T	152.0	<0.001	0.458	181.4	<0.001	2.59	0.109	0.014
	Negative	28.2 ± 23.9	22.9 ± 19.5	19.0 ± 15.4	15.9 ± 12.7	13.0 ± 9.4	10.6 ± 6.8	8.2 ± 4.5	T × S	0.708	0.644	0.024	0.276	T × S	0.788	0.418	0.004	0.848	0.358			
FBG	Positive	94.9 ± 11.1	93.0 ± 10.6	91.6 ± 9.8	94.4 ± 11.5	92.1 ± 9.5	94.5 ± 14.1	93.7 ± 9.0	T	3.52	0.003	0.108	0.945	T	2.77	0.016	0.015	2.753	0.11	0.974	0.325	0.005
	Negative	96.1 ± 11.6	93.0 ± 10.6	95.1 ± 9.3	96.0 ± 13.1	93.7 ± 9.7	92.9 ± 10.4	95.1 ± 8.4	T × S	1.48	0.187	0.048	0.565	T × S	1.56	0.168	0.009	0.443	0.507			
Calprotectin	Positive	515.0 ± 206.7		314.5 ± 166.3		157.4 ± 82.2		74.5 ± 29.3	T	253.0	<0.001	0.810	1.000	T	569.4	<0.001	0.760	753.5	<0.001	0.424	0.516	0.002
	Negative	517.4 ± 214.4		326.3 ± 139.4		172.0 ± 88.1		85.5 ± 66.9	T × S	0.157	0.925	0.003	0.078	T × S	0.108	0.854	0.001	0.073	0.787			
Hb	Positive	11.0 ± 1.4	11.1 ± 1.3	11.2 ± 1.2	11.5 ± 1.1	11.6 ± 1.0	11.7 ± 0.9	12.0 ± 0.9	T	49.7	<0.001	0.63	1	T	151.0	<0.001	0.456	279.2	<0.001	0.042	0.837	0.00024
	Negative	10.8 ± 1.4	11.0 ± 1.6	11.3 ± 1.1	1.5 ± 1.0	11.7 ± 1.0	12.0 ± 0.81	12.2 ± 0.75	T × S	3.1	0.007	0.096	0.91	T × S	3.75	0.012	0.02	5.61	0.019			
WBCs	Positive	6821.1 ± 1506.9	6701.1 ± 1349.8	6511.8 ± 1161.0	6597.6 ± 1271.7	6625.4 ± 1057.3	6497.2 ± 1025.5	6369.2 ± 1131.6	T	4.21	0.001	0.126	0.977	T	7.26	<0.001	0.039	2.44	0.120	14.7	<0.001	0.076
	Negative	6420.8 ± 1530.5	6249.0 ± 1385.3	8170.1 ± 1195.3	5890.8 ± 1066.8	5985.9 ± 1022.0	5873.3 ± 1033.1	5895.6 ± 979.3	T × S	1.05	0.394	0.035	0.409	T × S	1.18	0.318	0.007	1.65	0.200			
Platelets	Positive	296.2 ± 67.4	292.3 ± 66.3	287.0 ± 65.7	282.1 ± 57.9	282.5 ± 51.1	281.8 ± 50.2	284.2 ± 54.0	T	3.23	0.005	0.100	0.922	T	5.12	0.003	0.028	7.37	0.007	0.015	0.904	0.0001
	Negative	304.8 ± 61.7	283.0 ± 50.4	279.2 ± 44.3	282.0 ± 48.5	288.1 ± 46.5	280.0 ± 39.4	284.1 ± 44.2	T × S	1.02	0.415	0.034	0.396	T × S	1.22	0.302	0.007	0.559	0.456			
Total symptom score	Positive	20.9 ± 3.2	20.3 ± 3.4	14.2 ± 4.2	5.8 ± 3.1	2.9 ± 3.3	2.9 ± 3.0	0.7 ± 2.1	T	754.9	<0.001	0.964	1.000	T	1371.1	<0.001	0.890	432	<0.001	0.007	0.932	0.00004
	Negative	20.6 ± 3.1	20.4 ± 3.7	13.8 ± 4.6	5.4 ± 2.7	3.4 ± 3.0	3.3 ± 2.9	0.8 ± 1.6	T × S	0.901	0.496	0.031	0.35	T × S	0.728	0.502	0.004	0.003	0.955			
Body weight	Positive	68.3 ± 11.7	68.3 ± 11.8	69.1 ± 11.7	69.4 ± 11.5	69.4 ± 11.4	69.6 ± 11.1	69.3 ± 11.9	T	20.34	<0.001	0.411	1.000	T	16.67	<0.001	0.085	0.061	0.805	0.067	0.797	0.0004
	Negative	67.6 ± 12.2	67.6 ± 12.1	68.3 ± 12.1	68.0 ± 13.8	68.9 ± 12.1	69.6 ± 12.2	70.2 ± 12.0	T × S	2.08	0.058	0.067	0.740	T × S	3.95	0.013	0.021	7.73	0.006			
Pulse	Positive	80.8 ± 5.0	79.9 ± 4.3	78.3 ± 4.0	77.2 ± 4.8	78.3 ± 4.1	77.4 ± 4.1	78.5 ± 2.8	T	5.36	<0.001	0.155	0.995	T	8.24	<0.001	0.044	6.93	0.009	3.13	0.079	0.017
	Negative	80.5 ± 5.6	79.5 ± 5.5	78.9 ± 4.8	80.3 ± 5.0	78.7 ± 5.0	78.2 ± 5.0	78.3 ± 4.7	T × S	2.67	0.017	0.084	0.856	T × S	3.27	0.007	0.018	6.67	0.011			
Pulse pressure	Positive	41.0 ± 5.6	41.3 ± 6.7	39.7 ± 8.9	40.7 ± 8.6	41.1 ± 7.6	39.6 ± 6.9	41.7 ± 9.7	T	0.729	0.627	0.024	0.284	T	0.759	0.593	0.004	1.69	0.195	1.13	0.29	0.006
	Negative	41.5 ± 6.8	40.2 ± 6.8	41.6 ± 7.9	40.9 ± 8.1	41.8 ± 8.5	41.8 ± 8.1	42.0 ± 9.3	T × S	1.28	0.270	0.042	0.493	T × S	1.201	0.305	0.007	0.286	0.593			

H. pylori; *Helicobacter pylori*
IBD; inflammatory bowel disease
$p < 0.05$ is significant
[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)
[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant
[c] large effect if the value of partial Eta squared >0.1
T × S; time versus state of H. pylori infection

Table 4: Cox regression analysis of factors associated with IBD flare during follow-up

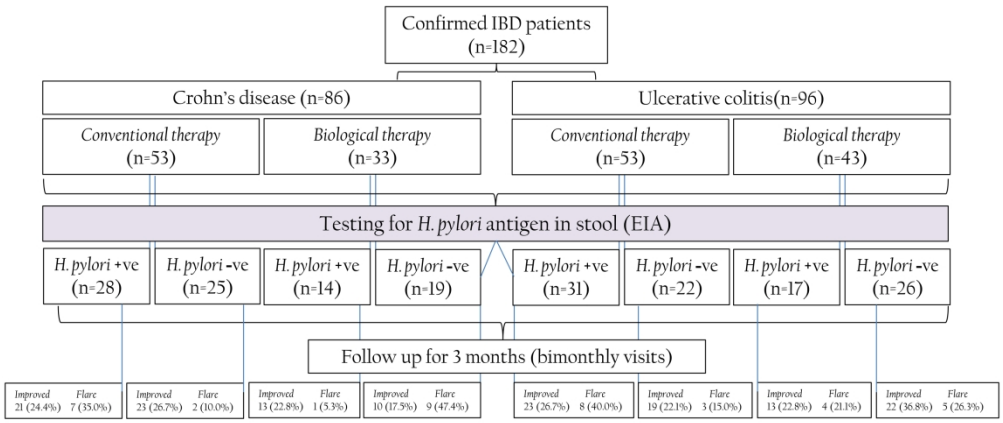
	Backward Stepwise (Wald) Logistic Regression	B	SE	Wald	df	Sig. (*p* value)	Exp(B)	95.0% CI for Exp(B) Lower Limit	95.0% CI for Exp(B) Upper Limit
Step 6	Age (Years)								
	16 - <20 Years			13.83	2	<0.001			
	20 - <35 Years	1.50	0.71	4.41	1	**0.036**	**4.49**	**1.11**	**18.21**
	35 - 55 Years	6.32	1.77	12.76	1	**<0.001**	**557.92**	**17.37**	**17922.78**
	Socioeconomic standard								
	High	1.08	0.50	4.71	1	**0.030**	**2.94**	**1.11**	**7.79**
	Middle	0.68	0.48	1.97	1	0.160	1.97	0.76	5.10
	Low			4.71	2	0.095			
	Food rich in insoluble fibers								
	Once per week			8.75	2	0.013			
	2-4 times per week	0.02	0.58	0.00	1	0.973	1.02	0.33	3.18
	Daily	1.62	0.69	5.61	1	**0.018**	**5.08**	**1.32**	**19.49**
	Fruits and Vegetables								
	Never			22.20	3	<0.001			
	Once per week	-7.07	1.63	18.74	1	**<0.001**	**0.00**	**0.00**	**0.02**
	2-4 times per week	-7.61	1.62	22.06	1	**<0.001**	**0.00**	**0.00**	**0.01**
	Daily	-7.47	1.68	19.76	1	**<0.001**	**0.00**	**0.00**	**0.02**
	Number of meals per day								
	Two			10.25	2	0.006			
	Three	-0.11	0.38	0.08	1	0.780	0.90	0.43	1.89
	Four	2.59	0.85	9.30	1	**0.002**	**13.33**	**2.52**	**70.46**
	Snacks between meals								
	Never			11.43	2	0.003			
	Occasionally	1.04	0.51	4.07	1	**0.044**	**2.82**	**1.03**	**7.72**
	Daily	-3.89	2.03	3.69	1	0.055	0.02	0.00	1.08

IBD; inflammatory bowel disease
p value significate at < 0.05

Table 5: Kaplan–Meier analysis of the probability of improvement in IBD symptoms in relation to with H. pylori infection and IBD treatment strategy

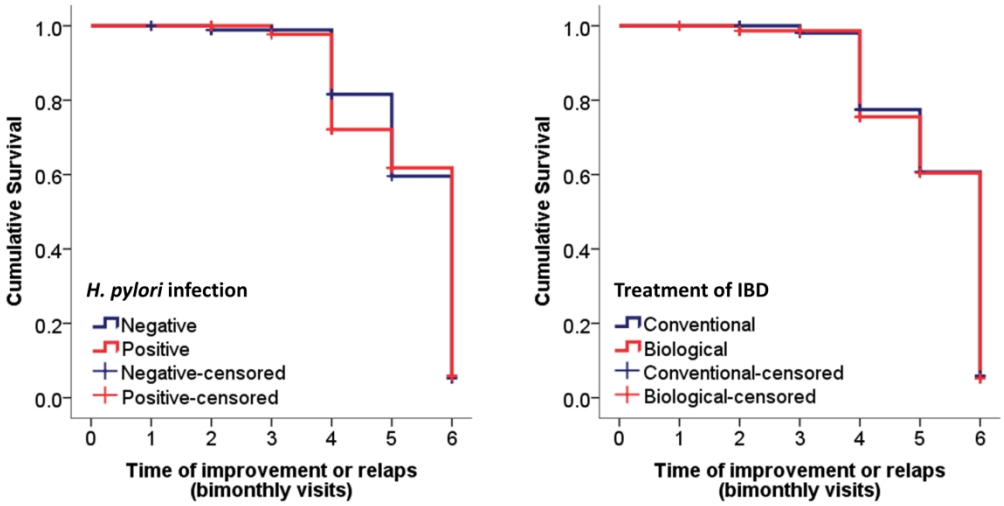
Variable	Group	Case summary	No of Events n(%)	Censored n(%)	Event Time (bimonthly visit)	No. of Events (recovery[a])	No. of relapse	No. at Risk (to recovery[a])	Probability of recovering[a]	Test of equality of recovery[a]		
										Log Rank (Mantel-Cox)	Breslow (Generalized Wilcoxon)	Tarone-Ware
										p value		
***H. pylori* infection in IBD patients**	Negative	n=92	73 (79.3)	19 (20.7)	1	0	2	92	0.000	0.969	0.708	0.833
					2	1	4	91	0.011			
					3	0	5	91	0.011			
					4	14	3	77	0.163			
					5	17	1	60	0.348			
					6	41	4	19	0.793			
	Positive	n=90	70 (77.8)	20 (22.2)	1	0	0	90	0.000			
					2	0	3	90	0.000			
					3	2	1	88	0.022			
					4	22	6	66	0.267			
					5	8	6	58	0.356			
					6	38	4	20	0.778			
Treatment of IBD	Conventional	n=106	86 (81.1)	20 (18.9)	1	0	0	106	0.000	0.893	0.867	0.880
					2	0	3	106	0.000			
					3	2	1	104	0.019			
					4	21	5	83	0.217			
					5	16	6	67	0.368			
					6	47	5	20	0.811			
	Biological	n=76	57 (75.0)	19 (25.0)	1	0	2	76	0.000			
					2	1	4	75	0.013			
					3	0	5	75	0.013			
					4	15	4	60	0.211			
					5	9	1	51	0.329			
					6	32	3	19	0.750			

H. pylori; *Helicobacter pylori*
IBD; inflammatory bowel disease
p value significate at <0.05
a: recovery reflects a state of remission of IBD condition



Patients' dispositions

266x114mm (300 x 300 DPI)



The equality of recovery (remission of IBD symptoms) during the follow-up periods associated with H. pylori infection status and IBD treatment strategies

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Supplementary Tables for online display

Table S1: Physical activity and dietary habit among the enrolled patients with IBD

		IBD patients		*H. pylori* infection in IBD patients				*p*~
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.	%	
Physical activity and physical exercise								
Transportation	not working	71	39.0	36	39.1	35	38.9	0.173
	On foot	19	10.4	14	15.2	5	5.6	
	By bicycle	4	2.2	2	2.2	2	2.2	
	Public transport or car	88	48.4	40	43.5	48	53.3	
Working activity	not working	65	35.7	30	32.6	35	38.9	0.001
	minimal	43	23.6	13	14.1	30	33.3	
	moderate	73	40.1	49	53.3	24	26.7	
	high	1	0.5	0	0.0	1	1.1	
Activity outside work	not working	59	32.4	27	29.3	32	35.6	0.451
	minimal	90	49.5	50	54.3	40	44.4	
	moderate	32	17.6	15	16.3	17	18.9	
	high	1	0.5	0	0.0	1	1.1	
Regular exercise	never	136	74.7	76	82.6	60	66.7	0.023
	yes frequent (>3 times/ week)	7	3.8	1	1.1	6	6.7	
	yes infrequent (<3 times/ week)	39	21.4	15	16.3	24	26.7	
Total physical activity score		2.8 ± 2.1		3.01 ± 2.2		2.5 ± 2.1		*t*=1.6, *p*= 0.107
Food habits								
Food source	Homemade	97	53.3	61	66.3	36	40.0	0.001
	Restaurant	6	3.3	4	4.3	2	2.2	
	Mixed	79	43.4	27	29.3	52	57.8	
Junk Food, Fast Food	never	50	27.5	25	27.2	25	27.8	0.995
	occasionally	128	70.3	65	70.7	63	70.0	
	daily	4	2.2	2	2.2	2	2.2	
Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	1	1.1	4	4.4	<0.001
	once per week	79	43.4	51	55.4	28	31.1	
	2-4 times per week	85	46.7	39	42.4	46	51.1	
	daily	13	7.1	1	1.1	12	13.3	
Trans fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	never	30	16.5	9	9.8	21	23.3	<0.001
	once per week	91	50.0	61	66.3	30	33.3	
	2-4 times per week	60	33.0	21	22.8	39	43.3	
	daily	1	0.5	1	1.1	0	0.0	
Food rich in insoluble fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs & spices)	never	0	0.0	0	0.0	0	0.0	<0.001
	once per week	39	21.4	28	30.4	11	12.2	
	2-4 times per week	88	48.4	49	53.3	39	43.3	
	daily	55	30.2	15	16.3	40	44.4	
Salty Food (pickled, salty cheese, salted fish, dokka, …)	never	27	14.8	16	17.4	11	12.2	<0.001
	once per week	96	52.7	61	66.3	35	38.9	
	2-4 times per week	54	29.7	12	13.0	42	46.7	

	daily	5	2.7	3	3.3	2	2.2	
	never	2	1.1	2	2.2	0	0.0	
Fruits and Vegetables	once per week	56	30.8	45	48.9	11	12.2	<0.001
	2-4 times per week	81	44.5	37	40.2	44	48.9	
	daily	43	23.6	8	8.7	35	38.9	
	never	16	8.8	4	4.3	12	13.3	
Red meat	once per week	113	62.1	66	71.7	47	52.2	0.013
	2-4 times per week	53	29.1	22	23.9	31	34.4	
	daily	0	0.0	0	0.0	0	0.0	
	never	157	86.3	80	87.0	77	85.6	
Under cooked meat	once per week	24	13.2	11	12.0	13	14.4	0.548
	2-4 times per week	1	0.5	1	1.1	0	0.0	
	daily	0	0.0	0	0.0	0	0.0	
	never	17	9.3	14	15.2	3	3.3	
Fish	once per week	91	50.0	38	41.3	53	58.9	0.007
	2-4 times per week	74	40.7	40	43.5	34	37.8	
	daily	0	0.0	0	0.0	0	0.0	
	never	25	13.7	17	18.5	8	8.9	
Consumption of caffeine in diet (tea, coffee)	once per week	20	11.0	17	18.5	3	3.3	<0.001
	2-4 times per week	61	33.5	30	32.6	31	34.4	
	daily	76	41.8	28	30.4	48	53.3	
	never	7	3.8	5	5.4	2	2.2	
Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	once per week	67	36.8	41	44.6	26	28.9	0.039
	2-4 times per week	91	50.0	41	44.6	50	55.6	
	daily	17	9.3	5	5.4	12	13.3	
	never	27	14.8	13	14.1	14	15.6	
Dairy products	once per week	49	26.9	33	35.9	16	17.8	0.034
	2-4 times per week	78	42.9	36	39.1	42	46.7	
	daily	28	15.4	10	10.9	18	20.0	
	one cup	8	4.4	3	3.3	5	6.7	
Average number of glasses of water consumed per day	2-3 cups	73	40.1	40	43.5	33	36.7	0.102
	at least 4 cups	73	40.1	41	44.6	32	35.6	
	4-8 cups	27	14.8	8	8.7	19	21.1	
	Never	60	33.0	33	35.9	27	30.0	
Snacks between meals	Occasionally	121	66.5	58	63.0	63	70.0	0.420
	Daily	1	0.5	1	1.1	0	0.0	
	Two	68	37.4	32	34.8	36	40.0	
Number of meals per day	Three	109	59.9	55	59.8	54	60.0	0.092
	Four	5	2.7	5	5.4	0	0.0	
Total food score (favorable food habits)		11.4 ± 4.5		12.2 ± 5.0		10.7 ± 3.8		t=2.4 , p= 0.018
Dietary restrictions	No	119	65.4	64	69.6	55	61.1	0.231
	Yes	63	34.6	28	30.4	35	38.9	
	Cereals	0	0.0	0	0.0	0	0.0	
	Brown rice	5	2.7	2	2.2	3	3.3	
	Whole grain bread	2	1.1	2	2.2	0	0.0	
	Seeds (beans, peas)	7	3.8	3	3.3	4	4.4	0.274
	Fruits (apples, plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0	
	High fat or protein food	34	18.7	18	19.6	16	17.8	

	Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	1.1	0	0.0	
	Raw green vegetables	6	3.3	3	3.3	3	3.3	
	Spices	9	4.9	3	3.3	6	6.7	
	Fried food	28	15.4	13	14.1	15	16.7	
	Baked dessert	1	0.5	0	0.0	1	1.1	
	Milk and dairy products	5	2.7	0	0.0	5	5.6	
	Carbonated drinks	14	7.7	4	4.3	10	11.1	
	Tea and coffee	1	0.5	1	1.1	0	0.0	
	Others	5	2.7	2	2.2	3	3.3	
Diet therapy	No	143	78.6	71	77.2	72	80.9	0.538
	Yes	38	20.9	21	22.8	17	19.1	
	Low fiber (bananas, cantaloupe)	7	3.8	2	2.2	5	5.6	
	Refined grains (white pasta, white rice, and oatmeal, potatoes)	13	7.1	3	3.3	10	11.1	
	Omega 3 rich food (fish)	29	15.9	17	18.5	12	13.3	
	Fully cooked, seedless, skinless, non-cruciferous vegetables (squash)	9	4.9	8	8.7	1	1.1	
	Lean sources of protein (poultry, soy, egg)	1	0.5	1	1.1	0	0.0	

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

~ *p* value for Chi Square test. Significant at < 0.05

Table S2: Baseline clinical and laboratory findings among the enrolled patients with IBD

		IBD patients		*H. pylori* infection in IBD patients				
		Total (n=182)		Negative (n=92)		Positive (n=90)		*p*~
		No.	%	No.	%	No.	%	
Clinical symptoms	Weight loss	125	68.7	68	73.9	57	63.3	0.124
	Diarrhea	178	97.8	89	96.7	89	98.9	0.323
	Constipation	12	6.6	6	6.5	6	6.7	0.969
	Flatulence	179	98.4	89	96.7	90	100.0	0.084
	Bloating/indigestion	177	97.3	88	95.7	89	98.9	0.182
	Hurt burn	176	96.7	90	97.8	86	95.6	0.391
	Urge incontinence	20	11.0	17	18.5	3	3.3	0.001
	Soiling	7	3.8	6	6.5	1	1.1	0.058
	Tenesmus	176	96.7	89	96.7	87	96.7	0.978
	Frequent bowel movements	166	91.2	85	92.4	81	90.0	0.569
	Abdominal cramps	160	87.9	78	84.8	82	91.1	0.190
	Epigastric pain	177	97.3	90	97.8	87	96.7	0.632
	Generalized abdominal pain	152	83.5	75	81.5	77	85.6	0.463
	Nausea	175	96.2	89	96.7	86	95.6	0.678
	Vomiting	168	92.3	85	92.4	83	92.2	0.966
	Loss of appetite	161	88.5	81	88.0	80	88.9	0.858
	Frequent bowel movement	171	94.0	89	96.7	82	91.1	0.111
	Blood in stool	155	85.2	75	81.5	80	88.9	0.162
	Bleeding per rectum	126	69.2	60	65.2	66	73.3	0.236
	Back pain	156	85.7	77	83.7	79	87.8	0.431
	Fever	54	29.7	24	26.1	30	33.3	0.285
	Chills	13	7.1	4	4.3	9	10.0	0.139
	Fatigue/lack of energy	143	78.6	63	68.5	80	88.9	0.001
	Headache	166	91.2	87	94.6	79	87.8	0.106
	Dizziness	148	81.3	76	82.6	72	80.0	0.652
	Insomnia/troubled sleep	155	85.2	82	89.1	73	81.1	0.791
	Limited sexual activity	65	35.7	32	34.8	33	36.7	0.128
	Infection	34	18.7	13	14.1	21	23.3	0.111
	Sick leaves/absenteeism	14	7.7	6	6.5	8	8.9	0.549
	Others	3	1.6	1	1.1	2	2.2	0.548
	Eye (stye, conjunctivitis, iridocyclitis)	4	2.2	1	1.1	3	3.3	0.301
	Joints (arthralgia, arthritis)	146	80.2	77	83.7	69	76.7	0.234
	Kidney (renal stones, hematuria)	5	2.7	3	3.3	2	2.2	0.668
	Liver (elevated liver enzymes, hepatitis B, hepatomegaly)	4	2.2	0	0.0	4	4.4	0.041
	Reproductive organs (delayed menstruation, polycystic ovary)	1	0.5	0	0.0	1	1.1	0.311

	Total symptom score	20.7 ± 3.2		20.6 ± 3.1		20.9 ± 3.2		*t*= -0.5 *p*=0.616
	ESR (males <15 mm/h, females <20 mm/hr)	34.1 ± 13.6		33.6 ± 14.1		34.6 ± 13.2		*t*= -0.49 *p*= 0.628
	CRP (< 10 mg/L)	30.6 ± 23.5		28.2 ± 23.9		33.0 ± 23.0		*t*= -1.4 *p*= 0.162
	FBG (70-100 mg/dl)	95.5 ± 11.4		96.1 ± 11.6		94.9 ± 11.1		*t*= 0.7 *p*= 0.504
	Fecal Calprotectin (<50 µg/g stool)	516.2 ± 210.0		517.4 ± 214.4		515.0 ± 206.7		*t*= -1.8 *p*= 0.077
	Hb (men 13.5 to 17.5 g/dl , women 12.0-15.5 g/dl)	10.9 ± 1.4		10.8 ± 1.4		11.0 ± 1.4		*t*= 0.8 *p*= 0.940
Laboratory findings	WBCs (4-11 k/ul)	6618.7 ± 1527.9		6420.8 ± 1530.5		6821.1 ± 1506.9		*t*= -0.8 *p*= 0.419
	Platelets (150-450 k/ul)	300.6 ± 64.5		304.8 ± 61.7		296.2 ± 67.4		*t*= 0.9 *p*= 0.372
	Body weight	67.9 ± 11.9		67.6 ± 12.2		68.3 ± 11.7		*t*= -0.4 *p*= 0.693
	Pulse (60-100 beats per minute)	80.6 ± 5.3		80.5 ± 5.6		80.8 ± 5.0		*t*= -0.3 *p*= 0.745
	Pulse pressure (40 and 60 mmHg)	41.3 ± 6.2		41.5 ± 6.8		41.0 ± 5.6		*t*= 0.6 *p*= 0.573
	Normal abdominal findings	23	12.6	12	13.0	11	12.2	
	Colonic distention	77	42.3	39	42.4	38	42.2	
	Diffuse bright liver	58	31.9	31	33.7	27	30.0	
	Diffuse hepatic fatty infiltration	31	17.0	15	16.3	16	17.8	
Abdominal ultrasound	Chronic noncalcular cholecystitis	14	7.7	8	8.7	6	6.7	0.987
	Renal stones	12	6.6	7	7.6	5	5.6	
	Chronic calcular cholecystitis	12	6.6	5	5.4	7	7.8	
	Splenomegaly	1	0.5	0	0.0	1	1.1	
	Cystitis	3	1.6	2	2.2	1	1.1	
	Unremarkable	21	11.5	11	12.0	10	11.1	
Endoscopy	Normal endoscopic findings	27	14.8	14	15.2	13	14.4	0.867

