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ORIGINAL RESEARCH

Acute *Helicobacter pylori* Infection Prevalence Among Renal Failure Patients and Its Potential Roles with Other Chronic Diseases: A Retrospective Cohort Study

Sari T Alhoufie[1], Nadir A Ibrahim[1], Areej A Alhhazmi[1], Hatim M Makhdoom[1], Hamza M Ali[1], Hassan A Hemeg[1], Yahya A Almutawif[1], Waleed H Mahallawi[1], Khalid O Alfarouk[2,3]

[1]Medical Laboratories Technology Department, College of Applied Medical Sciences, Taibah University, Al- Madinah Al-Munwarah, Saudi Arabia; [2]Zamzam Research Center, Zamzam Medical College, Khartoum, Sudan; [3]Alfarouk Biomedical Research LLC, Temple Terrace, FL, 33617, USA

Correspondence: Sari T Alhoufie, Medical Laboratories Technology Department, College of Applied Medical Sciences, Taibah University, Al- Madinah Al-Munwarah, Saudi Arabia, Email shoufie@taibahu.edu.sa

Background: *Helicobacter pylori* (*H. pylori*) infection is relevant to several chronic human diseases, from digestive diseases to renal, metabolic, and cancer diseases. *H. pylori* infections and chronic kidney diseases are in increasing, global records; if not well controlled in a specific population, these diseases might lead to more clinical complications.

Methods: In this retrospective study, we investigated the prevalence of acute *H. pylori* infections among 127 dialysis patients via subjecting their serums to the enzyme-linked immunosorbent assay (ELISA) to detect the human Immunoglobulin M (IgM) against *H. pylori* infections. Samples were from dialysis patients in a single hemodialysis center in Medina, Saudi Arabia, from January to August 2021.

Results: Our results indicated the significant prevalence of *H. pylori* acute infections among 33.1% of renal failure patients recruited in this study, chi-squared: 14.559, p-value: 0.0001. In addition, no significant occurrence of acute *H. pylori* infection among males and females, chi-squared: 1.823, p-value: 0.177. Furthermore, the prevalence of acute *H. pylori* infection was not significant in different age groups of renal failure patients. Chi-squared: 6.803, p-value: 0.147, despite *H. pylori*-infected cases predominantly represented in patients above 51 years. Moreover, we noticed that hypertension, followed by diabetes, was the most prevalent underlying medical condition among acute infected *H. pylori* and renal failure patients.

Conclusion: We documented the significant prevalence of acute *H. pylori* infection among renal failure patients. We also highlighted and discussed the possible potential roles of *H. pylori* in renal failure and other chronic diseases. Routine screening and treatment for acute *H. pylori* infection for chronic kidney diseases, hypertension, and diabetes patients would positively reduce the bacterium's progressive effects on them. They might even improve the control of these diseases.

Keywords: *Helicobacter pylori*, acute infection, chronic kidney disease, renal failure, hypertension, diabetes mellitus

Introduction

Helicobacter pylori is a gram-negative bacterium infecting both children and adults. It is the most common human chronic infection, causing gastrointestinal diseases such as gastric malignancies, gastritis, and ulcerative diseases. *H. pylori* can also be involved in other non-gastrointestinal infections such as diabetes and metabolic syndrome, heart disease, hematologic disorders, cancer, and chronic kidney disease (CKD) as well as chronic renal failure (CRF).[1–6]

Renal failure (RF), also termed end-stage kidney disease, is a kidney function decline of less than 15% compared to the normal kidney. When the kidney fails, the body loses its ability to remove waste, and water accumulates inside the body, leading to chemical imbalances that impact buffering capacity and electrolyte balances. Patients begin to receive hemodialysis.[7] RF could be acute or chronic; acute kidney failure can be initiated by different causes such as

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low blood pressure, urinary tract blockage, and hemolytic uremic syndrome after digestive tract bacterial infections caused by *E. coli* O157:H7. Chronic renal failure can be caused by prolonged urinary tract blockage, chronic inflammation, eg, Systemic Lupus Erythematosus (SLE), chronic high blood pressure, diabetes mellitus, and other factors.[8–11]

