BMC Endocrine Disorders

RESEARCH

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Association of *Helicobacter pylori* infection with complications of diabetes: a single-center retrospective study

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Abstract

Background Previous studies examined the association of *Helicobacter pylori* infection (*H. pylori*) with complications of diabetes, but the results have been inconsistent. The aim of this study of patients with type-2 diabetes (T2D) was to determine the association of *H. pylori* infection with the major complications of diabetes.

Methods This single-center retrospective study examined patients with T2D who received *H. pylori* testing between January 2016 and December 2021. Logistic regression analyses were used to evaluate the association of *H. pylori* infection with four major complications of diabetes.

Results We examined 960 patients with T2D, and 481 of them (50.1%) were positive for *H. pylori*. *H. pylori* infection was significantly associated with diabetic nephropathy (odds ratio [OR] = 1.462; 95% confidence interval [CI]: 1.006,2.126; $P = 0.046$). In addition, the co-occurrence of *H. pylori* positivity with hypertension (OR = 4.451; 95% CI: 2.351,8.427; $P < 0.001$), with glycated hemoglobin A1c (HbA1c) of at least 8% (OR = 2.925; 95% CI: 1.544,5.541; $P = 0.001$), and with diabetes duration of at least 9 years (OR = 3.305; 95% CI:1.823,5.993; $P < 0.001$) further increased the risk of diabetic nephropathy. There was no evidence of an association of *H. pylori* infection with retinopathy, neuropathy, or peripheral vascular disease.

Conclusions Our study of T2D patients indicated that those with *H. pylori* infections had an increased risk of nephropathy, and this risk was greater in patients who also had hypertension, an HbA1c level of 8% or more, and diabetes duration of 9 years or more.

Keywords *Helicobacter pylori*, Type-2 diabetes, Complication, Nephropathy

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Introduction

Helicobacter pylori is a Gram-negative bacterium that infects the gastric mucosa of the upper gastrointestinal tract, and is present in approximately half of all people worldwide. Although most infected individuals are asymptomatic, infection can lead to chronic gastritis, peptic ulcers, gastric adenocarcinomas, and mucosa-associated lymphoid tissue lymphoma [1]. A recent literature review concluded there were positive correlations of *H. pylori* infection with extra-gastroduodenal manifestations, such as diabetes, neurological diseases, hematological diseases, cardiovascular diseases, and autoimmune diseases [2].

Type-2 diabetes (T2D) is a major public health problem worldwide. In 2017, an estimated 451 million people between the ages of 18 and 99 years had diabetes, and this number is expected to increase to 693 million by 2045 [3]. The uncontrolled hyperglycemia in patients with diabetes can lead to serious microvascular and macrovascular complications, and these complications adversely affect the duration and quality of life [4, 5] and are a significant economic burden for healthcare systems. Strict glycemic control can prevent or delay these complications, and thereby improve long-term health and reduce treatment-associated costs. A meta-analysis of 13 studies concluded that diabetes was significantly associated with *H. pylori* infection [6]. Another meta-analysis of 41 case-control studies identified *H. pylori* as a risk factor for diabetes, particularly T2D [7]. *H. pylori* infection is also associated with higher levels of fasting plasma glucose (FPG) and glycated hemoglobin A1c (HbA1c) in patients with diabetes [8, 9]. The importance of these two indicators was emphasized in a longitudinal observational cohort study of Korean patients with newly diagnosed T2D, which found that early achievement of the target level of HbA1c was associated with long-term durable glycemic control and a decreased risk of complications [10]. A systematic review and meta-analysis from 2021 concluded that *H. pylori* eradication improved glycemic control in patients with T2D [11]. Other studies demonstrated that *H. pylori* eradication led to decreased levels of HbA1c and improved glycemic control [12, 13]. Therefore, many studies support the presence of an association of *H. pylori* infection with diabetes and hyperglycemia.

Although several studies have examined the relationship of *H. pylori* infection with diabetes complications (nephropathy, retinopathy, neuropathy, and peripheral vascular disease [PVD]), their conclusions have been inconsistent [14–23]. Demir et al. showed that diabetes patients with *H. pylori* infection had a higher incidence of neuropathy, but there was no association between retinopathy, nephropathy, and *H. pylori* infection [14]. A study in Turkey showed that *H. pylori* positivity was significantly associated with the presence of nephropathy and neuropathy [15]. Although some studies reported that the prevalences of nephropathy, neuropathy, retinopathy and PVD complications were significantly higher in diabetes patients who were *H. pylori*-positive [16–20], other studies reported contrary results [21–23]. These discordant results may be due to differences in study design, patient populations, sample size, or other factors. Therefore, clinical investigations with large samples are needed to investigate this topic. The aim of the present study was to investigate the association of *H. pylori* infection with complications of diabetes, especially diabetic nephropathy, retinopathy, neuropathy, PVD.

