Helicobacter pylori and Association between its Positivity and Anatomotopographic Settlement in the Stomach with the Host Age Range

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Abstract

Helicobacter pylori (H. pylori) is a Gram-negative, helically shaped flagellated bacterium. Major diseases associated with H. pylori infection include peptic ulcer, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma. The incidence of H. pylori in the anatomotopographic regions of the stomach, such as antrum, corpus, fundus, and incisura angularis, has been investigated. Do the rates of H. pylori in the settlements change over time according to the age ranges of the hosts? Does this change affect the diseases caused by or related to H. pylori? It is estimated that the outcomes, which have been obtained, may provide a new perspective in terms of understanding the etiopathogenesis of H. pylori-induced diseases. A comprehensive literature search of PubMed/MEDLINE databases had been conducted using a combination of terms, “Helicobacter pylori,” “Sydney System,” “stomach,” “pyloric antrum,” “gastric corpus,” “stomach cancer,” and “Helicobacter pylori and age.” There are very few articles examining the relationship between the topographic locations of H. pylori and host age range in the English language literature. Therefore, it is also purposed to emphasize the outcomes of our current research about the mentioned topic. In our opinion, similar studies should reveal the settlement and age range in the different geographic locations and societies as in our study. We believe that these findings will contribute to the efforts for understanding overtly of H. pylori-induced disease of the stomach.

Keywords: Antrum, biopsy, corpus, endoscopy, Helicobacter pylori, stomach, Sydney system

Résumé

Helicobacter pylori (H. pylori) est une bactérie flagellée à Gram négatif de forme hélicoïdale. Les principales maladies associées à l’infection à H. pylori comprennent l’ulcère gastro-duodénal, l’adénocarcinome gastrique et le lymphome du tissu lymphoïde associé à la muqueuse. L’incidence de H. pylori dans les régions anatomotopographiques de l’estomac, telles que l’antre, le corps, le fond d’œil et l’incisura angularis, a été étudiée. Les taux de H. pylori dans les colonies changent-ils avec le temps en fonction des tranches d’âge des hôtes? Ce changement affecte-t-il les maladies causées par ou liées à H. pylori? On estime que les résultats obtenus peuvent fournir une nouvelle perspective en termes de compréhension de l’étiopathogénèse des maladies induites par H. pylori. Une recherche documentaire complète des bases de données PubMed/MEDLINE a été effectuée en utilisant une combinaison de termes, “Helicobacter pylori”, “Sydney System”, “estomac”,

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bacterium associated with many gastric diseases.\textsuperscript{[1-2]} The Genus \textit{Helicobacter} includes about 35 species, consisting of one of them, \textit{H. pylori}.\textsuperscript{[3]} The most common and important diseases of \textit{H. pylori} infection are peptic ulcer (10%), gastric adenocarcinoma (1%-3%), and lymphoid tissue lymphoma associated with primary gastric mucosa (mucosa-associated lymphoid tissue [MALT]).\textsuperscript{[4]} \textit{H. pylori} is a microaerophilic bacterium living in the mucosal parts of the stomach.\textsuperscript{[5-7]} Colonization with \textit{H. pylori} is often associated with the progression of gastrointestinal disorders, i.e., gastritis, peptic ulcer disease, gastric cancer, and MALT lymphoma.\textsuperscript{[8]} The variety and severity of the diseases depend on the condition of the host’s immune system, the pathogenicity of \textit{H. pylori} and the presence of environmental factors, such as diet, stress, hygiene standard or presence of infections.\textsuperscript{[9]}

\textit{H. pylori}, fecal–oral or oral–oral contagion, is located in various parts of the stomach.\textsuperscript{[9]} \textit{H. pylori} involvement is present in approximately 50% of people in the upper gastrointestinal tract.\textsuperscript{[10]} \textit{H. pylori} has different mechanisms to escape the acidic gastric environment in which pH is about 2.0. These mechanisms are production of urease, flagellar mobility, and chemotaxis required for invasion of the stomach epithelium.\textsuperscript{[11]} Urease catalyzes the hydrolysis of urea to bicarbonate and ammonia. Urea is present in abundant amounts in the stomach; therefore, the pH approaches a neutral range.\textsuperscript{[12]}

