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The correlation between *Helicobacter pylori* infection and iron deficiency anemia in women

Z.-T. WANG, W.-T. TAN, M.-M. MENG, H. SU, Q. LI, C.-M. GUO, J. WANG, H. LIU

Department of Gastroenterology, Beijing Shijitan Hospital, Capital Medical University, Beijing, China

Abstract. – OBJECTIVE: In recent years, *Helicobacter pylori* (*H. pylori*) has been increasingly associated with extra-digestive manifestations, including scleroderma, rheumatism, and blood system diseases. Iron deficiency anemia (IDA) is a common chronic disease worldwide, with an insidious onset, but as the disease progresses, it will eventually seriously affect the quality of life of patients. The aim of our study was to investigate the relationship between *H. pylori* infection, iron deficiency (ID), and IDA, and to identify potential serological markers.

PATIENTS AND METHODS: We conducted a cross-sectional study of 998 individuals who had regular physical examinations at Beijing Shijitan Hospital from January 2021 to March 2022. We detected *H. pylori* infection by the ^{13}C breath test, and recorded the patient's serum iron, ferritin, transferrin saturation, blood count, etc. We assessed the association between IDA and *H. pylori* infection and related serum markers using logistic regression and multiple linear regression. Afterward, we analyzed the correlation between sex and potential serum biomarkers.

RESULTS: Among all study participants, 57.5% of patients had *H. pylori* and 42.5% did not have *H. pylori*. ID and IDA were significantly associated with *H. pylori* infection in women (p=0.031). This association persisted after further adjustment for sex, metabolic variables, liver function, and kidney function. Fasting blood glucose, triglycerides, and uric acid may be associated with IDA.

CONCLUSIONS: In women, *H. pylori* infection is associated with ID and IDA. The relationship between *H. pylori* and IDA may be mediated by glycometabolism, lipid metabolism, and uric acid metabolism.

Key Words:
Iron deficiency, Iron deficiency anemia, *Helicobacter pylori* infection, Breath test, Glycolipid metabolism.

Introduction

Helicobacter pylori (*H. pylori*) is a microaerobic, Gram-negative bacterium with a spiral shape. Within the complex ecosystem of the gastric flora, *H. pylori* stands out as a predominant bacterial species[1]. Humans serve as the exclusive host and source of infection for *H. pylori*. In the year 2015, it was estimated that approximately 4.4 billion people worldwide were affected by *H. pylori*[2]. The prevalence of *H. pylori* infection is notably concentrated in developing countries, where a significant portion of the population is affected. The infection rate of *H. pylori* in China is about 41.35%-72.3%[3]. *H. pylori* colonizes and thrives on the surface of the gastric mucosa, disrupting the integrity of the gastric mucosal barrier. This colonization process involves the production of vacuolar toxins, contributing to the development of diseases such as peptic ulcer disease and gastric cancer. Additionally, research has shown that the gut microbiota does impact bone metabolism[4]. In addition, recent reports[5,6] have described extragastrointestinal manifestations of *H. pylori*, including iron deficiency anemia (IDA)[7], idiopathic thrombocytopenic purpura, and vitamin B12 deficiency[8]. Studies[5,6] have additionally demonstrated that individuals with *H. pylori* infection face an increased risk of developing extraintestinal diseases, including conditions like coronary heart disease and growth retardation in children. Nevertheless, these symptoms are frequently overlooked in the context of *H. pylori* infection.

Iron deficiency (ID) is one of the most prevalent micronutrient deficiencies globally, affecting over 30% of the world's population[9]. IDA is the final stage of persistent negative iron balance[10]. Anemia poses a significant challenge to public health systems, particularly in developing countries. The World Health Organization (WHO) has set a goal to decrease the prevalence of anemia in women by 50% by the year 2025[11]. In infants and young children, ID is considered to be related to cognitive deficits. Adolescent women experience an elevated demand for iron due to growth and menstrual blood loss, contributing to

Corresponding Author: Hong Liu, MD; e-mail: liuhong_sjt@ccmu.edu.cn

the development of IDA[12]. Clinically advanced IDA increases patient mortality[13]. During the progression of IDA, there are typically no apparent symptoms in the early stages, and the primary clinical manifestations may not become apparent until the later stages. Therefore, early detection and prevention of IDA is particularly important. Most studies[12,13] support the idea that women have higher rates of IDA than men from age 15 to older age. Therefore, investigating the variations in the influencing factors of IDA between men and women will aid in understanding the pathogenesis of IDA and enable early-stage prevention of its onset and progression.

There are several acknowledged risk factors for the onset of anemia, including ID, inadequate levels of folic acid and vitamin B12, parasitic infections like schistosomiasis, deficiencies in other micronutrients such as riboflavin, and both acute and chronic infections[14]. Some scholars[5,6,15] have reported the correlation between *H. pylori* infection and IDA in children or adults and proposed the possible pathogenesis. The specific mechanism by which *H. pylori* infection of the gastric mucosa leads to IDA has not been fully elucidated. Iron serves as an essential growth factor for the proliferation of *H. pylori*. In the presence of *H. pylori* infection, there is an elevation in the level of milk protein in the gastric mucosa and gastric juice.

As a result, the absorption of iron by gastric mucosal lactoferrin and *H. pylori* is enhanced, leading to a heightened demand for iron. Thereby, this affects the body's iron requirements for hematopoiesis[16]. The traditional view suggests that *H. pylori* can induce atrophic gastritis, reduce gastric acid secretion, and lower levels of ascorbic acid, leading to decreased iron absorption. Autoimmune injury, resulting from antigen mimicry between *H. pylori* and human tissues, along with the damage inflicted on gastrointestinal epithelial cells through cellular immune mechanisms, contributes to the reduction of intestinal iron absorption. This represents a crucial aspect in the pathogenesis of *H. pylori* infection-related IDA. Recent data from a study[17] indicate that red cell distribution width (RDW) is a biomarker for predicting obesity in young populations. This provides a new perspective for our research. Although an association between IDA and *H. pylori* has been identified by many studies[12,13], there is still some disagreement. Presently, greater attention is given to understanding the relationship between *H. pylori* and IDA in children. Only a limited number of literature focus on the connection between adults, gender, *H. pylori,* and IDA. Hence, this study aims to investigate the relationship between *H. pylori* and IDA in adults of different genders. Simultaneously, it aims to explore potential serological markers and induction mechanisms.

