

World Journal of *Gastroenterology*

World J Gastroenterol 2022 July 28; 28(28): 3535-3752



REVIEW

- 3535 Peroxisome proliferator-activated receptor gamma as a therapeutic target for hepatocellular carcinoma: Experimental and clinical scenarios
Katoch S, Sharma V, Patial V
- 3555 Gut microbiota alteration and modulation in hepatitis B virus-related fibrosis and complications: Molecular mechanisms and therapeutic inventions
Li YG, Yu ZJ, Li A, Ren ZG

MINIREVIEWS

- 3573 Combination approaches in hepatocellular carcinoma: How systemic treatment can benefit candidates to locoregional modalities
da Fonseca LG, Araujo RLC
- 3586 Update on endoscopic ultrasound-guided liver biopsy
Rangwani S, Ardeshtina DR, Mumtaz K, Kelly SG, Han SY, Krishna SG
- 3595 Non-alcoholic fatty liver disease-related hepatocellular carcinoma: Is there a role for immunotherapy?
Mattos ÁZ, Debes JD, Vogel A, Arrese M, Revelo X, Pase THS, Manica M, Mattos AA
- 3608 Potassium-competitive acid blockers and gastroesophageal reflux disease
Leowattana W, Leowattana T
- 3620 Making the case for multidisciplinary pediatric aerodigestive programs
Kanotra SP, Weiner R, Rahhal R
- 3627 Therapeutic potential of mesenchymal stem cells in the treatment of acute liver failure
Harrell CR, Pavlovic D, Djonov V, Volarevic V
- 3637 Effective combinations of anti-cancer and targeted drugs for pancreatic cancer treatment
Nishimoto A

ORIGINAL ARTICLE

Basic Study

- 3644 Mechanism of electroacupuncture and herb-partitioned moxibustion on ulcerative colitis animal model: A study based on proteomics
Qi Q, Zhong R, Liu YN, Zhao C, Huang Y, Lu Y, Ma Z, Zheng HD, Wu LY

Retrospective Study

- 3666** How has the disease course of pediatric ulcerative colitis changed throughout the biologics era? A comparison with the IBSEN study

Kwon Y, Kim ES, Choe YH, Kim MJ

- 3682** Gastric mucosal precancerous lesions in *Helicobacter pylori*-infected pediatric patients in central China: A single-center, retrospective investigation

Yu M, Ma J, Song XX, Shao QQ, Yu XC, Khan MN, Qi YB, Hu RB, Wei PR, Xiao W, Jia BL, Cheng YB, Kong LF, Chen CL, Ding SZ

Observational Study

- 3695** Secular trends of intrahepatic cholangiocarcinoma in a high endemic area: A population-based study

Lin CR, Lee YK, Chiang CJ, Yang YW, Chang HC, You SL

- 3706** Family-based *Helicobacter pylori* infection status and transmission pattern in central China, and its clinical implications for related disease prevention

Yu XC, Shao QQ, Ma J, Yu M, Zhang C, Lei L, Zhou Y, Chen WC, Zhang W, Fang XH, Zhu YZ, Wu G, Wang XM, Han SY, Sun PC, Ding SZ

SCIENTOMETRICS

- 3720** Global research on *Clostridium difficile*-associated diarrhoea: A visualized study

Zyoud SH

CASE REPORT

- 3732** Delayed immune-related sclerosing cholangitis after discontinuation of pembrolizumab: A case report

Tanaka T, Sakai A, Tsujimae M, Yamada Y, Kobayashi T, Masuda A, Kodama Y

LETTER TO THE EDITOR

- 3739** Prednisolone induced pneumatosis coli and pneumoperitoneum

Goh SSN, Shelat V

- 3743** Is patient satisfaction sufficient to validate endoscopic anti-reflux treatments?

Bortolotti M

- 3747** Endoluminal vacuum-assisted therapy as a treatment for anastomotic leakage in colorectal surgery

Chiarello MM, Bianchi V, Fransvea P, Brisinda G

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Giovanna Ferraioli, MD, FAIUM, Researcher, Department of Clinical Surgical, Diagnostic and Pediatric Sciences, Medical School University of Pavia, Viale Brambilla 74, Pavia 27100, Italy. giovanna.ferraioli@unipv.it

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

July 28, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Retrospective Study

Gastric mucosal precancerous lesions in *Helicobacter pylori*-infected pediatric patients in central China: A single-center, retrospective investigation

Miao Yu, Jing Ma, Xiao-Xia Song, Qiao-Qiao Shao, Xue-Chun Yu, Muhammad Noman Khan, Ya-Bin Qi, Ruo-Bing Hu, Pei-Ru Wei, Wei Xiao, Bai-Ling Jia, Yan-Bo Cheng, Ling-Fei Kong, Chuan-Liang Chen, Song-Ze Ding

Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kirkik D, Turkey;
Miftahussurur M, Indonesia

Received: January 9, 2022

Peer-review started: January 9, 2022

First decision: March 8, 2022

Revised: April 2, 2022

Accepted: June 21, 2022

Article in press: June 21, 2022

Published online: July 28, 2022



Miao Yu, Jing Ma, Qiao-Qiao Shao, Xue-Chun Yu, Muhammad Noman Khan, Ya-Bin Qi, Ruo-Bing Hu, Pei-Ru Wei, Wei Xiao, Bai-Ling Jia, Song-Ze Ding, Department of Gastroenterology and Hepatology, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, Zhengzhou 450003, Henan Province, China

Xiao-Xia Song, Ling-Fei Kong, Department of Pathology, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, Zhengzhou 450003, Henan Province, China

Yan-Bo Cheng, Department of Pediatrics, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, Zhengzhou 450003, Henan Province, China

Chuan-Liang Chen, Department of Medical Imaging, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, Zhengzhou 450003, Henan Province, China

Corresponding author: Song-Ze Ding, MD, PhD, Professor, Department of Gastroenterology and Hepatology, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, No. 7 Weiwei Road, Jinshui District, Zhengzhou 450003, Henan Province, China. dingsongze@hotmail.com

Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) infects about 50% of the world population and is the major cause of chronic gastritis, peptic ulcers, and gastric cancer. Chronic *H. pylori* infection induces gastric mucosal precancerous lesions mostly in adulthood, and it is debatable whether these pathological conditions can occur in childhood and adolescents as well. Since this is a critical issue to determine if intervention should be offered for this population group, we investigated the gastric mucosal precancerous lesions in pediatric patients in an area in central China with a high prevalence of *H. pylori* and gastric cancer.

AIM

To investigate the relationship of *H. pylori* infection and gastric mucosal precancerous lesions in children and adolescents in central China.

METHODS

We screened 4258 ward-admitted children and adolescent patients with upper gastrointestinal symptoms, and finally enrolled 1015 pediatric patients with *H. pylori* infection and endoscopic and histological data. *H. pylori* infection status was determined by rapid urease test and histopathological examination. Both clinical and pathological data were collected and analyzed retrospectively. Occurrence of gastric mucosal precancerous lesions, inflammatory activity and degree of inflammatory cell infiltration between *H. pylori*-positive and -negative groups were compared.

RESULTS

Among the 1015 eligible children and adolescents, the overall *H. pylori* infection rate was 84.14% (854/1015). The infection rate increased with age. The incidence of gastric mucosal precancerous lesions in *H. pylori*-infected children was 4.33% (37/854), which included atrophic gastritis (17 cases), intestinal metaplasia (11 cases) and dysplasia (9 cases). In *H. pylori*-negative patients, only 1 atrophic gastritis case [0.62%, (1/161)] was found ($P < 0.05$). Active inflammation in *H. pylori*-infected patients was significantly higher than that in non-infected patients, and the *H. pylori*-infected group showed more severe lymphocyte and neutrophil granulocyte infiltration ($P < 0.001$). In addition, endoscopy revealed that the most common findings in *H. pylori*-positive patients were antral nodularity, but in *H. pylori*-negative patients only superficial gastritis was observed.

