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ORIGINAL RESEARCH

# *Helicobacter pylori*, Endoscopic, And Histologic Features Among Kidney Transplant Candidates In Southern Iran

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**Background:** The risks of gastrointestinal disorders and cancer are higher in chronic kidney disease (CKD) patients than the general population. There are only a few published reports on the association of *helicobacter pylori* (*H. pylori*) infection, endoscopic findings, and histology in these patients. This study was designed to address these controversial topics among kidney transplant candidates as the first study in southern Iran.

**Patients and methods:** In this cross-sectional study, patients undergoing renal transplantation in the largest center of southern Iran during 2016–2017 were evaluated for the frequency of *H. pylori* infection, endoscopic findings, and histology. Gastric endoscopic findings (normal, abnormal non-ulcerative, ulcerative) and histological findings of gastric biopsy (normal/non-significant, inflammation, premalignant lesions (PMLs), malignant lesions) were studied.

**Results:** In total, 293 patients underwent endoscopy for transplant work up. The mean age (SD) was 47.37 (13.14) years. The most common endoscopic finding was abnormal gastric lesions. Overall, 78.8% patients had abnormal gastric histologic findings, of which 6.1% had PMLs. There was no significant association between laboratory data of patients with *H. pylori* infection. Of these, 147 (50.2%) patients were positive and the others were *H. Pylori* negative. Positive *H. pylori* infection was significantly associated with gastric ulcerative lesions. Positive *H. pylori* infection was also strongly associated with inflammation ($P<0.01$), but not significantly associated with PMLs ($P=0.99$) in gastric histology.

**Conclusion:** The present study showed that abnormal endoscopic and histologic findings as well as positive *H. pylori* infection were observed in a large number of kidney transplant candidates, so upper endoscopy with biopsy is an acceptable procedure for these patients. However, further studies are recommended to determine the relationship of *H. pylori* with abnormal endoscopic and histologic findings considering other confounding factors in kidney transplant candidates as well as the efficacy of *H. pylori* eradication therapy to improve these abnormal findings.

**Keywords:** chronic kidney disease, transplantation, endoscopic findings, premalignant lesion, *Helicobacter pylori*

## Introduction

Chronic kidney disease (CKD) can be interpreted as an irreversible reduction in kidney function that could be as severe as being fatal in the case of no dialysis or transplantation. This condition is associated with several various pathological conditions of the gastrointestinal, cardiac, vascular, pulmonary and immunological systems.[1]

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The risk of gastrointestinal complications and cancer are higher in CKD patients than the general population.[2,3] Recent studies demonstrated the relationship between *helicobacter pylori* (*H. pylori*) infection and CKD,[4–8] but there is no evidence to approve direct association of *H. pylori* infection with renal disease.[9,10] *H. pylori* is the most common chronic bacterial infection of the gastrointestinal tract of humans.[11,12] The prevalence of *H. pylori* infection in the United States is estimated to be ~30–50%.[11,13] *H. pylori* infection is strongly associated with chronic active gastritis, peptic ulcer diseases, and malignancies.[11,14]

Gastric cancer, as the third highest cause of mortality, is a major public health problem.[15–17] Histologic pre-malignant lesions (PMLs) are precursors of cascade for the development of gastric cancer.[15,16] PMLs are classified as atrophic gastritis, complete or incomplete intestinal metaplasia, and gastric dysplasia.[15–17] Infection by *H. pylori* has been described in more than 90% of the cases of gastric mucosa associated lymphoid tissue.[18] Moreover, the role of upper GI endoscopy and the detection and/or treatment of *H. pylori* infection in non-dyspeptic renal transplant candidates are unclear, although some published studies have described the association or correlation between endoscopic findings and histologic changes.[19]

Like normal populations, PMLs are particularly important in patients with CKD and require careful endoscopic and histological follow-up to prevent further malignancy. It is reasonable to assume that eliminating malignancies or premalignant lesions prior to transplantation may help to reduce the incidence of post-transplant malignancy. Our center, like many other centers, routinely performs upper gastrointestinal endoscopy on all CKD patients that are candidates for kidney transplantation, but the usual role of endoscopy in these patients is unclear. On the other hand, there are only a few published reports on the association of *H. pylori* infection, endoscopic findings, and histology in these patients. Therefore, we designed this study to address these controversial topics among kidney transplant candidates as the first study in southern Iran.