**Geographic distribution**

The prevalence of \textit{H. pylori} infection is changing worldwide, roughly 10% in developed Western countries and 80% in developing countries such as India.\textsuperscript{[13,14]} Clinical findings are seen at approximately 20%. \textit{H. pylori} tends to decrease in many regions of the world. Evidence from the studies in Europe supports the downward trend. In some countries in the Middle East, the prevalence of \textit{H. pylori} remained relatively stable. In a meta-analysis published last year, \textit{H. pylori} prevalence was reported as very low in Australia and the surrounding regions (24.4%). However, the highest rate was observed in Africa (79.1%). The annual recurrence rate of \textit{H. pylori} infection was 4.3%. The prevalence of human development index and infection was related to the recurrence rate. Several studies have investigated the relationship between \textit{H. pylori} infection and the population data, social conditions, drinking water source, and dietary factors. In several studies, the insects and yeasts have been emphasized in the transmission of \textit{H. pylori}.\textsuperscript{[15]} Although there is an attenuation in gastric cancer rates in the developed countries, the most common cancer in the world is one of the causes of death.\textsuperscript{[16,17]} There is an increase in global mortality rates of gastric cancer due to population growth and life expectancy.\textsuperscript{[17]} Approximately 75% of total gastric cancer patients are presumed to be \textit{H. pylori}-induced inflammation and injury.\textsuperscript{[18]} \textit{H. pylori} colonized people for tens of thousands of years.\textsuperscript{[19]} During this time, they survived the aggressive environment of the stomach and survived the host immune system.\textsuperscript{[20]} \textit{H. pylori} invades the gastric epithelial surfaces by spreading to the mucus layer.\textsuperscript{[21]} Recently, it has been found that \textit{H. pylori} has proliferated in the glands, has a recurrent gastrointestinal spread, and can provide niche to bacteria.\textsuperscript{[22,23]}

In 2015, around 4.4 billion people were infected with \textit{H. pylori} worldwide and 950,000 new cases diagnosed with gastric cancer.\textsuperscript{[24]} In some parts of the world, it is quite common, for instance, the East Asian countries, Japan, China, and Korea. The incidence of gastric cancer in these countries is about ten times that of the United States. The incidence of gastric cancer is almost two times higher in males than in females and observed 66% in rural and 47% in urban areas.\textsuperscript{[25]} The successful colony of \textit{H. pylori} in the stomach requires an age-related gastric physiology and special characteristics related to the host. \textit{H. pylori} settles in childhood and continues for life.\textsuperscript{[26]}

**Diseases associated with \textit{Helicobacter pylori}**

\textit{H. pylori} infection is associated with some of the most common disorders of the upper gastrointestinal tract.\textsuperscript{[27]} Approximately 80% of the \textit{H. pylori} infections do not give clinical signs. Permanent \textit{H. pylori} colonization is the main risk factor for gastric and duodenal ulcer, lymphoid tissue lymphoma associated with gastric mucosa (MALT), and stomach adenocarcinoma.\textsuperscript{[28]} Different treatment modalities had been described for \textit{H. pylori}.\textsuperscript{[29,30]} The third leading cause of cancer deaths in the world is stomach adenocarcinoma and has been accepted as a cause of many disorders. \textit{H. pylori} is the main cause of chronic active gastritis. Duodenal and gastric ulcer, low-grade B-cell lymphoma, and MALT lymphoma are other important clinical diseases.\textsuperscript{[37,31,32]}

\textit{H. pylori}, a gram-negative, flagellated, microaerophilic bacterium that selectively colonizes the gastric mucosa layer, is a Class I carcinogenic bacterium, colonizing the stomach in childhood.\textsuperscript{[33,34]} Approximately 10% of individuals with gastric epithelial colonization develop clinical disease and 90% remain subclinical. If left untreated, the infection may persist throughout life.\textsuperscript{[15]} Up to now, about 20 different diseases associated with \textit{H. pylori} have been identified; duodenal ulcer, gastric ulcer, adenocarcinoma of the distal stomach, MALT lymphoma, diabetes mellitus, cardiovascular disease, and autoimmune diseases.\textsuperscript{[36]} Treatment failure of \textit{H. pylori}
Importance of gastric location for iron-deficiency anemia. H. pylori colonization is known to increase the risk of cancer in other parts of the stomach, except for the cardiac region. The relationship between H. pylori colonization and gastric cardia cancer varies according to geographical regions. In Western countries, there is a neutral or even negative relationship between gastric cardia cancer and H. pylori colonization, while high proportions reported for Eastern populations, namely China, Korea and Japan.

