Effects of Infections of *Helicobacter Pylori* With Different Virulent Factors on Severity of Gastrointestinal Diseases

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Research article

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Abstract

Background: *Helicobacter Pylori (H. pylori)* infection, one of the most common

chronic bacterial infections, has been considered as a major cause of diseases such as lymphoma, gastritis, peptic ulcers, and stomach cancer. Here, we aimed to determine whether *H. pylori* strains with different virulence contribute to the gastrointestinal diseases differentially in clinical settings, which may provide future direction for eradication of *H. pylori* infection.

Methods: We recruited 501 patients with gastrointestinal disorders for analysis of antibody types of *H. pylori* infection. Correlation analysis was done to determine the association of different virulence of *H. pylori* with patients' baseline parameters and personal disease history. Next, subjects with each type of anti- *H. pylori* infection antibody were subjected to esophagogastro duodenoscopy（EGD) and colonoscopy examinations. The pathological diagnosis was also conducted in endoscopic samples. Chi-squared test was employed to compare the differences in endoscopic assessments and pathological findings among three types of *H. pylori* infection determined by the presence of antibodies to virulent factors.

Results: There were 296 cases with Type I *H. pylori* infection, 120 cases with Type II *H. pylori* infection, and 85 cases without *H. pylori* infection (negative, Type III). No correlation was found between different virulence of *H. pylori* and participants' baseline data (*P > 0.05).* EGD results showed that the incidences of peptic ulcer, bleeding and malignant lesions in Type I group were significantly higher than that in Type II and Type III (P＜*0.05).* Despite of increased trends of incidences of precancerous alterations and the malignance in Type I group compared with type II and III groups, there was no significant difference (*P > 0.05*). In addition, coloscopic features were similar among three groups. On the other hand, infections of *H. pylori* with cytotoxin-associated gene A (CagA) and/or vacuolating cytotoxin A (VacA) virulent factors resulted in more severe histopathological diseases than that with only Ure A/B factor and without infection (*P < 0.05*).

Conclusions: Infections of *H. pylori* strains with CagA/VacA are likely to cause development of severe gastrointestinal diseases. These results are helpful to treat for *H. pylori* infection clinically.

Background

Helicobacter Pylori (H. pylori) infection contributes to the development of chronic gastritis, peptic ulcer, and even gastric cancer and gastric Mucosa-Associated Lymphoid Tissue lymphoma (MALT) [1, 2]. *H. pylori* has been declared and ratified as carcinogen I by the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO). In addition to diseases in its primary site of infection, a growing evidence demonstrates that *H. pylori* infection is involved in intestinal diseases, idiopathic thrombocytopenic purpura disease, iron deficiency anemia disease, coronary heart disease, infertility and other pathogeneses [3]. Therefore, accurate diagnosis and proper treatment of *H. pylori* infection are crucial to the progress and prognosis of clinical patients.

So far, *H. pylori* is determined using a variety of methods including urea breath test (UBT), serological test, stool antigen test, histological culture, etc.. Although UBT has been considered as a preferred non-invasive examination for diagnosis of *H. pylori* infection, many factors affect the accuracy of UBT, and lead to false negative and positive results. Besides that, UBT fails to categorize *H. pylori* into highly- and low-virulent strains based on the presence or absence of two key virulence factors, cytotoxin-associated gene A (CagA) and/or vacuolating cytotoxin A (VacA) [4].

In clinical practices, patients are often requested to eradicate *H. pylori* infection if the subject is tested positive using UBT. According to the 2019 Expert Consensus Opinion on Eradication, Prevention and Control of Gastric Cancer in *Helicobacter Pylori* China (Shanghai, 2019), the elimination of *H. pylori* helps to control the outcome of gastric cancer [5]. However, the role of different virulence of *H. pylori* in the development of gastrointestinal diseases remains unknown. Until now, based on antibodies against the bacterial virulence factors in serum, patients with *H. pylori* infection are classified into three types in accordance with the presence of CagA, VacA and Urease A/B (Ure A/B) or absence. We hypothesized that different virulent factors predict the severity and outcomes of gastrointestinal diseases in those patients with *H. pylori* infection. In this study, serum samples from 501 patients who had been hospitalized for gastrointestinal symptoms from September 2019 to June 2020 in the Department of gastroenterology at Puren Hospital in Wuhan were collected for evaluation of bacterial virulence. By doing so, we anticipate to solve the puzzle about the effects of different virulent factors of with *H. pylori* on gastrointestinal diseases.