Patients and methods

Study population

The electronic medical records of patients with T2D at Changzhou No. 2 People's Hospital, Affiliated with Nanjing Medical University between January 2016 and December 2021 were retrospectively examined. Diabetes was defined according to the 1999 criteria of the World Health Organization [24] as the presence of diabetic symptoms (such as polydipsia, polyuria, polyphagia, and unexplained weight loss) and a random plasma glucose of at least 11.1 mmol/L, or a FPG of at least 7.0 mmol/L, or a plasma glucose of at least 11.1 mmol/L at 2 h after a 75 g dose of oral glucose. *H. pylori* infection was diagnosed by a positive result from the ^{13}C-urea breath test (^{13}C-UBT), or the rapid urease test (RUT), or serological testing.

The inclusion criteria were diagnosis of T2D, age of at least 18 years, receipt of an *H. pylori* infection test, receipt of screening for diabetes complications (diabetic nephropathy, retinopathy, neuropathy, PVD), and complete data on demographics and serum biochemical indexes.

The exclusion criteria were type 1 diabetes, a history of *H. pylori* eradication therapy, any malignancy, chronic renal failure requiring dialysis treatment, treatment with a PPI, bismuth, or an antibiotic in the preceding 1 month, absence of an *H. pylori* infection test, and missing information regarding complications of diabetes (diabetic nephropathy, retinopathy, neuropathy, PVD).

Data collection

The baseline demographic data and serum biochemical indexes included age, gender, body mass index (BMI), smoking and alcohol habits, history of hypertension, known duration of T2D, HbA1c, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), calcium, endoscopic findings and comorbidities. BMI (kg/m^2) was calculated from body weight and height.

Assessment of diabetic complications

According to the American Diabetes Association [25], the diagnosis of diabetic nephropathy is based on the presence of a low estimated glomerular filtration rate (eGFR < 60 mL/min/1.73 m^2) and/or increased level of urinary albumin (≥30 mg/g creatinine) that persisted more than 3 months. Diabetic retinopathy is a common microvascular complication that leads to vision loss, and was determined by an ophthalmologist using a standard fundus examination [26]. Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations, and diagnosis is based on the exclusion of similar disorders [26]. The diagnosis of neuropathy was based on the results of electromyography and nerve fiber conduction examinations, as previously described [27]. PVD was diagnosed from clinical findings of a history of intermittent claudication pain, absence of pulse in a physical examinations, or both of these, with confirmation from a color-Doppler ultrasound examination [28].

Table 1 Clinical characteristics of diabetes patients who tested positive or negative for *H. pylori* infection*

Characteristic	Overall (*n* = 960)	H pylori (+) (*n* = 481)	H pylori (−) (*n* = 479)	*P* value**
Age, years	58.84 ± 10.32	58.56 ± 10.66	59.11 ± 9.98	0.410
Gender	594 (61.9)	311 (64.7)	283 (59.1)	0.075
Male	366 (38.1)	170 (35.3)	196 (40.9)	
Female				
BMI, kg/m^2	24.65 ± 3.33	24.59 ± 3.29	24.71 ± 3.38	0.601
Smoking history	336 (35.0)	182 (37.8)	154 (32.2)	0.065
Alcohol intake	211 (22.0)	117 (24.3)	94 (19.6)	0.079
Hypertension	491 (51.1)	249 (51.8)	242 (50.5)	0.700
Known diabetes duration, years	9.65 ± 7.34	9.54 ± 7.29	9.76 ± 7.41	0.642
HbA1c, %	8.81 ± 2.12	8.92 ± 2.13	8.70 ± 2.11	0.104
TC, mmol/L	4.49 ± 1.17	4.50 ± 1.16	4.48 ± 1.18	0.843
TG, mmol/L	1.55 [1.06, 2.27]	1.55 [1.07, 2.34]	1.54 [1.04, 2.20]	0.495
HDL-C, mmol/L	1.09 ± 0.38	1.09 ± 0.45	1.10 ± 0.29	0.880
LDL-C, mmol/L	2.51 ± 0.87	2.49 ± 0.83	2.53 ± 0.90	0.498
Calcium, mmol/L	2.25 ± 0.11	2.25 ± 0.10	2.24 ± 0.11	0.071
Gastroscopy	708 (73.8)	335 (69.6)	373 (77.9)	
Endoscopic findings	116 (12.1)	51(10.6)	65 (13.6)	**< 0.001**
	98 (10.2)	70 (14.6)	28 (5.8)	
Atrophic gastritis	494 (51.5)	214 (44.5)	280 (58.5)	
	252 (26.3)	146 (30.4)	106 (22.1)	
Peptic ulcer				
Others[a]				
No gastroscopy done				
Osteoporosis	149 (15.5)	70 (14.6)	79 (16.5)	0.407
Retinopathy	250 (26.0)	131 (27.2)	119 (24.8)	0.399
Nephropathy	147 (15.3)	85 (17.7)	62 (12.9)	**0.042**
Peripheral neuropathy	715 (74.5)	352 (73.2)	363 (75.8)	0.355
PVD	607 (63.2)	303 (63.0)	304 (63.5)	0.880

