

Preliminary single-center experience of *Helicobacter pylori* eradication among the liver transplant recipients

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Abstract

Objective: To investigate the prevalence of *Helicobacter pylori* infection among orthotopic liver transplant (LT) recipients and explore the efficacy and safety of *H. pylori* eradication therapy.

Methods: Liver transplant recipients receiving regular follow-up in our center were assessed by 13C-urea breath test between February 2018 and July 2020. A group of healthy tested patients were selected as control group at a rate of 1:3. All LT recipients with *H. pylori* were recommended to receive eradication therapy with bismuth-containing quadruple therapy (BQT), which included esomeprazole 20 mg + clarithromycin 500 mg + amoxicillin 1 g + bismuth 220 mg, twice daily for 14 days.

Results: The prevalence of *H. pylori* infection among the LT recipients was 19.6% (30/153), which was significantly lower than the control group (30/153 [19.6%] vs. 200/459 [43.6%], $p < 0.001$). In LT recipients who received transplantation at <1 year, 1–3 years, and >3 years, the prevalence of *H. pylori* infection was 10.6% (5/47), 17.5% (10/57), and 30.6% (15/49), respectively, which increased with the time after transplantation ($p = 0.04$). With BQT, the eradication rate of *H. pylori* was 91.3% (21/23). During the process of eradication, the blood trough concentration of immunosuppressants increased from 1.7 to 3.6 times, and reducing the dose of the drugs to one-third of what they were before the eradication therapy could avoid excessively elevated concentration of immunosuppressants. Adverse effects occurred in 55.2% (11/23), of the LT recipients and 21.0% (42/200) of the control group ($p < 0.01$), which was probably caused by the increased blood concentration of immunosuppressants. Normal liver function was observed, while transient abnormal kidney function was occurred in one recipient.

Conclusion: The prevalence of *H. pylori* infection was 19.6% among the LT recipients, which increased with the postoperative time. With BQT, *H. pylori* eradication was safe and effective in LT recipients.

KEYWORDS

bismuth-containing quadruple therapy, eradication therapy, *Helicobacter pylori*, immunosuppressant, liver transplantation, outcome

1 | INTRODUCTION

It has been reported that the incidence of de novo gastric cancer is significantly increased in liver transplant (LT) recipients, and the reported standardized incidence ratio is as high as 1.06–12.9.^{1–6} This phenomenon is more obvious in areas with a high incidence of gastric cancer, such as east-Asia, though the molecular mechanism is still unknown. At least 90% of non-cardia gastric cancers are related to *Helicobacter pylori* infection, and much evidence has shown a relationship between the increased incidence of gastric cancer (both intestinal type and diffuse type) and *H. pylori* infection.^{7,8} In recent years, it has been clearly established from many clinical trials that *H. pylori* eradication reduces the risk of gastric cancer, particular in patients with long-term follow-up.^{9–11} Therefore, it is necessary to know the prevalence of *H. pylori* infection in LT recipients and prescribe eradication therapy to decrease the risk of gastric cancer. However, clinical *H. pylori* eradication among LT recipients has rarely been reported.^{12,13} Here, we report the preliminary experience of eradication of *H. pylori* in liver transplant recipients from a single center.

2 | METHODS AND MATERIALS

2.1 | Patient enrollment

Liver transplant recipients who were regularly followed up in the Affiliated Hospital of Qingdao University and consented to receive a 13C-urea breath test (13-UBT) were recruited prospectively between February 2018 and July 2020; these patients were named the LT group. Meanwhile, a group of patients who received screening with 13-UBT in our medical examination center during the same period were chosen as the control group with propensity score matching. The control subjects were age- and sex-matched with the LT patients at a ratio of 1:3. Patients of both groups in our study had been living in Qingdao since birth and had similar diets and living habits. Data on the LT recipients included age, gender, indication for liver transplantation, date of operation, upper digestive tract symptoms, history of *H. pylori* eradication, and history of malignant tumors of the digestive system.