However, some CRF patients who have received hemodialysis for long periods complained of gastrointestinal troubles. It has been postulated that high urea concentration makes the gastric mucosa of these patients more susceptible to *H. pylori* colonization.[12,13] Previous observations in different countries reported the prevalence of *H. pylori* infection among patients with CRF ranging between 20 and 60%, and *H. pylori* infection can contribute to progressive renal dysfunction resulting in CKD development.[14–16]

In Saudi Arabia, the prevalence of CKD is 9892/100,000, which is higher compared to the North America 7919/100,000 and Western Europe 5446/100,000.[17,18] On the other hand, the prevalence of *H. pylori* in some areas in Saudi Arabia might reach almost 50% of the population.[19]

Little is known about the prevalence of acute *H. pylori* infection among RF patients in Saudi Arabia. Therefore, we aimed to investigate this prevalence in this study and shed light on the crucial role that *H. pylori* can play in initiating or aggravating chronic diseases such as RF, hypertension, and diabetes.

Methodology

Study Design and Samples Collections

In this retrospective study, serum samples from 127 renal failure patients collected in previous projects[20] were subjected to *H. pylori* IgM detection to investigate the prevalence of acute *H. pylori* infection among dialysis patients. Samples were collected from a single hemodialysis center in Madinah, Saudi Arabia, from January to August 2021 and preserved at −70 °C. Serum samples from patients whom undergoing hemodialysis were included in this study and those who not under dialysis procedure in the center were excluded. Demographic data, including patients' age, gender, and frequency of dialysis per week, were extracted from their records.

Ethical Consideration

Ethical approval was acquired from the Research Ethics Committee of the College of Applied Medical Sciences, Taibah University (2022/142/125/MLT). Patients' informed consents were waived by the Ethics Committee due to the retrospective nature of the study. Patients' privacy and confidentiality of data were maintained in accordance with the Declaration of Helsinki.

Serological Detection for *Helicobacter pylori* Infection

Anti-*Helicobacter pylori* IgM antibodies were determined qualitatively with SERION classic *Helicobacter pylori* IgM ELISA kit (Institut Virion\Serion GmbH, Würzburg, Germany) according to the manufacturers' guidelines. As part of the quality control of the assay, control and standard sera from the kits were included on each plate and were set up in duplicate. To avoid interference with rheumatoid factors, patient samples were pre-treated with rheumatoid factor absorbent by incubation the patient's sample in diluted rheumatoid factors – absorbent for 15 minutes at room temperature. According to the manufacturer's manual, all washing processes were carried out using a semi-automated ELISA washer and reader (Biotek, Winooski, US).

The ELISA is based on the specific interaction of antibodies in patient serum with their corresponding antigen with a sensitivity of 99% and 79.7% specificity. The SERION ELISA classic microtiter plate test strips were coated with specific antigens of *Helicobacter pylori*. In the first incubation, if antibodies in the patient's serum sample were present, they bind to the fixed antigen. After washing unbound antibodies, a secondary antibody, conjugated with the enzyme alkaline phosphatase detects attaches to the immune complex. A second washing step was performed then the substrate p-nitrophenyl phosphate was added. The colorless substrate was converted into the colored product p-nitrophenol. Finally, sodium hydroxide was then added to stop the reaction. The signal intensity of this reaction product was proportional to the concentration of the antibodies in the sample and was measured spectrophotometrically at a single

wavelength of 405 nm within 60 minutes. For qualitative evaluation, upper and lower cut-off ranges were calculated according to the user manual of the assay kits.

Statistical Analysis

H. pylori infection distributions to concerning sex, age and comorbidities were compared using the chi-squared ($\chi 2$) test. *P*-values of 0.05 were considered statistically significant. Descriptive statistics for categorical variables are presented as percentages and frequencies. Binary logistic regression analysis was performed to predict *H. pylori* infection with underlying diseases. Data were analyzed using the Statistical Package for the Social Sciences version 20 (IBM Corporation, Armonk, NY, USA).

