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NARRATIVE REVIEW

# Review on Helicobacter Pylori Associated Diseases

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## ABSTRACT

One of the most common and enduring bacterial infections globally, Helicobacter pylori (H. pylori) infects almost half of the world's population. The bacterium is described as a spiral microaerophilic gram-negative bacterium, it is commonly found in the stomach and can cause several categories of gastrointestinal conditions, such as gastritis, peptic ulcers, and in some circumstances, stomach cancer. There is also a growing knowledge that chronic H. pylori infection may be associated with an increased danger of extra-gastric disease that includes host iron deficiency anaemia, cardiovascular, autoimmune, metabolic, neurological and dermatological diseases. In this article, we examined the virulence factors of H. pylori and its correlation to gastrointestinal diseases, as well as the bacterium's potential involvement in extra-gastric diseases such as iron and vitamin B12 deficiency, in addition to neurological, cardiovascular, inflammatory bowel, and diabetes mellitus disorders.

**Keywords :** H pylori, Gastric Disease, Extra Gastric Manifestations

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## INTRODUCTION

Helicobacter pylori (H. pylori) is a spiral microaerophilic gram-negative bacterium, it is commonly found in the stomach and can cause several categories of gastrointestinal conditions, such as gastritis, peptic ulcers, and in some circumstances, stomach cancer. For a very long period of time and due to its extremely acidic environment, the human stomach was an organ devoid of germs where no microbe could survive in it. Warren and Marshall changed this idea in 1982 by isolating the bacteria of H. pylori from gastric biopsies of active chronic gastritis, gastric ulcer, or duodenal ulcer patients [1,2]. H. pylori Infection is considered as one of the most common chronic infections amongst humans since its isolation by Marshall and Warren[3]. Moreover, studies show that chronic H. pylori infection may be associated with an increased danger of extra-gastric disease that includes host iron deficiency (hematological)[4], cardiovascular, autoimmune, metabolic, neurological and dermatological diseases[5].

The virulence factors of H. pylori can be classified into three major pathogenic processes, involving colonization, immune escape, and disease induction[6]. The mode of transmission of the bacteria remains unclear, many authors have suggested that fecal-oral routes via contaminated water, food and dirty hands[7].

Many detection techniques for H. pylori have been developed. Non-invasive tests such as serology, urea breath test and stool antigen tests are usually preferred. Invasive tests including histology, culture media, rapid urease test and polymerase chain reaction (PCR) are also available. Each test has been associated with one or more advantages or disadvantages. However, PCR is considered the best way to detect H. pylori[8]. In this article, we highlight the associations between H. pylori and hematologic disorders such as iron and vitamin B12 deficiency, as well as the bacterium's potential involvement in neurological, cardiovascular, inflammatory bowel, and diabetes mellitus disorders.

**Major virulence factors of H. pylori**

Many virulence factors of H. pylori play an important role in the induction of inflammatory responses, control these responses, organizing them and maintaining chronic inflammation, these factors promote the survival and colonization of the bacterium within the gastric mucosa so H. pylori can escape from the immune system. This bacterium has many developed tools that changes host responses and signalling pathways[9]. Virulence factors of H. pylori includes:

1. **Adhesion factors:** blood group antigen-binding adhesin (BabA), SabA, H. pylori outer membrane protein (HopQ), and other outer membrane proteins interact with the receptors present on the host intestinal epithelial cells, thereby contributing significantly to the pathological events associated with chronic infections. The interaction guards the bacterium from being washed out throughout mucus discharge, facilitates nutrient access for the bacteria, and facilitates the delivery of bacterial toxins and other effector molecules to the host cells [10]. Lewis b blood group antigens produced on gastric epithelial cells are bound by BabA through a mediating mechanism. The associated SabA adhesin attaches itself to host sialyl-Lewis x antigens, which are mostly expressed on the surfaces of epithelial cells during inflammatory processes. HopQ appears to be crucial for Cag T4SS activity and binds to several cell adhesions molecules related to carcinoembryonic antigen. Binding to the glycoprotein laminin in the extracellular matrix is mediated by AlpA and AlpB[11].