This study was approved by the Ethical Affairs Committee of the Affiliated Hospital of Qingdao University, and the study adhered to the tenets of the Declaration of Helsinki, No. QYFYWZLL25994. Written informed consent was obtained from the patients or guardians for 13-UBT and treatment of *H. pylori* infection if present.

All liver transplant recipients underwent classical orthotopic LT with liver grafts from deceased donors. The immunosuppressive regimen after LT was mainly based on tacrolimus; a few patients received a sirolimus- or cyclosporine-based immunosuppressive regimen, and mycophenolate mofetil was combined as necessary to prevent acute rejection. The dose of the immunosuppressive drug and the most recent blood concentration of immunosuppressive drugs were recorded.

2.2 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) written consent for 13-UBT; (b) without severe comorbidities and life expectancy longer than 1 year; (c) liver transplantation performed at least 3 months before 13-UBT; and (d) complete clinical data and good adherence to follow-up.

The exclusion criteria were as follows: (a) previous diagnosis of malignant gastrointestinal tumors; (b) severe digestive symptoms (eg, hematochezia, hematemesis, and melena); (c) history of gastroduodenal surgery; and (d) history of *H. pylori* eradication therapy.

2.3 | 13C-urea breath test

The 13C-urea breath test is a noninvasive and very accurate test for the diagnosis of *H. pylori* infection. The tests were conducted using a 13-UBT analyzer according to the manufacturer's protocol. To reduce false-negative results, all patients were asked to fast for at least 4 hours and to not have taken proton pump inhibitors (PPIs) or antibiotics for one month before examination.

2.4 | *H. pylori* eradication therapy

Bismuth-containing quadruple therapy (BQT, esomeprazole 20 mg + clarithromycin 500 mg + amoxicillin 1 g + bismuth 220 mg, twice daily for 14 days) was used for treatment of all patients with documented *H. pylori* infection. Eradication of *H. pylori* was assessed with the 13-UBT one month after therapy. During *H. pylori* eradication therapy, blood concentrations of immunosuppressive agents were monitored on days 1, 4, 7, 15, 18, and 24, and the dose of the drugs was adjusted according to the results to prevent excessive fluctuation of blood concentrations by 2020. After 2020, immunosuppressants was reduced to one-third of what they were before eradication therapy. Blood concentrations of immunosuppressive agents were monitored on days 1, 4, 8, 12, 15, and 18. Liver function and kidney function were monitored during treatment and 4 to 6 weeks after the treatment.

2.5 | Statistical analysis

Data are presented as means \pm standard deviation. Independent sample *t* tests were used for analysis of continuous variables. Categorical variables were compared using the chi-square test or the Fisher exact test. All statistical analyses were performed with SPSS version 19.0 (IBM). $p > 0.05$ was considered statistically significant.

3 | RESULTS

In total, 153 LT recipients and 459 healthy tested controls were recruited, and the demographic data of the two groups were presented

in Table 1. Among the 153 LT recipients, 115 received liver transplantation for hepatitis B-related end-stage liver diseases, 10 for primary biliary cholangitis, 10 for alcoholic cirrhosis, 3 for HCV-related liver diseases, 3 for drug-induced liver disease, 3 for autoimmune hepatitis, 3 for cryptogenic cirrhosis, 2 for Wilson's disease, 2 for hilar cholangiocarcinoma, 1 for polycystic liver, and 1 for hepatolithiasis. One hundred and twenty-seven of the LT recipients received a tacrolimus-based immunosuppressive regimen, 14 received a sirolimus-based immunosuppressive regimen, and 12 received a cyclosporine-based immunosuppressive regimen.