Patients and Methods

Research Subjects

We selected patients aged 20 years and over who had regular check-ups at the Health Examination Center of Beijing Shijitan Hospital from January 2021 to March 2022. The blood chemistry was tested using a Roche electrochemiluminescence instrument (XS-1000i; Shenzhen Roche Biotechnology Co., Ltd; Shenzhen; China), which was in line with the reference range established by the Laboratory of Beijing Shijitan Hospital Affiliated with Capital Medical University. We excluded certain patients from the study if they met any of the following criteria:

1. They had a history of cancer.
2. They were taking drugs known to cause anemia such as antibiotics, anti-inflammatory drugs, analgesic drugs, phenytoin, etc.
3. They were pregnant or lactating women.
4. They had a history of digestive system tumors, surgery, or trauma, including gastrointestinal surgery.
5. They had taken anti-*H. pylori* drugs within the past 3 months.
6. They had a positive fecal occult blood test, indicating gastrointestinal bleeding.
7. They had blood diseases related to anemia or were taking antiplatelet or anticoagulant drugs.

Data Collection

A total of 998 eligible individuals gave informed consent and provided personal information, including personal medical history and medication use. All subjects were asked to fast after dinner the day before the blood sample was taken to ensure that the fasting period reached 6-12 hours. Blood samples were drawn in the morning, and 1-2 ml of venous whole blood was collected under fasting or resting conditions and tested as soon as possible after being placed in an anticoagulant tube. Test items include markers of glycometabolism and lipid metabolism, liver function, kidney function, ions (calcium, iron), etc. (XS-1000i; Shenzhen Roche Biotechnology

Co., Ltd; Shenzhen, China). All participants fasted 6-12 hours before the breathing experiment. On the morning of the same day, on an empty stomach, there was a mandatory non-smoking period of more than 12 hours, and the infection of *H. pylori* was detected by the ^{13}C breath test. The steps are as follows: (1) Prepare two collection bags and paste the patient's personal information. (2) The patient breathes quietly while holding his breath for ten seconds, and the exhaled air is collected in a bag as a 0-minute sample (HCBT-01 tester; Shenzhen Zhonghe Hengwo Biotechnology Co., Ltd; Shenzhen; China). (3) Give urea (C13) capsules and 50 ml of water; half an hour later, collect the second bag of breathing air. The results are expressed in delta over baseline (DOB), which means that $^{13}CO_2/^{12}CO_2$ and metabolic ratios mark urea-induced activity. DOB greater than 4% is considered an active *H. pylori* infection.

Diagnostic Criteria for Iron Deficiency and Iron Deficiency Anemia

Chinese experts[18] agree that to diagnose IDA, criterion (1) must be met along with any two of criteria (2)-(9) or multiple criteria among (2)-(9). (1) Small cell hypochromic anemia, male hemoglobin (Hb) concentration <120 g/dL, female hemoglobin concentration is less than 110 g/dL, erythrocyte morphology is hypochromic manifestations, mean corpuscular volume (MCV) <80 fL, mean corpuscular hemoglobin (MCH) <27 pg, mean corpuscular hemoglobin concentration (MCHC) <32%. (2) There are clear causes and clinical manifestations of ID. (3) Serum ferritin <14 ug/L. (4) Serum iron <8.95 umol/L, total iron binding capacity >64.44 umol/L. (5) Transferrin saturation <15%. (6) Bone marrow iron staining showed that small bone marrow granules could be dyed with iron and disappeared, and sideroblasts <15%. (7) Red blood cell-free protoporphyrin (FEP) >0.9 umol/L, blood zinc protoporphyrin (ZEP) > 0.9 umol/L, or FEP/Hb >4.5 ug/gHb. (8) Soluble transferrin receptor (sTfR) concentration > 26.5 nmol/L. (9) Iron treatment is effective.

Diagnostic criteria for ID: (1) serum ferritin <14 μg/L. (2) Hb concentration and serum iron are normal values.

Statistical Analysis

We used SPSS version 23.0 (IBM Corp., Armonk, NY, USA) statistical software for statistical analysis. The subjects were first divided into three groups: normal, ID, and IDA. Continuous variables are reported as mean±standard deviation, and the K-S test was used to verify that the data were normally distributed, while categorical variables are reported as percentages. Baseline characteristics and group data variables were compared using the *t*-test for continuous variables and Fisher's exact tests for categorical variables. The Chi-square test was used for comparisons of categorical variables in *H. pylori*-negative and positive groups. In addition, we divided the study population into two groups according to gender and used Fisher's exact test to verify whether there are gender differences in the relationship between *H. pylori* and ID, IDA.

We calculated multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CI) for IDA using logistic regression and multiple linear regression. The associations between ID, IDA, and *H. pylori* infection status were assessed by dichotomizing factor levels and calculating ORs. For a more in-depth analysis of the relationship between *H. pylori* infection status and IDA, we established a model using *H. pylori* infection status, complete blood cell differential, liver function, kidney function, glycometabolism, lipid metabolism, and IDA for analysis.

At the same time, we analyzed marker differences between men and women. We further analyzed gender differences in the relationship between *H. pylori* infection and IDA. Potential indicators include complete blood cell classification, liver function, kidney function, glycometabolism, and lipid metabolism, etc. Other serum biomarkers were factored into the model with their normal values. All models adjusted for age as a confounding factor. Two-tailed *p*-values lower than 0.05 were considered statistically significant.

