Gastrointestinal tuberculosis is not associated with proton pump inhibitors: A retrospective cohort study

Kyoung Sup Hong, Seung Joo Kang, Jong Kyoung Choi, Ju Han Kim, Heewon Seo, Suehyun Lee, Jae-Woo Jung, Hye-Ryun Kang, Sang-Heon Cho, Joo Sung Kim

Kyoung Sup Hong, Jae-Woo Jung, Hye-Ryun Kang, Sang-Heon Cho, Department of Internal Medicine, Drug Safety Monitoring Center, Seoul National University Hospital, Seoul National University College of Medicine, Seoul 110799, South Korea
Seung Joo Kang, Jong Kyoung Choi, Joo Sung Kim, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul 110799, South Korea
Ju Han Kim, Heewon Seo, Suehyun Lee, Division of Biomedical Informatics, Systems Biomedical Informatics Research Center, Seoul National University College of Medicine, Seoul 110799, South Korea

Author contributions: Hong KS and Kim JS designed the study and wrote the manuscript; Jung JW, Kang HR, and Cho SH contributed to the conception and design; Kang SJ contributed to the data analysis and interpretation; Kim JH contributed to the conception and data acquisition; and Choi JK, Seo H, and Lee S contributed to the data acquisition.

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Correspondence to: Dr. Joo Sung Kim, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul 110799, South Korea. jooskim@snu.ac.kr
Telephone: +82-2-20722228 Fax: +82-2-7629662
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Abstract

AIM: To evaluate the effect of proton pump inhibitors (PPIs) on the development of gastrointestinal tuberculosis.

METHODS: All patients who were more than 20 years old and who had received a prescription for PPIs among those who visited Seoul National University Hospital from January 1, 2005 to December 31, 2009 were identified. Due to the low sensitivity of the microbiologic test and the nonspecific pathologic findings, the diagnosis of gastrointestinal tuberculosis was confirmed through the presence of active ulcerations and the responses to anti-tuberculosis medications. The patients were divided into two groups according to treatment duration (group 1: ≤ 3 mo; group 2: > 3 mo) and were followed up from the time they took the first prescription of PPIs until their last visit. Logistic regression analysis was used to calculate the relative risks (RR) and 95%CI, adjusting for covariates.

RESULTS: Among the 61,834 patients exposed to PPIs (50,534 in group 1; 11,300 in group 2), 21 patients were diagnosed with PPI-associated gastrointestinal tuberculosis during 124,274 person-years of follow-up. Of 21 patients, 12 who revealed only scar changes in the colonoscopy were excluded from the statistical analyses. Of those who remained, 2 were excluded because they underwent gastrointestinal endoscopy within 4 wk of the first prescription for PPIs. Longer exposure to PPI was associated with a higher mean age (55.0 ± 14.5 in group 1 vs 58.2 ± 13.3 in group 2, P < 0.001) and a higher Charlson co-morbidity index (0.50 ± 0.93 in group 1 vs 0.77 ± 1.14 in group 2, P < 0.001). The true incidence of active gastrointestinal tuberculosis was 0.65 per 1000 person-years in group 1 and 0.03 per 1 000 person-years in group 2. Like the less-than-three-month PPI treatment period in group 1, the over-three-month PPI therapy period in group 2 was not associated with increased risk of acquiring gastrointestinal tuberculosis, after adjusting for age and co-morbidities, whereas the Charlson co-morbidity index was associated with increased risk of acquiring gastrointestinal tuberculosis based on the score [RR: (reference 1) in group 1 vs 1.518 in group 2; 95% CI: 1.040-2.216, P = 0.03].

CONCLUSION: Long-term PPI therapy does not seem to be associated with increased risk of acquiring gas-
trointestinal tuberculosis, but a higher Charlson co-morbidity index is associated with such.

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Key words: Proton pump inhibitor; Acid suppression; Tuberculosis; Gastrointestinal tuberculosis; Tuberculous colitis


INTRODUCTION

Gut flora is closely related to human health and disease[10]. The intestinal microflora is assumed to be affected by a series of factors that determine the intraluminal environment: the pH in the gastrointestinal tract, oxygen tension, nutrient availability, colonic physiology, bacterial interference, etc.[2]. One of the major factors controlling the bacterial distribution in the gastrointestinal tract is the gastric acid barrier, which may be affected by the use of inhibitors of gastric acid secretion, gastrectomy, and dietary indiscretion and stress.[3]. The establishment of enteric infection has been considered directly related to gastric acidity reduction[4-5]. Several recent studies associated proton pump inhibitors (PPIs) with a two- to three-fold increase in the risk of Clostridium difficile infection[6-9].