Abbreviations BMI, body mass index; HbA1c, glycated haemoglobin A1c; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; *H. pylori*, *Helicobacter pylori*

*Data are presented as number (percentage), mean ± standard deviation, or median [interquartile range]

**Calculated using the independent samples *t*-test, χ^2 test, or Mann-Whitney U test. Bold font indicates statistical significance

[a]Others include nodular gastritis, gastric erosion, and gastric polyp

Statistical analysis

Descriptive data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), or number (percentage). The independent samples *t*-test was used to compare continuous data that had normal distributions, the Mann-Whitney U test was used to compare continuous data that had non-normal distributions, and the χ^2 test was used to compare categorical data. Receiver operating characteristic (ROC) curves were constructed, and the Youden index was used to identify the optimal cutoff values for HbA1c, age, and known duration of diabetes for prediction of diabetic nephropathy and PVD. To assess the effect of different individual risk factors on T2D complications and the joint effects of *H. pylori* infection and other risk factors on these complications, binary logistic regression analysis was used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs). A *P* value below 0.05 was considered to be significant, and all statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA).

Results

We examined the records of 960 T2D patients who met all the eligibility criteria (Table 1). There were 481 *H. pylori*-positive patients and 479 *H. pylori*-negative patients. For the *H. pylori*-negative patients, the prevalence of atrophic gastritis was 13.6% and the prevalence of peptic ulcer was 5.8%. The other endoscopic findings of *H. pylori*-negative patients included nodular gastritis, gastric erosion, and gastric polyp. The *H. pylori*-positive group had a higher prevalence of diabetic nephropathy ($P = 0.042$), but the two groups had no statistically significant differences in retinopathy, neuropathy, or PVD.

We performed univariate and multivariate logistic regression to identify the risk factors for diabetic nephropathy (Table 2). The multivariate analysis showed that the significant and independent risk factors for diabetic nephropathy were *H. pylori* infection (aOR = 1.462, 95% CI: 1.006–2.126, $P = 0.046$), hypertension (aOR = 2.802, 95% CI: 1.829–4.293, $P < 0.001$), long duration of diabetes (aOR = 1.057, 95% CI: 1.031–1.084, $P < 0.001$), high level of HbA1c (aOR = 1.161, 95% CI: 1.065–1.267, $P < 0.001$), and high level of TG (aOR = 1.114, 95% CI, 1.044–1.188, $P = 0.001$).

ROC analysis of the continuous variables from the multivariable analysis for the prediction of diabetic

Table 2 Logistic regression analysis of factors associated with diabetic nephropathy*

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	aOR	95% CI	*P* value
Age	1.031	1.012,1.049	**0.001**	1.016	0.995,1.037	0.127
Gender (female)	1.105	0.772,1.582	0.585			
BMI	1.062	1.010,1.118	**0.020**	1.049	0.990,1.113	0.107
H. pylori (+)	1.444	1.012,2.059	**0.043**	1.462	1.006,2.126	**0.046**
Smoking history	0.679	0.461,1.001	0.051			
Alcohol intake	0.769	0.491,1.205	0.252			
Hypertension	3.236	2.182,4.800	**<0.001**	2.802	1.829,4.293	**<0.001**
Diabetes duration	1.057	1.034,1.081	**<0.001**	1.057	1.031,1.084	**<0.001**
HbA1c	1.124	1.039,1.216	**0.003**	1.161	1.065,1.267	**0.001**
TC	1.090	0.941,1.261	0.251			
TG	1.089	1.027,1.155	**0.005**	1.114	1.044,1.188	**0.001**
HDL-C	0.557	0.296,1.048	0.070			
LDL-C	1.007	0.822,1.233	0.946			
Calcium	0.584	0.118,2.879	0.509			

Abbreviations BMI, body mass index; HbA1c, glycated haemoglobin A1c; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; *H. pylori*, *Helicobacter pylori*