H. pylori infection is associated with the development of different gastrointestinal diseases such as gastric ulcer, gastric cancer, mucosal lymphoid tissue (MALT) lymphoma, and biliary cancer and extragastric diseases such as ischemic heart diseases, type 2 diabetes mellitus, anemia, inverse metabolic features in obese people, and insulin resistance. H. pylori-related diseases occur only in a small percentage of infected people. This suggests that it has been colonized in the stomach without any clear signs of disease and that H. pylori plays a beneficial role in human health. Recent studies have shown that the decrease in the incidence of H. pylori is parallel to the increase in the incidence of allergy and autoimmune disease. The absence of H. pylori is also associated with the incidence of multiple sclerosis and celiac disease.

H. pylori has also been associated with diseases of various nongastrointestinal organs, including coronary heart disease, rosacea and idiopathic urticaria, autoimmune thyroid disease, dermatological diseases such as thrombocytopenic purpura and iron-deficiency anemia.

Importance of gastric location for Helicobacter pylori

The virulence, anatomical location, environmental factors, and host genetics of H. pylori are important in transforming H. pylori infection into gastric cancer. In Western countries, cardia cancer frequently involves a mixture of gastric cardia and esophageal adenocarcinomas due to the prevalence of Barrett’s esophagus and adenocarcina of the esophagus. Taihang Mountains (China) are associated with a modest increase in the risk of both cardiac and noncardiac gastric adenocarcinoma in some high-risk regions worldwide for esophageal cancer. This is not the case for gastric cardia adenocarcinoma. Taihang Mountains (China) are associated with a modest increase in the risk of both cardiac and noncardiac gastric adenocarcinoma in some high-risk regions worldwide for esophageal cancer. Biopsy sampling is important for gastritis classification. However, the degree of inflammation and atrophy of different regions of the stomach with chronic gastritis has been discussed in just a few studies. Isajevs et al. analyzed the inflammatory, atrophic, and metaplastic changes in the big curvature and small curvature of the antrum and corpus mucosa. They examined the upper gastrointestinal endoscopy of a total of 420 patients, and the biopsy specimens were evaluated according to the updated Sydney classification. Histopathology revealed mononuclear and granulocyte inflammatory cells, which are more prominent in the curvature than the small curvature in the greater curvature. The degree of atrophy and intestinal metaplasia was more pronounced than the small curvature of the large curvature. The frequency of distribution of H. pylori did not differ in both the corpus and the curvature of the antrum. However, the degree of colonization of H. pylori is higher than the larger curvature in the small curvature. In addition, corpus atrophy was significantly higher than antrum atrophy. Severe atrophic, metaplastic, and inflammatory changes were more common in the small curvature than in the large curvature.

In a Russian study, conducted in Ryazan, the prevalence of H. pylori infection among the urban population was studied. 64.5% of the population studied were diagnosed as H. pylori infection. A total of 655 patients (638 adults and 17 children) were diagnosed with H. pylori infection. The prevalence of H. pylori infection was most commonly observed in 41–80 age group (66.9%). In addition, gender differences in the prevalence of H. pylori infection were detected in patients over 40 years of age. H. pylori infection in 41–80 years of age was 65.3% in men and 76.3% in women. Matsuhisa et al. reported that gastric ulcer was a common disease in Japan, whereas in Nepal, duodenal ulcers were common. Japanese patients infected with H. pylori have severe atrophic and metaplastic gastritis compared to Nepalese patients. The results may be related to the incidence of gastric cancer in Japanese. In older Japanese patients, dominant gastritis of the corpus was detected and antrum-dominant gastritis was found in all Nepalese patients. Matsuhisa et al. compared H. pylori-positive Asian adult populations with corpus-dominant gastritis, which is considered as one of the risk factors for gastric cancer. The incidence and mortality of gastric cancer is high among Japanese and Chinese populations.

