

World Journal of *Gastroenterology*

World J Gastroenterol 2024 February 28; 30(8): 779-993



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INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJG as 4.3; Quartile category: Q2. The WJG's CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xiang Li*; 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

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF**EDITORIAL BOARD MEMBERS**

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

PUBLICATION DATE

February 28, 2024

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PUBLISHING PARTNER

Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

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>

Xian-Jun Yu (Pancreatic Oncology), Jian-Gao Fan (Chronic Liver Disease), Hou-Bao Liu (Biliary Tract Disease)

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>

PUBLISHING PARTNER'S OFFICIAL WEBSITE

<https://www.shca.org.cn>
<https://www.zs-hospital.sh.cn>



Retrospective Study

Immunoglobulin G-mediated food intolerance and metabolic syndrome influence the occurrence of reflux esophagitis in *Helicobacter pylori*-infected patients

Li-Hui Wang, Bin-Bin Su, Sheng-Shu Wang, Guan-Chao Sun, Kun-Ming Lv, Yi Li, Hui Shi, Qian-Qian Chen

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): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ushiku T, Japan

Received: December 8, 2023

Peer-review started: December 8, 2023

First decision: December 27, 2023

Revised: January 4, 2024

Accepted: January 29, 2024

Article in press: January 29, 2024

Published online: February 28, 2024



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Abstract

BACKGROUND

Reflux esophagitis has an increasing prevalence and complex and diverse symptoms. Identifying its risk factors is crucial to understanding the etiology, prevention, and management of the disease. The occurrence of reflux esophagitis may be associated with food reactions, *Helicobacter pylori* (*H. pylori*) infection, and metabolic syndromes.

AIM

To investigate the risk factors for reflux esophagitis and analyze the effects of immunoglobulin (Ig) G-mediated food intolerance, *H. pylori* infection, and metabolic syndrome on reflux esophagitis.

METHODS

Outpatients attending the Second Medical Center of the PLA General Hospital between 2017 and 2021 were retrospectively enrolled. The patients' basic information, test results, gastroscopy results, *H. pylori* test results, and IgG-mediated food intolerance results were collected. Multivariate logistic regression analysis was used to analyze risk factors for reflux esophagitis. Statistical

mediation analysis was used to evaluate the effects of IgG-mediated food intolerance and metabolic syndrome on *H. pylori* infection affecting reflux esophagitis.

RESULTS

A total of 7954 outpatients were included; the prevalence of reflux esophagitis, IgG-mediated food intolerance, *H. pylori* infection, and metabolic syndrome were 20.84%, 61.77%, 35.91%, and 60.15%, respectively. Multivariate analysis showed that the independent risk factors for reflux esophagitis included IgG-mediated food intolerance (OR = 1.688, 95%CI: 1.497-1.903, $P < 0.00001$) and metabolic syndrome (OR = 1.165, 95%CI: 1.030-1.317, $P = 0.01484$), and the independent protective factor for reflux esophagitis was *H. pylori* infection (OR = 0.400, 95%CI: 0.351-0.456, $P < 0.00001$). IgG-mediated food intolerance had a partially positive mediating effect on *H. pylori* infection as it was associated with reduced occurrence of reflux esophagitis ($P = 0.0200$). Metabolic syndrome had a partially negative mediating effect on *H. pylori* infection and reduced the occurrence of reflux esophagitis ($P = 0.0220$).

CONCLUSION

Patients with IgG-mediated food intolerance and metabolic syndrome were at higher risk of developing reflux esophagitis, while patients with *H. pylori* infection were at lower risk. IgG-mediated food intolerance reduced the risk of reflux esophagitis pathogenesis in patients with *H. pylori* infection; however, metabolic syndrome increased the risk of patients with *H. pylori* infection developing reflux esophagitis.

Key Words: Gastroesophageal reflux; Esophagitis; Food intolerance; Metabolic syndrome; *Helicobacter pylori*; Chemokines

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Core Tip: This retrospective study investigated the effects of IgG-mediated food intolerance, *Helicobacter pylori* (*H. pylori*) infection, and metabolic syndrome on reflux esophagitis. In 7954 outpatients, the prevalence of reflux esophagitis was 20.84%. Patients with IgG-mediated food intolerance and metabolic syndrome are at higher risk of developing reflux esophagitis, while patients with *H. pylori* infection are at lower risk. IgG-mediated food intolerance reduces the risk of reflux esophagitis pathogenesis in patients with *H. pylori* infection; however, metabolic syndrome increases the risk of patients with *H. pylori* infection developing reflux esophagitis.