*Data are presented as odds ratios and 95% confidence intervals. Bold font indicates statistical significance

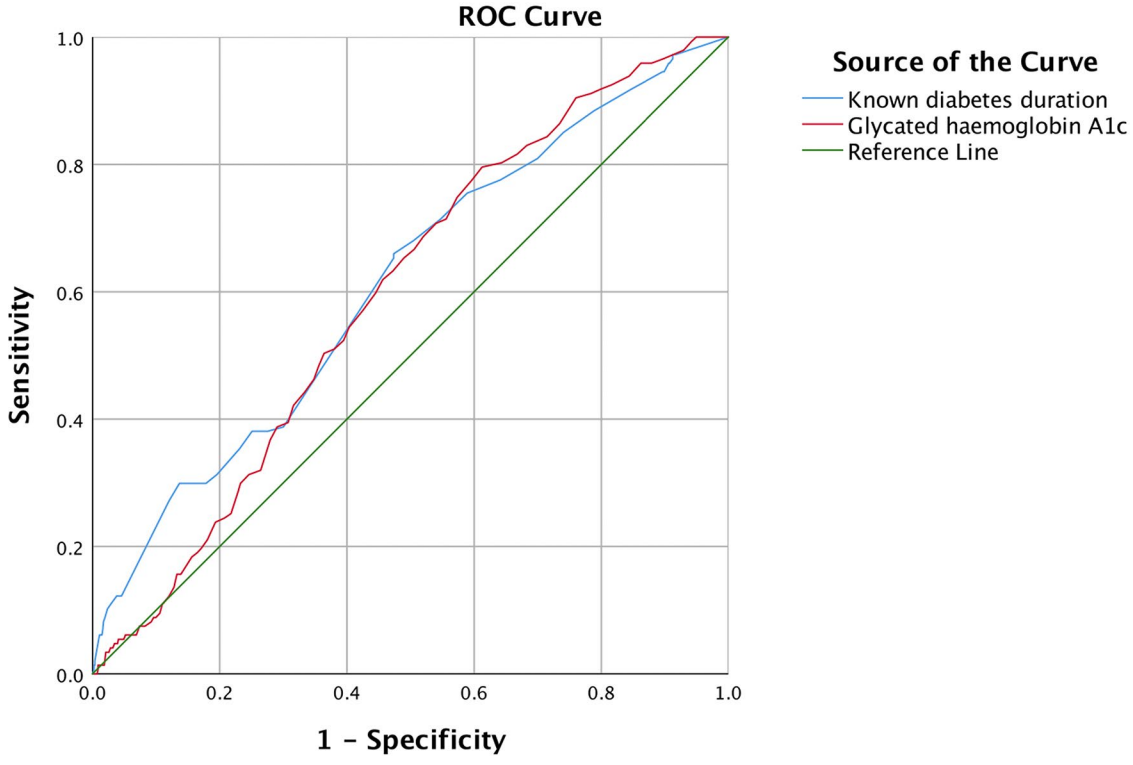

Fig. 1 Receiver operating characteristic curves for prediction of diabetic nephropathy

nephropathy indicated that the area under the curve (AUC) was 0.595 for HbA1c and 0.613 for diabetes duration (Fig. 1). Based on the Youden index, the cutoff value was 8% for HbA1c and 9 years for diabetes duration. The other 3 significant factors from the multivariable analysis were binary variables, including the TG level (<1.7 mmol/L vs. ≥1.7 mmol/L), which was classified according to the American Association of Clinical Endocrinology Clinical Practice Guideline [29].

We evaluated the joint effects of *H. pylori* infection with other factors on the risk of diabetic nephropathy (Table 3). The results demonstrated that the co-occurrence of *H. pylori* positivity with hypertension (aOR=4.451, 95% CI: 2.351–8.427, $P<0.001$), with an

Table 3 Joint effects of *H. Pylori* infection and traditional risk factors on diabetic nephropathy*