Results

The baseline characteristics of the patients are shown in Table I. 57.5% had *H. pylori* infection, and 42.5% did not. In the study population, 89 people (9.8%) had ID, and 36 people (3.6%) had IDA. The mean age of the population was 53.220±13.182 years old; 360 people were male (36.1%), and 638 people (63.9%) were female. The mean age of patients with and without *H. pylori* infection was 53.250±13.252 and 53.180±13.102, respectively; there was no significant difference in age. Table I shows that albumin (p=0.077), γ-glutamyl transferase (p=0.090), and Creatine

Table I. Baseline characteristics of the patients according to the *Helicobacter pylori* infection status.

	Total	*H. pylori* +	*H. pylori* -	*p*-value
Age (year)	53.220 ± 13.182	53.250 ± 13.252	53.180 ± 13.102	0.932
Sex (male)		21.3%	14.7%	0.428
Fe (ummol/L)	18.610 ± 7.997	18.480 ± 6.668	18.770 ± 9.446	0.606
WBC (*10^{12}/L)	6.009 ± 1.688	6.019 ± 1.672	5.995 ± 1.712	0.834
NE[#] (%)	59.333 ± 23.002	59.512 ± 28.054	59.091 ± 13.457	0.784
RBC (10^{12}/L)	4.775 ± 3.903	4.656 ± 0.455	4.935 ± 5.968	0.265
MCV (fL)	91.738 ± 37.464	91.628 ± 34.960	91.888 ± 40.665	0.914
MCH (pg)	30.292 ± 9.584	30.032 ± 2.270	30.646 ± 14.47	0.318
MCHC (g/L)	337.581 ± 136.972	331.251 ± 25.873	346.172 ± 207.949	0.143
HCT (L/L)	0.520 ± 3.100	0.426 ± 0.183	0.648 ± 4.755	0.337
RDW (%)	13.473 ± 13.586	13.462 ± 13.254	13.488 ± 14.040	0.976
PLT (*10^{9}/L)	241.402 ± 135.021	241.418 ± 136.766	241.381 ± 132.777	0.997
PDW (%)	12.556 ± 2.324	12.538 ± 2.331	12.581 ± 2.317	0.769
ALT (U/L)	22.340 ± 17.236	22.167 ± 16.885	22.571 ± 17.711	0.712
AST (U/L)	21.164 ± 10.135	21.470 ± 11.973	20.757 ± 6.965	0.234
GGT (U/L)	25.775 ± 25.639	24.589 ± 23.457	27.357 ± 28.238	0.090
TBiL (umol/L)	15.293 ± 7.765	15.299 ± 7.501	15.285 ± 8.114	0.978
DBiL (umol/L)	4.748 ± 8.882	4.969 ± 11.627	4.453 ± 1.921	0.361
IBiL (umol/L)	10.656 ± 4.480	10.682 ± 4.537	10.621 ± 4.408	0.836
Alb (g/L)	43.652 ± 4.664	43.876 ± 4.679	43.352 ± 4.631	0.077
ALP (U/L)	69.545 ± 22.533	68.940 ± 21.588	70.351 ± 23.735	0.325
Cr (umol/L)	63.725 ± 17.053	64.026 ± 18.682	63.325 ± 14.618	0.527
eGFR (ml/min/1.73 m^2)	101.994 ± 41.784	100.614 ± 20.848	103.812 ± 58.925	0.246
UA (umol/l)	324.649 ± 129.821	319.996 ± 90.627	330.801 ± 168.100	0.200
TC (mmol/L)	5.051 ± 11.839	4.643 ± 1.072	5.581 ± 17.918	0.258
TG (mmol/L)	2.021 ± 11.956	2.471 ± 15.893	1.440 ± 1.019	0.220
Glu (mmol/L)	6.096 ± 8.086	6.431 ± 10.689	5.663 ± 1.362	0.122
CK (U/L)	102.616 ± 72.974	107.014 ± 85.017	96.964 ± 53.263	0.051
LDH (U/L)	172.487 ± 37.548	172.018 ± 29.669	173.094 ± 45.814	0.686
Ca (mmol/L)	2.345 ± 0.861	2.346 ± 0.971	2.344 ± 0.694	0.977
Na (mmol/L)	140.850 ± 2.711	140.893 ± 2.331	140.794 ± 3.139	0.605
AMY (U/L)	68.667 ± 33.643	68.987 ± 26.670	68.256 ± 40.934	0.759
HDL-C (mmol/L)	1.327 ± 0.492	1.338 ± 0.590	1.311 ± 0.327	0.438
LDL-C (mmol/L)	3.156 ± 8.492	3.389 ± 11.298	2.856 ± 0.913	0.372

[#]Percentage; *Multiplied by. Fe, Serum Iron; Na, Sodium Ion; WBC, White Blood Cell; NE, Neutrophilic Granulocyte; RBC, Red Blood Cell; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; HCT, Hematocrit; RDW, Red Blood Cell Distribution Width; PLT, Platelet; PDW, Platelet Distribution Width; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, γ-Glutamyl Transferase; TBiL, Total Bilirubin; DBiL, Direct Bilirubin; IBiL, Indirect Bilirubin; Alb, Albumin; ALP, Alkaline Phosphatase; Cr, Creatinine; eGFR, Estimated Glomerular Filtration Rate; UA, Uric Acid; TC, Total cholesterol; TG, Triglyceride; Glu, Glucose; CK, Creatine phosphokinase; LDH, Lactic Dehydrogenase; Ca, Calcium Iron; AMY, Amylase; HDL-C, High-density Lipoprotein Cholesterol; LDL-C, Low-density Lipoprotein Cholesterol.

phosphokinase (p=0.051) were different between study participants with *H. pylori* infection and those without *H. pylori* infection, but the result is not significant.