CONCLUSION

In children and adolescents, gastric mucosal precancerous lesions occurred in 4.33% of *H. pylori*-infected patients in central China. These cases included atrophic gastritis, intestinal metaplasia, and dysplasia. The data revealed an obvious critical issue requiring future investigation and intervention for this population group.

Key Words: *Helicobacter pylori*; Gastric cancer; Precancerous lesions; Inflammation; Children and adolescents

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: *Helicobacter pylori* (*H. pylori*) infection induces gastric mucosal precancerous lesions mostly in adulthood. Whether these lesions can also occur in children and adolescents remains controversial. Our study showed that in a region in central China with a high prevalence of *H. pylori* and gastric cancer, the incidence of gastric mucosal precancerous lesions was 4.33% among *H. pylori*-infected children and adolescents, which is significantly higher than the non-infected pediatric patients. The precancerous lesions included atrophic gastritis, intestinal metaplasia, and dysplasia. These data provide an alarming alert and call for further investigation and intervention for this population group.

Citation: Yu M, Ma J, Song XX, Shao QQ, Yu XC, Khan MN, Qi YB, Hu RB, Wei PR, Xiao W, Jia BL, Cheng YB, Kong LF, Chen CL, Ding SZ. Gastric mucosal precancerous lesions in *Helicobacter pylori*-infected pediatric patients in central China: A single-center, retrospective investigation. *World J Gastroenterol* 2022; 28(28): 3682-3694

URL: <https://www.wjgnet.com/1007-9327/full/v28/i28/3682.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v28.i28.3682>

INTRODUCTION

Helicobacter pylori (*H. pylori*) has infected about 50% of the Chinese population and is responsible for 90% of non-cardia gastric cancer incidences. It is reported that one-third of asymptomatic or healthy children have serologically-confirmed *H. pylori* infection worldwide[1-3]. Although most *H. pylori*-infected children do not have obvious clinical symptoms, studies have shown that children with gastrointestinal symptoms have a higher rate of *H. pylori* infection, and the infection rates are affected by socioeconomic status, living habit, sanitary conditions, geographic region, etc.[4,5]. Despite the overall infection rate has slowly declined in China, the infection rate in rural areas is still much higher over that of city residents [6,7].

A recent meta-analysis in China in 2022 has indicated that *H. pylori* prevalence in children and adolescents is 28%[7]. Infection by *H. pylori* is closely associated with gastric mucosal inflammation and extra-gastrointestinal diseases[8-10]. A small portion of infected patients will follow Correa's cascade

and develop severe gastric mucosal lesions, such as atrophic gastritis, intestinal metaplasia (IM), and gastric cancer[11]. *H. pylori* CagA has been shown to be associated with gastric mucosal precancerous lesions in several epidemiological studies[5,12].

One 2006 review summarized the prevalence of gastric mucosal precancerous lesions in children and adolescents, ranging from 0% to 72% in *H. pylori*-infected patients[13]. Prevalence of gastric atrophy in different populations may also vary depending on different geographic/genetic origins or environmental factors in the pediatric population. For example, one Tunisian study in 2009 found that atrophic gastritis accounted for 9.3% (32/354) of enrolled children; of the 32 children with atrophic gastritis, 30 were infected with *H. pylori*[14]. In 2014, a Mexican study of 82 children with chronic gastritis found that 8.5% (7/82) children had antral atrophy and 6.1% (5/82) had IM; among the 7 children with atrophy, 6 had *H. pylori* infection[15]. Other studies carried out in different countries reported gastric atrophy was present in 4.4% to 10.7% of *H. pylori*-positive children[16,17]. However, large-scale investigation is lacking in this area.

H. pylori has the characteristics of family cluster infection and is transmissible among family members, including spouses and siblings[8,9,18]. The infected parents, especially mothers, play a major role in its transmission[19-21]. Most *H. pylori* infection is acquired during childhood and adolescents, and the infection will persist for decades unless proper treatment is offered. Because *H. pylori* infection usually does not cause or only causes mild gastric mucosal lesions in children and adolescents[22-24], the consequences were thought not to be as important as they were in adulthood. Hence, very few studies have focused on the relationships between *H. pylori* infection and gastric mucosa precancerous lesions in children and adolescents. Recent reports have begun to show that gastric mucosal atrophy and IM are also found in children and even in very young children, as mentioned above[13-15].

In this work, we retrospectively investigated a cohort of *H. pylori*-infected symptomatic pediatric inpatients on gastric mucosal inflammation status, incidence and pattern of gastric mucosal precancerous lesions in a major hospital in central China, which is an area with a high prevalence of *H. pylori* and gastric cancer (*H. pylori* infection rate is 49.6%[6], and gastric cancer incidence is 42.52/100000[25]). Studies in this area will be helpful to understand the pattern and prevalence of gastric mucosal precancerous lesions in pediatric patients and provide evidence for future *H. pylori* eradication recommendation and related disease prevention.

MATERIALS AND METHODS

Study population and patient enrollment

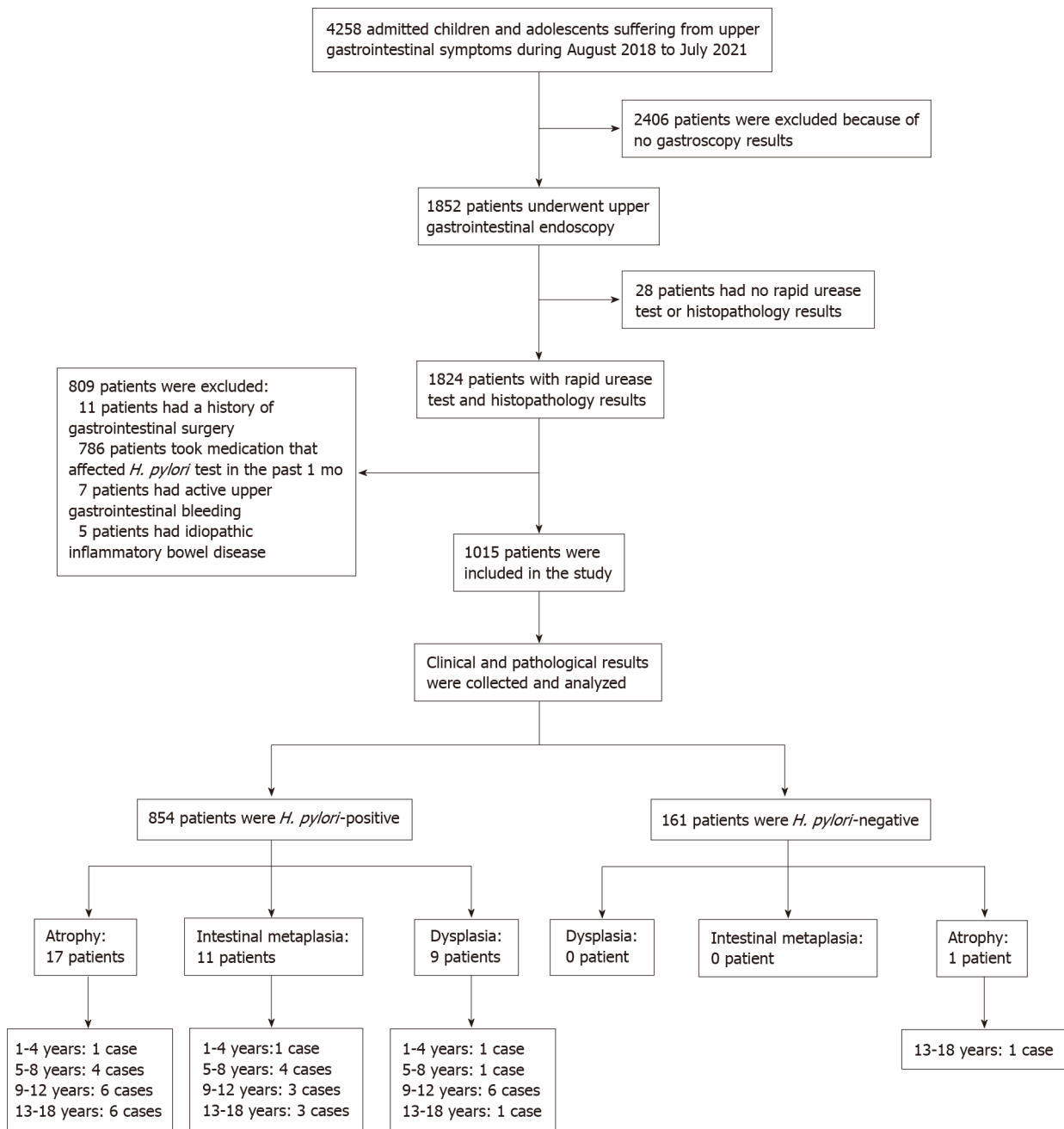
From August 1, 2018 to July 31, 2021, 4258 pediatric patients with an age less than 18-years-old who had upper gastrointestinal symptoms were admitted to the Department of Pediatrics, People's Hospital of Zhengzhou University; among them, 1852 underwent upper gastrointestinal endoscopy examination due to disease complaints, such as abdominal pain, abdominal distension, nausea, vomiting, hiccups, heartburn, *etc.* Patients who had taken biopsy specimens from the gastric mucosa for histopathological examination and rapid urease test were enrolled into the study. Exclusion criteria were as follows: (1) Use of antibiotics, bismuth salts, proton pump inhibitors, H2-receptor blockers, immunosuppressants and steroids over the past 1 mo; (2) History of gastrointestinal surgery; (3) Active upper gastrointestinal bleeding; and (4) Idiopathic inflammatory bowel disease.