H. pylori status	Variable	Nephropathy	No Nephropathy	OR[a] (95%CI)	*P* -trend
	Hypertension				
Negative	No	14(1.5)	223(23.2)	1.0	**< 0.001**
Negative	Yes	48(5.0)	194(20.2)	3.297 (1.707, 6.371)	
Positive	No	24(2.5)	208(21.7)	1.777 (0.882, 3.581)	
Positive	Yes	61(6.4)	188(19.6)	4.451 (2.351, 8.427)	
	HbA1c, %				
Negative	< 8	13(1.4)	153(15.9)	1.0	**0.001**
Negative	≥ 8	49(5.1)	264(27.5)	1.972 (1.018, 3.819)	
Positive	< 8	13(1.4)	115(12.0)	1.254 (0.547, 2.872)	
Positive	≥ 8	72(7.5)	281(29.3)	2.925 (1.544, 5.541)	
	Diabetes duration, years				
Negative	< 9	18(1.9)	206(21.5)	1.0	**< 0.001**
Negative	≥ 9	44(4.6)	211(22.0)	2.523 (1.368, 4.653)	
Positive	< 9	29(3.0)	197(20.5)	1.698 (0.895, 3.224)	
Positive	≥ 9	56(5.8)	199(20.7)	3.305 (1.823, 5.993)	
	TG, mmol/L				
Negative	< 1.7	33(3.4)	243(25.3)	1.0	0.090
Negative	≥ 1.7	29(3.0)	174(18.1)	0.988 (0.557, 1.753)	
Positive	< 1.7	44(4.6)	222(23.1)	1.359 (0.817, 2.260)	
Positive	≥ 1.7	41(4.3)	174(18.1)	1.588 (0.930, 2.712)	

Abbreviations HbA1c, glycated haemoglobin A1c; TG, triglycerides; *H. pylori*, *Helicobacter pylori*

*Data are presented as n (%) and odds ratios (95% confidence intervals). Bold font indicates statistical significance

[a]Adjusted for age, body mass index, HbA1c, TG, diabetes duration, and hypertension

HbA1c level of at least 8% (aOR=2.925, 95% CI: 1.544–5.541, *P*=0.001), and with diabetes duration of at least 9 years (aOR=3.305, 95% CI:1.823–5.993, *P*<0.001) were significantly associated with diabetic nephropathy.

We then performed univariate and multivariate logistic regression analyses of the risk factors for PVD (Table 4). The results of the multivariate analysis showed that *H. pylori* infection was not a significant risk factor for PVD (aOR=0.955, 95% CI: 0.718–1.270, *P*=0.752). However, greater age (aOR=1.063, 95% CI: 1.046–1.080, *P*<0.001), smoking (aOR=2.278, 95% CI: 1.584–3.277, *P*<0.001), hypertension (aOR=1.833, 95% CI: 1.372–2.449, *P*<0.001), and long duration of diabetes (OR=1.034, 95% CI: 1.011–1.057, *P*=0.003) were significantly and independently associated with PVD.

ROC analysis of significant continuous variables from the multivariable analysis indicated that the AUC value was 0.679 for age and 0.606 for diabetes duration for prediction of PVD (Fig. 2). Based on the Youden index, the cutoff values were 56-years-old for age and 8 years for diabetes duration.

As above, we also evaluated the joint effects of *H. pylori* infection with other factors on the risk of PVD (Table 5). The results showed that the co-occurrence of *H. pylori* positivity with age of at least 56 years (aOR=2.771, 95% CI: 1.807–4.250, *P*<0.001), history of smoking (aOR=2.344, 95% CI: 1.464–3.752, *P*<0.001) were significantly associated with PVD.

Discussion

The major result of this retrospective study is that infection by *H. pylori* was an independent risk factor for diabetic nephropathy. We also demonstrated that the co-occurrence of *H. pylori* infection with traditional risk

Table 4 Logistic regression analysis of factors associated with peripheral vascular disease*

Variable	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P* value	aOR	95% CI	*P* value
Age	1.069	1.054,1.085	**< 0.001**	1.063	1.046,1.080	**< 0.001**
Gender (female)	0.748	0.572,0.978	**0.034**	0.874	0.621,1.232	0.443
BMI	0.997	0.959,1.037	0.889			
H. pylori (+)	0.980	0.754,1.274	0.880	0.955	0.718,1.270	0.752
Smoking history	1.751	1.316,2.329	**< 0.001**	2.278	1.584,3.277	**< 0.001**
Alcohol intake	1.191	0.863,1.642	0.287			
Hypertension	2.206	1.687,2.884	**< 0.001**	1.833	1.372,2.449	**< 0.001**
Diabetes duration	1.058	1.037,1.079	**< 0.001**	1.034	1.011,1.057	**0.003**
HbA1c	0.988	0.929,1.050	0.691			
TC	0.920	0.823,1.029	0.144			
TG	0.970	0.920,1.023	0.260			
HDL-C	0.752	0.518,1.093	0.135			
LDL-C	1.021	0.877,1.188	0.792			
Calcium	0.811	0.244,2.698	0.732			

Abbreviations BMI, body mass index; HbA1c, glycated haemoglobin A1c; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; *H. pylori*, *Helicobacter pylori*

*Data are presented as odds ratios and 95% confidence intervals. Bold font indicates statistical significance