Although the body mass index (BMI) was similar between the two groups, the incidence of hypertension, diabetes mellitus, and hyperlipidemia was significantly higher in the LT recipients. In addition, the incidence of renal insufficiency was as high as 29.4% in LT recipients, and these data were 8.7% among the control group. Twenty-six (16.9%) of the LT recipients had mild digestive symptoms: intermittent epigastric pain ($n = 6$), regurgitation ($n = 6$), abdominal distention ($n = 5$), dyspepsia ($n = 4$), heartburn ($n = 3$), and belching ($n = 2$). The incidence of mild digestive disease was similar between the two groups, as well as gastroesophageal reflux disease (GERD). The prevalence of *H. pylori* infection was 19.6% (30/153) among the LT recipients, which was significantly lower than the control group (30/153 (19.6%) vs. 200/459 (43.6%), $p < 0.001$). For the LT recipients, the interval between the 13-C UBT to transplantation was 3.1 to 168.7 months, and the median interval was 31.9 months. Among the recipients who received LT in less than 1 year, 1–3 years, and more than 3 years, the prevalence of *H. pylori* infection was 10.6% (5/47), 17.5% (10/57), and 30.6% (15/49), respectively. The prevalence of *H. pylori* infection gradually increased after LT with

statistical significance ($p = 0.04$) (Figure 1). Digestive symptoms were present equally in LT patients with *H. pylori* infection and those without (7/30 vs. 19/123, $p = 0.219$).

Twenty-three of the 30 LT recipients who had *H. pylori* infection were treated with BQT for 14 days, while all of the 200 patients in control group received the same treatment. Successful eradication was achieved in 91.3% (21/23) of LT recipients versus 86.5% (173/200) of the control patients, as documented with the 13C-UBT ($p = 0.398$). Blood trough concentrations of immunosuppressants were recorded in 12 patients by 2020 (Figure 2). Ten of the 12 LT recipients were treated with tacrolimus; the other two were treated with sirolimus. Before eradication, the blood concentration of tacrolimus ranged from 2.2 to 7.2 ng/ml (Figure 2a), and the blood concentration of sirolimus in the two patients was 2.15 and 3.62 ng/ml, respectively (Figure 2b). Three days after *H. pylori* eradication, the blood concentrations of the immunosuppressants were 1.7–3.6 fold greater than baseline values. Adjustments in the dosages of immunosuppressive agents were applied to all twelve patients to decrease blood concentrations and prevent side effects. After 2020, four recipients were recorded with prophylactic immunosuppressant reduction, blood concentration was relatively stable without adjusting immunosuppressant during the process of eradication (Figure 3). Three of the LT recipients discontinued BQT on their own 8–11 days after therapy because of the elevated blood concentration of immunosuppressant, although no severe adverse effect was observed. Successful eradication was achieved in two of these three recipients. Lastly, another 4 LT recipient had not begun eradication therapy for personal reasons.

Adverse effects occurred in 12 of 23 LT recipients (52.2%) versus 42 of 200 control patients (21.0%), which was presented in Table 2. Although the adverse effects were more common in LT recipients, the frequency of adverse effects related to BQT was similar between the two groups (6/23 vs 42/200, $p = 0.370$). Six of the LT recipients had symptoms caused by increased blood concentrations of immunosuppressants, included headache, hypertension, insomnia, and irritability; all of them occurred before 2020 and resolved or diminished after dose reduction of the immunosuppressants. At the end of treatment (day 15), the mean dose of immunosuppressants was one-third to one-half of that before *H. pylori* eradication, and the routine dose was reapplied within 10 days after the completion of therapy. LT recipients' liver function tests remained stable during the treatment; however, temporary abnormal kidney function was observed in one recipient, and completely recovery was observed one month later.

TABLE 1 Demographic data of the two groups

	LT group (N = 153)	Control group (N = 459)	p-Value
Age ($\bar{x} \pm s$)	51.7 \pm 9.5	52.3 \pm 10.2	0.522
Sex (F/M)	30/123	97/362	0.391
BMI ($\bar{x} \pm s$)	23.11 \pm 3.25	23.76 \pm 2.85	0.286
Hypertension, n (%)	55 (35.9%)	113 (24.6%)	0.005
Diabetes mellitus, n (%)	49 (32.0%)	55 (11.9%)	<0.001
Hyperlipidemia, n (%)	60 (39.2%)	137 (29.8%)	0.021
Renal insufficiency ^a , n (%)	45 (29.4%)	40 (8.7%)	<0.001
Mild digestive symptom, n (%)	26 (16.9%)	62 (13.5%)	0.175
GERD, n (%)	9 (5.9%)	30 (6.5%)	0.473
<i>Helicobacter pylori</i> infection, n (%)	30 (19.6%)	200 (43.6%)	<0.001

Abbreviations: BMI, body mass index; GERD, gastroesophageal reflux disease; LT, liver transplant.