The study finally enrolled 1015 eligible children and adolescents. Patient information was collected only for the purpose of disease analysis and were kept confidential. As this is a retrospective study, no informed consent was required. The research protocol was approved by the Ethics Committee of People's Hospital of Zhengzhou University (2019-KY-No. 10). The flow chart of study design and patients' enrollment is shown in Figure 1. Patients were classified into four groups according to age: (1) 1-4 years; (2) 5-8 years; (3) 9-12 years; and (4) 13-18 years.

Endoscopic and histological evaluation of patients

At least two biopsy specimens were collected from the antrum or angulus during endoscopic examination. One biopsy sample was used for immediate rapid urease test. The other was oriented, fixed in formalin and embedded in paraffin blocks. After samples were sectioned, hematoxylin and eosin staining was applied for histological analysis. *H. pylori* infection was detected by immunohistochemical staining. Due to technique limitations, all patients were not given ¹³C-urea breath test, serological *H. pylori* antibody test or stool antigen test to determine *H. pylori* infection status at the time of their tests. Therefore, a patient was considered *H. pylori*-infected if either histological staining or rapid urease test was positive or if both were positive. Conversely, a patient was considered to be *H. pylori*-uninfected if either histological staining or rapid urease test was negative or if both were negative.

Histological variables (the activity of inflammation, lymphocyte and neutrophil granulocyte infiltration, glandular atrophy, IM and hyperplasia) were analyzed according to visual analog scale of the updated Sydney system[26]. Gastric mucosa changes were classified into absent, mild, moderate and severe levels according to the histological situation of each sample. Severity of lesions was determined by the most severe lesion in each patient. Atrophy of gastric mucosa was indicated by the destruction



DOI: 10.3748/wjg.v28.i28.3682 Copyright ©The Author(s) 2022.

Figure 1 Flow chart of patient enrollment on gastric mucosal precancerous lesions in children and adolescents in central China. There were 4258 patients with upper gastrointestinal symptoms under 18 year of age, 2406 patients were excluded for no gastroscopy examination, and the remaining 1852 children had underwent upper gastrointestinal endoscopy. Among these patients, 809 were excluded due to either surgery, medication, bleeding or idiopathic inflammatory bowel disease, and 28 patients were excluded due to no rapid urease test or histopathology test; the final enrolled patient number was 1015. In 854 *Helicobacter pylori* (*H. pylori*)-positive patients, 17 patients had atrophy, 11 patients had intestinal metaplasia and 9 patients had dysplasia, and only 1 of the 161 *H. pylori*-uninfected patients had atrophic gastritis. *H. pylori*: *Helicobacter pylori*.

and reduction in gastric glands of the stomach. IM is a condition in which cells that create the lining of the stomach are changed or replaced by intestinal cells. In many cases, when gastric atrophy and IM coexist, they were allocated into either the atrophy or IM category based on the major pathological presentations of the specific patients. Dysplasia refers to a proliferative lesion, abnormal hyperplasia of the gastric gland basement membrane epithelium and abnormal changes in morphology and structure. These specimens were evaluated by two pathologists in a blinded fashion.

Statistical analyses

Data were analyzed using SPSS for Windows version 25 (IBM Corp., Armonk, NY, United States). Continuous variables were described as mean $\pm$ SD or median (interquartile range), while categorical variables were described as percentages or frequencies. The χ^2 test or Fisher's exact test were used to

compare pathological changes of gastric mucosa, including activity of inflammation, presence of precancerous lesions and endoscopic pattern of gastric mucosa between patients with *H. pylori* infection and those without *H. pylori* infection. Grade data were analyzed using Wilcoxon signed-rank test, including degrees of inflammatory cell infiltration. A *P* value less than 0.05 (derived from two-tailed tests) was considered statistically significant.

RESULTS

Patients' demographic characteristics and clinical data

A total of 1852 selected patients were further examined from a pool of 4258 pediatric ward patients (Figure 1). Then, 809 patients were excluded due to surgery, medication, idiopathic inflammatory bowel disease or bleeding, and 28 more patients were excluded because of no rapid urease test or histopathological test. The remaining 1015 eligible patients were enrolled and analyzed. Patient demographic data were summarized in Table 1. Among the 1015 enrolled patients, 604 were males and 411 were females, with median age of 11-years-old, and 854 patients were infected by *H. pylori*, while 161 patients were not infected. The mean age of *H. pylori*-infected patients was significantly older than those of non-infected subjects (11 years *vs* 9 years, *P* < 0.05). There were no significant differences in sex distribution between the *H. pylori*-infected and non-infected groups.

The clinical characteristics of patients are also presented in Table 1. For endoscopic manifestations, superficial gastritis was observed in 255 (29.86%) cases among the *H. pylori*-positive patients and 76 (47.20%) cases among the *H. pylori*-negative patients (*P* < 0.05). There was no significant difference in the proportion of superficial gastritis with erosion, superficial gastritis with bile reflux and esophagitis regardless of the status of *H. pylori* infection (*P* > 0.05). Antral nodularity was observed in 131 (15.34%) *H. pylori*-positive patients and 4 (2.48%) *H. pylori*-negative patients (*P* < 0.05). In both *H. pylori*-infected and non-infected patients, most patients were clinically diagnosed with non-atrophic gastritis, and only a small percentage of patients developed atrophic gastritis or peptic ulcers.

H. pylori infection status in different age groups

In the 1-4 years, 5-8 years, 9-12 years and 13-18 years age groups (Table 2), the *H. pylori* infection rates were 40.74%, 78.39%, 88.05% and 89.60%, respectively. The trend of infection rate increasing as age increased was noted. Patient infection rates of the 5-8 years, 9-12 years and 13-18 years age groups were significantly higher than that of the 1-4 years age group. Infection rates of the 9-12 years and 13-18 years age groups were also significantly higher than that of the 5-8 years age group, but the infection rates had no significant difference between the 9-12 and 13-18 years age groups.

Gastric mucosal precancerous lesions in different age groups

Patient gastric mucosal precancerous lesions are shown in Table 3. Among the 854 *H. pylori*-infected patients, 4.33% (37/854) had gastric mucosa precancerous lesions; among which, 17 patients had atrophy, 11 patients had IM, and 9 patients had dysplasia. Only 1 of the 161 *H. pylori*-uninfected patients (0.62%) had atrophic gastritis. The incidence of precancerous lesions of gastric mucosa in *H. pylori*-infected patients was significantly more than those uninfected patients ($\chi^2 = 5.178$, *P* = 0.023). Among the *H. pylori*-positive patients, there were gastric mucosal precancerous lesions in each age group, whereas among the *H. pylori*-negative patients, only 1 patient with atrophic gastritis was found in the 13-18 years age group. Representative pictures of normal, gastritis, and gastric mucosal precancerous lesions are shown in Figure 2.