In Table II, we found a significant relationship between ID, IDA, and *H. pylori* infection, but only in females (p=0.031). We did not find this correlation in the male sex.

As shown in Table III, IDA is correlated with *H. pylori* (OR=0.579; 95% CI 0.341-0.982; p=0.043). Uric acid (OR=2.408; 95% CI 1.210-4.787; p=0.012), indirect bilirubin (OR=0.095; 95% CI 0.013-0.682; p=0.019), glucose (OR=0.420; 95% CI 0.207-0.852; p=0.016) and calcium ion (OR=0.444; 95% CI 0.212-0.982; p=0.031) had significant correlation with IDA.

Also, we analyzed marker differences between males and females, as shown in Table IV. We found that age (p=0.000), Hb concentration (p=0.000), serum iron (p=0.000), platelets (p=0.000), alanine aminotransferase (p=0.000), total bilirubin (p=0.000), indirect bilirubin (p=0.000), γ-glutamyl transferase (p=0.000), creatinine (p=0.000), estimated glomerular filtration

Table II. The relationship between the *Helicobacter pylori* infection and the iron deficiency in different genders.

		H. pylori infection (-)	*H. pylori* infection (+)	*p*-value
Female	Normal	230.000	317.000	**0.031**
	Iron Deficiency	36.000	25.000	
	Iron Deficiency Anemia	11.000	19.000	
Male	Normal	137.000	189.000	0.302
	Iron Deficiency	9.000	19.000	
	Iron Deficiency Anemia	1.000	5.000	

Bold indicates statistically significant values.

Table III. Multivariable analysis for different markers and iron deficiency anemia.

		OR	95% CI	*p*-value
RBC (*10^{12}/L)	Q1 (4.3-5.8)	1.100	0.479, 2.524	0.822
	Q2 (< 4.3)	0	0	
HCT (L/L)	Q1 (0.4-0.5)	0.715	0.332, 1.540	0.392
	Q2 (< 0.4)	0	0	
PCT (%)	Q1 (0.18-0.22)	0.848	0.378, 1.902	0.689
	Q2 (< 0.18)	0	0	
RDW (%)	Q1 (11.6-15)	1.528	0.292, 7.996	0.615
	Q2 (< 11.6)	0	0	
NE# (*10^9/L)	Q1 (1.8-6.3)	2.821	0.362, 21.977	0.322
	Q2 (> 6.3)	0	0	
PDW (%)	Q1 (9.8-17)	1.464	0.598, 3.586	0.405
	Q2 (< 9.8)	0	0	
PLT (*10^9/L)	Q1 (125-350)	6.044	0.037, 986.339	0.489
	Q2 (< 125)	0	0	
eGFR (ml/min/1.73 m^2)	Q1 (≥ 90)	0.867	0.364, 2.063	0.747
	Q2 (< 90)	0	0	
Cr (mmol/L)	Q1 (41-81)	0.230	0.028, 1.866	0.169
	Q12 (> 81)	0	0	
UA (mmol/L)	Q1 (187-357)	2.408	1.21, 4.787	**0.012**
	Q2 (358-571)	0	0	
AMY (U/L)	Q1 (35-135)	1.432	0.221, 9.263	0.706
	Q2 (> 135)	0	0	
ALP (U/L)	Q1 (50-135)	1.960	0.281, 13.667	0.497
	Q2 (> 135)	0	0	
AST (U/L)	Q1 (13-35)	0.880	0.134, 5.795	0.894
	Q12 (> 35)	0	0	
ALT (U/L)	Q1 (7-40)	0.694	0.135, 3.572	0.662
	Q2 (> 40)	0	0	
GGT (U/L)	Q1 (7-45)	0.717	0.182, 2.826	0.635
	Q2 (> 45)	0	0	
DBiL (mmol/L)	Q1 (0-7)	0.535	0.178, 1.608	0.266
	Q2 (> 7)	0	0	
IBiL (umol/L)	Q1 (5.6-20.8)	0.095	0.013, 0.682	**0.019**
	Q2 (> 20.8)	0	0	
Glu (mmol/L)	Q1 (0-6.00)	0.420	0.207, 0.852	**0.016**
	Q2 (> 6.00)	0	0	
CK (U/L)	Q1 (50-310)	1.397	0.685, 2.849	0.358
	Q2 (> 310)	0	0	
LDH (U/L)	Q1 (120-250)	0.442	0.04, 4.914	0.507
	Q2 (> 250)	0	0	
TC (mmol/L)	Q1 (3.00-5.70)	1.770	0.689, 4.554	0.236
	Q2 (> 5.70)	0	0	

Continued

Table III *(Continued)*. Multivariable analysis for different markers and iron deficiency anemia.

		TOR	95% CI	*p*-value
LDL-C (mmol/L)	Q1 (0-3.64)	0.668	0.240,1.859	0.440
	Q2 (> 3.64)	0	0	
TG (mmol/L)	Q1 (0-1.70)	0.741	0.325,1.692	0.477
	Q2 (> 1.70)	0	0	
HDL-C (mmol/L)	Q1 (1.10-1.74)	0.893	0.342,2.328	0.817
	Q2 (> 1.74)	0	0	
^{13}C	Q1 (without *H. pylori*)	0.579	0.341,0.982	**0.043**
	Q2 (with *H. pylori*)	0	0	
Ca (mmol/L)	Q1 (2.2-2.7)	0.444	0.212,0.928	**0.031**
	Q2 (< 2.2)	0	0	
Na (mmol/L)	Q1 (137-147)	1.682	0.544,5.197	0.367
	Q2 (< 137)	0	0	
Alb (g/L)	Q1 (40-55)	0.407	0.040,4.137	0.448
	Q2 (< 40)	0	0	