Results

Demographic Characteristics of the Study Cohort

One hundred and twenty-seven patients with chronic renal failure were recruited for the study. The mean ± SD of patients' ages was 48.28 ± 13.46 years (Minimum = 18, Maximum = 72). The majority (63%) of those patients were male (80 out of 127) patients, whereas (37%) were female (47 out of 127) (Table 1). Patients were grouped according to their ages, where most of them (47.2%) fall in the age of 51 years or older (60 out of 127), followed by patients aged between 41 and 50 years old with a percentage of 24.4% (31 out of 127). Patients between 21 and 30 years old were 19 patients with a percentage of 15%, and patients between the age of 31 and 40 were only 16, accounting for 12.6% of total patients (Table 2).

Patient's medical records indicated several other underlying medical conditions, where most of the patients suffered from hypertension, 66.9% (85 out of 127), diabetic Mellitus 4.7% (6 out of 127), or both 24.4% (31 out of 127), and few patients with other underlying medical conditions 3.9% (5 out of 127) (Table 3). Most of those patients, 95.3% (121 out of 127), had been undergoing dialysis therapy three times a week, whereas only 6 (4.7%) patients had dialysis therapy twice weekly.

H. pylori Prevalence Among Renal Failure Patients

Out of the 127 renal failure patients, 42 (33.1%) tested positive for *H. pylori* acute infection demonstrated by IgM seropositivity while 85 patients (66.9%) tested negative, chi-square: 14.559, p-value: 0.000136 (Figure 1). In addition,

Table 1 Distribution of *H. pylori* Infection Among Dialysis Patient's Gender

Patient's Genders	*H. pylori (%)*		Total	*p*-value
	ve +	ve -		
Male	23 (54.8%)	57(67.1%)	80 (63%)	0.177
Female	19 (45.2%)	28 (32.9%)	47 (37%)	
Total	42 (100%)	85 (100%)	127	

Table 2 Distribution of *H. pylori* Among Different Age Groups of Dialysis Patients

Patient's Genders	*H. pylori (%)*		Total	*p*-value
	ve +	ve -		
10–20 yrs	0 (0%)	1(1.2%)	1 (0.8%)	0.147
21–30 yrs	11 (26.2%)	8 (9.4%)	19 (15%)	
31–40 yrs	5 (11.9%)	11 (12.9%)	16 (12.6%)	
41–50 yrs	8 (19%)	23 (27.1%)	31(24.4%)	
>51 yrs	18 (42.9%)	42(49.4%)	60 (47.2%)	
Total	42 (100%)	85 (100%)	127	

Table 3 Distribution of *H. pylori* Infection with Other Underlying Medical Diseases

Underlying Diseases	*H. pylori*		Total	*p*-value
	ve +	ve -		
HTN	28 (66.7%)	57 (67.1%)	85 (66.9%)	0.926
DM	2 (4.7%)	4 (4.7%)	6 (4.7%)	
HTN & DM	11 (26.2)	20 (23.5%)	31 (24.4%)	
Others	1 (2.3%)	4 (4.7%)	5 (3.9%)	
Total	42 (100%)	85 (100%)	127	

there was no significant difference in the occurrence of *H. pylori* acute infection among males 54.8% (23 out of 42) and females 45.2% (19 out of 42), chi-squared: 1.823 and *P* values: 0.177 (Table 1).

Distribution of *H. pylori* Among Different Age Groups of Dialysis Patients

No significant variation was observed in the probability distribution of *H. pylori* infection among patients from different age groups (10–20, 21–30, 31–40, 40–50, and >50 years) (chi-squared: 6.803 and p-value: 0.147) (Table 2). However, by excluding the *H. pylori*-negative cases, we found that *H. pylori*-infected cases were predominantly represented in patients aged 51 years or older, with a percentage of 42.9% (18 out of 42), followed by 26.2% (11 out of 42) among 21–30-year-olds, 19% (8 out of 42) 41–50-year-olds and 11.9% (5 out of 42) among 31–40-year-old patients (chi-squared: 8.857, p-value: 0.031) (Figure 2).