2. **Urease:** as one of the most significant virulence factors involved in bacterial metabolism and colonization within the gastric mucosa, urease is the protein that H. pylori most commonly expresses. Because urease is present in both the intracellular compartment and the surface of H. pylori bacteria, internal and external urease can be distinguished from one another according to where they are located. Urease-negative mutants are not able to colonize the stomach mucosa by bacteria to the same degree as urease-positive H. pylori strains at physiological pH values and this refer to the urease which is necessary for this process[12].

3. **Flagellum:** H. pylori cannot enter the mucus layer or remain in a swimming reservoir within the mucus without flagella-driven movement. Due to a particular modification of their amino acid sequences, H. pylori's unipolar bundle of revolving sheathed flagella is made up of filaments made of two flagellin proteins that avoid activating the innate immune system via TLR5. Both chemotaxis and energy taxis regulate the movement direction, allowing bacteria to navigate through pH and bicarbonate and probably other gradients in the stomach mucus. Small molecule drugs that lower the density of H. pylori colonization can limit motility in vitro, suggesting that this method could be used in the future as a treatment[11].

4. **Catalase**: it is estimated to account for 4% to 5% of the total protein content of H. pylori, and it is one of the most highly expressed proteins in strains of the bacteria that are isolated from the stomach mucosa [9]. H. pylori catalase is greater resistance to cyanide or aminotriazole inhibition than catalase from other species[12].

5. **Cytotoxin-associated gene-A (Cag-A):** it is an effector protein that ranges in size from 125 to 145 kDa. Strains that express this protein are classified as highly virulent. CagA is translocated into the gastric epithelial cells through T4SS following its synthesis. Also, it acts as a stimulant for inflammatory responses, stimulates the releasing of two interleukins (IL-8 and Interleukin-12 (IL-12)), facilitates bacterial motility (Cag-A strains are more motile). The expression of CagA act as a promoter for the induction of gastritis, duodenal ulcers and increases the risk of gastric cancer, and the pathogenicity of the CagA protein leads to disruptions in cellular signaling[139].

6. **Vacuolating cytotoxin-A (Vac-A):** about half of all H. pylori strains release a 95 kDa protein (VacA) that encourages widespread hyalinization in epithelial cells. VacA protein implicated in the development of stomach cancer and peptic ulcers. The VacA protein regulates cellular processes in several ways, helping in H. pylori chronic colonization of the stomach mucosa and some of these way are the disruption of cytoskeleton-dependent cell functions, promotion of apoptosis, and immunological control[14].

7. **Phospholipases**: the mucus layer is broken down by H. pylori phospholipases, which eventually cause the stomach epithelial cells' physiological functions to disappear. Phospholipases not only damage mucosa but also promote persistent inflammation, that may aid in the progression of peptic ulcers. The environments of the gut can therefore support higher levels of bacterial colonization and survival[12].

8. **Blood group antigen binding adhesions (Bab A):** promotes the adherence of the pathogen, induces the toxins delivery into the host by facilitating the activity of bacterial type IV secretion system (T4SS), release extreme amounts of the proinflammatory factors resulting in the induction of carcinogenesis, stimulates numerous immune responses like IL-8, resulting in gastric inflammation[9].

**Gastrointestinal diseases caused by H. pylori**

## GASTRITIS

Two-thirds of the world's population is affected by H. pylori gastritis. Gastritis is among the most prevalent inflammatory chronic conditions that effect the stomach mucus and its infection is either acute or chronic (chronic active gastritis) [15]. Sour stomach or heartburn, and transient gastric suffering are the most common clinical manifestations of acute gastritis, which may lead to vomit and maybe hematemesis and bleed[11]. Peptic ulcer disease or gastroduodenal complications of chronic infection including gastric atrophy, intestinal metaplasia, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma are the most common complications presented in patients with chronic H. pylori gastritis [15].

## PEPTIC ULCER DISEASE (PUD

PUD includes esophageal, duodenal, and stomach ulcers, and the peptic ulcer, or stomach ulcer, is described as a condition in which the mucosa or lining of the stomach and/or duodenum is deeply damaged, extending beyond the muscular mucosa to the muscle layer. This damage is caused by the production of gastric acid in the environment[16]. Peptic ulcers are no longer thought to be caused by food neglect or genetic stress [2]. H. pylori continues to be the most common cause of PUD. It is estimated that 10% of people with H. pylori infection will experience PUD in their lifetime [11].