In Thailand, the incidence of gastric cancer is quite low, while in Vietnam, it is low. H. pylori-positive Chinese (Beijing), Thai, and Vietnamese patients were compared with Japanese patients with endoscopic diagnosis to compare antrum gastritis with corpus gastritis. The antrum gastritis rates of the Japanese were significantly higher than the other groups. The corpus-type gastritis was characteristic in the elderly Japanese and Chinese (Fuzhou).

However, Chinese (Beijing), Thai, and Vietnamese people (except those over 70 years of age) had antrum-type gastritis in all age groups. There is a similarity between the degree of H. pylori colonization and the neutrophil activity score. These results are parallel to the incidence of gastric cancer in Thailand and Vietnam populations. The incidence and mortality of gastric cancer is high among Japanese and Chinese people.
We, Sengul and Sengul, conducted a study to determine the *H. pylori* frequency and also to evaluate the connection of the location and age groups with the degree of *H. pylori* colonization, based on updated Sydney System for the histopathology results of endoscopic gastric mucosal samples of 373 cases, between February 2009 and February 2013. *H. pylori* was detected as at least one positive, 206 (55.2%), and negative, 167 (44.8%). *H. pylori* was positive for 73 of 147 (49.7%) in the corpus and 114 of 197 (57.9%) in the antrum. No difference was revealed, comparing the general stomach (*P* = 0.292), antrum (*P* = 0.896) and corpus (*P* = 0.184), age groups and also new subgroup (over and under 50, in the antrum), and the *H. pylori* colonization. We determined in our previous research that the *H. pylori* positivity was mostly present in the antrum and at the 45–64 age group, while no difference was detected between the location, six structured age groups, and subgroups with over and under 50 years, together with the degree of *H. pylori* colonization.

**Treatment modalities for Helicobacter pylori infections**

Multiple antibiotic regimens have been evaluated in order to eradicate *H. pylori*. However, a number of regimens have consistently achieved the acceptable high eradication rates to date. There are also limited data on *H. pylori* antibiotic resistance rates to guide therapy. The selected treatment regimen must regard to local antibiotic resistance patterns (if known, with their possible allergic effects), cost, side effects, and ease of administration for the medical agents. A resistance threshold of ≥15% is frequently utilized as an indicator in order to select an alternative empiric antibiotic regimen for *H. pylori* eradication purposes. In patients with risk factors for macrolide resistance, bismuth quadruple therapy is recommended to use, while clarithromycin-based triple therapy with a proton-pump inhibitor (PPI), amoxicillin, and clarithromycin for the ones without risk factors for that. Alternative potential first-line treatment regimens consist of clarithromycin-based hybrid or sequential therapy. Nevertheless, the clarithromycin-based hybrid therapy has not been universally endorsed; for instance, some North American guidelines recommendations run counter to utilization of the sequential therapy as a first-line regimen by adding proofs of the deprivation of data from North American trials. Recommendation for the duration of administration for clarithromycin-based triple therapy and bismuth quadruple treatment regimens is 14 days. Bismuth quadruple therapy includes bismuth subsalicylate, metronidazole, tetracycline, and a PPI given for 14 days, while clarithromycin triple therapy comprises clarithromycin, amoxicillin, and a PPI, with the recommendation for a duration of 14 days. Concomitant therapy involves clarithromycin, amoxicillin, nitroimidazole (tinidazole or metronidazole), and a PPI administered together with the duration of 10–14 days. Gisbert et al. reported that nonbismuth quadruple (concomitant) therapy was an effective, safe, and well-tolerated alternative to the triple therapy, while it was less complex than the sequential one. Therefore, they propounded that this regimen was being well suited for utilizing in settings, particularly where the efficacy of triple therapy would unacceptably low. Hybrid therapy subsumes amoxicillin and a PPI for 7 days, followed by the administration of amoxicillin, clarithromycin, nitroimidazole, and a PPI for 7 days. Besides, the 10-day-sequential therapy regimen comprises amoxicillin and a PPI for 5 days, followed by clarithromycin and nitroimidazole (e.g., metronidazole) plus a PPI for 5 days. In addition, levofloxacin resistance attenuates the eradication success rate of levofloxacin consisting of regimens by 20%–40%. However, levofloxacin triple therapy was revealed as might possess a role in the treatment of *H. pylori* species as a salvage regimen based on the results from international trials. In order to confirm eradication, urea breath test, fecal antigen test, or upper endoscopy, 4 weeks or more after fulfilling medical antibiotic therapy, should be performed in all patients treated for *H. pylori*.