Methods

Patients

We recruited consecutively 501 patients with gastrointestinal symptoms (abdominal pain, abdominal distension, acid reflux, etc.) in the Department of Gastroenterology at Puren Hospital from September 2019 to May 2020 for *H. pylori* antibody tests and other examinations. All patients were informed consent, including 260 males and 241 females, with a minimum age of 15 years and a maximum age of 90 years (average age of 57.02 ± 14.01). The baseline data of the patients included sex, age, smoking history, alcohol consumption history and family history of cancers.

Exclusion criteria: Patients with severe cardiovascular, hepatic, kidney dysfunction, immune deficiency disease, those with esophagogastric variceal hemorrhage, pregnant women or with mental illness, previous anti- *H. pylori* administration or those undergoing *H. pylori* eradication treatment were also excluded.

All subjects were briefed about this study, and had signed the informed consent form before the enrollment. The study protocol was also approved by the institutional review board (IRB) at the Puren Hospital.

Measurements of types of virulent factors of *H. pylori* infection

Types of *H. pylori* antibody in the patient serum were determined using a detection kit produced by Shenzhen Brautt Company, and Western blotting method. The manufacturer's instructions were followed. The kit classified the infections as Type I, Type II and Type III (negative) based on three types of antibody scenarios. Type I is positive for CagA and/or VacA antibody and Ure A/B antibody. Type II is positive for Ure A/B antibody, and negative for CagA and/or VacA antibody. Type III (Negative) is negative for CagA, VacA, and Ure A/B antibodies.

Esophagogastroduodenoscopy and colonoscopy

Of the 501 patients who underwent the antibody classification measurement, 384 patients received esophagogastroduodenoscopy (EGD) and 136 patients received colonoscopy. All participants signed the informed consent for their respective examinations. To those who would receive endoscopic therapy (such as: hemostasis with gastric and duodenal ulcer, excision of polyps), the informed consent for those operations were also obtained. EGD and colonoscopy were performed using the Olympus GIF-HQ290 and Olympus CF-H290L / I, respectively.

Endoscopists with more than 5 years of experience reviewed the endoscopic images and then made final endoscopic diagnosis.

Pathological examination

Except bearing the risk of hemorrhage in certain sorts of lesion locations by sampling, lesions of all patients who underwent endoscopy were collected by endoscopists and then were diagnosed by pathologists. The slides were reviewed by three pathologists who have worked for more than 5 years. If two pathologists disagreed with the diagnosis, the third pathologist then reviewed the slides to reach a consensus.

Statistical Analysis

First, SPSS 23.0 software was used to perform correlation analysis to determine the association between different antibody types of *H. pylori* infection and age, sex, smoking, alcohol consumption and family history of cancer according to the baseline data of 501 patients involved. Secondly, we conducted the Chi-squared test to compare the effects of presence or absence of antibodies to the virulent factors of *H. pylori* in those patients on gastrointestinal diseases via endoscopy and pathological measurements. A two-sided *P*-value less than 0.05 was considered statistically significant.

Results

H. pylori antibody types were not correlated with age, sex and personal history

Among 501 patients examined for the antibodies to the virulent factor of *H. pylori* infection, 296 cases were classified as Type I *H. pylori* infection, 120 cases were classified as Type II and 85 cases were classified as Type III (negative) *H. pylori* infection. Correlation analysis indicated that none of three groups (Type I, Type II and negative) showed any significant association with patients' baseline data (age, sex), and risk factors (e. g. smoking, alcohol consumption, family history of cancer) *(P > 0.05*) as shown in Table 1.

Table 1 Correlation analysis between different virulence of *H. pylori* infection and baseline parameters

Factors	Type I	Type II	Type III	Coefficient	P value
Age	57.35±14.02	57.78±13.30	54.78±14.89	0.05	0.229
Female/male	135(45.6%)/161(54.4%)	59(49.2%/61(50.8%)	47(55.3%)/38(44.7%)	0.07	0.09
smoking	81（27.2%）	25（20.8%）	15（17.6%）	0.08	0.073
alcohol	46（15.5%）	12（10%）	10（11.8%）	0.04	0.393
Cancer history	18（6.1%）	6（5%）	3（3.5%）	0.05	0.231