## GASTRIC CANCER

Some kinds of gastric carcinomas appear to be associated with H. pylori infection. The gastric cancer is the leading cause of cancer deaths worldwide, with gastric adenocarcinoma coming in second. The gastric cancer is far more common in some nations and regions, primarily Japan, Central Europe, the Scandinavian countries, South and Central America, the Soviet Union, China, and Korea as well [2]. Depending on their ethnicity and environmental circumstances, people with H. pylori infection have a 1-5% lifetime risk of developing stomach cancer. Following an H. pylori infection, certain cultures are more likely to develop stomach cancer. These communities most likely have higher rates of dietary habits, housing conditions, and genetic factors—for example, East Asian people tend to consume more salted or pickled foods. Although smoking and excessive salt consumption are two dietary and lifestyle factors that contribute to the development of gastric cancer, but it is considered that the presence of H. pylori infection is the most important cause[11].

## GASTRIC LYMPHOMA

A carcinoma of the lymphatic system is called lymphoma. The phrase "primary gastric lymphoma" refers to a kind of cancer that starts in the stomach and accounts for 3-6% of all

gastric cancers. Mucosa-Associated Lymphoid Tissue (MALT), a low-grade lymphoma, is closely linked to the infection of H. pylori. Normally, a healthy stomach does not contain lymphoid tissue, but an H. pylori infection can cause lymphoid clusters to form. It may be possible to resolve superficial mucosa-associated lymphoid tissue (MALT) by getting rid of H. pylori [2].

**Some of Extra Gastric Diseases caused by H. pylori**

Numerous studies conducted over the past few decades have revealed an association between infections caused by H. pylori and a range of extra-gastroduodenal problems [17,18].

**Iron Deficiency**

It is commonly acknowledged that iron deficiency is a common dietary deficit that affects around 500 million people globally. Many scientists have focused their attention on proving a link between iron deficiency and infection with H. pylori [2]. Regardless of gender, age, or other risk factors for iron deficiency, H. pylori infection lowers ferritin levels, which raises the possibility of anaemia. A recent research showed that when H. pylori is successfully eradicated, the efficacy of Iron-deficiency anaemia (IDA) medication increases. Following a successful eradication, ferritin and haemoglobin levels increased and mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) returned to normal with the use of iron supplements [19].

**Vitamin B12 Deficiency**

Vitamin B12, acts as a coenzyme in numerous metabolic pathways and contributes to DNA synthesis. The Vitamin B12 deficiency is a disorder caused by an absence of intake or absorption of the vitamin B12[20].

Though the precise mechanisms are still unclear, there is evidence pointing to a connection between deficiency of vitamin B12 and infection with H. pylori. For H. pylori to proliferate, vitamin B12 is necessary. There is a suggestion that the bacteria could collaborate with the host to absorb vitamin B12, which could limit the quantity of vitamin B12 that the host can[2]. Some research has connected improvements in vitamin B12 levels due to the successful elimination of H. pylori, which further supports the link between the illness and deficiency of B12 vitamin[2122].

**Diabetes mellitus**

Diabetes mellitus (DM) is a multifaceted metabolic disorder and it is the condition that is characterized by increased levels of glucose in the bloodstream, referred to as hyperglycemia. This occurs due to insufficient production of insulin by the body or inadequate utilization of the insulin it produces [23]. Diabetes is primarily divided into two categories: type 1 diabetes, an autoimmune disease, and type 2 diabetes, which is linked to insulin resistance [2]. Insulin action may be inhibited by phosphorylation of serine residues on the insulin receptor substrate due to elevated levels of inflammatory cytokines generated by H. pylori. This phosphorylation prevents the insulin receptor substrate from interacting with insulin receptors. The hormones leptin and ghrelin, which are produced by the mammalian

stomach, are involved in energy balance and their interactions impact glucose homeostasis and insulin sensitivity. There has been increasing evidence that H. pylori has a role in the control of these hormones [24]. Many studies showed that there is a relationship between H. pylori infection and DM. It's interesting to note that following H. pylori removal, the risk of DM dropped from 1.36 (95% CI, 1.10-1.67) to 0.92 (95% CI, 0.79-1.07) in Japan. This is consistent with research showing that H. pylori removal lowered HbA1c levels in diabetic individuals [18 25 26].