PPIs are currently the most powerful gastric acid suppressants and the drug of choice for the treatment of gastroesophageal reflux disease and peptic ulcer. PPIs are very powerful acid suppressors whose effects mean the percentage time intragastric pH > 4 may increase from 20% at baseline to over 60% within a week[10]. Today’s life expectancy is longer than ever before, and the number of patients who take antplatelet agents to prevent the onset of vascular diseases is increasing. Along with this, more and more patients are obliged to take prophylactic gastric acid suppressants, including PPIs, to prevent severe complications, such as peptic ulcer bleeding.

Tuberculosis is still an important health problem in many developing countries, including South Korea[10]. Unlike in developing countries, the disease used to be uncommon in developed countries, but it has re-emerged in the Western countries as a result of the acquired immunodeficiency syndrome (AIDS) epidemic therein as well as the influx of immigrants from developing countries[11-13]. Gastrectomy has been known to be a potential risk factor for tuberculosis for decades[14-16]. To these authors’ knowledge, however, there has been no report about a possible association between PPI use and gastrointestinal tuberculosis. This study was thus conducted to evaluate the effect of PPIs on the development of gastrointestinal tuberculosis.

MATERIALS AND METHODS

Setting and design

This study is part of a hospital-based longitudinal cohort study entitled “Seoul National University Hospital (SNUH) PPI Safety Study,” in which these authors analyzed the data regarding patients who visited SNUH and who were treated with PPI between January 1, 2005, and December 31, 2009. SNUH is a large urban tertiary care center in Seoul, South Korea. The hospital’s institutional review board approved the study with a waiver of informed consent.

Data sources

Data were obtained from a clinical data warehouse fully synchronized with the electronic medical recording (EMR) system created as part of the usual care. SNUH Clinical Data Warehouse (CDW) contains all the information from each visit, not only routine clinical data such as the demographics, diagnosis, medication profiles, laboratory results, and lengths of stay of inpatients since 2001 but also the electronic charts since 2004.

Patients and case definitions

All patients who were at least 20 years old at their first visit and who ingested PPI on prescription during the five-year screening period were included in the study. According to a large retrospective study including 225 Korean patients, histological examination of the colonscopic biopsy specimens revealed caseous necrosis in only 11.1% of the patients, and acid-fast bacilli (AFB) in 17.3% of the patients. Mycobacterium tuberculosis was isolated from the culture of biopsy specimens in 29.3% of the patients[17]. Even though granulomas were observed in 72.4% of the patients, granuloma is not a specific finding in intestinal tuberculosis. Due to the low sensitivity of the microbiologic test and the nonspecific pathologic findings, the diagnosis of active gastrointestinal tuberculosis was confirmed through both an endoscopic finding of active transverse ulcerations and a good response to anti-tuberculosis treatment, which was confirmed through a follow-up colonoscopy within three months from the initiation of the treatment. The definition of good therapeutic response was complete or near-complete healing of all the ulcerations in the follow-up colonoscopy.

The patients in whom colonoscopy revealed only scar changes were excluded from the statistical analysis for two reasons: (1) the exact temporal relationship between PPI ingestion and the development of gastrointestinal tuberculosis could not be verified; and (2) the diagnosis of tuberculosis could not be confirmed as there was no need for anti-tuberculosis treatment and due to the low sensitivity of the histological evaluation of the biopsy specimens. As tuberculosis is a chronic inflammatory disease, the patients who were diagnosed with gastrointestinal tuberculosis within four weeks of their first prescription for PPIs were also excluded from the statistical analyses.

The primary exposure of interest was receipt of PPIs. PPI
Table 1 Clinical information of the patients who were endoscopically diagnosed with suspicious tuberculosis