	GERD	75	41.2	35	38.0	40	44.4	
	Antral gastritis	33	18.1	15	16.3	18	20.0	
	Pangastritis	56	30.8	32	34.8	24	26.7	
	Pre-pyloric erosions	17	9.3	10	10.9	7	7.8	
	Superficial duodenal bulb ulcers	28	15.4	15	16.3	13	14.4	
	Incompetent cardia	10	5.5	7	7.6	3	3.3	
	Gastrodudonitis	21	11.5	9	9.8	12	13.3	
	Antral erosions	17	9.3	9	9.8	8	8.9	
	Duodenal inflammatory polyp	7	3.8	4	4.3	3	3.3	
	Erosive gastritis	1	0.5	0	0.0	1	1.1	
	Peptic ulcer	1	0.5	1	1.1	0	0.0	
	Erosive gastrodudonitis	4	2.2	2	2.2	2	2.2	
	Chronic active colitis	63	34.6	34	37.0	29	32.2	
	Chronic active ileocolitis-Ulcerative Colitis	25	13.7	11	12.0	14	15.6	
	Chronic active colitis with lymphoid hyperplasia	5	2.7	1	1.1	4	4.4	
	Chronic active colitis with multiple superficial ulcers	3	1.6	0	0.0	3	3.3	
	Internal piles	4	2.2	1	1.1	3	3.3	
	ulcerative proctitis	15	8.2	3	3.3	12	13.3	
	Chronic active ulcerative pancolitis	1	0.5	1	1.1	0	0.0	
Colonoscopy	multiple superficial aphthoid ulcers - mild ileitis of Crohn's disease	35	19.2	20	21.7	15	16.7	0.087
	Ileocolitis - Crohn's disease	31	17.0	14	15.2	17	18.9	
	Rectal Crohn's	10	5.5	5	5.4	5	5.6	
	Multiple superficial colonic ulcers and skip lesions with eosinophilic infiltration, terminal ileitis - Crohn's disease	13	7.1	9	9.8	4	4.4	
	Chronic active colitis with lymphoid hyperplasia - Crohn's disease	2	1.1	0	0.0	2	2.2	
	perianal fistula	1	0.5	1	1.1	0	0.0	
	None	137	75.3	77	83.7	60	66.7	
	Fistula	4	2.2	2	2.2	2	2.2	
	Stricture	4	2.2	1	1.1	3	3.3	
History of complications	Ulcer	26	14.3	10	10.9	16	17.8	0.066
	Intestinal perforation	0	0.0	0	0.0	0	0.0	
	GIT cancer	2	1.1	1	1.1	1	1.1	
	Abscess formation	5	2.7	0	0.0	5	5.6	

	Others	5	2.7	2	2.2	3	3.3	
	None	171	94.0	91	98.9	80	88.9	
	Stricturoplasty	3	1.6	1	1.1	2	2.2	
Surgical intervention	GIT cancer	1	0.5	0	0.0	1	1.1	0.061
	Abscess intervention	4	2.2	0	0.0	4	4.4	
	Others	3	1.6	0	0.0	3	3.3	

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

~ *p* value for Chi Square test. Significant at <0.05

Table S3: Repeated-measures ANOVA of clinical and laboratory findings among patients with IBD on biological treatment during follow-up

Parameter	*H. Pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA												
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects					Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12													
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T × S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	36.5 ± 12.6	29.8 ± 9.0	26.6 ± 8.4	23.2 ± 8.1	20.5 ± 7.3	17.7 ± 7.9	13.3 ± 7.1	T	33.9	<0.001	0.747	1.000	T	128.90	<0.001	0.635	199.6	<0.001	1.78	0.186	0.024
	Negative	33.2 ± 13.7	28.8 ± 10.7	24.4 ± 8.8	20.2 ± 7.8	18.8 ± 7.2	15.3 ± 5.0	13.1 ± 5.4	T × S	0.846	0.540	0.069	0.312	T × S	0.37	0.71	0.005	0.009	0.927			
CRP	Positive	31.2 ± 18.6	25.4 ± 14.7	22.0 ± 12.5	18.3 ± 8.7	14.4 ± 7.5	13.8 ± 7.3	12.2 ± 9.3	T	13.500	<0.001	0.540	1.000	T	60.54	<0.001	0.450	69.79	<0.001	0.225	0.637	0.003
	Negative	30.8 ± 26.2	25.4 ± 21.8	20.6 ± 16.6	17.1 ± 14.0	13.8 ± 10.1	11.4 ± 7.5	8.6 ± 4.5	T × S	0.893	0.505	0.072	0.330	T × S	0.420	0.581	0.006	0.35	0.556			
FBG	Positive	93.1 ± 9.5	91.2 ± 11.6	91.6 ± 9.6	94.5 ± 13.8	93.4 ± 11.8	93.4 ± 10.9	93.5 ± 10.4	T	1.530	0.182	0.117	0.554	T	1.56	0.172	0.021	0.665	0.417	0.136	0.713	0.002
	Negative	95.2 ± 8.8	92.3 ± 6.8	92.1 ± 7.7	93.6 ± 8.6	93.6 ± 8.7	92.5 ± 6.9	94.0 ± 5.9	T × S	0.385	0.886	0.032	0.153	T × S	0.42	0.832	0.006	0.289	0.593			
Calprotectin	Positive	573.8 ± 218.6		380.7 ± 190.6		171.3 ± 96.1		75.2 ± 30.8	T	113.0	<0.001	0.825	1.000	T	250.0	<0.001	0.772	347.5	<0.001	1.39	0.242	0.018
	Negative	508.6 ± 216.3		317.6 ± 153.5		168.3 ± 84.2		84.7 ± 49.8	T × S	1.350	0.266	0.053	0.344	T × S	2.31	0.11	0.030	2.87	0.037			
Hb	Positive	10.6 ± 1.3	10.7 ± 1.3	10.9 ± 1.3	11.3 ± 1.1	11.5 ± 0.9	11.6 ± 0.9	11.7 ± 1.0	T	29.00	<0.001	0.716	1.000	T	89.43	<0.001	0.547	172.7	<0.001	0.047	0.829	0.001
	Negative	10.5 ± 1.1	10.7 ± 1.2	10.9 ± 10.2	110.1 ± 10.1	11.4 ± 1.1	11.8 ± 0.84	1.0 ± 0.81	T × S	2.440	0.034	0.175	0.791	T × S	1.06	0.063	0.032	3.89	0.052			
WBCs	Positive	6385.5 ± 1029.0	6704.8 ± 1023.4	6512.9 ± 1013.5	6298.4 ± 1046.3	6582.3 ± 1075.4	6438.1 ± 1255.8	6125.5 ± 1092.8	T	2.520	0.029	0.180	0.806	T	2.51	0.035	0.033	0.093	0.761	2.85	0.096	0.037
	Negative	6326.7 ± 1479.9	6153.3 ± 1263.2	6062.2 ± 1102.1	5887.8 ± 966.4	6171.1 ± 1030.4	6038.7 ± 1093.6	5999.6 ± 1052.4	T × S	1.324	0.258	0.103	0.486	T × S	1.03	0.399	0.014	3.44	0.068			
Platelets	Positive	272.6 ± 51.0	286.9 ± 44.8	276.3 ± 40.5	279.1 ± 35.1	276.4 ± 31.5	277.1 ± 30.3	282.9 ± 40.5	T	0.738	0.621	0.060	0.273	T	0.41	0.875	0.005	0.605	0.439	5.56	0.021	0.07
	Negative	307.9 ± 69.6	291.8 ± 50.0	292.5 ± 41.8	293.1 ± 42.9	291.9 ± 41.2	288.2 ± 40.7	292.5 ± 44.1	T × S	0.753	0.610	0.061	0.278	T × S	1.18	0.317	0.016	0.527	0.47			
Total symptom score	Positive	21.6 ± 2.3	21.5 ± 2.6	16.4 ± 3.6	7.2 ± 3.0	3.7 ± 3.6	3.1 ± 2.4	0.1 ± 0.4	T	4.150	<0.001	0.973	1.000	T	551.50	<0.001	0.883	98.9	<0.001	4.6	0.035	0.06
	Negative	20.7 ± 3.5	20.2 ± 4.1	13.4 ± 5.6	5.9 ± 3.2	3.6 ± 3.4	3.3 ± 3.1	0.8 ± 1.9	T × S	2.040	0.072	0.153	0.702	T × S	2.85	0.052	0.038	7.61	0.094			
Body weight	Positive	63.9 ± 9.8	64.1 ± 10.1	65.0 ± 10.0	65.5 ± 10.0	65.8 ± 10.0	66.0 ± 10.0	66.1 ± 10.0	T	11.40	<0.001	0.498	1.000	T	33.70	<0.001	0.313	51.8	<0.001	0.055	0.816	0.001
	Negative	64.7 ± 11.0	64.9 ± 10.9	65.3 ± 10.8	65.6 ± 10.7	66.0 ± 10.6	66.6 ± 10.5	67.1 ± 10.4	T × S	2.280	0.046	0.166	0.759	T × S	1.40	0.252	0.018	11.1	0.001			
Pulse	Positive	80.8 ± 2.5	79.7 ± 2.5	76.8 ± 4.5	76.0 ± 4.7	77.7 ± 4.5	77.5 ± 4.4	78.8 ± 2.5	T	3.700	0.003	0.245	0.946	T	4.24	0.001	0.054	4.55	0.036	4.93	0.029	0.062

Pulse pressure	Negative	81.2 ± 6.8	79.2 ± 6.7	78.7 ± 5.3	81.1 ± 5.1	79.8 ± 5.1	78.8 ± 5.1	77.2 ± 4.6	T × S	3.010	0.011	0.208	0.882	T × S	3.90	0.003	0.050	12.81	0.001	0.009	0.924	0.0001
	Positive	39.7 ± 4.1	41.6 ± 5.8	38.7 ± 9.2	40.3 ± 8.3	42.6 ± 6.8	39.4 ± 6.8	41.3 ± 9.6	T	1.350	0.248	0.105	0.493	T	1.57	0.156	0.021	0.537	0.466			
	Negative	40.4 ± 7.4	39.6 ± 7.1	39.3 ± 7.5	39.3 ± 8.1	41.6 ± 8.5	40.9 ± 7.6	41.8 ± 10.1	T × S	0.728	0.628	0.060	0.270	T × S	0.59	0.740	0.008	0.604	0.440			

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

$p<0.05$ is significant

[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)

[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant

[c] large effect if the value of partial Eta squared >0.1

T × S; time versus state of H. pylori infection

Table S3: Repeated-measures ANOVA of clinical and laboratory findings among patients with IBD receiving conventional therapy during follow-up

Parameter	*H. pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA											
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects					Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12													
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	33.6 ± 13.5	30.8 ± 11.9	27.2 ± 11.1	24.8 ± 9.3	20.7 ± 7.4	17.0 ± 6.4	13.3 ± 3.9	T	64.2	<0.001	0.795	1.000	T	219.50	<0.001	0.679	359.3	<0.001	0.335	0.564	0.003
	Negative	34.1 ± 14.6	29.4 ± 12.0	26.0 ± 10.0	22.5 ± 8.2	19.5 ± 6.7	16.5 ± 5.7	12.9 ± 4.5	T × S	1.18	0.325	0.067	0.444	T × S	0.75	0.492	0.007	0.01	0.921			
CRP	Positive	34.0 ± 25.1	26.8 ± 20.2	22.9 ± 17.9	19.3 ± 14.8	15.4 ± 10.7	11.9 ± 6.7	9.1 ± 5.7	T	17.1	<0.001	0.508	1.000	T	83.80	<0.001	0.446	102.1	<0.001	3026	0.074	0.030
	Negative	25.7 ± 21.4	20.5 ± 16.9	17.5 ± 14.2	14.8 ± 11.4	12.3 ± 8.7	9.9 ± 6.1	7.7 ± 4.5	T × S	0.518	0.794	0.030	0.201	T × S	2.30	0.033	0.022	2.81	0.097			
FBG	Positive	95.9 ± 12.0	94.0 ± 10.1	92.2 ± 9.9	94.4 ± 10.3	91.4 ± 8.0	95.0 ± 15.0	93.8 ± 9.3	T	3.06	0.009	0.156	0.896	T	2.43	0.038	0.023	1.32	0.254	1.41	0.238	0.013
	Negative	96.9 ± 13.7	93.8 ± 13.2	97.9 ± 9.8	98.2 ± 16.1	93.9 ± 10.7	93.2 ± 13.0	96.3 ± 10.2	T × S	2.17	0.053	0.116	0.746	T × S	2.10	0.068	0.020	2.06	0.155			
Calprotectin	Positive	484.1 ± 195.0		279.7 ± 141.7		150.1 ± 73.7		74.1 ± 28.8	T	144.8	<0.001	0.810	1.000	T	325.50	<0.001	0.758	417	<0.001	3.23	0.075	0.030
	Negative	525.7 ± 214.2		334 ± 125.5		175.6 ± 92.5		86.3 ± 80.5	T × S	1.19	0.317	0.034	0.312	T × S	0.82	0.411	0.008	0.718	0.399			
Hb	Positive	11.1 ± 1.1	11.3 ± 1.3	11.4 ± 1.2	11.7 ± 1.1	11.7 ± 1.0	11.8 ± 1.0	12.1 ± 0.8	T	24.18	<0.001	0.594	1.000	T	65.83	<0.001	0.338	118.9	<0.001	0.508	0.477	0.005
	Negative	11.1 ± 1.5	11.3 ± 1.1	11.6 ± 1.0	11.8 ± 0.9	12.0 ± 0.8	12.1 ± 0.8	12.3 ± 0.7	T × S	2.19	0.050	0.117	0.753	T × S	1.90	0.137	0.018	2.12	0.148			
WBCs	Positive	7050.0 ± 1667.9	6699.2 ± 1501.3	6511.1 ± 1239.8	6754.7 ± 1357.3	6648.1 ± 1026.2	6528.3 ± 891.8	6497.3 ± 1138.6	T	3.61	0.003	0.179	0.944	T	6.95	<0.001	0.063	4.57	0.035	11.34	0.001	0.098
	Negative	7968.1 ± 1588.2	6340.4 ± 1500.8	6273.4 ± 1281.5	5893.6 ± 1165.3	5808.5 ± 992.5	5714.9 ± 956.7	5796.0 ± 903.8	T × S	1.67	0.137	0.092	0.612	T × S	1.99	0.118	0.019	0.118	0.732			
Platelets	Positive	308.6 ± 71.9	295.1 ± 75.4	292.6 ± 75.3	283.6 ± 67.1	285.7 ± 58.8	284.3 ± 58.1	284.9 ± 60.1	T	3.59	0.003	0.179	0.943	T	5.89	0.001	0.054	7.84	0.006	1.99	0.161	0.019
	Negative	301.8 ± 53.6	274.4 ± 49.9	266.4 ± 43.2	271.4 ± 51.5	284.5 ± 51.3	272.2 ± 36.8	276.1 ± 43.2	T × S	1.74	0.120	0.095	0.633	T × S	1.13	0.335	0.011	0.357	0.551			
Total symptom score	Positive	20.5 ± 3.6	19.7 ± 3.6	13.0 ± 4.0	5.0 ± 2.8	2.4 ± 3.1	2.8 ± 3.3	1.1 ± 2.5	T	360.0	<0.001	0.959	1.000	T	834.60	<0.001	0.895	424.6	<0.001	2.42	0.123	0.024
	Negative	20.5 ± 2.8	20.5 ± 3.3	14.2 ± 3.5	5.0 ± 1.9	3.2 ± 2.4	3.4 ± 2.7	0.7 ± 1.3	T × S	2.93	0.011	0.159	0.880	T × S	0.85	0.436	0.009	3.97	0.049			
Body weight	Positive	70.6 ± 12.0	70.4 ± 12.1	71.2 ± 12.1	71.5 ± 11.8	71.3 ± 11.8	71.5 ± 11.5	71.1 ± 12.6	T	11.15	<0.001	0.403	1.000	T	6.05	0.002	0.055	0.196	0.659	0.01	0.922	9.2×10^{-5}
	Negative	70.2 ± 12.8	70.3 ± 12.8	71.1 ± 12.8	70.2 ± 16.1	71.7 ± 12.9	72.4 ± 13.1	73.3 ± 12.8	T × S	2.32	0.039	0.123	0.779	T × S	3.43	0.029	0.032	4.26	0.042			
Pulse	Positive	80.7 ± 5.8	79.9 ± 5.1	79. ± 3.5	77.8 ± 4.7	78.6 ± 3.8	77.4 ± 4.0	78.3 ± 3.0	T	3.01	0.010	0.154	0.891	T	5.31	<0.001	0.049	4.6	0.034	0.141	0.079	0.017
	Negative	79.8 ± 4.1	79.8 ± 4.1	79.1 ± 4.2	79.6 ± 4.7	77.7 ± 4.9	77.7 ± 4.8	79.4 ± 4.6	T × S	1.50	0.189	0.083	0.555	T × S	1.53	0.184	0.015	0.111	0.739			

Pulse pressure	Positive	41.7 ± 6.2	41.2 ± 7.2	40.2 ± 8.8	40.8 ± 8.8	40.3 ± 7.9	39.7 ± 6.9	41.9 ± 9.9	T	0.481	0.821	0.028	0.188	T	0.43	0.844	0.004	0.599	0.441	0.141	0.708	0.001
	Negative	42.6 ± 6.1	40.9 ± 6.5	43.8 ± 7.7	42.3 ± 7.9	42.1 ± 8.6	42.8 ± 8.5	42.1 ± 8.6	T × S	1.026	0.413	0.059	0.388	T × S	1.11	0.349	0.011	2.04	0.156			

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

$p<0.05$ is significant

[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)

[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant

[c] large effect if the value of partial Eta squared >0.1

T × S; time versus state of H. pylori infection

Table S5: Univariate analysis for factor associated with IBD flare during follow up

		IBD patients		Flare during IBD therapy						95.0% C.I. for EXP(B)	
		Total (n=182)		No (n=143)		Yes (n=39)		*p*~	Exp(B)	Lower Limit	Upper Limit
		No.	%	No.	%	No.	%				
H pylori infection	Negative	92	50.5	73	51.0	19	48.7				
	Positive	90	49.5	70	49.0	20	51.3	0.820	1.08	0.57	2.02
	NA	92	50.5	73	51	19	48.7	0.837			
Onset of *H. pylori* infection	Few weeks ago	7	3.8	6	4.2	1	2.6	0.540	0.53	0.07	3.99
	3-6 months	10	5.5	7	4.9	3	7.7	0.488	1.54	0.45	5.21
	6 months - 1 year	35	19.2	29	20.3	6	15.4	0.789	0.88	0.35	2.21
	> 1 year	38	20.9	28	19.6	10	25.6	0.560	1.26	0.58	2.70
Type of IBD diagnosed	Crohn's disease	86	47.3	67	46.9	19	48.7				
	Ulcerative colitis	96	52.7	76	53.1	20	51.3	0.697	0.88	0.47	1.66
Crohn's disease	*H. pylori* Negative	44	24.2	33	23.1	11	28.2	0.526			
	H. pylori Positive	42	23.1	34	23.8	8	20.5	0.374	0.66	0.27	1.65
Ulcerative colitis	*H. pylori* Negative	48	26.4	40	28.0	8	20.5	0.196	0.55	0.22	1.36
	H. pylori Positive	48	26.4	36	25.2	12	30.8	0.853	0.93	0.41	2.10
Treatment of IBD	Conventional	106	58.2	86	60.1	20	51.3				
	Biological	76	41.8	57	39.9	19	48.7	0.254	1.44	0.77	2.70
Sex	Male	94	51.6	76	53.1	18	46.2				
	Female	88	48.4	67	46.9	21	53.8	0.241	1.46	0.78	2.74
Age	16 – <20 Years	20	11.0	15	10.5	5	12.8	0.708		ref	
	20 – <35 Years	136	74.7	106	74.1	30	76.9	0.814	0.89	0.35	2.30
	35 – 55 Years	26	14.3	22	15.4	4	10.3	0.440	0.60	0.16	2.22
	Mean ± SD	27.0 ± 7.3		27.8 ± 7.6		23.8 ± 4.9		0.008	*t*= 4.0, *p*< 0.001 0.92	0.87	0.98
Age at diagnosis	10 – >19	69	37.9	48	33.6	21	53.8	0.086			
	20 – <30	83	45.6	71	49.7	12	30.8	0.029	0.45	0.22	0.92
	30 – 45	30	16.5	24	16.8	6	15.4	0.341	0.64	0.26	1.60
	Mean ± SD	27.0 ± 7.3		22.3 ± 6.5		19.1 ± 4.8		0.01	*t*= 3.4, *p*= 0.001 0.92	0.87	0.98
Residence	Rural	88	48.4	74	51.7	14	35.9				
	Urban	94	51.6	69	48.3	25	64.1	0.051	1.92	1.00	3.70
Education	Illiterate	2	1.1	2	1.4	0	0.0	0.982	0.00	0.00	
	Read and Write	23	12.6	20	14.0	3	7.7	0.160	0.42	0.13	1.40
	Primary	4	2.2	4	2.8	0	0.0	0.978	0.00	0.00	
	Preparatory	13	7.1	11	7.7	2	5.1	0.309	0.47	0.11	2.00
	Secondary	44	24.2	35	24.5	9	23.1	0.487	0.76	0.36	1.64
	University education	96	52.7	71	49.7	25	64.1	0.715			
Working status	No	88	48.4	63	44.1	25	64.1				
	Yes	94	51.6	80	55.9	14	35.9	0.032	0.49	0.25	0.94
Occupation	Unemployed	37	20.3	31	21.7	6	15.4	0.024			
	Student	45	24.7	26	18.2	19	48.7	0.023	2.89	1.15	7.25
	Clerical	2	1.1	1	0.7	1	2.6	0.353	2.73	0.33	22.67
	Professional	39	21.4	33	23.1	6	15.4	0.962	0.97	0.31	3.02
	Housewife	21	11.5	19	13.3	2	5.1	0.566	0.63	0.13	3.10
	Auxiliary worker	22	12.1	19	13.3	3	7.7	0.701	0.76	0.19	3.05
	Farmer	16	8.8	14	9.8	2	5.1	0.643	0.69	0.14	3.40
Marital status	Married	73	40.1	50	35.0	23	59.0	0.110			
	Not married							0.016	2.20	1.16	4.21
	Single	106	58.2	91	63.6	15	38.5	0.018	2.20	1.15	4.21
	Widowed	2	1.1	1	0.7	1	2.6	0.276	3.08	0.41	23.35
	Divorced	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Socioeconomic standard	High	58	31.9	41	28.7	17	43.6	.015	2.730	1.215	6.14
	Middle	52	28.6	39	27.3	13	33.3	.127	1.938	.828	4.54
	Low	72	39.6	63	44.1	9	23.1	.052			
Consanguinity	No	144	79.1	114	79.7	30	76.9				
	Yes	38	20.9	29	20.3	9	23.1	0.888	0.95	0.45	2.00
Being breastfed	No	26	14.3	22	15.4	4	10.3				
	Yes	156	85.7	121	84.6	35	89.7	0.382	1.59	0.56	4.47
Smoking	Never	150	82.4	119	83.2	31	79.5	0.915			
	Current smoker	26	14.3	19	13.3	7	17.9	0.774	1.128	0.50	2.57
	Ex-Smoker	6	3.3	5	3.5	1	2.6	0.775	0.75	0.10	5.48
	NA	153	84.1	119	83.2	34	87.2	0.679			
Age of starting Smoking	< 20 Years	17	9.3	14	9.8	3	7.7	0.573	0.71	0.22	2.32
	20 – 30 Years	12	6.6	10	7.0	2	5.1	0.475	0.59	0.14	2.48
Smoking other than cigarette	Never	180	98.9	143	100.0	37	94.9				
	Shisha	2	1.1	0	0.0	2	5.1	0.079	3.59	0.86	14.94
Alcohol	No	182	100.0	143	100.0	39	100.0				
	Yes	0	0.0	0	0.0	0	0.0				
Drug Abuse	No	182	100.0	143	100.0	39	100.0				
	Yes	0	0.0	0	0.0	0	0.0				
Chronic diseases	No	82	45.1	64	44.8	18	46.2				
	Yes	100	54.9	79	55.2	21	53.8	0.811	0.93	0.49	1.74