Association of *H. pylori* Infection with Other Underlying Medical Diseases Among Dialysis Patients

Among dialysis patients recruited in this study, Hypertension noted in 66.9% (85 out of 127) of the patients and seropositivity for *H. pylori* IgM antibodies occurred in 32.9% of them (28 out of 85 patients) (Figure 3A). Furthermore, patients' medical records revealed that 24.4% (31/127) of the participants suffered from hypertension and diabetes (Table 3) and 35.5% (11/31) of them were infected with *H. pylori* (Figure 3B). Participants with only diabetes as an

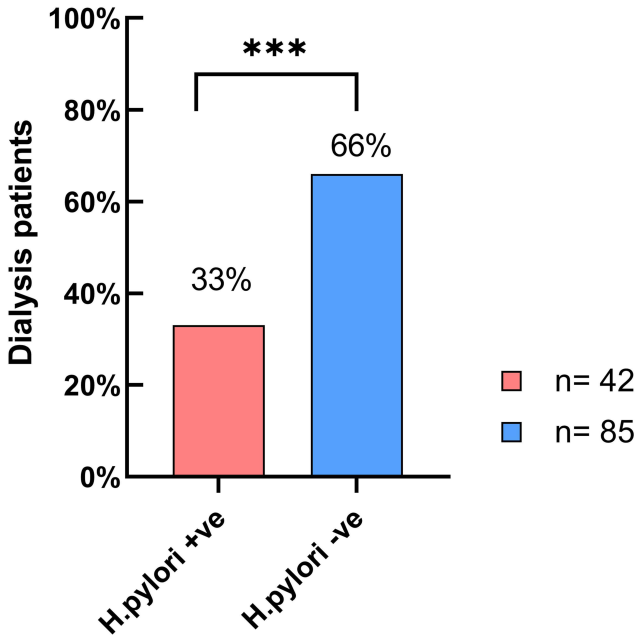

Figure 1 Prevalence of *H. pylori* acute infection among dialysis patients. (***) *p-value*: 0.0001.

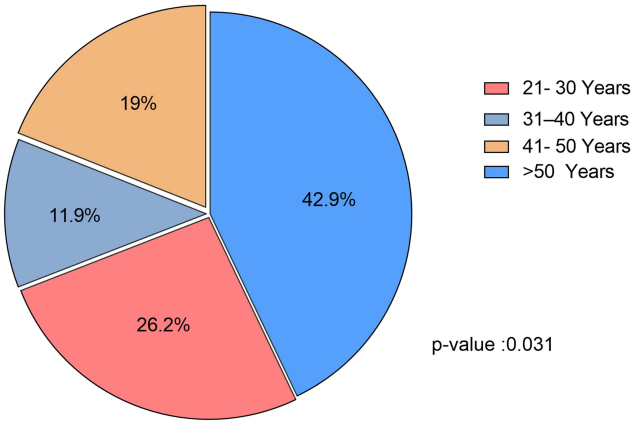

Figure 2 Distribution of *H. pylori* seropositivity among different age groups of 42 infected dialysis patients.

