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

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1 The relationship between *Helicobacter pylori* infection and inflammatory 2 bowel diseases: A real-life observation

3
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29 Abstract

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

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

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

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

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

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

49 Article summary

50 *Strengths and limitations of this study*

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

60 Introduction

61 Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease
62 (CD), are chronic, disabling, and progressive disorders characterized by lifelong treatment and a
63 significant growing global health burden (Ponder & Long, 2013). In recent decades, many developing
64 countries have seen a dramatic rise in the incidence of IBD¹. It is speculated that improved access to a
65 cleaner environment and the resulting decreased incidence of common childhood infections may be
66 contributing to this rise by altering susceptibility to certain diseases with an autoimmune component,
67 such as IBD^{2,3}. Thus, according to this speculation, microbial infections during childhood may
68 protect from IBD. This rise may partially be accounted for by the implementation of improved
69 diagnostic methods and heightened awareness of IBD.

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

74 *Helicobacter pylori* (*H. pylori*) is believed to be present in the upper gastrointestinal tract of
75 around 50 percent of the world's population. Of these, over 80 percent of cases are entirely without
76 symptoms⁶. In Egypt, the prevalence mounts to 80% among the general population⁷.

77 *H. pylori* can elicit a chronic systemic inflammatory response, which under certain conditions
78 may trigger autoimmune reactions and may be implicated in the pathogenesis of autoimmune
79 diseases. The inflammatory response of the gastric mucosa is mainly attributed to the stimulation of
80 the host's immune system caused by the bacterium. This results in cell mediated immune response
81 and elevated levels of cytokines. As a consequence, products of the local immune reactions may
82 migrate to extra-gastric sites and this may explain the link between *H. pylori* infection and a variety of
83 extra-gastric diseases, including autoimmune disorders⁸.

84 Numerous studies have examined the association between *H. pylori* infection and IBD.
85 However, the published literature is diverse^{8,9}. Whether the link between *H. pylori* and IBD is
86 coincidental, epiphenomenal or mechanistic remains uncertain. There are contradictory data regarding
87 both the causative and the protective role of *H. pylori* infection against IBD¹⁰⁻¹⁸.

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3 88 Based on the potential protective role of *H. pylori* infection on IBD, it is suggested that *H.*
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5 89 *pylori* eradication treatment can impact IBD course and thus should be administered with caution
6
7 90 although more prospective studies are needed ¹⁵.

9 91 IBD was found to be more prevalent in regions with lower rates of *H. pylori* colonization.
10
11 92 There is a steady rise in the incidence of IBD in *H. pylori* endemic regions which may reflect the era
12
13 93 of initiating anti-*H. pylori* therapy for peptic ulcer disease ¹². Furthermore, meta-analyses of relevant
14
15 94 studies have reported that the prevalence of *H. pylori* infection is lower in patients with IBD
16
17 95 compared to controls ^{8,9,12,18,19}. One study suggested that long-term treatment with sulphasalazine
18
19 96 leads to eradication of *H. pylori* infection ²⁰. Although this has not been confirmed by other studies,
20
21 97 evidence from most studies points to a protective role for this infection in the development of IBD ^{8,19}.

22
23
24 98 With the advances in the understanding of the pathological mechanisms involved in IBD, new
25
26 99 therapies have been proposed, with the most important development being the introduction of disease
27
28 100 response modifiers, also known as biological agents. The latter includes anti-tumor necrosis factor
29
30 101 (anti-TNF α), IL-1/IL-6 receptor antagonist and anti-CD20 antibody. They are generally well tolerated,
31
32 102 but their use was found to be associated with adverse effects, including risks of infection and
33
34 103 malignancies ²¹.

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36
37 104 This prompted us to further analyze the association between *H. pylori* infection and the flare
38
39 105 of IBD activity in a longitudinal study and to explore the possible impact of *H. pylori* infection on
40
41 106 response to conventional versus biological treatment of IBD.

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44 45 108 **Methods**

46 47 109 **Study population and sampling**

48
49 110 We conducted a prospective observational study at Alexandria University Student Hospital.
50
51 111 This hospital is affiliated with Alexandria University in Egypt and is serving all students, faculty and
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53 112 staff members at Alexandria University. It has a total bed capacity of 1000 beds and comprises
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55 113 outpatient clinics and inpatient and emergency departments. We enrolled in the study adult patients
56
57 114 with ages ≥ 18 years that were confirmed to have IBD [triphasic CT abdomen,

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3 115 endoscopy/colonoscopy and fecal calprotectin] and have started IBD treatment [conventional or
4
5 116 biological]. Patients having irritable bowel syndrome were excluded by applying Rome III criteria ²².

7 117 The treatment decision (standard vs biological) was made by clinicians at the Internal
8
9 118 Medicine department of the University student hospital. The prescribed treatment is the standards of
10
11 119 care adopted by the university hospital for treating IBD patients. Details of the treatment regimens
12
13 120 and the parameters used for standard vs biological decision are described in File S1.

15 121 The percentage of *H. pylori* infection among IBD patients can reach 10.0% ¹⁹. Since Egypt is
16
17 122 endemic for *H. pylori* infection ⁷. We assumed that this percentage could be higher. Using a using an
18
19 123 alpha error of 0.05, a 95% confidence level, and a study power of 80%; the minimum required sample
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21 124 size was found to be 138 patients. However, we ultimately enrolled a total of 182 IBD patients. The
22
23 125 sample size was calculated using Epi info 7 software. Confirmed IBD cases who accepted to
24
25 126 participate in the study were consecutively enrolled until the required sample size was fulfilled.
26
27 127 According to patient disposition depicted in Figure 1, the patients were assigned into two groups
28
29 128 according to the prescribed treatment regimen (File S1): Group 1 comprised patients on conventional
30
31 129 IBD treatment, whereas Group 2 included patients on biological IBD treatment.

33 130 To screen for *H. pylori* infection, all enrolled IBD patients were subjected to stool analysis to
34
35 131 detect *H. pylori* antigen in stool using a commercially available enzyme immunoassay (EIA) kit
36
37 132 [Foresight EIA test kit for qualitative and quantitative detection of *H. pylori* in the stool (ACON[®]
38
39 133 laboratories, Inc. San Diego, USA)]. Accordingly, each of the assigned groups included IBD patients
40
41 134 infected or not with *H. pylori*. IBD patients found positive for *H. pylori* were informed about their lab
42
43 135 results. We did not start *H. pylori* eradication therapy during the study period. Instead, after the three
44
45 136 months of follow up, IBD patients found positive for *H. pylori* were referred to a specialist for further
46
47 137 evaluation and management of their case according to the adopted standard of care.

51 52 53 138 **Patient and Public Involvement**

54
55 139 We informed the patients about the aims and concerns of the study and how it will add to
56
57 140 better understanding of the disease etiology and triggering factors, which was highly
58
59 141 appreciated by the patients, and the patients were motivated to be a part of the cohort
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3 142 intended for the long term follow-up by the clinicians. However, It was not appropriate or
4
5 143 possible to involve patients or the public in the design, or conduct, or reporting, or
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7
8 144 dissemination plans of our research. All the laboratory and clinical data were reported to the
9
10 145 participants and we discussed the study findings in a simple language.

12 146 **Assessments**

14 147 Baseline evaluation included thorough history taking, full clinical examination and laboratory
15
16 148 testing. A structured data collection form (File S2) was designed and used to collect the baseline data
17
18 149 [sociodemographic, personal habits, lifestyle, physical activity and exercise, dietary habits and
19
20 150 restrictions, family history, medical history, co-morbidities, medications] as well as clinical data
21
22 151 [Disease onset, history of the present complaints, frequency and duration of the attacks, past and
23
24 152 current IBD medications, history of switching therapeutic regimens, surgical interventions,
25
26 153 complications] from each patient at the initial visit. History of *H. pylori* infection and receiving *H.*
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28 154 *pylori* eradication therapy during the past 12 months was also recorded. at each follow-up visit. All
29
30 155 patients were followed bimonthly for three months (6 visits) during the period of IBD treatment.
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32 156 Patients were called weekly through their telephone numbers and were asked about the frequency, and
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34 157 severity of symptoms and if any side effects for the assigned treatment occurred during the previous
35
36 158 week.

39 159 All the participants were clinically checked. Trained investigators assessed for blood pressure
40
41 160 (BP) and performed the anthropometric measurements according to standard techniques²³⁻²⁵. Body
42
43 161 mass index (BMI) was calculated according to the Quetelet's index: $BMI = [\text{weight (kg)}/\text{height}^2$
44
45 162 $(\text{m}^2)]$. At each follow-up visit all enrolled IBD patients were subjected to laboratory measurement of
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47 163 complete blood count (CBC), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), fasting
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49 164 blood glucose (FBG), and fecal calprotectin²⁶. Imaging techniques including Triphasic CT and
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51 165 endoscopy/colonoscopy were done when indicated and their findings were recorded. Full length
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53 166 colonoscopy was performed for all patients, using Pentax colonoscopies. Colonoscopic biopsies were
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55 167 obtained from the rectal, sigmoid, descending, transverse, ascending colonic, and cecal mucosa of
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3 168 each patient. Histological assessment of the degree of inflammation in CD and UC was evaluated
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5 169 according to the European consensus on the histopathology of inflammatory bowel disease ²⁷.

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7 170 The socioeconomic status of the enrolled IBD patients was calculated and categorized as
8
9 171 high, middle, low and very low according to the modified social scoring of Fahmy and El-Sherbini ²⁸.

12 172 **Outcomes**

13
14 173 The enrolled patients in each group were evaluated clinically every two weeks for a total
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16 174 period of 3 months to record potential improvement/flare of the IBD condition. The primary outcome
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18 175 of the study is the number of patients with IBD who achieved remission at the end of the follow-up
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20 176 period.

23 177 **Statistical analysis**

24
25 178 The collected data were reviewed for accuracy and integrity and fed into computer software.
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27 179 Data were analyzed using a statistical software package (IBM SPSS statistics for windows, version
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29 180 21.0, Armonk, NY: IBM Corp., Released 2011). Continuous variables were presented as the mean \pm
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31 181 standard deviation (SD). Categorical variables were expressed as numbers with proportions, n (%).
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33 182 Variables relevant to laboratory data were dichotomized according to prefixed cutoffs, taking into
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35 183 consideration the normal reference values. Student's *t*-test was performed to compare quantitative
36
37 184 variables between two groups of normally distributed data. Chi Square (χ^2) test was performed to
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39 185 examine the association between qualitative variables. Fischer's Exact test with Yates Correction was
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41 186 used when cells were fewer than five. Repeated measures ANOVA was used to test the differences in
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43 187 means of quantitative variables measured at different time points. Multiple logistic regression
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45 188 analyses were conducted to identify independent risk factors of *H. Pylori* infection among IBD
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47 189 patients. Cox regression analysis (or proportional hazards regression) was used to investigating the
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49 190 effect of several variables upon the time a specified event takes to happen; thus to determine the
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51 191 factors associated with IBD flare/remission when testing variables that had statistically significant
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53 192 differences at significance levels <0.05 in the simple logistic regression analyses. Kaplan Meier
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55 193 analysis was used to determine the probability of recovery (improvement in IBD condition as the
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57 194 event-of-interest) considering the *H. pylori* infection status and treatment option given. Recovery

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3 195 defined improvement in IBD status based on clinical and laboratory data, whereas censored defined
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5 196 lack of improvement or flare of the inflammatory condition. All the statistical analyses were
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7 197 conducted with two-tailed tests and statistically significant levels were determined as being <0.05 .
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10 198 **Results**

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13 14 200 **Sociodemographics and clinical characteristics of the study cohort**

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16 201 A total of 182 IBD patients [96 (52.7%) UC and 86 (47.3%) CD] were enrolled in the study,
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18 202 being more frequently male (51.7%), married (58.2%), urban residents (51.6%), possessing high
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20 203 literacy levels (76.9%), and non-smokers (82.4%). The average age was 27.0 ± 7.3 years with the
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22 204 majority being in the age group 20 – 35 years. Overall, normal BMI was a predominant feature among
23
24 205 the study population (59.3%) while 31.9% were overweight. Other sociodemographic characteristics
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26 206 of the study participants are shown in (Table 1).
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28
29 207 The study participants did not differ significantly in relation to their total physical activity
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31 208 score. However, IBD patients found free of *H. pylori* infection deemed to have a more favorable food
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33 209 habit score compared to IBD patients with *H. pylori* infection (12.2 ± 5.0 vs 10.7 ± 3.8 , $p = 0.018$)
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35 210 (Table S1)
36

37
38 211 Baseline clinical and laboratory findings of all IBD patients are demonstrated in Table S2.
39
40 212 IBD patients with *H. pylori* infection had higher rates of abdominal pain, abdominal cramps, bloating,
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42 213 indigestion, flatulence, diarrhea, bleeding per rectum, fever, chills, infection, fatigue/lack of energy,
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44 214 sick leaves/absenteeism as well as higher mean CRP and ESR levels than those found free of *H.*
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46 215 *pylori* infection although the differences were not statistically significant. GIT endoscopy and
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48 216 colonoscopy for the enrolled patients proved to have features of CD and UC in the form of superficial
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50 217 ulcerations and mild infiltration.
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53 218 ***H. pylori* infection among IBD patients**

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55 219 We detected *H. pylori* infection in almost half (49.5%) of the enrolled IBD patients, being
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57 220 almost equally presented among UD [48 (50.0%)] and CD [42 (48.8%)] patients [OR (95% CI)= 1.05
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59 221 (0.59 – 1.88)], although most of them (82.8%) admitted receiving *H. pylori* eradication therapy during
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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

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3 248 therapy vs 0.750 in biological therapy). The number of people who recovered among *H. pylori*
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5 249 negative patients was almost equal to that in *H. pylori* positive patients. On the other hand, the
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7 250 proportion of recovered IBD patients under conventional therapy was relatively higher than those
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9 251 receiving biological therapy although the difference was not statistically significant. In total, 39
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11 252 subjects did not recover until the end of the study. The Log Rank, Breslow and Tarone-Ware tests of
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13 253 equality of recovery did not differ significantly among the enrolled IBD patients in relation *H. pylori*
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15 254 infection status or the IBD treatment option ($p > 0.05$) (Table 5 and Figure 2).

18 19 255 **Discussion**

20
21 256 In recent decades, improving hygienic conditions and socioeconomic status have reduced *H.*
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23 257 *pylori* infection rates and this trend has concurrently been accompanied by an increased IBD
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25 258 incidence in most countries. However, the role of *H. pylori* in IBD remains unresolved yet ^{1,15,29}.
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27 259 Numerous studies have reported a lower *H. pylori* infection rate in patients with CD and/or UC than
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29 260 in non-IBD control individuals, although a small number of studies showed no significant association
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31 261 ^{8,9,12,19,29}. Recently, emerging epidemiologic studies and animal experiments revealed an inverse
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33 262 correlation between *H. pylori* infection and IBD onset, suggesting that *H. pylori* colonization exerts a
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35 263 special protective effect on autoimmune diseases ^{12,21}.

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37 264 In attempting to further explain the negative association between *H. pylori* infection and IBD,
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39 265 we enrolled in a longitudinal study IBD patients having or not *H. pylori* infection and observed the
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41 266 possible impact of *H. pylori* infection on response to conventional versus biological treatment of IBD.

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43 267 In our IBD cohort, *H. pylori* was detected in almost half of the patients. These numbers are
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45 268 relatively low compared to the prevalence among the general population in Egypt where the disease
46
47 269 tends to be endemic ³⁰⁻³³. This supports previous reports of lower rates *H. pylori* of in IBD patients
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49 270 and suggests a possible link between *H. pylori* and IBD ^{8,19}. The rate *H. pylori* infection was
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51 271 significantly higher among IBD patients on conventional treatment which disagrees with studies
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53 272 suggesting that 5-aminosalicylates or sulphasalazine interfere with the adhesion of *H. pylori* to the
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55 273 mucosa and block its replication ^{20,34-36}. In fact, several studies did not support the aspect that as
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57 274 treatment with sulfasalazine or any other medical therapy such as 5-aminosalicylic acid (5-ASA),
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3 275 thiopurines steroids, antibiotics had an influence on *H. pylori* colonization rate ^{12,37-39}. The same holds
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5 276 for novel therapeutic modalities, such as anti-tumor necrosis factor alpha (TNF- α) treatment ⁴⁰.

7 277 In the present study, the majority of *H. pylori* positive IBD patients admitted receiving *H.*
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9 278 *pylori* eradication therapy in the past 2 months which brings into question the effectiveness of the
10
11 279 eradication therapy in treated cases or highlights the occurrence of reinfection among this group of
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13 280 patients. It is noteworthy that most of the previous studies did not inquire into the participants' past
14
15 281 history of treatment for *H. pylori* infection ¹². It is therefore possible that their IBD patients had been
16
17 282 treated for *H. pylori* prior to enrollment in the study, thereby producing a falsely low *H. pylori*
18
19 283 infection rate.

22 284 Accumulating evidence suggests that *H. pylori* through its immune regulation capacity
23
24 285 protects human from various diseases with an auto-immune nature including IBD ⁴¹. Such speculation
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26 286 has been explored in various studies and the results are controversial. Certainly, the heterogeneity
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28 287 among studies accounted for by methods of IBD and *H. pylori* diagnosis, study location, or study
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30 288 population and the possibility of publication bias limit the certainty of this conclusion and bring into
31
32 289 question the robustness of their findings. We extended previous work by investigating the association
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34 290 between *H. pylori* infection and IBD disease from a different angle in a prospective study. A potential
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36 291 avenue for extending our study involved broadening the inclusion criteria to gain further insight into
37
38 292 the local variation of the protective effects of *H. pylori* on IBD. Differing from previous studies, we
39
40 293 added subgroup analysis on *H. pylori* infection and the type of IBD treatment. However, we did not
41
42 294 observe a significant relationship between the existence of the two conditions. For instance, the course
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44 295 of the disease was similar in all IBD patients regardless of their *H. pylori* infection status or when
45
46 296 considering the type of treatment given (conventional or biological). There also seemed a trend that
47
48 297 the extent and severity of IBD increased with *H. pylori* infection decreasing. Intriguingly, the
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50 298 proportion of recovered IBD patients under conventional therapy was relatively higher than those
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52 299 receiving biological therapy. This might be ascribed to the higher *H. pylori* infection among IBD
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54 300 patients under conventional therapy or that patients receiving biological therapy are those who were
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56 301 refractory to previous conventional therapy, thus having a more severe disease activity. Although our
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3 302 findings do not support the inverse association between *H. pylori* infection and IBD disease, they
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5 303 increase in some part the credibility of previous studies.

6
7 304 IBD is thought to be triggered by a complex interplay of environmental and genetic factors.
8
9 305 The growing burden of IBD could be a proxy of the hygiene hypothesis and improved sanitary living
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11 306 conditions, lifestyle and dietary changes, more frequent antibiotic use, enhanced diagnostic methods
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13 307 and heightened awareness of IBD⁴²⁻⁴⁴. In this regard, we examined in addition to *H. pylori* infection
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15 308 the role of some host and environmental cofactors that have been reported as either alleviating or
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17 309 inciting factors for IBD flare. These included diet, smoking, physical activity, breastfeeding,
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19 310 socioeconomic standard, education, occupation, urban versus rural lifestyle, and exposure to
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21 311 medication⁴⁴. In this context, we were guided by existing studies that recognized differences in
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23 312 potential risk factors or unique features to certain populations, such as the Mediterranean diet. Indeed,
24
25 313 dietary factors play a crucial role in disease initiation or relapse⁴⁵, although certain diets, such as the
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27 314 Mediterranean diet, are purported to be protective of IBD⁴⁶⁻⁴⁸. The Mediterranean diet, plant-based
28
29 315 diet and semi-vegetarian diet have been shown by some studies to alleviate symptoms of IBD and
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31 316 keep patients in remission potentially through reducing inflammation and improving microbiota^{49,50}.
32
33 317 In the present cohort, IBD patients negative for *H. pylori* infection and those experiencing less flare
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35 318 had a more favorable overall dietary habit score. In line with Kakodkar's recommendations⁴⁹, which
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37 319 encourage the consumption of all vegetables and fruits in an IBD diet, we observed a strong protective
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39 320 role for the daily as well as 2-3 times per week intake of vegetables and fruits on IBD flare. In a
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41 321 recent meta-analysis, the beneficial effect of *H. pylori* against IBD in Mediterranean populations was
42
43 322 lower compared to East Asian and European regions¹⁸. Nevertheless, the included studies did not
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45 323 explicitly incorporate dietary information or study the putative beneficial effect of diet as a
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47 324 confounder in their analyses. Moreover, this positive effect could be attributed to the relative
48
49 325 abundance of *CagA H. pylori* in these populations, a strain with specific constituents that modulate
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51 326 host immune defenses⁵¹.

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53 327 Fiber has a potential anti-inflammatory role in IBD, although a converse effect can occur⁴⁴.
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55 328 Our cox regression model revealed that consumption of food rich in insoluble fibers such as whole
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57 329 bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs and

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3 330 spices, on daily basis significantly increased the risk of IBD flare particularly in patients consuming
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5 331 four meals per day with occasional snacks between meals.

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7 332 In agreement with Gentschew et al.,⁵² trans fat intake was also associated with higher odds of
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9 333 IBD flare although this did not appear in our final model. Although our findings might suggest a role
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11 334 for diet in IBD flare, the effect of diet is questionable due to limitations in terms of recall bias and
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13 335 multifactorial exposures. Moreover, IBD patients may alter their dietary habits based on the
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15 336 symptoms that vary with disease activity. This raises the need for further explicit research into the role
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17 337 of diet in IBD.

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19 338 Variation in the protective effect of *H. pylori* on IBD could also be ascribed to socioeconomic
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21 339 factors. In the present study, IBD patients with higher socioeconomic standards who were mostly
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23 340 urban residents had a higher chance of disease flares. Importantly, *H. pylori* infection did not
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25 341 significantly vary in relation to the socioeconomic standard in our IBD cohort. These findings lend
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27 342 support to those factors associated with an urban lifestyle and industrialization can influence one's
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29 343 risk of IBD.

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31 344 Furthermore, the rate of *H. pylori* gastric colonization was significantly higher in adults older
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33 345 than 20 years although there was no significant difference in the IBD average age of onset between
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35 346 positive and negative *H. pylori* groups. This age group has also higher disease flares. These findings
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37 347 are probably due to their co-morbid history or other aspects of their lifestyle or which affects IBD
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39 348 occurrence. Apart from the age, other demographic variables did not show any effects on our results.

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41 349 Collectively, the association between IBD and the presence of *H. pylori* infection seems to be
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43 350 uncertain and remains to be explored. Looking forward, there is still much to be learned about the
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45 351 etiology of IBD and how specific environmental exposures intimately impact the development of
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47 352 disease and also the potential for relapse.