Active inflammation in H. pylori-infected and -uninfected patients

As described in Table 4, active inflammation was observed in 16.04% (137/854) of the *H. pylori*-infected patients and only 3.73% (6/161) of the -uninfected patients. A significant difference was noticed between these two groups ($\chi^2 = 16.975$, *P* < 0.001). But in the 1-4 years age group, there was no significant difference in inflammatory activity between the *H. pylori*-infected and -uninfected patients (13.64% *vs* 6.25%, $\chi^2 = 0.196$, *P* = 0.658). Whereas in the 5-8 years, 9-12 years and 13-18 years age groups, the proportion of active inflammation in the *H. pylori*-positive patients was significantly higher than that in the *H. pylori*-negative patients ($\chi^2 = 4.901$, *P* = 0.027; $\chi^2 = 3.987$, *P* = 0.046; $\chi^2 = 6.012$, *P* = 0.014).

Characteristics of inflammatory cell infiltration in H. pylori-infected and -uninfected groups

The degree of neutrophil granulocyte infiltration with different *H. pylori* infection status is shown in Table 5. For the 854 infected patients, the proportions of absent, mild and moderate neutrophil granulocyte infiltration were 83.96%, 13.58% and 2.46%, respectively. While for the -uninfected patients, they were 96.27%, 3.73% and 0%, respectively. Compared with *H. pylori*-infected patients, the prevalence of neutrophil granulocyte infiltration in gastric mucosa was significantly higher than that in uninfected patients (*Z* = 4.319, *P* < 0.001). This difference between *H. pylori*-positive and -negative patients was also indicated in different age groups, with the exception of the 1-4 years age group.

Table 1 Demographic and clinical data of patients

Variables	Total	<i>H. pylori</i> +	<i>H. pylori</i> -	<i>P</i> value
Patients, <i>n</i>	1015	854	161	
Age in year, median (IQR)	11 (9-13)	11 (9-13)	9 (6-12)	< 0.001 ^a
Sex, <i>n</i> (%)				
Female	411 (40.49)	346 (40.52)	65 (40.37)	
Male	604 (59.51)	508 (59.48)	96 (59.63)	0.973
Endoscopic pattern, <i>n</i> (%)				
Esophagitis	28 (2.76)	23 (2.69)	5 (3.11)	0.975
Superficial gastritis	331 (32.61)	255 (29.86)	76 (47.20)	< 0.001 ^b
Superficial gastritis with erosion	236 (23.25)	200 (23.42)	36 (22.36)	0.77
Superficial gastritis with bile reflux	295 (29.06)	251 (29.39)	44 (27.33)	0.597
Antral nodularity	135 (13.30)	131 (15.34)	4 (2.48)	< 0.001 ^b
Peptic ulcer	90 (8.87)	80 (9.37)	10 (6.21)	0.196
Atrophic gastritis	18 (1.77)	17 (1.99)	1 (0.62)	0.378
Clinical diagnosis, <i>n</i> (%)				
Esophagitis	28 (2.76)	23 (2.69)	5 (3.11)	0.975
Non atrophic gastritis	997 (98.23)	837 (98.01)	160 (99.38)	0.378
Atrophic gastritis	18 (1.77)	17 (1.99)	1 (0.62)	0.378
Gastric ulcer	18 (1.77)	16 (1.87)	2 (1.24)	0.817
Duodenal ulcer	72 (7.09)	64 (7.49)	8 (4.97)	0.252

^a*P* < 0.05: Median age was compared between *Helicobacter pylori* (*H. pylori*)-positive and -negative groups.

^b*P* < 0.05: When compared between *H. pylori*-positive and -negative within each disease group.

IQR: Interquartile range; *H. pylori*: *Helicobacter pylori*.

Table 2 *Helicobacter pylori* infection status in different age groups

Age group	Sex, <i>n</i> (male/female)	<i>H. pylori</i> +, <i>n</i> (%)	<i>H. pylori</i> -, <i>n</i> (%)
1-4	54 (29/25)	22 (40.74)	32 (59.26)
5-8	199 (111/88)	156 (78.39) ^a	43 (21.61)
9-12	435 (286/149)	383 (88.05) ^{a,b}	52 (11.95)
13-18	327 (178/149)	293 (89.60) ^{a,b}	34 (10.40)
Total	1015 (604/411)	854 (84.14)	161 (15.86)

^a*P* < 0.05: When *Helicobacter pylori* (*H. pylori*) infection rates were compared with the 1-4 years age group.

^b*P* < 0.05: When *H. pylori* infection rates were compared with the 5-8 years age group.

H. pylori: *Helicobacter pylori*.

As for lymphocyte infiltration, patients with *H. pylori* infection had more severe lymphocyte infiltration than uninfected patients ($Z = 3.997$, $P < 0.001$). In the *H. pylori*-positive group, 40.98%, 50.59% and 8.43% of mild, moderate and marked lymphocyte infiltration, respectively, were found, while in the *H. pylori*-negative group, the rates were 56.52%, 40.99% and 2.48%, respectively. In *H. pylori*-infected patients, the 9-12 years and 13-18 years age groups also showed more severe lymphocyte infiltration compared to the uninfected patients ($Z = 2.539$, $P = 0.011$; $Z = 2.164$, $P = 0.030$), but this difference was not significant between the 1-4 years and 5-8 years age groups ($Z = 0.570$, $P = 0.569$; $Z = 1.737$, $P = 0.082$) (Table 6). Representative pictures of gastric mucosal inflammatory cell infiltration are shown in Figure 2.

Table 3 Precancerous lesions in the gastric mucosa in children and adolescents

Age group	<i>H. pylori</i> +				Subtotal	<i>H. pylori</i> -				Subtotal
	<i>n</i>	Atrophy	IM	Dysplasia		<i>n</i>	Atrophy	IM	Dysplasia	
1-4	22	1	1	1	3	32	0	0	0	0
5-8	156	4	4	1	9	43	0	0	0	0
9-12	383	6	3	6	15	52	0	0	0	0
13-18	293	6	3	1	10	34	1	0	0	1
Total	854	37 (4.33%) ^a				161	1 (0.62%)			

^a*P* < 0.05: The incidence of gastric mucosal precancerous lesions was compared between *Helicobacter pylori* (*H. pylori*)-positive and *H. pylori*-negative patients.

IM: Intestinal metaplasia; *H. pylori*: *Helicobacter pylori*.

Table 4 Comparison of active inflammation between *Helicobacter pylori*-positive and -negative patients

Age group	<i>H. pylori</i> +			<i>H. pylori</i> -		
	<i>n</i>	Active inflammation	Non-active inflammation	<i>n</i>	Active inflammation	Non-active inflammation
1-4	22	3 (13.64)	19 (86.36)	32	2 (6.25)	30 (93.75)
5-8	156	23 (14.74) ^a	133 (85.26)	43	1 (2.33)	42 (97.67)
9-12	383	52 (13.58) ^b	331 (86.42)	52	2 (3.85)	50 (96.15)
13-18	293	59 (20.14) ^c	234 (79.86)	34	1 (2.94)	33 (97.06)
Total	854	137 (16.04) ^d	717 (83.96)	161	6 (3.73)	155 (96.27)

^a*P* < 0.05: Active inflammation in *Helicobacter pylori* (*H. pylori*)-positive patients were compared with -negative patients in the 5-8 years age group.

^b*P* < 0.05: Active inflammation in *H. pylori*-positive patients was compared with -negative patients in the 9-12 years age group.

^c*P* < 0.05: Active inflammation in *H. pylori*-positive patients was compared with -negative patients in the 13-18 years age group.