Citation: Wang LH, Su BB, Wang SS, Sun GC, Lv KM, Li Y, Shi H, Chen QQ. Immunoglobulin G-mediated food intolerance and metabolic syndrome influence the occurrence of reflux esophagitis in *Helicobacter pylori*-infected patients. *World J Gastroenterol* 2024; 30(8): 855-862

URL: <https://www.wjgnet.com/1007-9327/full/v30/i8/855.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v30.i8.855>

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a range of diseases arising from the reflux of gastroduodenal content, and its pathogenesis is related to the immuno-inflammatory cascade[1]. Reflux esophagitis (RE), a phenotype of GERD, is defined as a visible mucosal rupture in the distal esophagus[2]. RE accounts for 30% of GERD cases, with an increasing prevalence and complex and diverse symptoms which greatly affect the quality of life; its long-term treatment requirements consume significant healthcare resources and create a socioeconomic burden[3]. Identifying the risk factors for RE is crucial to understanding the etiology, prevention, and management of the disease.

Food intolerance (FI) refers to the discomfort caused by a food or food component at a dose that is normally tolerated; this is responsible for most adverse food reactions. FI can be asymptomatic and manifest only as a high immunoglobulin (Ig) G response to stimulation by specific food antigens[4]. Certain foods can cause an imbalance between pro-inflammatory and anti-inflammatory cytokines, which is conducive to the production of an inflammatory environment and activation of the immune system[5]; this phenomenon may affect the development of RE. Metabolic syndrome is a risk factor for RE[6,7]. The effects of *Helicobacter pylori* (*H. pylori*) infection on reflux remain controversial[8-10]. This study aimed to explore the risk factors for RE and analyze the effects of IgG-mediated FI, *H. pylori* infection, and metabolic syndrome on RE.

MATERIALS AND METHODS

Research methods

This was a retrospective cross-sectional study. Outpatients attending the Second Medical Center of PLA General Hospital between 2017 and 2021 were enrolled.

The inclusion criteria were as follows: (1) Successful gastroscopy at our hospital; (2) successful completion of the IgG-mediated FI test; and (3) successful completion of the *H. pylori* test.

The exclusion criteria were as follows: (1) Missing test results; and (2) severe cardiovascular, cerebrovascular, or consciousness impairment preventing completion of the examination.

Basic information

The data collected from outpatient records included the following: (1) Basic information: age, sex, systolic blood pressure, diastolic blood pressure, smoking history, and drinking history; (2) test results: white blood cell count, hemoglobin, C-reactive protein, folic acid, homocysteine, brain natriuretic peptide precursor, total cholesterol, fasting blood glucose, creatinine, total protein, and 25-hydroxyvitamin D3; (3) diseases: metabolic syndrome and *H. pylori* infection; (4) gastroscopy results: presence of RE; and (5) IgG-mediated FI results.

Diagnostic criteria

Diagnostic criteria for reflux esophagitis: RE, diagnosed by the presence of mucosal rupture, was detected by gastroscopy and classified according to the current international common Los Angeles grading (LA) standard. LA-A type is categorized by the presence of one or more mucosal breakages ≤ 5 mm in length, LA-B type is categorized by the presence of one or more mucosal breakages > 5 mm in length with no fusion lesion, LA-C type is categorized by the presence of mucosal breakages with fusion lesions $< 75\%$ of the esophageal circumference, and LA-D type is categorized by the presence of mucosal breakages with fusion lesions $\geq 75\%$ of the esophageal circumference[3].