^aGlomerular filtration rate <60 ml/min/1.73 m².

4 | DISCUSSION

Our study showed that the prevalence of *H. pylori* infection was significantly lower in LT recipients than in the general population, and a steadily increasing trend was observed during the 3 or more years after LT with a significant difference observed (10.6% in <1 year, while 30.6% in >3 years). *H. pylori* eradication therapy was effective

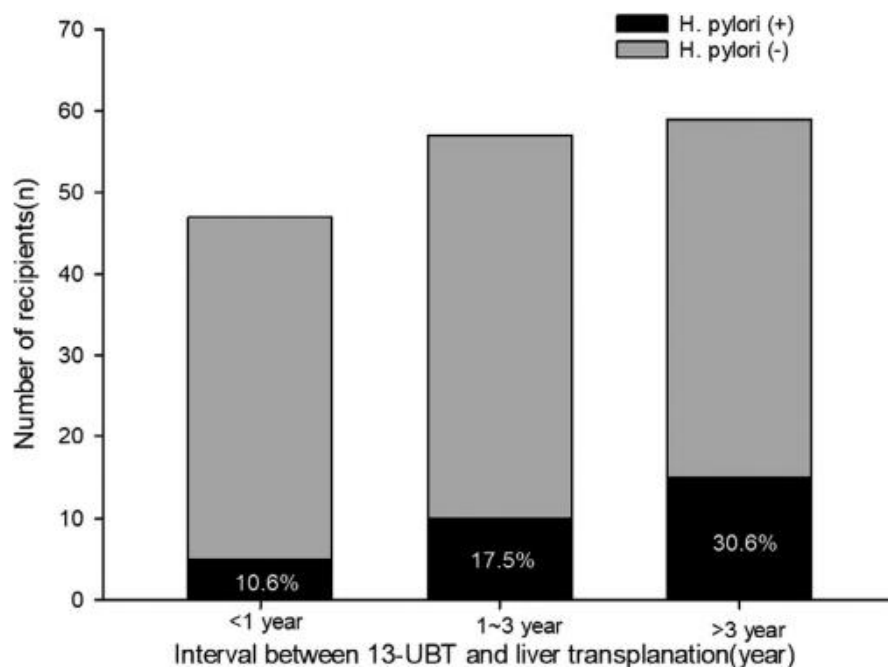


FIGURE 1 The trend of *Helicobacter pylori* infection after liver transplantation