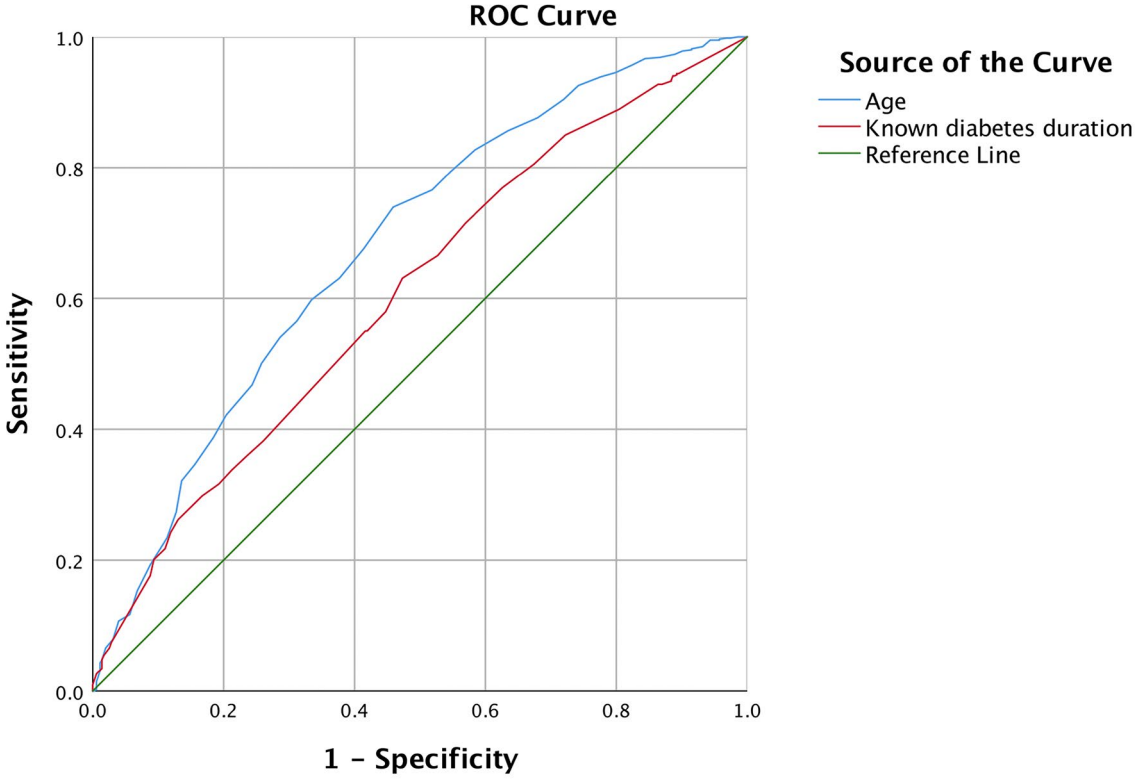

Fig. 2 Receiver operating characteristic curves for prediction of peripheral vascular disease

factors (hypertension, long duration of diabetes duration, high level of HbA1c) further increased the risk of diabetic nephropathy. Although our results showed that *H. pylori* infection was not associated with retinopathy, neuropathy, or PVD, we found that the co-occurrence of *H. pylori* infection with several traditional risk factors (age, smoking) increased the risk of PVD. In addition, although our control diabetic group was *H. pylori*-negative, these individuals had many gastric alterations, such as atrophic gastritis and peptic ulcer, suggesting that T2D patients are more vulnerable to gastric mucosal injuries.

Table 5 Joint effects of *H. Pylori* infection and traditional risk factors on peripheral vascular disease

H. pylori status	Variable	PVD	No PVD	OR[a](95%CI)*	*P* -trend
	Age, years				
Negative	< 56	79(8.2)	88(9.2)	1.0	**< 0.001**
Negative	≥ 56	225(23.4)	87(9.1)	2.477(1.624, 3.776)	
Positive	< 56	79(8.2)	103(10.7)		
Positive	≥ 56	224(23.3)	75(7.8)	0.760(0.488, 1.182)	
				2.771(1.807, 4.250)	
	Smoking history				
Negative	No	198(20.6)	127(13.2)	1.0	**< 0.001**
Negative	Yes	106(11.0)	48(5.0)	1.791(1.110, 2.888)	
Positive	No	169(17.6)	130(13.5)		
Positive	Yes	134(14.0)	48(5.0)	0.821(0.580, 1.163)	
				2.344(1.464, 3.752)	
	Diabetes duration, years				
Negative	< 8	121(12.6)	88(9.2)	1.0	0.190
Negative	≥ 8	183(19.1)	87(9.1)	1.168(0.774, 1.760)	
Positive	< 8	103(10.7)	98(10.2)		
Positive	≥ 8	200(20.8)	80(8.3)	0.764(0.501, 1.167)	
				1.315(0.873, 1.979)	
	Hypertension				
Negative	No	124(12.9)	113(11.8)	1.0	**0.006**
Negative	Yes	180(18.8)	62(6.5)	2.037(1.352, 3.068)	
Positive	No	129(13.4)	103(10.7)		
Positive	Yes	174(18.1)	75(7.8)	1.053(0.712, 1.558)	
				1.740(1.172, 2.586)	