Diagnostic criteria for IgG-mediated FI: ELISA was performed to detect delayed allergens, namely, specific IgG antibodies for 21 foods (beef, chicken, cod, corn, crab, egg, mushroom, milk, pork, rice, shrimp, soybean, tomatoes, wheat, brewer's yeast, garlic, ginger, onion, cottage cheese, red pepper, and sesame). All reagents were equilibrated to room temperature (20 °C–28 °C) and a standard curve was drawn. The absorbance value of each microwell was read with a microplate reader and the concentration of IgG antibodies was evaluated based on the absorbance of each well and the standard curve. IgG-positive food was defined as IgG antibody concentrations ≥ 50 U/mL. IgG-mediated FI was diagnosed when there was ≥ 1 IgG-positive food[11].

Diagnostic criteria for metabolic syndrome: Metabolic syndrome was diagnosed by the presence of at least three of the following: (1) Abdominal obesity (namely, central obesity): waist circumference ≥ 90 cm for men and ≥ 85 cm for women; (2) hyperglycemia: fasting blood glucose ≥ 6.1 mmol/L or blood glucose ≥ 7.8 mmol/L obtained 2 h after sugar loading or patients diagnosed with diabetes who were receiving treatment; (3) hypertension: blood pressure $\geq 130/85$ mmHg (1 mmHg = 0.133 kPa) or patients diagnosed with hypertension who were receiving treatment; (4) fasting triacylglycerol ≥ 1.70 mmol/L; and (5) fasting high-density lipoprotein cholesterol < 1.04 mmol/L[12].

Diagnostic criteria for *H. pylori* infection: The diagnostic criteria for *H. pylori* infection included the use of a ^{13}C -urea breath test or the histologic examination of gastric biopsy specimens as diagnostic tools[13].

Statistical analysis

Normally distributed continuous variables are presented as means \pm SD, and independent *t*-tests were used for between-group comparisons. Categorical variables are presented as numbers or percentages, and χ^2 tests were used for between-group comparisons. Multivariate logistic regression analysis was used to analyze risk factors for RE. Mediation effect analysis was used to evaluate the effects of IgG-mediated FI and metabolic syndrome on the occurrence of RE caused by *H. pylori* infection. In this study, SPSS (version 26.0; IBM Corp., Armonk, NY, United States) was applied to organize and statistically analyze the data; a *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 7954 outpatients were included; 1658 (20.84%) had RE. Notably, RE had a high prevalence among older patients, men, and patients with smoking and alcohol consumption histories. Furthermore, comparing the diseases and test results between the non-RE and RE groups, the RE group demonstrated higher positive IgG-mediated FI, metabolic syndrome, white blood cell count, hemoglobin, homocysteine, fasting blood glucose, and creatinine levels and a lower rate of *H. pylori* infection; all *P*-values were < 0.05 (Table 1).

Multivariate analysis of influencing factors in reflux esophagitis

Multivariate analysis showed that the risk factors for RE included IgG-mediated FI and metabolic syndrome and that *H. pylori* infection was a protective factor for RE (Figure 1).

Mediation effect analysis of IgG-mediated FI on *H. pylori* infection affecting reflux esophagitis

The χ^2 test was used to analyze IgG-mediated FI and *H. pylori* infection. The incidence of IgG-mediated FI was significantly lower in the *H. pylori*-infected group (1700/2856, 59.52%) than in the *H. pylori*-non-infected group (3213/5098, 63.02%; *P* = 0.002). The exposure variable was *H. pylori* infection, the outcome variable was RE, and IgG-mediated FI was used as the mediating variable in the mediation effect analysis. The results showed that the total effect of *H. pylori*