# Patients And Methods

## Population And Study Design

After obtaining the approval of the University Ethics Committee of Shiraz University of Medical Sciences and the Institutional Review Board (reference code: 96-01-01-14984), we conducted a retrospective cross-sectional study of patients with CKD on the transplant waiting list performed at two major referral centers in southern Iran—during 2016 and 2017. This study was conducted following the declaration of Helsinki regarding ethical principles for medical research. Written informed consent was obtained from all patients to review their medical records. The frequency of *H. pylori* infection, endoscopic findings, and histology in consecutive renal transplant candidates were evaluated.

We included all adult patients with a definitive CKD diagnosis who were on the transplant waiting list and we excluded patients with incomplete medical reports. Data for each patient were recorded in a checklist. We collected and evaluated various variables, including age, sex, pre-transplant screening data, endoscopy, and histology reports. For endoscopic evaluation, endoscopic findings of different parts of the upper gastrointestinal tract, including the esophagus, stomach, and duodenum, were examined. Our patients were then categorized, based on gastric endoscopic findings, into three groups of normal, abnormal non-ulcerative (any evidence of mucosal lesion without ulcer, eg, erosion, erythema, nodularity, atrophy, white plaque, and petechiae), and ulcerative.

Given the retrospective nature of our study, endoscopic biopsies of abnormal gastric mucosa as well as random gastric biopsies in all patients with normal mucosa were examined by a pathologist. The histologic findings were categorized into four groups of normal/non-significant, inflammation, PMLs, and malignant lesions. *H. pylori* infection was established by Giemsa stain and hematoxylin and eosin staining by the same pathologist. The frequency of *H. pylori* infection was studied in different types of gastric endoscopic findings as well as other parts of the upper gastrointestinal tract. Finally, three groups of gastric endoscopic findings were compared for the existence of different groups of histological findings.

## Statistical Analysis

Means±standard deviations were reported for quantitative variables, and frequencies were reported for qualitative variables. Univariate analysis was done by chi-square test, and two independent sample t-tests. A *P*-value less than 0.050 was considered as significant. All data analysis was performed under IBM SPSS statistics for Windows, version 25.0 (Chicago, IL).

# Results

In total, 293 patients were included. The mean (SD) age was 47.37 (14.15) years, ranging from 18–81 years. Of these, 183 (62.5%) and 110 (37.5%) patients were male

and female, respectively. Mean ages in females and males were 45.66±13.84 and 41±14.27 years, respectively. The most common causes of CKD were hypertension and diabetes mellitus. The clinical and demographic characteristics of the participants are shown in Table 1.

Overall, 249 (84.98%) and 44 (15.02%) patients had abnormal and normal upper gastrointestinal endoscopic findings, respectively; 94, 203, and 34 of the abnormal upper gastrointestinal endoscopic findings were gastroesophageal reflux disease, abnormal gastric lesions, and duodenal ulcer, respectively. Some patients had more than one endoscopic finding.

One hundred and forty-seven (50.2%) patients were positive and the others were *H. pylori* negative. There was no significant association between laboratory data of patients with *H. pylori* infection (Table 2). Overall, 94 patients had GERD, of whom 50 (53.19%) were positive for *H. pylori* infection. In the stomach, 90 (30.7%) of the patients with *H. pylori* infection had abnormal non-ulcerative lesions, while only 17 (5.5%) of them had gastric ulcer and 40 (13.6%) were normal. With the ratio the same as the stomach, duodenal abnormal non-ulcerative findings (12.6%) were greater than duodenal ulcers (7.1%) in patients with *H. pylori* infection. Table 3 shows the association between *H. pylori* infection and endoscopic findings. Positive *H. pylori* infection was significantly associated with gastric ulcerative lesions. Our data showed no significant association between other endoscopic findings with *H. pylori* infection.

Overall, 231 (78.8%) had abnormal gastric histologic findings, of which 213 (72.6%) and 18 (6.1%) had inflammatory changes and PMLs, respectively. Sixty-two patients had normal/non-significant histology. The evidence of PMLs was seen in 16 and two patients with abnormal non-ulcerative and ulcerative gastric endoscopic findings, respectively. On the other hand, no normal endoscopy was associated with PMLs. Table 4 shows the association between gastric endoscopic findings and histology. Positive *H. pylori* infection was strongly associated with inflammation ($P$<0.01), but not significantly associated with PMLs ($P$=0.99) in gastric histology (Table 5).