^d*P* < 0.05: Active inflammation was compared between the *H. pylori*-positive and -negative groups.

Data are *n* (%), unless otherwise indicated. *H. pylori*: *Helicobacter pylori*.

Table 5 Degree of neutrophil granulocyte infiltration in *Helicobacter pylori*-positive and -negative patients

Age group	<i>H. pylori</i> +				<i>H. pylori</i> -				<i>Z</i>	<i>P</i> value
	<i>n</i>	Absent	Mild	Moderate	<i>n</i>	Absent	Mild	Moderate		
1-4	22	19 (86.36)	3 (13.64)	0 (0)	32	30 (93.75)	2 (6.25)	0 (0)	0.912	0.362
5-8	156	133 (85.26)	21 (13.46)	2 (1.28)	43	42 (97.67)	1 (2.33)	0 (0)	2.212	0.027 ^a
9-12	383	331 (86.42)	44 (11.49)	8 (2.09)	52	50 (96.15)	2 (3.85)	0 (0)	2.009	0.045 ^b
13-18	293	234 (79.86)	48 (16.38)	11 (3.76)	34	33 (97.06)	1 (2.94)	0 (0)	2.456	0.014 ^c
Total	854	717 (83.96)	116 (13.58)	21 (2.46)	161	155 (96.27)	6 (3.73)	0 (0)	4.319	< 0.001 ^d

^a*P* < 0.05: Degree of neutrophil granulocyte infiltration in *Helicobacter pylori* (*H. pylori*)-positive patients were compared with -negative patients in the 5-8 years age group.

^b*P* < 0.05: Degree of neutrophil granulocyte infiltration in *H. pylori*-positive patients was compared with -negative patients in the 9-12 years age group.

^c*P* < 0.05: Degree of neutrophil granulocyte infiltration in *H. pylori*-positive patients was compared with -negative patients in the 13-18 years age group.

^d*P* < 0.05: Degree of neutrophil granulocyte infiltration was compared between *H. pylori*-positive and -negative groups.

Data are *n* (%), unless otherwise indicated. *H. pylori*: *Helicobacter pylori*.

DISCUSSION

In the current study, we investigated gastric mucosal inflammation and precancerous lesions in pediatric patients who were hospitalized for gastrointestinal symptoms. Among the 1015 children in our study who underwent upper gastrointestinal endoscopy, gastric mucosa precancerous lesions occurred

Table 6 Degree of lymphocyte infiltration in *Helicobacter pylori*-positive and -negative patients

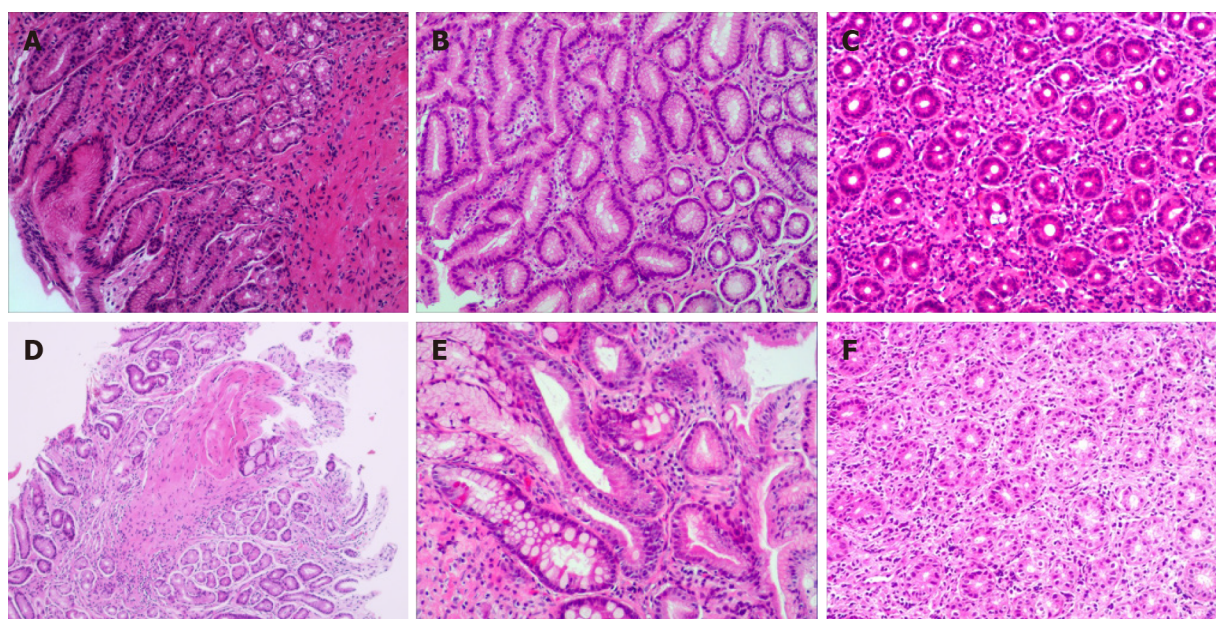
Age group	<i>H. pylori</i> ⁺				<i>H. pylori</i> ⁻				Z	P value
	n	Mild	Moderate	Marked	n	Mild	Moderate	Marked		
1-4	22	10 (45.45)	11 (50)	1 (4.55)	32	17 (53.12)	14 (43.75)	1 (3.13)	0.57	0.569
5-8	156	67 (42.95)	75 (48.08)	14 (8.97)	43	24 (55.81)	18 (41.86)	1 (2.33)	1.737	0.082
9-12	383	161 (42.04)	195 (50.91)	27 (7.05)	52	31 (59.62)	20 (38.46)	1 (1.92)	2.539	0.01 ^a
13-18	293	112 (38.23)	151 (51.54)	30 (10.24)	34	19 (55.88)	14 (41.18)	1 (2.94)	2.164	0.03 ^b
Total	854	350 (40.98)	432 (50.59)	72 (8.43)	161	91 (56.52)	66 (40.99)	4 (2.48)	3.997	< 0.00 ^c

^a*P* < 0.05: Degree of lymphocyte infiltration in *Helicobacter pylori* (*H. pylori*)-positive patients were compared with -negative patients in 9-12 years age group.

^b*P* < 0.05: Degree of lymphocyte infiltration in *H. pylori*-positive patients were compared with -negative patients in 13-18 years age group.

^c*P* < 0.05: Degree of lymphocyte infiltration was compared between *H. pylori*-positive and -negative groups.

Data are n (%), unless otherwise indicated. *H. pylori*: *Helicobacter pylori*.



DOI: 10.3748/wjg.v28.i28.3682 Copyright ©The Author(s) 2022.

Figure 2 Representative pictures of normal and pathological gastric mucosa manifestations in children and adolescents. A: Normal gastric mucosa; B: Chronic inflammation of the gastric mucosa; C: Active inflammation of the gastric mucosa; D: Gastric mucosal atrophy; E: Intestinal metaplasia; F: Mild dysplasia. Hematoxylin and eosin, × 400.

in 4.33% of *H. pylori*-infected children, in which the proportions of atrophy, IM and dysplasia were 1.99%, 1.29%, 1.05%, respectively, significantly higher than findings from *H. pylori*-negative patients.

Under endoscopy evaluation, *H. pylori*-positive children presented more nodular gastritis, which is an important feature of *H. pylori* infection in children. But, the proportions of esophagitis, chronic superficial gastritis with erosions, chronic superficial gastritis with bile reflux and esophagitis were not significantly different between the infected and non-infected groups. The results also showed that children with *H. pylori* infection had a significantly higher incidence of gastric mucosal inflammation, and the degrees of neutrophil and lymphocyte infiltration were also much more serious than in *H. pylori*-negative children. These results are in line with previous studies that showed various degrees of inflammation in *H. pylori*-infected pediatric patients. For example, in 2017, Broide *et al*[27] showed that monocyte and neutrophil infiltration was more severe in the infected children group with chronic gastritis in Israel. One retrospective study of 196 children in Japan in 2006 also reached a similar conclusion[17].