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52 354 **Study limitations**

53
54 355 Several limitations of the current work should be listed. First, we did not test *H. pylori* in colon
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56 356 biopsy, which may decrease the disease prevalence rate. However, this would cause additional
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58 357 burdens of an invasive procedure to the patients which is against medical ethics. A urea breath test

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3 358 would have been a better alternative, but we did not have access to it in our centers. Second, the small
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5 359 sample size was a major limitation and might have impacted the estimation of the effect size. Third,
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7 360 the trend of decreased *H. pylori* infection in patients under biological therapy thus paralleling with
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9 361 increased severity of IBD should be investigated in a larger randomized controlled trial for statistical
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11 362 significance. Also, our results merit reassessment in a cohort of patients from a background
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13 363 population with a low prevalence of *H. pylori* and with explicit information about eradication
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15 364 treatment and exposure to other antibiotics. Finally, the causal relationship between *H. pylori*
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17 365 infection and IBD cannot be established through a non-controlled study and further large scale
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19 366 prospective clinical trials are needed. Towards this, studies investigating the effect of eradication of
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21 367 *H. pylori* on the development of IBD and considering environmental exposures, hygiene diet, physical
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23 368 activity and intestinal microbiota as strong confounders are warranted. An ideal study would be
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25 369 conducted at the time of IBD diagnosis and proceed prospectively.
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372 **Ethical consideration**

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

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

381 **Conflict of Interest**

382 All authors declare no conflict of interest.

383 **Data sharing statement**

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3 384 All data are fully available without restriction by the corresponding author at
4
5 385 ekram.wassim@alexu.edu.eg
6
7

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9

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11
12 388 ***Acknowledgements***

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15 389 We would like to acknowledge the study participants for accepting to participate in the study.
16
17 390

18
19 391 **Author contribution**

20
21 392 EWAW: Conceptualization, developed the theoretical framework and study design, took the lead for
22
23 393 overall direction and planning of the study implementation, data curation, statistical analysis and
24
25 394 interpretation of data, major contribution to writing, revised and approved final version of the
26
27 395 manuscript
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29 396

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31 397 EIY: Study implementation and recruitment of the study participants, data collection, clinical
32
33 398 evaluation and follow up, analysis and interpretation of data, contributed to the writing of the
34
35 399 manuscript, revised and approved final version of the of the manuscript.
36
37 400

38 400

39
40 401 EMH: Supervised the study implementation and data collection, facilitated the recruitment of the
41
42 402 study participants, clinical evaluation and follow up, data curation, contributed to the writing of the
43
44 403 manuscript, revised and approved final version of the manuscript.
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3 540 **Figure legend**
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6 541 Figure 1: Patients' disposition throughout the study
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9 542 Figure 2: The equality of recovery (improvement in IBD condition) over the follow-up periods in
10 543 relation to *H. pylori* infection status and the IBD treatment option
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13 544 Figure S1: clinical and laboratory findings of IBD patients over the follow-up periods in relation to *H.*
14 545 *pylori* infection status and the IBD treatment option
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		IBD patients		H pylori infection in IBD patients				<i>p</i> ~
		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 <i>H. pylori</i> 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 <i>H. pylori</i> 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 ± 7.5		<i>t</i> =1.3, <i>p</i> = 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		<i>t</i> = -0.583, <i>p</i> = 0.560

List of Tables

Table 1: Characteristic of the study population

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	

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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

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

Backward Stepwise (Wald) Logistic Regression		B	S.E.	Wald	df	Sig. (<i>p</i> 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 significant at <0.05

IBD; inflammatory bowel disease

Parameter	<i>H. pylori</i> 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	Wilks' Lambda	Fa	p	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	Fa	Effect Size (Partial Eta Squared) ^b	Linearity (F value) ^b	p	F	p	Effect Size (Partial Eta Squared) ^b	
			Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
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 x S	1.156	0.322	0.038	0.448	T x 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 x S	0.708	0.644	0.024	0.276	T x 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 x S	1.48	0.187	0.048	0.565	T x 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 x S	0.157	0.925	0.003	0.078	T x 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	11.5 ± 1.0	11.7 ± 1.0	12.0 ± 0.81	12.2 ± 0.75	T x S	3.1	0.007	0.096	0.91	T x 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 x S	1.05	0.394	0.035	0.409	T x 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 ± 64.3	279.2 ± 44.3	282.0 ± 48.5	288.1 ± 46.5	280.0 ± 39.4	284.1 ± 44.2	T x S	1.02	0.415	0.034	0.396	T x 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 x S	0.901	0.496	0.031	0.35	T x 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 x S	2.08	0.058	0.067	0.740	T x 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

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	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

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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 significant at <0.05

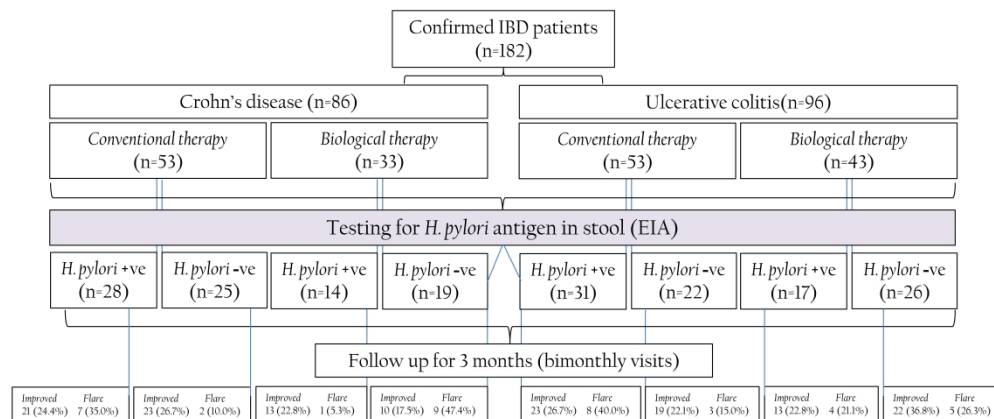
547 Table 5: Kaplan Meier analysis of the probability of improvement in IBD condition in
 548 relation to *H. pylori* infection and IBD treatment option

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 <i>H. pylori</i> infection/treatment option		
										Log Rank (Mantel-Cox)	Breslow (Generalized Wilcoxon)	Tarone-Ware
										p value		
<i>H. pylori</i> 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			

549 p value significant at <0.05
 550 IBD; inflammatory bowel disease

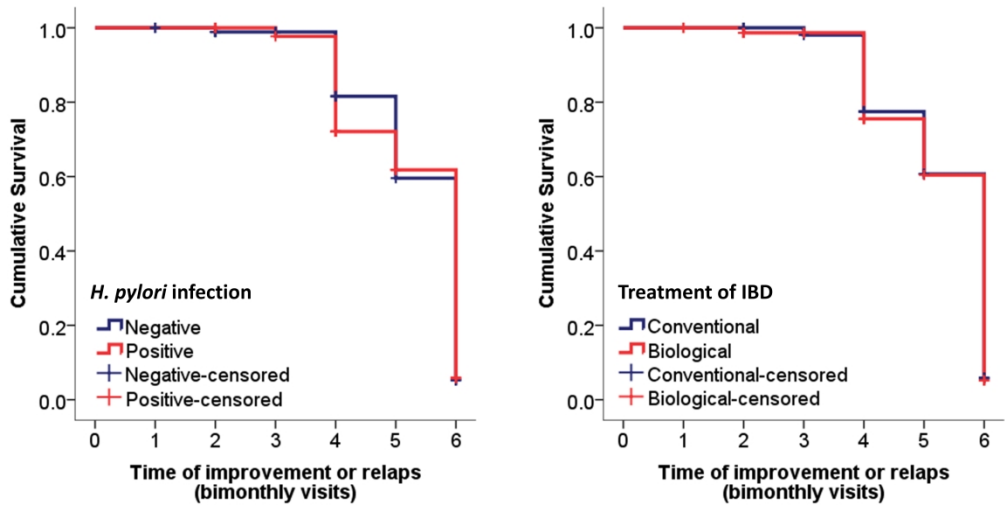
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H. pylori infection

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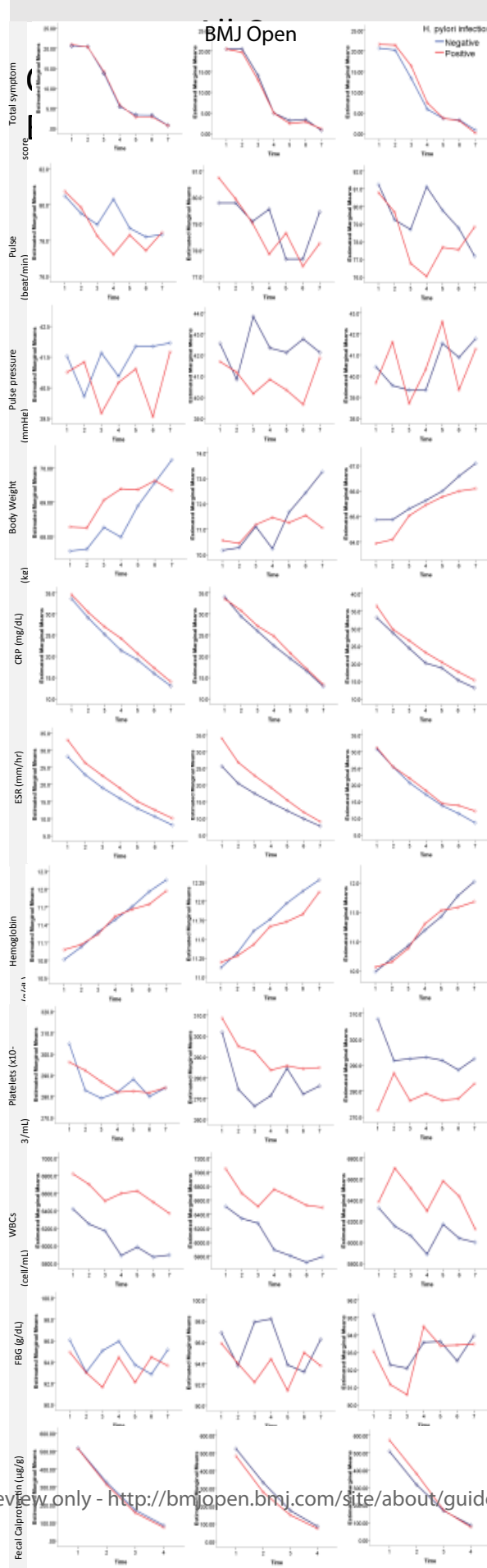


Table S1: Physical activity and dietary habit among the IBD patients

		IBD patients		H pylori infection in IBD patients				<i>p</i> ~
		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		<i>t</i> =1.6, <i>p</i> = 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	2	2.2	
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	12.2	<0.001
	once per week	96	52.7	61	66.3	38.9	
	2-4 times per week	54	29.7	12	13.0	46.7	
	daily	5	2.7	3	3.3	2.2	
Fruits and Vegetables	never	2	1.1	2	2.2	0.0	<0.001
	once per week	56	30.8	45	48.9	12.2	
	2-4 times per week	81	44.5	37	40.2	48.9	
	daily	43	23.6	8	8.7	38.9	
Red meat	never	16	8.8	4	4.3	13.3	0.013
	once per week	113	62.1	66	71.7	52.2	
	2-4 times per week	53	29.1	22	23.9	34.4	
	daily	0	0.0	0	0.0	0.0	
Under cooked meat	never	157	86.3	80	87.0	85.6	0.548
	once per week	24	13.2	11	12.0	14.4	
	2-4 times per week	1	0.5	1	1.1	0.0	
	daily	0	0.0	0	0.0	0.0	
Fish	never	17	9.3	14	15.2	3.3	0.007
	once per week	91	50.0	38	41.3	58.9	
	2-4 times per week	74	40.7	40	43.5	37.8	
	daily	0	0.0	0	0.0	0.0	
Consumption of caffeine in diet (tea, coffee)	never	25	13.7	17	18.5	8.9	<0.001
	once per week	20	11.0	17	18.5	3.3	
	2-4 times per week	61	33.5	30	32.6	34.4	
	daily	76	41.8	28	30.4	53.3	
Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	never	7	3.8	5	5.4	2.2	0.039
	once per week	67	36.8	41	44.6	28.9	
	2-4 times per week	91	50.0	41	44.6	55.6	
	daily	17	9.3	5	5.4	13.3	
Dairy products	never	27	14.8	13	14.1	15.6	0.034
	once per week	49	26.9	33	35.9	17.8	
	2-4 times per week	78	42.9	36	39.1	46.7	
	daily	28	15.4	10	10.9	20.0	
Average number of glasses of water consumed per day	one cup	8	4.4	3	3.3	6.7	0.102
	2-3 cups	73	40.1	40	43.5	36.7	
	at least 4 cups	73	40.1	41	44.6	35.6	
	4-8 cups	27	14.8	8	8.7	21.1	
Snacks between meals	Never	60	33.0	33	35.9	30.0	0.420
	Occasionally	121	66.5	58	63.0	70.0	
	Daily	1	0.5	1	1.1	0.0	
Number of meals per day	Two	68	37.4	32	34.8	40.0	0.092
	Three	109	59.9	55	59.8	60.0	
	Four	5	2.7	5	5.4	0.0	
Total food score (favorable food habits)		11.4 ± 4.5		12.2 ± 5.0		10.7 ± 3.8	<i>t</i> =2.4 , <i>p</i> = 0.018

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Dietary restrictions	No	119	65.4	64	69.6	55	61.1	0.231
	Yes	63	34.6	28	30.4	55	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	6	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	5	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	0	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	22	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	0	11.1	
	Omega 3 rich food (fish)	29	15.9	17	18.5	2	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

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

	IBD patients		H pylori infection in IBD patients				<i>p</i> ~	
	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	

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Laboratory findings	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		$t = 0.8$ $p = 0.940$
	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
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
	Strictureplasty	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	<i>H. Pylori</i> 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	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
			Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD														
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	0.81	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	0.72	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	0.32	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 ± 1.0	11.0 ± 1.1	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	0.63	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	0.35	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	0.99	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	0.75	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	0.17	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	0.52	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	0.52	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	0.56	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	0.40	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

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

Parameter	<i>H. pylori</i> 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	Wilks' Lambda	F ^a	p	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F ^a	Effect Size (Partial Eta Squared) ^b	Linearity (F value) ^b	p	F	p	Effect Size (Partial Eta Squared) ^c	
			Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD														
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	0.92	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	0.333	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	0.338	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	0.668	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	0.511	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	0.37	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	0.18	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	0.35	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	0.36	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	0.02	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	0.29	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	0.01	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	0.484	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	0.444	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	0.449	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

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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.	%					
8	<i>H. pylori</i> infection	Negative	92	50.5	73	51.0	19	48.7	0.820	1.08	0.57	2.02
		Positive	90	49.5	70	49.0	20	51.3	0.837			
9		NA	92	50.5	73	51	19	48.7				
10	Onset of <i>H. pylori</i> infection	Few weeks ago	7	3.8	6	4.2	1	2.6	0.540	0.53	0.07	3.99
11		3-6 months	10	5.5	7	4.9	3	7.7	0.488	1.54	0.45	5.21
12		6 months - 1 year	35	19.2	29	20.3	6	15.4	0.789	0.88	0.35	2.21
13		> 1 year	38	20.9	28	19.6	10	25.6	0.560	1.26	0.58	2.70
14	Type of IBD diagnosed	Crohn's disease	86	47.3	67	46.9	19	48.7				
15		Ulcerative colitis	96	52.7	76	53.1	20	51.3	0.697	0.88	0.47	1.66
16	Crohn's disease	<i>H. pylori</i> Negative	44	24.2	33	23.1	11	28.2	0.526			
17		<i>H. pylori</i> Positive	42	23.1	34	23.8	8	20.5	0.374	0.66	0.27	1.65
18	Ulcerative colitis	<i>H. pylori</i> Negative	48	26.4	40	28.0	8	20.5	0.196	0.55	0.22	1.36
19		<i>H. pylori</i> Positive	48	26.4	36	25.2	12	30.8	0.853	0.93	0.41	2.10
20	Treatment of IBD	Conventional	106	58.2	86	60.1	20	51.3				
21		Biological	76	41.8	57	39.9	19	48.7	0.254	1.44	0.77	2.70
22	Sex	Male	94	51.6	76	53.1	18	46.2				
23		Female	88	48.4	67	46.9	21	53.8	0.241	1.46	0.78	2.74
24	Age	16 - <20 Years	20	11.0	15	10.5	5	12.8	0.708	ref		
25		20 - <35 Years	136	74.7	106	74.1	30	76.9	0.814	0.89	0.35	2.30
26		35 - 55 Years	26	14.3	22	15.4	4	10.3	0.440	0.60	0.16	2.22
27	Mean ± SD		27.0 ± 7.3		27.8 ± 7.6		23.8 ± 4.9		$t=4.0, p<0.001$			
28								0.008	0.92	0.87	0.98	
29	Age at diagnosis	10 - >19	69	37.9	48	33.6	21	53.8	0.086			
30		20 - <30	83	45.6	71	49.7	12	30.8	0.029	0.45	0.22	0.92
31		30 - 45	30	16.5	24	16.8	6	15.4	0.341	0.64	0.26	1.60
32	Mean ± SD		27.0 ± 7.3		22.3 ± 6.5		19.1 ± 4.8		$t=3.4, p=0.001$			
33								0.01	0.92	0.87	0.98	
34	Residence	Rural	88	48.4	74	51.7	14	35.9				
35		Urban	94	51.6	69	48.3	25	64.1	0.051	1.92	1.00	3.70
36	Education	Illiterate	2	1.1	2	1.4	0	0.0	0.982	0.00	0.00	
37		Read and Write	23	12.6	20	14.0	3	7.7	0.160	0.42	0.13	1.40
38		Primary	4	2.2	4	2.8	0	0.0	0.978	0.00	0.00	
39		Preparatory	13	7.1	11	7.7	2	5.1	0.309	0.47	0.11	2.00
40		Secondary	44	24.2	35	24.5	9	23.1	0.487	0.76	0.36	1.64
41		University education	96	52.7	71	49.7	25	64.1	0.715			
42	Working status	No	88	48.4	63	44.1	25	64.1				
43		Yes	94	51.6	80	55.9	14	35.9	0.032	0.49	0.25	0.94
44	Occupation	Unemployed	37	20.3	31	21.7	6	15.4	0.024			
45		Student	45	24.7	26	18.2	19	48.7	0.023	2.89	1.15	7.25
46		Clerical	2	1.1	1	0.7	1	2.6	0.353	2.73	0.33	22.67
47		Professional	39	21.4	33	23.1	6	15.4	0.962	0.97	0.31	3.02
48		Housewife	21	11.5	19	13.3	2	5.1	0.566	0.63	0.13	3.10
49		Auxiliary worker	22	12.1	19	13.3	3	7.7	0.701	0.76	0.19	3.05
50		Farmer	16	8.8	14	9.8	2	5.1	0.643	0.69	0.14	3.40
51	Marital status	Married	73	40.1	50	35.0	23	59.0	0.110			
52		Not married						0.016	2.20	1.16	4.21	
53		Single	106	58.2	91	63.6	15	38.5	0.018	2.20	1.15	4.21
54		Widowed	2	1.1	1	0.7	1	2.6	0.276	3.08	0.41	23.35
55		Divorced	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
56	Socioeconomic standard	High	58	31.9	41	28.7	17	43.6	.015	2.730	1.215	6.14
57		Middle	52	28.6	39	27.3	13	33.3	.127	1.938	.828	4.54
58		Low	72	39.6	63	44.1	9	23.1	.052			
59	Consanguinity	No	144	79.1	114	79.7	30	76.9				
60		Yes	38	20.9	29	20.3	9	23.1	0.888	0.95	0.45	2.00
61	Being breastfed	No	26	14.3	22	15.4	4	10.3				
62		Yes	156	85.7	121	84.6	35	89.7	0.382	1.59	0.56	4.47
63	Smoking	Never	150	82.4	119	83.2	31	79.5	0.915			
64		Current smoker	26	14.3	19	13.3	7	17.9	0.774	1.128	0.50	2.57
65		Ex-Smoker	6	3.3	5	3.5	1	2.6	0.775	0.75	0.10	5.48
66	Age of starting Smoking	NA	153	84.1	119	83.2	34	87.2	0.679			
67		< 20 Years	17	9.3	14	9.8	3	7.7	0.573	0.71	0.22	2.32
68		20 - 30 Years	12	6.6	10	7.0	2	5.1	0.475	0.59	0.14	2.48
69	Smoking other than cigarette	Never	180	98.9	143	100.0	37	94.9				
70		Shisha	2	1.1	0	0.0	2	5.1	0.079	3.59	0.86	14.94
71	Alcohol	No	182	100.0	143	100.0	39	100.0				
72		Yes	0	0.0	0	0.0	0	0.0				

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3 Drug Abuse	No	182	100.0	143	100.0	39	100.0					
4	Yes	0	0.0	0	0.0	0	0.0					
5	No	82	45.1	64	44.8	18	46.2					
6	Yes	100	54.9	79	55.2	21	53.8	0.811	0.93	0.49	1.74	
7	Diabetes Mellitus	10	5.5	8	5.6	2	5.1					
8	Hypertension	30	16.5	25	17.5	5	12.8					
9	Bronchial Asthma/COPD	15	8.2	13	9.1	2	5.1					
10	Heart disease	1	0.5	1	0.7	0	0.0					
11	Renal disease	1	0.5	0	0.0	1	2.6					
12	Liver disease	1	0.5	1	0.7	0	0.0					
13	SLE	0	0.0	0	0.0	0	0.0					
14	rheumatoid arthritis	6	3.3	5	3.5	1	2.6					
15	Skin allergy	18	9.9	16	11.2	2	5.1					
16	Hyperthyroidism	4	2.2	3	2.1	1	2.6					
17	Hypothyroidism	8	4.4	5	3.5	3	7.7					
18	Other autoimmune diseases	1	0.5	1	0.7	0	0.0					
19	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					
20												
21												
22												
23 Autoimmune diseases	No	163	89.6	129	90.2	34	87.2					
24	Yes	19	10.4	14	9.8	5	12.8	0.555	1.33	0.52	3.39	
25	None	13	7.1	10	7.0	3	7.7					
26	Analgesic (NSAIDs)	12	6.6	7	4.9	5	12.8					
27	Antidiabetics	6	3.3	6	4.2	0	0.0					
28	Antihypertensives	32	17.6	27	18.9	5	12.8					
29	corticosteroids	10	5.5	5	3.5	5	12.8					
30	IBD therapy	151	83.0	118	82.5	33	84.6					
31	Hormonal contraceptives	2	1.1	0	0.0	2	5.1					
32	Thyroxin	9	4.9	6	4.2	3	7.7					
33	Others	37	20.3	28	19.6	9	23.1					
34	No	141	77.5	108	75.5	33	84.6					
35	Yes	41	22.5	35	24.5	6	15.4	0.279	0.62	0.26	1.48	
36	Yes; first degree relatives	40	22.0	34	23.8	6	15.4					
37	Yes; other relatives	1	0.5	1	0.7	0	0.0					
38	Other autoimmune disease	3	1.6	3	2.1	0	0.0					
39	Physical activity											
40	not working	71	39.0	60	42.0	11	28.2	0.208				
41	On foot	19	10.4	17	11.9	2	5.1	0.503	0.60	0.13	2.70	
42	By bicycle	4	2.2	3	2.1	1	2.6	0.709	1.48	0.19	11.47	
43	Public transport or car	88	48.4	63	44.1	25	64.1	0.090	1.85	0.91	3.76	
44	not working	65	35.7	53	37.1	12	30.8	0.655				
45	minimal	43	23.6	31	21.7	12	30.8	0.249	1.60	0.72	3.57	
46	moderate	73	40.1	58	40.6	15	38.5	0.882	1.06	0.50	2.26	
47	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00		
48	not working	59	32.4	48	33.6	11	28.2	0.733				
49	minimal	90	49.5	71	49.7	19	48.7	0.838	1.08	0.51	2.27	
50	moderate	32	17.6	23	16.1	9	23.1	0.293	1.60	0.66	3.87	
51	high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00		
52	never	136	74.7	109	76.2	27	69.2	0.397				
53	yes frequent (>3 times/ week)	7	3.8	5	3.5	2	5.1	0.758	1.25	0.30	5.27	
54	yes infrequent (<3 times/ week)	39	21.4	29	20.3	10	25.6	0.176	1.66	0.80	3.45	
55	Total physical activity score	2.8 ± 2.1		2.7 ± 2.2		2.9 ± 2.0		$t= 0.40, p= 0.695$				
56								0.855	1.01	0.88	1.17	
57	Dietary habits											
58	Food source	Homemade	97	53.3	78	54.5	19	48.7	0.858			
59		Restaurant	6	3.3	5	3.5	1	2.6	0.829	0.80	0.11	5.99
60		Mixed	79	43.4	60	42.0	19	48.7	0.639	1.16	0.62	2.20
61	Junk Food, Fast Food	never	50	27.5	41	28.7	9	23.1	0.806			
62		occasionally	128	70.3	99	69.2	29	74.4	0.535	1.27	0.60	2.68
63		daily	4	2.2	3	2.1	1	2.6	0.706	1.49	0.19	11.75
64	Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	5	3.5	0	0.0	0.399			
65		once per week	79	43.4	65	45.5	14	35.9	0.898	2383.0	0.00	1.6×10 ⁶⁸
66		2-4 times per week	85	46.7	62	43.4	23	59.0	0.891	4190.1	0.00	2.9×10 ⁶⁸
67		daily	13	7.1	11	7.7	2	5.1	0.898	2475.2	0.00	1.7×10 ⁶⁸
68	Transfat (such as in cake, cookies, pies, dessert,	never	30	16.5	27	18.9	3	7.7	0.017			
69		once per week	91	50.0	75	52.4	16	41.0	0.506	1.52	0.44	5.22

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

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	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	0.982	0.99	0.46	2.16
	Yes	38	20.9	30	21.0	8	20.5				
	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
	Strictureplasty	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
AMI 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 ileitis - 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				

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	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

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3 If no response or complication (surgery)
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7 **B. Treatment of Crohn's Disease**

8 According to disease severity

9 a- Mild to moderate

10 Treatment of active symptoms (antidiarrheal, nutrition, careful observation)
11 Ileocaecal (budesonide 3-4 mg/day)
12 Clonic sulfasalazine 2-4 g/day
13
14

15 b- Moderate to severe

16 Induction therapy (oral corticosteroids 40-60 mg / day with dose tapering over 8
17 weeks + AZA 2-2.5 mg/kg)

18 1- Response (maintain on

19 AZA 1.5-2.5 mg/kg/day

20 Methotrexate 2.5 mg/kg S.C or IM

21 Refractory cases will shift to biologicals (Ustekinumab)
22
23
24

25 2- Steroid resistant

26 Give anti INF (biological)

27 +AZA (2-2.5 g/kg)