**Table 1** Clinical And Demographic Characteristics Of The Participants Among Kidney Transplant Candidates (n=293)

| Characteristics | | Frequency (%) |
|---|---|---|
| Mean age (years) | 47.37±14.15 | |
| Gender | | |
| Male | | 183 (62.5) |
| Female | | 110 (37.5) |
| Age distribution (years) | <30 | 44 (15.02) |
| | 30–50 | 111 (37.88) |
| | >50 | 138 (47.10) |
| Etiology of chronic kidney disease | | |
| Hypertension | | 115 (39.25) |
| Diabetes mellitus | | 54 (18.43) |
| Nephrotic and nephritic syndrome | | 46 (15.70) |
| Urinary Tract Obstruction | | 28 (9.56) |
| Others | | 12 (4.09) |
| Unknown | | 38 (12.97) |
| Anemia (Hemoglobin<12) | | 61.7 |
| Cigarette smoking | | 4.1 |
| BMI (Kg/m$^2$) | 23.74±3.85 | |
| Heavy drinking | | 0 |
| Dyspepsia symptoms | | 65 (22.18) |

**Table 2** The Comparison Of Laboratory Data Between Positive And Negative *helicobacter pylori (H. pylori)* Among Kidney Transplant Candidates

| Laboratory Data Variables* | Positive *H. pylori* (n=146) | Negative *H. pylori* (n=147) | *P*-value |
|---|---|---|---|
| Bloor urea nitrogen (mg/dL) | 76.5 (6.7) | 75.7 (5.9) | 0.28 |
| Serum creatinine (mg/dL) | 7.0 (0.4) | 6.9 (0.7) | 0.14 |
| Serum potassium (mEq/L) | 5.3 (0.8) | 5.4 (0.9) | 0.32 |
| Serum calcium (mg/dL) | 8.5 (1.5) | 8.4 (1.3) | 0.54 |
| Serum aspartate transaminase (IU/L) | 19.8 (12.4) | 18.6 (13.5) | 0.43 |
| Serum alanine transaminase (IU/L) | 18.2 (11.3) | 19.2 (12.6) | 0.48 |
| Serum albumin (mg/dL) | 4.2 (0.5) | 4.1 (0.8) | 0.20 |
| Serum total cholesterol (mg/dL) | 181 (35.4) | 172 (64.3) | 0.14 |
| Serum triglyceride (mg/dL) | 164 (70.2) | 153 (61.7) | 0.16 |

**Notes:** *Mean (standard deviation); Test: Independent *t*-test.

## Discussion

*H. pylori* infection has been reported to be strongly associated with various gastroduodenal diseases.[11,15] The prevalence of *H. pylori* infection in the study differs from country

**Table 3** The Association Between *Helicobacter pylori* (*H. pylori*) Infection And Endoscopic Findings Among Kidney Transplant Candidates (n=293)

| Endoscopic Findings | Positive *H. pylori* | Negative *H. pylori* | *P*-value |
|---|---|---|---|
| **Esophagus** | **151 (%)** | **142 (%)** | |
| Normal | 99 (65.56) | 94 (66.20) | 0.91 |
| Gastroesophageal reflux disease | 50 (33.11) | 44 (30.98) | 0.70 |
| Others | 2 (1.33) | 4 (2.82) | 0.37 |
| **Stomach** | **147 (%)** | **146 (%)** | |
| Normal | 40 (27.21) | 50 (34.25) | 0.19 |
| Abnormal non-ulcerative | 90 (61.22) | 89 (60.96) | 0.96 |
| Ulcerative | 17 (11.57) | 7 (4.79) | 0.03 |
| **Duodenum** | **147 (%)** | **146 (%)** | |
| Normal | 89 (60.54) | 92 (63.02) | 0.66 |
| Abnormal non-ulcerative | 37 (25.17) | 41(28.08) | 0.57 |
| Ulcerative | 21 (14.29) | 13 (8.90) | 0.15 |

**Notes:** Test: Chi-squared test.

**Table 4** The Association Between Gastric Endoscopic Findings And Histology Of Gastric Biopsy Samples Among Kidney Transplant Candidates (n=293)

| Histology Of Gastric Biopsy Samples* | Normal Endoscopy (%) | Abnormal Endoscopy** (%) | *P*-value |
|---|---|---|---|
| Normal/non-significant | 26 (29.21) | 36 (17.65) | 0.03 |
| Inflammation | 63 (70.79) | 150 (73.53) | 0.63 |
| Pre-malignant lesions | 0 | 18 (8.82) | <0.01 |

**Notes:** Test: Chi-squared test. *Endoscopic biopsies of abnormal gastric mucosa as well as random biopsies in all participants with normal mucosa. **Abnormal Endoscopy including ulcerative lesions or abnormal non-ulcerative lesions.