The above results indicate that *H. pylori* infection is closely related to gastric mucosal inflammation, which might be the basis for development of gastric precancerous lesions, as both basic experiments and clinical investigations have confirmed that certain bacterial components, such as CagA and VacA, have detrimental effects on gastric epithelial cells. In addition, CagA is a bacterial oncoprotein, which can cause epithelial cell oncogenic transformation *in vivo*[28-30]. Therefore, future experiments for more

detailed analysis of the *H. pylori* component on the pathogenesis of gastric precancerous lesions in children will be very helpful to understand the carcinogenesis and provide more rational for precise intervention and prevention.

The significance of this study is that it provides evidence to demonstrate that *H. pylori* infection is associated with the occurrence of precancerous lesions in pediatric patients, and these lesions increase with increase in age. Furthermore, the pediatric population might present in a similar way to adults with *H. pylori* infection, suggesting a healthcare threat to the pediatric patients. As eradication of *H. pylori* has been shown to prevent the development of atrophic gastritis, IM and gastric malignancy in adults[31,32], it is expected that proper intervention in pediatric patients could prevent the development of future diseases. Future investigation on the rationale and health economic evaluation would be required to provide more supporting evidence.

These results are also in line with previous reports. For example, in 2006, a study of 131 *H. pylori*-infected children in Japan showed that the proportion of gastric antrum atrophy was 10.7%[17]. In a 2020 study in Romania, the *H. pylori* infection rate was 33.06% (82/248); among 82 infected children, 9 (11%) had atrophic gastritis and 2 (2.4%) had IM[33]. A survey of 1634 children in China in 2014 found that atrophic gastritis accounted for 4.4% (23/524 cases) of the *H. pylori*-infected children[16]. However, one Austrian study in 2011 found gastric atrophy was rare (1/84) in children infected with *H. pylori*[34]. In addition, no gastric atrophy was found in 66 French children infected with *H. pylori* in 2009[35], and no precancerous lesions were found in 132 gastric biopsies from 22 symptomatic *H. pylori*-infected children in a 2009 study in Brazil[36].

As *H. pylori*-induced disease presentations are mostly present in adulthood, the presence of precancerous lesions in children unveiled a critical issue that was largely neglected previously[13,15,37]. Although there are still controversies on the significance and consequence of *H. pylori*-induced serious gastric mucosal lesions in children[13], current consensus reports from the Asia-Pacific region[38], China[8,39] and Japan[18] have indicated that *H. pylori* should be eradicated when such conditions are present, and their family members should also receive screening and treatment if confirmed positive. It is hypothesized that gastric mucosal atrophy and IM in children and adolescents might be present in a similar way to adult *H. pylori* infection and is probably more common in areas with high *H. pylori* infection rates than previously thought.

One of the major shortfalls of this retrospective study is that the rapid urease test was the primary test used to detect *H. pylori* infection because ¹³C-urea breath test, serological *H. pylori* antibody tests and stool antigen tests were not available for more accurate diagnosis. This could result in the underestimation of *H. pylori* infection rates or have false negative results in the uninfected children group. Two perplexing results might be attributed to these drawbacks as there are 8 duodenal ulcer patients (Table 1) and few patients had active gastric inflammation (Tables 4 and 5) in the *H. pylori*-negative group. Due to the strong relationship of *H. pylori* in causing these diseases, it is unlikely these patients were not infected by *H. pylori*. Furthermore, it is likely because of the limitation of the rapid urease test, which is unable to detect patchy distribution of *H. pylori* in the stomach. Therefore, future studies will be required to confirm these discrepancies. Even with these drawbacks, the overall conclusions and significance of the investigation were not affected.

Although the current work provides novel points on *H. pylori*-induced gastric mucosal precancerous lesions in children, due to its retrospective nature, the investigation has limitations. First, this study only discussed the relationship between *H. pylori* infection and gastric mucosa precancerous lesions and was unable to analyze the effects of different genotypes of infected *H. pylori* strains. Therefore, more detailed information on *H. pylori* strains are not available. Nonetheless, our previous work demonstrated that type I *H. pylori* (CagA- and VacA-positive) is the primary type of *H. pylori* infection in this region[40]. It is expected that the pediatric population is similar to the adult population. Second, not all cases had biopsy specimens from both the gastric antrum and body. Some of the precancerous lesions and *H. pylori* infection may have been missed due to histopathological presentation of the stomach, and patchy *H. pylori* infection status in other places of the stomach were unable to be examined. In the future, multiple biopsies might be helpful to overcome these drawbacks. Third, this was a single-center, retrospective analysis, and all the children were hospitalized due to gastrointestinal symptoms, which may be the reason why the infection rate was much higher than among the general population. In the future, large-scale investigations in the general public and multi-center, prospective and randomized control analyses are needed to comprehensively assess the risk of *H. pylori* infection and precancerous lesions in children and adolescents in order to understand the overall precancerous lesions of *H. pylori*-infected pediatric patients.

CONCLUSION

Our results show that *H. pylori*-infected children have more active inflammation and inflammatory cell infiltration in the gastric mucosa, and infection rate increases with patient age. The incidence of precancerous lesions in *H. pylori*-infected patients is also significantly higher compared to that in -uninfected patients. Although the percentage is only 4.33%, it provides an alarming alert and call for further invest-

igation and intervention for this population group.

ARTICLE HIGHLIGHTS

Research background

Chronic *Helicobacter pylori* (*H. pylori*) infection causes gastric mucosal precancerous lesions and gastric cancer in adult patients. It remains to be determined, however, whether gastric mucosal precancerous lesions may also occur in children and adolescents, as this remains an important issue for clinical intervention.

Research motivation

Investigating the relationship between *H. pylori* infection and gastric mucosal precancerous lesions in pediatric patients will provide important evidence on whether intervention should be offered to prevent related disease development in this population group.

Research objectives

H. pylori infection status, gastric mucosal inflammation and gastric precancerous lesions in hospitalized pediatric patients were investigated in central China.

Research methods

We retrospectively enrolled 1015 symptomatic pediatric patients to analyze their clinical and pathological data. The endoscopic and histological findings, occurrence of gastric mucosal precancerous lesions, inflammatory activity and degree of inflammatory cell infiltration were analyzed between *H. pylori*-positive and -negative patient groups.

Research results

The overall *H. pylori* infection rate was 84.14% for the 1015 enrolled pediatric patients, and infection rate increased with age. The incidence of gastric mucosal precancerous lesions in *H. pylori*-infected children was 4.33%, which was significantly higher than that in *H. pylori*-negative children. Infected patients showed more active inflammation as well as more severe inflammatory cell infiltration compared to the non-infected patients. Additionally, endoscopy revealed that the most common presentation was antral nodularity in *H. pylori*-positive patients, whereas superficial gastritis was a marked feature for *H. pylori*-negative patients.

Research conclusions

In children and adolescents, gastric mucosal precancerous lesions occurred in 4.33% of *H. pylori*-infected patients in central China. The data revealed an obvious critical issue that requires future investigation and intervention for this population group.

Research perspectives

The results provide insights on *H. pylori* infection status and its relationship with gastric mucosal precancerous in symptomatic pediatric patients in central China. Further investigation and intervention for related disease prevention are required in this population group.

ACKNOWLEDGEMENTS

The authors are grateful to the staff of the Department of Gastroenterology and Hepatology, People's Hospital of Zhengzhou University for their valuable assistance in this work.

FOOTNOTES

Author contributions: Yu M, Cheng YB, Jia BL, Kong LF, Chen CL and Ding SZ designed the research; Yu M, Song XX, Ma J, Shao QQ, Yu XC, Khan MN, Qi YB, Hu RB, Wei PR and Xiao W collected the clinical data and performed the experiments; Yu M analyzed the data; Yu M and Ding SZ wrote the paper; Ding SZ revised the article; all authors approved the final version of the manuscript.