28 Maintenance like induction therapy
29
30

31 3- Steroid dependent

32 Methotrexate 25 mg/kg S.C or IM +/- biologicals
33
34

35 c- Severe/fulminate disease

36 I.V steroids (hydrocortisone 400 mg/day pr methylprednisolone 60 mg/day

37 + Anti INF
38

39 d- Perianal / fistula disease

40 Antibiotics

41 Drainage of abscess

42 + biologics (infliximab, adalimumab)
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List of Biologics used

- Infliximab (Remicade)
IV 5 mg/kg or 10 mg/kg if severe
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 severe
- 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	

1	broccoli, dried herbs & spices, fruits, vegetables)	
2	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
3		
4	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
5		
6	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
7		
8	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
9		
10	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
11		
12	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
13		
14	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
15		
16	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
17		
18	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
19		
20	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
21		
22	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.....
23		
24	39. Food preparation method	(0) No preference (1) boiling (2) grilling (3) steaming (4) frying
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26	40. Number of meals per day
27		
28	41. Snackes between meals	(0) Never (1) occasionally (2) daily; per day
29		
30	II- Clinical data	
31		
32	42. Type of IBD diagnosed	(0) Crohn's disease (1) ulcerative colitis
33		
34	43. Age at diagnosisyears old
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36	44. History of H. pylori infection	
37		
38	45. If yes mention the onset	(-1) NA (1) few weeks (2) 3-6 months (3) 6 months- 1 year (4) ≥ 1 year
39		
40	46. History of receiving H. pylori eradication therapy during the past 12 months	(0) No (1) Yes;
41		
42	47. History of complications	(0) None (1) fistula (2) stricture (3) ulcers (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others.....
43		
44	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
45		
46	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) Moltillium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others.....
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1		(00) None (01) 5-ASA "Pentasa (Mesalamine)" (02) 6-mercaptopurine	
2		"Purinethol" (03) Methotrexate "Trexall, Rasuvo, Otrexup"	
3	50. Medications used in the past to control IBD	(04) Cyclosporine "Sandimmune, Neoral" (05) Corticosteroids "Prednisone"	
4		(06) Sulfasalazine (07) Azathiopurines "Imuran" (08) Librax	
5		(09) Imodium (10) Azithromycin "Zithromax" (11) Ciprofloxacin	
6		(12) Rifabutin (13) Clarithromycin "Biaxin" (14) Flagyl	
7		(15) probiotics (16) multivitamin supplements (17) Infliximab	
8		(18)PPI (19) Moltilium (20) H2 receptor antagonist (21) antacids	
9	51. How do you describe the effectiveness of the prescribed medications	(0) no difference (1) slight improved (2) dramatic improvement	
10		(3) slightly worsened condition (4) dramatic deterioration	
11	52. How do you describe the side effects of the prescribed medications	(0) none (1) few and tolerable (2) many but tolerable	
12		(3) difficult to tolerate and interfere with daily life	

III- Examination

16	53. Baseline Body Weight kg	
17	54. Heightcm	

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	Follow Up					
	treatment	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							

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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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3
4 1 **Helicobacter pylori infection in patients with inflammatory bowel diseases:**
5 2 **a single-centre, prospective, observational study in Egypt**
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10 4 **Running title:** Inflammatory bowel disease and *Helicobacter pylori* infection
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1
2
3 **29 Abstract**
4

5 **30 Objective:** Conflicting results have been reported by numerous epidemiological studies investigating
6
7 **31** the association between *Helicobacter pylori* infection and inflammatory bowel disease (IBD). We
8
9 **32** aimed in this study to assess the possible association between *H. pylori* infection and IBD and its
10
11 **33** effects on disease progression.
12

13
14 **34 Design:** Prospective observational study

15
16 **35 Setting:** Specialized IBD care clinics at Alexandria University Student Hospital in northern Egypt,
17
18 **36** between March and June 2019.

19
20 **37 Participants:** Patients with IBD.

21
22 **38 Analysis and outcome measures:** IBD participants were screened for *H. pylori* infection and
23
24 **39** clinically evaluated at the initial visit and bimonthly for 3 months to record any potential
25
26 **40** improvement/flare of the IBD condition.
27

28
29 **41 Results:** Overall, 49.5% of patients with IBD had evidence of *H. pylori* infection. The course of IBD
30
31 **42** did not significantly differ in association with *H. pylori* infection or IBD treatment strategy. Cox
32
33 **43** regression analysis revealed that patients aged 20–35 years (OR, 95% CI= 6.20 [1.74–22.12]) and 35–
34
35 **44** 55 years (OR, 95% CI = 557.9, [17.4–17922.8]), high socioeconomic status (OR 95% CI = 2.9 [1.11–
36
37 **45** 7.8]), daily consumption of fiber-rich food (OR, 95% CI = 5.1 [1.32–19.5]), occasional consumption
38
39 **46** of snacks between meals (OR, 95% CI = 2.8 [2.5–70.5]), and eating four meals per day (OR, 95% CI
40
41 **47** = 13.3 (1.0–7.7]) predicted IBD flare. In contrast, eating fruits and vegetables was strongly protective.
42
43 **48** the probabilities of improvement of IBD symptoms after 12 weeks of follow-up were comparable,
44
45 **49** considering *H. pylori* infection status (0.793, *H. pylori*-negative vs. 0.778, *H. pylori*-positive) or IBD
46
47 **50** treatment option (0.811, conventional therapy vs. 0.750, biological therapy).
48

49
50 **51 Conclusion:** The association between IBD and *H. pylori* infection is unresolved and must be further
51
52 **52** evaluated in the context of specific environmental exposures that influence the development or relapse
53
54 **53** of IBD.
55

56

57
58 **55 Keywords:** Inflammatory Bowel Disease; Crohn's disease; Ulcerative colitis; *Helicobacter pylori*
59
60

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2
3 57 **Article summary**
4

5 58 *Strengths and limitations of this study*
6

- 7 59
- 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
11 61 between *H. pylori* infection and IBD cannot be established.
 - The need of reliable diagnostic tests for *H. pylori* infection to better estimate the disease
14 62 prevalence.
16 63
 - We report the effect of *H. pylori* infection on the response to conventional *versus* biological
18 64 treatment of IBD.
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67 Introduction

68 Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease
69 (CD), comprises chronic, disabling, and progressive disorders characterized by lifelong treatment that
70 impose a significant globally increasing threat to human health¹. Numerous economically low-
71 income countries have experienced a dramatic increase in the incidence of IBD². Improved access to
72 a more hygienic environment and the resulting decreased incidence of common childhood infections
73 may represent a contributing factor through altering susceptibility to diseases with an autoimmune
74 component, such as IBD^{3,4}. Accordingly, microbial infections during childhood may protect against
75 IBD. This rise may partially be accounted for by, the implementation of improved diagnostic methods
76 and heightened awareness of IBD.

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

81 Evidence indicates that *Helicobacter pylori* resides in the upper gastrointestinal tract of
82 approximately 50% of the world's population, among which >80% of people lack symptoms⁷. In
83 Egypt, the prevalence is approximately 80%⁸. *H. pylori* can elicit a chronic systemic inflammatory
84 response, which may trigger autoimmune reactions that may contribute to the pathogenesis of
85 autoimmune diseases. The inflammatory response of the gastric mucosa mainly involves stimulation
86 of the host's immune system in response to *H. pylori*, which induces a cell-mediated immune
87 response characterized by elevated levels of cytokines. Consequently, products of local immune
88 reactions may migrate to extra-gastric sites, which may account for the association between *H. pylori*
89 infection and extra-gastric diseases, including autoimmune disorders⁹.

90 Although numerous, diverse studies analyzed the association between *H. pylori* infection and
91 IBD^{9,10}, a causal association between *H. pylori* and IBD remains to be established; and the are
92 contradictory data related to the potential causative and the protective roles of *H. pylori* infection
93 associated with IBD¹¹⁻¹⁹.

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3 94 Assuming a potential protective role of *H. pylori* infection against IBD, *H. pylori* eradication
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5 95 treatment may influence the progression of IBD course and thus should be carefully administered,
6
7 96 considering the findings of future prospective studies ^{16 20}.

8
9 97 IBD occurs more frequently in regions with lower rates of *H. pylori* colonization. The steady
10
11 98 increase in the incidence of IBD in *H. pylori*-endemic regions may reflect the advent of initiating anti-
12
13 99 *H. pylori* therapy to treat peptic ulcers ¹³. Furthermore, meta-analyses show that the prevalence of *H.*
14
15 100 *pylori* infection is lower in patients with IBD compared with controls ^{9 10 13 19 21}. For example, long-
16
17 101 term treatment with sulphasalazine contributes to the eradication of *H. pylori* infection ²². Although
18
19 102 unconfirmed, most studies indicate a protective role for *H. pylori* infection against the development of
20
21 103 IBD ^{9 21}.

22
23
24 104 With advances in identifying the pathological mechanisms underlying IBD, new therapies
25
26 105 have been proposed, particularly those involving biological response modifiers. These include anti-
27
28 106 tumor necrosis factor antibodies (anti-TNF α), IL-1/IL-6 receptor antagonists, and an anti-CD20
29
30 107 antibody. These therapies are generally well tolerated, although they may be associated with adverse
31
32 108 effects, including increased susceptibility to infection and increased risk of malignancies ²³.

33
34
35 109 These considerations inspired us to conduct a longitudinal study to further analyze the
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37 110 association between *H. pylori* infection and the flare of IBD and to investigate possible effects of *H.*
38
39 111 *pylori* infection on the response to conventional *versus* biological treatment of IBD.

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42 43 113 **Methods**

44 45 114 **Study population and sampling**

46
47 115 We conducted a prospective observational study at Alexandria University Student Hospital
48
49 116 (AUSH) that is affiliated with Alexandria University, Egypt and serves students, faculty, and staff
50
51 117 members. AUSH comprises outpatient clinics and inpatient and emergency departments with a bed
52
53 118 capacity of 1000. We enrolled patients aged ≥ 18 years with confirmed IBD (triphasic CT abdomen,
54
55 119 endoscopy/colonoscopy, and fecal calprotectin) and commenced IBD treatment (conventional or
56
57 120 biological). Patients with irritable bowel syndrome were excluded according to the Rome III criteria
58
59 121 ²⁴.

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3 122 Clinicians on the staff of the Internal Medicine Department of the AUSH selected the
4
5 123 treatment (standard vs. biological). The prescribed treatment is the standard of care adopted by the
6
7 124 AUSH for treating patients with IBD. Details of the treatment regimens and the parameters employed
8
9 125 to select standard or biological treatment are described in File S1.

11 126 The frequency of *H. pylori* infection among patients with IBD is as high as 10.0%²¹. Using
12
13 127 an alpha error = 0.05 and a 95% confidence level, the minimum required sample size was 138
14
15 128 patients. However, we ultimately enrolled 182 patients with IBD, because we predicted that the
16
17 129 prevalence of *H. pylori* infection might be higher because of the endemicity of *H. pylori* infection in
18
19 130 Egypt⁸, and to compensate for possible dropouts during the follow-up. The sample size was
20
21 131 calculated using Epi info 7 software. Patients with confirmed IBD who agreed to participate in the
22
23 132 study were consecutively enrolled. According to their characteristics (Figure 1), the patients were
24
25 133 assigned into groups according to the prescribed treatment regimen (File S1) as follows: Group 1
26
27 134 comprised patients administered conventional IBD treatment, and Group 2 included patients
28
29 135 undergoing biological IBD treatment.

32 136 Stool samples was used to detect *H. pylori* antigen using a commercially available enzyme
33
34 137 immunoassay (EIA) kit (Foresight EIA test kit for qualitative and quantitative detection of *H. pylori*
35
36 138 in the stool; ACON Laboratories, Inc. San Diego, CA, USA). Each assigned group included patients
37
38 139 with IBD with or without *H. pylori* infection, and *H. pylori*-positive patients were shown their
39
40 140 laboratory findings. We did not commence *H. pylori* eradication therapy during the study period.
41
42 141 After a 3-month follow-up, *H. pylori*-positive patients were referred to a specialist for further
43
44 142 evaluation and case management according to the adopted standard of care.

48 143 **Patient and Public Involvement**

50 144 We informed the patients about the aims and concerns of the study and how it will add to
51
52 145 better understanding of their disease etiology and triggering factors, which was highly appreciated by
53
54 146 the patients, and motivated them to be a part of the cohort intended for the long term follow-up by the
55
56 147 clinicians. However, It was not appropriate or possible to involve patients or the public in the design,
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3 148 conduct, reporting, or dissemination plans of our research. All the laboratory and clinical data were
4
5 149 reported to the study participants, where we discussed the study findings in a simple language.
6

7 150 **Assessments**

8
9 151 Baseline evaluation included the patient's history, full clinical examination, and laboratory
10
11 152 tests. A data collection form (File S2) was used to collect baseline data as follows:
12
13 153 sociodemographics, personal habits, lifestyle, physical activity and exercise, dietary habits and
14
15 154 restrictions, family history, medical history, comorbidities, and medications. Clinical data collected
16
17 155 were from each patient during the initial visit were as follows: Disease onset, history of present
18
19 156 complaints, frequency and duration of IBD attacks, past and current IBD medications, history of
20
21 157 changing therapy, surgical intervention, and complications. History of *H. pylori* infection and
22
23 158 undergoing *H. pylori* eradication therapy during the past 12 months were recorded during each
24
25 159 follow-up visit. All patients were followed bimonthly for three months (6 visits) during IBD
26
27 160 treatment. Patients were contacted weekly via telephone and asked about the frequency and severity
28
29 161 of symptoms and if adverse effects associated with treatment occurred during the previous week.
30
31

32 162 Blood pressure (BP) and anthropometric measurements were measured according to standard
33
34 163 techniques²⁵⁻²⁷. Body mass index (BMI) was calculated according to the Quetelet's index: BMI =
35
36 164 (weight [kg]/height² [m²]). At each follow-up visit, laboratory tests were performed as follows:
37
38 165 complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting
39
40 166 blood glucose (FBG), and fecal calprotectin²⁸. Imaging techniques included triphasic CT and
41
42 167 endoscopy/colonoscopy when indicated. All patients underwent full-length colonoscopy (Pentax
43
44 168 colonoscopies). Colonoscopic biopsies acquired from the rectum and sigmoid; descending, transverse,
45
46 169 ascending colon; as well as the cecal mucosa. Histological analyses of the degree of inflammation
47
48 170 associated with CD and UC were evaluated according to the European consensus on the
49
50 171 histopathology of IBD²⁹.
51

52
53 172 The socioeconomic status of the enrolled patients with IBD was calculated and categorized as
54
55 173 high, middle, low, and very low, according to a modified social scoring system³⁰.
56
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175 **Outcomes**

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

179 **Statistical analysis**

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

200

201

202 Results

203 Patients' sociodemographics and clinical characteristics

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

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

212 Patients' baseline clinical and laboratory findings are presented in Table S2. Compared with
213 patients without *H. pylori* infection, infected patients had higher rates of abdominal cramps (91.1% vs.
214 84.8%), abdominal pain (85.6% vs. 81.5%), bloating/indigestion (98.9% vs. 95.7%), flatulence
215 (100.0% vs. 96.7%), diarrhea (98.9% vs. 96.7%), rectal bleeding (73.3% vs. 65.2%), fever (33.3% vs.
216 26.1%), chills (10.0% vs. 4.3%), infection (23.3% vs. 14.1%), fatigue/lack of energy (88.9% vs.
217 68.5%), sick leave/absenteeism (8.9% vs. 6.5%), and higher mean CRP (33.0 ± 23.0 vs. 28.2 ± 23.9)
218 and ESR (34.6 ± 13.2 vs. 33.6 ± 14.1) levels. However, the differences were not statistically
219 significant. GIT endoscopy and colonoscopy revealed features of CD and UC, indicated by superficial
220 ulcerations and mild infiltration.

221 *H. pylori* infection among patients with IBD

222 We detected *H. pylori* infection in 49.5% of patients, including those with UD (48, 50.0%)
223 and CD (42, 48.8%) (OR, 95% CI = 1.05, 0.59–1.88), although 85.6% reported undergoing *H. pylori*
224 eradication therapy during the past 12 months. The infection rate was highest (82.2%) among the age
225 group 20 to <35 years (Table 1). Regression analysis revealed that conventional treatment of IBD
226 (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
227 35–55 years (OR, 95% CI = 11.1 [1.18–104.64]), and mixed food source (OR, 95% CI = 3.12 [1.60–
228 6.06]) predicted *H. pylori* infection ($p < 0.05$) (Table 2).

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

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

238 **Factors associated with improvement in IBD symptoms**

239 Cox regression analysis revealed that subjects aged 20–35 years (OR, 95% CI= 6.20 [1.74–
240 22.12]) and 35–55 years (OR, 95% CI = 557.9, [17.4–17922.8]), high socioeconomic status (OR, 95%
241 CI = 2.9 [1.11–7.8]), daily consumption of fiber-rich food (OR, 95% CI = 5.1 [1.32–19.5]), occasional
242 consumption of snacks between meals (OR, 95% CI = 2.8 [2.5–70.5]), and eating four meals per day
243 (OR, 95% CI = 13.3 (1.0–7.7)) were significantly associated with IBD flare ($p < 0.05$). In contrast,
244 eating fruits and vegetables protected against IBD flare (Tables 4 and Table S5).

245 **Probability of improvement of IBD symptoms in relation to *H. pylori* infection and IBD** 246 **treatment strategy**

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

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

257 Discussion

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

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

270 *H. pylori* was detected in approximately 50% of the patients, which is low compared with the
271 prevalence among the population of Egypt, where disease is endemic³³⁻³⁶. These findings support the
272 results of studies showing that lower rates *H. pylori* infection of patients with IBD, suggesting an
273 association between *H. pylori* and IBD^{9 21}. The rate *H. pylori* infection is significantly higher among
274 patients with IBD who undergo conventional treatment, which conflicts with studies suggesting that
275 5-aminosalicylates or sulphasalazine interfere with the adhesion of *H. pylori* to the mucosa and block
276 its proliferation^{22 37-39}. For example, the results of multiple studies do not support the conclusion that
277 treatment with sulfasalazine or other drugs such as 5-aminosalicylic acid (5-ASA), thiopurines,
278 steroids, and antibiotics influence the colonization rate of *H. pylori*^{13 40-42}. It is worth noting that
279 although the treatment of IBD patients with anti-TNF- α agents, immunosuppressant and/ or
280 corticosteroid increases the risk of infections, there is no direct evidence that novel therapeutic
281 strategies such as anti-tumor necrosis factor alpha (TNF- α) and immunosuppressants result in

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2
3 282 exacerbating or influence the prevalence of *H. pylori* infection Similar findings were reported by a
4
5 283 study of novel therapeutic strategies such as anti-tumor necrosis factor alpha (TNF- α) treatment
6
7 284 {Singh, 2011 #145; Triantafyllidis, 2014 #29; Zhong, 2021 #144}.

9 285 Here we show that the majority of *H. pylori*-positive patients with IBD admitted undergoing
10
11 286 *H. pylori* eradication therapy during the previous 12 months, which raises questions about the efficacy
12
13 287 of eradication therapy or reveals reinfection among this group of patients. Notably, most studies do not
14
15 288 report subjects' history of treatment of *H. pylori* infection¹³. It is therefore possible that such patients
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17 289 with IBD were treated for *H. pylori* infection before enrollment, culminating in an incorrectly low rate
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19 290 of *H. pylori* infection.

21
22 291 Accumulating evidence suggests that *H. pylori*, through its ability to regulate the immune
23
24 292 response, protects human from diseases with an autoimmune component, including IBD⁴³. The
25
26 293 results of investigations designed to confirm this possibility are controversial. For example, the
27
28 294 heterogeneity among studies accounted for by methods used to diagnose IBD and *H. pylori* infection,
29
30 295 study location, study population, and the possibility of publication bias limit the validity of this
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32 296 conclusion and raise questions concerning the robustness of their findings.

33
34 297 Here we conducted a prospective study to extended previous work through investigations of
35
36 298 the association between *H. pylori* infection and IBD. A potential avenue for extending our study
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38 299 involved broadening the inclusion criteria to gain further insight into local variations of the protective
39
40 300 effects of *H. pylori* against IBD. In contrast to previous studies, we added subgroup analysis of *H.*
41
42 301 *pylori* infection and the type of IBD treatment. However, we did not detect a significant relationship
43
44 302 between the two conditions. For example, disease course was similar among all patients with IBD
45
46 303 regardless of their *H. pylori* infection status or conventional or biological treatment. Moreover, the
47
48 304 extent, and severity of IBD increased with a decrease in *H. pylori* infection. We were intrigued by our
49
50 305 findings that that the proportion of patients administered conventional therapy who recovered from
51
52 306 IBD was higher than those administered biological therapy. This may be explained by the higher rate
53
54 307 of *H. pylori* infection among patients with IBD administered conventional therapy or that patients
55
56 308 administered biological therapy were refractory to previous conventional therapy and therefore
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58 309 suffered from increased disease severity.

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3 310 Evidence indicates that IBD is induced through complex interactions between environmental
4
5 311 and genetic factors. The growing burden of IBD may serve as a proxy for the hygiene hypothesis and
6
7 312 improvements in the sanitation of living conditions, lifestyle and dietary changes, more frequent
8
9 313 antibiotic use, enhanced diagnostic methods, and heightened awareness of IBD^{1 44 45}. Accordingly, we
10
11 314 further investigated the role of host and environmental cofactors reported to ameliorate or incite
12
13 315 factors for IBD flare (e.g., diet, smoking, physical activity, breastfeeding, socioeconomic status,
14
15 316 education, occupation, urban versus rural lifestyle, and medication¹). In this context, we were guided
16
17 317 by existing studies that recognized differences in potential risk factors or features unique to certain
18
19 318 populations, such as the Mediterranean diet. Indeed, dietary factors play a crucial role in disease
20
21 319 initiation or relapse⁴⁶, although certain diets such as the Mediterranean diet are purported to protect
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23 320 against IBD⁴⁷⁻⁴⁹.

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25
26 321 The plant-based, semi-vegetarian Mediterranean diet alleviates symptoms of IBD and
27
28 322 maintains patients in remission, potentially through reducing inflammation and improving the
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30 323 microbiota^{50 51}. In our present cohort, *H. pylori*-negative patients with IBD and those experiencing
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32 324 less flare had a more favorable overall dietary habit score. Consistent with Kakodkar's
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34 325 recommendations⁵⁰, which encourage the consumption of all vegetables and fruits in an IBD diet, we
35
36 326 observed a strong protective role on IBD flare of daily and 2–3-times weekly consumption of
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38 327 vegetables and fruits. Moreover, a recent meta-analysis shows that the beneficial effect of *H. pylori*
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40 328 experienced by Mediterranean populations with IBD is lower compared with residents of East Asian
41
42 329 and European regions¹⁹. Nevertheless, the analysis did not explicitly incorporate dietary information
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44 330 or study the putative beneficial effect of diet as a confounder. Moreover, this positive effect may be
45
46 331 attributed to the relative abundance of CagA *H. pylori* in these populations, a strain that produces
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48 332 specific constituents that modulate host immune defenses⁵².

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50
51 333 Fiber may serve as an anti-inflammatory component of IBD treatment, although a converse
52
53 334 effect can occur¹. Our Cox regression analysis revealed that daily consumption of foods rich in
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55 335 insoluble fibers, such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower,
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57 336 broccoli, dried herbs, and spices, significantly increased the risk of IBD flare, particularly in patients
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59 337 who consume four daily meals interspersed with occasional snacks.

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3 338 In agreement with Gentschew et al.,⁵³ trans-fat consumption was associated with a higher
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5 339 probability of IBD flare, although this was not a variable included in our final model. Although our
6
7 340 findings suggest a role for diet in IBD flare, its effect is questionable because of the limitations of
8
9 341 recall bias and multifactorial exposures. Moreover, patients with IBD may alter their dietary habits in
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11 342 response to symptoms that vary with disease activity, which requires further direct research into the
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13 343 role of diet in IBD.

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15 344 Variations in the protective effects of *H. pylori* on IBD may be explained by socioeconomic
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17 345 factors. For example, here we show that patients with IBD with higher socioeconomic status and
18
19 346 mainly urban residents had a higher chance of disease flares. Moreover, the frequency of *H. pylori*
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21 347 infection did not significantly vary in association with socioeconomic status. These findings support
22
23 348 the argument that factors associated with an urban lifestyle and industrialization influence risk of IBD.
24
25 349 Furthermore, the rate of gastric colonization by *H. pylori* was significantly higher in adults aged >20
26
27 350 years, although there was no significant difference in the average age of IBD onset between *H. pylori*-
28
29 351 positive and -negative groups. This age group experienced a higher frequency of disease flares. These
30
31 352 findings may be explained by patients' histories of comorbidities or lifestyle, which affect the
32
33 353 occurrence of IBD. Demographic variables other than age did not exert detectable effects.