#Percentage; *Multiplied by. RBC, Red Blood Cell; HCT, Hematocrit; PCT, Platelet Crit; RDW, Red Blood Cell Distribution Width; NE, Neutrophilic Granulocyte; PDW, Platelet Distribution Width; PLT, Platelet; eGFR, Estimated Glomerular Filtration Rate; Cr, Creatinine; UA, Uric Acid; AMY, Amylase; ALP, Alkaline Phosphatase; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; GGT, γ-Glutamyl Transferase; DBiL, Direct Bilirubin; IBiL, Indirect Bilirubin; Glu, Glucose; CK, Creatine phosphokinase; LDH, Lactic Dehydrogenase; TC, Total cholesterol; LDL-C, Low-density Lipoprotein Cholesterol; TG, Triglyceride; HDL-C, High-density Lipoprotein Cholesterol; ^{13}C, breathing test positive; Ca, Calcium Iron; Na, Sodium Ion; Alb, Albumin; OR, Odds ratio; CI, Confidence Interval. Bold indicates statistically significant values.

rate (p=0.000), uric acid (p=0.000), lactic dehydrogenase (p=0.040), creatine phosphokinase (p=0.000), high-density lipoprotein cholesterol (p=0.000) are significantly different between men and women.

The relationship between different serum markers and IDA is shown in Table V. We found *H. pylori* (OR=0.54; 95% CI 0.300-0.970; p=0.041), uric acid (OR=2.870; 95% CI 1.330-6.210; p=0.007), glucose (OR=0.490; 95% CI 0.260-0.950; p=0.034), triglyceride (OR=0.400; 95% CI 0.180-0.880; p=0.023), calcium ion (OR=0.460; 95% CI 0.220-0.970; p=0.041), indirect bilirubin (OR=0.02; 95% CI 0.000-0.210; p=0.001). There may be a significant difference in gender, adjusted for age as a confounding factor.

Discussion

ID is one of the major contributors to the global burden of disease, especially affecting children, women, and people in low and developing countries. ID is the most common micronutrient deficiency worldwide. Insufficient iron supply leads to the depletion of body stores. Iron deprivation of erythrocytes and other tissues occurs through the action of hepcidin, which potentially impairs oxygen transport and enzymatic reactions in almost all major metabolic pathways. Anemia, one of the many consequences of ID, only eventually develops as iron becomes progressively depleted and functional impairment[19,20]. In 2011, a total of 528 million women of childbearing age had IDA worldwide, of which 496 million were non-pregnant women and 32.4 million were pregnant women, of whom 20 million had severe anemia[21]. According to the 2016 WHO statistics[19], more than 1.24 billion people worldwide suffer from IDA, which has become the 5th highest prevalence of disease and the 4th leading economic burden of the disease worldwide. Whereas the prevalence of ID is at least twice that of IDA, with more than 2 billion people affected. Common signs and symptoms of IDA include fatigue and somnolence, distractibility, pica, cold sensitivity in women, dizziness, headache, and neurologic deafness[22,23].

There are many etiologies of ID, such as inadequate intake of iron, such as a vegetarian diet, malabsorption of iron, atrophic gastritis, loss of iron elements, and increased demand for iron elements in young children during growth and development as well as in menstrual women. And occult blood loss, such as gastrointestinal bleeding can also lead to ID and ultimately to IDA[23]. Currently, the gender differences in IDA remain a topic of controversy. Our study found a significant association between *H. pylori* and

Table IV. Baseline characteristics of the patients in different genders.

	Total	Male	Female	*p*-value
Age (year)	53.220 ± 13.182	56.230 ± 12.042	51.530 ± 13.502	**0.000**
WBC (*10^{12}/L)	6.009 ± 1.688	6.147 ± 1.533	5.928 ± 1.769	0.057
NE# (%)	59.333 ± 23.001	58.587 ± 10.074	59.767 ± 27.884	0.454
RBC (*10^{12}/L)	4.775 ± 3.903	4.981 ± 0.447	4.659 ± 4.864	0.212
MCV (fL)	91.738 ± 37.464	90.458 ± 5.882	92.456 ± 46.600	0.420
MCH (pg)	30.292 ± 9.583	30.541 ± 1.675	30.153 ± 11.916	0.540
MCHC (g/L)	337.581 ± 136.971	344.688 ± 160.044	333.582 ± 122.044	0.219
HCT (L/L)	0.520 ± 3.100	0.461 ± 0.226	0.554 ± 3.872	0.650
RDW (%)	13.473 ± 13.586	13.402 ± 15.129	13.513 ± 12.648	0.901
PLT (*10^{9}/L)	241.402 ± 135.021	214.688 ± 53.097	256.434 ± 162.148	**0.000**
PDW (%)	12.556 ± 2.324	12.649 ± 2.284	12.504 ± 2.34601	0.347
ALT (U/L)	22.340 ± 17.236	25.582 ± 16.167	20.459 ± 17.558	**0.000**
AST (U/L)	21.164 ± 10.135	21.642 ± 8.730	20.879 ± 10.853	0.248
TBiL (umol/L)	15.293 ± 7.765	16.567 ± 7.207	14.561 ± 7.976	**0.000**
DBiL (umol/L)	4.748 ± 8.882	5.076 ± 2.217	4.561 ± 11.007	0.375
IBiL (umol/L)	10.656 ± 4.480	11.488 ± 5.246	10.166 ± 3.884	**0.000**
Alb (g/L)	43.652 ± 4.664	43.720 ± 4.011	43.612 ± 4.998	0.708
ALP (U/L)	69.545 ± 22.533	69.855 ± 17.893	69.388 ± 24.809	0.730
GGT (U/L)	25.775 ± 25.639	33.207 ± 31.451	21.545 ± 20.451	**0.000**
Cr (umol/L)	63.725 ± 17.053	74.699 ± 13.754	57.194 ± 15.393	**0.000**
eGFR (ml/min/1.73 m^2)	101.994 ± 41.784	96.861 ± 14.578	104.960 ± 51.134	**0.000**
UA (umol/l)	324.649 ± 129.821	370.482 ± 84.602	297.361 ± 143.610	**0.000**
TC (mmol/L)	5.051 ± 11.839	4.441 ± 1.053	5.450 ± 15.205	0.228
TG (mmol/L)	2.021 ± 11.956	1.621 ± 1.026	2.284 ± 15.382	0.435
Glu (mmol/L)	6.096 ± 8.086	5.899 ± 1.431	6.230 ± 10.333	0.563
CK (U/L)	102.616 ± 72.974	123.506 ± 91.497	88.584 ± 52.968	**0.000**
LDH (U/L)	172.487 ± 37.548	169.218 ± 27.421	174.728 ± 42.884	**0.040**
Ca (mmol/L)	2.345 ± 0.861	2.300 ± 0.083	2.376 ± 1.111	0.215
Fe (mmol/L)	18.610 ± 7.997	19.880 ± 6.671	17.740 ± 8.673	**0.000**
Na (mmol/L)	140.850 ± 2.711	140.733 ± 2.998	140.929 ± 2.500	0.307
AMY (U/L)	68.667 ± 33.643	68.563 ± 43.258	68.715 ± 25.189	0.950
HDL-C (mmol/L)	1.327 ± 0.492	1.162 ± 0.323	1.435 ± 0.551	**0.000**
LDL-C (mmol/L)	3.156 ± 8.492	2.837 ± 0.906	3.366 ± 10.918	0.382