Supported by the National Natural Science Foundation of China, No. U1604174; Henan Provincial Government-Health and Family Planning Commission, No. 20170123 and No. SBGJ202002004; and Henan Provincial Government-Health and Family Planning Commission Research Innovative Talents Project, No. 51282.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of People's Hospital of Zhengzhou University (2019-KY-No. 10).

Informed consent statement: The study was performed retrospectively. Patients were not required to give informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors declare that there are no conflicts of interests related to this work.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Miao Yu 0000-0002-3587-2760; Jing Ma 0000-0003-1172-527X; Xiao-Xia Song 0000-0003-4633-9862; Qiao-Qiao Shao 0000-0002-4900-9394; Xue-Chun Yu 0000-0003-4425-6019; Muhammad Noman Khan 0000-0003-4814-7768; Ya-Bin Qi 0000-0002-7736-4043; Ruo-Bing Hu 0000-0003-4735-1310; Pei-Ru Wei 0000-0001-6306-590X; Wei Xiao 0000-0002-6814-9261; Bai-Ling Jia 0000-0002-2920-2322; Yan-Bo Cheng 0000-0003-3203-4603; Ling-Fei Kong 0000-0003-1710-8344; Chuan-Liang Chen 0000-0002-5566-7297; Song-Ze Ding 0000-0002-4589-6942.

S-Editor: Yan JP

L-Editor: A

P-Editor: Yan JP

REFERENCES

- 1 **Yuan C**, Adeloje D, Luk TT, Huang L, He Y, Xu Y, Ye X, Yi Q, Song P, Rudan I; Global Health Epidemiology Research Group. The global prevalence of and factors associated with *Helicobacter pylori* infection in children: a systematic review and meta-analysis. *Lancet Child Adolesc Health* 2022; **6**: 185-194 [PMID: 35085494 DOI: 10.1016/S2352-4642(21)00400-4]
- 2 **Park JS**, Jun JS, Seo JH, Youn HS, Rhee KH. Changing prevalence of *Helicobacter pylori* infection in children and adolescents. *Clin Exp Pediatr* 2021; **64**: 21-25 [PMID: 32668822 DOI: 10.3345/cep.2019.01543]
- 3 **Li XC**, Wang HD, Zhang N, Wang YP, Zhou YN. Systematic review and meta-analysis of epidemiological investigation of *Helicobacter pylori* infection in children and adolescents in China. *Linchuang Erke Zazhi* 2017; **35**: 782-787 [DOI: 10.3969/j.issn.1000-3606.2017.10.016]
- 4 **Seo JH**, Bortolin K, Jones NL. Review: *Helicobacter pylori* infection in children. *Helicobacter* 2020; **25** Suppl 1: e12742 [PMID: 32918353 DOI: 10.1111/hel.12742]
- 5 **Subsomwong P**, Miftahussurur M, Uchida T, Vilaichone RK, Ratanachu-Ek T, Mahachai V, Yamaoka Y. Prevalence, risk factors, and virulence genes of *Helicobacter pylori* among dyspeptic patients in two different gastric cancer risk regions of Thailand. *PLoS One* 2017; **12**: e0187113 [PMID: 29084246 DOI: 10.1371/journal.pone.0187113]
- 6 **Li M**, Sun Y, Yang J, de Martel C, Charvat H, Clifford GM, Vaccarella S, Wang L. Time trends and other sources of variation in *Helicobacter pylori* infection in mainland China: A systematic review and meta-analysis. *Helicobacter* 2020; **25**: e12729 [PMID: 32686261 DOI: 10.1111/hel.12729]
- 7 **Ren S**, Cai P, Liu Y, Wang T, Zhang Y, Li Q, Gu Y, Wei L, Yan C, Jin G. Prevalence of *Helicobacter pylori* infection in China: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2022; **37**: 464-470 [PMID: 34862656 DOI: 10.1111/jgh.15751]
- 8 **Liu WZ**, Xie Y, Lu H, Cheng H, Zeng ZR, Zhou LY, Chen Y, Wang JB, Du YQ, Lu NH; Chinese Society of Gastroenterology, Chinese Study Group on *Helicobacter pylori* and Peptic Ulcer. Fifth Chinese National Consensus Report on the management of *Helicobacter pylori* infection. *Helicobacter* 2018; **23**: e12475 [PMID: 29512258 DOI: 10.1111/hel.12475]
- 9 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European *Helicobacter* and Microbiota Study Group and Consensus panel. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]
- 10 **Jones NL**, Koletzko S, Goodman K, Bontems P, Cadranet S, Casswall T, Czinn S, Gold BD, Guarner J, Elitsur Y, Homan M, Kalach N, Kori M, Madrazo A, Megraud F, Papadopoulou A, Rowland M; ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN Guidelines for the Management of *Helicobacter pylori* in Children and Adolescents (Update 2016). *J Pediatr Gastroenterol Nutr* 2017; **64**: 991-1003 [PMID: 28541262 DOI: 10.1097/MPG.0000000000001594]
- 11 **Correa P**. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554-3560 [PMID: 3288329]
- 12 **Miftahussurur M**, Sharma RP, Shrestha PK, Maharjan RK, Shiota S, Uchida T, Sato H, Yamaoka Y. *Helicobacter pylori* Infection and Gastric Mucosal Atrophy in Two Ethnic Groups in Nepal. *Asian Pac J Cancer Prev* 2015; **16**: 7911-7916