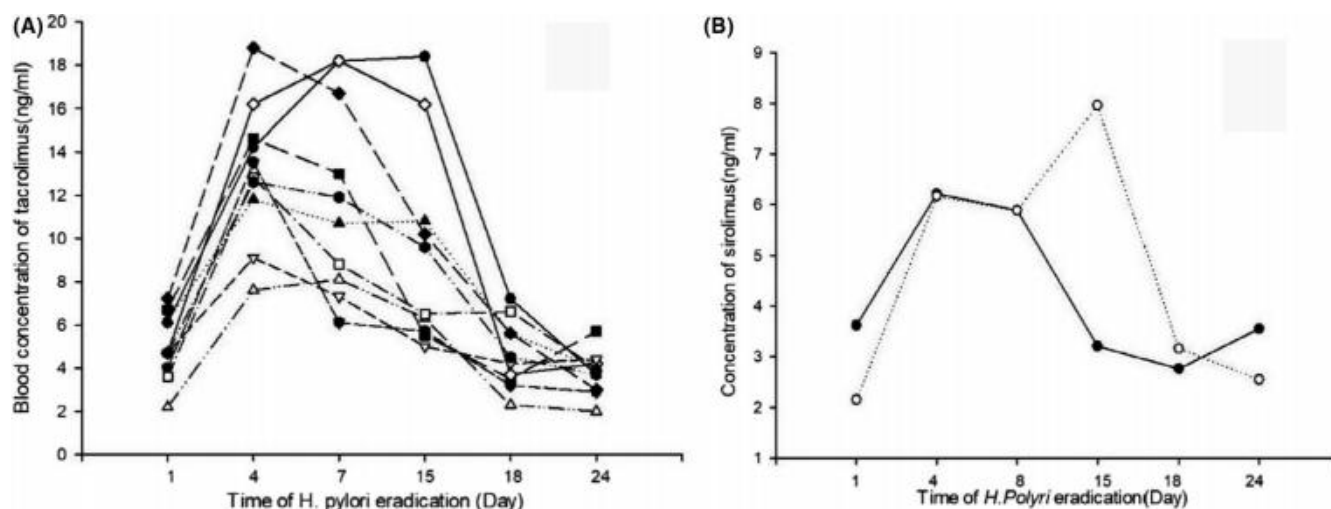


FIGURE 2 Concentration of immunosuppressive agents (A: Tacrolimus and B: Sirolimus) during the process of *Helicobacter pylori* eradication with adjusting immunosuppressants during the process

in LT recipients, and special attention should be paid to the interaction between drugs during this process.

In our study, the prevalence of *H. pylori* infection was 19.6% in LT recipients, which was a little higher than the previous reported prevalence of 5.6% to 18.6%,¹⁴⁻¹⁶ and significantly lower than in the control group. Although epidemiological investigations into *H. pylori* infection after liver transplantation are limited, and there is discrepancy caused by different diagnostic methods (eg, histology, urea breath test, and serology), a significantly lower prevalence of *H. pylori* infection was observed in LT recipients compared with the general population and patients with cirrhosis (50%).^{15,17} A longitudinal comparative study of 29 LT recipients found that the preoperative prevalence of *H. pylori* infection was 50%, which declined to 5.6% eight weeks after transplantation.¹⁵ This phenomenon could be explained by the fact that LT recipients took several advanced

antibiotics during the perioperative period, and PPIs were usually prescribed to prevent gastrointestinal bleeding at the same time, which may have been equivalent to *H. pylori* eradication therapy. At present, the necessity and efficacy of *H. pylori* eradication in liver transplant candidates are unclear, but our study suggests that *H. pylori* eradication therapy before liver transplantation should not be advocated because of the high spontaneous elimination rate of *H. pylori* after LT.

Our study found that the prevalence of *H. pylori* infection was gradually increased with the time after liver transplantation, from 10.6% in recipients at less than one year to the 30.6% in recipients after more than three years. This phenomenon indicated that a high recurrence rate of *H. pylori* infection may exist in LT recipients; it has been reported that the international average annual recurrence rate of *H. pylori* infection after eradication therapy is 4.3% (95% CI,

FIGURE 3 Concentration of immunosuppressive agents during the process of *Helicobacter pylori* eradication with adjusting immunosuppressants before eradication therapy