**Discussion**

*H. pylori* is a spiral-shaped, Gram-negative special bacterium that selectively holds the gastric mucosa, living in a microaerophilic environment which usually leads to a pronounced disease condition and persistent inflammation. However, in some cases, chronic active gastritis, peptic ulcer, lymphoid tissue lymphoma due to mucosa, and even gastric adenocarcinoma may develop. The evidence of oral–oral transmission is reported, though human–human passage has not been fully established.

*H. pylori* prevalence varies concerning the ethnicity and the geographic regions. Lee et al. reported that the positivity of *H. pylori* was recognized as 48.3%, 67.4%, and 77.9% in the American, Korean, and Japan cases, respectively, and the antrum was the most common location. In the studies, conducted in different regions in Turkey, *H. pylori* positivity was detected as 52.8%, 62.7%, 71%, 78.4%, 87%, 89.8%, 25.2%, 64%, 58.4%, and 70.1% in Thrace region, Istanbul, Erzurum, Erzincan, Van, Sanliurfa, Kuscehir, Konya, Kayseri, and Sivas. In December 2018, we reported the *H. pylori* positivity as 55.2% in Giresun. Our positivity is just between the positivity of American and Korean-Japan groups with the frequent location of the antrum (57.9%), concerning the corpus (49.7%).

*H. pylori* has been found to colonize the most common gastric antrum as a result of various studies conducted in different parts of the world. It colonizes some parts of the stomach. *H. pylori* localization is being more intense in the antrum. We reported that *H. pylori* positivity was 49.7% in the corpus, while 57.9% in the antrum. There was no significant association between *H. pylori* localization and *H. pylori* colonization degree. *H. pylori* localization in the antrum did not reveal a significant age.

The EUROGAST study group examines the prevalence of *H. pylori* infection in Europe, North Africa, North America, and Japan covering 17 different geographically defined
populations in two age groups, 25–34 and 55–64.\cite{33} The EUROGAST study detected the higher infection prevalence in the older group (61.4%) than the younger one (34.9%).\cite{33} Sengul and Sengul\cite{34} studied six age groups at the end of 2018 and reported the frequency of \textit{H. pylori}, regarding the age groups as 15–34 age group (57.1%), 35–44 age group (49.1%), 45–64 age group (64.5%), 65–74 age group (53.7%), 75–84 age group (59.4%), and above 85 years (3.3%).\cite{33} There was no significant relationship between \textit{H. pylori} colonization and age groups \cite{36} (\textit{P}>0.05). Reported the highest positivity in the 3rd group, 45–65 age group, 64.5%, which revealed so similarity with the positivity of EUROGAST study group, 61.4% for their 55-64 age group.\cite{36,38}

The prevalence of \textit{H. pylori}, ethnic group, and geographical varies according to regions.\cite{39} A Chile study reported 29\% \textit{H. pylori} positivity using the fast urease test and endoscopic biopsy samples. The infection prevalence of the age group of 40–49 years was 38.1\%, the highest rate. They also reported the attenuation of the prevalence of \textit{H. pylori} to 28.9\% from 44.9\% during the period of 11 years.\cite{33}

\textit{H. pylori}-related diseases are increasing in proximal stomach parts with increasing age. The pathogenesis and mechanism of \textit{H. pylori}-related diseases in the proximal stomach has not been explained. Stomach environment changes with age. \textit{H. pylori} colonization appears to be affected by this change.