Table 1 Baseline characteristics

Characteristics	Non-reflux esophagitis (n = 6296)	Reflux esophagitis (n = 1658)	P value
Basic information			
Age (yr), mean ± SD	49.76 ± 8.00	50.81 ± 7.83	< 0.001
Sex (male) [n (%)]	4177 (66.34)	1504 (90.71)	< 0.001
Systolic blood pressure (mmHg), mean ± SD	123.40 ± 137.49	126.12 ± 16.78	0.421
Diastolic blood pressure (mmHg), mean ± SD	80.58 ± 11.57	82.63 ± 11.06	< 0.001
Drinking history [n (%)]			< 0.001
No	2567 (40.77)	387 (23.34)	
Yes	3592 (57.05)	1231 (74.25)	
Abstain	137 (2.17)	40 (2.41)	
Smoking history [n (%)]			< 0.001
No	4073 (64.69)	788 (47.53)	
Yes	1777 (28.22)	720 (43.43)	
Abstain	446 (7.08)	150 (9.05)	
Test results			
White blood cell count (10 ⁹ /L), mean ± SD	5.87 ± 1.44	6.21 ± 1.55	< 0.001
Hemoglobin (g/L), mean ± SD	143.31 ± 15.33	150.17 ± 12.61	< 0.001
C-reactive protein (mg/L), mean ± SD	0.16 ± 0.36	0.16 ± 0.31	0.999
Folic acid (ng/mL), mean ± SD	9.50 ± 4.39	8.58 ± 4.05	< 0.001
Homocysteine (μmol/L), mean ± SD	12.35 ± 9.38	13.46 ± 6.96	< 0.001
Brain natriuretic peptide precursor (pg/mL), mean ± SD	34.59 ± 41.53	30.29 ± 49.06	< 0.001
Total cholesterol (mmol/L), mean ± SD	4.76 ± 0.90	4.72 ± 0.95	0.103
Fasting blood glucose (mmol/L), mean ± SD	5.50 ± 1.17	5.68 ± 1.20	< 0.001
Creatinine (μmol/L), mean ± SD	67.92 ± 13.97	72.21 ± 12.79	< 0.001
Total protein (g/L), mean ± SD	70.14 ± 5.39	69.82 ± 5.25	0.031
25-hydroxyvitamin D3 (ng/mL), mean ± SD	19.79 ± 6.01	20.13 ± 6.14	0.040
Diseases [n (%)]			
IgG-mediated food intolerance	3781 (60.05)	1132 (68.28)	< 0.001
<i>Helicobacter pylori</i> infection	2478 (39.36)	378 (22.80)	< 0.001
Metabolic syndrome	3671 (58.31)	1113 (67.13)	< 0.001

Ig: Immunoglobulin.

infection on RE was -0.122064, the direct effect of *H. pylori* infection on RE was -0.119349, the mediation effect of *H. pylori* infection on RE through IgG-mediated FI was -0.002715, and the mediation effect accounted for 0.022242 of the total effect; the effects showed statistically significant differences (all *P* values < 0.05) (Table 2). IgG-mediated FI had a partially positive mediating effect on *H. pylori* infection in reducing the occurrence of RE.

Mediation effect analysis of metabolic syndrome on *H. pylori* infection affecting reflux esophagitis

The χ^2 test was used to analyze metabolic syndrome and *H. pylori* infection; the incidence of metabolic syndrome was significantly higher in the *H. pylori*-infected group (1767/2856, 61.87%) than in the *H. pylori*-non-infected group (3017/5098, 59.18%; *P* = 0.019). The exposure variable was *H. pylori* infection, the outcome variable was RE, and metabolic syndrome was used as the mediating variable for the mediation effect analysis. The results showed that the total effect of *H. pylori* infection on RE was -0.121571, the direct effect of *H. pylori* infection on RE was -0.122715, the mediation effect of *H. pylori* infection on RE through metabolic syndrome was 0.001144, and the mediation effect accounted for -0.009413 in the total effect; the effects showed statistically significant differences (all *P*-values < 0.05) (Table 3). Metabolic syndrome had a partially negative mediating effect on *H. pylori* infection in reducing the occurrence of RE.

Table 2 Mediation effect analysis: Immunoglobulin G-mediated food intolerance

Indicators	Effect value	95%CI	P value
Total effect	-0.122064	-0.138193, -0.104456	< 0.0001
Average direct effect	-0.119349	-0.135905, -0.102256	< 0.0001
Average mediation effect	-0.002715	-0.004145, -0.000316	0.0200
Average mediation effect percentage	0.022242	0.002679, 0.034859	0.0200

Table 3 Mediation effect analysis: Metabolic syndrome

Indicators	Effect value	95%CI	P value
Total effect	-0.121571	-0.138064, -0.104781	< 0.0001
Average direct effect	-0.122715	-0.139268, -0.105907	< 0.0001
Average mediation effect	0.001144	0.000182, 0.002307	0.0220
Average mediation effect percentage	-0.009413	-0.018807, -0.001479	0.0220