Gastroscopic features of three groups based on antibody detection

Out of 501 subjects, 384 patients received EGD examination. In them, we found 234 (79.1%) in type I group, 86 (71.7%) in type II, and 64 (75.3%) in the negative group. After statistical analysis, the percentage numbers of patients receiving gastroscopic examinations were not different among three types ($P > 0.05$). As shown in Table 2, in type I group, we found 47 cases of chronic gastritis (20.1%) confirmed by EGD, 19 cases with reflux esophagitis (RE, 8.1%), 91 cases with peptic ulcer with hemorrhage (38.9%), 62 cases with polyps in esophagus, gastric or duodenum (26.5%), 15 cases with gastric malignancies (6.4%). Of the 86 cases in type II, we found 15 cases (17.4%) with chronic gastritis, 20 cases (23.3%) with esophagitis, 17 cases (19.8%) with peptic ulcer with hemorrhage, 33 cases (38.4%) with polyps in esophagus, gastric and duodenum, and only 1 case (1.2%) with gastric malignancies. In the negative group, we found 17 cases (26.6%) with chronic gastritis, 9 cases with (14.1%) reflux esophagitis, 8 cases (12.5%) with peptic ulcer with hemorrhage, 28 cases (43.8%) with polyps in esophagus, stomach or duodenum, and 2 cases (3.1%) with possible gastric malignant change. As shown in Table 2, the primary gastroscopic characteristics of type I group were gastric and duodenal ulcers with or without hemorrhage, which had a total rate of 38.9%. This number in type I group was significantly higher than that in type II and negative groups ($P < 0.05$). More interestingly, the ratio of neoplasia findings in type I group was also significantly higher than that in the other two groups ($P < 0.05$). On the other hand, the combined rate of polyps in esophagus, stomach and duodenum was comparatively added in type II and negative group, which accompanied with reduction of incidence of ulcers, bleeding and neoplasia findings.

Table 2
Gastroscopic features with different virulence factors of *H. pylori*

Type	Gastritis	RE	Peptic ulcer/ Bleeding	Polyps	Cancer
I	47(20.1%)	19(8.1%)	91(38.9%)*	62(26.5%)	15(6.4%)*
II	15(17.4%)	20(23.3%)	17(19.8%)	33(38.4%)	1(1.2%)
III	17(26.6%)	9(14.1%)	8(12.5%)	28(43.8%)	2(3.1%)

* : $P < 0.05$, compared with type II and negative ones, the incidences of peptic ulcer, hemorrhage, and malignant diseases in type I group were higher significantly.

Pathological results with different virulence factors of *H. pylori*

Exclusion of high risk in hemorrhage, 294 lesions were sampled to identify pathological alterations in patients of the three types. As shown in Table 3, these included 173 cases (73.9%) in type I group, 72 cases (83.7%) in type II group, and 49 cases (76.6%) in negative group. There was no significant difference in rates of patients with pathological changes ($P > 0.05$). Firstly, we divided pathological results into three phenotypes comprising mucosal atrophy and/or intestinal metaplasia, intraepithelial Neoplasia/gastric cancer, and other benign pathological findings. As was shown in Table 3, there were 41 (23.7%) cases with atrophy /intestinal metaplasia, 17 (9.8%) cases with intraepithelial neoplasia and carcinoma, and 115 (66.5%) with benign lesions in type I group. Of the 72 patients in type II group, there were 14 (19.4%) cases with atrophy and/or intestinal metaplasia, 3 (4.2%) cases with intraepithelial neoplasia/carcinoma, and 55 (76.4%) cases with diagnosed benign lesions. Of the 49 negative cases, there were 9 (18.4%) cases with atrophy and/or intestinal metaplasia, 2 (4.1%) cases with intraepithelial neoplasia/carcinoma, and 38 (77.6%) cases with other benign lesions. Statistical analysis indicated that the incidences of precancerous alterations and the malignance in type I group were elevated in comparison with that in type II and negative groups. There was no significant difference of any of these parameters among three groups as shown in Table 3 ($P > 0.05$).