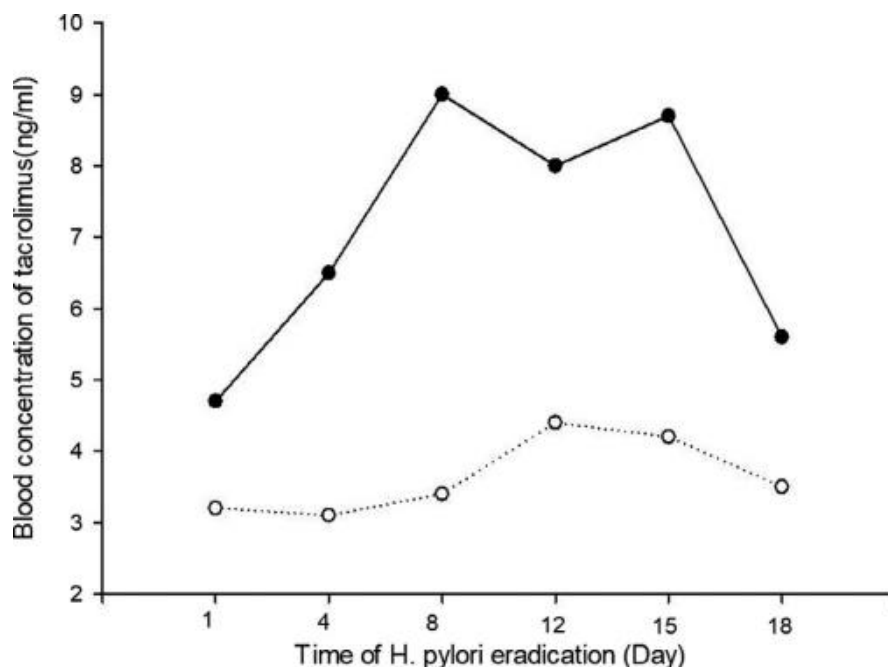


TABLE 2 Occurrence of new or aggravated symptoms during eradication therapy in the two groups

	LT group (N = 23)	Control group (N = 200)	p-Value
Adverse effect, n (%)	12 (52.2%)	42 (21.0%)	0.007
Nausea/ vomiting, n (%)	1 (4.3%)	12 (6.0%)	0.603
Dry mouth, n (%)	0	2 (1%)	0.804
Epigastric pain, n (%)	2 (8.7%)	5 (2.5%)	0.155
Dyspepsia, n (%)	0	8 (4.0%)	0.412
Heartburn, n (%)	2 (8.7%)	2 (1%)	0.054
Bloating, n (%)	0	4 (2%)	0.645
Belching, n (%)	0	2 (1%)	0.804
Diarrhea, n (%)	0	3 (1.5%)	0.720
Constipation, n (%)	1 (4.3%)	3 (1.5%)	0.355
Skin rash, n (%)	0	1 (0.5%)	0.897
Headache, n (%) ^a	3 (13.0%)	0	0.001
Hypertension, n (%) ^a	3 (13.0%)	0	0.001
Insomnia, n (%)	1 (4.3%)	0	0.103
Irritability, n (%)	2 (8.7%)	0	0.010

Abbreviation: LT, liver transplant.

^aThese three LT recipients suffered from headache were also proved to have hypertension.

4%–5%),¹⁸ and it varies from place to place, associated with local socioeconomic levels and the local *H. pylori* infection prevalence. For example, the recurrence rate of *H. pylori* infection after eradication in Colombia has been reported to be as high as 18.1%, while it is only 0.6% in the Netherlands.¹⁹ Recently, a study in China showed

that the 1-year and 3-year recurrence rates of *H. pylori* infection after eradication therapy are 1.75% and 4.61%, respectively.²⁰ Poor hygienic conditions in restaurants and contact with other infected individuals are thought to be risk factors of *H. pylori* recurrence, while family members receiving treatment may reduce the risk of recurrence.^{20,21} Considering the immunocompromised status after transplantation and the high prevalence of *H. pylori* infection among the general population in China (50%), the risk of *H. pylori* recurrence among LT recipients may be significantly elevated compared with the general population. In addition, a significant proportion of LT recipients have metabolic syndrome, which may also increase the likelihood of *H. pylori* re-infection.^{22,23} Therefore, screening and treating infected family members and improving sanitary conditions are recommended to reduce the risk of *H. pylori* recurrence in LT recipients.

With the frequency and long-time survival rates of liver transplantation increasing, de novo malignancies have become an important factor threatening recipients' survival. De novo gastric cancer has been found to be one of the most common malignancies in east-Asian nations, such as Korea and Japan.^{3,6} Moreover, the prognosis of de novo gastric cancer after LT is relatively poor due to the immunosuppressive status.¹ In recent decades, the relationship between *H. pylori* infection and gastric cancer has been fully documented, and *H. pylori* eradication therapy has been proven to decrease the risk of gastric cancer by 46%–54%.^{9–11} Currently, *H. pylori* “screen-and-treat” strategies are recommended in communities at high risk of gastric cancer in the Maastricht IV guidelines.²⁴ Although the mechanism of de novo gastric cancer is unknown and it is unclear whether *H. pylori* is responsible for the steep rise in gastric cancer after LT, the monitoring of *H. pylori* status regularly with highly sensitive methods and *H. pylori* eradication are recommended for LT recipients to minimize the incidence of de novo gastric cancer.