34
35 354 The findings of this study must be interpreted in view of its limitations. First, we did not
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37 355 test gastric biopsies for *H. pylori*, which may have decreased the disease prevalence rate. However,
38
39 356 this would incur the burdens of an ethically questionable invasive procedure. A urea breath test may
40
41 357 serve as a better alternative, although we did not have access to this test in our centers. Second, the
42
43 358 small sample size was a major limitation and may have influenced the estimation of effect size. Third,
44
45 359 the trend of decreased *H. pylori* infection in patients administered biological therapy coincided with
46
47 360 increased severity of IBD, which should be investigated by a larger, statistically robust randomized
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49 361 controlled trial. Moreover, our results merit reassessment in a cohort of patients from a background
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51 362 population with a low prevalence of *H. pylori* that includes detailed information about eradication
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53 363 treatment and administration of other antibiotics. Fourth, a causal relationship between *H. pylori*
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55 364 infection and IBD cannot be established through an uncontrolled study (control group without IBD),
56
57 365 and further large scale prospective clinical trials are required. Thus, studies are warranted to

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2
3 366 investigate the effects of eradication of *H. pylori* on the development of IBD combined with analyses
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5 367 of environmental exposures, hygiene diet, physical activity, and intestinal microbiota as significant
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7 368 confounders. An ideal study would be prospective and initiated when IBD is diagnosed.
8

9 369 **Conclusions**

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11 370 Together, the findings of our present analysis of the association between IBD and *H. pylori*
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13 371 infection are inconclusive, and further studies are required. Thus, much remains to be learned about
14
15 372 the causes of IBD and whether specific environmental exposures influence the development of disease
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17 373 and its course.
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20 21 375 **Ethical considerations**

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23
24 376 The study was approved by the institutional review board and the ethics committee of the
25
26 377 High Institute of Public Health affiliated with Alexandria University, Egypt [Ref no. 603 - 2019]. The
27
28 378 study was conducted in accordance with the international ethical guidelines and that of the
29
30 379 Declaration of Helsinki. Informed written consent was obtained from each participant after explaining
31
32 380 the aim and concerns of the study. The datasheets were coded by number to ensure anonymity and
33
34 381 confidentiality of the participants' data.
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36

37 382

38 39 383 **Conflict of Interest**

40
41 384 All authors declare no conflict of interest.
42
43

44 45 385 **Data availability statement**

46 386 All data are fully available without restriction by the corresponding author at
47
48 387 ekram.wassim@alexu.edu.eg
49

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52

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56
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59

60 392

1
2
3 393 **Author contribution**
4

5 394 EWAW: Conceptualization, developed the theoretical framework and study design, took the lead for
6
7 395 overall direction and planning of the study implementation, data curation, statistical analysis and
8
9 396 interpretation of data, major contribution to writing, revised and approved final version of the
10
11 397 manuscript
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14 398

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16 399 EIY: Study implementation and recruitment of the study participants, data collection, clinical
17
18 400 evaluation and follow up, analysis and interpretation of data, contributed to the writing of the
19
20 401 manuscript, revised and approved final version of the of the manuscript.
21

22 402

23
24 403 EMH: Supervised the study implementation and data collection, facilitated the recruitment of the
25
26 404 study participants, clinical evaluation and follow up, data curation, contributed to the writing of the
27
28 405 manuscript, revised and approved final version of the manuscript.
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3 542 **Figure legends**
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6 543 Figure 1: Patients' dispositions
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9 544 Figure 2: The equality of recovery (remission of IBD symptoms) during the follow-up periods
10 545 associated with *H. pylori* infection status and IBD treatment strategies.
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13 546 Figure S1: Patients' clinical and laboratory findings during follow-up periods associated with *H.*
14 547 *pylori* infection status and the IBD treatment strategy.
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For peer review only

List of Tables

Table 1: Characteristic of the study population

		IBD patients		<i>H. pylori</i> infection in IBD patients				<i>p</i> ~
		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	
	Few weeks ago	7	3.8	0	0	7	7.8	
Onset of <i>H. pylori</i> infection	3 – 6 months	10	5.5	0	0	10	11.1	<0.001
	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 <i>H. pylori</i> 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	<i>t</i> =1.3, <i>p</i> = 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	
Residence	Mean ± SD	21.6 ± 6.4	21.4 ± 6.3	22.0 ± 6.5	<i>t</i> = -0.583, <i>p</i> = 0.560			
	Rural	88	48.4	51	55.4	37	41.1	0.053
Education	Urban	94	51.6	41	44.6	53	58.9	0.096
	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	
Working status	Preparatory	13	7.1	9	9.8	4	4.4	0.104
	Secondary	44	24.2	24	26.1	20	22.2	
	University education	96	52.7	43	46.7	53	58.9	
Occupation	No	88	48.4	39	42.4	49	54.4	0.012
	Yes	94	51.6	53	57.6	41	45.6	
	Unemployed	37	20.3	21	22.8	16	17.8	
	Student	45	24.7	16	17.4	29	32.2	
Marital status	Clerical	2	1.1	2	2.2	0	0	0.370
	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	
Socioeconomic standard	Single	73	40.1	37	40.2	36	40	0.206
	Married	106	58.2	55	59.8	51	56.7	
	Widowed	2	1.1	0	0	2	2.2	
Consanguinity	Divorced	1	0.5	0	0	1	1.1	0.309
	High	58	31.9	24	26.1	34	37.8	
	Middle	52	28.6	30	32.6	22	24.4	
History of being breastfed	Low	72	39.6	38	41.3	34	37.8	0.716
	No	144	79.1	70	76.1	74	82.2	
	Yes	38	20.9	22	23.9	16	17.8	
	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 dyslipidemia, hemorrhoids, scleritis, HCV, anemia, fatty liver, steatosis, psoriasis, peripheral neuropathy, chronic cholecystitis)

Table 1 continued

		IBD patients		<i>H. pylori</i> infection in IBD patients				<i>p</i> ~
		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	
	None	13	7.1	12	13	1	1.1	
Medications	Analgesic (NSAIDs)	12	6.6	3	3.3	9	10	0.002
	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 significant 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	<i>H. pylori</i> infection	Follow-up period (3 Months)						Repeated Measures ANOVA																	
		Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test				Within Subject Effects				Between Subject Effects								
		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 x S	1.156	0.322	0.038	0.448	T x 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 x S	0.708	0.644	0.024	0.276	T x 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 x S	1.48	0.187	0.048	0.565	T x 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 x S	0.157	0.925	0.003	0.078	T x 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 x S	3.1	0.007	0.096	0.91	T x 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 x S	1.05	0.394	0.035	0.409	T x 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 x S	1.02	0.415	0.034	0.396	T x 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 x S	0.901	0.496	0.031	0.35	T x 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 x S	2.08	0.058	0.067	0.740	T x 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 x S	2.67	0.017	0.084	0.856	T x 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 x S	1.28	0.270	0.042	0.493	T x S	1.201	0.305	0.007	0.286	0.593						

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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 \times S; time versus state of *H. pylori* infection

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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	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 significant 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

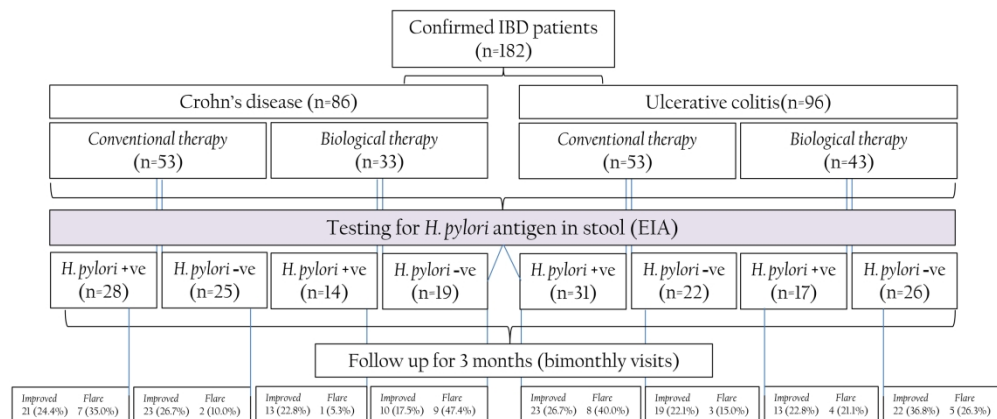
Variable	Group	Case summary	No of Events n(%)	Censored n(%)	Event Time (bimonthly visit)	No. of Events (recovery ^a)	No. of relapse	No. at Risk (to recovery ^a)	Probability of recovering ^a	Test of equality of recovery ^a		
										Log Rank (Mantel- Cox)	Breslow (Generalized Wilcoxon)	Tarone-Ware
										<i>p</i> value		
<i>H. pylori</i> 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				
Treatment of IBD	Conventional	n=106	86 (81.1)	20 (18.9)	6	38	4	20	0.778			
					1	0	0	106	0.000			
					2	0	3	106	0.000			
					3	2	1	104	0.019			
					4	21	5	83	0.217			
	5	16	6	67	0.368							
	Biological	n=76	57 (75.0)	19 (25.0)	6	47	5	20	0.811			
					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 significant at <0.05

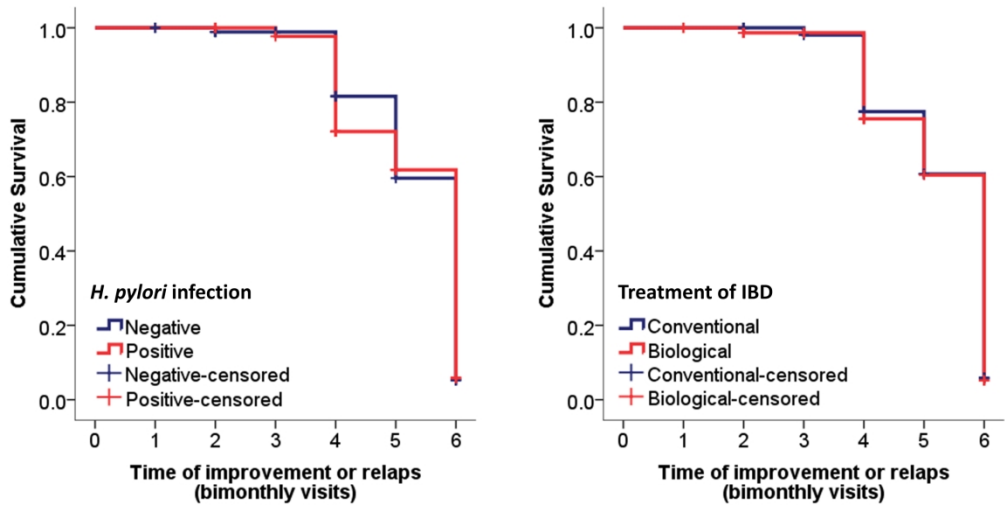
a: recovery reflects a state of remission of IBD condition



Patients' dispositions

266x114mm (300 x 300 DPI)

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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

257x129mm (300 x 300 DPI)

Supplementary Tables for online display

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

		IBD patients		<i>H. pylori</i> infection in IBD patients			<i>p</i> ~	
		Total (n=182)		Negative (n=92)		Positive (n=90)		
		No.	%	No.	%	No.		%
Physical activity and physical exercise								
	not working	71	39.0	36	39.1	35	38.9	0.173
Transportation	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	
Activity outside work	high	1	0.5	0	0.0	1	1.1	0.451
	not working	59	32.4	27	29.3	32	35.6	
	minimal	90	49.5	50	54.3	40	44.4	
Regular exercise	moderate	32	17.6	15	16.3	17	18.9	0.023
	high	1	0.5	0	0.0	1	1.1	
	never	136	74.7	76	82.6	60	66.7	
Total physical activity score	yes frequent (>3 times/ week)	7	3.8	1	1.1	6	6.7	0.023
	yes infrequent (<3 times/ week)	39	21.4	15	16.3	24	26.7	
		2.8 ± 2.1		3.01 ± 2.2		2.5 ± 2.1		<i>t</i> =1.6, <i>p</i> = 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	
Trans fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	daily	13	7.1	1	1.1	12	13.3	<0.001
	never	30	16.5	9	9.8	21	23.3	
	once per week	91	50.0	61	66.3	30	33.3	
Food rich in insoluble fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs & spices)	2-4 times per week	60	33.0	21	22.8	39	43.3	<0.001
	daily	1	0.5	1	1.1	0	0.0	
	never	0	0.0	0	0.0	0	0.0	
Salty Food (pickled, salty cheese, salted fish, dokka, ...)	once per week	39	21.4	28	30.4	11	12.2	<0.001
	2-4 times per week	88	48.4	49	53.3	39	43.3	
	never	55	30.2	15	16.3	40	44.4	
	once per week	27	14.8	16	17.4	11	12.2	<0.001
	2-4 times per week	96	52.7	61	66.3	35	38.9	
	never	54	29.7	12	13.0	42	46.7	

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

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

17 *H. pylori*; *Helicobacter pylori*

18 IBD; inflammatory bowel disease

19 ~ *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		<i>H. pylori</i> infection in IBD patients				<i>p</i> ~
	Total (n=182)		Negative (n=92)		Positive (n=90)		
	No.	%	No.	%	No.	%	
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	<i>t</i> = -0.5 <i>p</i> = 0.616			
	ESR (males <15 mm/h, females <20 mm/hr)	34.1 ± 13.6	33.6 ± 14.1	34.6 ± 13.2	<i>t</i> = -0.49 <i>p</i> = 0.628			
	CRP (< 10 mg/L)	30.6 ± 23.5	28.2 ± 23.9	33.0 ± 23.0	<i>t</i> = -1.4 <i>p</i> = 0.162			
	FBG (70-100 mg/dl)	95.5 ± 11.4	96.1 ± 11.6	94.9 ± 11.1	<i>t</i> = 0.7 <i>p</i> = 0.504			
	Fecal Calprotectin (<50 µg/g stool)	516.2 ± 210.0	517.4 ± 214.4	515.0 ± 206.7	<i>t</i> = -1.8 <i>p</i> = 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	<i>t</i> = 0.8 <i>p</i> = 0.940			
Laboratory findings	WBCs (4-11 k/ul)	6618.7 ± 1527.9	6420.8 ± 1530.5	6821.1 ± 1506.9	<i>t</i> = -0.8 <i>p</i> = 0.419			
	Platelets (150-450 k/ul)	300.6 ± 64.5	304.8 ± 61.7	296.2 ± 67.4	<i>t</i> = 0.9 <i>p</i> = 0.372			
	Body weight	67.9 ± 11.9	67.6 ± 12.2	68.3 ± 11.7	<i>t</i> = -0.4 <i>p</i> = 0.693			
	Pulse (60-100 beats per minute)	80.6 ± 5.3	80.5 ± 5.6	80.8 ± 5.0	<i>t</i> = -0.3 <i>p</i> = 0.745			
	Pulse pressure (40 and 60 mmHg)	41.3 ± 6.2	41.5 ± 6.8	41.0 ± 5.6	<i>t</i> = 0.6 <i>p</i> = 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

1								
2								
3		GERD	75	41.2	35	38.0	40	44.4
4		Antral gastritis	33	18.1	15	16.3	18	20.0
5		Pangastritis	56	30.8	32	34.8	24	26.7
6		Pre-pyloric erosions	17	9.3	10	10.9	7	7.8
7		Superficial duodenal bulb ulcers	28	15.4	15	16.3	13	14.4
8		Incompetent cardia	10	5.5	7	7.6	3	3.3
9		Gastrodudonitis	21	11.5	9	9.8	12	13.3
10		Antral erosions	17	9.3	9	9.8	8	8.9
11		Duodenal inflammatory polyp	7	3.8	4	4.3	3	3.3
12		Erosive gastritis	1	0.5	0	0.0	1	1.1
13		Peptic ulcer	1	0.5	1	1.1	0	0.0
14		Erosive gastrodudonitis	4	2.2	2	2.2	2	2.2
15		Chronic active colitis	63	34.6	34	37.0	29	32.2
16		Chronic active ileocolitis-						
17		Ulcerative Colitis	25	13.7	11	12.0	14	15.6
18		Chronic active colitis with						
19		lymphoid hyperplasia	5	2.7	1	1.1	4	4.4
20		Chronic active colitis with						
21		multiple superficial ulcers	3	1.6	0	0.0	3	3.3
22		Internal piles	4	2.2	1	1.1	3	3.3
23		ulcerative proctitis	15	8.2	3	3.3	12	13.3
24		Chronic active ulcerative						
25		pancolitis	1	0.5	1	1.1	0	0.0
26	Colonoscopy	multiple superficial aphthoid						
27		ulcers - mild ileitis of Crohn's	35	19.2	20	21.7	15	16.7
28		disease						0.087
29		Ileocolitis - Crohn's disease	31	17.0	14	15.2	17	18.9
30		Rectal Crohn's	10	5.5	5	5.4	5	5.6
31		Multiple superficial colonic						
32		ulcers and skip lesions with						
33		eosinophilic infiltration, terminal	13	7.1	9	9.8	4	4.4
34		ileitis - Crohn's disease						
35		Chronic active colitis with						
36		lymphoid hyperplasia - Crohn's	2	1.1	0	0.0	2	2.2
37		disease						
38		perianal fistula	1	0.5	1	1.1	0	0.0
39		None	137	75.3	77	83.7	60	66.7
40		Fistula	4	2.2	2	2.2	2	2.2
41		Stricture	4	2.2	1	1.1	3	3.3
42	History of	Ulcer	26	14.3	10	10.9	16	17.8
43	complications	Intestinal perforation	0	0.0	0	0.0	0	0.0
44		GIT cancer	2	1.1	1	1.1	1	1.1
45		Abscess formation	5	2.7	0	0.0	5	5.6
46								

	Others	5	2.7	2	2.2	3	3.3	
	None	171	94.0	91	98.9	80	88.9	
	Strictureplasty	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

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

Parameter	<i>H. Pylori</i> infection	Follow-up period (3 Months)						Repeated Measures ANOVA														
		Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test				Within Subject Effects					Between Subject Effects				
		Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Wilks' Lambda	F ^a	p	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T \times 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 \pm 12.6	29.8 \pm 9.0	26.6 \pm 8.4	23.2 \pm 8.1	20.5 \pm 7.3	17.7 \pm 7.1	7.9	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 \pm 13.7	28.8 \pm 10.7	24.4 \pm 8.8	20.2 \pm 7.8	18.8 \pm 7.2	15.3 \pm 5.4	5.0	T \times S	0.846	0.540	0.069	0.312	T \times S	0.37	0.71	0.005	0.009	0.927			
CRP	Positive	31.2 \pm 18.6	25.4 \pm 14.7	22.0 \pm 12.5	18.3 \pm 8.7	14.4 \pm 7.5	13.8 \pm 9.3	7.3	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 \pm 26.2	25.4 \pm 21.8	20.6 \pm 16.6	17.1 \pm 14.0	13.8 \pm 10.1	11.4 \pm 7.5	6.9	T \times S	0.893	0.505	0.072	0.330	T \times S	0.420	0.581	0.006	0.35	0.556			
FBG	Positive	93.1 \pm 9.5	91.2 \pm 11.6	91.6 \pm 9.6	94.5 \pm 13.8	93.4 \pm 11.8	93.4 \pm 10.9	6.9	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 \pm 8.8	92.3 \pm 6.8	92.1 \pm 7.7	93.6 \pm 8.6	93.6 \pm 8.7	92.5 \pm 5.9	6.9	T \times S	0.385	0.886	0.032	0.153	T \times S	0.42	0.832	0.006	0.289	0.593			
Calprotectin	Positive	573.8 \pm 218.6	380.7 \pm 190.6	171.3 \pm 96.1	75.2 \pm 30.8	30.8	T	113.0	<0.001	0.825	1.000	1.000	T	250.0	<0.001	0.772	347.5	<0.001	1.39	0.242	0.018	
	Negative	508.6 \pm 216.3	317.6 \pm 153.5	168.3 \pm 84.2	84.2	T \times S	1.350	0.266	0.053	0.344	T \times S	2.31	0.11	0.030	2.87	0.037						
Hb	Positive	10.6 \pm 1.3	10.7 \pm 1.3	10.9 \pm 1.3	11.3 \pm 1.1	11.5 \pm 0.9	11.6 \pm 1.0	0.9	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 \pm 1.1	10.7 \pm 1.2	10.9 \pm 1.02	110.1 \pm 10.1	11.4 \pm 1.1	11.8 \pm 0.84	0.84	T \times S	2.440	0.034	0.175	0.791	T \times S	1.06	0.063	0.032	3.89	0.052			
WBCs	Positive	6385.5 \pm 1029.0	6704.8 \pm 1023.4	6512.9 \pm 1013.5	6298.4 \pm 1046.3	6582.3 \pm 1075.4	6438.1 \pm 1255.8	6125.5 \pm 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 \pm 1479.9	6153.3 \pm 1263.2	6062.2 \pm 1102.1	5887.8 \pm 966.4	6171.1 \pm 1030.4	6038.7 \pm 1093.6	5999.6 \pm 1052.4	T \times S	1.324	0.258	0.103	0.486	T \times S	1.03	0.399	0.014	3.44	0.068			
Platelets	Positive	272.6 \pm 51.0	286.9 \pm 44.8	276.3 \pm 40.5	279.1 \pm 35.1	276.4 \pm 31.5	277.1 \pm 30.3	282.9 \pm 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 \pm 69.6	291.8 \pm 50.0	292.5 \pm 41.8	293.1 \pm 42.9	291.9 \pm 41.2	288.2 \pm 40.7	292.5 \pm 44.1	T \times S	0.753	0.610	0.061	0.278	T \times S	1.18	0.317	0.016	0.527	0.47			
Total symptom score	Positive	21.6 \pm 2.3	21.5 \pm 2.6	16.4 \pm 3.6	7.2 \pm 3.0	3.7 \pm 3.6	3.1 \pm 2.4	0.1 \pm 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 \pm 3.5	20.2 \pm 4.1	13.4 \pm 5.6	5.9 \pm 3.2	3.6 \pm 3.4	3.3 \pm 3.1	0.8 \pm 1.9	T \times S	2.040	0.072	0.153	0.702	T \times S	2.85	0.052	0.038	7.61	0.094			
Body weight	Positive	63.9 \pm 9.8	64.1 \pm 10.1	65.0 \pm 10.0	65.5 \pm 10.0	65.8 \pm 10.0	66.0 \pm 10.0	66.1 \pm 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 \pm 11.0	64.9 \pm 10.9	65.3 \pm 10.8	65.6 \pm 10.7	66.0 \pm 10.6	66.6 \pm 10.5	67.1 \pm 10.4	T \times S	2.280	0.046	0.166	0.759	T \times S	1.40	0.252	0.018	11.1	0.001			
Pulse	Positive	80.8 \pm 2.5	79.7 \pm 2.5	76.8 \pm 4.5	76.0 \pm 4.7	77.7 \pm 4.5	77.5 \pm 4.4	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
	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
Pulse pressure	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

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

Parameter	<i>H. pylori</i> infection	Follow-up period (3 Months)							Repeated Measures ANOVA															
		Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test				Within Subject Effects					Between Subject Effects						
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Wilks' Lambda	F [†]	p	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T x S)	F [‡]	p	Effect Size (Partial Eta Squared) [§]	Linearity (F value) ^b	p	F	p	Effect Size (Partial Eta Squared) [§]		
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 x S	1.18	0.325	0.067	0.444	T x 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 x S	0.518	0.794	0.030	0.201	T x 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 ± 9.1	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 x S	2.17	0.053	0.116	0.746	T x 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	150.1 ± 73.7	74.1 ± 28.8	74.1 ± 28.8	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	175.6 ± 92.5	86.3 ± 80.5	86.3 ± 80.5	86.3 ± 80.5	T x S	1.19	0.317	0.034	0.312	T x 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 x S	2.19	0.050	0.117	0.753	T x 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 x S	1.67	0.137	0.092	0.612	T x 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 x S	1.74	0.120	0.095	0.633	T x 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 x S	2.93	0.011	0.159	0.880	T x 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	71.1 ± 16.1	71.7 ± 12.9	72.4 ± 13.1	73.3 ± 12.8	T x S	2.32	0.039	0.123	0.779	T x 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 x S	1.50	0.189	0.083	0.555	T x S	1.53	0.184	0.015	0.111	0.739					

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Pulse pressure	Positive	41.7 ±	41.2 ±	40.2 ±	40.8 ±	40.3 ±	39.7 ±	41.9 ±	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 ±	40.9 ±	43.8 ±	42.3 ±	42.1 ±	42.8 ±	42.1 ±										T × S	1.026			