	Diabetes Mellitus	10	5.5	8	5.6	2	5.1				
	Hypertension	30	16.5	25	17.5	5	12.8				
	Bronchial Asthma/COPD	15	8.2	13	9.1	2	5.1				
	Heart disease	1	0.5	1	0.7	0	0.0				
	Renal disease	1	0.5	0	0.0	1	2.6				
	Liver disease	1	0.5	1	0.7	0	0.0				
	SLE	0	0.0	0	0.0	0	0.0				
	rheumatoid arthritis	6	3.3	5	3.5	1	2.6				
	Skin allergy	18	9.9	16	11.2	2	5.1				
	Hyperthyroidism	4	2.2	3	2.1	1	2.6				
	Hypothyroidism	8	4.4	5	3.5	3	7.7				
	Other autoimmune diseases	1	0.5	1	0.7	0	0.0				
	Others (Chronic sinusitis, vertigo, lumbar disc prolapse, familial dyslipidemia, hemorrhoids, scleritis, HCV, anemia, fatty liver, steatosis, psoriasis, peripheral neuropathy, chronic cholecystitis)	27	14.8	21	14.7	6	15.4				
Autoimmune diseases	No	163	89.6	129	90.2	34	87.2				
	Yes	19	10.4	14	9.8	5	12.8	0.555	1.33	0.52	3.39
Medications	None	13	7.1	10	7.0	3	7.7				
	Analgesic (NSAIDs)	12	6.6	7	4.9	5	12.8				
	Antidiabetics	6	3.3	6	4.2	0	0.0				
	Antihypertensives	32	17.6	27	18.9	5	12.8				
	corticosteroids	10	5.5	5	3.5	5	12.8				
	IBD therapy	151	83.0	118	82.5	33	84.6				
	Hormonal contraceptives	2	1.1	0	0.0	2	5.1				
	Thyroxin	9	4.9	6	4.2	3	7.7				
	Others	37	20.3	28	19.6	9	23.1				
Family history of similar condition	No	141	77.5	108	75.5	33	84.6				
	Yes	41	22.5	35	24.5	6	15.4	0.279	0.62	0.26	1.48
	Yes; first degree relatives	40	22.0	34	23.8	6	15.4				
	Yes; other relatives	1	0.5	1	0.7	0	0.0				
	Other autoimmune disease	3	1.6	3	2.1	0	0.0				
Physical activity											
Transportation	not working	71	39.0	60	42.0	11	28.2	0.208			
	On foot	19	10.4	17	11.9	2	5.1	0.503	0.60	0.13	2.70
	By bicycle	4	2.2	3	2.1	1	2.6	0.709	1.48	0.19	11.47
	Public transport or car	88	48.4	63	44.1	25	64.1	0.090	1.85	0.91	3.76
Working activity	not working	65	35.7	53	37.1	12	30.8	0.655			
	minimal	43	23.6	31	21.7	12	30.8	0.249	1.60	0.72	3.57
	moderate	73	40.1	58	40.6	15	38.5	0.882	1.06	0.50	2.26
	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Activity outside work	not working	59	32.4	48	33.6	11	28.2	0.733			
	minimal	90	49.5	71	49.7	19	48.7	0.838	1.08	0.51	2.27
	moderate	32	17.6	23	16.1	9	23.1	0.293	1.60	0.66	3.87
	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Regular exercise	never	136	74.7	109	76.2	27	69.2	0.397			
	yes frequent (>3 times/ week)	7	3.8	5	3.5	2	5.1	0.758	1.25	0.30	5.27
	yes infrequent (<3 times/ week)	39	21.4	29	20.3	10	25.6	0.176	1.66	0.80	3.45
Total physical activity score		2.8 ± 2.1		2.7 ± 2.2		2.9 ± 2.0			t= 0.40, p= 0.695		
								0.855	1.01	0.88	1.17
Dietary habits											
Food source	Homemade	97	53.3	78	54.5	19	48.7	0.858			
	Restaurant	6	3.3	5	3.5	1	2.6	0.829	0.80	0.11	5.99
	Mixed	79	43.4	60	42.0	19	48.7	0.639	1.16	0.62	2.20
Junk Food, Fast Food	never	50	27.5	41	28.7	9	23.1	0.806			
	occasionally	128	70.3	99	69.2	29	74.4	0.535	1.27	0.60	2.68
	daily	4	2.2	3	2.1	1	2.6	0.706	1.49	0.19	11.75
Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	5	3.5	0	0.0	0.399			
	once per week	79	43.4	65	45.5	14	35.9	0.898	2383.0	0.00	1.6×10^{68}
	2-4 times per week	85	46.7	62	43.4	23	59.0	0.891	4190.1	0.00	2.9×10^{68}
	daily	13	7.1	11	7.7	2	5.1	0.898	2475.2	0.00	1.7×10^{68}
Transfat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	never	30	16.5	27	18.9	3	7.7	0.017			
	once per week	91	50.0	75	52.4	16	41.0	0.506	1.52	0.44	5.22
	2-4 times per week	60	33.0	41	28.7	19	48.7	0.061	3.21	0.95	10.85
	daily	1	0.5	0	0.0	2	5.1	0.020	14.82	1.52	144.45
Food rich in insoluble fibers (such as whole bread, cereals, beans, peas, wheat, oat,	never	0	0.0	0	0.0	0	0.0				
	once per week	39	21.4	31	21.7	8	20.5	0.022			
	2-4 times per week	88	48.4	76	53.1	12	30.8	0.362	0.66	0.27	1.61
	daily	55	30.2	36	25.2	19	48.7	0.163	1.80	0.79	4.12

artichoke, squash, cabbage, cauliflower, broccoli, dried herbs & spices, fruits, vegetables)											
Salty Food (pickled, salty cheese, salted fish, dokka)	never	27	14.8	22	15.4	5	12.8	0.470			
	once per week	96	52.7	78	54.5	18	46.2	0.885	0.93	0.34	2.51
	2-4 times per week	54	29.7	40	28.0	14	35.9	0.516	1.40	0.51	3.90
	daily	5	2.7	3	2.1	2	5.1	0.299	2.38	0.46	12.29
Fruits and Vegetables	never	2	1.1	0	0.0	2	5.1	0.005			
	once per week	56	30.8	44	30.8	12	30.8	0.001	0.07	0.01	0.31
	2-4 times per week	81	44.5	64	44.8	17	43.6	0.000	0.07	0.02	0.31
	daily	43	23.6	35	24.5	8	20.5	0.001	0.07	0.01	0.34
Red meat	never	16	8.8	13	9.1	3	7.7	0.959			
	once per week	113	62.1	88	61.5	25	64.1	0.950	0.96	0.29	3.20
	2-4 times per week	53	29.1	42	29.4	11	28.2	0.835	0.87	0.24	3.14
	daily	0	0.0	0	0.0	0	0.0				
Under cooked meat	never	157	86.3	120	83.9	37	94.9	0.259			
	once per week	24	13.2	22	15.4	2	5.1	0.100	0.30	0.07	1.26
	2-4 times per week	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
	daily	0	0.0	0	0.0	0	0.0				
Fish	never	17	9.3	16	11.2	1	2.6	0.220			
	once per week	91	50.0	67	46.9	24	61.5	0.102	5.30	0.72	39.19
	2-4 times per week	74	40.7	60	42.0	14	35.9	0.176	4.06	0.53	30.95
	daily	0	0.0	0	0.0	0	0.0				
Consumption of caffeine in diet (tea, coffee)	never	25	13.7	22	15.4	3	7.7	0.027			
	once per week	20	11.0	16	11.2	4	10.3	0.571	1.54	0.34	6.89
	2-4 times per week	61	33.5	54	37.8	7	17.9	0.949	0.96	0.25	3.70
	daily	76	41.8	51	35.7	25	64.1	0.078	2.94	0.89	9.74
Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	never	7	3.8	7	4.9	1	2.6	0.181			
	once per week	67	36.8	56	39.2	11	28.2	0.780	1.34	0.17	10.48
	2-4 times per week	91	50.0	70	49.0	21	53.8	0.519	1.93	0.26	14.38
	daily	17	9.3	10	7.0	7	17.9	0.215	3.77	0.46	30.66
Dairy products	never	27	14.8	22	15.4	5	12.8	0.552			
	once per week	49	26.9	41	28.7	8	20.5	0.831	0.89	0.29	2.71
	2-4 times per week	78	42.9	58	40.6	20	51.3	0.409	1.51	0.57	4.03
	daily	28	15.4	22	15.4	6	15.4	0.497	1.51	0.46	4.98
Average number of glasses of water consumed per day	one cup	9	4.9	6	4.2	3	7.7	0.346			
	2-3 cups	73	40.1	59	41.3	14	35.9	0.367	0.56	0.16	1.96
	at least 4 cups	73	40.1	54	37.8	19	48.7	0.734	0.81	0.24	2.74
	4-8 cups	27	14.8	24	16.8	3	7.7	0.156	0.31	0.06	1.56
Snacks between meals	Never	60	33.0	54	37.8	6	15.4	0.009			
	Occasionally	121	66.5	89	62.2	32	82.1	0.014	2.99	1.25	7.14
	Daily	1	0.5	0	0.0	1	2.6	0.009	17.12	2.02	144.86
Number of meals per day	2	68	37.4	55	38.5	13	33.3	0.058			
	3	109	59.9	86	60.1	23	59.0	0.857	1.06	0.54	2.10
	4	5	2.7	2	1.4	3	7.7	0.022	4.37	1.24	15.37
Total food score (favorable food habits)		11.4 ± 4.5		11.9 ± 4.3		9.9 ± 5.0			t=2.2 , p=0.029		
								0.029	0.93	0.86	0.99
	No	119	65.4	95	66.4	24	61.5				
	Yes	63	34.6	48	33.6	15	38.5	0.406	1.32	0.69	2.51
Dietary restrictions	Cereals	0	0.0	0	0.0	0	0.0				
	Brown rice	5	2.7	4	2.8	1	2.6				
	Whole grain bread	2	1.1	2	1.4	0	0.0				
	Seeds (beans, peas)	7	3.8	3	2.1	4	10.3				
	Fruits (apples; plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0				
	High fat or protein food	34	18.7	25	17.5	9	23.1				
	Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	0.7	0	0.0				
	Raw green vegetables	6	3.3	6	4.2	0	0.0				
	Spices	9	4.9	7	4.9	2	5.1				
	Fried food	28	15.4	22	15.4	6	15.4				
	Baked dessert	1	0.5	1	0.7	0	0.0				
	Milk and dairy products	5	2.7	3	2.1	2	5.1				
	Carbonated drinks	14	7.7	11	7.7	3	7.7				
	Tea and coffee	1	0.5	1	0.7	0	0.0				
	Others	5	2.7	4	2.8	1	2.6				
Diet therapy	No	143	78.6	113	79.0	31	79.5				
	Yes	38	20.9	30	21.0	8	20.5	0.982	0.99	0.46	2.16
	Low fiber (bananas, cantaloupe)			5	3.5	2	5.1				
	Refined grains (white pasta, white rice, and oatmeal, potatoes)			10	7	3	7.7				

	Omega 3 rich food (fish)			24	16.8	5	12.8				
	Fully cooked, seedless, skinless, non-cruciferous vegetables (squash)			6	4.2	3	7.7				
	Lean sources of protein (poultry, soy, egg)			1	0.7	0	0.0				
	Others			0	0.0	0	0.0				
	None	137	75.3	109	76.2	28	71.8	0.689			
	Yes	41	22.5	31	21.7	10	25.6	0.818	1.09	0.53	2.23
	Fistula	4	2.2	3	2.1	1	2.6	0.949	1.07	0.15	7.86
	Stricture	4	2.2	3	2.1	1	2.6	0.964	1.05	0.14	7.70
History of complications	Ulcer	26	14.3	21	14.7	4	10.3	0.546	0.72	0.25	2.07
	Intestinal perforation	0	0.0	0	0.0	0	0.0				
	GIT cancer	2	1.1	2	1.4	0	0.0	0.974	0.00	0.00	1.3×10^{250}
	Abscess formation	5	2.7	3	2.1	2	5.1	0.304	2.12	0.50	8.94
	Others	5	2.7	2	1.4	3	7.7	0.126	2.54	0.77	8.35
	None	171	94.0	136	95.1	35	89.7	0.711			
	Yes							0.297	1.73	0.62	4.88
	Stricturoplasty	3	1.6	2	1.4	1	2.6	0.657	1.57	0.21	11.47
	Endoscopic balloon dilatation	0	0.0	0	0.0	0	0.0				
Surgical intervention	Surgical resection	0	0.0	0	0.0	0	0.0				
	Intestinal perforation	0	0.0	0	0.0	0	0.0				
	GIT cancer	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
	Abscess formation	4	2.2	3	2.1	1	2.6	0.668	1.55	0.21	11.37
	Others (appendectomy, cholecystectomy	3	1.6	1	0.7	2	5.1	0.175	2.68	0.64	11.17
	< 18.5 (underweight)	3	1.6	2	1.4	1	2.6	0.687			
BMI categories	18.5-24.99 (Normal weight)	108	59.3	85	59.4	23	59.0	0.297	0.34	0.05	2.56
	25-29.99 (Overweight)	58	31.9	47	32.9	11	28.2	0.268	0.31	0.04	2.44
	30-39.99 (Obese)	13	7.1	9	6.3	4	10.3	0.474	0.45	0.05	4.04
	Chronic active colitis	63	34.6	49	34.3	14	35.9				
	Chronic active ileocolitis-UC	25	13.7	20	14	5	12.8				
	Chronic active colitis with lymphoid hyperplasia	5	2.7	4	2.8	1	2.6				
	Chronic active colitis with multiple superficial ulcers	3	1.6	2	1.4	1	2.6				
	Internal piles	4	2.2	3	2.1	1	2.6				
	ulcerative proctitis	15	8.2	13	9.1	2	5.1				
	Chronic active ulcerative pancolitis	1	0.5	0	0	1	2.6				
Colonoscopy	multiple superficial aphthoid ulcers - mild ileitis of Crohn's disease	35	19.2	26	18.2	9	23.1				
	Ileocolitis - Crohn's disease	31	17.0	27	18.9	4	10.3				
	Rectal Crohn's	10	5.5	7	4.9	3	7.7				
	Multiple superficial colonic ulcers and skip lesions with eosinophilic infiltration, terminal ileiltis - Crohn's disease	13	7.1	11	7.7	2	5.1				
	Chronic active colitis with lymphoid hyperplasia - CD	2	1.1	2	1.4	0	0				
	perianal fistula	1	0.5	0	0	1	2.6				
	Normal endoscopic findings	27	14.8	19	13.3	8	20.5				
	GERD	75	41.2	61	42.7	14	35.9				
	Antral gastritis	33	18.1	27	18.9	6	15.4				
	Pangastritis	56	30.8	45	31.5	11	28.2				
	Pre-pyloric erosions	17	9.3	13	9.1	4	10.3				
	Superficial duodenal bulb ulcers	28	15.4	21	14.7	7	17.9				
Endoscopy	Incompetent cardia	10	5.5	10	7.0	0	0.0				
	Gastrodudonitis	21	11.5	18	12.6	3	7.7				
	Antral erosions	17	9.3	13	9.1	4	10.3				
	Duodenal inflammatory polyp	7	3.8	5	3.5	2	5.1				
	Erosive gastritis	1	0.5	1	0.7	0	0.0				
	Peptic ulcer	1	0.5	0	0.0	1	2.6				
	Erosive gastrodudonitis	4	2.2	2	1.4	2	5.1				
	Normal abdominal findings	23	12.6	19	13.3	4	10.3				
	Colonic distention	77	42.3	60	42.0	17	43.6				
	Diffuse bright liver	58	31.9	46	32.2	12	30.8				
Abdominal Ultrasound	Diffuse hepatic fatty infiltration	31	17.0	0	0.0	0	0.0				
	Chronic noncalcular cholecystitis	14	7.7	10	7.0	4	10.3				

	Renal stones	12	6.6	9	6.3	3	7.7
	Chronic calcular cholecystitis	12	6.6	10	7.0	2	5.1
	Splenomegaly	1	0.5	1	0.7	0	0.0
	Cystitis	3	1.6	3	2.1	0	0.0
	Unremarkable	21	11.5	16	11.1	5	12.8

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

~ *p* value for Chi Square test. Significant at <0.05

NA; non-applicable

All Cases | Conventional Therapy | Biological Therapy

Total symptom score

Pulse rate (time/min)

Body Weight (kg)

CRP (mg/dL)

ESR (mm/hr)

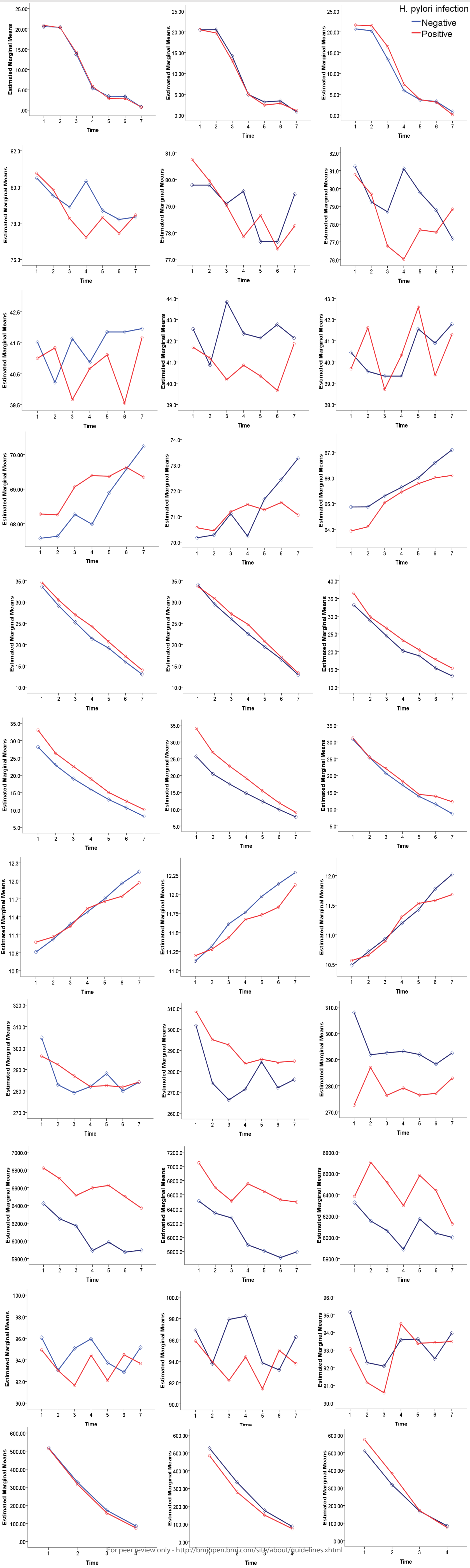
Hemoglobin (g/dL)

Platelets (x10^3/mL)

WBCs (cell/mL)

FBG (g/dL)

Fecal Calprotectin (μg/g)



File S1

Protocol for treating inflammatory bowel diseases

A. Treatment of ulcerative colitis

Depend on

1- Disease activity (clinical and endoscopic)
2- Extend (distal, left sided, extensive)

I- Mild, moderate + distal extend (proctosigmoiditis)
Topical methotrexate 4g/day
+ oral mesalazine (2-4 g/day)
+ steroid (oral prednisolone 40-60 mg/day with dose tapering over 8 weeks
If no remission (or unstable remission) occurs
The patient is treated as sever disease

If stable remission occurs
So stop steroids and maintain on mesalazine + AZA or 6-mp (for lifelong or 2 years then ….)

II- Mild, moderate + left sided extend (proctosigmoiditis)
5 ASA
+ oral mesalazine (2-4 g/day)
+ topical
If unsatisfactory response occurs
+ steroid (oral prednisolone 40-60 mg/day with dose tapering over 8 weeks
If no remission (or unstable remission or unsatisfactory response) occurs

The patient is treated as sever disease

If stable remission occurs
maintain lifelong on 5 ASA (1-2 g/day)+ AZA (2-2.5 mg/kg for 3-4 years)
sever disease (need hospitalization)
vital signs/ 6 hrs, CBC, ESR, CRP, electrolytes, stool chart, Abd US
antidiarrheal, anticholinergic, antibiotics, nutrition, blood transfusion, fluids
I.V steroids (hydrocortisone 400 mg/day pr methylprednisolone 60 mg/day
If stable remission occurs
Maintain lifelong on 5 ASA 1-2 g/day
+AZA 2-2.5 mg/kg

If unstable remission

Add AZA or methotrexate if still unstable remission occurs shift to biological

If no remission occurs shift to biological
If no response or complication (surgery)

B. Treatment of Crohn's Disease

According to disease severity

a- Mild to moderate
Treatment of active symptoms (antidiarrheal, nutrition, careful observation)
Ileocaecal (budesonide 3-4 mg/day)
Clonic sulfasalazine 2-4 g/day

b- Moderate to severe
Induction therapy (oral corticosteroids 40-60 mg / day with dose tapering over 8 weeks + AZA 2-2.5 mg/kg)

1- Response (maintain on
AZA 1.5-2.5 mg/kg/day
Methotrexate 2.5 mg/kg S.C or IM
Refractory cases will shift to biologicals (Ustekinumab)

2- Steroid resistant
Give anti INF (biological)
+AZA (2-2.5 g/kg)
Maintenance like induction therapy

3- Steroid dependent
Methotrexate 25 mg/kg S.C or IM +/- biologicals

c- Severe/fulminate disease
I.V steroids (hydrocortisone 400 mg/day pr methylprednisolone 60 mg/day
+ Anti INF

d- Perianal / fistula disease
Antibiotics
Drainage of abcess
+ biologics (infliximab, adalimumab)

List of Biologics used

- Infliximab (Remicode)
  IV 5 mg/kg or 10 mg/kg if sever
  Induction : 0, 2, 6 weeks
  Maintained : 8 weeks (4-12 week)

- Adalimumab (Humira)
  S.C 40 mg 80 mg 160 mg
  Induction : week 0; 160 mg
  Week 2; 80 mg
  Maintenance : 2 weeks 40 mg
  1 week 40 mg

- Golimumab (Simponi)
  S.C 50 mg 100 mg 200 mg
  Induction: Week 0; 200 mg
  Week 2; 100 mg
  Week 6; 50 mg (if weight < 70 kg) and 100 mg if weight > 70 kg

- Ustekinumab (Stelara)
  S.C or I.V
  260 mg or 390 mg or 520 mg
  Induction: week 0 I.V
  Week 8 S.C
  Maintenance: 8 – 12 weeks S.C

- Vedolizumab (Entyvio)
  IV
  300 mg
  Induction: 0, 2, 6 weeks
  Maintenance: week 8
  For 4 weeks if sever

- Certolizumab (Cimzia)
  S.C
  400 mg
  Induction : week 0; 400 mg
  Week 2; 400 mg
  Week 4; 400 mg
  Maintenance: 4 weeks 400 mg

File S2

Questionnaire: The Relationship between Helicobacter Pylori Infection and Inflammatory Bowel Disease

Pt no:	Name:	tel:

Group no:		H. Pylori (0) -ve (1) +ve	Treatment: (0) Conventional (1) Biologic

I- Sociodemographic Data		Code
1. Gender	(0) Male (1) Female	
2. Age in years	……..	
3. Residence	(0) Rural (1) Urban	
4. Education	(0) Illiterate (1) Read and Write (2) Primary (3) Preparatory (4) Secondary (5) University Education	
5. Occupation	(0) Not working (1) Student (2) Clerical (3) Professional (4) HCW (5) House wife (6) Craft (7) Auxiliary worker (8) Farmer (9) Retired (10) Other……..	
6. Marital status	(0) Single (1) Married (2) Widowed (3) Divorced	
7. Parent Consanguinity	(0) No (1) Yes	
8. Had been breast fed	(0) No (1) Yes	
9. Smoking	(0) Never (1) Current smoker (2) Ex-smoker	
10. Smoking index	no. of smoked cigarettes per day…… x no. of smoking years …… x 365	
11. Age of starting Smoking	(0) N/A (1) <20 years old (2) 20-30 years old (3) > 30 years old	
12. Smoking other than cigarette	(0) Never (1) Shisha (2) Snuff	
13. Alcohol Intake	(0) NA (1) Occasional (2) <3 cups/ day (3) >3 cups/ day (4) ex-drinker	
14. Drug Abuse	(0) NA (1) Never (2) Cannabis (3) Opium (4) tablets "tamols" (5) powder(heroin, cocaine) (6) IV drugs (7) others: ----------	
15. Chronic diseases	(00) No (01) DM (02) Hypertension (03) Bronchial Asthma/COPD (04) Heart disease (05) Renal Disease (06) liver disease (07) SLE (08) rheumatoid arthritis (09) skin allergy (10) hyperthyroidism (11) hypothyroidism (12) other autoimmune …….. (13) others……	
16. Family history of similar condition	(0) No (1) Yes; first degree relatives (2) Yes; other relatives (3) Other autoimmune disease……	
17. Medications	(0) None (1) Analgesic (NSAIDs) (2) anti DM (3) anti HTN (4) corticosteroids (5) IBD therapy (6) hormonal/oral contraceptives (7)thyroxin (8)others ……	
18. Transportation	(-1) not working (1) on foot (2) by bicycle (3) public transport/car	
19. Working activity	(-1) not working (1) Minimal (2) Moderate (3) High	
20. Activity outside work	(-1) not working (1) Minimal (2) Moderate (3) High	
21. Regular exercise	(0) Never (1) Yes Frequent (>3 times/week) (2) Yes Infrequent (<3 times/week)	
22. If yes, mention time spent in min/day	…… (-1) N/A	
23. Food source	(0) Homemade (1) restaurants (2) Mixed	
24. Junk Food, Fast Food	(0) Never (1) occasionally (2) daily If **daily**, mention the number of servings per day ……	
25. Saturated Fat (butter, ghee, cream, ..etc)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
26. trans Fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
27. Food rich in fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, squash, cabbage, cauliflower,	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	

broccoli, dried herbs & spices, fruits, vegetables)		
28. Salty Food (pickled, salty cheese, salted fish, dokka, ...	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
29. Fruits & Vegetables	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
30. Red meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
31. Under cooked meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
32. Fish	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
33. Consumption of caffeine in diet (tea, coffee)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
34. Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
35. Dairy products	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
36. On average, how many glasses of water consumed per day?	(1) one cup (2) 2-3 cups (3) at least 4 cups (4) 4 to 8 cups	
37. Dietary restrictions	(00) none (01) cereals (02) brown rice (03) whole grain bread (04) seeds (beans, peas) (05) fruits (apples, plums, peaches, skin removed) (06) high fat or protein food (07) vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper) (08) raw green vegetables (09) spices (10) fried food (11)baked dessert (12) milk and dairy products (13) carbonated drinks (14) tea and coffee (15) others ……	
38. Diet therapy	(0) none (1) low fiber (bananas, cantaloupe) (2) refined grains (white pasta, white rice, and oatmeal, potatoes) (3) Omega 3 rich food (fish) (4) Fully cooked, seedless, skinless, non-cruciferous vegetables (squash) (5) Lean sources of protein (poultry, soy, egg) (6) others……	
39. Food preparation method	(0) No preference (1) boiling (2) grilling (3) steaming (4) frying	
40. Number of meals per day	……	
41. Snackes between meals	(0) Never (1) occasionally (2) daily; ……. per day	
II- Clinical data		
42. Type of IBD diagnosed	(0) Crohn's disease (1) ulcerative colitis	
43. Age at diagnosis	**……..years old**	
44. History of H. pylori infection		
45. If yes mention the onset	(-1) NA (1) few weeks (2) 3-6 months (3) 6 months- 1 year (4)≥ 1 year	
46. History of receiving H. pylori eradication therapy during the past 12 months	(0) No (1) Yes; ……	
47. History of complications	(0) None (1) fistula (2) stricture (3) ulcers (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others……	
48. Surgical intervention	(0) None (1) stricturoplasty (2) Endoscopic balloon dilatation (3) surgical resection (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others	
49. Current medications used to control IBD	(00) None (01) 5-ASA "Pentasa (Mesalamine)" (02) 6-mercaptopurine "Purinethol" (03) Methotrexate "Trexall, Rasuvo, Otrexup" (04) Cyclosporine "Sandimmune, Neoral" (05) Corticosteroids "Prednisone" (06) Sulfasalazine (07) Azathiopurines "Imuran" (08) Librax (09) Imodium (10) Azithromycin "Zithromax" (11) Ciprofloxacin (12) Rifabutin (13) Clarithromycin "Biaxin" (14) Flagyl (15) probiotics (16) multivitamin supplements (17) Infliximab (18)PPI (19) Moltilium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others……	

50. Medications used in the past to control IBD	(00) None (01) 5-ASA "Pentasa (Mesalamine)" (02) 6-mercaptopurine "Purinethol" (03) Methotrexate "Trexall, Rasuvo, Otrexup" (04) Cyclosporine "Sandimmune, Neoral" (05) Corticosteroids "Prednisone" (06) Sulfasalazine (07) Azathiopurines "Imuran" (08) Librax (09) Imodium (10) Azithromycin "Zithromax" (11) Ciprofloxacin (12) Rifabutin (13) Clarithromycin "Biaxin" (14) Flagyl (15) probiotics (16) multivitamin supplements (17) Infliximab (18)PPI (19) Moltilium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others……	
51. How do you describe the effectiveness of the prescribed medications	(0) no difference (1) slight improved (2) dramatic improvement (3) slightly worsened condition (4) dramatic deterioration	
52. How do you describe the side effects of the prescribed medications	(0) none (1) few and tolerable (2) many but tolerable (3) difficult to tolerate and interfere with daily life	

III- Examination		
53. Baseline Body Weight	**…….. kg**	
54. Height	**……..cm**	

55. Fahmy and El Sherbini Socioeconomic standard scoring

1- Education		**Score**
	1.Father	**2.Mother**
Read and write or illiterate non working	1	1
Read and write or illiterate working	2	2
Primary education non working	3	3
Primary education working	4	4
Preparatory education non working	5	5
Preparatory education working	6	6
Secondary education non working	7	7
Secondary education working	8	8
University higher non working	9	9
University higher working	10	10
3- Family income		
Satisfactory and saving		8
Satisfactory		6
Satisfactory and debt		4
Unsatisfactory		2
6- Family size		
3-4 members		4
5 members		3
6 members		2
7 or more members		1
4- Crowding index		
5 or more/ room		0
4-		1
2-		2
<2		3
5- Sanitation		
According to the presence of pure water supply all through the day, electricity and special water closets inside the house:		
All the three present		3
2 out of three		2
One out of three		1
1- Total Score		
1- High (≥31.5)		
2- Middle (21 - <31.5)		
3- Low (<21)		

Follow-up sheet

	Pre treatment	Follow Up					
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
	0	week 2	Week 4	week 6	Week 8	Week 10	week 12
Body weight							
Blood pressure							
Pulse							
CRP							
ESR							
Hb							
Plts							
WBCs							
FBS							
Abd US							
CT							
MRI							
GIT Endoscopy							
Colonoscopy							
Others							
Symptoms (frequency per day)							
Weight loss							
Diarrhea							
Constipation							
Flatulence							
Bloating/indigestion							
Hurt burn							
Urge incontinence							
Soiling							
Tenesmus							
Frequent bowel movements							
Abd cramps							
Epigastric pain							
Generalized abdominal pain							
Nausea							
Vomiting							
Loss of appetite							
Bowel movement interfere with ability to eat							
Blood in stool							
Bleeding per rectum							

	Pre treatment	Follow Up					
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
	0	week 2	Week 4	week 6	Week 8	Week 10	week 12
Back pain							
Fever							
Chills							
Night sweating							
Fatigue/lack of energy							
Headache							
Dizziness							
Insomnia/troubled sleep							
Limited sexual activity							
Infection							
Sick leaves/absenteeism							
Others							
Signs of other system affection							
Eye							
Joints							
Kidney							
Skin							
Liver							
Reproductive organs							

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5 (lines 115-121)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5-6 (lines 115-125)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Page 5 (lines 118-121)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6-8
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at Page 6 (lines 126-135)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 8 (lines 170-189)
		(*b*) Describe any methods used to examine subgroups and interactions Page 7 (lines 179-199)
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 9-11 and all tables

		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 9-10 Table 1
		(b) Indicate number of participants with missing data for each variable of interest Page 9-11 and all tables
Outcome data	15*	Report numbers of outcome events or summary measures Page 9-11 and all tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 9-11 and all tables
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 10-11 and tables 2-5 and suppl tables
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 13
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Helicobacter pylori infection in patients with inflammatory bowel diseases: a single-centre, prospective, observational study in Egypt

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057214.R2
Article Type:	Original research
Date Submitted by the Author:	25-Mar-2022
Complete List of Authors:	Abd El-Wahab, Ekram; Alexandria University High Institute of Public Health, Tropical Health Youssef, Ebtessam; Alexandria University High Institute of Public Health, Tropical Health Hassouna, Ehab; Alexandria Medical School, Internal Medicine
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Epidemiology
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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Helicobacter pylori infection in patients with inflammatory bowel diseases: a single-centre, prospective, observational study in Egypt

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- **word count**: 3995

- **number of references**: 53

- **number of tables**: 5

- **number of figures** : 2

Abstract

Objective: Conflicting results have been reported by numerous epidemiological studies investigating the association between *Helicobacter pylori* (*H. pylori*) infection and inflammatory bowel disease (IBD). We aimed in this study to assess the possible association between *H. pylori* infection and IBD and its effects on disease progression.

Design: Prospective observational study.

Setting: Specialized IBD care clinics at Alexandria University Student Hospital in northern Egypt, between March and June 2019.

Participants: 182 patients with IBD.

Analysis and outcome measures: IBD participants were screened for *H. pylori* infection and clinically evaluated at the initial visit and bimonthly for 3 months to record any potential improvement/flare of the IBD condition.

Results: Overall, 90 (49.5%) patients with IBD had evidence of *H. pylori* infection. The course of IBD did not significantly differ in association with *H. pylori* infection or IBD treatment strategy. Cox regression analysis revealed that patients aged 20–35 years (OR = 6.20 [95% CI 1.74–22.12]) and 35–55 years (557.9 [17.4–17922.8]), high socioeconomic status (2.9 [1.11–7.8]), daily consumption of fibre-rich food (5.1 [1.32–19.5]), occasional consumption of snacks between meals (2.8 [2.5–70.5]) and eating four meals per day (13.3 (1.0–7.7]) were predictive of IBD flare. By contrast, eating fruits and vegetables showed a strongly protective association (OR = 0.001 (95% CI 0.0002–0.02]). The probabilities of improvement of IBD symptoms after 12 weeks of follow-up were comparable in assessments based on *H. pylori* infection status (0.793 for *H. pylori*-negative *vs*. 0.778 for *H. pylori*-positive) and IBD treatment option (0.811 for conventional therapy *vs*. 0.750 for biological therapy).

Conclusion: The association between IBD and *H. pylori* infection is unresolved and should be further investigated in the context of specific environmental exposures that influence the development or relapse of IBD.

Keywords: Inflammatory Bowel Disease; Crohn's disease; Ulcerative colitis; *Helicobacter pylori*

Article summary

Strengths and limitations of this study

- We were able to report the effect of *Helicobacter pylori* (*H. pylori*) infection on the response to conventional *versus* biological treatment of inflammatory bowel disease (IBD).
- The relatively small sample size and single-centre setting may limit the generalizability of the results.
- The study lacks a lack of a non-IBD healthy control group, and a causal link between *H. pylori* infection and IBD cannot be established.
- Estimation of the prevalence of *H. pylori* in IBD patients was limited by the detection method.

Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), comprises chronic, disabling, and progressive disorders characterized by lifelong treatment that impose a significant globally increasing threat to human health [1]. Numerous economically low-income countries have experienced a dramatic increase in the incidence of IBD [2]. Improved access to a more hygienic environment and the resulting decreased incidence of common childhood infections may represent a contributing factor through altering susceptibility to diseases with an autoimmune component, such as IBD [3 4]. Accordingly, microbial infections during childhood may protect against IBD. This rise may partially be accounted for by, the implementation of improved diagnostic methods and heightened awareness of IBD.

Although the pathogenesis of IBD is unknown, evidence indicates that it involves complex and unidentified interactions between environmental factors (such as infections, medicines, tobacco, food components) as well as host genetic factors that induce abnormal or inappropriate immunological reactions, or both, to components of the intestinal flora [5 6].

Evidence indicates that *Helicobacter pylori* (*H. pylori*) resides in the upper gastrointestinal tract of approximately 50% of the world's population, among which >80% of people lack symptoms [7]. In Egypt, the prevalence is approximately 80% [8]. *H. pylori* can elicit a chronic systemic inflammatory response, which may trigger autoimmune reactions that may contribute to the pathogenesis of autoimmune diseases. The inflammatory response of the gastric mucosa mainly involves stimulation of the host's immune system in response to *H. pylori*, which induces a cell-mediated immune response characterized by elevated levels of cytokines. Consequently, products of local immune reactions may migrate to extra-gastric sites, which may account for the association between *H. pylori* infection and extra-gastric diseases, including autoimmune disorders [9].

Although numerous, diverse studies analysed the association between *H. pylori* infection and IBD [9 10], a causal association between *H. pylori* and IBD remains to be established; and the are contradictory data related to the potential causative and the protective roles of *H. pylori* infection associated with IBD [11-19].

Assuming a potential protective role of *H. pylori* infection against IBD, *H. pylori* eradication treatment may influence the progression of IBD course and thus should be carefully administered, considering the findings of future prospective studies [16 20].

IBD occurs more frequently in regions with lower rates of *H. pylori* colonization. The steady increase in the incidence of IBD in *H. pylori*-endemic regions may reflect the advent of initiating anti-*H. pylori* therapy to treat peptic ulcers [13]. Furthermore, meta-analyses show that the prevalence of *H. pylori* infection is lower in patients with IBD compared with controls [9 10 13 19 21]. For example, long-term treatment with sulphasalazine contributes to the eradication of *H. pylori* infection [22]. Although unconfirmed, most studies indicate a protective role for *H. pylori* infection against the development of IBD [9 21].

With advances in identifying the pathological mechanisms underlying IBD, new therapies have been proposed, particularly those involving biological response modifiers. These include anti-tumor necrosis factor antibodies (anti-TNFα), IL-1/IL-6 receptor antagonists, and an anti-CD20 antibody. These therapies are generally well tolerated, although they may be associated with adverse effects, including increased susceptibility to infection and increased risk of malignancies [23].

These considerations inspired us to conduct a prospective, longitudinal study to further analyse the association between *H. pylori* infection and the flare of IBD and to investigate possible effects of *H. pylori* infection on the response to conventional *versus* biological treatment of IBD.

Methods

Study population and sampling

We conducted a prospective observational study at Alexandria University Student Hospital (AUSH) that is affiliated with Alexandria University, Egypt and serves students, faculty, and staff members. AUSH comprises outpatient clinics and inpatient and emergency departments with a bed capacity of 1000. We enrolled patients aged ≥18 years with confirmed IBD (triphasic CT abdomen, endoscopy/colonoscopy, and fecal calprotectin) and commenced IBD treatment (conventional or biological). Patients with irritable bowel syndrome were excluded according to the Rome III criteria [24].

Clinicians on the staff of the Internal Medicine Department of the AUSH selected the treatment (standard *vs*. biological). The prescribed treatment is the standard of care adopted by the AUSH for treating patients with IBD. Details of the treatment regimens and the parameters employed to select standard or biological treatment are described in File S1.

The frequency of *H. pylori* infection among patients with IBD is as high as 10.0% [21]. Using a margin of error=5.0%, an alpha error = 0.05 and a 95% confidence level, the minimum required sample size was 138 [8]. However, we ultimately enrolled 182 patients with IBD, because we expected that the prevalence of *H. pylori* infection might be higher because of the endemicity of *H. pylori* infection in Egypt [8], and to compensate for possible dropouts during the follow-up. The sample size was calculated using Epi info 7 software. Patients with confirmed IBD who agreed to participate in the study were consecutively enrolled. According to their characteristics (Figure 1), the patients were assigned into groups according to the prescribed treatment regimen (File S1) as follows: Group 1 comprised patients administered conventional IBD treatment, and Group 2 included patients undergoing biological IBD treatment.

Stool samples was used to detect *H. pylori* antigen using a commercially available enzyme immunoassay (EIA) kit (Foresight EIA test kit for qualitative and quantitative detection of *H. pylori* in the stool; ACON Laboratories, Inc. San Diego, CA, USA). Each assigned group included patients with IBD with or without *H. pylori* infection, and *H. pylori*-positive patients were shown their laboratory findings. We did not commence *H. pylori* eradication therapy during the study period. After a 3-month follow-up, *H. pylori*-positive patients were referred to a specialist for further evaluation and case management according to the adopted standard of care.

Patient and public involvement

We informed the patients about the aims and concerns of the study and how it will add to better understanding of their disease aetiology and triggering factors, which was highly appreciated by the patients, and motivated them to be a part of the cohort intended for the long-term follow-up by the clinicians. However, it was not appropriate or possible to involve patients or the public in the design,

conduct, reporting, or dissemination plans of our research. All the laboratory and clinical data were reported to the study participants, where we discussed the study findings in a simple language.

Assessments

Baseline evaluation included the patient's history, full clinical examination, and laboratory tests. A data collection form (File S2) was used to collect baseline data as follows: sociodemographic characteristics, personal habits, lifestyle, physical activity and exercise, dietary habits and restrictions, family history, medical history, comorbidities, and medications. Clinical data collected were from each patient during the initial visit were as follows: Disease onset, history of present complaints, frequency and duration of IBD attacks, past and current IBD medications, history of changing therapy, surgical intervention, and complications. History of *H. pylori* infection and undergoing *H. pylori* eradication therapy during the past 12 months were recorded during each follow-up visit. All patients were followed bimonthly for three months (6 visits) during IBD treatment. Patients were contacted weekly via telephone and asked about the frequency and severity of symptoms and if adverse effects associated with treatment occurred during the previous week.

Blood pressure (BP) and anthropometric measurements were measured according to standard techniques [25-27]. Body mass index (BMI) was calculated according to the Quetelet's index: BMI = (weight [kg]/height^2 [m^2]). At each follow-up visit, laboratory tests were performed as follows: complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting blood glucose (FBG), and fecal calprotectin [28]. Imaging techniques included triphasic CT and endoscopy/colonoscopy when indicated. All patients underwent full-length colonoscopy (Pentax colonoscopies). Colonoscopic biopsies acquired from the rectum and sigmoid; descending, transverse, ascending colon; as well as the cecal mucosa. Histological analyses of the degree of inflammation associated with CD and UC were evaluated according to the European consensus on the histopathology of IBD [29].

The socioeconomic status of the enrolled patients with IBD was calculated and categorized as high, middle, low, and very low, according to a modified social scoring system [30].

Outcomes

Patients in each group were clinically evaluated every two weeks for 3 months to record potential improvement/flare of IBD. The primary outcome of the study was the number of patients with IBD who achieved remission (improvement of IBD symptoms and normalization of the laboratory tests) at the end of the follow-up period.

Statistical analysis

Data were reviewed for accuracy and integrity and analysed using SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Continuous variables are presented as the mean ± standard deviation, and categorical variables are expressed as numbers with proportion, n (%). Variables relevant to laboratory data were dichotomized according to prefixed cut-offs, considering the normal reference values. The Student's *t* test was performed to compare quantitative variables between two groups of normally distributed data. The chi squared (χ^2) test was performed to evaluate the association between qualitative variables. Fisher's exact test with Yates correction was used when cell count was < 5. Reponses that have non-applicable (NA) values were coded with "-1" and we use the SPSS program strategy for handling missing values in the analysis. Repeated-measures ANOVA was used to test the significance of differences in the means of quantitative variables measured at different times. Multivariate logistic regression analyses were conducted to identify independent risk factors for *H. pylori* infection among patients with IBD. Cox regression analysis (or proportional hazards regression) was used to evaluate the effects of several variables at the time of occurrence of a specified event. Factors associated with IBD flare/remission were thus identified when testing variables with significant differences (significance levels <0.05) in the simple logistic regression analyses. Kaplan–Meier analysis was used to estimate the probability of recovery (remission of IBD as the event-of-interest) considering *H. pylori* infection status and treatment option. Recovery-defined remission/improvement in IBD status was based on clinical and laboratory data, whereas censored data defined lack of improvement or flare of the inflammatory condition. Statistical analyses were conducted using two-tailed tests (level of significance <0.05).

Results

Sociodemographic and clinical characteristics

Patients with IBD (n = 182) (n = 96 [52.7%] UC and n = 86 [47.3%] CD) included 51.7% males, 58.2% married, 51.6% resided in urban areas, 76.9% highly literate, and 82.4% non-smokers. The average age was 27.0 ± 7.3 years, with the majority ranging from 20 to 35 years. Normal BMI was a predominant feature (59.3%), and 31.9% were overweight. Patients' other sociodemographic characteristics are shown in (Table 1).

The physical activity scores were comparable between the study participants. However, those without *H. pylori* infection were judged to have a favourable food-habit score compared with those with *H. pylori* infection (12.2 ± 5.0 *vs*. 10.7 ± 3.8) (Table S1).

Patients' baseline clinical and laboratory findings are presented in Table S2. Compared with patients without *H. pylori* infection, infected patients had higher rates of abdominal cramps (91.1% *vs*. 84.8%), abdominal pain (85.6% *vs*. 81.5%), bloating/indigestion (98.9% *vs*. 95.7%), flatulence (100.0% *vs*. 96.7%), diarrhoea (98.9% *vs*. 96.7%), rectal bleeding (73.3% *vs*. 65.2%), fever (33.3% *vs*. 26.1%), chills (10.0% *vs*. 4.3%), infection (23.3% *vs*. 14.1%), fatigue/lack of energy (88.9% *vs*. 68.5%), sick leave/absenteeism (8.9% *vs*. 6.5%), and higher mean CRP (33.0 ± 23.0 *vs*. 28.2 ± 23.9) and ESR (34.6 ± 13.2 *vs*. 33.6 ± 14.1) levels. GIT endoscopy and colonoscopy revealed features of CD and UC, indicated by superficial ulcerations and mild infiltration.

H. pylori infection among patients with IBD

We detected *H. pylori* infection in 49.5% of patients, including those with UD (48, 50.0%) and CD (42, 48.8%) (OR = 1.05 [95% CI 0.59–1.88]), although 85.6% of them reported undergoing *H. pylori* eradication therapy in the past 12 months prior to the study. The infection rate was highest (74, 82.2%) among the age group 20 to <35 years (Table 1). Logistic regression analysis revealed that conventional treatment of IBD (OR = 1.99 [95% CI 1.03–3.85]), adults aged 20 or <35 years (6.20 [1.74–22.12]) and 35–55 years (11.1 [1.18–104.64]), and mixed food sources (3.12 [1.60–6.06]) predicted *H. pylori* infection ($p < 0.05$) (Table 2).

Assessment of IBD improvement/flare in relation to *H. pylori* infection

The total symptom scores of all patients, as well as the levels of ESR, CRP, Hb, and fecal calprotectin, significantly and linearly declined throughout the follow-up of all patients, independent of the status of *H. pylori* infection ($p < 0.05$). The values of other parameters (body weight, pulse, BP, WBCs, platelet count, and FBG) fluctuated in a nonlinear pattern, although the levels were within normal range. Overall, the changes (effect size) varied with time, because the pattern did not significantly differ relative to *H. pylori* infection (Table 3 and Figure S1). Subgroup analyses yielded similar results associated with the type of treatment (conventional, Table S3 and Figure S1 or biological, Table S4 and Figure S1).

Factors associated with improvement in IBD symptoms

Cox regression analysis revealed that subjects aged 20–35 years (OR = 6.20 [95% CI 1.74–22.12]) and 35–55 years (557.9 [17.4–17922.8]), high socioeconomic status (2.9 [1.11–7.8]), daily consumption of fibre-rich food (5.1 [1.32–19.5]), occasional consumption of snacks between meals (2.8 [2.5–70.5]), and eating four meals per day (13.3 [1.0–7.7]) were significantly associated with IBD flare ($p < 0.05$). By contrast, eating fruits and vegetables protected against IBD flare (Tables 4 and Table S5).

Probability of improvement of IBD symptoms in relation to *H. pylori* infection and IBD treatment strategy

Kaplan–Meier analysis revealed that the probabilities of recovery (remission) among the patients after 12 weeks of follow-up were comparable, considering *H. pylori* infection status (0.793 for *H. pylori*-negative *vs*. 0.778 for *H. pylori*-positive) or IBD treatment option (0.811 for conventional therapy *vs*. 0.750 for biological therapy). The number of patients who recovered from IBD among *H. pylori*-negative patients was similar to that of *H. pylori*-positive patients. By contrast, the proportion of recovered patients with IBD who underwent conventional therapy was higher compared with those administered biological therapy, although the difference was not significant. Thirty-nine subjects did not recover until the end of the study. The results of log-rank, Breslow, and Tarone-Ware tests of

equality of recovery (remission) did not significantly differ in relation to *H. pylori* infection status or IBD treatment strategy ($p > 0.05$) (Table 5 and Figure 2).

Discussion

Recent improvements in hygienic conditions and socioeconomic status have reduced *H. pylori* infection rates, and this trend accompanies increased IBD incidence in most countries. However, the role of *H. pylori* in IBD is unknown [2 16 31]. Numerous studies found lower *H. pylori* infection rates in patients with CD, UC, or both, compared with non-IBD controls, although a few studies did not detect a significant association [9 10 13 21 31]. Recent epidemiological studies, animal experiments, and meta-analyses reveal an inverse correlation between *H. pylori* infection and the onset of IBD onset, suggesting that colonization by *H. pylori* confers a protective effect against autoimmune diseases [13 23 32].

To further explain the negative association between *H. pylori* infection and IBD, we conducted a longitudinal study of patients with IBD, with or without *H. pylori* infection, to determine the influence *H. pylori* infection on patients' responses to conventional *vs*. biological treatment of IBD.