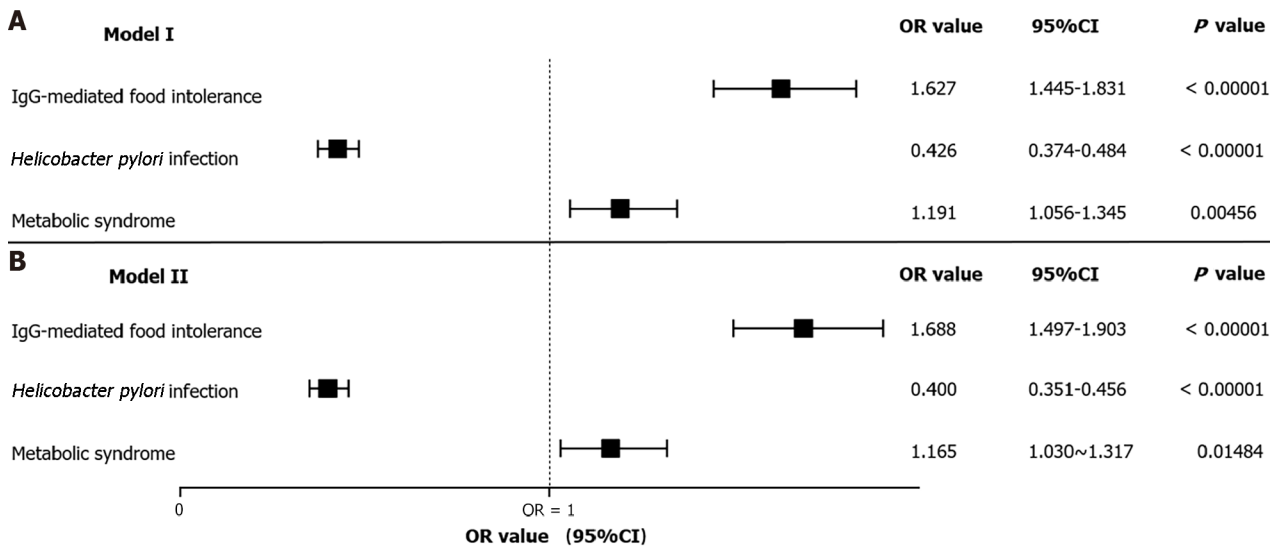


Figure 1 Multivariate analysis of influencing factors in reflux esophagitis. A: Model I was adjusted for age and sex; B: Model II was adjusted for age, sex, white blood cell count, hemoglobin, C-reactive protein, homocysteine, brain natriuretic peptide precursor, total protein, creatinine, 25-hydroxyvitamin D3, smoking history, and drinking history. Ig: Immunoglobulin.

DISCUSSION

RE, also known as erosive esophagitis, is a type of GERD with a complex etiology and an increasing prevalence. Research on its pathogenesis has progressed in recent years, ranging from the invasion of reflux and the destruction of the anti-reflux barrier to immunity, inflammation and biomarkers on a systemic scale[14]. RE demonstrates a high rate of relapse after treatment and is associated with esophageal strictures, bleeding, carcinogenesis, and other complications, which affect the quality of life and long-term prognosis of patients. Therefore, it is critical to explore the risk factors for RE and implement early clinical interventions. The population prevalence of FI is 20% [4], resulting from reactions to food components, non-celiac gluten sensitivity, or defects in enzymes and transport[15]. Furthermore, food may induce inflammatory responses, which are crucial in the development of RE. Metabolic syndrome and its associated components are also risk factors for RE[6], and *H. pylori* infection plays an essential role in RE[8,10]. Therefore, the occurrence of RE may be associated with food reactions, *H. pylori* infection, and metabolic syndromes. This study focused on three relatively common clinical diseases, evaluated risk factors associated with the occurrence of RE, and explored the pathogenic effects of IgG-mediated FI, *H. pylori* infection, and metabolic syndrome on RE to provide a clinical basis for the etiology of the disease; this is crucial knowledge to prevent the occurrence of reflux and improve patients' quality of life.

