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Eradication of *Helicobacter pylori* that contributes to hepatogenic ulcer is beneficial to the healing of hepatogenic ulcer

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Abstract

Background This study aimed to explore the role of *Helicobacter pylori* (Hp) eradication in patients with hepatogenic ulcer (HU).

Methods Patients with HU, patients with liver cirrhosis without peptic ulcer and patients with functional dyspepsia (FD) were selected and the relationship between complications of liver cirrhosis and Hp infection in HU patients was evaluated retrospectively. Furthermore, 60 HU patients with Hp infection were randomly divided into the treatment group with rabeprazole plus amoxicillin and levofloxacin, and the control group with rabeprazole alone and the therapeutic effects then were recorded. This trial was registered at the China Clinical Research Registration Center (Trial registration number: ChiCTR2200061355, 2022/06/21).

Results The Hp positive rate in the HU group was significantly higher compared with the liver cirrhosis without ulcer group or the FD group. Moreover, the positive rate of Hp in HU patients with mild esophageal varices was higher than that in HU patients with moderate and severe esophageal varices. Additionally, the rate of Hp eradication and ulcer healing in the treatment group was significantly higher than that in the control group. Importantly, the remission time of ulcer-related symptoms in the treatment group was shorter compared with the control group.

Conclusion Hp is a contributor to HU and an integrated strategy consisting of rabeprazole, amoxicillin and levofloxacin is effective in the treatment of HU, providing a potential application for HU patients.

Keywords Cirrhosis, Peptic ulcer, Helicobacter pylori

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Introduction

Hepatogenic ulcer (HU), a peptic ulcer (PU) that occurs on the basis of liver cirrhosis, is a leading cause of upper gastrointestinal bleeding in patients with liver cirrhosis, which is featured by epigastric pain, acid regurgitation, belching, abdominal distension, anorexia, etc [1, 2]. However, the majority of these symptoms are easily masked by the manifestations of cirrhosis itself [3]. Unfortunately, it is worth noting that general acid suppression therapy is difficult to achieve satisfactory results, which has been a difficult issue in clinical treatment [4]. Therefore, alternative therapeutic strategies, especially easy-to-promote solutions, are urgently needed.

Helicobacter pylori (Hp) is responsible for gastritis, PU and gastric cancer, transmission routes of which include oral-oral or fecal-oral transmission [5, 6]. Hp eradication exerts an essential role in the treatment and prevention of PU [7]. Nowadays, the majority of used first-line therapies do not achieve expected results in more than 20% of patients, which might be attributed to a growing body of factors that affect the ability of patients to cure Hp is infection antibiotic resistance which is growing evidently in several geographic areas [8, 9]. More important, it should be noted that the pathogenesis of HU is not completely the same as that of common PU, and it is associated with multiple factors, such as portal hypertension and liver function, but the exact mechanism is still unclear [10, 11]. Notably, whether Hp is the cause of HU remains controversial.

In the present study, we identified that it was Hp infection that was a high-risk factor that resulted in HU. Moreover, the rate of Hp eradication and ulcer healing in the group of rabeprazole combined with amoxicillin and levofloxacin was remarkably higher than that in the group of rabeprazole alone. The present work, collectively, paves a new road to developing an alternative treatment option for HU patients with Hp infection.

Materials and methods

Experimental procedures

The present study included two experiments. We collected HU patients, liver cirrhosis without PU, and patients with functional dyspepsia (FD) to retrospectively analyze the relationship between Hp and HU in experiment 1. In experiment 2, recollected additional HU patients were randomly divided into treatment group and control group to prospectively evaluate the effect of Hp eradication on HU.

Experiment 1: the relationship between Helicobacter pylori and hepatogenic ulcer

General information

From January 2010 to December 2019, a total of 80 patients with HU were enrolled, including 52 males and 28 females, aged 22–69 years, with an average of 48.2 years; 48 patients with Child-Pugh class A and 32 patients with Child-Pugh class B. 45 cases of mild esophageal varices and 35 cases of moderate to severe esophageal varices. All patients with liver cirrhosis were diagnosed by clinical manifestations and laboratory tests, in addition to imaging examinations (partially confirmed by pathology). Patients with primary heart, lung, brain, kidney and other serious diseases or digestive tract malignant tumors were excluded. The diagnosis of PU was active ulcer under endoscopy; the diagnosis of Hp infection was evaluated via ^{14}C urea breath test. In addition, 80 patients with liver cirrhosis without PU and 80 patients with FD were selected as the control group. All patients with FD were based on Rome III criteria: one or more of epigastric pain, epigastric burning, postprandial fullness, and early satiety symptoms, presenting a persistent or recurrent chronic course. The disease duration was > 6 months, and the symptoms persisted for the past 3 months. The above symptoms cannot be relieved after defecation. Hepatobiliary, pancreatic, and spleen diseases were excluded by abdominal color doppler ultrasonography, and no obvious abnormality was found in gastroscopy. All subjects did not take antibiotics and non-steroidal anti-inflammatory drugs in recent one month (as nonsteroidal anti-inflammatory drugs affect ulcers), and did not take acid inhibitors and gastric mucosal protectors (including bismuth) for two weeks.