**Cardiovascular Diseases**

Chronic bacterial infection of the gastrointestinal organs stimulates dyslipidemia, raises fibrinogen levels, induces CRP release, rapidly raises blood leukocyte and homocysteine levels, stimulates hypercoagulability, induces immune cross-reactivity, and raises proinflammatory cytokines. According to scientific study, inflammatory conditions have a major effect on atherosclerosis, so chronic infection with H. pylori could lead to atherosclerosis and cardiovascular disease[1].

**Neurological Disorders**

It has been proposed that H. pylori enter the brain via an oro-nasal route, resulting in neurodegeneration. Alternatively, H. pylori-infected monocytes could enter the brain via a pro-inflammatory cytokine-induced breakdown of the blood-brain barrier (BBB). Finally, H. pylori might get to the brain via the enteric nervous system[20]. Recent studies have found a link between infection with H. pylori and various neurological disorders, including Parkinson's disease (PD) and Alzheimer's disease (AD) [2]. A meta-analysis of research on the connection between intestinal diseases and PD or AD found that the OR for H. pylori infection in PD and AD patients was 1.65 (95% CI, 1.43–1.91) and 1.40 (95% CI, 1.12–1.76), respectively [18]. According to studies, eradicating the infectious agent improved AD-related problems. The pathogenic relationship could be a higher incidence of the apolipoprotein E (ApoE) polymorphism in H. pylori-infected individuals, which is a risk factor for Alzheimer's disease [20]. It has been demonstrated that eradicating H. pylori in Parkinson's disease patients improved the efficacy of clinical symptoms and the general quality of life [2]. Moreover, Guillain-Barré syndrome, also known as (GBS) is an autoimmune, acute neuropathy characterized by distal limb paralysis. The illness is frequently started by an infectious disease, and H. pylori infection has been recognized as related with GBS, through the pathogenic relationship and molecular mimicry between H. pylori LPS and peripheral nerve gangliosides. A recent meta-analysis showed that the Guillain-Barré's syndrome patients had significantly higher levels of anti-H. pylori IgG in CSF ($P < 00001$) and serum ($P = 0.004$) compared to controls [18].

**Chronic Urticaria (CU)**

Chronic Urticaria (CU) is a skin disorder characterized by distinct itching spots known as wheal. CU is thought to be an autoimmune basis in its pathophysiology, with the generation of autoantibodies triggering histamine release via IgE epitopes or FceRI receptor binding[20].

Chronic Urticaria is one skin disease that H. pylori has been linked to it[2], there are many processes have been linked to H. pylori with CU; such as an increase in gastrointestinal mucosal permeability for antigens, immunomodulation, autoimmunity, or vascular wall dysfunction might be involved in this association. Moreover, different immunopathogenesis during the H. pylori infection can cause illness might be caused by an unstable Th1 or Th2 mediated response post an infection[27]. The clinical improvement of skin condition following H. pylori eradication is critical. In this regard, some researchers demonstrated a good outcome of skin lesions following anti-H. pylori treatment[20].

**Inflammatory bowel disease**

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, debilitating, and progressive condition that requires continuous treatment and poses a growing global hazard to human health[28]. A number of observational investigations have looked into the potential link between the presence of H. pylori colonization and inflammatory bowel disorders [29]. The pathophysiologic contribution of H. pylori in a situation of IBD may be linked to the fact that the infection with the bacteria induces a systemic Th1-mediated immunological response, stimulating both specific and non-specific immune responses, which may start a chain of immunologic reactions that contribute to IBD. Another potential modifying mechanism is direct contact of the gut mucosa with urease and cytotoxins. On the other hand, the bacterium's protective role could be attributed to its influence on a tolerogenic phenotype of dendritic cells and T-regulatory cells with immunosuppressive properties, besides that, H. pylori generates peptides that help preserve the inflamed gut[20]. Although many research investigations have examined the relationship between H. pylori infection and IBD, a causal relationship between the two has yet to be established, and there is conflicting evidence regarding the potential causative and protective roles of H. pylori infection in IBD[28].

## CONCLUSION

H. pylori gastritis affects approximately two-thirds of the global population and it is linked to certain types of gastric carcinomas, hematologic disorders like Vitamin B12 and iron-deficiency anaemia. Furthermore, there is a suspected association between the bacterium and different diseases such as inflammatory bowel syndrome, cardiovascular diseases, neurologic diseases, and Diabetes mellitus.