In a Chinese study, 180 cases with the symptoms of dyspepsia were divided into the young, middle-aged, and old groups and the endoscopic gastric biopsies had been obtained from five locations in each case as the large curvature (middle corpus, mid-antrum), small curvature (middle corpus, mid-antrum), and incisura angularis. The results of this study revealed that the \textit{H. pylori} infection rate had increased with age in the corpus location. In addition, \textit{H. pylori} density had increased in the corpus in the elderly patients while the antrum and incisura angularis had not increased. A significant positive relationship between \textit{H. pylori} infection, mucosal inflammation, and pyloric metaplasia severity with increasing age in the corpus was reported. \textit{H. pylori} involvement had shifted from the distal to proximal with increased age. In this case, the spread of the pyloric glands increases from distal to proximal. In the same way, the rate of pyloric metaplasia increased with the risk of aggravated \textit{H. pylori} infection with associated inflammation in the elderly.\cite{36} In a US study, the age-related changes in the gastric mucosa and their association with \textit{H. pylori} had been examined. They collected data from a large national pathology database of 895,323 cases who underwent esophagogastroduodenoscopy between January 2008 and December 2013. Various gastric histopathologies were expressed as a percentage according to prevalence, sex, and age. Throughout life, gastric mucosa became abnormal in 50\% of participants. Gastric mucosa abnormalities were also found to be high in patients with high \textit{H. pylori} infection. The chronic active gastritis was detected in 22\% of the biopsies associated with \textit{H. pylori}. The reactive gastropathy was observed in 18\% of biopsies. It is increasing with age. Most of the pathological conditions detected in histological analysis are caused by \textit{H. pylori} infection.\cite{39}

On December 2018, we reported our 4-year single-center experience with 373 cases, of which 344 had the endoscopic gastric biopsies, obtained from the antrum and corpus locations. \textit{H. pylori} positivity had revealed 57.9\% in the antrum and 49.7\% in the corpus.\cite{40} The rest of 29 cases had the results from the locations of fundus, corpus and antrum, and fundus and corpus and antrum. No significant association between the anatomic localization and \textit{H. pylori} positivity could be exhibited. An alternate taxonomy in terms of the subgroups, under and over 50 years old, had been performed, and no statistical difference had been detected as the antrum localization, the most common location for \textit{H. pylori} positivity, was selected as the anatomic pilot region.\cite{41} \textit{H. pylori} infection is estimated to affect approximately 50\% of the world population.\cite{42} In another estimate, the average prevalence of \textit{H. pylori} infection in the world was given as 58\%.\cite{43} In our study, the overall \textit{H. pylori} positivity was 55.2\%.\cite{44} Because of the irregular distribution of \textit{H. pylori} in the gastric mucosa, biopsies from various regions of the stomach may increase the diagnostic yield for detection of \textit{H. pylori}.\cite{45} \textit{H. pylori} infection is a major health problem in China and its prevalence ranges from 41.5\% to 72.3\% according to population and geographic region.\cite{46} According to geographical regions, age, and socioeconomic status, it ranges between 39.9\% and 84.2\%.\cite{47}

\textit{H. pylori} has been found to colonize the most common gastric antrum as a result of various studies conducted in different parts of the world. It colonizes some parts of the stomach.\cite{48} Zhang \textit{et al.} reported that \textit{H. pylori} localization is being more intense in the antrum.\cite{49} We reported the \textit{H. pylori} positivity of 49.7\% in the corpus, while 57.9\% in the antrum. No significant association was recognized between \textit{H. pylori} localization and \textit{H. pylori} colonization degree. \textit{H. pylori} localization in the antrum did not reveal a significant age.\cite{42}

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The prevalence of *H. pylori*, ethnic group, and geographical varies according to regions. A Chile study reported 29% *H. pylori* positivity using the fast urease test and endoscopic biopsy samples. The infection prevalence of the age group of 40–49 years was 38.1%, the highest rate. They also reported the attenuation of the prevalence of *H. pylori* to 28.9% from 44.9% during the period of 11 years. *H. pylori*-related diseases are increasing in proximal stomach parts with increasing age. The pathogenesis and mechanism of *H. pylori*-related diseases in the proximal stomach has not been explained. Stomach environment changes with age.

**CONCLUSION**

*H. pylori* leads to important diseases in the stomach and gastrointestinal tract. Although quite a few researches have been performed to date about *H. pylori*, few studies exist in the English language literature about whether its anatomo-topographic gastric settlements in the stomach during the aging process alter its positivity [Figure 1]. We reported in our current previous study that the *H. pylori* positivity was being mostly in the antrum and at 45–64 age group, while no difference was observed between the location, six structured age groups, and subgroups with over and under 50 years, together with the degree of colonization for *H. pylori*. We assert that the advanced multicentric studies should be performed on the topographic gastric localization and relevant age groups related to assessment evaluation of *H. pylori* which we suppose that it could be beneficial and essential for the progressive evaluation and follow-up of its leading diseases in the stomach.

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**Conflicts of interest**

There are no conflicts of interest.

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