#Percentage; *Multiplied by. WBC, White Blood Cell; NE, Neutrophilic Granulocyte; RBC, Red Blood Cell; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; MCHC, Mean Corpuscular Hemoglobin Concentration; HCT, Hematocrit; RDW, Red Blood Cell Distribution Width; PLT, Platelet; PDW, Platelet Distribution Width; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; TBiL, Total Bilirubin; DBiL, Direct Bilirubin; IBiL, Indirect Bilirubin; Alb, Albumin; ALP, Alkaline Phosphatase; GGT, γ-Glutamyl Transferase; Cr, Creatinine; eGFR, Estimated Glomerular Filtration Rate; UA, Uric Acid; TC, Total cholesterol; TG, Triglyceride; Glu, Glucose; CK, Creatine phosphokinase; LDH, Lactic Dehydrogenase; Ca, Calcium Iron; Fe, Serum Iron; Na, Sodium Ion; AMY, Amylase; HDL-C, High-density Lipoprotein Cholesterol; LDL-C, Low-density Lipoprotein Cholesterol. Bold indicates statistically significant values.

IDA in females, but no correlation in males. The reasons for these gender differences may be attributed to the following factors: firstly, based on the reference intakes published in 2023 by the Chinese Nutrition Society[24], women require a larger daily intake of iron than men. Studies have found that women's recipes generally consume less meat than men[25]. Therefore, women are more likely to develop IDA. Second, study[26] has found that women lose a portion of their iron as a result of bleeding from a physiological cycle compared with men, and male hormones (androgens, such as testosterone) have a role in promoting Hb synthesis, whereas female hormones (estrogens, such as estriol) do not. Finally, women will devote their own iron stores to their children through physiological processes such as pregnancy and lactation, and if not promptly replenished, they will be predisposed to IDA.

However, the relationship between *H. pylori* infection and IDA currently remains incompletely defined. Research[27] argues that *H. pylori* is associated with IDA only in men. A study by Hou et al[27] of 646 male elderly individuals found that *H. pylori*-positive patients were more likely to develop IDA (p=0.009). Others have consid-

ered *H. pylori* to be associated with IDA only in women. Lee et al[15] found that female sex and *H. pylori* infection were factors associated with ID. Women infected with *H. pylori* had fewer body iron stores. Mulayim et al[28] found that *H. pylori* in pregnant women was associated with Hb concentration. IDA was associated with fetal growth retardation and a higher risk of *H. pylori* infection. Our study analyzed the association between *H. pylori* infection and IDA in different genders. We found that IDA resulting from ID was significantly associated with *H. pylori* infection in females, but not in males. In female patients, those with *H. pylori* infection are more prone to

Table V. Multivariable analysis for different markers and gender.