H. pylori was detected in approximately 50% of the patients, which is low compared with the prevalence among the population of Egypt, where disease is endemic [33-36]. These findings support the results of studies showing that lower rates *H. pylori* infection of patients with IBD, suggesting an association between *H. pylori* and IBD [9 21]. The rate *H. pylori* infection is significantly higher among patients with IBD who undergo conventional treatment, which conflicts with studies suggesting that 5-aminosalicylates or sulphasalazine interfere with the adhesion of *H. pylori* to the mucosa and block its proliferation [22 37-39]. For example, the results of multiple studies do not support the conclusion that treatment with sulfasalazine or other drugs such as 5-aminosalicylic acid (5-ASA), thiopurines, steroids, and antibiotics influence the colonization rate of *H. pylori* [13 40-42]. It is wort noting that although the treatment of IBD patients with anti-TNF-α agents, immunosuppressant and/ or corticosteroid increases the risk of infections, there is no direct evidence that novel therapeutic strategies such as anti-tumor necrosis factor alpha (TNF-α) and immunosuppressants result in

exacerbating or influence the prevalence of H. pylori infection Similar findings were reported by a study of novel therapeutic strategies such as anti-tumor necrosis factor alpha (TNF-α) treatment {Singh, 2011 #145;Triantafillidis, 2014 #29;Zhong, 2021 #144}.

Here we show that the majority of *H. pylori*-positive patients with IBD admitted undergoing *H. pylori* eradication therapy during the previous 12 months, which raises questions about the efficacy of eradication therapy or revels reinfection among this group of patients. Notably, most studies do not report subjects' history of treatment of *H. pylori* infection [13]. It is therefore possible that such patients with IBD were treated for *H. pylori* infection before enrolment, culminating in an incorrectly low rate of *H. pylori* infection.

Accumulating evidence suggests that *H. pylori*, through its ability to regulate the immune response, protects human from diseases with an autoimmune component, including IBD [43]. The results of investigations designed to confirm this possibility are controversial. For example, the heterogeneity among studies accounted for by methods used to diagnose IBD and *H. pylori* infection, study location, study population, and the possibility of publication bias limit the validity of this conclusion and raise questions concerning the robustness of their findings.

Here we conducted a prospective study to extended previous work through investigations of the association between *H. pylori* infection and IBD. A potential avenue for extending our study involved broadening the inclusion criteria to gain further insight into local variations of the protective effects of *H. pylori* against IBD. In contrast to previous studies, we added subgroup analysis of *H. pylori* infection and the type of IBD treatment. However, we did not detect a significant relationship between the two conditions. For example, disease course was similar among all patients with IBD regardless of their *H. pylori* infection status or conventional or biological treatment. Moreover, the extent, and severity of IBD increased with a decrease in *H. pylori* infection. We were intrigued by our findings that that the proportion of patients administered conventional therapy who recovered from IBD was higher than those administered biological therapy. This may be explained by the higher rate of *H. pylori* infection among patients with IBD administered conventional therapy or that patients administered biological therapy were refractory to previous conventional therapy and therefore suffered from increased disease severity.

Evidence indicates that IBD is induced through complex interactions between environmental and genetic factors. The growing burden of IBD may serve as a proxy for the hygiene hypothesis and improvements in the sanitation of living conditions, lifestyle and dietary changes, more frequent antibiotic use, enhanced diagnostic methods, and heightened awareness of IBD [1 44 45]. Accordingly, we further investigated the role of host and environmental cofactors reported to ameliorate or incite factors for IBD flare (e.g., diet, smoking, physical activity, breastfeeding, socioeconomic status, education, occupation, urban versus rural lifestyle, and medication [1]). In this context, we were guided by existing studies that recognized differences in potential risk factors or features unique to certain populations, such as the Mediterranean diet. Indeed, dietary factors play a crucial role in disease initiation or relapse [46], although certain diets such as the Mediterranean diet are purported to protect against IBD [47-49].

The plant-based, semi-vegetarian Mediterranean diet alleviates symptoms of IBD and maintains patients in remission, potentially through reducing inflammation and improving the microbiota [50 51]. In our present cohort, *H. pylori*-negative patients with IBD and those experiencing less flare had a more favourable overall dietary habit score. Consistent with Kakodkar's recommendations [50], which encourage the consumption of all vegetables and fruits in an IBD diet, we observed a strong protective role on IBD flare of daily and 2–3-times weekly consumption of vegetables and fruits. Moreover, a recent meta-analysis shows that the beneficial effect of *H. pylori* experienced by Mediterranean populations with IBD is lower compared with residents of East Asian and European regions [19]. Nevertheless, the analysis did not explicitly incorporate dietary information or study the putative beneficial effect of diet as a confounder. Moreover, this positive effect may be attributed to the relative abundance of CagA *H. pylori* in these populations, a strain that produces specific constituents that modulate host immune defences [52].

Fibre may serve as an anti-inflammatory component of IBD treatment, although a converse effect can occur [1]. Our Cox regression analysis revealed that daily consumption of foods rich in insoluble fibre, such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs, and spices, significantly increased the risk of IBD flare, particularly in patients who consume four daily meals interspersed with occasional snacks.

In agreement with Gentschew et al., [53] trans-fat consumption was associated with a higher probability of IBD flare, although this was not a variable included in our final model. Although our findings suggest a role for diet in IBD flare, its effect is questionable because of the limitations of recall bias and multifactorial exposures. Moreover, patients with IBD may alter their dietary habits in response to symptoms that vary with disease activity, which requires further direct research into the role of diet in IBD.

Variations in the protective effects of *H. pylori* on IBD may be explained by socioeconomic factors. For example, here we show that patients with IBD with higher socioeconomic status and mainly urban residents had a higher chance of disease flares. Moreover, the frequency of *H. pylori* infection did not significantly vary in association with socioeconomic status. These findings support the argument that factors associated with an urban lifestyle and industrialization influence risk of IBD. Furthermore, the rate of gastric colonization by *H. pylori* was significantly higher in adults aged >20 years, although there was no significant difference in the average age of IBD onset between *H. pylori*-positive and -negative groups. This age group experienced a higher frequency of disease flares. These findings may be explained by patients' histories of comorbidities or lifestyle, which affect the occurrence of IBD. Demographic variables other than age did not exert detectable effects.

The findings of this study must be interpreted in view of its limitations. First, we did not test gastric biopsies for *H. pylori*, which may have decreased the disease prevalence rate. However, this would incur the burdens of an ethically questionable invasive procedure. A urea breath test may serve as a better alternative, although we did not have access to this test in our centres. Second, the small sample size was a major limitation and may have influenced the estimation of effect size. Third, the trend of decreased *H. pylori* infection in patients administered biological therapy coincided with increased severity of IBD, which should be investigated by a larger, statistically robust randomized controlled trial. Moreover, our results merit reassessment in a cohort of patients from a background population with a low prevalence of *H. pylori* that includes detailed information about eradication treatment and administration of other antibiotics. Fourth, a causal relationship between *H. pylori* infection and IBD cannot be established through an uncontrolled study (control group without IBD), and further large scale prospective studies are required. Thus, studies are warranted to investigate the

effects of eradication of *H. pylori* on the development of IBD combined with analyses of environmental exposures, hygiene diet, physical activity, and intestinal microbiota as significant confounders. An ideal study would be prospective and initiated when IBD is diagnosed.

Conclusions

Together, the findings of our present analysis of the association between IBD and *H. pylori* infection are inconclusive, and further studies are required. Thus, much remains to be learned about the causes of IBD and whether specific environmental exposures influence the development of disease and its course.

Ethics approval

The study was approved by the institutional review board and the ethics committee of the High Institute of Public Health affiliated with Alexandria University, Egypt. The study was conducted in accordance with the international ethical guidelines and that of the Declaration of Helsinki. Informed written consent was obtained from each participant after explaining the aim and concerns of the study. The datasheets were coded by number to ensure anonymity and confidentiality of the participants' data.

Contributors

EWAW: Conceptualization, developed the theoretical framework and study design, took the lead for overall direction and planning of the study implementation, data curation, statistical analysis and interpretation of data, major contribution to writing, revised and approved final version of the manuscript. EIY: Study implementation and recruitment of the study participants, data collection, clinical evaluation and follow up, analysis and interpretation of data, contributed to the writing of the manuscript, revised and approved final version of the of the manuscript. EMH: Supervised the study implementation and data collection, facilitated the recruitment of the study participants, clinical

evaluation and follow up, data curation, contributed to the writing of the manuscript, revised and approved final version of the manuscript.

Competing interests

All authors declare no conflict of interest.

Data availability statement

All data are fully available without restriction by the corresponding author at ekram.wassim@alexu.edu.eg.

Funding: None.

Acknowledgments

We would like to acknowledge the study participants for accepting to participate in the study.

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Figure legends

Figure 1: Patient dispositions

Figure 2: The equality of recovery (remission of IBD symptoms) during the follow-up periods associated with *H. pylori* infection status and IBD treatment strategies

Figure S1 (supplementary material): Patients' clinical and laboratory findings during follow-up periods associated with *H. pylori* infection status and the IBD treatment strategy

Table 1: Characteristics of the study population

	IBD patients		*H. pylori* infection in IBD patients			
	Total (n=182)		Negative (n=92)		Positive (n=90)	
	No.	%	No.	%	No.	%
Type of IBD diagnosed						
Crohn's disease	86	47.3	44	47.8	42	46.7
Ulcerative colitis	96	52.7	48	52.2	48	53.3
Onset of *H. pylori* infection						
None	92	50.5	92	100	0	0
Few weeks ago	7	3.8	0	0	7	7.8
3 – 6 months	10	5.5	0	0	10	11.1
6 months – 1 year	35	19.2	0	0	35	38.9
> 1 year	38	20.9	0	0	38	42.2
History of receiving *H. pylori* eradication therapy in the past 12 months prior to the study						
No	89	48.9	76	82.6	13	14.4
Yes	93	51.1	16	17.4	77	85.6
Treatment option given						
Conventional	106	58.2	47	51.1	59	65.6
Biological	76	41.8	45	48.9	31	34.4
Sex						
Male	94	51.6	46	50	48	53.3
Female	88	48.4	46	50	42	46.7
Age (Years)						
16 – <20 Years	20	11	15	16.3	5	5.6
20 – <35 Years	136	74.7	62	67.4	74	82.2
35 – 55 Years	26	14.3	15	16.3	11	12.2
Mean ± SD	27.0 ± 7.3		27.6 ± 8.0		26.3 ± 6.5	
Age at IBD diagnosis						
10 – >19	69	37.9	35	38	34	37.8
20 – <30	83	45.6	46	50	37	41.1
30 – 45	30	16.5	11	12	19	21.1
Mean ± SD	21.6 ± 6.4		21.4 ± 6.3		22.0 ± 6.5	
Residence						
Rural	88	48.4	51	55.4	37	41.1
Urban	94	51.6	41	44.6	53	58.9
Education						
Illiterate	2	1.1	0	0	2	2.2
Read and write	23	12.6	12	13	11	12.2
Primary	4	2.2	4	4.3	0	0
Preparatory	13	7.1	9	9.8	4	4.4
Secondary	44	24.2	24	26.1	20	22.2
University education	96	52.7	43	46.7	53	58.9
Working status						
No	88	48.4	39	42.4	49	54.4
Yes	94	51.6	53	57.6	41	45.6
Occupation						
Unemployed	37	20.3	21	22.8	16	17.8
Student	45	24.7	16	17.4	29	32.2
Clerical	2	1.1	2	2.2	0	0
Professional	39	21.4	17	18.5	22	24.4
Housewife	21	11.5	10	10.9	11	12.2
Auxiliary worker	22	12.1	12	13	10	11.1
Farmer	16	8.8	14	15.2	2	2.2
Marital status						
Single	73	40.1	37	40.2	36	40
Married	106	58.2	55	59.8	51	56.7
Widowed	2	1.1	0	0	2	2.2
Divorced	1	0.5	0	0	1	1.1
Socioeconomic standard						
High	58	31.9	24	26.1	34	37.8
Middle	52	28.6	30	32.6	22	24.4
Low	72	39.6	38	41.3	34	37.8
Consanguinity						
No	144	79.1	70	76.1	74	82.2
Yes	38	20.9	22	23.9	16	17.8
History of being breastfed						
No	26	14.3	14	15.2	12	13.3
Yes	156	85.7	78	84.8	78	86.7

a; Included chronic sinusitis, vertigo, lumbar disc prolapse, familial dyslipidaemia, haemorrhoids, scleritis, HCV, anaemia, fatty liver, steatosis, psoriasis, peripheral neuropathy, chronic cholecystitis)

Table 1 continued

	IBD patients		*H. pylori* infection in IBD patients			
	Total (n=182)		Negative (n=92)		Positive (n=90)	
	No.	%	No.	%	No.	%
Smoking						
Never	150	82.4	75	81.5	75	83.3
Current smoker	26	14.3	13	14.1	13	14.4
Ex-Smoker	6	3.3	4	4.3	2	2.2
Age of starting Smoking						
Non-smoker	153	84.1	77	83.7	76	84.4
< 20 Years	17	9.3	10	10.9	7	7.8
20-30 Years	12	6.6	5	5.4	7	7.8
>30 Years	0	0	0	0	0	0
Smoking other than cigarette						
Never	180	98.9	90	97.8	90	100
Shisha	2	1.1	2	2.2	0	0
BMI categories						
< 18.5 (underweight)	3	1.6	2	2.2	1	1.1
18.5-24.99 (Normal weight)	108	59.3	58	63	50	55.6
25-29.99 (Overweight)	58	31.9	24	26.1	34	37.8
30-39.99 (Obese)	13	7.1	8	8.7	5	5.6
Co-morbidities						
No	82	45.1	43	46.7	39	43.3
Yes	100	54.9	49	53.3	51	56.7
Diabetes Mellitus	10	5.5	4	4.3	6	6.7
Hypertension	30	16.5	15	16.3	15	16.7
Bronchial Asthma/COPD	15	8.2	11	12	4	4.4
Heart disease	1	0.5	0	0	1	1.1
Renal disease	1	0.5	1	1.1	0	0
Liver disease	1	0.5	0	0	1	1.1
Skin allergy	18	9.9	11	12	7	7.8
Hyperthyroidism	4	2.2	1	1.1	3	3.3
Hypothyroidism	8	4.4	0	0	8	8.9
Other autoimmune diseases	1	0.5	0	0	1	1.1
Others[a]	27	14.8	8	8.7	19	21.1
Autoimmune diseases						
No	163	89.6	85	92.4	78	86.7
Yes	19	10.4	7	7.6	12	13.3
Medications						
None	13	7.1	12	13	1	1.1
Analgesic (NSAIDs)	12	6.6	3	3.3	9	10
Antidiabetics	6	3.3	3	3.3	3	3.3
Antihypertensives	32	17.6	16	17.4	16	17.8
Corticosteroids	10	5.5	4	4.3	6	6.7
IBD therapy	151	83	70	76.1	81	90
Hormonal contraceptives	2	1.1	0	0	2	2.2
Thyroxin	9	4.9	2	2.2	7	7.8
Others	37	20.3	15	16.3	22	24.4

~ *p* value for Chi Square test. Significant at <0.05

IBD; inflammatory bowel disease

H. pylori; *Helicobacter pylori*

No history of alcohol or drug abuse was reported

Table 2: Predictors of *H. pylori* infection in patients with IBD

Backward Stepwise (Wald) Logistic Regression		B	S.E.	Wald	df	Sig. (*p* value)	Exp(B)	95.0% C.I. for EXP(B)	
								Lower Limit	Upper Limit
Step 5	Treatment of IBD								
	Biological treatment	-0.686	0.337	4.14	1	0.042	0.50	0.26	0.98
	Conventional treatment	0.686	0.337	4.14	1	0.042	1.99	1.03	3.85
	Age group (Years)								
	16 - <20			7.93	2	0.019		ref	
	20 - <35	1.825	0.649	7.92	1	0.005	6.20	1.74	22.12
	35 - 55	2.408	1.144	4.43	1	0.035	11.11	1.18	104.64
	Food source								
	Homemade			11.48	2	0.003		ref	
	Restaurant	-0.024	0.915	0.00	1	0.979	0.98	0.16	5.87
	Mixed	1.137	0.339	11.25	1	<0.001	3.12	1.60	6.06
	Constant	0.108	1.015	0.01	1	0.915	1.11		

p value significate at <0.05
H. pylori; *Helicobacter pylori*
IBD; inflammatory bowel disease
ref; reference category

Table 3: Repeated-measures ANOVA of clinical and laboratory findings among patients with IBD during follow-up

Parameter	*H. pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA												
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects					Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12													
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	34.6 ± 13.2	30.5 ± 10.9	27.0 ± 10.3	24.2 ± 8.9	20.6 ± 27.3	17.3 ± 6.9	14.0 ± 5.3	T	96.93	<0.001	0.769	1.000	T	350.0	<0.001	0.660	570.0	<0.001	1.75	0.188	0.010
	Negative	33.6 ± 14.1	29.1 ± 11.3	25.2 ± 9.4	21.4 ± 8.6	19.2 ± 6.9	15.9 ± 5.3	13.0 ± 4.9	T × S	1.156	0.322	0.038	0.448	T × S	0.666	0.538	0.004	0.001	0.974			
CRP	Positive	33.0 ± 23.0	26.4 ± 18.4	22.8 ± 16.1	18.9 ± 13.0	15.1 ± 9.7	12.5 ± 6.9	10.1 ± 7.2	T	31.74	<0.001	0.521	1.000	T	152.0	<0.001	0.458	181.4	<0.001	2.59	0.109	0.014
	Negative	28.2 ± 23.9	22.9 ± 19.5	19.0 ± 15.4	15.9 ± 12.7	13.0 ± 9.4	10.6 ± 6.8	8.2 ± 4.5	T × S	0.708	0.644	0.024	0.276	T × S	0.788	0.418	0.004	0.848	0.358			
FBG	Positive	94.9 ± 11.1	93.0 ± 10.6	91.6 ± 9.8	94.4 ± 11.5	92.1 ± 9.5	94.5 ± 14.1	93.7 ± 9.0	T	3.52	0.003	0.108	0.945	T	2.77	0.016	0.015	2.753	0.11	0.974	0.325	0.005
	Negative	96.1 ± 11.6	93.0 ± 10.6	95.1 ± 9.3	96.0 ± 13.1	93.7 ± 9.7	92.9 ± 10.4	95.1 ± 8.4	T × S	1.48	0.187	0.048	0.565	T × S	1.56	0.168	0.009	0.443	0.507			
Calprotectin	Positive	515.0 ± 206.7		314.5 ± 166.3		157.4 ± 82.2		74.5 ± 29.3	T	253.0	<0.001	0.810	1.000	T	569.4	<0.001	0.760	753.5	<0.001	0.424	0.516	0.002
	Negative	517.4 ± 214.4		326.3 ± 139.4		172.0 ± 88.1		85.5 ± 66.9	T × S	0.157	0.925	0.003	0.078	T × S	0.108	0.854	0.001	0.073	0.787			
Hb	Positive	11.0 ± 1.4	11.1 ± 1.3	11.2 ± 1.2	11.5 ± 1.1	11.6 ± 1.0	11.7 ± 0.9	12.0 ± 0.9	T	49.7	<0.001	0.63	1	T	151.0	<0.001	0.456	279.2	<0.001	0.042	0.837	0.00024
	Negative	10.8 ± 1.4	11.0 ± 1.6	11.3 ± 1.1	1.5 ± 1.0	11.7 ± 1.0	12.0 ± 0.81	12.2 ± 0.75	T × S	3.1	0.007	0.096	0.91	T × S	3.75	0.012	0.02	5.61	0.019			
WBCs	Positive	6821.1 ± 1506.9	6701.1 ± 1349.8	6511.8 ± 1161.0	6597.6 ± 1271.7	6625.4 ± 1057.3	6497.2 ± 1025.5	6369.2 ± 1131.6	T	4.21	0.001	0.126	0.977	T	7.26	<0.001	0.039	2.44	0.120	14.7	<0.001	0.076
	Negative	6420.8 ± 1530.5	6249.0 ± 1385.3	8170.1 ± 1195.3	5890.8 ± 1066.8	5985.9 ± 1022.0	5873.3 ± 1033.1	5895.6 ± 979.3	T × S	1.05	0.394	0.035	0.409	T × S	1.18	0.318	0.007	1.65	0.200			
Platelets	Positive	296.2 ± 67.4	292.3 ± 66.3	287.0 ± 65.7	282.1 ± 57.9	282.5 ± 51.1	281.8 ± 50.2	284.2 ± 54.0	T	3.23	0.005	0.100	0.922	T	5.12	0.003	0.028	7.37	0.007	0.015	0.904	0.0001
	Negative	304.8 ± 61.7	283.0 ± 50.4	279.2 ± 44.3	282.0 ± 48.5	288.1 ± 46.5	280.0 ± 39.4	284.1 ± 44.2	T × S	1.02	0.415	0.034	0.396	T × S	1.22	0.302	0.007	0.559	0.456			
Total symptom score	Positive	20.9 ± 3.2	20.3 ± 3.4	14.2 ± 4.2	5.8 ± 3.1	2.9 ± 3.3	2.9 ± 3.0	0.7 ± 2.1	T	754.9	<0.001	0.964	1.000	T	1371.1	<0.001	0.890	432	<0.001	0.007	0.932	0.00004
	Negative	20.6 ± 3.1	20.4 ± 3.7	13.8 ± 4.6	5.4 ± 2.7	3.4 ± 3.0	3.3 ± 2.9	0.8 ± 1.6	T × S	0.901	0.496	0.031	0.35	T × S	0.728	0.502	0.004	0.003	0.955			
Body weight	Positive	68.3 ± 11.7	68.3 ± 11.8	69.1 ± 11.7	69.4 ± 11.5	69.4 ± 11.4	69.6 ± 11.1	69.3 ± 11.9	T	20.34	<0.001	0.411	1.000	T	16.67	<0.001	0.085	0.061	0.805	0.067	0.797	0.0004
	Negative	67.6 ± 12.2	67.6 ± 12.1	68.3 ± 12.1	68.0 ± 13.8	68.9 ± 12.1	69.6 ± 12.2	70.2 ± 12.0	T × S	2.08	0.058	0.067	0.740	T × S	3.95	0.013	0.021	7.73	0.006			
Pulse	Positive	80.8 ± 5.0	79.9 ± 4.3	78.3 ± 4.0	77.2 ± 4.8	78.3 ± 4.1	77.4 ± 4.1	78.5 ± 2.8	T	5.36	<0.001	0.155	0.995	T	8.24	<0.001	0.044	6.93	0.009	3.13	0.079	0.017
	Negative	80.5 ± 5.6	79.5 ± 5.5	78.9 ± 4.8	80.3 ± 5.0	78.7 ± 5.0	78.2 ± 5.0	78.3 ± 4.7	T × S	2.67	0.017	0.084	0.856	T × S	3.27	0.007	0.018	6.67	0.011			
Pulse pressure	Positive	41.0 ± 5.6	41.3 ± 6.7	39.7 ± 8.9	40.7 ± 8.6	41.1 ± 7.6	39.6 ± 6.9	41.7 ± 9.7	T	0.729	0.627	0.024	0.284	T	0.759	0.593	0.004	1.69	0.195	1.13	0.29	0.006
	Negative	41.5 ± 6.8	40.2 ± 6.8	41.6 ± 7.9	40.9 ± 8.1	41.8 ± 8.5	41.8 ± 8.1	42.0 ± 9.3	T × S	1.28	0.270	0.042	0.493	T × S	1.201	0.305	0.007	0.286	0.593			

H. pylori; *Helicobacter pylori*
IBD; inflammatory bowel disease
$p < 0.05$ is significant
[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)
[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant
[c] large effect if the value of partial Eta squared >0.1
T × S; time versus state of H. pylori infection
ref; reference category

Table 4: Cox regression analysis of factors associated with IBD flare during follow-up

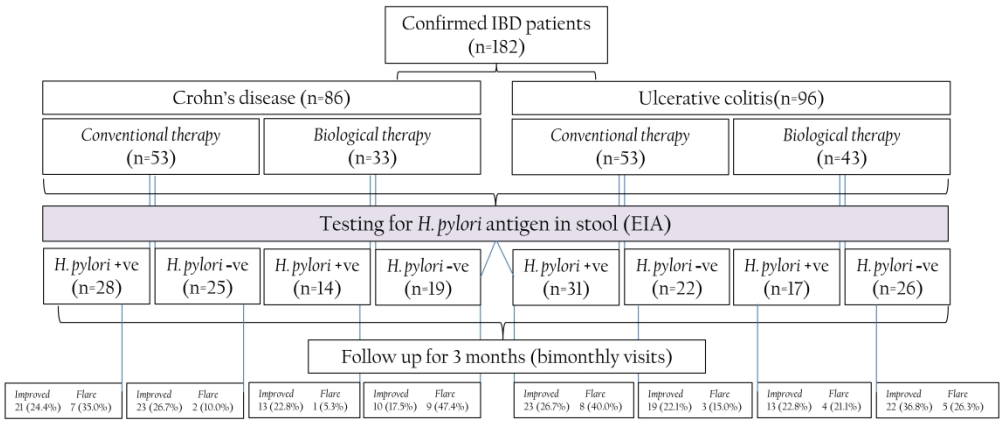
	Backward Stepwise (Wald) Logistic Regression	B	SE	Wald	df	Sig. (*p* value)	Exp(B)	95.0% CI for Exp(B) Lower Limit	95.0% CI for Exp(B) Upper Limit
Step 6	Age (Years)								
	16 - <20 Years			13.83	2	<0.001		ref	
	20 - <35 Years	1.50	0.71	4.41	1	0.036	4.49	1.11	18.21
	35 - 55 Years	6.32	1.77	12.76	1	<0.001	557.92	17.37	17922.78
	Socioeconomic standard								
	High	1.08	0.50	4.71	1	0.030	2.94	1.11	7.79
	Middle	0.68	0.48	1.97	1	0.160	1.97	0.76	5.10
	Low			4.71	2	0.095			
	Food rich in insoluble fibre								
	Once per week			8.75	2	0.013		ref	
	2-4 times per week	0.02	0.58	0.00	1	0.973	1.02	0.33	3.18
	Daily	1.62	0.69	5.61	1	0.018	5.08	1.32	19.49
	Fruits and vegetables								
	Never			22.20	3	<0.001		ref	
	Once per week	-7.07	1.63	18.74	1	<0.001	0.001	0.00003	0.02
	2-4 times per week	-7.61	1.62	22.06	1	<0.001	0.001	0.00002	0.01
	Daily	-7.47	1.68	19.76	1	<0.001	0.001	0.00002	0.02
	Number of meals per day								
	Two			10.25	2	0.006		ref	
	Three	-0.11	0.38	0.08	1	0.780	0.90	0.43	1.89
	Four	2.59	0.85	9.30	1	0.002	13.33	2.52	70.46
	Snacks between meals								
	Never			11.43	2	0.003		ref	
	Occasionally	1.04	0.51	4.07	1	0.044	2.82	1.03	7.72
	Daily	-3.89	2.03	3.69	1	0.055	0.02	0.00	1.08