**Table 5** The Association Between *Helicobacter pylori* (*H. pylori*) Infection And Histology Of Gastric Biopsy Samples Among Kidney Transplant Candidates (n=293)

| Histology Of Gastric Biopsy Samples* | Positive *H. pylori* (%) | Negative *H. pylori* (%) | *P*-value |
|---|---|---|---|
| Normal/non-significant | 4 (2.74) | 58 (39.46) | <0.01 |
| Inflammation | 133 (91.10) | 80 (54.42) | <0.01 |
| Premalignant lesions | 9 (6.16) | 9 (6.12) | 0.99 |

**Notes:** Test: Chi-squared test. *Endoscopic biopsies of abnormal gastric mucosa as well as random biopsies in all participants with normal mucosa.

to country, ethnicity to ethnicity, even in the same country.[12,20–22] Our study revealed that 50.2% of our population were *H. pylori* positive, which was lower and at the same time higher compared to local and international studies. *H. pylori* infection causes a spectrum of both gastric and extra gastrointestinal diseases with acute and chronic gastritis, peptic ulcer disease, gastric atrophy, intestinal metaplasia, MALT lymphoma, and gastric adenocarcinoma.[21]

In previous reports ~85% of the adults were IgG carriers of the *H. pylori*[11] and histological evidence of *H. pylori* was noted in 89.2% of biopsies in the north of Iran.[24] Both of these studies indicate the lower rate of *H. pylori* prevalence in our study compared to normal population compared to in previous studies. In a cross-sectional study, Asl et al[25] determined the *H. pylori* frequency in patients with stable chronic hemodialysis with non-ulcer dyspepsia. Based on microscopic evaluation, the prevalence of *H. pylori* in dyspeptic patients on dialysis was 70% and 57.5% in dyspeptic patients with normal renal function. Both results are higher than our report. Gu et al[26] conducted a meta-analysis on chronic renal failure patients who received hemodialysis and found that the *H. pylori* infection rate was about 50.8%, which is almost the same as our report.

The vast majority of our patients had abnormality in their upper endoscopy, including GERD, gastric lesions, and duodenal lesions. Ponticelli et al[27] found that the most common gastrointestinal complications in transplant recipients are oral, esophageal, and gastric lesions. In a study by Ihamaki et al[28] upper gastrointestinal lesions were evaluated in the general population. According to their study, the prevalence of peptic ulcer, duodenal ulcer, and gastric ulcer were 1.68%, 1.4% and 0.28%, respectively. Our study showed a higher incidence of ulcer in both positive and negative groups of *H. pylori*.

Gu et al[26] showed that the incidence of ulcerative diseases in dialysis patients was 13.7% and in the control group was 24.9%. According to our study compared with their study, the frequency of ulcerative lesions in our population was lower.

The prevalence of erosive gastritis, erosive duodenitis, gastric ulcer, and duodenal ulcer was 12%, 10%, 2%, and 2%, respectively; according to the Akdamar et al[29] study. In our study, the prevalence of gastric non-ulcerative abnormalities, duodenal non-ulcerative abnormalities, gastric ulcer, and duodenal ulcer was higher than that reported.

In a report[15] the association of gastric endoscopic findings and histologic pre-malignant lesions was evaluated; this showed that abnormal gastric endoscopic findings can be considered as a risk factor for PMLs. Endoscopy and histological changes in the upper gastrointestinal tract of patients with chronic renal failure were

studied by Mirsa et al[30] who showed that the most frequent histological changes in gastric histology were mucosal edema (82.35%) and gastritis (23.5%). Homse Netto et al22 conducted a study of 96 patients to evaluate gastrointestinal alterations in renal transplant candidates, and found that intestinal metaplasia was present in 8.33% of their population, which was most consistent with our study. But in this study, *H. pylori* was significantly associated with non-ulcerative gastric findings, which was not consistent with our study.