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

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2													
3		Diabetes Mellitus	10	5.5	8	5.6	2	5.1					
4		Hypertension	30	16.5	25	17.5	5	12.8					
5		Bronchial Asthma/COPD	15	8.2	13	9.1	2	5.1					
6		Heart disease	1	0.5	1	0.7	0	0.0					
7		Renal disease	1	0.5	0	0.0	1	2.6					
8		Liver disease	1	0.5	1	0.7	0	0.0					
9		SLE	0	0.0	0	0.0	0	0.0					
10		rheumatoid arthritis	6	3.3	5	3.5	1	2.6					
11		Skin allergy	18	9.9	16	11.2	2	5.1					
12		Hyperthyroidism	4	2.2	3	2.1	1	2.6					
13		Hypothyroidism	8	4.4	5	3.5	3	7.7					
14		Other autoimmune diseases	1	0.5	1	0.7	0	0.0					
15		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					
16		No	163	89.6	129	90.2	34	87.2					
17	Autoimmune diseases	Yes	19	10.4	14	9.8	5	12.8	0.555	1.33	0.52	3.39	
18		None	13	7.1	10	7.0	3	7.7					
19		Analgesic (NSAIDs)	12	6.6	7	4.9	5	12.8					
20		Antidiabetics	6	3.3	6	4.2	0	0.0					
21		Antihypertensives	32	17.6	27	18.9	5	12.8					
22	Medications	corticosteroids	10	5.5	5	3.5	5	12.8					
23		IBD therapy	151	83.0	118	82.5	33	84.6					
24		Hormonal contraceptives	2	1.1	0	0.0	2	5.1					
25		Thyroxin	9	4.9	6	4.2	3	7.7					
26		Others	37	20.3	28	19.6	9	23.1					
27		No	141	77.5	108	75.5	33	84.6					
28	Family history of similar condition	Yes	41	22.5	35	24.5	6	15.4	0.279	0.62	0.26	1.48	
29		Yes; first degree relatives	40	22.0	34	23.8	6	15.4					
30		Yes; other relatives	1	0.5	1	0.7	0	0.0					
31		Other autoimmune disease	3	1.6	3	2.1	0	0.0					
32													
33													
34	Transportation	not working	71	39.0	60	42.0	11	28.2	0.208				
35		On foot	19	10.4	17	11.9	2	5.1	0.503	0.60	0.13	2.70	
36		By bicycle	4	2.2	3	2.1	1	2.6	0.709	1.48	0.19	11.47	
37		Public transport or car	88	48.4	63	44.1	25	64.1	0.090	1.85	0.91	3.76	
38	Working activity	not working	65	35.7	53	37.1	12	30.8	0.655				
39		minimal	43	23.6	31	21.7	12	30.8	0.249	1.60	0.72	3.57	
40		moderate	73	40.1	58	40.6	15	38.5	0.882	1.06	0.50	2.26	
41		high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00		
42	Activity outside work	not working	59	32.4	48	33.6	11	28.2	0.733				
43		minimal	90	49.5	71	49.7	19	48.7	0.838	1.08	0.51	2.27	
44		moderate	32	17.6	23	16.1	9	23.1	0.293	1.60	0.66	3.87	
45		high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00		
46	Regular exercise	never	136	74.7	109	76.2	27	69.2	0.397				
47		yes frequent (>3 times/ week)	7	3.8	5	3.5	2	5.1	0.758	1.25	0.30	5.27	
48		yes infrequent (<3 times/ week)	39	21.4	29	20.3	10	25.6	0.176	1.66	0.80	3.45	
49	Total physical activity score		2.8 ± 2.1		2.7 ± 2.2		2.9 ± 2.0		0.855	t= 0.40, p= 0.695	1.01	0.88	1.17
50	Dietary habits												
51	Food source	Homemade	97	53.3	78	54.5	19	48.7	0.858				
52		Restaurant	6	3.3	5	3.5	1	2.6	0.829	0.80	0.11	5.99	
53		Mixed	79	43.4	60	42.0	19	48.7	0.639	1.16	0.62	2.20	
54	Junk Food, Fast Food	never	50	27.5	41	28.7	9	23.1	0.806				
55		occasionally	128	70.3	99	69.2	29	74.4	0.535	1.27	0.60	2.68	
56		daily	4	2.2	3	2.1	1	2.6	0.706	1.49	0.19	11.75	
57	Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	5	3.5	0	0.0	0.399				
58		once per week	79	43.4	65	45.5	14	35.9	0.898	2383.0	0.00	1.6×10 ⁶⁸	
59		2-4 times per week	85	46.7	62	43.4	23	59.0	0.891	4190.1	0.00	2.9×10 ⁶⁸	
60		daily	13	7.1	11	7.7	2	5.1	0.898	2475.2	0.00	1.7×10 ⁶⁸	
61	Transfat (such as in cake, cookies, pies, dessert, cream, mayonnaise,	never	30	16.5	27	18.9	3	7.7	0.017				
62		once per week	91	50.0	75	52.4	16	41.0	0.506	1.52	0.44	5.22	
63		2-4 times per week	60	33.0	41	28.7	19	48.7	0.061	3.21	0.95	10.85	
64	Processed meat as burger & sausage)	daily	1	0.5	0	0.0	2	5.1	0.020	14.82	1.52	144.45	
65	Food rich in insoluble fibers (such as whole bread, cereals, beans,	never	0	0.0	0	0.0	0	0.0					
66		once per week	39	21.4	31	21.7	8	20.5	0.022				
67		2-4 times per week	88	48.4	76	53.1	12	30.8	0.362	0.66	0.27	1.61	
68		daily	55	30.2	36	25.2	19	48.7	0.163	1.80	0.79	4.12	

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3	Artichoke, squash,												
4	cabbage, cauliflower,												
5	broccoli, dried herbs & spices, fruits, vegetables)												
6	Salty Food (pickled,	never	27	14.8	22	15.4	5	12.8	0.470				
7	salty cheese, salted fish,	once per week	96	52.7	78	54.5	18	46.2	0.885	0.93	0.34	2.51	
8	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	
9	Fruits and Vegetables	never	2	1.1	0	0.0	2	5.1	0.005				
10		once per week	56	30.8	44	30.8	12	30.8	0.001	0.07	0.01	0.31	
11		2-4 times per week	81	44.5	64	44.8	17	43.6	0.000	0.07	0.02	0.31	
12		daily	43	23.6	35	24.5	8	20.5	0.001	0.07	0.01	0.34	
13	Red meat	never	16	8.8	13	9.1	3	7.7	0.959				
14		once per week	113	62.1	88	61.5	25	64.1	0.950	0.96	0.29	3.20	
15		2-4 times per week	53	29.1	42	29.4	11	28.2	0.835	0.87	0.24	3.14	
16		daily	0	0.0	0	0.0	0	0.0					
17	Under cooked meat	never	157	86.3	120	83.9	37	94.9	0.259				
18		once per week	24	13.2	22	15.4	2	5.1	0.100	0.30	0.07	1.26	
19		2-4 times per week	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00		
20		daily	0	0.0	0	0.0	0	0.0					
21	Fish	never	17	9.3	16	11.2	1	2.6	0.220				
22		once per week	91	50.0	67	46.9	24	61.5	0.102	5.30	0.72	39.19	
23		2-4 times per week	74	40.7	60	42.0	14	35.9	0.176	4.06	0.53	30.95	
24		daily	0	0.0	0	0.0	0	0.0					
25	Consumption of caffeine in diet (tea, coffee)	never	25	13.7	22	15.4	3	7.7	0.027				
26		once per week	20	11.0	16	11.2	4	10.3	0.571	1.54	0.34	6.89	
27		2-4 times per week	61	33.5	54	37.8	7	17.9	0.949	0.96	0.25	3.70	
28		daily	76	41.8	51	35.7	25	64.1	0.078	2.94	0.89	9.74	
29	Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	never	7	3.8	7	4.9	1	2.6	0.181				
30		once per week	67	36.8	56	39.2	11	28.2	0.780	1.34	0.17	10.48	
31		2-4 times per week	91	50.0	70	49.0	21	53.8	0.519	1.93	0.26	14.38	
32		daily	17	9.3	10	7.0	7	17.9	0.215	3.77	0.46	30.66	
33	Dairy products	never	27	14.8	22	15.4	5	12.8	0.552				
34		once per week	49	26.9	41	28.7	8	20.5	0.831	0.89	0.29	2.71	
35		2-4 times per week	78	42.9	58	40.6	20	51.3	0.409	1.51	0.57	4.03	
36		daily	28	15.4	22	15.4	6	15.4	0.497	1.51	0.46	4.98	
37	Average number of glasses of water consumed per day	one cup	9	4.9	6	4.2	3	7.7	0.346				
38		2-3 cups	73	40.1	59	41.3	14	35.9	0.367	0.56	0.16	1.96	
39		at least 4 cups	73	40.1	54	37.8	19	48.7	0.734	0.81	0.24	2.74	
40		4-8 cups	27	14.8	24	16.8	3	7.7	0.156	0.31	0.06	1.56	
41	Snacks between meals	Never	60	33.0	54	37.8	6	15.4	0.009				
42		Occasionally	121	66.5	89	62.2	32	82.1	0.014	2.99	1.25	7.14	
43		Daily	1	0.5	0	0.0	1	2.6	0.009	17.12	2.02	144.86	
44	Number of meals per day	2	68	37.4	55	38.5	13	33.3	0.058				
45		3	109	59.9	86	60.1	23	59.0	0.857	1.06	0.54	2.10	
46		4	5	2.7	2	1.4	3	7.7	0.022	4.37	1.24	15.37	
47	Total food score (favorable food habits)		11.4 ± 4.5		11.9 ± 4.3		9.9 ± 5.0		0.029	t=2.2, p=0.029	0.93	0.86	0.99
48		No	119	65.4	95	66.4	24	61.5					
49		Yes	63	34.6	48	33.6	15	38.5	0.406	1.32	0.69	2.51	
50		Cereals	0	0.0	0	0.0	0	0.0					
51		Brown rice	5	2.7	4	2.8	1	2.6					
52		Whole grain bread	2	1.1	2	1.4	0	0.0					
53		Seeds (beans, peas)	7	3.8	3	2.1	4	10.3					
54		Fruits (apples; plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0					
55		High fat or protein food	34	18.7	25	17.5	9	23.1					
56		Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	0.7	0	0.0					
57		Raw green vegetables	6	3.3	6	4.2	0	0.0					
58		Spices	9	4.9	7	4.9	2	5.1					
59		Fried food	28	15.4	22	15.4	6	15.4					
60		Baked dessert	1	0.5	1	0.7	0	0.0					
61		Milk and dairy products	5	2.7	3	2.1	2	5.1					
62		Carbonated drinks	14	7.7	11	7.7	3	7.7					
63		Tea and coffee	1	0.5	1	0.7	0	0.0					
64		Others	5	2.7	4	2.8	1	2.6					
65		No	143	78.6	113	79.0	31	79.5					
66		Yes	38	20.9	30	21.0	8	20.5	0.982	0.99	0.46	2.16	
67		Low fiber (bananas, cantaloupe)			5	3.5	2	5.1					
68		Refined grains (white pasta, white rice, and oatmeal, potatoes)			10	7	3	7.7					

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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

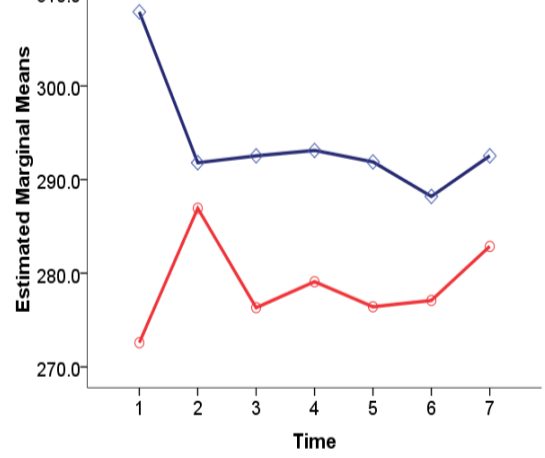
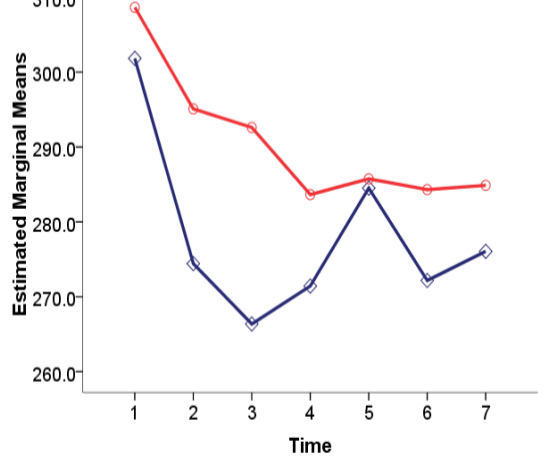
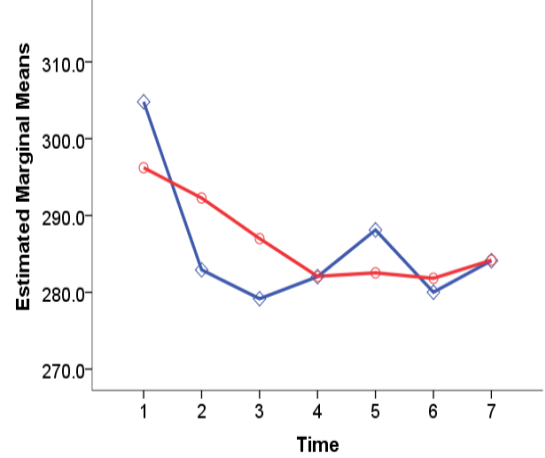
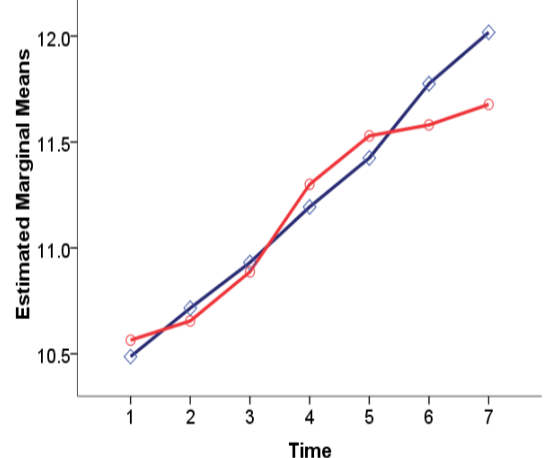
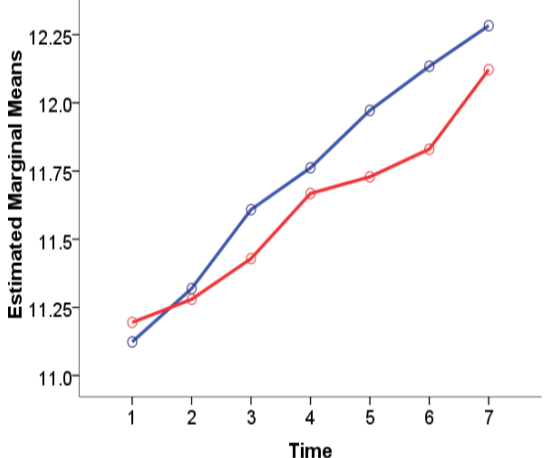
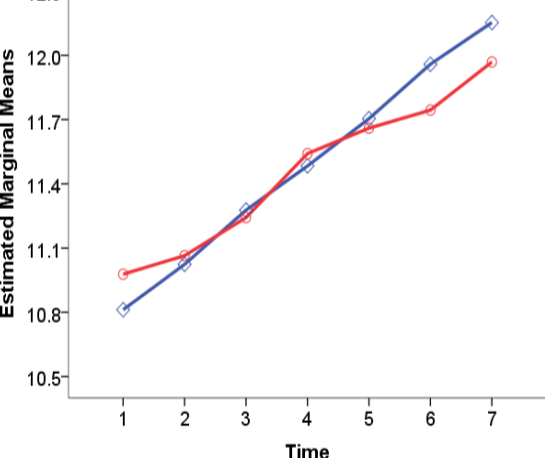
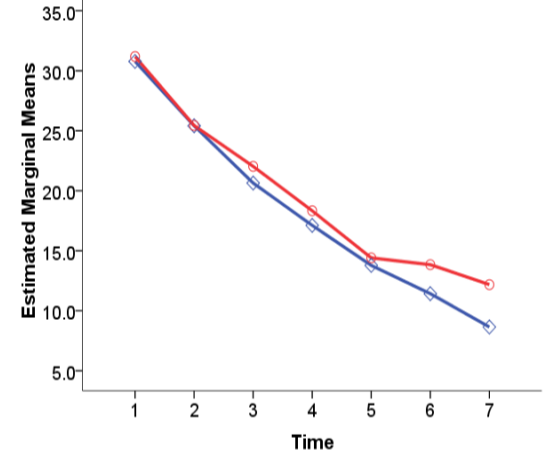
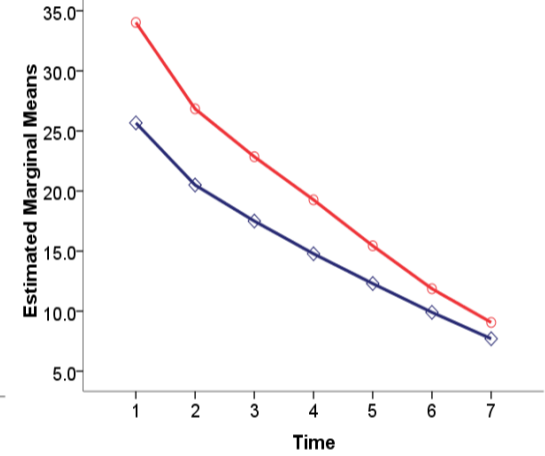
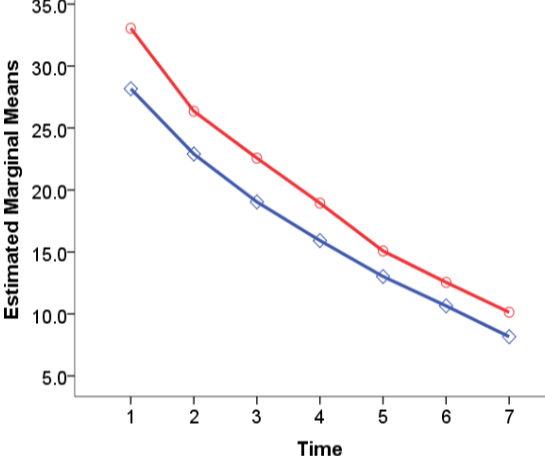
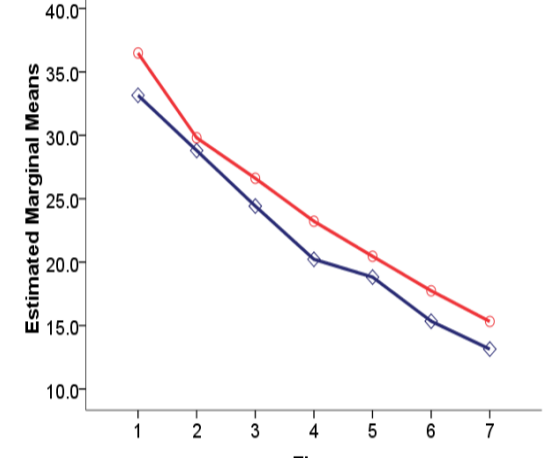
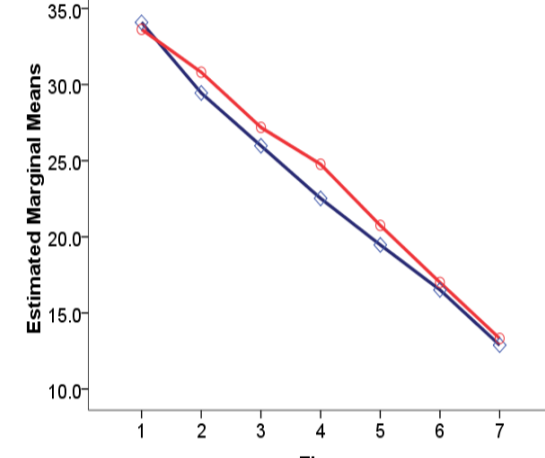
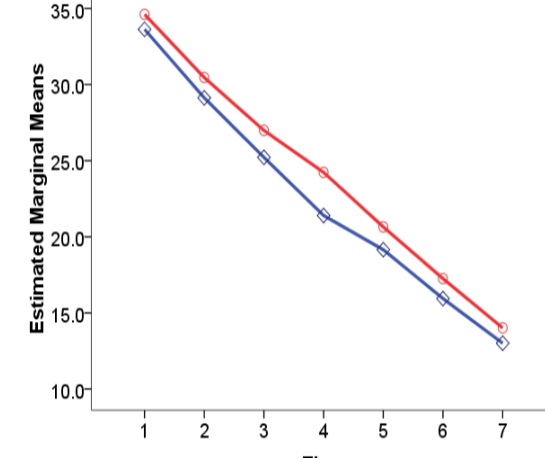
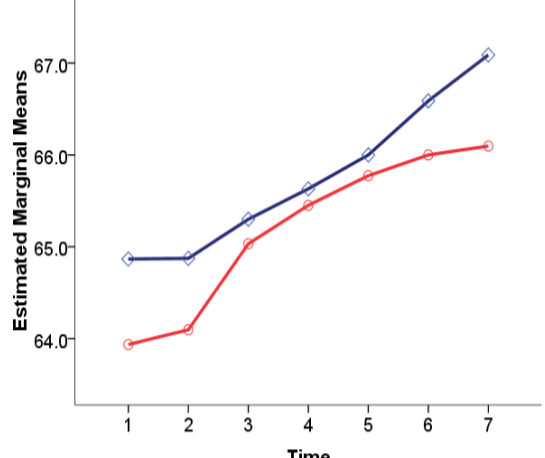
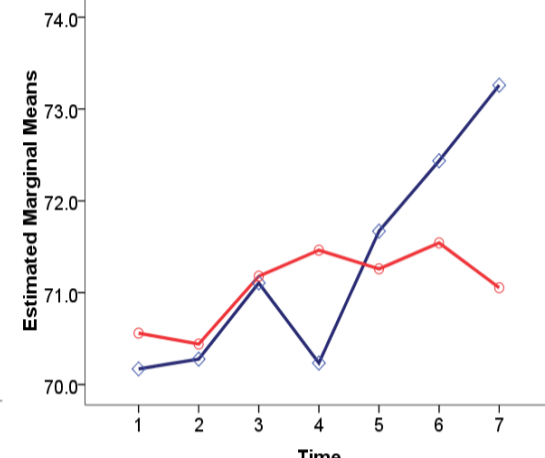
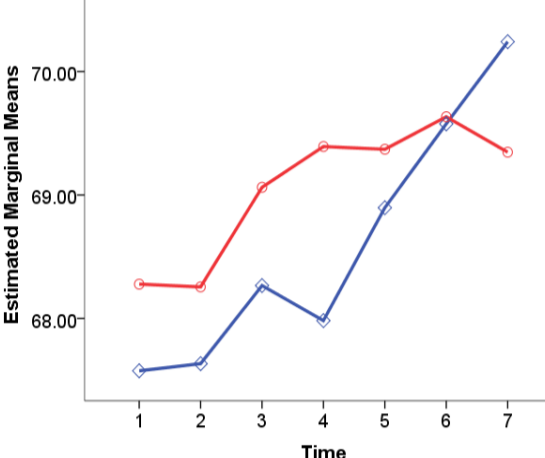
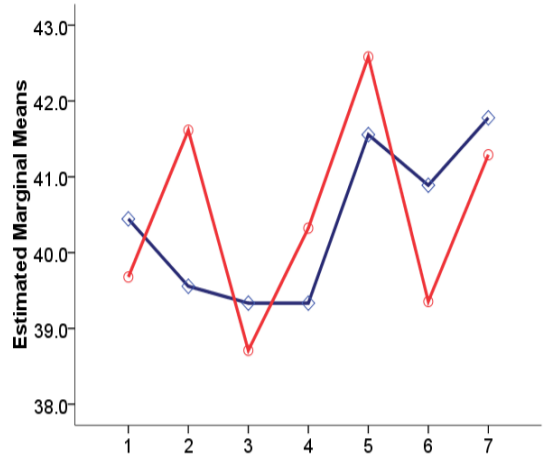
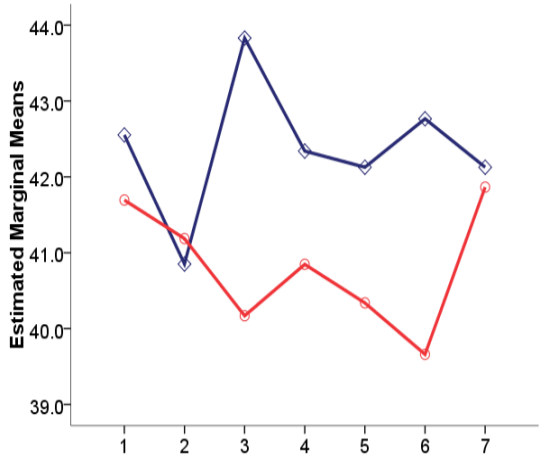
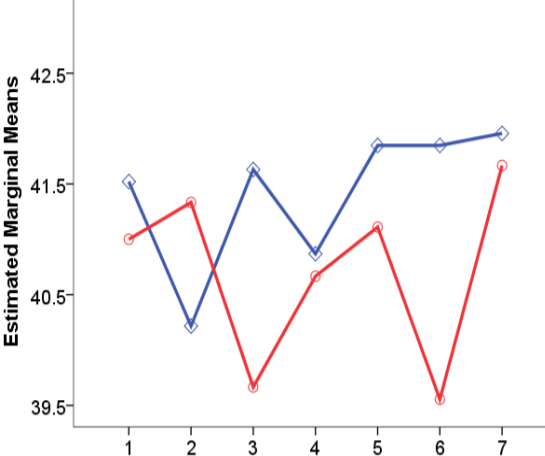
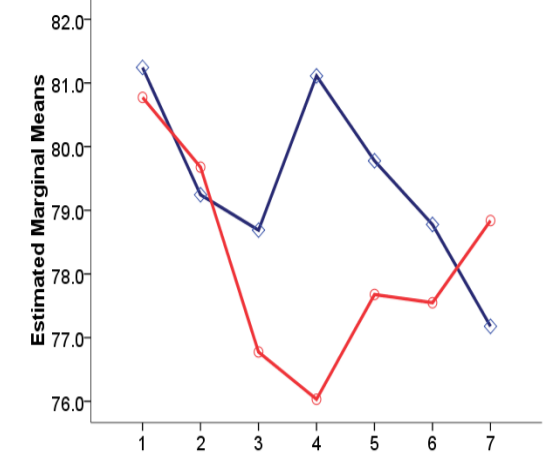
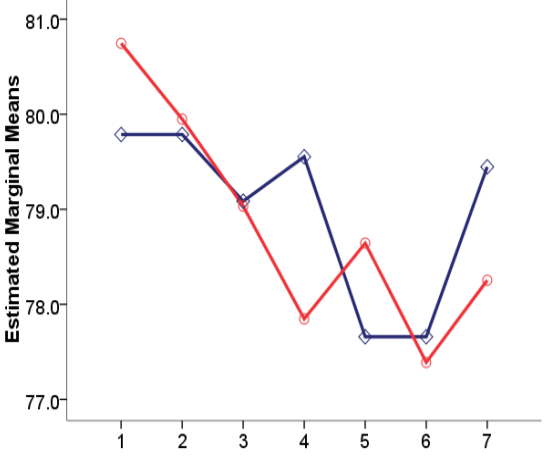
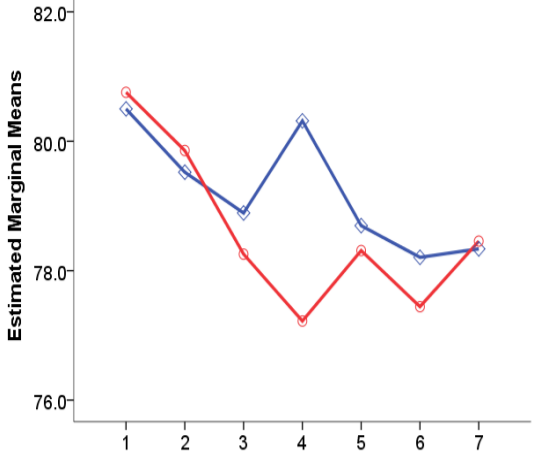
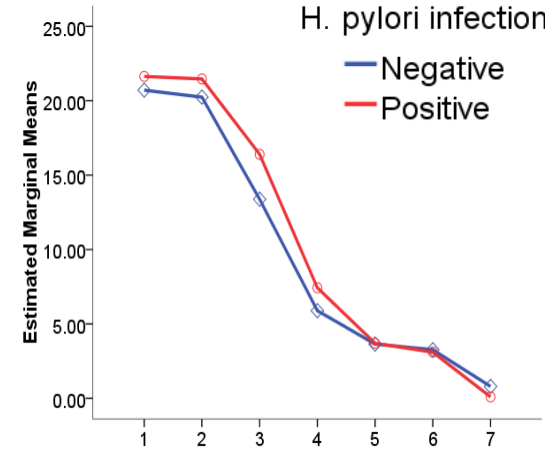
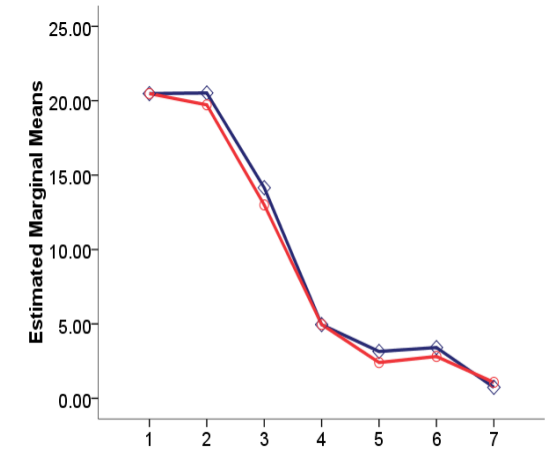
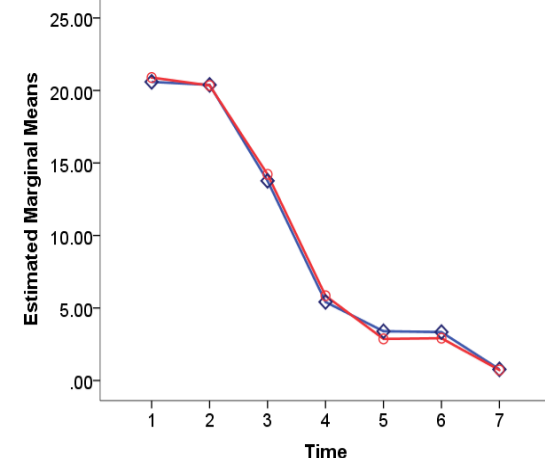
For peer review only