<table>
<thead>
<tr>
<th>Gender/age</th>
<th>Group</th>
<th>PPI duration before diagnosis (d)</th>
<th>Reason for endoscopy</th>
<th>Endoscopy findings</th>
<th>Pathology findings</th>
<th>Decision for analysis</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/65</td>
<td>1</td>
<td>639</td>
<td>Diarrhea</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/73</td>
<td>2</td>
<td>844</td>
<td>Abdominal pain</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/65</td>
<td>1</td>
<td>1377</td>
<td>Routine check</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/60</td>
<td>1</td>
<td>415</td>
<td>Routine check</td>
<td>Scar, terminal ileum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/64</td>
<td>1</td>
<td>616</td>
<td>Anemia</td>
<td>Scar, descending colon</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/67</td>
<td>1</td>
<td>56</td>
<td>Abdominal pain</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/55</td>
<td>2</td>
<td>87</td>
<td>Routine check</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/82</td>
<td>1</td>
<td>523</td>
<td>Constipation</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/58</td>
<td>1</td>
<td>65</td>
<td>Lower abdominal pain</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/55</td>
<td>1</td>
<td>612</td>
<td>Routine check</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>M/52</td>
<td>1</td>
<td>894</td>
<td>Blood-tinged stool</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/61</td>
<td>2</td>
<td>29</td>
<td>Bloating</td>
<td>Scar, cecum</td>
<td>No biopsy</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>F/72</td>
<td>1</td>
<td>125</td>
<td>Hematochezia</td>
<td>Ulcers, cecum</td>
<td>Chronic active colitis</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>M/44</td>
<td>1</td>
<td>28</td>
<td>Anemia</td>
<td>Ulcers, cecum/transverse colon</td>
<td>Non-caseating granuloma, positive PCR</td>
<td>Included</td>
<td>Palpable right supraclavicular lymph node</td>
</tr>
<tr>
<td>F/63</td>
<td>1</td>
<td>55</td>
<td>Epigastric pain</td>
<td>Ulcer, gastric cardia</td>
<td>Non-caseating granuloma, positive PCR</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>M/49</td>
<td>1</td>
<td>7</td>
<td>Melena</td>
<td>Ulcers, terminal ileum Ulcers, cecum</td>
<td>Chronic active ileitis, Non-caseating granuloma, positive PCR</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>M/41</td>
<td>1</td>
<td>574</td>
<td>Loose stool</td>
<td>Ulcers, terminal ileum Ulcers, cecum</td>
<td>Chronic active ileitis, Non-caseating granuloma, positive PCR</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>M/20</td>
<td>1</td>
<td>49</td>
<td>Lower abdominal pain</td>
<td>Ulcers, ileocecal valve</td>
<td>Chronic active colitis</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>F/66</td>
<td>1</td>
<td>1</td>
<td>Melena</td>
<td>Ulcers, terminal ileum Ulcers, ileocecal valve</td>
<td>Chronic active ileitis, Chronic active colitis</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>F/59</td>
<td>1</td>
<td>224</td>
<td>Lower abdominal pain</td>
<td>Ulcers, ileocecal valve</td>
<td>Chronic active colitis, Chronic active colitis</td>
<td>Included</td>
<td></td>
</tr>
<tr>
<td>F/46</td>
<td>1</td>
<td>28</td>
<td>Epigastric pain</td>
<td>Ulcers, mid-esophagus</td>
<td>Non-caseating granuloma, positive PCR</td>
<td>Included</td>
<td></td>
</tr>
</tbody>
</table>

1 Patients with PPI treatment for three months or less as group 1, and patients with more-than-three-month PPI treatment as group 2; 2 Polymerase chain reaction (PCR) for Mycobacterium tuberculosis. PPI: Proton pump inhibitor; M: Male; F: Female.

exposure was classified by overall dosing period before the first endoscopy showing suspicious gastrointestinal tuberculosis or the last prescription date in patients without gastrointestinal tuberculosis. The patients with less than three months of PPI treatment were defined as group 1, and those with three or more months of PPI treatment were defined as group 2. To normalize the different acid-suppressive capacities among the PPI regimens, omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, pantoprazole 40 mg, and esomeprazole 40 mg were defined as standard daily doses of PPI. To calculate the adjusted dosing period, the period of the half-dose regimen was multiplied by 0.5, and the period for the double-dose regimen was multiplied by 2.

Statistical analysis
The covariates that may influence the risk of acquiring gastrointestinal tuberculosis and those that may influence the exposure to PPIs were included in the analysis. These variables were age, sex, and co-morbidities. The co-morbidities were determined from the registered diagnosis by the attending physician using the International Classification of Diseases 10th Revision code. Quan’s algorithm was used to define the 17 Charlson co-morbidities, and the Charlson index was calculated[18,19].

Unadjusted comparisons were performed using the t-test, ANOVA test, Mann-Whitney test, χ² test, or Fisher exact test, as appropriate. Logistic regression modeling was used to estimate the relative risk of acquiring gastrointestinal tuberculosis in multivariate analyses. Statistical analysis was performed using the SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS
Among the patients who visited SNUH during the five-year study period, 61,834 patients received PPIs and 7 gastrointestinal tuberculosis cases were identified. After excluding the patients who were diagnosed with suspicious gastrointestinal tuberculosis through endoscopy prior to the first prescription of PPIs, a total of 21 patients were screened. Of these, 12 patients who revealed only scar changes in colonoscopy were excluded from the statistical analyses. Of those who remained, 2 were excluded because they underwent gastrointestinal endoscopy within 4 wk of the first prescription of PPIs (Table...
1. Anti-tuberculosis medications (isoniazid, rifampicin, ethambutol, and pyrazinamide) were prescribed to the finally selected 7 patients. Follow-up endoscopy was performed 2 or 3 mo after the start of the anti-tuberculosis treatment, and revealed complete healing or almost-healed ulcerations in all 7 patients.