*H. pylori* infection has been reported to be strongly associated with various gastroduodenal diseases.[11,14] The important question is how useful the eradication therapy of *H. pylori* can be in patients with CKD. In a recent study by Sugimoto et al[23] they concluded that, since patients with CKD have a higher risk of gastroduodenal diseases, all hemodialysis patients are advised to use endoscopic examinations and *H. pylori* eradication therapies. In a study by Hsu et al[31] on pre-ESRD patients and matched patients on ESRD, they concluded that early *H. pylori* eradication has a lower risk of peptic ulcer bleeding in positive *H. pylori* infection.

The role of *H. pylori* eradication therapies in improving the nutritional status of patients with CKD has also been studied. Some studies have shown that infection with *H. pylori* in CKD patients is associated with malnutrition, and it is recommended that eradication of *H. pylori* may improve nutritional status.[23,32] In a pilot study,[32] the effect of *H. pylori* eradication therapy on nutritional status in *H. pylori* positive hemodialysis patients was investigated. They concluded that eradication of *H. pylori* may improve nutritional status by increasing serum cholinesterase and cholesterol levels in hemodialysis patients, especially in patients with mild-to-moderate gastric mucosal atrophy.

There was no consensus on the type of *H. pylori* eradication regimen for patients with CKD,[23,33–36] but a study by Alimadadi et al[37] to investigate the effect of creatinine clearance on *H. pylori* eradication showed no association between the success rate of *H. pylori* eradication and renal function. In a study by Seyyed Majidi et al[34] CKD patients with positive *H. pylori* were divided into four groups treated for 2 weeks to evaluate different treatment regimens. There was no significant difference between the success rates of *H. pylori* eradication regimens in the different groups. They conclude that, with fewer drugs and less risk of side-effects and drug interactions, a sequential regimen is the best. In another study by Itatsu et al,[35] hemodialysis patients with positive *H. pylori* were divided into two groups treated for 1 week to evaluate different treatment regimens. They concluded that a low-dose lansoprazole, amoxicillin, and clarithromycin regimen is safe, effective, and recommended in these patients. The long-term effect of *H. pylori* eradication in patients with peptic ulcer with and without CKD was evaluated by Tseng et al.[36] They concluded that the recurrence of peptic ulcer after *H. pylori* eradication was higher in patients with CKD than in patients without renal disease. Although there are several studies on the eradication of *H. pylori* treatment in CKD, the clinical protocol and appropriate eradication regimens are controversial and further studies are needed to better elucidate this issue.

As far as we know, this is the first study to investigate the association between *H. pylori* infection, gastric endoscopy, and histological changes in kidney transplant candidates in Iran. Our research had some important limitations. This study was a retrospective study that was conducted in only two centers. *H. pylori* infection was diagnosed with only one method. Except for the results presented, we did not have further documentation to evaluate other potential risk factors and confounding factors that make patients susceptible to abnormal endoscopy or histology. Given these limitations and to determine the significance of our results, multi-center research can be used. Compared to other studies,[22] one of the strengths of our study was the significant size of the sample with important variables available including pre-transplant laboratory data, endoscopy, and histological reports. Another strength of our study was that endoscopic and histologic findings were classified into different groups and the frequency of *H. pylori* infection was evaluated in different types of endoscopic and histological findings. The findings of this study showed a lower prevalence of *H. pylori* infection compared to many studies. The majority of our patients had abnormal endoscopic findings. Abnormal non-ulcerative and ulcerative changes constituted the dominant endoscopic findings in *H. pylori*-positive patients. Abnormal histology findings were especially significant in abnormal endoscopic findings. Until further studies are revealed, this study could send a message to nephrologists and gastroenterologists that upper gastrointestinal endoscopy is an acceptable procedure for all kidney transplant candidates with or without gastrointestinal symptoms, and in all patients, even with normal endoscopic findings, random biopsy for evaluation of *H. pylori* and abnormal histology can be helpful.

## Conclusions

The present study showed that abnormal endoscopic and histologic findings as well as positive *H. pylori* infection were observed in a large number of kidney transplant candidates, so upper endoscopy with biopsy is an acceptable procedure for these patients. However, further studies are recommended to determine the relationship of *H. pylori* with abnormal endoscopic and histologic findings considering other confounding factors in kidney transplant candidates as well as the efficacy of *H. pylori* eradication therapy to improve these abnormal findings.

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## Disclosure

The authors report no conflicts of interest in this work.

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