Table 3
Pathological manifestations with different types of *H. pylori* infection

Type	Atrophy/Metaplasia	Neoplasia/Cancer	Benign	Total
I	41(23.7%)	17(9.8%)	115(66.6%)	173(100%)
II	14(19.4%)	3(4.2%)	55(76.4%)	72(100%)
III	9(18.4%)	2(4.1%)	38(77.6%)	49(100%)

Colonoscopy features in *H. pylori* positive patients with different virulent factors

Of 501 patients involved in antibody classification, 136 cases received the colonoscopy examination, which included 72 (24.3%) cases in type I group, 40 (33.3%) cases in type II group and 24 (28.2%) subjects in the negative group. The percentage numbers of examined cases among three type groups are not different ($P > 0.05$). As shown in Table 4, 46 (63.9%) cases in type I group had polyps, adenomatous polyps and cancer. In type I patients, 6(8.3%) cases had inflammatory alteration and inflammatory bowel disease (IBD), and 20 (27.8%) cases appeared to be normal under the colonoscopy examination. Among the 40 subjects in type II group, 23 cases (57.5%) had polyps, adenomatous polyps and malignance endoscopic features. There were 3 cases (7.5%) with inflammatory alteration and IBD, while 14 cases (25%) had normal colonoscopy results. Lastly, 15 patients out of 24 (62.5%) examined had polyps, adenomas and malignant morphologic types in the negative group. There were 3 cases (12.5%) with inflammatory alterations and IBD, and 6 cases (25%) with normal colonoscopy results. Results of Chi-square test indicated that colonoscopy results were not significantly different among three groups ($P > 0.05$).

Table 4
Colonoscopic findings with different types of *H. pylori* infection

Type	Polyps/Adenoma/Cancer	Inflammation	Normal	Total
I	46(63.9%)	6(8.3%)	20(27.8%)	72(100%)
II	23(57.5%)	3(7.5%)	14(35%)	40(100%)
III	15(62.5%)	3(13.5%)	6(25%)	24(100%)

Histopathology difference of colonoscopy results from patients in different virulence factor groups

Tissue samples from 55 subjects out of the 130 patients receiving colonoscopy examination were evaluated for pathological changes. As shown in Fig. 1, 10 (38.5%) out of 26 cases in type I group were diagnosed pathologically as mild to moderate inflammation and hyperplastic polyp. The remaining 16 cases (61.5%) were considered to have severe inflammation, adenomatous polyps, atypical hyperplasia and cancer. In type II group, 14 (70%) out of the 20 cases had mild and moderate inflammation, while the remaining 6 cases (30%) had severe inflammation, and adenomatous polyps. Of 9 subjects in the negative group, 7 (77.8%) cases were diagnosed as mild to moderate inflammation, and hyperplastic polyps, while the remaining 2 cases (22.2%) had severe inflammation phenotypes. Statistical analysis demonstrated that infection of *H. pylori* with CagA and/or VacA resulted in significantly more severe histopathological alterations in comparison with that with only Ure A/B virulent factor or without infection ($P < 0.05$).

Discussion

H. pylori is a group of gram-negative spirochetes widely colonized in the stomach. More than 50% of the world's population is currently infected with the bacteria, which have been identified by the International Cancer Organization as the leading cause of gastroduodenal ulcers, chronic gastritis and stomach cancer [6]. The genome of *H. pylori* has high genetic diversity which affects its invasion to the gastric mucosa of the host. The mechanism of its pathogenicity is related to the interactions among virulence factors, host genes and environmental factors. The genome of *H. pylori* encodes more than 1,500 proteins, of which more than 500 genes are specific for *H. pylori*. The pathogenic ability of *H. pylori* strains is diverse, so the development and progression of host diseases caused by *H. pylori* strains vary. So far, the known virulence factors of *H. pylori* strains have included CagA, VacA, Urease A/B, DupA, OMPs and ICEA, of which CagA, VacA and Urease A/B are the best characterized and investigated ones [7–9].

Based on the presence or absence of the major three virulence factors (CagA, VacA and Urease A/B), patients with *H. pylori* infection can be divided into three types. The data presented in this manuscript are from 501 participants. We observed that the incidence of type I infection is higher than that of Type II and negative group. The correlation analysis revealed that there is no association between different virulence of *H. pylori* and patients' baseline parameters and personal history including age, sex, history of smoking, alcohol consumption, and family history of cancer. In the future, we plan to recruit more participants to further evaluate whether any of the risk factors of hypertension, diabetes and hyperlipidemia is related to the different virulence of *H. pylori* infection.