The true incidence of gastrointestinal tuberculosis was 0.65 per 1000 person-years in group 1 and 0.03 per 1000 person-years in group 2 (Table 2). The characteristics of each group are shown in Table 3. The mean age (± SD) was 55.0 ± 14.5 years in group 1 and 58.2 ± 13.3 years in group 2. Longer exposure to PPI was associated with a higher Charlson co-morbidity index and a higher age (Table 3).

Table 4 presents the demographic and clinical characteristics of the active-gastrointestinal-tuberculosis and non-tuberculosis groups. Due to the small number of patients in the active-tuberculosis group, there was no significant difference between the two groups.

Table 5 shows the results of the multivariable analysis using logistic regression. A longer PPI treatment period (over three months) was not associated with increased risk of acquiring active gastrointestinal tuberculosis. The Charlson index was associated with significantly increased risk of acquiring active gastrointestinal tuberculosis by over 50% per score 1.

**DISCUSSION**

This cohort study was conducted not only to evaluate the possible role of more-than-three-month PPI treatment but also to calculate the incidence rate of, and to find the risk factors for, acquiring active gastrointestinal tuberculosis in all the at-least-20-year-old patients who visited SNUH and who were treated with PPI between January 1, 2005 and December 31, 2009. As a result, more-than-three-month PPI treatment was found not to be associated with increased risk of acquiring active gastrointestinal tuberculosis. The incidence rate of tuberculosis was reported to be 97 per 100 000 in 2010 in the South Korean general population[20]. The calculated incidence rate of active gastrointestinal tuberculosis seems to be much lower in PPI-treated patients in the present study (Table 2), even considering the reportedly small proportion of gastrointestinal tuberculosis in the whole tuberculosis population[21].

A diagnosis of gastrointestinal tuberculosis can be confirmed if a characteristic caseous granuloma, positive smear of AFB, or positive culture of mycobacterium is observed in the biopsy specimen[12]. Compared to pulmonary tuberculosis, however, there is a relatively small absolute number of AFB in gastrointestinal tuberculosis[21], and caseous granuloma is infrequently observed in patients with an early-stage disease or who have been treated with anti-tuberculosis medications[22].

Many studies have been performed to assess the diagnostic accuracy of such histological markers, and there have been a number of reports showing granuloma in 41%-48%, caseous granuloma in 8%-18%, positive smear of AFB in 0%-100%, and positive culture of AFB in 0%-69% of gastrointestinal tuberculosis patients. As there have been many reports showing variable results, it seems impossible to set universal standards for diagnosing gastrointestinal tuberculosis. There are adjacent diagnostic modalities, such as polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*, and endoscopic findings. Although PCR is a method that shows over 50% diagnostic sensitivity, its substantial false positivity limits its role to that of an adjunctive test for the diagnosis of gastrointestinal tuberculosis[21]. In the present study, both non-caseating granuloma and positive PCR were observed in two patients with gastrointestinal tuberculosis.
tuberculosis, but non-caseating granuloma was observed in only 2 of the 7 patients with intestinal tuberculosis, and PCR was positive in 1 of the 2 patients who showed granuloma.

The endoscopic findings of gastrointestinal tuberculosis are often nonspecific[12,20]. Intestinal tuberculosis and Crohn's disease are chronic inflammatory bowel disorders that are difficult to differentiate from each other[19,28]. A study on colonoscopic findings reported that four parameters (involvement of fewer than 4 segments, a patulous ileocecal valve, transverse ulcers, and scars or pseudopolyps) were more frequently observed in intestinal tuberculosis patients than in Crohn's disease patients. Four parameters (anorectal lesions, longitudinal ulcers, aphthous ulcers, and cobblestone appearance) were significantly more common in Crohn's disease patients than in intestinal tuberculosis patients. A systematic analysis of the 8 parameters of colonoscopy was very useful in the differential diagnosis as it could differentiate between intestinal tuberculosis and Crohn's disease with 87.5% accuracy[10]. In the endemic areas of tuberculosis, it seems reasonable to prescribe anti-tuberculosis medications for patients with endoscopic findings favoring intestinal tuberculosis even if there is no specific histological finding from the biopsy specimens[15]. In the present study, anti-tuberculosis medications were also prescribed for 5 patients with only nonspecific chronic inflammations found through biopsy. Intestinal tuberculosis was confirmed in all 5 patients through follow-up colonoscopy, which revealed good therapeutic responses as well as symptom relief.