		OR	95% CI	*p*-value
RBC (*10^{12}/L)	Q1 (4.3-5.8)	0.840	0.370, 1.890	0.671
	Q2 (< 4.3)	0	0	
HCT (L/L)	Q1 (0.4-0.5)	0.660	0.300, 1.430	0.291
	Q2 (< 0.4)	0	0	
RDW (%)	Q1 (11.6-15)	2.620	0.400, 17.430	0.318
	Q2 (< 11.6)	0	0	
PDW (%)	Q1 (9.8-17)	1.540	0.630, 3.780	0.350
	Q2 (< 9.8)	0	0	
NE# (*10^9/L)	Q1 (1.8-6.3)	3.110	0.380, 25.530	0.291
	Q2 (> 6.3)	0	0	
PCT (%)	Q1 (0.18-0.22)	0.890	0.400, 1.990	0.777
	Q2 (< 0.18)	0	0	
^{13}C	Q1 (without *H. pylori*)	0.540	0.300, 0.970	**0.041**
	Q2 (with *H. pylori*)	0	0	
Cr (mmol/L)	Q1 (41-81)	0.590	0.070, 5.060	0.631
	Q12 (> 81)	0	0	
eGFR (ml/min/1.73 m^2)	Q1 (≥ 90)	0.820	0.330, 2.030	0.675
	Q2 (< 90)	0	0	
UA (mmol/L)	Q1 (187-357)	2.870	1.330, 6.210	**0.007**
	Q2 (358-571)	0	0	
CK (U/L)	Q1 (40-200)	6.310	0.100, 384.140	0.380
	Q2 (> 200)	0	0	
LDH (U/L)	Q1 (120-250)	0.270	0.020, 2.990	0.285
	Q2 (> 250)	0	0	
Glu (mmol/L)	Q1 (0-6.00)	0.490	0.260, 0.950	**0.034**
	Q2 (> 6.00)	0	0	
HDL-C (mmol/L)	Q1 (1.10-1.74)	0.770	0.290, 2.040	0.597
	Q2 (> 1.74)	0	0	
AMY (U/L)	Q1 (35-135)	1.500	0.240, 9.420	0.666
	Q2 (> 135)	0	0	
LDL-C (mmol/L)	Q1 (0-3.64)	0.720	0.250, 2.040	0.532
	Q2 (>3.64)	0	0	
Na (mmol/L)	Q1 (137-147)	1.620	0.520, 5.050	0.402
	Q2 (< 137)	0	0	
TC (mmol/L)	Q1 (3.00-5.70)	1.670	0.640, 4.340	0.292
	Q2 (> 5.70)	0	0	
Alb (g/L)	Q1 (40-55)	0.390	0.040, 3.980	0.426
	Q2 (< 40)	0	0	
TG (mmol/L)	Q1 (0-1.70)	0.400	0.180, 0.880	**0.023**
	Q2 (> 1.70)	0	0	
AST (U/L)	Q1 (13-35)	0.930	0.140, 6.200	0.944
	Q12 (> 35)	0	0	
ALT (U/L)	Q1 (7-40)	0.360	0.060, 2.280	0.279
	Q2 (> 40)	0	0	
ALP (U/L)	Q1 (50-135)	2.510	0.290, 21.710	0.404
	Q2 (> 135)	0	0	
Glb (g/L)	Q1 (20-40)	0.410	0.010, 16.710	0.637
	Q2 (> 40)	0	0	

Continued

Table V *(Continued)*. Multivariable analysis for different markers and gender.

		OR	95% CI	*p*-value
Ca (mmol/L)	Q1 (2.2-2.7)	0.460	0.220, 0.970	**0.041**
	Q2 (< 2.2)	0	0	
IBiL (mmol/L)	Q1 (5.6-20.8)	0.020	0.000, 0.210	**0.001**
	Q2 (> 20.8)	0	0	
DBiL (mmol/L)	Q1 (0-7)	0.570	0.180, 1.780	0.334
	Q2 (> 7)	0	0	
TBiL (umol/L)	Q1 (5-21)	0.180	0.030, 1.020	0.053
	Q2 (> 21)	0	0	
GGT (U/L)	Q1 (7-45)	0.900	0.190, 4.270	0.896
	Q2 (> 45)	0	0	

#Percentage; *Multiplied by. RBC, Red Blood Cell; HCT, Hematocrit; RDW, Red Blood Cell Distribution Width; PDW, Platelet Distribution Width; NE, Neutrophilic Granulocyte; PCT, Platelet Crit; ^{13}C, breathing test positive; Cr, Creatinine; eGFR, Estimated Glomerular Filtration Rate; UA, Uric Acid; CK, Creatine phosphokinase; LDH, Lactic Dehydrogenase; Glu, Glucose; HDL-C, High-density Lipoprotein Cholesterol; LDL-C, Low-density Lipoprotein Cholesterol; AMY, Amylase; Na, Sodium Ion; TC, Total cholesterol; Alb, Albumin; TG, Triglyceride; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; GLb, Globulin; ALP, Alkaline Phosphatase; Ca, Calcium Iron; IBiL, Indirect Bilirubin; DBiL, Direct Bilirubin; TBiL, Total Bilirubin; GGT, γ-Glutamyl Transferase; OR, Odds ratio; CI Confidence Interval. Bold indicates statistically significant values. Male and female have different normal value in UA, UA 149-416 umol/L in male, 89-357 umol/L in female.

developing IDA. Therefore, the eradication of *H. pylori* infection can mitigate the occurrence of IDA to a certain extent, offering protective benefits for women. We believe that this might be attributed to the distinct etiology of IDA between men and women. However, we did not find any other studies on this topic, suggesting the need for more comprehensive research and analysis. Upon scrutinizing gender differences, we observed significant variations in uric acid, glucose, triglycerides, indirect bilirubin, and calcium ions. These findings indicate the involvement of factors related to glycolipid metabolism in the development and progression of IDA in different genders. This study establishes a foundation for future investigations into sex differences in the relationship between *H. pylori* and IDA.

In our study, we discovered an association between *H. pylori* infection and IDA, and the underlying mechanism may be linked to metabolic syndrome. This association is supported by several factors. Firstly, *H. pylori* infection can induce an inflammatory response, leading to oxidative stress. Proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1, and interleukin-6, contribute to an increase in xanthine oxidase (XO) activity[29]. Elevated serum uric acid levels, induced by XO overexpression, trigger the body's oxidative stress response. This, in turn, results in the activation of serum ferritin. Increased expression and activity of xanthine oxidase after iron exposure has been observed in both *in vivo* and *in vitro* studies[29,30]. Hyperuricemia plays an important role in the occurrence and development of body iron metabolism[31]. Hyperuricemia is one of the common metabolic diseases in Chinese adults, and its prevalence increases with age in adult women in a nationwide study[32], which first reported that the levels of serum ferritin, transferrin, and Hb concentrations were associated with the risk of serum uric acid and hyperuricemia ($p<0.05$). Mainous et al[33] reported a positive association between serum uric acid levels and serum ferritin levels in the same population. Serum uric acid levels may function as a variable for stratifying the risk of iron overload. The risk of hyperuricemia and IDA was found to be significantly associated in the current study, which was the same as the results of a previous small sample study[34].