All Cases

Conventional Therapy

Biological Therapy

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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 abscess

+ biologics (infliximab, adalimumab)

List of Biologics used

- Infliximab (Remicade)
IV 5 mg/kg or 10 mg/kg if severe
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 severe

- 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	

1	broccoli, dried herbs & spices, fruits, vegetables)		
2	28. Salty Food (pickled, salty cheese, salted fish, dokka, ...	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
3		If daily , mention the number of servings per day	
4	29. Fruits & Vegetables	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
5		If daily , mention the number of servings per day	
6	30. Red meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
7		If daily , mention the number of servings per day	
8	31. Under cooked meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
9		If daily , mention the number of servings per day	
10	32. Fish	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
11		If daily , mention the number of servings per day	
12	33. Consumption of caffeine in diet (tea, coffee)	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
13		If daily , mention the number of servings per day	
14	34. Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
15		If daily , mention the number of servings per day	
16	35. Dairy products	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
17		If daily , mention the number of servings per day	
18	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	
19	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	
20	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.....	
21	39. Food preparation method	(0) No preference (1) boiling (2) grilling (3) steaming (4) frying	
22	40. Number of meals per day	
23	41. Snacks between meals	(0) Never (1) occasionally (2) daily; per day	
24	II- Clinical data		
25	42. Type of IBD diagnosed	(0) Crohn's disease (1) ulcerative colitis	
26	43. Age at diagnosisyears old	
27	44. History of H. pylori infection		
28	45. If yes mention the onset	(-1) NA (1) few weeks (2) 3-6 months (3) 6 months- 1 year (4) ≥ 1 year	
29	46. History of receiving H. pylori eradication therapy during the past 12 months	(0) No (1) Yes;	
30	47. History of complications	(0) None (1) fistula (2) stricture (3) ulcers (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others.....	
31	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	
32	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) Moltium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others.....	

1 2 3 4 5 6 7 8	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.....	
9 10	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	
11 12	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

16 17	53. Baseline Body Weight kg	
18	54. Heightcm	

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	Follow Up					
	treatment	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							

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60STROBE 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.

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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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4 1 ***Helicobacter pylori* infection in patients with inflammatory bowel diseases:**
5 2 **a single-centre, prospective, observational study in Egypt**
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10 4 **Ekram W. Abd El-Wahab^{1 ^}, Ebtessam I. Youssef^{2,3}, Ehab M. Hassouna⁴**

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22 - **word count:** 3995

23 - **number of references:** 53

24 - **number of tables:** 5

25 - **number of figures :** 2

1
2
3 **27 Abstract**
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5 **28 Objective:** Conflicting results have been reported by numerous epidemiological studies investigating
6
7 **29** the association between *Helicobacter pylori* (*H. pylori*) infection and inflammatory bowel disease
8
9 **30** (IBD). We aimed in this study to assess the possible association between *H. pylori* infection and IBD
10
11 **31** and its effects on disease progression.

12
13 **32 Design:** Prospective observational study.

14
15 **33 Setting:** Specialized IBD care clinics at Alexandria University Student Hospital in northern Egypt,
16
17 **34** between March and June 2019.

18
19 **35 Participants:** 182 patients with IBD.

20
21 **36 Analysis and outcome measures:** IBD participants were screened for *H. pylori* infection and
22
23 **37** clinically evaluated at the initial visit and bimonthly for 3 months to record any potential
24
25 **38** improvement/flare of the IBD condition.

26
27 **39 Results:** Overall, 90 (49.5%) patients with IBD had evidence of *H. pylori* infection. The course of
28
29 **40** IBD did not significantly differ in association with *H. pylori* infection or IBD treatment strategy. Cox
30
31 **41** regression analysis revealed that patients aged 20–35 years (OR = 6.20 [95% CI 1.74–22.12]) and 35–
32
33 **42** 55 years (557.9 [17.4–17922.8]), high socioeconomic status (2.9 [1.11–7.8]), daily consumption of
34
35 **43** fibre-rich food (5.1 [1.32–19.5]), occasional consumption of snacks between meals (2.8 [2.5–70.5])
36
37 **44** and eating four meals per day (13.3 (1.0–7.7)) were predictive of IBD flare. By contrast, eating fruits
38
39 **45** and vegetables showed a strongly protective association (OR = 0.001 (95% CI 0.0002–0.02)). The
40
41 **46** probabilities of improvement of IBD symptoms after 12 weeks of follow-up were comparable in
42
43 **47** assessments based on *H. pylori* infection status (0.793 for *H. pylori*-negative vs. 0.778 for *H. pylori*-
44
45 **48** positive) and IBD treatment option (0.811 for conventional therapy vs. 0.750 for biological therapy).

46
47 **49 Conclusion:** The association between IBD and *H. pylori* infection is unresolved and should be further
48
49 **50** investigated in the context of specific environmental exposures that influence the development or
50
51 **51** relapse of IBD.

52
53 **54 Keywords:** Inflammatory Bowel Disease; Crohn's disease; Ulcerative colitis; *Helicobacter pylori*
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1
2
3 54 **Article summary**
4

5 55 ***Strengths and limitations of this study***
6

- 7 56 • We were able to report the effect of *Helicobacter pylori* (*H. pylori*) infection on the response
8 to conventional *versus* biological treatment of inflammatory bowel disease (IBD).
9 57
10
11 58 • The relatively small sample size and single-centre setting may limit the generalizability of the
12 results.
13 59
14
15 60 • The study lacks a lack of a non-IBD healthy control group, and a causal link between *H.*
16 *pylori* infection and IBD cannot be established.
17 61
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19 62 • Estimation of the prevalence of *H. pylori* in IBD patients was limited by the detection
20 method.
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65 Introduction

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

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

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

88 Although numerous, diverse studies analysed the association between *H. pylori* infection and
89 IBD ^{9 10}, a causal association between *H. pylori* and IBD remains to be established; and the are
90 contradictory data related to the potential causative and the protective roles of *H. pylori* infection
91 associated with IBD ¹¹⁻¹⁹.

1
2
3 92 Assuming a potential protective role of *H. pylori* infection against IBD, *H. pylori* eradication
4
5 93 treatment may influence the progression of IBD course and thus should be carefully administered,
6
7 94 considering the findings of future prospective studies ^{16 20}.

8
9 95 IBD occurs more frequently in regions with lower rates of *H. pylori* colonization. The steady
10
11 96 increase in the incidence of IBD in *H. pylori*-endemic regions may reflect the advent of initiating anti-
12
13 97 *H. pylori* therapy to treat peptic ulcers ¹³. Furthermore, meta-analyses show that the prevalence of *H.*
14
15 98 *pylori* infection is lower in patients with IBD compared with controls ^{9 10 13 19 21}. For example, long-
16
17 99 term treatment with sulphasalazine contributes to the eradication of *H. pylori* infection ²². Although
18
19 100 unconfirmed, most studies indicate a protective role for *H. pylori* infection against the development of
20
21 101 IBD ^{9 21}.

22
23
24 102 With advances in identifying the pathological mechanisms underlying IBD, new therapies
25
26 103 have been proposed, particularly those involving biological response modifiers. These include anti-
27
28 104 tumor necrosis factor antibodies (anti-TNF α), IL-1/IL-6 receptor antagonists, and an anti-CD20
29
30 105 antibody. These therapies are generally well tolerated, although they may be associated with adverse
31
32 106 effects, including increased susceptibility to infection and increased risk of malignancies ²³.

33
34
35 107 These considerations inspired us to conduct a prospective, longitudinal study to further
36
37 108 analyse the association between *H. pylori* infection and the flare of IBD and to investigate possible
38
39 109 effects of *H. pylori* infection on the response to conventional *versus* biological treatment of IBD.
40

41 110

42 43 111 **Methods**

44 45 112 **Study population and sampling**

46
47 113 We conducted a prospective observational study at Alexandria University Student Hospital (AUSH)
48
49 114 that is affiliated with Alexandria University, Egypt and serves students, faculty, and staff members.

50
51 115 AUSH comprises outpatient clinics and inpatient and emergency departments with a bed capacity of
52
53 116 1000. We enrolled patients aged ≥ 18 years with confirmed IBD (triphasic CT abdomen,
54
55 117 endoscopy/colonoscopy, and fecal calprotectin) and commenced IBD treatment (conventional or
56
57 118 biological). Patients with irritable bowel syndrome were excluded according to the Rome III criteria
58
59 119 ²⁴.

1
2
3 120 Clinicians on the staff of the Internal Medicine Department of the AUSH selected the
4
5 121 treatment (standard vs. biological). The prescribed treatment is the standard of care adopted by the
6
7 122 AUSH for treating patients with IBD. Details of the treatment regimens and the parameters employed
8
9 123 to select standard or biological treatment are described in File S1.

11 124 The frequency of *H. pylori* infection among patients with IBD is as high as 10.0% ²¹. Using a
12
13 125 margin of error=5.0%, an alpha error = 0.05 and a 95% confidence level, the minimum required
14
15 126 sample size was 138 ⁸. However, we ultimately enrolled 182 patients with IBD, because we expected
16
17 127 that the prevalence of *H. pylori* infection might be higher because of the endemicity of *H. pylori*
18
19 128 infection in Egypt ⁸, and to compensate for possible dropouts during the follow-up. The sample size
20
21 129 was calculated using Epi info 7 software. Patients with confirmed IBD who agreed to participate in
22
23 130 the study were consecutively enrolled. According to their characteristics (Figure 1), the patients were
24
25 131 assigned into groups according to the prescribed treatment regimen (File S1) as follows: Group 1
26
27 132 comprised patients administered conventional IBD treatment, and Group 2 included patients
28
29 133 undergoing biological IBD treatment.

32 134 Stool samples was used to detect *H. pylori* antigen using a commercially available enzyme
33
34 135 immunoassay (EIA) kit (Foresight EIA test kit for qualitative and quantitative detection of *H. pylori*
35
36 136 in the stool; ACON Laboratories, Inc. San Diego, CA, USA). Each assigned group included patients
37
38 137 with IBD with or without *H. pylori* infection, and *H. pylori*-positive patients were shown their
39
40 138 laboratory findings. We did not commence *H. pylori* eradication therapy during the study period.
41
42 139 After a 3-month follow-up, *H. pylori*-positive patients were referred to a specialist for further
43
44 140 evaluation and case management according to the adopted standard of care.

48 141 **Patient and public involvement**

50 142 We informed the patients about the aims and concerns of the study and how it will add to better
51
52 143 understanding of their disease aetiology and triggering factors, which was highly appreciated by the
53
54 144 patients, and motivated them to be a part of the cohort intended for the long-term follow-up by the
55
56 145 clinicians. However, it was not appropriate or possible to involve patients or the public in the design,
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1
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3 146 conduct, reporting, or dissemination plans of our research. All the laboratory and clinical data were
4
5 147 reported to the study participants, where we discussed the study findings in a simple language.
6

7 148 **Assessments**

9 149 Baseline evaluation included the patient's history, full clinical examination, and laboratory tests. A
10
11 150 data collection form (File S2) was used to collect baseline data as follows: sociodemographic
12
13 151 characteristics, personal habits, lifestyle, physical activity and exercise, dietary habits and restrictions,
14
15 152 family history, medical history, comorbidities, and medications. Clinical data collected were from
16
17 153 each patient during the initial visit were as follows: Disease onset, history of present complaints,
18
19 154 frequency and duration of IBD attacks, past and current IBD medications, history of changing
20
21 155 therapy, surgical intervention, and complications. History of *H. pylori* infection and undergoing *H.*
22
23 156 *pylori* eradication therapy during the past 12 months were recorded during each follow-up visit. All
24
25 157 patients were followed bimonthly for three months (6 visits) during IBD treatment. Patients were
26
27 158 contacted weekly via telephone and asked about the frequency and severity of symptoms and if
28
29 159 adverse effects associated with treatment occurred during the previous week.
30
31

32
33 160 Blood pressure (BP) and anthropometric measurements were measured according to standard
34
35 161 techniques²⁵⁻²⁷. Body mass index (BMI) was calculated according to the Quetelet's index: $BMI =$
36
37 162 $(\text{weight [kg]}/\text{height}^2 [\text{m}^2])$. At each follow-up visit, laboratory tests were performed as follows:
38
39 163 complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting
40
41 164 blood glucose (FBG), and fecal calprotectin²⁸. Imaging techniques included triphasic CT and
42
43 165 endoscopy/colonoscopy when indicated. All patients underwent full-length colonoscopy (Pentax
44
45 166 colonoscopies). Colonoscopic biopsies acquired from the rectum and sigmoid; descending, transverse,
46
47 167 ascending colon; as well as the cecal mucosa. Histological analyses of the degree of inflammation
48
49 168 associated with CD and UC were evaluated according to the European consensus on the
50
51 169 histopathology of IBD²⁹.

52
53
54 170 The socioeconomic status of the enrolled patients with IBD was calculated and categorized as
55
56 171 high, middle, low, and very low, according to a modified social scoring system³⁰.

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59 172
60

173 **Outcomes**

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

178 **Statistical analysis**

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

199

200 **Results**

201 **Sociodemographic and clinical characteristics**

202 Patients with IBD (n = 182) (n = 96 [52.7%] UC and n = 86 [47.3%] CD) included 51.7% males,
203 58.2% married, 51.6% resided in urban areas, 76.9% highly literate, and 82.4% non-smokers. The
204 average age was 27.0 ± 7.3 years, with the majority ranging from 20 to 35 years. Normal BMI was a
205 predominant feature (59.3%), and 31.9% were overweight. Patients' other sociodemographic
206 characteristics are shown in (Table 1).

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

210 Patients' baseline clinical and laboratory findings are presented in Table S2. Compared with
211 patients without *H. pylori* infection, infected patients had higher rates of abdominal cramps (91.1% vs.
212 84.8%), abdominal pain (85.6% vs. 81.5%), bloating/indigestion (98.9% vs. 95.7%), flatulence
213 (100.0% vs. 96.7%), diarrhoea (98.9% vs. 96.7%), rectal bleeding (73.3% vs. 65.2%), fever (33.3% vs.
214 26.1%), chills (10.0% vs. 4.3%), infection (23.3% vs. 14.1%), fatigue/lack of energy (88.9% vs.
215 68.5%), sick leave/absenteeism (8.9% vs. 6.5%), and higher mean CRP (33.0 ± 23.0 vs. 28.2 ± 23.9)
216 and ESR (34.6 ± 13.2 vs. 33.6 ± 14.1) levels. GIT endoscopy and colonoscopy revealed features of
217 CD and UC, indicated by superficial ulcerations and mild infiltration.

218 ***H. pylori* infection among patients with IBD**

219 We detected *H. pylori* infection in 49.5% of patients, including those with UD (48, 50.0%) and CD
220 (42, 48.8%) (OR = 1.05 [95% CI 0.59–1.88]), although 85.6% of them reported undergoing *H. pylori*
221 eradication therapy in the past 12 months prior to the study. The infection rate was highest (74,
222 82.2%) among the age group 20 to <35 years (Table 1). Logistic regression analysis revealed that
223 conventional treatment of IBD (OR = 1.99 [95% CI 1.03–3.85]), adults aged 20 or <35 years (6.20
224 [1.74–22.12]) and 35–55 years (11.1 [1.18–104.64]), and mixed food sources (3.12 [1.60–6.06])
225 predicted *H. pylori* infection ($p < 0.05$) (Table 2).

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

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

236 **Factors associated with improvement in IBD symptoms**

237 Cox regression analysis revealed that subjects aged 20–35 years (OR = 6.20 [95% CI 1.74–22.12])
238 and 35–55 years (557.9 [17.4–17922.8]), high socioeconomic status (2.9 [1.11–7.8]), daily
239 consumption of fibre-rich food (5.1 [1.32–19.5]), occasional consumption of snacks between meals
240 (2.8 [2.5–70.5]), and eating four meals per day (13.3 [1.0–7.7]) were significantly associated with
241 IBD flare ($p < 0.05$). By contrast, eating fruits and vegetables protected against IBD flare (Tables 4
242 and Table S5).

243 **Probability of improvement of IBD symptoms in relation to *H. pylori* infection and IBD** 244 **treatment strategy**

245 Kaplan–Meier analysis revealed that the probabilities of recovery (remission) among the patients after
246 12 weeks of follow-up were comparable, considering *H. pylori* infection status (0.793 for *H. pylori*-
247 negative vs. 0.778 for *H. pylori*-positive) or IBD treatment option (0.811 for conventional therapy vs.
248 0.750 for biological therapy). The number of patients who recovered from IBD among *H. pylori*-
249 negative patients was similar to that of *H. pylori*-positive patients. By contrast, the proportion of
250 recovered patients with IBD who underwent conventional therapy was higher compared with those
251 administered biological therapy, although the difference was not significant. Thirty-nine subjects did
252 not recover until the end of the study. The results of log-rank, Breslow, and Tarone-Ware tests of

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

255 Discussion

256 Recent improvements in hygienic conditions and socioeconomic status have reduced *H. pylori*
257 infection rates, and this trend accompanies increased IBD incidence in most countries. However, the
258 role of *H. pylori* in IBD is unknown^{2 16 31}. Numerous studies found lower *H. pylori* infection rates in
259 patients with CD, UC, or both, compared with non-IBD controls, although a few studies did not detect
260 a significant association^{9 10 13 21 31}. Recent epidemiological studies, animal experiments, and meta-
261 analyses reveal an inverse correlation between *H. pylori* infection and the onset of IBD onset,
262 suggesting that colonization by *H. pylori* confers a protective effect against autoimmune diseases^{13 23}
263³².

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

268 *H. pylori* was detected in approximately 50% of the patients, which is low compared with the
269 prevalence among the population of Egypt, where disease is endemic³³⁻³⁶. These findings support the
270 results of studies showing that lower rates *H. pylori* infection of patients with IBD, suggesting an
271 association between *H. pylori* and IBD^{9 21}. The rate *H. pylori* infection is significantly higher among
272 patients with IBD who undergo conventional treatment, which conflicts with studies suggesting that
273 5-aminosalicylates or sulphasalazine interfere with the adhesion of *H. pylori* to the mucosa and block
274 its proliferation^{22 37-39}. For example, the results of multiple studies do not support the conclusion that
275 treatment with sulfasalazine or other drugs such as 5-aminosalicylic acid (5-ASA), thiopurines,
276 steroids, and antibiotics influence the colonization rate of *H. pylori*^{13 40-42}. It is worth noting that
277 although the treatment of IBD patients with anti-TNF- α agents, immunosuppressant and/ or
278 corticosteroid increases the risk of infections, there is no direct evidence that novel therapeutic
279 strategies such as anti-tumor necrosis factor alpha (TNF- α) and immunosuppressants result in

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3 280 exacerbating or influence the prevalence of *H. pylori* infection Similar findings were reported by a
4
5 281 study of novel therapeutic strategies such as anti-tumor necrosis factor alpha (TNF- α) treatment
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7 282 {Singh, 2011 #145; Triantafyllidis, 2014 #29; Zhong, 2021 #144}.