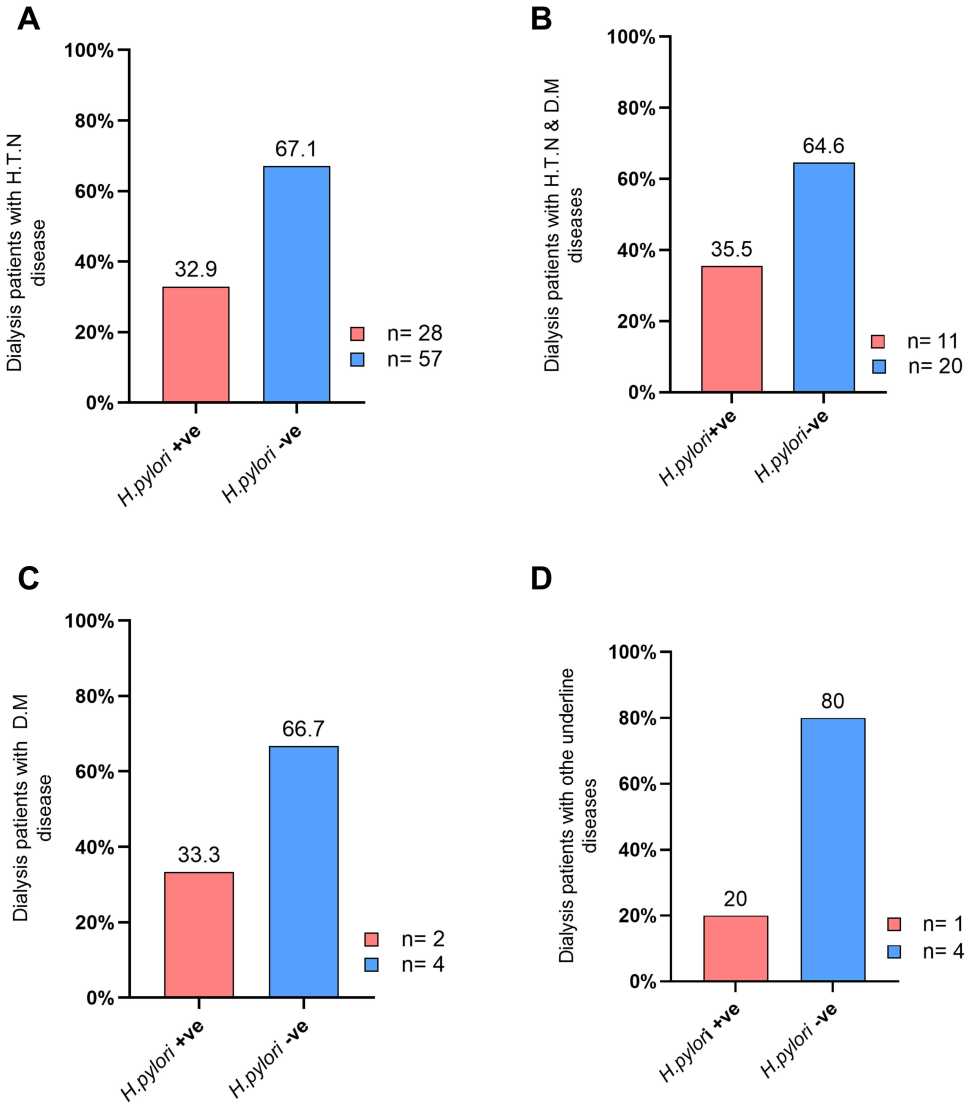

Figure 3 Association of *H. pylori* acute infection with other underlying medical diseases among dialysis patients. (**A**) Dialysis patients with hypertension (HTN), (**B**) dialysis patients with hypertension and diabetes mellitus, (**C**) dialysis patients with diabetes mellitus only (DM), (**D**) dialysis patients with other underlying medical conditions.

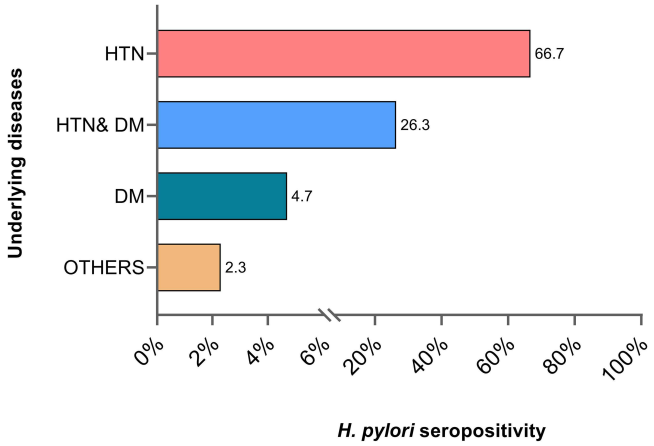

Figure 4 Distribution of different underlying medical diseases among positive *H. pylori* dialysis patients (p-value: <0.0001).

Table 4 Predictors of Change in *H. pylori* Infectivity

	B	S.E.	Degree of Freedom	*p*-value	95% Confidence Interval
Underlying diseases			3	0.918	
HTN	−0.675	1.142	1	0.554	0.054 to 4.769
HTN & DM	−0.788	1.179	1	0.504	0.045 to 4.586
DM	−0.693	1.414	1	0.624	0.031 to 7.994

underlying medical condition were 6 out of 127, and only two were infected with *H. pylori* (Figure 3C). Few patients have other distinctive underlying medical conditions (Table 3) such as systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibody (ANCA), and ischemic heart disease (IHD) those patients were negative for *H. pylori* infection, except for one patient who suffered from hypertension and ischemic heart disease (Figure 3D).