It has been established that the highly virulent *H. pylori* strains comprise the cytotoxin-associated genes pathogenicity island (CagPAI), which is a 40 kb region containing 31 genes encoding the elements of a type IV secretion system, participating in CagA toxic activity and following a series of inflammatory responses [10]. Research has shown that infections with CagA positive strains are more virulent than the strains without this genotype in gastric colonization and proliferation [11]. In the process of infection, CagA is localized on the plasma membrane, in which it is phosphorylated at specific Glu-Pro-Ile-Tyr-Ala (EPIYA)-motifs through Src and Abl kinases in host [12, 13]. The degree of toxicity with CagA is associated highly with numbers and types of the EPIYA-motifs at the C-terminal region. After translocation, CagA interacts with multiple host cell molecules and induces the dysregulation involved in the homeostatic signal transduction of gastric epithelial cells, triggering chronic pro-inflammatory responses involving apoptosis, disruption of cell polarity and promotion of genetic instability, through which carcinogenesis then takes place. Owing to such cancer-inducing traits, CagA therefore has been designated as the first bacterial oncoprotein [14].

The vacuolating cytotoxin A (VacA) is known for its capacity to induce the formation of vacuoles in eukaryotic cells. VacA gene exists in all *H. pylori* strains, with different vacuolating ability, which is conferred by variations in five VacA regions: s-region (s1 and s2), i-region (i1, i2, i3), m-region (m1 and m2), d-region (d1 and d2), and the recently identified c-region (c1 and c2). Different variants of VacA like s1, s2, m1 and others could bring about varied toxic effects from cellular vacuolation, oxidative stress to apoptosis induction [15, 16]. According to results from Ogiwara H, the potential risk of developing peptic ulcers and cancer in patients carrying s1 or m1 is significantly higher than those carrying other toxins [17]. In Iran, for example, the d1 was identified as a novel oncogenic factor for gastric cancer [18]. Additionally d1 and i1 have displayed a synergistic effect on the progress of gastric cancer [19]. Once infected, VacA induces the vacuolation of epithelial cells, triggers the release of mitochondrial cytochrome C and then initiates apoptosis [20]. Moreover, it also confers the formation of membrane channels, through which cytochrome C is released and then binds to extracellular receptors. As a result, cellular inflammatory responses occur consequently [21, 22].

In our present study, we found that the probability of peptic ulcer, gastrointestinal bleeding and malignancy increased significantly in the type I patients carrying *H. pylori* with CagA/Vaga compared with type II and negative counterparts. At the same time, infections of *H. pylori* with UreA/B show primarily as relative mild gastroscopic manifestations like gastritis, reflux esophagitis, polypoid changes. In regard to mechanism, we reason that the main virulent factors CagA and VagA act on the gastric and duodenal mucosa, and trigger a series of inflammatory reactions, which lead to relatively severe gastroscopic outcomes such as peptic ulcer, bleeding, and even cancer. UreA/B in Type II group is less virulent than CagA/VacA in type I group, which could only influence vesicular transport and cell cycles [23]. As a result, gastroscopic characteristics are based on chronic inflammatory cell infiltration of the mild to moderate inflammatory response without ulcers and malignant changes. Although precancerous changes (atrophy, intestinal metaplasia, intraepithelial neoplasia) and cancers in type I group show a trend of increase compared with that in type II and negative groups, the difference among them is not significant. The inadequate number of participants maybe a factor attributing to this nonsignificant result. In future studies, we should further subdivide the pathological results based on severity of inflammation, and various precancerous changes from mild to severe. By analyzing histopathological results like that, a definite link between the different virulence of *H. pylori* strains and pathologic abnormalities may be established accurately.

There have been increasing documents showing that the prevalence of colorectal ailments has been linked to the infection with *H. pylori*, whereas no consistent conclusion has been drawn by far [24–27]. Boyuk B et al investigated 341 subjects and showed that the progression of colorectal adenoma and carcinoma is independent of *H. pylori* infection [24]. From our colonoscopic results, the incidences of colorectal polyps, and carcinoma with different virulent factors of *H. pylori* infection are not different among the three groups. However, the pathological diagnosis revealed that rates of severe inflammation, adenomatous polyp and colorectal cancer in patients with CagA/VacA toxins are much higher than that with UreA/B and negative group. Infection with *H. pylori* causes the secretion of gastrin in the blood, which can act as a hormone to stimulate the growth of the colonic mucosa cells. *H. pylori* can cause hypergastrinemia only or in combination with changes in the normal gastrointestinal flora, suggesting an acceptable mechanism for its carcinogenicity [28, 29]. The limitation of our study is the relatively small number of patients who received colonoscopy examinations. If we further group the colonoscopic findings according to size, location and morphology of intestinal lesions, the exact relationship could be defined.