Clinical eradication of *H. pylori* among LT recipients is rare. In the general population, the efficacy of *H. pylori* treatment regimens has

decreased because of increasing antibiotic resistance.²⁵ At present, BQT is recommended as a first-line treatment for eradicating *H. pylori* in China due to its high efficacy, safety, and tolerance.²⁶ It has been reported that the eradication rate of BQT ranges from 85% to 94% in the general population.²⁶ Additionally, these four drugs have few adverse effects on liver and kidney function; therefore, BQT was prescribed to eradicate *H. pylori* in LT recipients in our study. The majority of recipients received LT due to end-stage liver diseases, so a medical history of multiple antibiotics was an unavoidable issue, and a long duration of therapy (14 days) was chosen to improve the success rate. In agreement with the general population, the eradication rate in LT recipients was 91.3% (21/23), which indicated that BQT was effective in LT recipients, even if a considerable portion had *H. pylori* reinfections. In fact, a previous study has revealed that BQT is effective for *H. pylori* reinfection.²⁷

No severe adverse effects that led to discontinuation were observed in our study; however, the blood concentrations of immunosuppressant agents were sharply increased during *H. pylori* eradication treatment, which were caused by drug interactions. Most immunosuppressants, such as tacrolimus and cyclosporine, are calcineurin inhibitors and substrates of cytochrome P450 3A (CYP3A). Clarithromycin, a commonly used antibiotic for *H. pylori* eradication, strongly inhibits CYP3A and increases the blood concentrations of those immunosuppressants. Besides, the incidence of renal insufficiency was higher than control group in our study, which might also lead to an increasing supratherapeutic levels of immunosuppressant. Recently, a report showed that the trough level of cyclosporine was significantly increased in a LT recipient treated with a clarithromycin-containing regimen.¹² Furthermore, polymorphisms of CYP3A5 were tested in LT recipients in our study; however, no significant difference was observed in the extent of immunosuppressant concentration arising among recipients with different polymorphisms at the first test after initiation of *H. pylori* eradication therapy. It was speculated that the inhibition of Clarithromycin to CYP3A5 was stronger than the effect of the differentiation of CYP3A5 polymorphisms to immunosuppressant metabolism. Therefore, prophylactic immunosuppressants reduction was given to avoid excessively elevated blood concentration after 2020, and a good response was observed. As our preliminary results confirmed that under the premise of closely monitoring and pre-emptive drug reduction, the quadruple therapy containing clarithromycin could obtain eradication rate as to 91.3% with acceptable side effects, it was strongly recommended that, either very close monitoring of immunosuppression level or adjustment of immunosuppression before starting the treatment especially in the renal insufficiency patients, would be able to maximize security during the *H. pylori* eradication treatment in LT recipients.

Our study has several limitations. First, the sample size was relatively small. In the future, the sample size will be expanded to verify our conclusions. Second, propensity score matching was used to set the control group, which may have introduced selection bias. Third, this was a cross-sectional study and lacked longitudinal comparisons, so it was impossible to determine the trend of *H. pylori* infection with the time after liver transplantation. Despite these limitations, our

study provides preliminary results for *H. pylori* infection in LT patients and the experience of *H. pylori* eradication.

5 | CONCLUSIONS

Our study showed that the prevalence of *H. pylori* infection was 19.6% in LT recipients, which gradually increased with the time the after transplantation. *H. pylori* eradication therapy with BQT was safe and effective in LT recipients, and adjusting immunosuppressants to one-third of what they were before eradication therapy was suggested to reduce the adverse effects caused by their elevated blood concentrations.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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