This study has a number of strengths. First, to these authors' knowledge, this study is the first study that evaluated PPI's role in the development of gastrointestinal tuberculosis. Second, all the data in this study were extracted from the SNUH CDW system that is fully synchronized with the EMR system and is optimized for research. Using the SNUH CDW system, 61 834 patients among the over one million patients who visited SNUH during the 5-year study period were rapidly screened, and the patients with gastrointestinal tuberculosis were sensitively sought out via browsing endoscopy and pathology reports. Most of all, compared to cohort studies using a public database, through which only the cumulative incidence rate could be estimated, it is notable that the true incidence rate of gastrointestinal tuberculosis in PPI-treated patients was calculated. The calculated incidence rate was as low as 0.65 per 1000 person-years in group 1 and 0.03 per 1000 person-years in group 2, and anti-tuberculosis medications were shown to be effective in all the patients with active gastrointestinal tuberculosis. Therefore, the risk of acquiring gastrointestinal tuberculosis does not seem to be clinically significant in PPI-treated patients.

This study, however, has several key limitations. First, the study was performed with patients from a single urbanized tertiary care hospital. In general, a hospital cohort is vulnerable to selection bias, and the results have poor generalizability. In South Korea, a single compulsory medical insurance takes effect. Due to the open medical delivery system, all the patients are practically free to visit tertiary care hospitals. In this study, 64% of the patients fall under Charlson index 0. Therefore, their possible difference from primary care patients in the aspect of clinical severity does not seem substantial. Another limitation of a hospital cohort is its dynamic nature, which enables the members to easily join or drop out. Fortunately, even if this study was performed in PPI-treated patients during a 5-year period, the patients could be followed up for 21.8 mo in group 1 and for 34.4 mo in group 2. Therefore, the adherence of the patients in this study seems to have been good.

The second limitation is the potentially different diagnostic sensitivity. This study is an observational study. Therefore, the patients did not necessarily undergo gastrointestinal endoscopy. The implementation of endoscopy was determined according to the patient's symptoms/signs, patient's will, and doctor's decision. Therefore, the adherence of the patients in this study seems to have been good.

Table 4 Demographic and clinical characteristics of the active-tuberculosis and non-tuberculosis groups (mean ± SD)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>50.6 ± 17.7</td>
<td>55.6 ± 14.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>3 (43)</td>
<td>31 803 (51)</td>
<td></td>
</tr>
<tr>
<td>PPI duration</td>
<td>47.7 ± 97.9</td>
<td>72.8 ± 213.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.29 ± 2.56</td>
<td>0.55 ± 0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>Score = 0.2 (%)</td>
<td>5 (71)</td>
<td>39 459 (64)</td>
<td></td>
</tr>
<tr>
<td>Score &gt; 1.2 (%)</td>
<td>0 (0)</td>
<td>19 899 (32)</td>
<td></td>
</tr>
<tr>
<td>Score &gt; 3 n (%)</td>
<td>2 (29)</td>
<td>2467 (4)</td>
<td></td>
</tr>
<tr>
<td>History of admission</td>
<td>6 (86)</td>
<td>35 824 (58)</td>
<td></td>
</tr>
</tbody>
</table>

PPI: Proton pump inhibitor.

Table 5 Results of the multivariable analysis using logistic regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reference 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, increase by year</td>
<td>0.972 (0.923-1.023)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Charlson index, increase by score 1</td>
<td>1.518 (1.040-2.216)</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1 (0.374-7.689)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>History of admission</td>
<td>4.317 (0.501-37.220)</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

PPI: Proton pump inhibitor.
strict adherence to the hospital of female patients than male patients. In the 9 patients diagnosed with active gastrointestinal tuberculosis, however, there were nearly equal numbers of male and female patients. Endoscopy was performed to assess bloody diarrhea, anemia, and severe pain, which seemed to be symptoms suggesting active gastrointestinal tuberculosis (Table 1). In this study, statistical analysis was performed in the patients with active gastrointestinal tuberculosis, which could suggest that the results of this study were not highly biased by the patients’ will or adherence.

In conclusion, long-term PPI therapy does not seem to be associated with increased risk of acquiring gastrointestinal tuberculosis whereas a higher Charlson co-morbidity index is associated with such. These results, however, may not exempt further monitoring due to the small case number.

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