Our study is the first to investigate the effects of IgG-mediated FI on RE in a large population and confirm that IgG-mediated FI contributes to the development of RE. Studies have suggested that diet may activate the immune system and alter the levels of inflammatory markers in the blood; increased pro-inflammatory cytokines and decreased anti-inflam-

matory cytokines have been linked to diet-associated immune system activation[16]. Furthermore, the promotion and release of inflammatory cytokines and cells during inflammatory reactions involve continuous interdependent cellular communication, which is crucial in the pathogenesis of GERD[1,17]. When FI occurs, a decrease in anti-inflammatory cytokines and the release of inflammatory cells and factors cause reflux; however, further studies are necessary to better understand this phenomenon. Most patients with FI are asymptomatic, which results in such patients receiving less attention[18]. In this study, the prevalence of IgG-mediated FI, which is crucial in the development of RE, was 61.77%; therefore, it is imperative to critically evaluate IgG-mediated FI. Screening for IgG-mediated FI in patients diagnosed with RE or in high-risk groups and avoiding related foods that induce FI in daily life may be crucial in reducing the occurrence of reflux.

This study suggests that metabolic syndrome is a risk factor for RE, consistent with other studies[6,7]. The pathological commonality between the diseases associated with metabolic syndrome is a chronic low-grade inflammation state, which activates various inflammatory signal cascades and leads to the activation of NF- κ B, Jun amino-terminal kinase, and inflammatory processes; this results in the recruitment of immune cells, which further aggravates inflammation[19,20]. The mechanism by which metabolic syndrome promotes the development of RE may be associated with the mechanical effect of increased abdominal pressure caused by a large amount of adipose tissue. Furthermore, substances secreted by adipose tissue, such as TNF- α , IL-6, leptin, and insulin-like growth factor-1, significantly contribute to the occurrence, development, and carcinogenesis of GERD[6]. Therefore, controlling metabolic factors such as blood glucose, blood pressure, lipid levels, and body weight can significantly reduce the occurrence of RE.

In this study, *H. pylori* infection was considered a protective factor against RE. The possible mechanism has been analyzed: *H. pylori* infection causes gastric mucosal atrophy and acid production damage, and bacterial ammonia production neutralizes acidic substances and reduces acid reflux. Additionally, it leads to the activation of vagal receptors on the fundus and cardia, consequently increasing serum gastrin secretion, improving lower esophageal sphincter pressure, reducing reflux of gastric contents, and protecting the esophageal mucosa. The effect of *H. pylori* infection on reflux is controversial; some studies have suggested that *H. pylori* infection is a risk factor for RE, while others suggested that there is no relationship between them[8-10]. The possible reasons for the controversy between this study and other studies could be that other studies mostly assessed the impact of *H. pylori* eradication on RE through quality of life and reflux symptoms, and the drugs used to eradicate *H. pylori* significantly reduced the symptoms of reflux, which affected accuracy and confidence in the results. Therefore, screening for *H. pylori* infection is not routinely required for the clinical treatment of RE, and the treatment options for *H. pylori* infection are not indicated as anti-reflux therapy; this is consistent with the recommendations of the 2013 guidelines of the American College of Gastroenterology[21].

This study confirmed the effect of IgG-mediated FI and metabolic syndrome in reducing the occurrence of RE caused by *H. pylori* infection. A study conducted in southwest China revealed that *H. pylori* infection was negatively associated with food-specific IgG in eggs, milk, and wheat; this is consistent with the results of this study[22]. *H. pylori* infection stimulates the production of Foxp3+ regulatory T cells, which have strong immunosuppressive properties, control the degree of self and non-autoantigen reactions, and produce immune tolerance, consequently protecting against *H. pylori* infection. Immune tolerance suppresses the immune response caused by FI, which reduces the occurrence of RE. In people with FI, increased intestinal permeability allows food substances to enter the circulation; concurrently, the immune system recognizes certain food molecules as harmful substances and initiates an immune response to these substances, resulting in food-specific IgG[23], which further activates the immune effect and enhances the protective effect of *H. pylori* infection against the occurrence of RE. Therefore, IgG-mediated FI reduces the incidence of RE in patients with *H. pylori* infection. In addition, the results showed that *H. pylori* infection increased the incidence of metabolic syndrome. *H. pylori* infection can upregulate the expression of various inflammatory factors (including C-reactive protein, tumor necrosis factor, and various interleukins), promote insulin resistance, and initiate metabolic syndromes[24]. Metabolic syndrome results in chronic over-nutrition and excess energy, exceeding the metabolic capacity of tissues, which leads to metabolic stress and weakens the protective effect of *H. pylori* infection against reflux. Therefore, metabolic syndrome increases the incidence of RE in patients with *H. pylori* infection.