9 283 Here we show that the majority of *H. pylori*-positive patients with IBD admitted undergoing
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11 284 *H. pylori* eradication therapy during the previous 12 months, which raises questions about the efficacy
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13 285 of eradication therapy or reveals reinfection among this group of patients. Notably, most studies do not
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15 286 report subjects' history of treatment of *H. pylori* infection¹³. It is therefore possible that such patients
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17 287 with IBD were treated for *H. pylori* infection before enrolment, culminating in an incorrectly low rate
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19 288 of *H. pylori* infection.

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22 289 Accumulating evidence suggests that *H. pylori*, through its ability to regulate the immune
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24 290 response, protects human from diseases with an autoimmune component, including IBD⁴³. The
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26 291 results of investigations designed to confirm this possibility are controversial. For example, the
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28 292 heterogeneity among studies accounted for by methods used to diagnose IBD and *H. pylori* infection,
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30 293 study location, study population, and the possibility of publication bias limit the validity of this
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32 294 conclusion and raise questions concerning the robustness of their findings.

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35 295 Here we conducted a prospective study to extended previous work through investigations of
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37 296 the association between *H. pylori* infection and IBD. A potential avenue for extending our study
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39 297 involved broadening the inclusion criteria to gain further insight into local variations of the protective
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41 298 effects of *H. pylori* against IBD. In contrast to previous studies, we added subgroup analysis of *H.*
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43 299 *pylori* infection and the type of IBD treatment. However, we did not detect a significant relationship
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45 300 between the two conditions. For example, disease course was similar among all patients with IBD
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47 301 regardless of their *H. pylori* infection status or conventional or biological treatment. Moreover, the
48
49 302 extent, and severity of IBD increased with a decrease in *H. pylori* infection. We were intrigued by our
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51 303 findings that that the proportion of patients administered conventional therapy who recovered from
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53 304 IBD was higher than those administered biological therapy. This may be explained by the higher rate
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55 305 of *H. pylori* infection among patients with IBD administered conventional therapy or that patients
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57 306 administered biological therapy were refractory to previous conventional therapy and therefore
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59 307 suffered from increased disease severity.

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3 308 Evidence indicates that IBD is induced through complex interactions between environmental
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5 309 and genetic factors. The growing burden of IBD may serve as a proxy for the hygiene hypothesis and
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7 310 improvements in the sanitation of living conditions, lifestyle and dietary changes, more frequent
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9 311 antibiotic use, enhanced diagnostic methods, and heightened awareness of IBD^{1 44 45}. Accordingly, we
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11 312 further investigated the role of host and environmental cofactors reported to ameliorate or incite
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13 313 factors for IBD flare (e.g., diet, smoking, physical activity, breastfeeding, socioeconomic status,
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15 314 education, occupation, urban versus rural lifestyle, and medication¹). In this context, we were guided
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17 315 by existing studies that recognized differences in potential risk factors or features unique to certain
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19 316 populations, such as the Mediterranean diet. Indeed, dietary factors play a crucial role in disease
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21 317 initiation or relapse⁴⁶, although certain diets such as the Mediterranean diet are purported to protect
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23 318 against IBD⁴⁷⁻⁴⁹.

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26 319 The plant-based, semi-vegetarian Mediterranean diet alleviates symptoms of IBD and
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28 320 maintains patients in remission, potentially through reducing inflammation and improving the
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30 321 microbiota^{50 51}. In our present cohort, *H. pylori*-negative patients with IBD and those experiencing
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32 322 less flare had a more favourable overall dietary habit score. Consistent with Kakodkar's
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34 323 recommendations⁵⁰, which encourage the consumption of all vegetables and fruits in an IBD diet, we
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36 324 observed a strong protective role on IBD flare of daily and 2–3-times weekly consumption of
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38 325 vegetables and fruits. Moreover, a recent meta-analysis shows that the beneficial effect of *H. pylori*
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40 326 experienced by Mediterranean populations with IBD is lower compared with residents of East Asian
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42 327 and European regions¹⁹. Nevertheless, the analysis did not explicitly incorporate dietary information
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44 328 or study the putative beneficial effect of diet as a confounder. Moreover, this positive effect may be
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46 329 attributed to the relative abundance of CagA *H. pylori* in these populations, a strain that produces
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48 330 specific constituents that modulate host immune defences⁵².

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51 331 Fibre may serve as an anti-inflammatory component of IBD treatment, although a converse
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53 332 effect can occur¹. Our Cox regression analysis revealed that daily consumption of foods rich in
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55 333 insoluble fibre, such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower,
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57 334 broccoli, dried herbs, and spices, significantly increased the risk of IBD flare, particularly in patients
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59 335 who consume four daily meals interspersed with occasional snacks.

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3 336 In agreement with Gentschew et al.,⁵³ trans-fat consumption was associated with a higher
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5 337 probability of IBD flare, although this was not a variable included in our final model. Although our
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7 338 findings suggest a role for diet in IBD flare, its effect is questionable because of the limitations of
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9 339 recall bias and multifactorial exposures. Moreover, patients with IBD may alter their dietary habits in
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11 340 response to symptoms that vary with disease activity, which requires further direct research into the
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13 341 role of diet in IBD.

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15 342 Variations in the protective effects of *H. pylori* on IBD may be explained by socioeconomic
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17 343 factors. For example, here we show that patients with IBD with higher socioeconomic status and
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19 344 mainly urban residents had a higher chance of disease flares. Moreover, the frequency of *H. pylori*
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21 345 infection did not significantly vary in association with socioeconomic status. These findings support
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23 346 the argument that factors associated with an urban lifestyle and industrialization influence risk of IBD.
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25 347 Furthermore, the rate of gastric colonization by *H. pylori* was significantly higher in adults aged >20
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27 348 years, although there was no significant difference in the average age of IBD onset between *H. pylori*-
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29 349 positive and -negative groups. This age group experienced a higher frequency of disease flares. These
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31 350 findings may be explained by patients' histories of comorbidities or lifestyle, which affect the
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33 351 occurrence of IBD. Demographic variables other than age did not exert detectable effects.

34
35 352 The findings of this study must be interpreted in view of its limitations. First, we did not
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37 353 test gastric biopsies for *H. pylori*, which may have decreased the disease prevalence rate. However,
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39 354 this would incur the burdens of an ethically questionable invasive procedure. A urea breath test may
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41 355 serve as a better alternative, although we did not have access to this test in our centres. Second, the
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43 356 small sample size was a major limitation and may have influenced the estimation of effect size. Third,
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45 357 the trend of decreased *H. pylori* infection in patients administered biological therapy coincided with
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47 358 increased severity of IBD, which should be investigated by a larger, statistically robust randomized
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49 359 controlled trial. Moreover, our results merit reassessment in a cohort of patients from a background
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51 360 population with a low prevalence of *H. pylori* that includes detailed information about eradication
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53 361 treatment and administration of other antibiotics. Fourth, a causal relationship between *H. pylori*
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55 362 infection and IBD cannot be established through an uncontrolled study (control group without IBD),
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57 363 and further large scale prospective studies are required. Thus, studies are warranted to investigate the

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3 364 effects of eradication of *H. pylori* on the development of IBD combined with analyses of
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5 365 environmental exposures, hygiene diet, physical activity, and intestinal microbiota as significant
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7 366 confounders. An ideal study would be prospective and initiated when IBD is diagnosed.
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9 367 **Conclusions**

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11 368 Together, the findings of our present analysis of the association between IBD and *H. pylori* infection
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13 369 are inconclusive, and further studies are required. Thus, much remains to be learned about the causes
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15 370 of IBD and whether specific environmental exposures influence the development of disease and its
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17 371 course.
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22 375 **Ethics approval**

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27
28 376 The study was approved by the institutional review board and the ethics committee of the High
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30 377 Institute of Public Health affiliated with Alexandria University, Egypt. The study was conducted in
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32 378 accordance with the international ethical guidelines and that of the Declaration of Helsinki. Informed
33
34 379 written consent was obtained from each participant after explaining the aim and concerns of the study.
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36 380 The datasheets were coded by number to ensure anonymity and confidentiality of the participants'
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38 381 data.
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41 383 **Contributors**

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45 384 EWAW: Conceptualization, developed the theoretical framework and study design, took the lead for
46
47 385 overall direction and planning of the study implementation, data curation, statistical analysis and
48
49 386 interpretation of data, major contribution to writing, revised and approved final version of the
50
51 387 manuscript. EIY: Study implementation and recruitment of the study participants, data collection,
52
53 388 clinical evaluation and follow up, analysis and interpretation of data, contributed to the writing of the
54
55 389 manuscript, revised and approved final version of the of the manuscript. EMH: Supervised the study
56
57 390 implementation and data collection, facilitated the recruitment of the study participants, clinical
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3 391 evaluation and follow up, data curation, contributed to the writing of the manuscript, revised and
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5 392 approved final version of the manuscript.
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9 394 **Competing interests**

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11 395 All authors declare no conflict of interest.
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15 396 **Data availability statement**

16 397 All data are fully available without restriction by the corresponding author at
17
18 398 ekram.wassim@alexu.edu.eg.
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27
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32 404 **References**

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3 538 **Figure legends**
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6 539 **Figure 1: Patient dispositions**
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9 540 **Figure 2: The equality of recovery (remission of IBD symptoms) during the follow-up periods**
10 **associated with *H. pylori* infection status and IBD treatment strategies**
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13 542 **Figure S1 (supplementary material): Patients' clinical and laboratory findings during follow-up**
14 **periods associated with *H. pylori* infection status and the IBD treatment strategy**
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Table 1: Characteristics of the study population

	IBD patients		<i>H. pylori</i> 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 <i>H. pylori</i> 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 <i>H. pylori</i> 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		<i>H. pylori</i> 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. (<i>p</i> 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 significant 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	<i>H. pylori</i> infection	Follow-up period (3 Months)						Repeated Measures ANOVA																	
		Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test				Within Subject Effects				Between Subject Effects								
		Mean ± SD	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	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 x S	1.156	0.322	0.038	0.448	T x 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 x S	0.708	0.644	0.024	0.276	T x 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 x S	1.48	0.187	0.048	0.565	T x 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 x S	0.157	0.925	0.003	0.078	T x 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 x S	3.1	0.007	0.096	0.91	T x 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 x S	1.05	0.394	0.035	0.409	T x 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 x S	1.02	0.415	0.034	0.396	T x 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 x S	0.901	0.496	0.031	0.35	T x 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 x S	2.08	0.058	0.067	0.740	T x 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 x S	2.67	0.017	0.084	0.856	T x 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 x S	1.28	0.270	0.042	0.493	T x 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 \times S; time versus state of *H. pylori* infection

ref; reference category

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For peer review only

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	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 significant 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

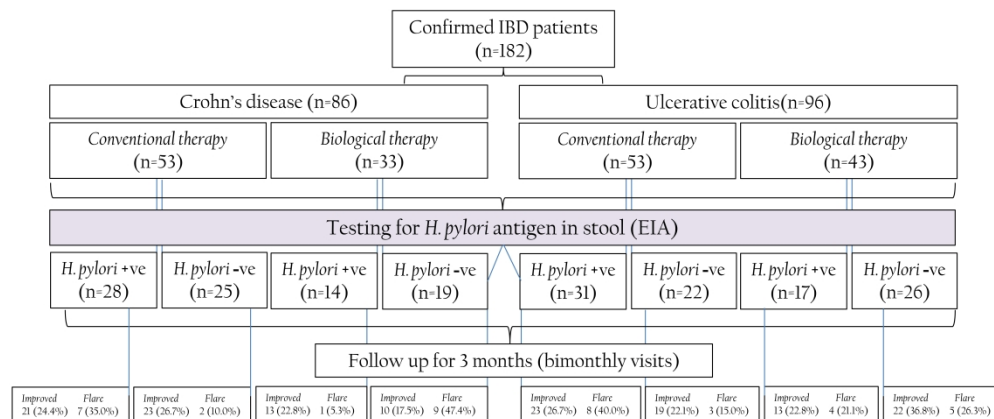
Variable	Group	Case summary	No of Events n(%)	Censored n(%)	Event Time (bimonthly visit)	No. of Events (recovery ^a)	No. of relapse	No. at Risk (to recovery ^a)	Probability of recovering ^a	Test of equality of recovery ^a		
										Log Rank (Mantel- Cox)	Breslow (Generalized Wilcoxon)	Tarone-Ware
										<i>p</i> value		
<i>H. pylori</i> 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				
Treatment of IBD	Conventional	n=106	86 (81.1)	20 (18.9)	6	38	4	20	0.778			
					1	0	0	106	0.000			
					2	0	3	106	0.000			
					3	2	1	104	0.019			
					4	21	5	83	0.217			
	5	16	6	67	0.368							
	Biological	n=76	57 (75.0)	19 (25.0)	6	47	5	20	0.811			
					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

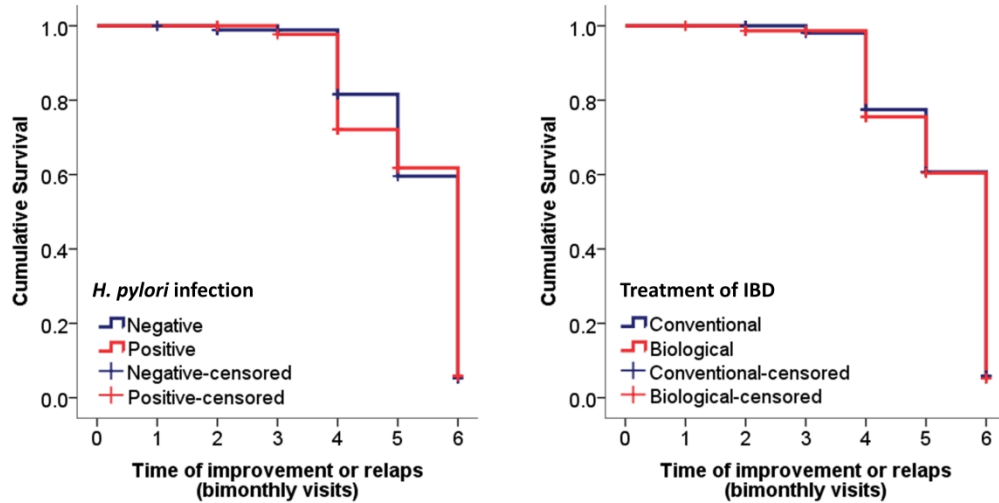
p value significant at <0.05

a: recovery reflects a state of remission of IBD condition



Patients' dispositions

266x114mm (600 x 600 DPI)



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

257x129mm (600 x 600 DPI)

Supplementary Tables for online display

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

		IBD patients		<i>H. pylori</i> infection in IBD patients			<i>p</i> ~
		Total (n=182)		Negative (n=92)		Positive (n=90)	
		No.	%	No.	%	No.	
Physical activity and physical exercise							
	not working	71	39.0	36	39.1	35	38.9
Transportation	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
	minimal	43	23.6	13	14.1	30	33.3
	moderate	73	40.1	49	53.3	24	26.7
Activity outside work	high	1	0.5	0	0.0	1	1.1
	not working	59	32.4	27	29.3	32	35.6
	minimal	90	49.5	50	54.3	40	44.4
Regular exercise	moderate	32	17.6	15	16.3	17	18.9
	high	1	0.5	0	0.0	1	1.1
	never	136	74.7	76	82.6	60	66.7
Total physical activity score	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
		2.8 ± 2.1		3.01 ± 2.2		2.5 ± 2.1	
Food habits							
Food source	Homemade	97	53.3	61	66.3	36	40.0
	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
	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
	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
Trans fat (such as in cake, cookies, pies, dessert, cream, mayonnaise, processed meat as burger & sausage)	daily	13	7.1	1	1.1	12	13.3
	never	30	16.5	9	9.8	21	23.3
	once per week	91	50.0	61	66.3	30	33.3
Food rich in insoluble fibers (such as whole bread, cereals, beans, peas, wheat, oat, artichoke, cabbage, cauliflower, broccoli, dried herbs & spices)	2-4 times per week	60	33.0	21	22.8	39	43.3
	daily	1	0.5	1	1.1	0	0.0
	never	0	0.0	0	0.0	0	0.0
Salty Food (pickled, salty cheese, salted fish, dokka, ...)	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
	never	55	30.2	15	16.3	40	44.4
		27		16		11	
		96		61		35	
		54		12		42	

t=1.6, *p*= 0.107

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

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

17 *H. pylori*; *Helicobacter pylori*

18 IBD; inflammatory bowel disease

19 ~ *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		<i>H. pylori</i> infection in IBD patients				<i>p</i> ~
	Total (n=182)		Negative (n=92)		Positive (n=90)		
	No.	%	No.	%	No.	%	
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	<i>t</i> = -0.5 <i>p</i> = 0.616			
	ESR (males <15 mm/h, females <20 mm/hr)	34.1 ± 13.6	33.6 ± 14.1	34.6 ± 13.2	<i>t</i> = -0.49 <i>p</i> = 0.628			
	CRP (< 10 mg/L)	30.6 ± 23.5	28.2 ± 23.9	33.0 ± 23.0	<i>t</i> = -1.4 <i>p</i> = 0.162			
	FBG (70-100 mg/dl)	95.5 ± 11.4	96.1 ± 11.6	94.9 ± 11.1	<i>t</i> = 0.7 <i>p</i> = 0.504			
	Fecal Calprotectin (<50 µg/g stool)	516.2 ± 210.0	517.4 ± 214.4	515.0 ± 206.7	<i>t</i> = -1.8 <i>p</i> = 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	<i>t</i> = 0.8 <i>p</i> = 0.940			
Laboratory findings	WBCs (4-11 k/ul)	6618.7 ± 1527.9	6420.8 ± 1530.5	6821.1 ± 1506.9	<i>t</i> = -0.8 <i>p</i> = 0.419			
	Platelets (150-450 k/ul)	300.6 ± 64.5	304.8 ± 61.7	296.2 ± 67.4	<i>t</i> = 0.9 <i>p</i> = 0.372			
	Body weight	67.9 ± 11.9	67.6 ± 12.2	68.3 ± 11.7	<i>t</i> = -0.4 <i>p</i> = 0.693			
	Pulse (60-100 beats per minute)	80.6 ± 5.3	80.5 ± 5.6	80.8 ± 5.0	<i>t</i> = -0.3 <i>p</i> = 0.745			
	Pulse pressure (40 and 60 mmHg)	41.3 ± 6.2	41.5 ± 6.8	41.0 ± 5.6	<i>t</i> = 0.6 <i>p</i> = 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

1									
2									
3		GERD	75	41.2	35	38.0	40	44.4	
4		Antral gastritis	33	18.1	15	16.3	18	20.0	
5		Pangastritis	56	30.8	32	34.8	24	26.7	
6		Pre-pyloric erosions	17	9.3	10	10.9	7	7.8	
7		Superficial duodenal bulb ulcers	28	15.4	15	16.3	13	14.4	
8		Incompetent cardia	10	5.5	7	7.6	3	3.3	
9		Gastrodudonitis	21	11.5	9	9.8	12	13.3	
10		Antral erosions	17	9.3	9	9.8	8	8.9	
11		Duodenal inflammatory polyp	7	3.8	4	4.3	3	3.3	
12		Erosive gastritis	1	0.5	0	0.0	1	1.1	
13		Peptic ulcer	1	0.5	1	1.1	0	0.0	
14		Erosive gastrodudonitis	4	2.2	2	2.2	2	2.2	
15		Chronic active colitis	63	34.6	34	37.0	29	32.2	
16		Chronic active ileocolitis- Ulcerative Colitis	25	13.7	11	12.0	14	15.6	
17		Chronic active colitis with lymphoid hyperplasia	5	2.7	1	1.1	4	4.4	
18		Chronic active colitis with multiple superficial ulcers	3	1.6	0	0.0	3	3.3	
19		Internal piles	4	2.2	1	1.1	3	3.3	
20		ulcerative proctitis	15	8.2	3	3.3	12	13.3	
21		Chronic active ulcerative pancolitis	1	0.5	1	1.1	0	0.0	
22		multiple superficial aphthoid ulcers - mild ileitis of Crohn's disease	35	19.2	20	21.7	15	16.7	0.087
23	Colonoscopy	Ileocolitis - Crohn's disease	31	17.0	14	15.2	17	18.9	
24		Rectal Crohn's	10	5.5	5	5.4	5	5.6	
25		Multiple superficial colonic ulcers and skip lesions with eosinophilic infiltration, terminal ileitis - Crohn's disease	13	7.1	9	9.8	4	4.4	
26		Chronic active colitis with lymphoid hyperplasia - Crohn's disease	2	1.1	0	0.0	2	2.2	
27		perianal fistula	1	0.5	1	1.1	0	0.0	
28		None	137	75.3	77	83.7	60	66.7	
29		Fistula	4	2.2	2	2.2	2	2.2	
30		Stricture	4	2.2	1	1.1	3	3.3	
31	History of complications	Ulcer	26	14.3	10	10.9	16	17.8	0.066
32		Intestinal perforation	0	0.0	0	0.0	0	0.0	
33		GIT cancer	2	1.1	1	1.1	1	1.1	
34		Abscess formation	5	2.7	0	0.0	5	5.6	
35									
36									
37									
38									
39									
40									
41									
42									
43									
44									
45									
46									

	Others	5	2.7	2	2.2	3	3.3	
	None	171	94.0	91	98.9	80	88.9	
	Strictureplasty	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

For peer review only

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

Parameter	<i>H. Pylori</i> infection	Follow-up period (3 Months)						Repeated Measures ANOVA														
		Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test				Within Subject Effects					Between Subject Effects				
		Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Wilks' Lambda	F ^a	p	Partial Eta Squared	Observed power	Effect of Time (T) versus State (T \times 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 \pm 12.6	29.8 \pm 9.0	26.6 \pm 8.4	23.2 \pm 8.1	20.5 \pm 7.3	17.7 \pm 7.1	7.9	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 \pm 13.7	28.8 \pm 10.7	24.4 \pm 8.8	20.2 \pm 7.8	18.8 \pm 7.2	15.3 \pm 5.4	5.0	T \times S	0.846	0.540	0.069	0.312	T \times S	0.37	0.71	0.005	0.009	0.927			
CRP	Positive	31.2 \pm 18.6	25.4 \pm 14.7	22.0 \pm 12.5	18.3 \pm 8.7	14.4 \pm 7.5	13.8 \pm 7.3	7.3	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 \pm 26.2	25.4 \pm 21.8	20.6 \pm 16.6	17.1 \pm 14.0	13.8 \pm 10.1	11.4 \pm 7.5	6.9	T \times S	0.893	0.505	0.072	0.330	T \times S	0.420	0.581	0.006	0.35	0.556			
FBG	Positive	93.1 \pm 9.5	91.2 \pm 11.6	91.6 \pm 9.6	94.5 \pm 13.8	93.4 \pm 11.8	93.4 \pm 10.9	6.9	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 \pm 8.8	92.3 \pm 6.8	92.1 \pm 7.7	93.6 \pm 8.6	93.6 \pm 8.7	92.5 \pm 5.9	6.9	T \times S	0.385	0.886	0.032	0.153	T \times S	0.42	0.832	0.006	0.289	0.593			
Calprotectin	Positive	573.8 \pm 218.6	380.7 \pm 190.6	171.3 \pm 96.1	75.2 \pm 30.8	30.8	0.9	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 \pm 216.3	317.6 \pm 153.5	168.3 \pm 84.2	84.2	49.8	0.9	T \times S	1.350	0.266	0.053	0.344	T \times S	2.31	0.11	0.030	2.87	0.037				
Hb	Positive	10.6 \pm 1.3	10.7 \pm 1.3	10.9 \pm 1.3	11.3 \pm 1.1	11.5 \pm 0.9	11.6 \pm 1.0	0.9	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 \pm 1.1	10.7 \pm 1.2	10.9 \pm 1.02	110.1 \pm 10.1	11.4 \pm 1.1	11.8 \pm 0.84	0.84	T \times S	2.440	0.034	0.175	0.791	T \times S	1.06	0.063	0.032	3.89	0.052			
WBCs	Positive	6385.5 \pm 1029.0	6704.8 \pm 1023.4	6512.9 \pm 1013.5	6298.4 \pm 1046.3	6582.3 \pm 1075.4	6438.1 \pm 1255.8	6125.5 \pm 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 \pm 1479.9	6153.3 \pm 1263.2	6062.2 \pm 1102.1	5887.8 \pm 966.4	6171.1 \pm 1030.4	6038.7 \pm 1093.6	5999.6 \pm 1052.4	T \times S	1.324	0.258	0.103	0.486	T \times S	1.03	0.399	0.014	3.44	0.068			
Platelets	Positive	272.6 \pm 51.0	286.9 \pm 44.8	276.3 \pm 40.5	279.1 \pm 35.1	276.4 \pm 31.5	277.1 \pm 30.3	282.9 \pm 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 \pm 69.6	291.8 \pm 50.0	292.5 \pm 41.8	293.1 \pm 42.9	291.9 \pm 41.2	288.2 \pm 40.7	292.5 \pm 44.1	T \times S	0.753	0.610	0.061	0.278	T \times S	1.18	0.317	0.016	0.527	0.47			
Total symptom score	Positive	21.6 \pm 2.3	21.5 \pm 2.6	16.4 \pm 3.6	7.2 \pm 3.0	3.7 \pm 3.6	3.1 \pm 2.4	0.1 \pm 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 \pm 3.5	20.2 \pm 4.1	13.4 \pm 5.6	5.9 \pm 3.2	3.6 \pm 3.4	3.3 \pm 3.1	0.8 \pm 1.9	T \times S	2.040	0.072	0.153	0.702	T \times S	2.85	0.052	0.038	7.61	0.094			
Body weight	Positive	63.9 \pm 9.8	64.1 \pm 10.1	65.0 \pm 10.0	65.5 \pm 10.0	65.8 \pm 10.0	66.0 \pm 10.0	66.1 \pm 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 \pm 11.0	64.9 \pm 10.9	65.3 \pm 10.8	65.6 \pm 10.7	66.0 \pm 10.6	66.6 \pm 10.5	67.1 \pm 10.4	T \times S	2.280	0.046	0.166	0.759	T \times S	1.40	0.252	0.018	11.1	0.001			
Pulse	Positive	80.8 \pm 2.5	79.7 \pm 2.5	76.8 \pm 4.5	76.0 \pm 4.7	77.7 \pm 4.5	77.5 \pm 4.4	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
	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