Abbreviations PVD, peripheral vascular disease; *H. pylori*, *Helicobacter pylori*

*Data are presented as n (%) and odds ratios (95% confidence intervals). Bold font indicates statistical significance

[a]Adjusted for age, gender, smoking history, diabetes duration, and hypertension

It is uncertain how *H. pylori* infection in the gut affects the pathogenic processes that are responsible for diabetic nephropathy, although there are several possible mechanisms. First, several studies suggested that inflammatory responses that are secondary to infection could lead to systemic inflammation, and systemic inflammation is an established risk factor for diabetic nephropathy [30]. In support of this interpretation, patients with diabetes are more vulnerable to *H. pylori* infections, and several studies reported that T2D patients with *H. pylori* infections were more likely to have elevated levels of multiple inflammatory cytokines, including C-reactive protein, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8) [15, 16, 21]. There is also a close relationship of T2D with dysfunctional endothelial cells, increased insulin resistance, disrupted lipid metabolism, and proteinuria [31–34].

Second, chronic *H. pylori* infection can lead to atrophic gastritis, which reduces the absorption of folate and vitamin-B_{12}. The conversion of homocysteine (HCY) into methionine requires these two co-factors, and their depletion leads to an increased level of HCY. An elevated level of HCY can contribute to vascular endothelial damage, in that it increases atherosclerosis and thrombogenesis and it inhibits the secretion of nitric oxide (NO) by endothelial cells. These responses can cause platelet aggregation and vasoconstriction, and increase the risk for arteriosclerosis and hypertension [35, 36], which can lead to diabetic nephropathy.

Our results also demonstrated that *H. pylori* infection, hypertension, diabetes duration, HbA1c level, and TG level were independent risk factors for diabetic nephropathy. Moreover, we showed that the co-occurrence of *H. pylori* positivity with hypertension, with an HbA1c level of 8% or more, and with diabetes duration of 9 or more years further increased the risk of diabetic nephropathy. These additive or synergistic effects are biologically plausible. In particular, nuclear factor-kappa B (NF-κB) is a transcription factor that regulates the level of many chemokines, cell adhesion proteins, inflammatory cytokines, and other molecules that function in the pathogenesis of diabetic nephropathy [30]. In addition, the NF-κB-mediated stimulation of the expression of pro-inflammatory genes and their signaling pathways has a major effect in promoting the progression of hypertension to diabetic nephropathy [37], and *H. pylori* infection can activate NF-κB signaling [38]. Taken together with our results, we suggest that the NF-κB-mediated secretion of inflammatory cytokines may be responsible for kidney damage in patients who have concomitant *H. pylori*

infection and hypertension. This alternative interpretation can also explain why T2D patients with hypertension and *H. pylori* infection have a greater risk of diabetic nephropathy.

HbA1c is the best single biomarker of long-term glycemic control, and higher levels reflect long-term hyperglycemia [39]. Hyperglycemia is a well-established risk factor for diabetic nephropathy [40], and several studies reported that *H. pylori* infection was associated with increased levels of plasma glucose and HbA1c in patients with T2D [8, 9, 41]. These previous studies suggest that the combination of an elevated level of HbA1c and *H. pylori* infection is a biologically plausible explanation for the increased risk of diabetic nephropathy.

A prolonged duration of diabetes is another significant risk factor for diabetic nephropathy [40], and there is evidence that diabetes duration is positively associated with *H. pylori* infection [42]. This is consistent with our finding that the co-occurrence of a longer duration of diabetes and *H. pylori* infection further increased the risk of diabetic nephropathy. However, we found no elevated risk of diabetic nephropathy in patients who had *H. pylori* infection with an elevated TG level (≥1.7 mmol/L). This may be because of our small sample size, in that only 41 of our patients (4.3%) had both *H. pylori* infection and an elevated TG level. We therefore suggest that future studies with larger samples examine this relationship.