IBD; inflammatory bowel disease
p value significate at < 0.05
ref; reference category

Table 5: Kaplan–Meier analysis of the probability of improvement in IBD symptoms in relation to with H. pylori infection and IBD treatment strategy

Variable	Group	Case summary	No of Events n(%)	Censored n(%)	Event Time (bimonthly visit)	No. of Events (recovery[a])	No. of relapse	No. at Risk (to recovery[a])	Probability of recovering[a]	Test of equality of recovery[a]		
										Log Rank (Mantel-Cox)	Breslow (Generalized Wilcoxon)	Tarone-Ware
										p value		
***H. pylori* infection in IBD patients**	Negative	n=92	73 (79.3)	19 (20.7)	1	0	2	92	0.000	0.969	0.708	0.833
					2	1	4	91	0.011			
					3	0	5	91	0.011			
					4	14	3	77	0.163			
					5	17	1	60	0.348			
					6	41	4	19	0.793			
	Positive	n=90	70 (77.8)	20 (22.2)	1	0	0	90	0.000			
					2	0	3	90	0.000			
					3	2	1	88	0.022			
					4	22	6	66	0.267			
					5	8	6	58	0.356			
					6	38	4	20	0.778			
Treatment of IBD	Conventional	n=106	86 (81.1)	20 (18.9)	1	0	0	106	0.000	0.893	0.867	0.880
					2	0	3	106	0.000			
					3	2	1	104	0.019			
					4	21	5	83	0.217			
					5	16	6	67	0.368			
					6	47	5	20	0.811			
	Biological	n=76	57 (75.0)	19 (25.0)	1	0	2	76	0.000			
					2	1	4	75	0.013			
					3	0	5	75	0.013			
					4	15	4	60	0.211			
					5	9	1	51	0.329			
					6	32	3	19	0.750			

H. pylori; *Helicobacter pylori*
IBD; inflammatory bowel disease
p value significate at <0.05
a: recovery reflects a state of remission of IBD condition



Patients' dispositions

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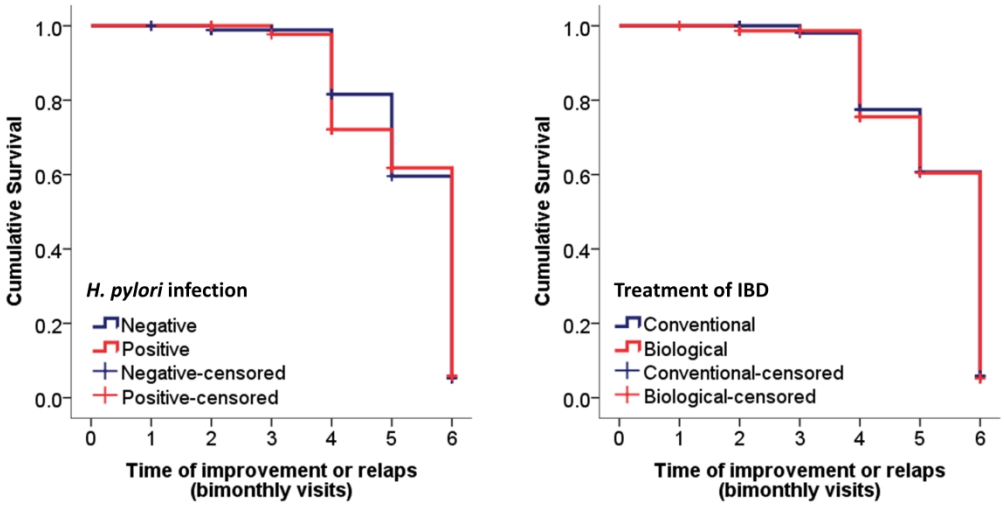

The equality of recovery (remission of IBD symptoms) during the follow-up periods associated with H. pylori infection status and IBD treatment strategies

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Supplementary Tables for online display

Table S1: Physical activity and dietary habit among the enrolled patients with IBD

		IBD patients		*H. pylori* infection in IBD patients				*p*~
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.	%	
Physical activity and physical exercise								
Transportation	not working	71	39.0	36	39.1	35	38.9	0.173
	On foot	19	10.4	14	15.2	5	5.6	
	By bicycle	4	2.2	2	2.2	2	2.2	
	Public transport or car	88	48.4	40	43.5	48	53.3	
Working activity	not working	65	35.7	30	32.6	35	38.9	0.001
	minimal	43	23.6	13	14.1	30	33.3	
	moderate	73	40.1	49	53.3	24	26.7	
	high	1	0.5	0	0.0	1	1.1	
Activity outside work	not working	59	32.4	27	29.3	32	35.6	0.451
	minimal	90	49.5	50	54.3	40	44.4	
	moderate	32	17.6	15	16.3	17	18.9	
	high	1	0.5	0	0.0	1	1.1	
Regular exercise	never	136	74.7	76	82.6	60	66.7	0.023
	yes frequent (>3 times/ week)	7	3.8	1	1.1	6	6.7	
	yes infrequent (<3 times/ week)	39	21.4	15	16.3	24	26.7	
Total physical activity score		2.8 ± 2.1		3.01 ± 2.2		2.5 ± 2.1		*t*=1.6, *p*= 0.107
Food habits								
Food source	Homemade	97	53.3	61	66.3	36	40.0	0.001
	Restaurant	6	3.3	4	4.3	2	2.2	
	Mixed	79	43.4	27	29.3	52	57.8	
Junk Food, Fast Food	never	50	27.5	25	27.2	25	27.8	0.995
	occasionally	128	70.3	65	70.7	63	70.0	
	daily	4	2.2	2	2.2	2	2.2	
Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	1	1.1	4	4.4	<0.001
	once per week	79	43.4	51	55.4	28	31.1	
	2-4 times per week	85	46.7	39	42.4	46	51.1	
	daily	13	7.1	1	1.1	12	13.3	
Trans fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	never	30	16.5	9	9.8	21	23.3	<0.001
	once per week	91	50.0	61	66.3	30	33.3	
	2-4 times per week	60	33.0	21	22.8	39	43.3	
	daily	1	0.5	1	1.1	0	0.0	
Food rich in insoluble fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs & spices)	never	0	0.0	0	0.0	0	0.0	<0.001
	once per week	39	21.4	28	30.4	11	12.2	
	2-4 times per week	88	48.4	49	53.3	39	43.3	
	daily	55	30.2	15	16.3	40	44.4	
Salty Food (pickled, salty cheese, salted fish, dokka, …)	never	27	14.8	16	17.4	11	12.2	<0.001
	once per week	96	52.7	61	66.3	35	38.9	
	2-4 times per week	54	29.7	12	13.0	42	46.7	

	daily	5	2.7	3	3.3	2	2.2	
	never	2	1.1	2	2.2	0	0.0	
Fruits and Vegetables	once per week	56	30.8	45	48.9	11	12.2	<0.001
	2-4 times per week	81	44.5	37	40.2	44	48.9	
	daily	43	23.6	8	8.7	35	38.9	
	never	16	8.8	4	4.3	12	13.3	
Red meat	once per week	113	62.1	66	71.7	47	52.2	0.013
	2-4 times per week	53	29.1	22	23.9	31	34.4	
	daily	0	0.0	0	0.0	0	0.0	
	never	157	86.3	80	87.0	77	85.6	
Under cooked meat	once per week	24	13.2	11	12.0	13	14.4	0.548
	2-4 times per week	1	0.5	1	1.1	0	0.0	
	daily	0	0.0	0	0.0	0	0.0	
	never	17	9.3	14	15.2	3	3.3	
Fish	once per week	91	50.0	38	41.3	53	58.9	0.007
	2-4 times per week	74	40.7	40	43.5	34	37.8	
	daily	0	0.0	0	0.0	0	0.0	
	never	25	13.7	17	18.5	8	8.9	
Consumption of caffeine in diet (tea, coffee)	once per week	20	11.0	17	18.5	3	3.3	<0.001
	2-4 times per week	61	33.5	30	32.6	31	34.4	
	daily	76	41.8	28	30.4	48	53.3	
	never	7	3.8	5	5.4	2	2.2	
Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	once per week	67	36.8	41	44.6	26	28.9	0.039
	2-4 times per week	91	50.0	41	44.6	50	55.6	
	daily	17	9.3	5	5.4	12	13.3	
	never	27	14.8	13	14.1	14	15.6	
Dairy products	once per week	49	26.9	33	35.9	16	17.8	0.034
	2-4 times per week	78	42.9	36	39.1	42	46.7	
	daily	28	15.4	10	10.9	18	20.0	
	one cup	8	4.4	3	3.3	5	6.7	
Average number of glasses of water consumed per day	2-3 cups	73	40.1	40	43.5	33	36.7	0.102
	at least 4 cups	73	40.1	41	44.6	32	35.6	
	4-8 cups	27	14.8	8	8.7	19	21.1	
	Never	60	33.0	33	35.9	27	30.0	
Snacks between meals	Occasionally	121	66.5	58	63.0	63	70.0	0.420
	Daily	1	0.5	1	1.1	0	0.0	
	Two	68	37.4	32	34.8	36	40.0	
Number of meals per day	Three	109	59.9	55	59.8	54	60.0	0.092
	Four	5	2.7	5	5.4	0	0.0	
Total food score (favorable food habits)		11.4 ± 4.5		12.2 ± 5.0		10.7 ± 3.8		t=2.4 , p= 0.018
Dietary restrictions	No	119	65.4	64	69.6	55	61.1	0.231
	Yes	63	34.6	28	30.4	35	38.9	
	Cereals	0	0.0	0	0.0	0	0.0	
	Brown rice	5	2.7	2	2.2	3	3.3	
	Whole grain bread	2	1.1	2	2.2	0	0.0	
	Seeds (beans, peas)	7	3.8	3	3.3	4	4.4	0.274
	Fruits (apples, plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0	
	High fat or protein food	34	18.7	18	19.6	16	17.8	

	Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	1.1	0	0.0	
	Raw green vegetables	6	3.3	3	3.3	3	3.3	
	Spices	9	4.9	3	3.3	6	6.7	
	Fried food	28	15.4	13	14.1	15	16.7	
	Baked dessert	1	0.5	0	0.0	1	1.1	
	Milk and dairy products	5	2.7	0	0.0	5	5.6	
	Carbonated drinks	14	7.7	4	4.3	10	11.1	
	Tea and coffee	1	0.5	1	1.1	0	0.0	
	Others	5	2.7	2	2.2	3	3.3	
Diet therapy	No	143	78.6	71	77.2	72	80.9	0.538
	Yes	38	20.9	21	22.8	17	19.1	
	Low fiber (bananas, cantaloupe)	7	3.8	2	2.2	5	5.6	
	Refined grains (white pasta, white rice, and oatmeal, potatoes)	13	7.1	3	3.3	10	11.1	
	Omega 3 rich food (fish)	29	15.9	17	18.5	12	13.3	
	Fully cooked, seedless, skinless, non-cruciferous vegetables (squash)	9	4.9	8	8.7	1	1.1	
	Lean sources of protein (poultry, soy, egg)	1	0.5	1	1.1	0	0.0	

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

~ *p* value for Chi Square test. Significant at < 0.05

Table S2: Baseline clinical and laboratory findings among the enrolled patients with IBD

		IBD patients		*H. pylori* infection in IBD patients				
		Total (n=182)		Negative (n=92)		Positive (n=90)		*p*~
		No.	%	No.	%	No.	%	
Clinical symptoms	Weight loss	125	68.7	68	73.9	57	63.3	0.124
	Diarrhea	178	97.8	89	96.7	89	98.9	0.323
	Constipation	12	6.6	6	6.5	6	6.7	0.969
	Flatulence	179	98.4	89	96.7	90	100.0	0.084
	Bloating/indigestion	177	97.3	88	95.7	89	98.9	0.182
	Hurt burn	176	96.7	90	97.8	86	95.6	0.391
	Urge incontinence	20	11.0	17	18.5	3	3.3	0.001
	Soiling	7	3.8	6	6.5	1	1.1	0.058
	Tenesmus	176	96.7	89	96.7	87	96.7	0.978
	Frequent bowel movements	166	91.2	85	92.4	81	90.0	0.569
	Abdominal cramps	160	87.9	78	84.8	82	91.1	0.190
	Epigastric pain	177	97.3	90	97.8	87	96.7	0.632
	Generalized abdominal pain	152	83.5	75	81.5	77	85.6	0.463
	Nausea	175	96.2	89	96.7	86	95.6	0.678
	Vomiting	168	92.3	85	92.4	83	92.2	0.966
	Loss of appetite	161	88.5	81	88.0	80	88.9	0.858
	Frequent bowel movement	171	94.0	89	96.7	82	91.1	0.111
	Blood in stool	155	85.2	75	81.5	80	88.9	0.162
	Bleeding per rectum	126	69.2	60	65.2	66	73.3	0.236
	Back pain	156	85.7	77	83.7	79	87.8	0.431
	Fever	54	29.7	24	26.1	30	33.3	0.285
	Chills	13	7.1	4	4.3	9	10.0	0.139
	Fatigue/lack of energy	143	78.6	63	68.5	80	88.9	0.001
	Headache	166	91.2	87	94.6	79	87.8	0.106
	Dizziness	148	81.3	76	82.6	72	80.0	0.652
	Insomnia/troubled sleep	155	85.2	82	89.1	73	81.1	0.791
	Limited sexual activity	65	35.7	32	34.8	33	36.7	0.128
	Infection	34	18.7	13	14.1	21	23.3	0.111
	Sick leaves/absenteeism	14	7.7	6	6.5	8	8.9	0.549
	Others	3	1.6	1	1.1	2	2.2	0.548
	Eye (stye, conjunctivitis, iridocyclitis)	4	2.2	1	1.1	3	3.3	0.301
	Joints (arthralgia, arthritis)	146	80.2	77	83.7	69	76.7	0.234
	Kidney (renal stones, hematuria)	5	2.7	3	3.3	2	2.2	0.668
	Liver (elevated liver enzymes, hepatitis B, hepatomegaly)	4	2.2	0	0.0	4	4.4	0.041
	Reproductive organs (delayed menstruation, polycystic ovary)	1	0.5	0	0.0	1	1.1	0.311

	Total symptom score	20.7 ± 3.2		20.6 ± 3.1		20.9 ± 3.2		*t*= -0.5 *p*=0.616
	ESR (males <15 mm/h, females <20 mm/hr)	34.1 ± 13.6		33.6 ± 14.1		34.6 ± 13.2		*t*= -0.49 *p*= 0.628
	CRP (< 10 mg/L)	30.6 ± 23.5		28.2 ± 23.9		33.0 ± 23.0		*t*= -1.4 *p*= 0.162
	FBG (70-100 mg/dl)	95.5 ± 11.4		96.1 ± 11.6		94.9 ± 11.1		*t*= 0.7 *p*= 0.504
	Fecal Calprotectin (<50 µg/g stool)	516.2 ± 210.0		517.4 ± 214.4		515.0 ± 206.7		*t*= -1.8 *p*= 0.077
	Hb (men 13.5 to 17.5 g/dl , women 12.0-15.5 g/dl)	10.9 ± 1.4		10.8 ± 1.4		11.0 ± 1.4		*t*= 0.8 *p*= 0.940
Laboratory findings	WBCs (4-11 k/ul)	6618.7 ± 1527.9		6420.8 ± 1530.5		6821.1 ± 1506.9		*t*= -0.8 *p*= 0.419
	Platelets (150-450 k/ul)	300.6 ± 64.5		304.8 ± 61.7		296.2 ± 67.4		*t*= 0.9 *p*= 0.372
	Body weight	67.9 ± 11.9		67.6 ± 12.2		68.3 ± 11.7		*t*= -0.4 *p*= 0.693
	Pulse (60-100 beats per minute)	80.6 ± 5.3		80.5 ± 5.6		80.8 ± 5.0		*t*= -0.3 *p*= 0.745
	Pulse pressure (40 and 60 mmHg)	41.3 ± 6.2		41.5 ± 6.8		41.0 ± 5.6		*t*= 0.6 *p*= 0.573
	Normal abdominal findings	23	12.6	12	13.0	11	12.2	
	Colonic distention	77	42.3	39	42.4	38	42.2	
	Diffuse bright liver	58	31.9	31	33.7	27	30.0	
	Diffuse hepatic fatty infiltration	31	17.0	15	16.3	16	17.8	
Abdominal ultrasound	Chronic noncalcular cholecystitis	14	7.7	8	8.7	6	6.7	0.987
	Renal stones	12	6.6	7	7.6	5	5.6	
	Chronic calcular cholecystitis	12	6.6	5	5.4	7	7.8	
	Splenomegaly	1	0.5	0	0.0	1	1.1	
	Cystitis	3	1.6	2	2.2	1	1.1	
	Unremarkable	21	11.5	11	12.0	10	11.1	
Endoscopy	Normal endoscopic findings	27	14.8	14	15.2	13	14.4	0.867

	GERD	75	41.2	35	38.0	40	44.4	
	Antral gastritis	33	18.1	15	16.3	18	20.0	
	Pangastritis	56	30.8	32	34.8	24	26.7	
	Pre-pyloric erosions	17	9.3	10	10.9	7	7.8	
	Superficial duodenal bulb ulcers	28	15.4	15	16.3	13	14.4	
	Incompetent cardia	10	5.5	7	7.6	3	3.3	
	Gastrodudonitis	21	11.5	9	9.8	12	13.3	
	Antral erosions	17	9.3	9	9.8	8	8.9	
	Duodenal inflammatory polyp	7	3.8	4	4.3	3	3.3	
	Erosive gastritis	1	0.5	0	0.0	1	1.1	
	Peptic ulcer	1	0.5	1	1.1	0	0.0	
	Erosive gastrodudonitis	4	2.2	2	2.2	2	2.2	
	Chronic active colitis	63	34.6	34	37.0	29	32.2	
	Chronic active ileocolitis-Ulcerative Colitis	25	13.7	11	12.0	14	15.6	
	Chronic active colitis with lymphoid hyperplasia	5	2.7	1	1.1	4	4.4	
	Chronic active colitis with multiple superficial ulcers	3	1.6	0	0.0	3	3.3	
	Internal piles	4	2.2	1	1.1	3	3.3	
	ulcerative proctitis	15	8.2	3	3.3	12	13.3	
	Chronic active ulcerative pancolitis	1	0.5	1	1.1	0	0.0	
Colonoscopy	multiple superficial aphthoid ulcers - mild ileitis of Crohn's disease	35	19.2	20	21.7	15	16.7	0.087
	Ileocolitis - Crohn's disease	31	17.0	14	15.2	17	18.9	
	Rectal Crohn's	10	5.5	5	5.4	5	5.6	
	Multiple superficial colonic ulcers and skip lesions with eosinophilic infiltration, terminal ileitis - Crohn's disease	13	7.1	9	9.8	4	4.4	
	Chronic active colitis with lymphoid hyperplasia - Crohn's disease	2	1.1	0	0.0	2	2.2	
	perianal fistula	1	0.5	1	1.1	0	0.0	
	None	137	75.3	77	83.7	60	66.7	
	Fistula	4	2.2	2	2.2	2	2.2	
	Stricture	4	2.2	1	1.1	3	3.3	
History of complications	Ulcer	26	14.3	10	10.9	16	17.8	0.066
	Intestinal perforation	0	0.0	0	0.0	0	0.0	
	GIT cancer	2	1.1	1	1.1	1	1.1	
	Abscess formation	5	2.7	0	0.0	5	5.6	

	Others	5	2.7	2	2.2	3	3.3	
	None	171	94.0	91	98.9	80	88.9	
	Stricturoplasty	3	1.6	1	1.1	2	2.2	
Surgical intervention	GIT cancer	1	0.5	0	0.0	1	1.1	0.061
	Abscess intervention	4	2.2	0	0.0	4	4.4	
	Others	3	1.6	0	0.0	3	3.3	

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

~ *p* value for Chi Square test. Significant at <0.05

Table S3: Repeated-measures ANOVA of clinical and laboratory findings among patients with IBD on biological treatment during follow-up

Parameter	*H. Pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA												
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects					Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12													
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T × S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	36.5 ± 12.6	29.8 ± 9.0	26.6 ± 8.4	23.2 ± 8.1	20.5 ± 7.3	17.7 ± 7.9	13.3 ± 7.1	T	33.9	<0.001	0.747	1.000	T	128.90	<0.001	0.635	199.6	<0.001	1.78	0.186	0.024
	Negative	33.2 ± 13.7	28.8 ± 10.7	24.4 ± 8.8	20.2 ± 7.8	18.8 ± 7.2	15.3 ± 5.0	13.1 ± 5.4	T × S	0.846	0.540	0.069	0.312	T × S	0.37	0.71	0.005	0.009	0.927			
CRP	Positive	31.2 ± 18.6	25.4 ± 14.7	22.0 ± 12.5	18.3 ± 8.7	14.4 ± 7.5	13.8 ± 7.3	12.2 ± 9.3	T	13.500	<0.001	0.540	1.000	T	60.54	<0.001	0.450	69.79	<0.001	0.225	0.637	0.003
	Negative	30.8 ± 26.2	25.4 ± 21.8	20.6 ± 16.6	17.1 ± 14.0	13.8 ± 10.1	11.4 ± 7.5	8.6 ± 4.5	T × S	0.893	0.505	0.072	0.330	T × S	0.420	0.581	0.006	0.35	0.556			
FBG	Positive	93.1 ± 9.5	91.2 ± 11.6	91.6 ± 9.6	94.5 ± 13.8	93.4 ± 11.8	93.4 ± 10.9	93.5 ± 10.4	T	1.530	0.182	0.117	0.554	T	1.56	0.172	0.021	0.665	0.417	0.136	0.713	0.002
	Negative	95.2 ± 8.8	92.3 ± 6.8	92.1 ± 7.7	93.6 ± 8.6	93.6 ± 8.7	92.5 ± 6.9	94.0 ± 5.9	T × S	0.385	0.886	0.032	0.153	T × S	0.42	0.832	0.006	0.289	0.593			
Calprotectin	Positive	573.8 ± 218.6		380.7 ± 190.6		171.3 ± 96.1		75.2 ± 30.8	T	113.0	<0.001	0.825	1.000	T	250.0	<0.001	0.772	347.5	<0.001	1.39	0.242	0.018
	Negative	508.6 ± 216.3		317.6 ± 153.5		168.3 ± 84.2		84.7 ± 49.8	T × S	1.350	0.266	0.053	0.344	T × S	2.31	0.11	0.030	2.87	0.037			
Hb	Positive	10.6 ± 1.3	10.7 ± 1.3	10.9 ± 1.3	11.3 ± 1.1	11.5 ± 0.9	11.6 ± 0.9	11.7 ± 1.0	T	29.00	<0.001	0.716	1.000	T	89.43	<0.001	0.547	172.7	<0.001	0.047	0.829	0.001
	Negative	10.5 ± 1.1	10.7 ± 1.2	10.9 ± 10.2	110.1 ± 10.1	11.4 ± 1.1	11.8 ± 0.84	1.0 ± 0.81	T × S	2.440	0.034	0.175	0.791	T × S	1.06	0.063	0.032	3.89	0.052			
WBCs	Positive	6385.5 ± 1029.0	6704.8 ± 1023.4	6512.9 ± 1013.5	6298.4 ± 1046.3	6582.3 ± 1075.4	6438.1 ± 1255.8	6125.5 ± 1092.8	T	2.520	0.029	0.180	0.806	T	2.51	0.035	0.033	0.093	0.761	2.85	0.096	0.037
	Negative	6326.7 ± 1479.9	6153.3 ± 1263.2	6062.2 ± 1102.1	5887.8 ± 966.4	6171.1 ± 1030.4	6038.7 ± 1093.6	5999.6 ± 1052.4	T × S	1.324	0.258	0.103	0.486	T × S	1.03	0.399	0.014	3.44	0.068			
Platelets	Positive	272.6 ± 51.0	286.9 ± 44.8	276.3 ± 40.5	279.1 ± 35.1	276.4 ± 31.5	277.1 ± 30.3	282.9 ± 40.5	T	0.738	0.621	0.060	0.273	T	0.41	0.875	0.005	0.605	0.439	5.56	0.021	0.07
	Negative	307.9 ± 69.6	291.8 ± 50.0	292.5 ± 41.8	293.1 ± 42.9	291.9 ± 41.2	288.2 ± 40.7	292.5 ± 44.1	T × S	0.753	0.610	0.061	0.278	T × S	1.18	0.317	0.016	0.527	0.47			
Total symptom score	Positive	21.6 ± 2.3	21.5 ± 2.6	16.4 ± 3.6	7.2 ± 3.0	3.7 ± 3.6	3.1 ± 2.4	0.1 ± 0.4	T	4.150	<0.001	0.973	1.000	T	551.50	<0.001	0.883	98.9	<0.001	4.6	0.035	0.06
	Negative	20.7 ± 3.5	20.2 ± 4.1	13.4 ± 5.6	5.9 ± 3.2	3.6 ± 3.4	3.3 ± 3.1	0.8 ± 1.9	T × S	2.040	0.072	0.153	0.702	T × S	2.85	0.052	0.038	7.61	0.094			
Body weight	Positive	63.9 ± 9.8	64.1 ± 10.1	65.0 ± 10.0	65.5 ± 10.0	65.8 ± 10.0	66.0 ± 10.0	66.1 ± 10.0	T	11.40	<0.001	0.498	1.000	T	33.70	<0.001	0.313	51.8	<0.001	0.055	0.816	0.001
	Negative	64.7 ± 11.0	64.9 ± 10.9	65.3 ± 10.8	65.6 ± 10.7	66.0 ± 10.6	66.6 ± 10.5	67.1 ± 10.4	T × S	2.280	0.046	0.166	0.759	T × S	1.40	0.252	0.018	11.1	0.001			
Pulse	Positive	80.8 ± 2.5	79.7 ± 2.5	76.8 ± 4.5	76.0 ± 4.7	77.7 ± 4.5	77.5 ± 4.4	78.8 ± 2.5	T	3.700	0.003	0.245	0.946	T	4.24	0.001	0.054	4.55	0.036	4.93	0.029	0.062