## DECLARATIONS

1. All authors contributed equally to the paper, with tasks divided collaboratively, including research and writing. Each author shares equal responsibility for the content and conclusions.

2. Conflict of interest

The authors declares no conflict of interest

3. Ethical Approval

(Institutional ethical approvals and informed consent)

This research does not conflict with our university's ethical standards, nor with any known ethical criteria.

4. Funding resources

This research is self-funded

## REFERENCES

1. Muhi SH, Abd WS, Abd NS. THE EFFECT OF HELICOBACTER PYLORI ON INTERLEUKIN-6 IN PATIENTS WITH ISCHEMIC HEART DISEASE. Iraqi Journal of Agricultural Sciences. 2023;54(5):1243–1251.
2. Almashhadany DA, Mohammed HI, Abdullah AD. Review on Helicobacteriosis Associated Diseases. International Journal. 2023;10(5):24–34. Available from: https://cosmosscholars.com/phms/index.php/ijmst/ar...
3. Jabbar HS, Adulsamed A. Gene detection of Helicobacter-pylori by use real-time PCR in patients from Wasit province: Iraq. Journal of Entomology and Zoology Studies. 2018;6(2):640–643.
4. Flores SE, Aitchison A, Day AS, Keenan JI. Helicobacter pylori infection perturbs iron homeostasis in gastric epithelial cells. PLoS One. 2017;12(9):184026–184026. 10.1371/journal.pone.0184026.
5. Lewinska A, Wnuk M. Helicobacter pylori-induced premature senescence of extragastric cells may contribute to chronic skin diseases. Biogerontology. 2017;18(2):293–299. doi.org/10.1007/s10522-017-9676-x.
6. Salman AH, Hawezy AA. Prevalence of vacA, cagA, and iceA Virulence Factors of Helicobacter Pylori Isolated from Gastro-duodenal Patients. Journal of Biotechnology Research Center. 2020;14(1).
7. Idowu A, Mzukwa A, Harrison U, Palamides P, Haas R, Mbao M, et al. Detection of Helicobacter pylori and its virulence genes (cag A, dup A, and vac A) among patients with gastroduodenal diseases in Chris Hani Baragwanath Academic Hospital, South Africa. BMC gastroenterology. 2019;19(1):1–10. 10.1186/s12876-019-0986-0.
8. Patel SK, Pratap CB, Jain AK, Gulati AK, Nath G. Diagnosis of Helicobacter pylori: what should be the gold standard? World journal of gastroenterology. 2014;20(36):12847–12847. 10.3748/wjg.v20.i36.12847.
9. Baj J, Forma A, Sitarz M, Portincasa P, Garruti G, Krasowska D, et al. Helicobacter pylori virulence factors-mechanisms of bacterial pathogenicity in the gastric microenvironment. Cells. 2020;10(1):27–27. 10.3390/cells10010027.