A recent systematic review and meta-analysis concluded that infection by *H. pylori* was associated with atherosclerosis [43]. An earlier study by Hamed et al. demonstrated that the prevalence of PVD was significantly greater in *H. pylori*-positive patients who had diabetes, and that this effect may be mediated by the increased levels of inflammatory cytokines [16]. Even though we found no evidence that *H. pylori* infection affected the risk for PVD, we did find that T2D patients who had *H. pylori* infection combined with an age of 56 years or more or with a history of smoking had a much higher risk of PVD. Therefore, we suggest that physicians should consider the use of *H. pylori* eradication therapy to reduce the risk of PVD in diabetes patients who are elderly or have a history of smoking. If these patients are positive for *H. pylori*, then eradication therapy should be implemented.

This study had two major strengths. First, to our best knowledge, this is the first study to demonstrate that the combination of *H. pylori* infection with traditional risk factors increased the risk for complications of T2D. This finding may be helpful for improving the treatments and outcomes of patients with T2D complications in clinical settings. Second, we had a relatively large sample of T2D patients, all of whom were tested for *H. pylori* infection, and we adjusted for the major traditional risk factors in our statistical analyses, and this increased the reliability of the results.

Nevertheless, there were also some limitations in our study. First, because this was a retrospective observational study, we could only evaluate the significance of associations, and could not identify causal relationships. Second, all patients were from a single medical center, and therefore might not be representative of the general population of China. Therefore, large, multicenter, prospective studies of this topic are warranted. Third, there were differences in the sensitivity and specificity of the three different tests used to diagnose *H. pylori* infection, and these differences could have affected the reported associations. Fourth, vacuolating cytotoxin-A (VacA) and cytotoxin-associated gene A protein (CagA) play a role in the pathogenesis of *H. pylori*-related diseases. Due to the lack of VacA/CagA data, we are unable to determine the association of these virulence factors with the major complications of diabetes. Fifth, although our control diabetic group was *H. pylori*-negative, these individuals had many gastric alterations, such as atrophic gastritis and peptic ulcer. Comparison with a diabetic control group that had no gastric alterations would likely lead to more significant findings. Finally, we did not assess the effect of *H. pylori* eradication and medication on diabetic nephropathy because we did not have access to follow-up data.

Conclusions

In conclusion, our results suggest that *H. pylori* infection of patients with T2D is an independent risk factor for diabetic nephropathy. We also found that the co-occurrence of *H. pylori* infection with hypertension, with diabetes duration of 9 years or more, and with an HbA1c level of 8% or more further increased the risk for diabetic nephropathy. We suggest that clinicians should pay more attention to T2D patients with *H. pylori* infections to better prevent the progression to diabetic nephropathy, and should also consider *H. pylori* eradication therapy to prevent or slow the development of diabetic nephropathy.

Abbreviations

H. Pylori	*Helicobacter pylori*
T2D	Type-2 diabetes
OR	Odds ratio
CI	Confidence interval
HbA1c	Glycated hemoglobin A1c
PVD	Peripheral vascular disease
^{13}C-UBT	^{13}C-urea breath test
RUT	Rapid urease test
BMI	Body mass index
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol,
TG	Triglycerides
SD	Standard deviation
IQR	Interquartile range
ROC	Receiver operating characteristic curves

TNF-α	Tumor necrosis factor-α
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-8	Interleukin-8
HCY	Homocysteine
NO	Nitric oxide
NF-κB	Nuclear factor-kappa B
VacA	Vacuolating cytotoxin A
CagA	Cytotoxin-associated gene-A

Acknowledgements
Not applicable.

Author contributions
Z. L. and J. Z. : acquisition of data, analysis and interpretation of data, drafting the article. Y.J. and K. M. : acquisition of data, analysis and interpretation of data. C. C. : interpretation of data, revising the article. X. W. : conception and design of the study, critical revision, analysis and interpretation of data, final approval.All authors read and approved the final manuscript.

Funding
The Top Talent of Changzhou "The 14th Five-Year Plan" High-Level Health Talents Training Project, NO. 2022CZBJ051; Clinical Research Project of Changzhou Medical Center of Nanjing Medical University (CMCC202309); Changzhou commission of health Science and Technology Project (ZD202336).

Data availability
It is possible to access the data after coordination with the corresponding author by email.

Declarations

Ethics approval and consent to participate
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. This study was approved by the Institutional Review Board of Changzhou No. 2 People's Hospital, Affiliated with Nanjing Medical University, Changzhou, China ([2022] KY010-01). Since the present study is a retrospective analysis of patient data, the need for informed consent was waived by the Institutional Review Board of Changzhou No. 2 People's Hospital, Affiliated with Nanjing Medical University.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Received: 3 January 2024 / Accepted: 2 August 2024
Published online: 14 August 2024

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