No significant distribution of *H. pylori* seropositivity observed among different underlying medical conditions for the dialysis patients (chi-squared: 0.572; p-value 0.903) (Table 3).

However, by excluding *H. pylori*-negative cases, significant distribution of *H. pylori* seropositivity occurred among different underlying medical condition patients (Chi-squared: 44.667 p-value: <0.0001). In addition, we found that hypertension cases were predominantly represented among *H. pylori*-infected dialysis patients 66.7% (28 out of 42), followed by hypertension and diabetes patients 26.2% (11/42) of *H. pylori*-infected dialysis cases and diabetic patient with *H. pylori* seropositivity were 4.7% (2 out of 24) and other diseases were 2.3% (1 out of 42) (Figure 4).

Nevertheless, binary logistic regression analysis was performed to predict *H. pylori* infection with comorbid status, underlying medical condition variable which is classified into 4 classes (HTN, DM, HTN and DM, and others) was included in the model. The results of the logistic regression analysis showed that the model which considered the independent variable, underlying medical condition, was not statistically significant (p value = 0.918), log-likelihood =160.706 (Table 4).

Discussion

In this work, we conducted a retrospective study to investigate the prevalence of acute *H. pylori* infections among 127 randomly selected renal failure patients from a single hemodialysis center in Medina, Saudi Arabia, from January to August 2021. Our results revealed seropositivity (IgM) for *H. pylori* acute infections among 33% of dialysis patients indicating significant prevalence (*p*-value: 0.0001). In addition, we found no significant difference in the occurrence of