10. Ansari S, Yamaoka Y. Helicobacter pylori virulence factors exploiting gastric colonization and its pathogenicity. Toxins. 2019;11(11):677–677. doi.org/10.3390/toxins11110677.
11. Malfertheiner P, Camargo MC, El-Omar E, Liou JM, Peek R, Schulz C, et al. Helicobacter pylori infection. Nature reviews Disease primers. 2023;9(1):19–19. 10.1038/s41572-023-00431-8.
12. Najee HB, Zainulabdeen SM, Atiyah IA. Virulence factors of Helicobacter pylori. Muthanna Medical Journal. 2023;(1):10–10. dx.doi.org/10.52113/1/1/2023-67-74.
13. Ansari S, Yamaoka Y. Helicobacter pylori virulence factor cytotoxin-associated gene A (CagA)-mediated gastric pathogenicity. International journal of molecular sciences. 2020;21(19):7430–7430. 10.3390/ijms21197430.
14. Kadhim AS, Al-Karawi AS. Insights into the Pathogenesis, Virulence Factors, and Diagnosis of Helicobacter pylori: A Comprehensive Review. American Journal of Bioscience and Bioinformatics. 2023;2(1):31–37. Available from: https://inlibrary.uz/index.php/archive/article/view/30690.
15. Jensen PJ, Feldman M, Lamont JT, Grover S. Acute and chronic gastritis due to Helicobacter pylori. 2019;.
16. Chaudhry A, Cuthrell KM, Thornton OR. Peptic Ulcer Disease; Stomach and Gastric Ulcers, a Concise Review. International Research Journal of Gastroenterology and Hepatology. 2023;6(1):30–39. Available from: http://geographical.go2journals.com/id/eprint/1607.
17. Sowaid YI, Ali OM, Hussian SSA. Extra-Gastroduodenal Manifestation and Helicobacter pylori Infection. Archives of Razi Institute. 2022;77(3):1017–1026. 10.22092/ARI.2022.357387.2027.
18. Pellicano R, Ianiro G, Fagoonee S, Settanni CR, Gasbarrini A. Extragastric diseases and Helicobacter pylori. Helicobacter. 2020;25:12741–12741. doi.org/10.1111/hel.12741.
19. Makhmonov LS, Mamatkulova FK, Berdiyarova MB, Shomurodov KE. The main causes of anemia in iron and vitamin b 12 deficiency associated with helicobacter pylori. Nveo-natural volatiles & essential oils Journal| NVEO. 2021;p. 10167–10174.
20. Gravina AG, Priadko K, Ciamarra P, Granata L, Facchiano A, Miranda A, et al. Extragastric manifestations of Helicobacter pylori infection. Journal of Clinical Medicine. 2020;9(12):3887–3887. doi.org/10.3390/jcm9123887.
21. Cai X, Li X, Jin Y, Zhang M, Xu Y, Liang C, et al. Vitamins and Helicobacter pylori: an updated comprehensive meta-analysis and systematic review. Frontiers in Nutrition. 2022;8:781333–781333. 10.3389/fnut.2021.781333.
22. Ulasoglu C, Temiz HE, Sağlam ZA. The Relation of Cytotoxin-Associated Gene-A Seropositivity with Vitamin B12 Deficiency in Helicobacter pylori- Positive Patients. BioMed Research International. 2019;2019(1):1450536–1450536. doi.org/10.1155/2019/1450536.
23. Sugandh FNU, Chandio M, Raveena FNU, Kumar L, Karishma FNU, Khuwaja S, et al. Advances in the management of diabetes mellitus: a focus on personalized medicine.

Cureus. 2023;(8):15–15. 10.7759/cureus.43697.

24. Bajaj S, Rekwal L, Misra SP, Misra V, Yadav RK, Srivastava A. Association of helicobacter pylori infection with type 2 diabetes. Indian journal of endocrinology and metabolism. 2014;18(5):694–699. 10.4103/2230-8210.139235.
25. Cheng KP, Yang YJ, Hung HC, Lin CH, Wu CT, Hung MH, et al. Helicobacter pylori eradication improves glycemic control in type 2 diabetes patients with asymptomatic active Helicobacter pylori infection. Journal of Diabetes Investigation. 2019;10(4):1092–1101. doi.org/10.1111/jdi.12991.
26. Kato M, Toda A, Yamamoto-Honda R, Arase Y, Sone H. Association between Helicobacter pylori infection, eradication and diabetes mellitus. Journal of diabetes investigation. 2019;10(5):1341–1346. doi.org/10.1111/jdi.13011.
27. Kareem MA, Abd-Alrahman TZ, Aboud RS, Al-Ahmer SD, Muhammad TY. The role of Helicobacter pylori infection in skin disorders. Iraqi Journal of Science. 2016;p. 2406–2411. Available from: https://www.ijs.uobaghdad.edu.iq/index.php/eijs/article/view/6336.
28. El-Wahab A, Youssef EW, Hassouna EI, E. Helicobacter pylori infection in patients with inflammatory bowel diseases: a single-centre, prospective, observational study in Egypt. BMJ open. 2022;12(5):57214–57214. doi.org/10.1136/bmjopen-2021-057214.
29. Shirzad-Aski H, Besharat S, Kienesberger S, Sohrabi A, Roshandel G, Amiriani T, et al. Association between Helicobacter pylori colonization and inflammatory bowel disease: a systematic review and meta-analysis. Journal of Clinical Gastroenterology. 2021;55(5):380–392. 10.1097/MCG.0000000000001415.