Pulse pressure	Negative	81.2 ± 6.8	79.2 ± 6.7	78.7 ± 5.3	81.1 ± 5.1	79.8 ± 5.1	78.8 ± 5.1	77.2 ± 4.6	T × S	3.010	0.011	0.208	0.882	T × S	3.90	0.003	0.050	12.81	0.001	0.009	0.924	0.0001
	Positive	39.7 ± 4.1	41.6 ± 5.8	38.7 ± 9.2	40.3 ± 8.3	42.6 ± 6.8	39.4 ± 6.8	41.3 ± 9.6	T	1.350	0.248	0.105	0.493	T	1.57	0.156	0.021	0.537	0.466			
	Negative	40.4 ± 7.4	39.6 ± 7.1	39.3 ± 7.5	39.3 ± 8.1	41.6 ± 8.5	40.9 ± 7.6	41.8 ± 10.1	T × S	0.728	0.628	0.060	0.270	T × S	0.59	0.740	0.008	0.604	0.440			

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

$p<0.05$ is significant

[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)

[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant

[c] large effect if the value of partial Eta squared >0.1

T × S; time versus state of H. pylori infection

Table S3: Repeated-measures ANOVA of clinical and laboratory findings among patients with IBD receiving conventional therapy during follow-up

Parameter	*H. pylori* infection	Baseline	Follow-up period (3 Months)						Repeated Measures ANOVA											
			Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test					Within Subject Effects					Between Subject Effects		
			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12													
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F[a]	*p*	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F[a]	*p*	Effect Size (Partial Eta Squared)[c]	Linearity (F value)[b]	*p*	F	*p*	Effect Size (Partial Eta Squared)[c]
ESR	Positive	33.6 ± 13.5	30.8 ± 11.9	27.2 ± 11.1	24.8 ± 9.3	20.7 ± 7.4	17.0 ± 6.4	13.3 ± 3.9	T	64.2	<0.001	0.795	1.000	T	219.50	<0.001	0.679	359.3	<0.001	0.335	0.564	0.003
	Negative	34.1 ± 14.6	29.4 ± 12.0	26.0 ± 10.0	22.5 ± 8.2	19.5 ± 6.7	16.5 ± 5.7	12.9 ± 4.5	T × S	1.18	0.325	0.067	0.444	T × S	0.75	0.492	0.007	0.01	0.921			
CRP	Positive	34.0 ± 25.1	26.8 ± 20.2	22.9 ± 17.9	19.3 ± 14.8	15.4 ± 10.7	11.9 ± 6.7	9.1 ± 5.7	T	17.1	<0.001	0.508	1.000	T	83.80	<0.001	0.446	102.1	<0.001	3026	0.074	0.030
	Negative	25.7 ± 21.4	20.5 ± 16.9	17.5 ± 14.2	14.8 ± 11.4	12.3 ± 8.7	9.9 ± 6.1	7.7 ± 4.5	T × S	0.518	0.794	0.030	0.201	T × S	2.30	0.033	0.022	2.81	0.097			
FBG	Positive	95.9 ± 12.0	94.0 ± 10.1	92.2 ± 9.9	94.4 ± 10.3	91.4 ± 8.0	95.0 ± 15.0	93.8 ± 9.3	T	3.06	0.009	0.156	0.896	T	2.43	0.038	0.023	1.32	0.254	1.41	0.238	0.013
	Negative	96.9 ± 13.7	93.8 ± 13.2	97.9 ± 9.8	98.2 ± 16.1	93.9 ± 10.7	93.2 ± 13.0	96.3 ± 10.2	T × S	2.17	0.053	0.116	0.746	T × S	2.10	0.068	0.020	2.06	0.155			
Calprotectin	Positive	484.1 ± 195.0		279.7 ± 141.7		150.1 ± 73.7		74.1 ± 28.8	T	144.8	<0.001	0.810	1.000	T	325.50	<0.001	0.758	417	<0.001	3.23	0.075	0.030
	Negative	525.7 ± 214.2		334 ± 125.5		175.6 ± 92.5		86.3 ± 80.5	T × S	1.19	0.317	0.034	0.312	T × S	0.82	0.411	0.008	0.718	0.399			
Hb	Positive	11.1 ± 1.1	11.3 ± 1.3	11.4 ± 1.2	11.7 ± 1.1	11.7 ± 1.0	11.8 ± 1.0	12.1 ± 0.8	T	24.18	<0.001	0.594	1.000	T	65.83	<0.001	0.338	118.9	<0.001	0.508	0.477	0.005
	Negative	11.1 ± 1.5	11.3 ± 1.1	11.6 ± 1.0	11.8 ± 0.9	12.0 ± 0.8	12.1 ± 0.8	12.3 ± 0.7	T × S	2.19	0.050	0.117	0.753	T × S	1.90	0.137	0.018	2.12	0.148			
WBCs	Positive	7050.0 ± 1667.9	6699.2 ± 1501.3	6511.1 ± 1239.8	6754.7 ± 1357.3	6648.1 ± 1026.2	6528.3 ± 891.8	6497.3 ± 1138.6	T	3.61	0.003	0.179	0.944	T	6.95	<0.001	0.063	4.57	0.035	11.34	0.001	0.098
	Negative	7968.1 ± 1588.2	6340.4 ± 1500.8	6273.4 ± 1281.5	5893.6 ± 1165.3	5808.5 ± 992.5	5714.9 ± 956.7	5796.0 ± 903.8	T × S	1.67	0.137	0.092	0.612	T × S	1.99	0.118	0.019	0.118	0.732			
Platelets	Positive	308.6 ± 71.9	295.1 ± 75.4	292.6 ± 75.3	283.6 ± 67.1	285.7 ± 58.8	284.3 ± 58.1	284.9 ± 60.1	T	3.59	0.003	0.179	0.943	T	5.89	0.001	0.054	7.84	0.006	1.99	0.161	0.019
	Negative	301.8 ± 53.6	274.4 ± 49.9	266.4 ± 43.2	271.4 ± 51.5	284.5 ± 51.3	272.2 ± 36.8	276.1 ± 43.2	T × S	1.74	0.120	0.095	0.633	T × S	1.13	0.335	0.011	0.357	0.551			
Total symptom score	Positive	20.5 ± 3.6	19.7 ± 3.6	13.0 ± 4.0	5.0 ± 2.8	2.4 ± 3.1	2.8 ± 3.3	1.1 ± 2.5	T	360.0	<0.001	0.959	1.000	T	834.60	<0.001	0.895	424.6	<0.001	2.42	0.123	0.024
	Negative	20.5 ± 2.8	20.5 ± 3.3	14.2 ± 3.5	5.0 ± 1.9	3.2 ± 2.4	3.4 ± 2.7	0.7 ± 1.3	T × S	2.93	0.011	0.159	0.880	T × S	0.85	0.436	0.009	3.97	0.049			
Body weight	Positive	70.6 ± 12.0	70.4 ± 12.1	71.2 ± 12.1	71.5 ± 11.8	71.3 ± 11.8	71.5 ± 11.5	71.1 ± 12.6	T	11.15	<0.001	0.403	1.000	T	6.05	0.002	0.055	0.196	0.659	0.01	0.922	9.2×10^{-5}
	Negative	70.2 ± 12.8	70.3 ± 12.8	71.1 ± 12.8	70.2 ± 16.1	71.7 ± 12.9	72.4 ± 13.1	73.3 ± 12.8	T × S	2.32	0.039	0.123	0.779	T × S	3.43	0.029	0.032	4.26	0.042			
Pulse	Positive	80.7 ± 5.8	79.9 ± 5.1	79. ± 3.5	77.8 ± 4.7	78.6 ± 3.8	77.4 ± 4.0	78.3 ± 3.0	T	3.01	0.010	0.154	0.891	T	5.31	<0.001	0.049	4.6	0.034	0.141	0.079	0.017
	Negative	79.8 ± 4.1	79.8 ± 4.1	79.1 ± 4.2	79.6 ± 4.7	77.7 ± 4.9	77.7 ± 4.8	79.4 ± 4.6	T × S	1.50	0.189	0.083	0.555	T × S	1.53	0.184	0.015	0.111	0.739			

Pulse pressure	Positive	41.7 ± 6.2	41.2 ± 7.2	40.2 ± 8.8	40.8 ± 8.8	40.3 ± 7.9	39.7 ± 6.9	41.9 ± 9.9	T	0.481	0.821	0.028	0.188	T	0.43	0.844	0.004	0.599	0.441	0.141	0.708	0.001
	Negative	42.6 ± 6.1	40.9 ± 6.5	43.8 ± 7.7	42.3 ± 7.9	42.1 ± 8.6	42.8 ± 8.5	42.1 ± 8.6	T × S	1.026	0.413	0.059	0.388	T × S	1.11	0.349	0.011	2.04	0.156			

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

$p<0.05$ is significant

[a] F value based on Greenhouse-Geisser test was considered in highlighted cells when Mauchly's test is significant (<0.05)

[b] significant Quadratic effect was considered in highlighted cells when linear effect was insignificant

[c] large effect if the value of partial Eta squared >0.1

T × S; time versus state of H. pylori infection

Table S5: Univariate analysis for factor associated with IBD flare during follow up

		IBD patients		Flare during IBD therapy						95.0% C.I. for EXP(B)	
		Total (n=182)		No (n=143)		Yes (n=39)		*p*~	Exp(B)	Lower Limit	Upper Limit
		No.	%	No.	%	No.	%				
H pylori infection	Negative	92	50.5	73	51.0	19	48.7				
	Positive	90	49.5	70	49.0	20	51.3	0.820	1.08	0.57	2.02
	NA	92	50.5	73	51	19	48.7	0.837			
Onset of *H. pylori* infection	Few weeks ago	7	3.8	6	4.2	1	2.6	0.540	0.53	0.07	3.99
	3-6 months	10	5.5	7	4.9	3	7.7	0.488	1.54	0.45	5.21
	6 months - 1 year	35	19.2	29	20.3	6	15.4	0.789	0.88	0.35	2.21
	> 1 year	38	20.9	28	19.6	10	25.6	0.560	1.26	0.58	2.70
Type of IBD diagnosed	Crohn's disease	86	47.3	67	46.9	19	48.7				
	Ulcerative colitis	96	52.7	76	53.1	20	51.3	0.697	0.88	0.47	1.66
Crohn's disease	*H. pylori* Negative	44	24.2	33	23.1	11	28.2	0.526			
	H. pylori Positive	42	23.1	34	23.8	8	20.5	0.374	0.66	0.27	1.65
Ulcerative colitis	*H. pylori* Negative	48	26.4	40	28.0	8	20.5	0.196	0.55	0.22	1.36
	H. pylori Positive	48	26.4	36	25.2	12	30.8	0.853	0.93	0.41	2.10
Treatment of IBD	Conventional	106	58.2	86	60.1	20	51.3				
	Biological	76	41.8	57	39.9	19	48.7	0.254	1.44	0.77	2.70
Sex	Male	94	51.6	76	53.1	18	46.2				
	Female	88	48.4	67	46.9	21	53.8	0.241	1.46	0.78	2.74
Age	16 – <20 Years	20	11.0	15	10.5	5	12.8	0.708		ref	
	20 – <35 Years	136	74.7	106	74.1	30	76.9	0.814	0.89	0.35	2.30
	35 – 55 Years	26	14.3	22	15.4	4	10.3	0.440	0.60	0.16	2.22
	Mean ± SD	27.0 ± 7.3		27.8 ± 7.6		23.8 ± 4.9		0.008	*t*= 4.0, *p*< 0.001 0.92	0.87	0.98
Age at diagnosis	10 – >19	69	37.9	48	33.6	21	53.8	0.086			
	20 – <30	83	45.6	71	49.7	12	30.8	0.029	0.45	0.22	0.92
	30 – 45	30	16.5	24	16.8	6	15.4	0.341	0.64	0.26	1.60
	Mean ± SD	27.0 ± 7.3		22.3 ± 6.5		19.1 ± 4.8		0.01	*t*= 3.4, *p*= 0.001 0.92	0.87	0.98
Residence	Rural	88	48.4	74	51.7	14	35.9				
	Urban	94	51.6	69	48.3	25	64.1	0.051	1.92	1.00	3.70
Education	Illiterate	2	1.1	2	1.4	0	0.0	0.982	0.00	0.00	
	Read and Write	23	12.6	20	14.0	3	7.7	0.160	0.42	0.13	1.40
	Primary	4	2.2	4	2.8	0	0.0	0.978	0.00	0.00	
	Preparatory	13	7.1	11	7.7	2	5.1	0.309	0.47	0.11	2.00
	Secondary	44	24.2	35	24.5	9	23.1	0.487	0.76	0.36	1.64
	University education	96	52.7	71	49.7	25	64.1	0.715			
Working status	No	88	48.4	63	44.1	25	64.1				
	Yes	94	51.6	80	55.9	14	35.9	0.032	0.49	0.25	0.94
Occupation	Unemployed	37	20.3	31	21.7	6	15.4	0.024			
	Student	45	24.7	26	18.2	19	48.7	0.023	2.89	1.15	7.25
	Clerical	2	1.1	1	0.7	1	2.6	0.353	2.73	0.33	22.67
	Professional	39	21.4	33	23.1	6	15.4	0.962	0.97	0.31	3.02
	Housewife	21	11.5	19	13.3	2	5.1	0.566	0.63	0.13	3.10
	Auxiliary worker	22	12.1	19	13.3	3	7.7	0.701	0.76	0.19	3.05
	Farmer	16	8.8	14	9.8	2	5.1	0.643	0.69	0.14	3.40
Marital status	Married	73	40.1	50	35.0	23	59.0	0.110			
	Not married							0.016	2.20	1.16	4.21
	Single	106	58.2	91	63.6	15	38.5	0.018	2.20	1.15	4.21
	Widowed	2	1.1	1	0.7	1	2.6	0.276	3.08	0.41	23.35
	Divorced	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Socioeconomic standard	High	58	31.9	41	28.7	17	43.6	.015	2.730	1.215	6.14
	Middle	52	28.6	39	27.3	13	33.3	.127	1.938	.828	4.54
	Low	72	39.6	63	44.1	9	23.1	.052			
Consanguinity	No	144	79.1	114	79.7	30	76.9				
	Yes	38	20.9	29	20.3	9	23.1	0.888	0.95	0.45	2.00
Being breastfed	No	26	14.3	22	15.4	4	10.3				
	Yes	156	85.7	121	84.6	35	89.7	0.382	1.59	0.56	4.47
Smoking	Never	150	82.4	119	83.2	31	79.5	0.915			
	Current smoker	26	14.3	19	13.3	7	17.9	0.774	1.128	0.50	2.57
	Ex-Smoker	6	3.3	5	3.5	1	2.6	0.775	0.75	0.10	5.48
	NA	153	84.1	119	83.2	34	87.2	0.679			
Age of starting Smoking	< 20 Years	17	9.3	14	9.8	3	7.7	0.573	0.71	0.22	2.32
	20 – 30 Years	12	6.6	10	7.0	2	5.1	0.475	0.59	0.14	2.48
Smoking other than cigarette	Never	180	98.9	143	100.0	37	94.9				
	Shisha	2	1.1	0	0.0	2	5.1	0.079	3.59	0.86	14.94
Alcohol	No	182	100.0	143	100.0	39	100.0				
	Yes	0	0.0	0	0.0	0	0.0				
Drug Abuse	No	182	100.0	143	100.0	39	100.0				
	Yes	0	0.0	0	0.0	0	0.0				
Chronic diseases	No	82	45.1	64	44.8	18	46.2				
	Yes	100	54.9	79	55.2	21	53.8	0.811	0.93	0.49	1.74

	Diabetes Mellitus	10	5.5	8	5.6	2	5.1				
	Hypertension	30	16.5	25	17.5	5	12.8				
	Bronchial Asthma/COPD	15	8.2	13	9.1	2	5.1				
	Heart disease	1	0.5	1	0.7	0	0.0				
	Renal disease	1	0.5	0	0.0	1	2.6				
	Liver disease	1	0.5	1	0.7	0	0.0				
	SLE	0	0.0	0	0.0	0	0.0				
	rheumatoid arthritis	6	3.3	5	3.5	1	2.6				
	Skin allergy	18	9.9	16	11.2	2	5.1				
	Hyperthyroidism	4	2.2	3	2.1	1	2.6				
	Hypothyroidism	8	4.4	5	3.5	3	7.7				
	Other autoimmune diseases	1	0.5	1	0.7	0	0.0				
	Others (Chronic sinusitis, vertigo, lumbar disc prolapse, familial dyslipidemia, hemorrhoids, scleritis, HCV, anemia, fatty liver, steatosis, psoriasis, peripheral neuropathy, chronic cholecystitis)	27	14.8	21	14.7	6	15.4				
Autoimmune diseases	No	163	89.6	129	90.2	34	87.2				
	Yes	19	10.4	14	9.8	5	12.8	0.555	1.33	0.52	3.39
Medications	None	13	7.1	10	7.0	3	7.7				
	Analgesic (NSAIDs)	12	6.6	7	4.9	5	12.8				
	Antidiabetics	6	3.3	6	4.2	0	0.0				
	Antihypertensives	32	17.6	27	18.9	5	12.8				
	corticosteroids	10	5.5	5	3.5	5	12.8				
	IBD therapy	151	83.0	118	82.5	33	84.6				
	Hormonal contraceptives	2	1.1	0	0.0	2	5.1				
	Thyroxin	9	4.9	6	4.2	3	7.7				
	Others	37	20.3	28	19.6	9	23.1				
Family history of similar condition	No	141	77.5	108	75.5	33	84.6				
	Yes	41	22.5	35	24.5	6	15.4	0.279	0.62	0.26	1.48
	Yes; first degree relatives	40	22.0	34	23.8	6	15.4				
	Yes; other relatives	1	0.5	1	0.7	0	0.0				
	Other autoimmune disease	3	1.6	3	2.1	0	0.0				
Physical activity											
Transportation	not working	71	39.0	60	42.0	11	28.2	0.208			
	On foot	19	10.4	17	11.9	2	5.1	0.503	0.60	0.13	2.70
	By bicycle	4	2.2	3	2.1	1	2.6	0.709	1.48	0.19	11.47
	Public transport or car	88	48.4	63	44.1	25	64.1	0.090	1.85	0.91	3.76
Working activity	not working	65	35.7	53	37.1	12	30.8	0.655			
	minimal	43	23.6	31	21.7	12	30.8	0.249	1.60	0.72	3.57
	moderate	73	40.1	58	40.6	15	38.5	0.882	1.06	0.50	2.26
	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Activity outside work	not working	59	32.4	48	33.6	11	28.2	0.733			
	minimal	90	49.5	71	49.7	19	48.7	0.838	1.08	0.51	2.27
	moderate	32	17.6	23	16.1	9	23.1	0.293	1.60	0.66	3.87
	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
Regular exercise	never	136	74.7	109	76.2	27	69.2	0.397			
	yes frequent (>3 times/ week)	7	3.8	5	3.5	2	5.1	0.758	1.25	0.30	5.27
	yes infrequent (<3 times/ week)	39	21.4	29	20.3	10	25.6	0.176	1.66	0.80	3.45
Total physical activity score		2.8 ± 2.1		2.7 ± 2.2		2.9 ± 2.0			t= 0.40, p= 0.695		
								0.855	1.01	0.88	1.17
Dietary habits											
Food source	Homemade	97	53.3	78	54.5	19	48.7	0.858			
	Restaurant	6	3.3	5	3.5	1	2.6	0.829	0.80	0.11	5.99
	Mixed	79	43.4	60	42.0	19	48.7	0.639	1.16	0.62	2.20
Junk Food, Fast Food	never	50	27.5	41	28.7	9	23.1	0.806			
	occasionally	128	70.3	99	69.2	29	74.4	0.535	1.27	0.60	2.68
	daily	4	2.2	3	2.1	1	2.6	0.706	1.49	0.19	11.75
Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	5	3.5	0	0.0	0.399			
	once per week	79	43.4	65	45.5	14	35.9	0.898	2383.0	0.00	1.6×10^{68}
	2-4 times per week	85	46.7	62	43.4	23	59.0	0.891	4190.1	0.00	2.9×10^{68}
	daily	13	7.1	11	7.7	2	5.1	0.898	2475.2	0.00	1.7×10^{68}
Transfat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	never	30	16.5	27	18.9	3	7.7	0.017			
	once per week	91	50.0	75	52.4	16	41.0	0.506	1.52	0.44	5.22
	2-4 times per week	60	33.0	41	28.7	19	48.7	0.061	3.21	0.95	10.85
	daily	1	0.5	0	0.0	2	5.1	0.020	14.82	1.52	144.45
Food rich in insoluble fibers (such as whole bread, cereals, beans, peas, wheat, oat,	never	0	0.0	0	0.0	0	0.0				
	once per week	39	21.4	31	21.7	8	20.5	0.022			
	2-4 times per week	88	48.4	76	53.1	12	30.8	0.362	0.66	0.27	1.61
	daily	55	30.2	36	25.2	19	48.7	0.163	1.80	0.79	4.12

artichoke, squash, cabbage, cauliflower, broccoli, dried herbs & spices, fruits, vegetables)											
Salty Food (pickled, salty cheese, salted fish, dokka)	never	27	14.8	22	15.4	5	12.8	0.470			
	once per week	96	52.7	78	54.5	18	46.2	0.885	0.93	0.34	2.51
	2-4 times per week	54	29.7	40	28.0	14	35.9	0.516	1.40	0.51	3.90
	daily	5	2.7	3	2.1	2	5.1	0.299	2.38	0.46	12.29
Fruits and Vegetables	never	2	1.1	0	0.0	2	5.1	0.005			
	once per week	56	30.8	44	30.8	12	30.8	0.001	0.07	0.01	0.31
	2-4 times per week	81	44.5	64	44.8	17	43.6	0.000	0.07	0.02	0.31
	daily	43	23.6	35	24.5	8	20.5	0.001	0.07	0.01	0.34
Red meat	never	16	8.8	13	9.1	3	7.7	0.959			
	once per week	113	62.1	88	61.5	25	64.1	0.950	0.96	0.29	3.20
	2-4 times per week	53	29.1	42	29.4	11	28.2	0.835	0.87	0.24	3.14
	daily	0	0.0	0	0.0	0	0.0				
Under cooked meat	never	157	86.3	120	83.9	37	94.9	0.259			
	once per week	24	13.2	22	15.4	2	5.1	0.100	0.30	0.07	1.26
	2-4 times per week	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
	daily	0	0.0	0	0.0	0	0.0				
Fish	never	17	9.3	16	11.2	1	2.6	0.220			
	once per week	91	50.0	67	46.9	24	61.5	0.102	5.30	0.72	39.19
	2-4 times per week	74	40.7	60	42.0	14	35.9	0.176	4.06	0.53	30.95
	daily	0	0.0	0	0.0	0	0.0				
Consumption of caffeine in diet (tea, coffee)	never	25	13.7	22	15.4	3	7.7	0.027			
	once per week	20	11.0	16	11.2	4	10.3	0.571	1.54	0.34	6.89
	2-4 times per week	61	33.5	54	37.8	7	17.9	0.949	0.96	0.25	3.70
	daily	76	41.8	51	35.7	25	64.1	0.078	2.94	0.89	9.74
Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	never	7	3.8	7	4.9	1	2.6	0.181			
	once per week	67	36.8	56	39.2	11	28.2	0.780	1.34	0.17	10.48
	2-4 times per week	91	50.0	70	49.0	21	53.8	0.519	1.93	0.26	14.38
	daily	17	9.3	10	7.0	7	17.9	0.215	3.77	0.46	30.66
Dairy products	never	27	14.8	22	15.4	5	12.8	0.552			
	once per week	49	26.9	41	28.7	8	20.5	0.831	0.89	0.29	2.71
	2-4 times per week	78	42.9	58	40.6	20	51.3	0.409	1.51	0.57	4.03
	daily	28	15.4	22	15.4	6	15.4	0.497	1.51	0.46	4.98
Average number of glasses of water consumed per day	one cup	9	4.9	6	4.2	3	7.7	0.346			
	2-3 cups	73	40.1	59	41.3	14	35.9	0.367	0.56	0.16	1.96
	at least 4 cups	73	40.1	54	37.8	19	48.7	0.734	0.81	0.24	2.74
	4-8 cups	27	14.8	24	16.8	3	7.7	0.156	0.31	0.06	1.56
Snacks between meals	Never	60	33.0	54	37.8	6	15.4	0.009			
	Occasionally	121	66.5	89	62.2	32	82.1	0.014	2.99	1.25	7.14
	Daily	1	0.5	0	0.0	1	2.6	0.009	17.12	2.02	144.86
Number of meals per day	2	68	37.4	55	38.5	13	33.3	0.058			
	3	109	59.9	86	60.1	23	59.0	0.857	1.06	0.54	2.10
	4	5	2.7	2	1.4	3	7.7	0.022	4.37	1.24	15.37
Total food score (favorable food habits)		11.4 ± 4.5		11.9 ± 4.3		9.9 ± 5.0			t=2.2 , p=0.029		
								0.029	0.93	0.86	0.99
	No	119	65.4	95	66.4	24	61.5				
	Yes	63	34.6	48	33.6	15	38.5	0.406	1.32	0.69	2.51
Dietary restrictions	Cereals	0	0.0	0	0.0	0	0.0				
	Brown rice	5	2.7	4	2.8	1	2.6				
	Whole grain bread	2	1.1	2	1.4	0	0.0				
	Seeds (beans, peas)	7	3.8	3	2.1	4	10.3				
	Fruits (apples; plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0				
	High fat or protein food	34	18.7	25	17.5	9	23.1				
	Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	0.7	0	0.0				
	Raw green vegetables	6	3.3	6	4.2	0	0.0				
	Spices	9	4.9	7	4.9	2	5.1				
	Fried food	28	15.4	22	15.4	6	15.4				
	Baked dessert	1	0.5	1	0.7	0	0.0				
	Milk and dairy products	5	2.7	3	2.1	2	5.1				
	Carbonated drinks	14	7.7	11	7.7	3	7.7				
	Tea and coffee	1	0.5	1	0.7	0	0.0				
	Others	5	2.7	4	2.8	1	2.6				
Diet therapy	No	143	78.6	113	79.0	31	79.5				
	Yes	38	20.9	30	21.0	8	20.5	0.982	0.99	0.46	2.16
	Low fiber (bananas, cantaloupe)			5	3.5	2	5.1				
	Refined grains (white pasta, white rice, and oatmeal, potatoes)			10	7	3	7.7				