- [PMID: 26625820 DOI: 10.7314/apjcp.2015.16.17.7911]
- 13 **Dimitrov G**, Gottrand F. Does gastric atrophy exist in children? *World J Gastroenterol* 2006; **12**: 6274-6279 [PMID: 17072948 DOI: 10.3748/wjg.v12.i39.6274]
 - 14 **Boukthir S**, Mrad SM, Kalach N, Sammoud A. Gastric atrophy and *Helicobacter pylori* infection in children. *Trop Gastroenterol* 2009; **30**: 107-109 [PMID: 19760998]
 - 15 **Villarreal-Calderon R**, Luévano-González A, Aragón-Flores M, Zhu H, Yuan Y, Xiang Q, Yan B, Stoll KA, Cross JV, Iczkowski KA, Mackinnon AC Jr. Antral atrophy, intestinal metaplasia, and preneoplastic markers in Mexican children with *Helicobacter pylori*-positive and *Helicobacter pylori*-negative gastritis. *Ann Diagn Pathol* 2014; **18**: 129-135 [PMID: 24656654 DOI: 10.1016/j.anndiagpath.2014.02.003]
 - 16 **Yu Y**, Su L, Wang X, Xu C. Association between *Helicobacter pylori* infection and pathological changes in the gastric mucosa in Chinese children. *Intern Med* 2014; **53**: 83-88 [PMID: 24429445 DOI: 10.2169/internalmedicine.53.0918]
 - 17 **Kato S**, Nakajima S, Nishino Y, Ozawa K, Minoura T, Konno M, Maisawa S, Toyoda S, Yoshimura N, Vaid A, Genta RM. Association between gastric atrophy and *Helicobacter pylori* infection in Japanese children: a retrospective multicenter study. *Dig Dis Sci* 2006; **51**: 99-104 [PMID: 16416219 DOI: 10.1007/s10620-006-3091-5]
 - 18 **Sugano K**, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P; faculty members of Kyoto Global Consensus Conference. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 2015; **64**: 1353-1367 [PMID: 26187502 DOI: 10.1136/gutjnl-2015-309252]
 - 19 **Osaki T**, Konno M, Yonezawa H, Hojo F, Zaman C, Takahashi M, Fujiwara S, Kamiya S. Analysis of intra-familial transmission of *Helicobacter pylori* in Japanese families. *J Med Microbiol* 2015; **64**: 67-73 [PMID: 25351712 DOI: 10.1099/jmm.0.080507-0]
 - 20 **Rothbacher D**, Winkler M, Gonser T, Adler G, Brenner H. Role of infected parents in transmission of *Helicobacter pylori* to their children. *Pediatr Infect Dis J* 2002; **21**: 674-679 [PMID: 12237602 DOI: 10.1097/00006454-200207000-00014]
 - 21 **Kienesberger S**, Perez-Perez GI, Olivares AZ, Bardhan P, Sarker SA, Hasan KZ, Sack RB, Blaser MJ. When is *Helicobacter pylori* acquired in populations in developing countries? *Gut Microbes* 2018; **9**: 252-263 [PMID: 29494270 DOI: 10.1080/19490976.2017.1421887]
 - 22 **Jaramillo-Rodríguez Y**, Nares-Cisneros J, Martínez-Ordaz VA, Velasco-Rodríguez VM, Márquez FC, Manríquez-Covarrubias LE. Chronic gastritis associated with *Helicobacter pylori* in Mexican children: histopathological patterns. *Pediatr Dev Pathol* 2011; **14**: 93-98 [PMID: 20658934 DOI: 10.2350/09-12-0754-OA.1]
 - 23 **Okuda M**, Lin Y, Kikuchi S. *Helicobacter pylori* Infection in Children and Adolescents. *Adv Exp Med Biol* 2019; **1149**: 107-120 [PMID: 31037557 DOI: 10.1007/5584_2019_361]
 - 24 **Whitney AE**, Guarner J, Hutwagner L, Gold BD. *Helicobacter pylori* gastritis in children and adults: comparative histopathologic study. *Ann Diagn Pathol* 2000; **4**: 279-285 [PMID: 11073332 DOI: 10.1053/adpa.2000.17871]
 - 25 **Liu S**, Chen Q, Quan P, Zhang M, Zhang S, Guo L, Sun X, Wang C. Cancer incidence and mortality in Henan province, 2012. *Chin J Cancer Res* 2016; **28**: 275-285 [PMID: 27478313 DOI: 10.21147/j.issn.1000-9604.2016.03.02]
 - 26 **Dixon MF**, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; **20**: 1161-1181 [PMID: 8827022 DOI: 10.1097/00000478-199610000-00001]
 - 27 **Broide E**, Richter V, Mendlovic S, Shalem T, Eindor-Abarbanel A, Moss SF, Shirin H. Lymphoid follicles in children with *Helicobacter pylori*-negative gastritis. *Clin Exp Gastroenterol* 2017; **10**: 195-201 [PMID: 28860835 DOI: 10.2147/CEG.S133421]
 - 28 **Hatakeyama M**. *Helicobacter pylori* and gastric carcinogenesis. *J Gastroenterol* 2009; **44**: 239-248 [PMID: 19271114 DOI: 10.1007/s00535-009-0014-1]
 - 29 **Myint T**, Miftahussurur M, Vilaichone RK, Ni N, Aye TT, Subsomwong P, Uchida T, Mahachai V, Yamaoka Y. Characterizing *Helicobacter pylori cagA* in Myanmar. *Gut Liver* 2018; **12**: 51-57 [PMID: 29069889 DOI: 10.5009/gnl17053]
 - 30 **Hatakeyama M**. Linking epithelial polarity and carcinogenesis by multitasking *Helicobacter pylori* virulence factor CagA. *Oncogene* 2008; **27**: 7047-7054 [PMID: 19029944 DOI: 10.1038/onc.2008.353]
 - 31 **Kong YJ**, Yi HG, Dai JC, Wei MX. Histological changes of gastric mucosa after *Helicobacter pylori* eradication: a systematic review and meta-analysis. *World J Gastroenterol* 2014; **20**: 5903-5911 [PMID: 24914352 DOI: 10.3748/wjg.v20.i19.5903]
 - 32 **Ford AC**, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014; **348**: g3174 [PMID: 24846275 DOI: 10.1136/bmj.g3174]
 - 33 **Domşa AT**, Lupuşoru R, Gheban D, Şerban R, Borzan CM. *Helicobacter pylori* Gastritis in Children-The Link between Endoscopy and Histology. *J Clin Med* 2020; **9** [PMID: 32183130 DOI: 10.3390/jcm9030784]
 - 34 **Hoepler W**, Hammer K, Hammer J. Gastric phenotype in children with *Helicobacter pylori* infection undergoing upper endoscopy. *Scand J Gastroenterol* 2011; **46**: 293-298 [PMID: 21073375 DOI: 10.3109/00365521.2010.533383]
 - 35 **Kalach N**, Papadopoulos S, Asmar E, Spyckerelle C, Gosset P, Raymond J, Dehecq A, Decoster A, Creusy C, Dupont C. In French children, primary gastritis is more frequent than *Helicobacter pylori* gastritis. *Dig Dis Sci* 2009; **54**: 1958-1965 [PMID: 19003529 DOI: 10.1007/s10620-008-0553-y]
 - 36 **Langner M**, Machado RS, Patrício FR, Kawakami E. Evaluation of gastric histology in children and adolescents with *Helicobacter pylori* gastritis using the Update Sydney System. *Arq Gastroenterol* 2009; **46**: 328-332 [PMID: 20232015 DOI: 10.1590/s0004-28032009000400015]
 - 37 **Kara N**, Urganci N, Kalyoncu D, Yilmaz B. The association between *Helicobacter pylori* gastritis and lymphoid aggregates, lymphoid follicles and intestinal metaplasia in gastric mucosa of children. *J Paediatr Child Health* 2014; **50**: 605-609 [PMID: 24925694 DOI: 10.1111/jpc.12609]
 - 38 **Mahachai V**, Vilaichone RK, Pittayanon R, Rojborwonwitaya J, Leelakusolvong S, Maneerattanaporn M, Chotivitayatarakorn P, Treeprasertsuk S, Kositchaiwat C, Pisespongsa P, Mairiang P, Rani A, Leow A, Mya SM, Lee YC,

- Vannarath S, Rasachak B, Chakravuth O, Aung MM, Ang TL, Sollano JD, Trong Quach D, Sansak I, Wiwattanachang O, Harnsomburana P, Syam AF, Yamaoka Y, Fock KM, Goh KL, Sugano K, Graham D. *Helicobacter pylori* management in ASEAN: The Bangkok consensus report. *J Gastroenterol Hepatol* 2018; **33**: 37-56 [PMID: [28762251](#) DOI: [10.1111/jgh.13911](#)]
- 39 **Ding SZ**, Du YQ, Lu H, Wang WH, Cheng H, Chen SY, Chen MH, Chen WC, Chen Y, Fang JY, Gao HJ, Guo MZ, Han Y, Hou XH, Hu FL, Jiang B, Jiang HX, Lan CH, Li JN, Li Y, Li YQ, Liu J, Li YM, Lyu B, Lu YY, Miao YL, Nie YZ, Qian JM, Sheng JQ, Tang CW, Wang F, Wang HH, Wang JB, Wang JT, Wang JP, Wang XH, Wu KC, Xia XZ, Xie WF, Xie Y, Xu JM, Yang CQ, Yang GB, Yuan Y, Zeng ZR, Zhang BY, Zhang GY, Zhang GX, Zhang JZ, Zhang ZY, Zheng PY, Zhu Y, Zuo XL, Zhou LY, Lyu NH, Yang YS, Li ZS; National Clinical Research Center for Digestive Diseases (Shanghai), Gastrointestinal Early Cancer Prevention & Treatment Alliance of China (GECA), *Helicobacter pylori* Study Group of Chinese Society of Gastroenterology, and Chinese Alliance for *Helicobacter pylori* Study. Chinese Consensus Report on Family-Based *Helicobacter pylori* Infection Control and Management (2021 Edition). *Gut* 2022; **71**: 238-253 [PMID: [34836916](#) DOI: [10.1136/gutjnl-2021-325630](#)]
- 40 **Yuan L**, Zhao JB, Zhou YL, Qi YB, Guo QY, Zhang HH, Khan MN, Lan L, Jia CH, Zhang YR, Ding SZ. Type I and type II *Helicobacter pylori* infection status and their impact on gastrin and pepsinogen level in a gastric cancer prevalent area. *World J Gastroenterol* 2020; **26**: 3673-3685 [PMID: [32742135](#) DOI: [10.3748/wjg.v26.i25.3673](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