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

Parameter	<i>H. pylori</i> infection	Follow-up period (3 Months)								Repeated Measures ANOVA														
		Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Multivariate test	Within Subject Effects					Between Subject Effects									
		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 ± 9.1	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	150.1 ± 73.7	74.1 ± 28.8	74.1 ± 28.8	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	175.6 ± 92.5	86.3 ± 80.5	86.3 ± 80.5	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	71.1 ± 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					

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Pulse pressure	Positive	41.7 ±	41.2 ±	40.2 ±	40.8 ±	40.3 ±	39.7 ±	41.9 ±	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	6.2	7.2	8.8	8.8	7.9	6.9	9.9										T × S	1.026			

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

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Table S5: Univariate analysis for factor associated with IBD flare during 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.	%					
8	<i>H. pylori</i> infection	Negative	92	50.5	73	51.0	19	48.7	0.820	1.08	0.57	2.02
		Positive	90	49.5	70	49.0	20	51.3	0.837			
9		NA	92	50.5	73	51	19	48.7	0.540	0.53	0.07	3.99
10	Onset of <i>H. pylori</i> infection	Few weeks ago	7	3.8	6	4.2	1	2.6	0.488	1.54	0.45	5.21
		3-6 months	10	5.5	7	4.9	3	7.7	0.789	0.88	0.35	2.21
12		6 months - 1 year	35	19.2	29	20.3	6	15.4	0.560	1.26	0.58	2.70
		> 1 year	38	20.9	28	19.6	10	25.6				
13	Type of IBD diagnosed	Crohn's disease	86	47.3	67	46.9	19	48.7	0.697	0.88	0.47	1.66
		Ulcerative colitis	96	52.7	76	53.1	20	51.3	0.526			
14		<i>H. pylori</i> Negative	44	24.2	33	23.1	11	28.2	0.374	0.66	0.27	1.65
15	Crohn's disease	<i>H. pylori</i> Positive	42	23.1	34	23.8	8	20.5	0.196	0.55	0.22	1.36
16		<i>H. pylori</i> Negative	48	26.4	40	28.0	8	20.5	0.853	0.93	0.41	2.10
		<i>H. pylori</i> Positive	48	26.4	36	25.2	12	30.8				
17		Conventional	106	58.2	86	60.1	20	51.3	0.254	1.44	0.77	2.70
18	Treatment of IBD	Biological	76	41.8	57	39.9	19	48.7				
19		Male	94	51.6	76	53.1	18	46.2	0.241	1.46	0.78	2.74
20	Sex	Female	88	48.4	67	46.9	21	53.8	0.708		ref	
21		16 - <20 Years	20	11.0	15	10.5	5	12.8	0.814	0.89	0.35	2.30
22	Age	20 - <35 Years	136	74.7	106	74.1	30	76.9	0.440	4.60	0.16	2.22
		35 - 55 Years	26	14.3	22	15.4	4	10.3				
23		Mean ± SD	27.0 ± 7.3		27.8 ± 7.6		23.8 ± 4.9		0.008	$t = 4.0, p < 0.001$		0.92
24		10 - >19	69	37.9	48	33.6	21	53.8	0.086			0.98
25	Age at diagnosis	20 - <30	83	45.6	71	49.7	12	30.8	0.029	0.45	0.22	0.92
26		30 - 45	30	16.5	24	16.8	6	15.4	0.341	0.64	0.26	1.60
27		Mean ± SD	27.0 ± 7.3		22.3 ± 6.5		19.1 ± 4.8		0.01	$t = 3.4, p = 0.001$		0.92
28												0.98
28	Residence	Rural	88	48.4	74	51.7	14	35.9	0.051	1.92	1.00	3.70
29		Urban	94	51.6	69	48.3	25	64.1	0.982	0.00	0.00	
30		Illiterate	2	1.1	2	1.4	0	0.0	0.160	0.42	0.13	1.40
31		Read and Write	23	12.6	20	14.0	3	7.7	0.978	0.00	0.00	
31	Education	Primary	4	2.2	4	2.8	0	0.0	0.309	0.47	0.11	2.00
32		Preparatory	13	7.1	11	7.7	2	5.1	0.487	0.76	0.36	1.64
33		Secondary	44	24.2	35	24.5	9	23.1	0.715			
34		University education	96	52.7	71	49.7	25	64.1				
34	Working status	No	88	48.4	63	44.1	25	64.1	0.032	0.49	0.25	0.94
35		Yes	94	51.6	80	55.9	14	35.9	0.024			
36		Unemployed	37	20.3	31	21.7	6	15.4	0.023	2.89	1.15	7.25
37		Student	45	24.7	26	18.2	19	48.7	0.353	2.73	0.33	22.67
38	Occupation	Clerical	2	1.1	1	0.7	1	2.6	0.962	0.97	0.31	3.02
39		Professional	39	21.4	33	23.1	6	15.4	0.566	0.63	0.13	3.10
40		Housewife	21	11.5	19	13.3	2	5.1	0.701	0.76	0.19	3.05
41		Auxiliary worker	22	12.1	19	13.3	3	7.7	0.643	0.69	0.14	3.40
41		Farmer	16	8.8	14	9.8	2	5.1	0.016	2.20	1.16	4.21
42		Married	73	40.1	50	35.0	23	59.0	0.018	2.20	1.15	4.21
42	Marital status	Not married							0.276	3.08	0.41	23.35
43		Single	106	58.2	91	63.6	15	38.5	0.981	0.00	0.00	
44		Widowed	2	1.1	1	0.7	1	2.6				
44		Divorced	1	0.5	1	0.7	0	0.0	.015	2.730	1.215	6.14
45		High	58	31.9	41	28.7	17	43.6	.127	1.938	.828	4.54
46	Socioeconomic standard	Middle	52	28.6	39	27.3	13	33.3	.052			
47		Low	72	39.6	63	44.1	9	23.1				
47	Consanguinity	No	144	79.1	114	79.7	30	76.9	0.888	0.95	0.45	2.00
48		Yes	38	20.9	29	20.3	9	23.1				
49	Being breastfed	No	26	14.3	22	15.4	4	10.3	0.382	1.59	0.56	4.47
50		Yes	156	85.7	121	84.6	35	89.7	0.915			
51	Smoking	Never	150	82.4	119	83.2	31	79.5	0.774	1.128	0.50	2.57
52		Current smoker	26	14.3	19	13.3	7	17.9	0.775	0.75	0.10	5.48
52		Ex-Smoker	6	3.3	5	3.5	1	2.6	0.679			
53		NA	153	84.1	119	83.2	34	87.2	0.573	0.71	0.22	2.32
53	Age of starting Smoking	< 20 Years	17	9.3	14	9.8	3	7.7	0.475	0.59	0.14	2.48
54		20 - 30 Years	12	6.6	10	7.0	2	5.1				
55		Never	180	98.9	143	100.0	37	94.9	0.079	3.59	0.86	14.94
56	Smoking other than cigarette	Shisha	2	1.1	0	0.0	2	5.1				
57	Alcohol	No	182	100.0	143	100.0	39	100.0				
58		Yes	0	0.0	0	0.0	0	0.0				
58	Drug Abuse	No	182	100.0	143	100.0	39	100.0				
59		Yes	0	0.0	0	0.0	0	0.0				
60	Chronic diseases	No	82	45.1	64	44.8	18	46.2	0.811	0.93	0.49	1.74
60		Yes	100	54.9	79	55.2	21	53.8				

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3		Diabetes Mellitus	10	5.5	8	5.6	2	5.1				
4		Hypertension	30	16.5	25	17.5	5	12.8				
5		Bronchial Asthma/COPD	15	8.2	13	9.1	2	5.1				
6		Heart disease	1	0.5	1	0.7	0	0.0				
7		Renal disease	1	0.5	0	0.0	1	2.6				
8		Liver disease	1	0.5	1	0.7	0	0.0				
9		SLE	0	0.0	0	0.0	0	0.0				
10		rheumatoid arthritis	6	3.3	5	3.5	1	2.6				
11		Skin allergy	18	9.9	16	11.2	2	5.1				
12		Hyperthyroidism	4	2.2	3	2.1	1	2.6				
13		Hypothyroidism	8	4.4	5	3.5	3	7.7				
14		Other autoimmune diseases	1	0.5	1	0.7	0	0.0				
15		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				
16		No	163	89.6	129	90.2	34	87.2				
17	Autoimmune diseases	Yes	19	10.4	14	9.8	5	12.8	0.555	1.33	0.52	3.39
18		None	13	7.1	10	7.0	3	7.7				
19		Analgesic (NSAIDs)	12	6.6	7	4.9	5	12.8				
20		Antidiabetics	6	3.3	6	4.2	0	0.0				
21		Antihypertensives	32	17.6	27	18.9	5	12.8				
22	Medications	corticosteroids	10	5.5	5	3.5	5	12.8				
23		IBD therapy	151	83.0	118	82.5	33	84.6				
24		Hormonal contraceptives	2	1.1	0	0.0	2	5.1				
25		Thyroxin	9	4.9	6	4.2	3	7.7				
26		Others	37	20.3	28	19.6	9	23.1				
27		No	141	77.5	108	75.5	33	84.6				
28	Family history of similar condition	Yes	41	22.5	35	24.5	6	15.4	0.279	0.62	0.26	1.48
29		Yes; first degree relatives	40	22.0	34	23.8	6	15.4				
30		Yes; other relatives	1	0.5	1	0.7	0	0.0				
31		Other autoimmune disease	3	1.6	3	2.1	0	0.0				
32												
33												
34	Transportation	not working	71	39.0	60	42.0	11	28.2	0.208			
35		On foot	19	10.4	17	11.9	2	5.1	0.503	0.60	0.13	2.70
36		By bicycle	4	2.2	3	2.1	1	2.6	0.709	1.48	0.19	11.47
37		Public transport or car	88	48.4	63	44.1	25	64.1	0.090	1.85	0.91	3.76
38	Working activity	not working	65	35.7	53	37.1	12	30.8	0.655			
39		minimal	43	23.6	31	21.7	12	30.8	0.249	1.60	0.72	3.57
40		moderate	73	40.1	58	40.6	15	38.5	0.882	1.06	0.50	2.26
41		high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
42	Activity outside work	not working	59	32.4	48	33.6	11	28.2	0.733			
43		minimal	90	49.5	71	49.7	19	48.7	0.838	1.08	0.51	2.27
44		moderate	32	17.6	23	16.1	9	23.1	0.293	1.60	0.66	3.87
45		high	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00	
46	Regular exercise	never	136	74.7	109	76.2	27	69.2	0.397			
47		yes frequent (>3 times/ week)	7	3.8	5	3.5	2	5.1	0.758	1.25	0.30	5.27
48		yes infrequent (<3 times/ week)	39	21.4	29	20.3	10	25.6	0.176	1.66	0.80	3.45
49	Total physical activity score		2.8 ± 2.1		2.7 ± 2.2		2.9 ± 2.0		0.855	t= 0.40, p= 0.695	1.01	0.88
50												
51	Dietary habits											
52	Food source	Homemade	97	53.3	78	54.5	19	48.7	0.858			
53		Restaurant	6	3.3	5	3.5	1	2.6	0.829	0.80	0.11	5.99
54		Mixed	79	43.4	60	42.0	19	48.7	0.639	1.16	0.62	2.20
55	Junk Food, Fast Food	never	50	27.5	41	28.7	9	23.1	0.806			
56		occasionally	128	70.3	99	69.2	29	74.4	0.535	1.27	0.60	2.68
57		daily	4	2.2	3	2.1	1	2.6	0.706	1.49	0.19	11.75
58	Saturated Fat (butter, ghee, cream, ..etc)	never	5	2.7	5	3.5	0	0.0	0.399			
59		once per week	79	43.4	65	45.5	14	35.9	0.898	2383.0	0.00	1.6×10 ⁶⁸
60		2-4 times per week	85	46.7	62	43.4	23	59.0	0.891	4190.1	0.00	2.9×10 ⁶⁸
61		daily	13	7.1	11	7.7	2	5.1	0.898	2475.2	0.00	1.7×10 ⁶⁸
62	Transfat (such as in cake, cookies, pies, dessert, cream, mayonnaise,	never	30	16.5	27	18.9	3	7.7	0.017			
63		once per week	91	50.0	75	52.4	16	41.0	0.506	1.52	0.44	5.22
64		2-4 times per week	60	33.0	41	28.7	19	48.7	0.061	3.21	0.95	10.85
65	Processed meat as burger & sausage)	daily	1	0.5	0	0.0	2	5.1	0.020	14.82	1.52	144.45
66	Food rich in insoluble fibers (such as whole bread, cereals, beans,	never	0	0.0	0	0.0	0	0.0				
67		once per week	39	21.4	31	21.7	8	20.5	0.022			
68		2-4 times per week	88	48.4	76	53.1	12	30.8	0.362	0.66	0.27	1.61
69		daily	55	30.2	36	25.2	19	48.7	0.163	1.80	0.79	4.12

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3	Artichoke, squash,												
4	cabbage, cauliflower,												
5	broccoli, dried herbs & spices, fruits, vegetables)												
6	Salty Food (pickled,	never	27	14.8	22	15.4	5	12.8	0.470				
7	salty cheese, salted fish,	once per week	96	52.7	78	54.5	18	46.2	0.885	0.93	0.34	2.51	
8	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	
9	Fruits and Vegetables	never	2	1.1	0	0.0	2	5.1	0.005				
10		once per week	56	30.8	44	30.8	12	30.8	0.001	0.07	0.01	0.31	
11		2-4 times per week	81	44.5	64	44.8	17	43.6	0.000	0.07	0.02	0.31	
12		daily	43	23.6	35	24.5	8	20.5	0.001	0.07	0.01	0.34	
13	Red meat	never	16	8.8	13	9.1	3	7.7	0.959				
14		once per week	113	62.1	88	61.5	25	64.1	0.950	0.96	0.29	3.20	
15		2-4 times per week	53	29.1	42	29.4	11	28.2	0.835	0.87	0.24	3.14	
16		daily	0	0.0	0	0.0	0	0.0					
17	Under cooked meat	never	157	86.3	120	83.9	37	94.9	0.259				
18		once per week	24	13.2	22	15.4	2	5.1	0.100	0.30	0.07	1.26	
19		2-4 times per week	1	0.5	1	0.7	0	0.0	0.981	0.00	0.00		
20		daily	0	0.0	0	0.0	0	0.0					
21	Fish	never	17	9.3	16	11.2	1	2.6	0.220				
22		once per week	91	50.0	67	46.9	24	61.5	0.102	5.30	0.72	39.19	
23		2-4 times per week	74	40.7	60	42.0	14	35.9	0.176	4.06	0.53	30.95	
24		daily	0	0.0	0	0.0	0	0.0					
25	Consumption of caffeine in diet (tea, coffee)	never	25	13.7	22	15.4	3	7.7	0.027				
26		once per week	20	11.0	16	11.2	4	10.3	0.571	1.54	0.34	6.89	
27		2-4 times per week	61	33.5	54	37.8	7	17.9	0.949	0.96	0.25	3.70	
28		daily	76	41.8	51	35.7	25	64.1	0.078	2.94	0.89	9.74	
29	Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	never	7	3.8	7	4.9	1	2.6	0.181				
30		once per week	67	36.8	56	39.2	11	28.2	0.780	1.34	0.17	10.48	
31		2-4 times per week	91	50.0	70	49.0	21	53.8	0.519	1.93	0.26	14.38	
32		daily	17	9.3	10	7.0	7	17.9	0.215	3.77	0.46	30.66	
33	Dairy products	never	27	14.8	22	15.4	5	12.8	0.552				
34		once per week	49	26.9	41	28.7	8	20.5	0.831	0.89	0.29	2.71	
35		2-4 times per week	78	42.9	58	40.6	20	51.3	0.409	1.51	0.57	4.03	
36		daily	28	15.4	22	15.4	6	15.4	0.497	1.51	0.46	4.98	
37	Average number of glasses of water consumed per day	one cup	9	4.9	6	4.2	3	7.7	0.346				
38		2-3 cups	73	40.1	59	41.3	14	35.9	0.367	0.56	0.16	1.96	
39		at least 4 cups	73	40.1	54	37.8	19	48.7	0.734	0.81	0.24	2.74	
40		4-8 cups	27	14.8	24	16.8	3	7.7	0.156	0.31	0.06	1.56	
41	Snacks between meals	Never	60	33.0	54	37.8	6	15.4	0.009				
42		Occasionally	121	66.5	89	62.2	32	82.1	0.014	2.99	1.25	7.14	
43		Daily	1	0.5	0	0.0	1	2.6	0.009	17.12	2.02	144.86	
44	Number of meals per day	2	68	37.4	55	38.5	13	33.3	0.058				
45		3	109	59.9	86	60.1	23	59.0	0.857	1.06	0.54	2.10	
46		4	5	2.7	2	1.4	3	7.7	0.022	4.37	1.24	15.37	
47	Total food score (favorable food habits)		11.4 ± 4.5		11.9 ± 4.3		9.9 ± 5.0		0.029	t=2.2, p=0.029	0.93	0.86	0.99
48		No	119	65.4	95	66.4	24	61.5					
49		Yes	63	34.6	48	33.6	15	38.5	0.406	1.32	0.69	2.51	
50		Cereals	0	0.0	0	0.0	0	0.0					
51		Brown rice	5	2.7	4	2.8	1	2.6					
52		Whole grain bread	2	1.1	2	1.4	0	0.0					
53		Seeds (beans, peas)	7	3.8	3	2.1	4	10.3					
54		Fruits (apples; plums, peaches; skin removed)	0	0.0	0	0.0	0	0.0					
55		High fat or protein food	34	18.7	25	17.5	9	23.1					
56		Vegetables (beets, broccoli, cabbage, cauliflower, onions, garlic, pepper)	1	0.5	1	0.7	0	0.0					
57		Raw green vegetables	6	3.3	6	4.2	0	0.0					
58		Spices	9	4.9	7	4.9	2	5.1					
59		Fried food	28	15.4	22	15.4	6	15.4					
60		Baked dessert	1	0.5	1	0.7	0	0.0					
61		Milk and dairy products	5	2.7	3	2.1	2	5.1					
62		Carbonated drinks	14	7.7	11	7.7	3	7.7					
63		Tea and coffee	1	0.5	1	0.7	0	0.0					
64		Others	5	2.7	4	2.8	1	2.6					
65		No	143	78.6	113	79.0	31	79.5					
66		Yes	38	20.9	30	21.0	8	20.5	0.982	0.99	0.46	2.16	
67		Low fiber (bananas, cantaloupe)			5	3.5	2	5.1					
68		Refined grains (white pasta, white rice, and oatmeal, potatoes)			10	7	3	7.7					

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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

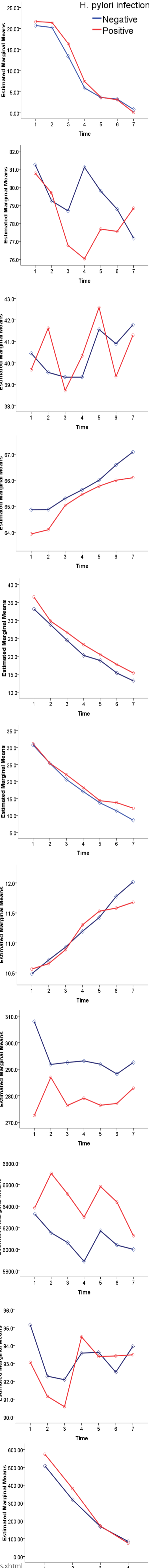
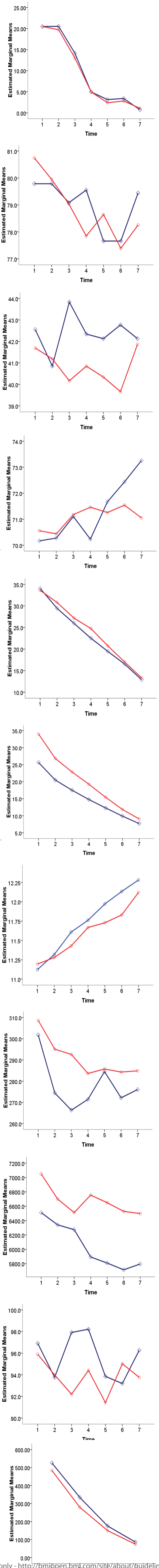
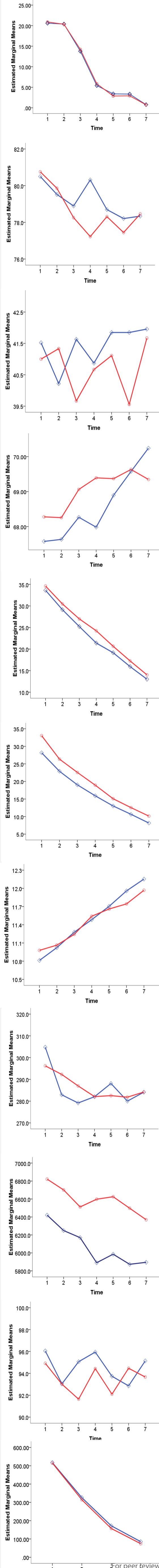
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All Cases

Conventional Therapy

Biological Therapy

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H. pylori infection

— Negative
— Positive

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 abscess

+ biologics (infliximab, adalimumab)

List of Biologics used

- Infliximab (Remicade)
IV 5 mg/kg or 10 mg/kg if severe
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 severe
- 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	

1	broccoli, dried herbs & spices, fruits, vegetables)		
2	28. Salty Food (pickled, salty cheese, salted fish, dokka, ...	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
3		If daily , mention the number of servings per day	
4	29. Fruits & Vegetables	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
5		If daily , mention the number of servings per day	
6	30. Red meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
7		If daily , mention the number of servings per day	
8	31. Under cooked meat	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
9		If daily , mention the number of servings per day	
10	32. Fish	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
11		If daily , mention the number of servings per day	
12	33. Consumption of caffeine in diet (tea, coffee)	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
13		If daily , mention the number of servings per day	
14	34. Soft drinks (carbonated drinks, cola, canned and sweetened drinks)	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
15		If daily , mention the number of servings per day	
16	35. Dairy products	(0) Never (1) once per week (2) 2-4 times per week (3) daily	
17		If daily , mention the number of servings per day	
18	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	
19	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	
20	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.....	
21	39. Food preparation method	(0) No preference (1) boiling (2) grilling (3) steaming (4) frying	
22	40. Number of meals per day	
23	41. Snacks between meals	(0) Never (1) occasionally (2) daily; per day	
24	II- Clinical data		
25	42. Type of IBD diagnosed	(0) Crohn's disease (1) ulcerative colitis	
26	43. Age at diagnosisyears old	
27	44. History of H. pylori infection		
28	45. If yes mention the onset	(-1) NA (1) few weeks (2) 3-6 months (3) 6 months- 1 year (4) ≥ 1 year	
29	46. History of receiving H. pylori eradication therapy during the past 12 months	(0) No (1) Yes;	
30	47. History of complications	(0) None (1) fistula (2) stricture (3) ulcers (4) intestinal perforation (5) GIT cancer (6) abscess formation (7) others.....	
31	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	
32	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) Moltium (20) H2 receptor antagonist (21) antacids (22) antispasmodics (23) others.....	

1 2 3 4 5 6 7 8	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.....	
9 10	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	
11 12	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

16 17	53. Baseline Body Weight kg	
18	54. Heightcm	

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	Follow Up					
	treatment	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							

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60STROBE 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.