Lifestyle modification, dietary control, and pharmacotherapy are the primary treatment options for RE; however, the complex pathogenesis of RE and the critical role of the immuno-inflammatory cascade in its development may complicate the management of symptoms and increase susceptibility to relapse after treatment. This study evaluated the risk factors for RE and explored the effects of IgG-mediated FI, *H. pylori* infection, and metabolic syndrome on RE. Patients with IgG-mediated FI and metabolic syndrome were at a higher risk of RE; however, patients with *H. pylori* infection had a lower risk of RE. IgG-mediated FI reduced the risk of RE in patients with *H. pylori* infection; however, metabolic syndrome increased the risk of RE in patients with *H. pylori* infection. Therefore, in the management of RE, preventing the induction of IgG-mediated FI and optimal diagnosis and treatment of metabolic syndrome may reduce the occurrence of RE; this represents a strategy to achieve prevention and early treatment of RE in the future.

This was a single-center retrospective clinical study, and the test results showed certain deviations. Therefore, prospective and multicenter studies should be conducted to evaluate the factors influencing RE. The mechanisms underlying the effects of IgG-mediated FI, *H. pylori* infection, and metabolic syndrome in RE should be evaluated regarding the molecular perspective and the associated pathways.

CONCLUSION

Patients with IgG-mediated FI and metabolic syndrome are at a higher risk of RE; however, patients with *H. pylori* infection have a lower risk of RE. IgG-mediated FI reduces the risk of RE in patients with *H. pylori* infection; however,

metabolic syndrome increases the risk of RE in patients with *H. pylori* infection.

ARTICLE HIGHLIGHTS

Research background

Reflux esophagitis has an increasing prevalence and complex and diverse symptoms. Identifying its risk factors is crucial to understanding the etiology, prevention, and management of the disease.

Research motivation

The occurrence of reflux esophagitis may be associated with food reactions, *Helicobacter pylori* (*H. pylori*) infection, and metabolic syndromes.

Research objectives

To investigate the risk factors for reflux esophagitis and analyze the effects of IgG-mediated food intolerance, *H. pylori* infection, and metabolic syndrome on reflux esophagitis.

Research methods

This retrospective study analyzed endoscopic images of outpatients attending the Second Medical Center of PLA General Hospital between 2017 and 2021, classified them into non-RE and RE groups, and further explored the differences in IgG-mediated food intolerance, *H. pylori* infection, and metabolic syndrome of the different groups.

Research results

In 7954 outpatients, the prevalence of reflux esophagitis was 20.84%.

Research conclusions

Patients with IgG-mediated food intolerance and metabolic syndrome are at higher risk of developing reflux esophagitis, while those with *H. pylori* infection are at lower risk. IgG-mediated FI reduces the risk of RE in patients with *H. pylori* infection, while metabolic syndrome increases the risk of RE in these patients.

Research perspectives

In the management of RE, preventing the induction of IgG-mediated FI and optimal diagnosis and treatment of metabolic syndrome may reduce the occurrence of RE.

FOOTNOTES

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Author contributions: Su BB, Lv KM, Li Y, Shi H, and Chen QQ are gastroenterologists; Wang SS is a statistician; Wang LH and Sun GC are master degree candidates; Shi H and Chen QQ performed the disease diagnosis; Wang LH, Su BB, Shi H, and Chen QQ designed the research study; Su BB and Wang SS performed the primary literature and data extraction; Wang LH, Su BB, and Wang SS analyzed the data and wrote the manuscript; Sun GC, Lv KM, Li Y, Shi H, and Chen QQ revised the manuscript for important intellectual content; and all authors read and approved the final version.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the PLA General Hospital (Ethics audits No. S2022-414-01).

Informed consent statement: Patients were not required to provide informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to test by written consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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S-Editor: Gong ZM

L-Editor: A

P-Editor: Yu HG

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