Secondly, another potential mechanism could be related to the body's glycometabolism and insulin sensitivity. Accumulating evidence[35] indicates that serum ferritin levels are associated with increased fasting insulin levels, insulin resistance, and an increased risk of diabetes. After analyzing 1,013 middle-aged Finnish men, one study[36] found a correlation between elevated fasting glucose and serum insulin levels and high serum ferritin levels. In the NHANES III survey[37], elevated serum ferritin was associated with diabetes. One study[38] evaluated insulin resistance, inflammatory factors, liver function, and parameters of iron metabolism in animals by feeding rats

a high-glucose diet. This study found that the rats pass activation of NF-κB/P65 and JAK2/STAT3 signaling stimulates Hepcidin expression in the liver, which in turn affects reduced iron absorption and systemic ID, which demonstrates that a high sugar diet induces systemic ID. This result is consistent with our study indicating that high glucose levels *in vivo* may lead to the occurrence of iron deficiency, providing a new direction for the disorder of iron metabolism caused by glycometabolism.

Third, several studies[39,40] in humans and animals have shown that lipid levels have a correlation with iron status *in vivo*. In animal models[40], hypertriglyceridemia can be reversed by iron element supplementation. It has been suggested that Hb concentration may influence cholesterol synthesis or mobilization from tissues to plasma. It is also possible that an iron-deficient state reduces the activity of enzymes that contribute to cholesterol synthesis. Wrede et al[41] conducted a study on 1,070 probands and found significant differences in serum ferritin levels in patients with high cholesterol (>200 mg/dL) and diabetes. This confirmed a correlation between serum ferritin levels and the presence of insulin receptor substrate criteria. While blood ferritin is often found to be positively associated with unhealthy lipid profiles[41]. ID has a high incidence in obese individuals[42], and there is also ID in diet-induced obese animals[43], suggesting that lipid metabolism is involved in IDA.

Fourth, study[44] has found that the liver, which is involved in the entire metabolic process, induces the degradation of ferritin *via* Hepcidin, thereby regulating the amount of iron ingested from food and influencing iron metabolism within macrophages, as well as the body's iron stores. Excessive suppression of Hepcidin leads to iron-loading anemia, while excessive induction of ferroptosis results in iron-restricted erythropoiesis and anemia. Our study offers a clinical foundation for this metabolic direction, which represents an intermediate mediating pathway. However, further in-depth studies are still needed to clarify the metabolic mechanisms involved.

Finally, *H. pylori* colonizes the gastric mucosa, invades the host's immune defense system, the direct effects of toxins, and the induced inflammatory and immune responses, leading to various degrees of reduced gastric acid secretion and ultimately to atrophy of the gastric mucosa[45]. Calcium ions are absorbed by the small intestine under acidic conditions. Therefore, calcium ions absorption is impaired in either hypochlorhydria or achlorhydria[46]. Studies[47,48] have demonstrated a mechanistic interaction between *H. pylori* Vacuolating cytotoxin A (VacA) and the endolysosomal calcium channel Transient Receptor Potential Channel Mucolipin-1 (Trpml-1). Research[48] raised the possibility that endolysosomal calcium channel Trpml-1 activity could serve as a potential therapeutic target for the treatment of chronic *H. pylori* infection. Trpml-1 is essential for maintaining adequate ion homeostasis and membrane trafficking in the endolysosomal pathway by mediating the release of calcium from late endosomes and lysosomes. Our results suggest that calcium iron has a correlation with IDA. This suggests an interaction between calcium absorption and iron metabolism, but there are currently no relevant studies to confirm this theory, and further studies are needed in the future.

Despite the findings of our study, several limitations remain. First, some patients could not clearly recall the precise time point at which they were first examined for *H. pylori* infection, so the length of infection may have had an impact on the results. Second, our study population only included patients who seek medical advice from our hospital, and the results may be affected by the difference in the distribution of the population. Thus, the results of this study still need to be further verified by the enlarged sample size. Third, the situation after *H. pylori* eradication in patients, including blood test indicators, was not obtained in this study, so it is also necessary to follow up on the situation of anemia in patients after treating *H. pylori* in the future. In addition, we found some differences between genders for IDA *vs. H. pylori* but did not further investigate the pathophysiological mechanisms; we discovered that this effect may be exerted through markers of glycolipid metabolism, which provides a new therapeutic direction for the future treatment of IDA.

Conclusions

There is a correlation between *H. pylori,* female ID, and IDA. Glycolipid metabolism may be a pathway mediating their interactions. Uric acid, glucose, triglycerides, indirect bilirubin, and calcium ions are associated with IDA in women. Oxidative stress response caused by chronic inflammation and activation of the autoimmune system may be involved in *H. pylori* and IDA in females.

Conflict of Interest
The authors declare that they have no conflict of interests.

Availability of Data and Materials
The data set analyzed in the study is not disclosed due to the inclusion of the personal information of the research population. However, the complete dataset can be obtained from the corresponding author upon reasonable request.

Authors' Contribution
LH has made significant contributions to the design of the works. WZT analyzed the preliminary data and drafted the manuscript. TWT has revised the article. MMM, SH, GCM, LQ and WJ conducted a final review of the article. All authors have read and approved the manuscript.

Ethics Approval
The study was conducted in accordance with the Helsinki Declaration and has been approved by the Ethics Committee of Beijing Shijitan Hospital, Affiliated with Capital Medical University [registration number: sjtky11-1x-2022 (63)]. All participants in this study were from the outpatient Department of Shijitan Hospital and lived in Beijing.

Informed Consent
We obtained informed consent from patients or their immediate family members after informing them of the purpose and significance of the study.

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ORCID ID
Hong Liu: 0000-0001-5424-3305
Ziteng Wang: 0000-0002-1543-1933
Wentao Tan: 0009-0005-3343-1696
Mingming Meng: 0000-0003-3560-1052
Hui Su: 0000-0002-0517-9981
Qian Li: 0000-0002-6671-1556
Chunmei Guo: 0000-0002-6103-7849
Jing Wang: 0000-0002-5723-0566

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