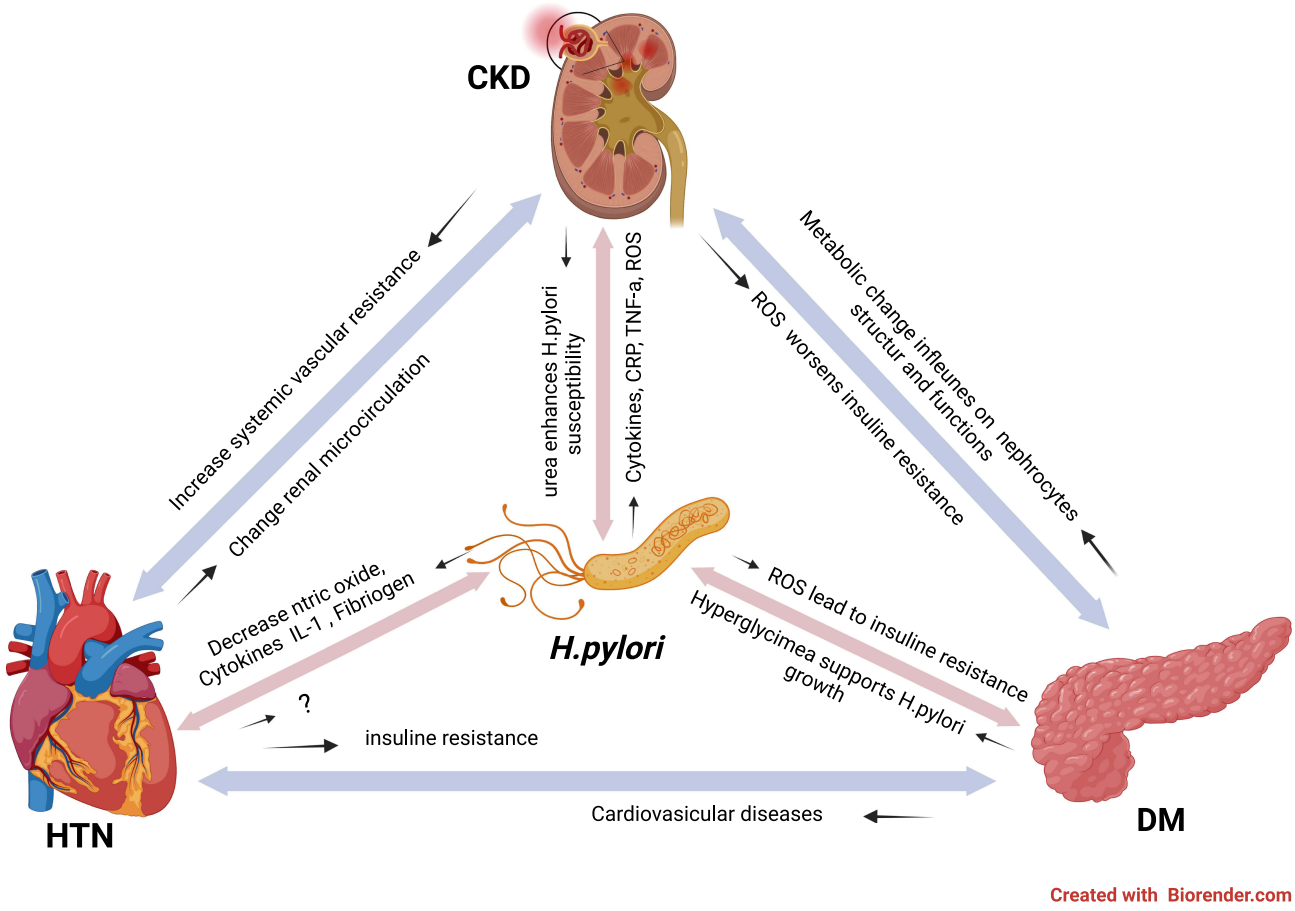

Figure 5 Potential roles of *H. pylori* infection and its interventions in the cyclic relation between chronic kidney disease (CKD), diabetes mellitus (DM) and hypertension (HTN).

H. pylori infection among males and females (*p*-values: 0.177), as well as among different age groups of renal failure patients (*p*-value: 0.147). Nevertheless, we noticed that *H. pylori*-infected cases were predominantly represented in patients aged 51 years old. Moreover, significant distribution (p-value:<0.0001) of *H. pylori* seropositivity occurred between different underlying medical conditions, whereas logistic regression analysis showed no predictors of change for *H. pylori* infectivity.

We conducted serological detection for *H. pylori* IgM, indicating acute and recent *H. pylori* infection. Alem and his colleagues found that the detection of *H. pylori* IgM is highly specific to indicate acute infection among 9043 symptomatic and asymptomatic individuals. Other researchers claimed that IgM detection reflects the bacterium's recent infection and mucosal invasion phase. In addition, IgM antibodies can occur in the first 18 days of *H. pylori* infection.[21–23]

The significant prevalence of *H. pylori* in this study among renal failure patients (Figure 1) agrees with several previous studies.[24–27] *H. pylori* infection is relevant to renal diseases such as membranous nephropathy (MN), immunoglobulin A nephropathy (IgAN), lupus nephritis, and diabetic nephropathy.[28–34] Furthermore, Qian and colleagues detected *H. pylori* antigens in renal biopsy specimens of kidney patients.[35,36] The bacterium can trigger renal diseases via inducing chronic inflammation, a significant cause of renal diseases. For instance, *H. pylori* induce inflammatory cytokines, chemokines, and growth factors that can damage a vascular endothelial structure in the kidney. In addition, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-a), interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 8 (IL-8), heat shock protein (HSP) is also induced by *H. pylori* infection which might aggravate microvascular damage in the kidney (Figure 5).[37,38] However, other epidemiologic observations noticed an inconsistent association of *H. pylori* infection among such a group of patients.[39–41] These contradictory findings can be attributed to several reasons. For instance, *H. pylori* prevalence varies clearly across

different demographic and geographic areas due to the sanitary conditions, cultural habits, and economic situations. In addition, some medications commonly prescribed for renal failure patients, such as antibiotics, proton pump inhibitors, and bismuth, can affect the reliability of these diagnostic methods by increasing the possibility of false-negative results.[42,43] Furthermore, there are several diagnostic methods for *H. pylori* infection, including a urea breath test, stool antigen, urease test, histology, and bacterium culturing, and the different used tests to detect *H. pylori* infection in each study might raise these paradoxical results.