Conclusions

In conclusion, the H. Pylori strains carrying CagA/VacA are more likely to cause severe gastrointestinal diseases. However, the antibody measurement only reflects *H. pylori* infection, which does not differentiate whether it is due to previous infection or currently being infected status. Therefore, an accurate diagnosis of *H. pylori* infection should effectively be UBT and antibody tests simultaneously. Our findings further identify the exact effects of different virulence pathogenicity (CagA, VacA and UreA/B) on the development of gastrointestinal diseases. These may provide some clues and direction for the precise eradication of *H. pylori* in infected patients, and prevent gastrointestinal diseases in the future.

Abbreviations

H. pylori
Helicobacter Pylori
EGD
Esophagogastro duodenoscopy

VacA
Vacuolating cytotoxin A
MALT
Mucosa-Associated Lymphoid Tissue lymphoma
UreA/B
Urease A/B
IARC
International Agency for Research on Cancer
WHO
World Health Organization
UBT
Urea breath test

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Affiliated Puren Hospital of Wuhan University of Science and Technology. All participants gave written informed consent.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

All authors declared no conflict of interest.

Author contributions

YZ, KT and XMF designed the experiments. KT and YZ summarized and wrote the draft. All authors read and approved the manuscript submission.

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Figures

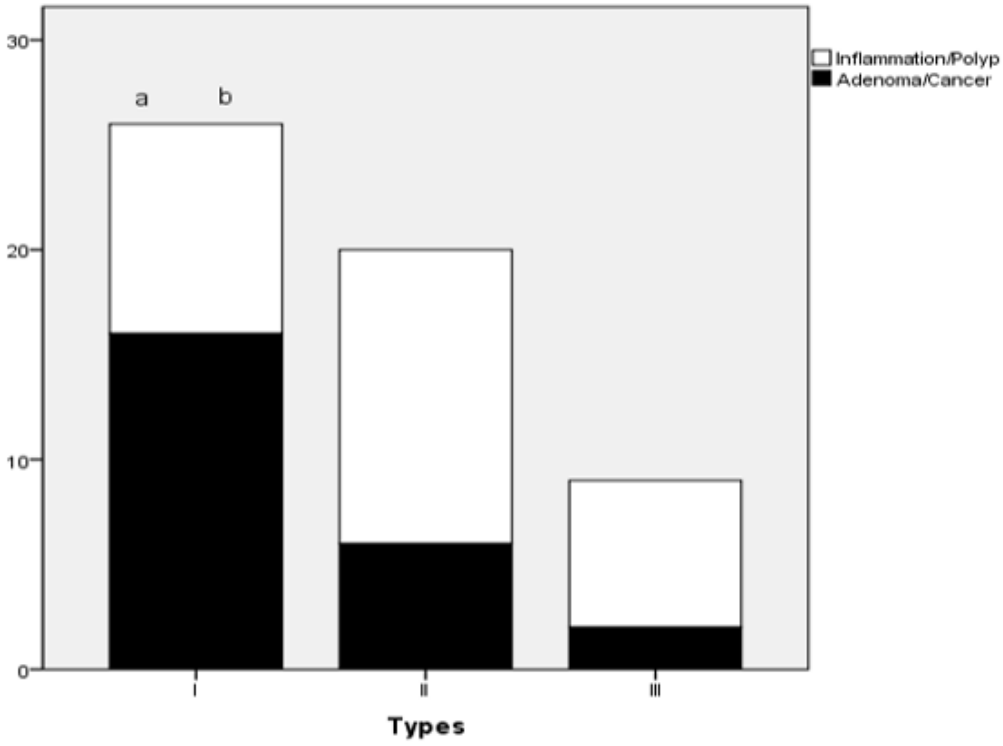

Figure 1

Pathological results of colonoscopy among different types of H. pylori infection. a: P < 0.05, for comparing Type I and Type II groups. The incidences of severe inflammation, precancerous lesions and colorectal cancer were significantly increased. b:P□0.01 for comparing Type I and the negative groups. There was significant difference between the type I infection and negative groups.