	Omega 3 rich food (fish)			24	16.8	5	12.8				
	Fully cooked, seedless, skinless, non-cruciferous vegetables (squash)			6	4.2	3	7.7				
	Lean sources of protein (poultry, soy, egg)			1	0.7	0	0.0				
	Others			0	0.0	0	0.0				
	None	137	75.3	109	76.2	28	71.8	0.689			
	Yes	41	22.5	31	21.7	10	25.6	0.818	1.09	0.53	2.23
	Fistula	4	2.2	3	2.1	1	2.6	0.949	1.07	0.15	7.86
	Stricture	4	2.2	3	2.1	1	2.6	0.964	1.05	0.14	7.70
History of complications	Ulcer	26	14.3	21	14.7	4	10.3	0.546	0.72	0.25	2.07
	Intestinal perforation	0	0.0	0	0.0	0	0.0				
	GIT cancer	2	1.1	2	1.4	0	0.0	0.974	0.00	0.00	1.3×10^{250}
	Abscess formation	5	2.7	3	2.1	2	5.1	0.304	2.12	0.50	8.94
	Others	5	2.7	2	1.4	3	7.7	0.126	2.54	0.77	8.35
	None	171	94.0	136	95.1	35	89.7	0.711			
	Yes							0.297	1.73	0.62	4.88
	Stricturoplasty	3	1.6	2	1.4	1	2.6	0.657	1.57	0.21	11.47
	Endoscopic balloon dilatation	0	0.0	0	0.0	0	0.0				
Surgical intervention	Surgical resection	0	0.0	0	0.0	0	0.0				
	Intestinal perforation	0	0.0	0	0.0	0	0.0				
	GIT cancer	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
	Abscess formation	4	2.2	3	2.1	1	2.6	0.668	1.55	0.21	11.37
	Others (appendectomy, cholecystectomy	3	1.6	1	0.7	2	5.1	0.175	2.68	0.64	11.17
	< 18.5 (underweight)	3	1.6	2	1.4	1	2.6	0.687			
BMI categories	18.5-24.99 (Normal weight)	108	59.3	85	59.4	23	59.0	0.297	0.34	0.05	2.56
	25-29.99 (Overweight)	58	31.9	47	32.9	11	28.2	0.268	0.31	0.04	2.44
	30-39.99 (Obese)	13	7.1	9	6.3	4	10.3	0.474	0.45	0.05	4.04
	Chronic active colitis	63	34.6	49	34.3	14	35.9				
	Chronic active ileocolitis-UC	25	13.7	20	14	5	12.8				
	Chronic active colitis with lymphoid hyperplasia	5	2.7	4	2.8	1	2.6				
	Chronic active colitis with multiple superficial ulcers	3	1.6	2	1.4	1	2.6				
	Internal piles	4	2.2	3	2.1	1	2.6				
	ulcerative proctitis	15	8.2	13	9.1	2	5.1				
	Chronic active ulcerative pancolitis	1	0.5	0	0	1	2.6				
Colonoscopy	multiple superficial aphthoid ulcers - mild ileitis of Crohn's disease	35	19.2	26	18.2	9	23.1				
	Ileocolitis - Crohn's disease	31	17.0	27	18.9	4	10.3				
	Rectal Crohn's	10	5.5	7	4.9	3	7.7				
	Multiple superficial colonic ulcers and skip lesions with eosinophilic infiltration, terminal ileiltis - Crohn's disease	13	7.1	11	7.7	2	5.1				
	Chronic active colitis with lymphoid hyperplasia - CD	2	1.1	2	1.4	0	0				
	perianal fistula	1	0.5	0	0	1	2.6				
	Normal endoscopic findings	27	14.8	19	13.3	8	20.5				
	GERD	75	41.2	61	42.7	14	35.9				
	Antral gastritis	33	18.1	27	18.9	6	15.4				
	Pangastritis	56	30.8	45	31.5	11	28.2				
	Pre-pyloric erosions	17	9.3	13	9.1	4	10.3				
	Superficial duodenal bulb ulcers	28	15.4	21	14.7	7	17.9				
Endoscopy	Incompetent cardia	10	5.5	10	7.0	0	0.0				
	Gastrodudonitis	21	11.5	18	12.6	3	7.7				
	Antral erosions	17	9.3	13	9.1	4	10.3				
	Duodenal inflammatory polyp	7	3.8	5	3.5	2	5.1				
	Erosive gastritis	1	0.5	1	0.7	0	0.0				
	Peptic ulcer	1	0.5	0	0.0	1	2.6				
	Erosive gastrodudonitis	4	2.2	2	1.4	2	5.1				
	Normal abdominal findings	23	12.6	19	13.3	4	10.3				
	Colonic distention	77	42.3	60	42.0	17	43.6				
	Diffuse bright liver	58	31.9	46	32.2	12	30.8				
Abdominal Ultrasound	Diffuse hepatic fatty infiltration	31	17.0	0	0.0	0	0.0				
	Chronic noncalcular cholecystitis	14	7.7	10	7.0	4	10.3				

	Renal stones	12	6.6	9	6.3	3	7.7
	Chronic calcular cholecystitis	12	6.6	10	7.0	2	5.1
	Splenomegaly	1	0.5	1	0.7	0	0.0
	Cystitis	3	1.6	3	2.1	0	0.0
	Unremarkable	21	11.5	16	11.1	5	12.8

H. pylori; *Helicobacter pylori*

IBD; inflammatory bowel disease

~ *p* value for Chi Square test. Significant at <0.05

NA; non-applicable

All Cases | Conventional Therapy | Biological Therapy

Total symptom score

Pulse rate (time/min)

Body Weight (kg)

CRP (mg/dL)

ESR (mm/hr)

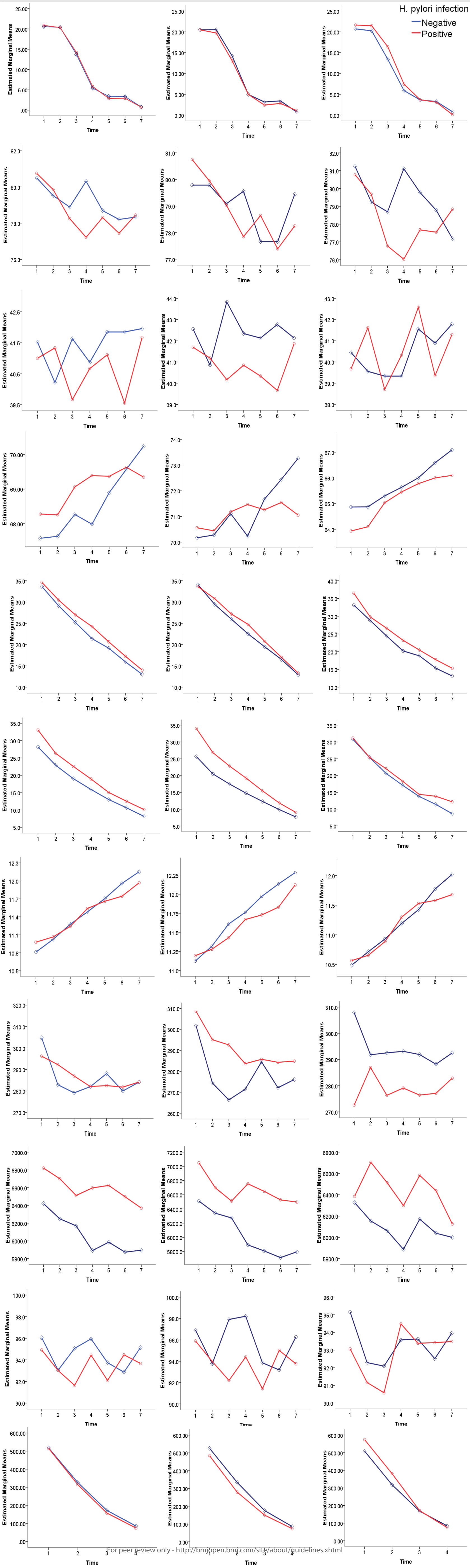
Hemoglobin (g/dL)

Platelets (x10^3/mL)

WBCs (cell/mL)

FBG (g/dL)

Fecal Calprotectin (μg/g)



File S1

Protocol for treating inflammatory bowel diseases

A. Treatment of ulcerative colitis

Depend on

1- Disease activity (clinical and endoscopic)
2- Extend (distal, left sided, extensive)

I- Mild, moderate + distal extend (proctosigmoiditis)
Topical methotrexate 4g/day
+ oral mesalazine (2-4 g/day)
+ steroid (oral prednisolone 40-60 mg/day with dose tapering over 8 weeks
If no remission (or unstable remission) occurs
The patient is treated as sever disease

If stable remission occurs
So stop steroids and maintain on mesalazine + AZA or 6-mp (for lifelong or 2 years then ….)

II- Mild, moderate + left sided extend (proctosigmoiditis)
5 ASA
+ oral mesalazine (2-4 g/day)
+ topical
If unsatisfactory response occurs
+ steroid (oral prednisolone 40-60 mg/day with dose tapering over 8 weeks
If no remission (or unstable remission or unsatisfactory response) occurs

The patient is treated as sever disease

If stable remission occurs
maintain lifelong on 5 ASA (1-2 g/day)+ AZA (2-2.5 mg/kg for 3-4 years)
sever disease (need hospitalization)
vital signs/ 6 hrs, CBC, ESR, CRP, electrolytes, stool chart, Abd US
antidiarrheal, anticholinergic, antibiotics, nutrition, blood transfusion, fluids
I.V steroids (hydrocortisone 400 mg/day pr methylprednisolone 60 mg/day
If stable remission occurs
Maintain lifelong on 5 ASA 1-2 g/day
+AZA 2-2.5 mg/kg

If unstable remission

Add AZA or methotrexate if still unstable remission occurs shift to biological

If no remission occurs shift to biological
If no response or complication (surgery)

B. Treatment of Crohn's Disease

According to disease severity

a- Mild to moderate
Treatment of active symptoms (antidiarrheal, nutrition, careful observation)
Ileocaecal (budesonide 3-4 mg/day)
Clonic sulfasalazine 2-4 g/day

b- Moderate to severe
Induction therapy (oral corticosteroids 40-60 mg / day with dose tapering over 8 weeks + AZA 2-2.5 mg/kg)

1- Response (maintain on
AZA 1.5-2.5 mg/kg/day
Methotrexate 2.5 mg/kg S.C or IM
Refractory cases will shift to biologicals (Ustekinumab)

2- Steroid resistant
Give anti INF (biological)
+AZA (2-2.5 g/kg)
Maintenance like induction therapy

3- Steroid dependent
Methotrexate 25 mg/kg S.C or IM +/- biologicals

c- Severe/fulminate disease
I.V steroids (hydrocortisone 400 mg/day pr methylprednisolone 60 mg/day
+ Anti INF

d- Perianal / fistula disease
Antibiotics
Drainage of abcess
+ biologics (infliximab, adalimumab)

List of Biologics used

- Infliximab (Remicode)
  IV 5 mg/kg or 10 mg/kg if sever
  Induction : 0, 2, 6 weeks
  Maintained : 8 weeks (4-12 week)

- Adalimumab (Humira)
  S.C 40 mg 80 mg 160 mg
  Induction : week 0; 160 mg
  Week 2; 80 mg
  Maintenance : 2 weeks 40 mg
  1 week 40 mg

- Golimumab (Simponi)
  S.C 50 mg 100 mg 200 mg
  Induction: Week 0; 200 mg
  Week 2; 100 mg
  Week 6; 50 mg (if weight < 70 kg) and 100 mg if weight > 70 kg

- Ustekinumab (Stelara)
  S.C or I.V
  260 mg or 390 mg or 520 mg
  Induction: week 0 I.V
  Week 8 S.C
  Maintenance: 8 – 12 weeks S.C

- Vedolizumab (Entyvio)
  IV
  300 mg
  Induction: 0, 2, 6 weeks
  Maintenance: week 8
  For 4 weeks if sever

- Certolizumab (Cimzia)
  S.C
  400 mg
  Induction : week 0; 400 mg
  Week 2; 400 mg
  Week 4; 400 mg
  Maintenance: 4 weeks 400 mg

File S2

Questionnaire: The Relationship between Helicobacter Pylori Infection and Inflammatory Bowel Disease

Pt no:	Name:	tel:

Group no:		H. Pylori (0) -ve (1) +ve	Treatment: (0) Conventional (1) Biologic

I- Sociodemographic Data		Code
1. Gender	(0) Male (1) Female	
2. Age in years	……..	
3. Residence	(0) Rural (1) Urban	
4. Education	(0) Illiterate (1) Read and Write (2) Primary (3) Preparatory (4) Secondary (5) University Education	
5. Occupation	(0) Not working (1) Student (2) Clerical (3) Professional (4) HCW (5) House wife (6) Craft (7) Auxiliary worker (8) Farmer (9) Retired (10) Other……..	
6. Marital status	(0) Single (1) Married (2) Widowed (3) Divorced	
7. Parent Consanguinity	(0) No (1) Yes	
8. Had been breast fed	(0) No (1) Yes	
9. Smoking	(0) Never (1) Current smoker (2) Ex-smoker	
10. Smoking index	no. of smoked cigarettes per day…… x no. of smoking years …… x 365	
11. Age of starting Smoking	(0) N/A (1) <20 years old (2) 20-30 years old (3) > 30 years old	
12. Smoking other than cigarette	(0) Never (1) Shisha (2) Snuff	
13. Alcohol Intake	(0) NA (1) Occasional (2) <3 cups/ day (3) >3 cups/ day (4) ex-drinker	
14. Drug Abuse	(0) NA (1) Never (2) Cannabis (3) Opium (4) tablets "tamols" (5) powder(heroin, cocaine) (6) IV drugs (7) others: ----------	
15. Chronic diseases	(00) No (01) DM (02) Hypertension (03) Bronchial Asthma/COPD (04) Heart disease (05) Renal Disease (06) liver disease (07) SLE (08) rheumatoid arthritis (09) skin allergy (10) hyperthyroidism (11) hypothyroidism (12) other autoimmune …….. (13) others……	
16. Family history of similar condition	(0) No (1) Yes; first degree relatives (2) Yes; other relatives (3) Other autoimmune disease……	
17. Medications	(0) None (1) Analgesic (NSAIDs) (2) anti DM (3) anti HTN (4) corticosteroids (5) IBD therapy (6) hormonal/oral contraceptives (7)thyroxin (8)others ……	
18. Transportation	(-1) not working (1) on foot (2) by bicycle (3) public transport/car	
19. Working activity	(-1) not working (1) Minimal (2) Moderate (3) High	
20. Activity outside work	(-1) not working (1) Minimal (2) Moderate (3) High	
21. Regular exercise	(0) Never (1) Yes Frequent (>3 times/week) (2) Yes Infrequent (<3 times/week)	
22. If yes, mention time spent in min/day	…… (-1) N/A	
23. Food source	(0) Homemade (1) restaurants (2) Mixed	
24. Junk Food, Fast Food	(0) Never (1) occasionally (2) daily If **daily**, mention the number of servings per day ……	
25. Saturated Fat (butter, ghee, cream, ..etc)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
26. trans Fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
27. Food rich in fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, squash, cabbage, cauliflower,	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	

broccoli, dried herbs & spices, fruits, vegetables)		
28. Salty Food (pickled, salty cheese, salted fish, dokka, ...	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
29. Fruits & Vegetables	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
30. Red meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
31. Under cooked meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
32. Fish	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
33. Consumption of caffeine in diet (tea, coffee)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
34. Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
35. Dairy products	(0) Never (1) once per week (2) 2-4 times per week (3) daily If **daily**, mention the number of servings per day ……	
36. On average, how many glasses of water consumed per day?	(1) one cup (2) 2-3 cups (3) at least 4 cups (4) 4 to 8 cups	
37. Dietary restrictions	(00) none (01) cereals (02) brown rice (03) whole grain bread (04) seeds (beans, peas) (05) fruits (apples, plums, peaches, skin removed) (06) high fat or protein food (07) vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper) (08) raw green vegetables (09) spices (10) fried food (11)baked dessert (12) milk and dairy products (13) carbonated drinks (14) tea and coffee (15) others ……	
38. Diet therapy	(0) none (1) low fiber (bananas, cantaloupe) (2) refined grains (white pasta, white rice, and oatmeal, potatoes) (3) Omega 3 rich food (fish) (4) Fully cooked, seedless, skinless, non-cruciferous vegetables (squash) (5) Lean sources of protein (poultry, soy, egg) (6) others……	
39. Food preparation method	(0) No preference (1) boiling (2) grilling (3) steaming (4) frying	
40. Number of meals per day	……	
41. Snackes between meals	(0) Never (1) occasionally (2) daily; ……. per day	
II- Clinical data		
42. Type of IBD diagnosed	(0) Crohn's disease (1) ulcerative colitis	
43. Age at diagnosis	**……..years old**	
44. History of H. pylori infection		
45. If yes mention the onset	(-1) NA (1) few weeks (2) 3-6 months (3) 6 months- 1 year (4)≥ 1 year	
46. History of receiving H. pylori eradication therapy during the past 12 months	(0) No (1) Yes; ……	
47. History of complications	(0) None (1) fistula (2) stricture (3) ulcers (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others……	
48. Surgical intervention	(0) None (1) stricturoplasty (2) Endoscopic balloon dilatation (3) surgical resection (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others	
49. Current medications used to control IBD	(00) None (01) 5-ASA "Pentasa (Mesalamine)" (02) 6-mercaptopurine "Purinethol" (03) Methotrexate "Trexall, Rasuvo, Otrexup" (04) Cyclosporine "Sandimmune, Neoral" (05) Corticosteroids "Prednisone" (06) Sulfasalazine (07) Azathiopurines "Imuran" (08) Librax (09) Imodium (10) Azithromycin "Zithromax" (11) Ciprofloxacin (12) Rifabutin (13) Clarithromycin "Biaxin" (14) Flagyl (15) probiotics (16) multivitamin supplements (17) Infliximab (18)PPI (19) Moltilium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others……	

50. Medications used in the past to control IBD	(00) None (01) 5-ASA "Pentasa (Mesalamine)" (02) 6-mercaptopurine "Purinethol" (03) Methotrexate "Trexall, Rasuvo, Otrexup" (04) Cyclosporine "Sandimmune, Neoral" (05) Corticosteroids "Prednisone" (06) Sulfasalazine (07) Azathiopurines "Imuran" (08) Librax (09) Imodium (10) Azithromycin "Zithromax" (11) Ciprofloxacin (12) Rifabutin (13) Clarithromycin "Biaxin" (14) Flagyl (15) probiotics (16) multivitamin supplements (17) Infliximab (18)PPI (19) Moltilium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others……	
51. How do you describe the effectiveness of the prescribed medications	(0) no difference (1) slight improved (2) dramatic improvement (3) slightly worsened condition (4) dramatic deterioration	
52. How do you describe the side effects of the prescribed medications	(0) none (1) few and tolerable (2) many but tolerable (3) difficult to tolerate and interfere with daily life	

III- Examination		
53. Baseline Body Weight	**…….. kg**	
54. Height	**……..cm**	

55. Fahmy and El Sherbini Socioeconomic standard scoring

1- Education		**Score**
	1.Father	**2.Mother**
Read and write or illiterate non working	1	1
Read and write or illiterate working	2	2
Primary education non working	3	3
Primary education working	4	4
Preparatory education non working	5	5
Preparatory education working	6	6
Secondary education non working	7	7
Secondary education working	8	8
University higher non working	9	9
University higher working	10	10
3- Family income		
Satisfactory and saving		8
Satisfactory		6
Satisfactory and debt		4
Unsatisfactory		2
6- Family size		
3-4 members		4
5 members		3
6 members		2
7 or more members		1
4- Crowding index		
5 or more/ room		0
4-		1
2-		2
<2		3
5- Sanitation		
According to the presence of pure water supply all through the day, electricity and special water closets inside the house:		
All the three present		3
2 out of three		2
One out of three		1
1- Total Score		
1- High (≥31.5)		
2- Middle (21 - <31.5)		
3- Low (<21)		

Follow-up sheet

	Pre treatment	Follow Up					
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
	0	week 2	Week 4	week 6	Week 8	Week 10	week 12
Body weight							
Blood pressure							
Pulse							
CRP							
ESR							
Hb							
Plts							
WBCs							
FBS							
Abd US							
CT							
MRI							
GIT Endoscopy							
Colonoscopy							
Others							
Symptoms (frequency per day)							
Weight loss							
Diarrhea							
Constipation							
Flatulence							
Bloating/indigestion							
Hurt burn							
Urge incontinence							
Soiling							
Tenesmus							
Frequent bowel movements							
Abd cramps							
Epigastric pain							
Generalized abdominal pain							
Nausea							
Vomiting							
Loss of appetite							
Bowel movement interfere with ability to eat							
Blood in stool							
Bleeding per rectum							

	Pre treatment	Follow Up					
		visit 1	visit 2	visit 3	visit 4	visit 5	visit 6
	0	week 2	Week 4	week 6	Week 8	Week 10	week 12
Back pain							
Fever							
Chills							
Night sweating							
Fatigue/lack of energy							
Headache							
Dizziness							
Insomnia/troubled sleep							
Limited sexual activity							
Infection							
Sick leaves/absenteeism							
Others							
Signs of other system affection							
Eye							
Joints							
Kidney							
Skin							
Liver							
Reproductive organs							

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 5
Methods		
Study design	4	Present key elements of study design early in the paper Page 5 (lines 115-121)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 5-6 (lines 115-125)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants Page 5 (lines 118-121)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6-8
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at Page 6 (lines 126-135)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Page 8 (lines 170-189)
		(*b*) Describe any methods used to examine subgroups and interactions Page 7 (lines 179-199)
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 9-11 and all tables

		(b) Give reasons for non-participation at each stage NA
		(c) Consider use of a flow diagram Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 9-10 Table 1
		(b) Indicate number of participants with missing data for each variable of interest Page 9-11 and all tables
Outcome data	15*	Report numbers of outcome events or summary measures Page 9-11 and all tables
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 9-11 and all tables
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 10-11 and tables 2-5 and suppl tables
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 13
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.