Early diagnosis and treatment for *H. pylori* infection might prevent its impact on renal function. A recent observation by Pan and colleagues reported a remarkable decrease in the albumin-to-creatinine ratio (ACR) in the urine after eradicating *H. pylori* infection for renal disease patients with peptic ulcers.[44] Other studies noticed reduced proteinuria in patients with membranous nephropathy, patients suffering from dyspeptic complaints, and type 2 diabetic patients after eradicating *H. pylori* infection.[35,45,46]

Our result revealed no significant distribution (p-value: 0.147) of acute *H. pylori* infection among different age groups of renal failure patients. However, *H. pylori*-seropositivity was observed predominantly in the age group >51 years (Figure 2). Several studies reported a high prevalence of *H. pylori* incidences among elderly patients with gastroduodenal diseases up to 70% and might range from 40 to 60% in asymptomatic elderly individuals,[47–49] which might stand behind the predominancy of *H. pylori*-seropositivity among renal failure patients age group >51 years in this work.

We also noted 32.9% of *H. pylori*-seropositivity for renal failure patients suffering from hypertension as underlying disease (Figure 3A) which concurs with recent observations.[50,51] In addition, among *H. pylori* seropositive cases, hypertension was more common than others underlying diseases (Figure 4). The association between *H. pylori* and hypertension can be attributed to several factors. For instance, *H. pylori* can initiate the cascades of many disease pathways, including hypertension and atherosclerosis, as it decreases nitric oxide (NO) production and prevents the vasodilatation property resulting in diastolic blood pressure.[52] In addition, *H. pylori* trigger many mediators that support hypertension pathogenicities such as fibrinogen, interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), as they are related to insulin resistant which is one of the major causes that leads to hypertension and diabetes mellitus type 2 (Figure 5).[53,54] Whether hypertension contributes to *H. pylori* infection or not is still unclear and needs to be investigated. Some studies claimed that *H. pylori* eradication improved blood pressure values among hypertension patients,[55,56] indicating the importance of routine investigation for *H. pylori* infection.

Diabetes was reported among 37 renal failure patients, and *H. pylori* seropositivity occurred in 13 of them, 11 patients suffered from diabetes-hypertension, and 2 patients have diabetes only (Figure 3B and C). Early studies showed that hyperglycemia might play a role in *H. pylori* stomach infectivity via different aspects such as increasing endothelial permeability, altering basement membrane composition and structure, and enhancing *H. pylori* adhesion and other virulence factors expressions.[57,58] *H. pylori* supports ROS production, leading to insulin resistance and developing DM type 2 (Figure 5). Moreover, ROS leads to kidney injury; at the same time, CKD increases ROS production and worsens insulin resistance.[59,60] A recent study on type 2 diabetes patients with active *H. pylori* infection showed glycemic control improvement after eradicating such infection.[61]

From all above, *H. pylori* infections were reported among patients with underlying cycling-related diseases, such as CKD, DM, and HPT. Emerging results from different studies mentioned above revealed that *H. pylori* infections could trigger these chronic diseases either directly or indirectly; meanwhile, these diseases can make patients more susceptible to *H. pylori* infection, as illustrated in (Figure 5). In addition, in several observations, *H. pylori* infection eradication positively impacted these underlying diseases, including restoring renal functions and improving glycemic control and blood pressure values.

There were some limitations in this work; firstly, the patient's medical report did not provide some essential details such as the patient's medications, gastrointestinal discomfort complaints, and some chemical indicators for CKD such as ACR that would be useful in comparison between *H. pylori*-infected and non-infected renal failure patients. Secondly, we observed *H. pylori* prevalence in relatively small samples from a single dialysis center. Finally, a prospective study would consider conducting other confirmatory tests for *H. pylori* detection. However, our study highlights the prevalence of *H. pylori* acute infection among dialysis patients in Saudi Arabia, considering the impact of other underlying diseases that had not been discussed before.

Concluding Remarks and Recommendations

This study showed the significant prevalence of acute *H. pylori* infection among renal failure patients. We illustrated the potential role of the bacterium in aggravating other commonly associated diseases with CKD, such as diabetes and hypertension. Understanding the pathogenic impact of *H. pylori* on other chronic diseases would open a new milieu that presents proper management of gut ecology and might represent a potential and rational approach to managing these diseases. Therefore, implementing routine screening for *H. pylori* infection and treatments for renal failure and diabetes and hypertension patients, in general, would minimize the potential prognosis that *H. pylori* might result, as emerging studies have shown.

Data Sharing Statement

All data and materials generated during the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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