Upper gastrointestinal endoscopy

Routine gastrointestinal endoscopy was performed with an Olympus EVIS260 electronic gastroscope, and all diagnoses were confirmed by more than 2 endoscopists. A piece of gastric mucosa tissue was taken from the gastric antrum within 3 cm far from the pylorus with the same size of biopsy forceps for rapid urease test (RUT). To be specific, the RUT kit (Fujian Sanqiang Biochemical Company, Fujian, China) was placed at room temperature for 30 min. Subsequently, the cover of the substrate enzyme labeling strip was removed and 100 μL of the enzymatic reaction solution was then added to each well. Finally, the collected gastric mucosal tissues were placed into the drug solution with a specimen stick. The results were observed under natural light after 5 min of incubation. Negative: the color of the medicinal solution at the edge of gastric mucosal tissue is yellow without color reaction. Positive: the color of the medicinal solution at the edge of gastric mucosal tissue is light red or rose red.

^{14}C Urea breath test

Subjects were subjected to ^{14}C urea breath test via ^{14}C-UBT mass spectrometer and urea ^{14}C breath test box (Shenzhen China Nuclear Headway Biotechnology Co., Ltd, Shenzhen, China) to evaluate Hp infection one day

after gastroscopy. Briefly, all patients were tested on an empty stomach and gargled followed by taking 1 capsule of 14 C-urea. After sitting for 25 min, the patients were blown into the liquid scintillation bottle containing CO_2 absorbent through a gas tube. The color of the CO_2 absorbing agent has changed to colorless or it has taken 5 min, but the color has not completely faded, and the tester stopped blowing air. A total of 4.5 mL of diluted scintillation fluid was added to the sample vial. After fully dissolving in the sample vial, the ^{14}C radioactivity (dpm) of the sample was measured on a flash meter for 2 min. On the condition that ^{14}C-UBT > 100 dpm, it was determined to be Hp positive.

Hp infection diagnostic criteria

Patients who met the positive criteria of RUT and ^{14}C urea breath test criteria were considered positive for Hp infection. Patients who were negative on both tests were judged to be negative for Hp infection.

Experiment 2: effect of Helicobacter pylori eradication on hepatogenic ulcer

General information and pharmacological intervention

In total, 60 patients with Hp-positive HU were selected from June 2022 through June 2023, including 39 males and 21 females, aged 25–68 years, with an average of 49.6 years. The inclusion criteria were patients diagnosed with HU and Hp infection. Exclusion criteria: (1) Non-HU and Hp infection; (2) Patients with gastrointestinal cancer; (3) Taking antibiotics and non-steroidal anti-inflammatory drugs within the last month, and acid inhibitors and gastric mucosal protectants within two weeks. HU patients were randomly divided into the treatment group and control group, with 30 cases in each group. The age, gender, liver function grade, ulcer location, number and combined bleeding of the two groups were comparable. Compared to bismuth-based quadruple therapy, standard triple therapy exerts a lesser impact on liver function and is thus more appropriate for patients with hepatic conditions. Consequently, we selected the standard triple therapy for the eradication of Hp. The treatment group was given rabeprazole (20 mg), amoxicillin (1.0 g) and levofloxacin (0.2 g) twice a day for 2 weeks. The control group was treated with rabeprazole (20 mg), twice a day, orally for 2 weeks. All cases were given appropriate liver protection and nutritional support according to the clinical situation. Gastroscopy and ^{14}C urea breath test were rechecked one month after the end of the course of treatment.

Criterion standard for the effect of pharmacological intervention

Healing: the symptoms disappeared, and the ulcer healed or showed scar stage by gastroscopy. Effective: the symptoms basically disappeared, and the ulcer area was reduced by more than 1 / 2. Ineffective: no improvement in symptoms, less than 1 / 2 reduction in ulcer area, or no significant change. Healing plus effectiveness is the total effective rate. The eradication standard of Hp was ^{14}C urea breath test turned negative. Adverse reactions during treatment were recorded.

Statistical treatment

SPSS 18.0 software (IBM, SPSS, Chicago, IL, USA) was used for processing and analysis. The measurement data were expressed in mean ± standard deviation, and Student's *t*-test was used between groups; the counting data were expressed in rate (%), and the χ^2 test was used for comparison between groups.

Results

Hp infection is a high-risk factor that is responsible for HU

Due to a paucity of strong evidence that Hp has given the contribution of HU has been reported, we decided to attach importance to the relationship between Hp and HU (Fig. 1). At first, we collected patients with HU, liver cirrhosis without PU, and FD were selected, with 80 cases in each group. As shown in Table 1, the Hp-positive infection rate in the HU group (80.00%) was significantly higher than that in the cirrhosis without ulceration group (60.00%) or the FU group (43.75%). Subsequently, liver function classification and Hp infection in HU patients were analyzed. The results of the statistical analysis witnessed that the Hp-positive patients with Child-Pugh class A and B were 79.17% (38/48) and 81.25% (26/32), nevertheless, in which no significant differences were found. Furthermore, we compared the difference between Hp infection rates in HU patients with different degrees of esophageal varices. Interestingly, the positive rate of Hp in patients with mild esophageal varices was 88.89% (40/45), which was significantly higher than that in patients with moderate and severe esophageal varices (68.57%, 24/35). Collectively, we might put forward a conclusion that the development of HU was attributed to Hp infection, which was supported by the observation that HU patients displayed a higher Hp infection rate.

Anti-Hp treatment can effectively improve HU on the basis of liver protection and acid suppression

It has been well-established that patients with PU will be beneficial from therapy in the treatment of Hp infection [12]. However, there is still controversy as to whether eradication therapy is required for Hp-positive HU patients. Intending to cope with this issue, we divided the 60 HU patients into the treatment group with rabeprazole plus amoxicillin ($n = 30$) and the control group with rabeprazole alone ($n = 30$), in which we recorded the time it took for ulcer-related symptoms to resolve. Based on

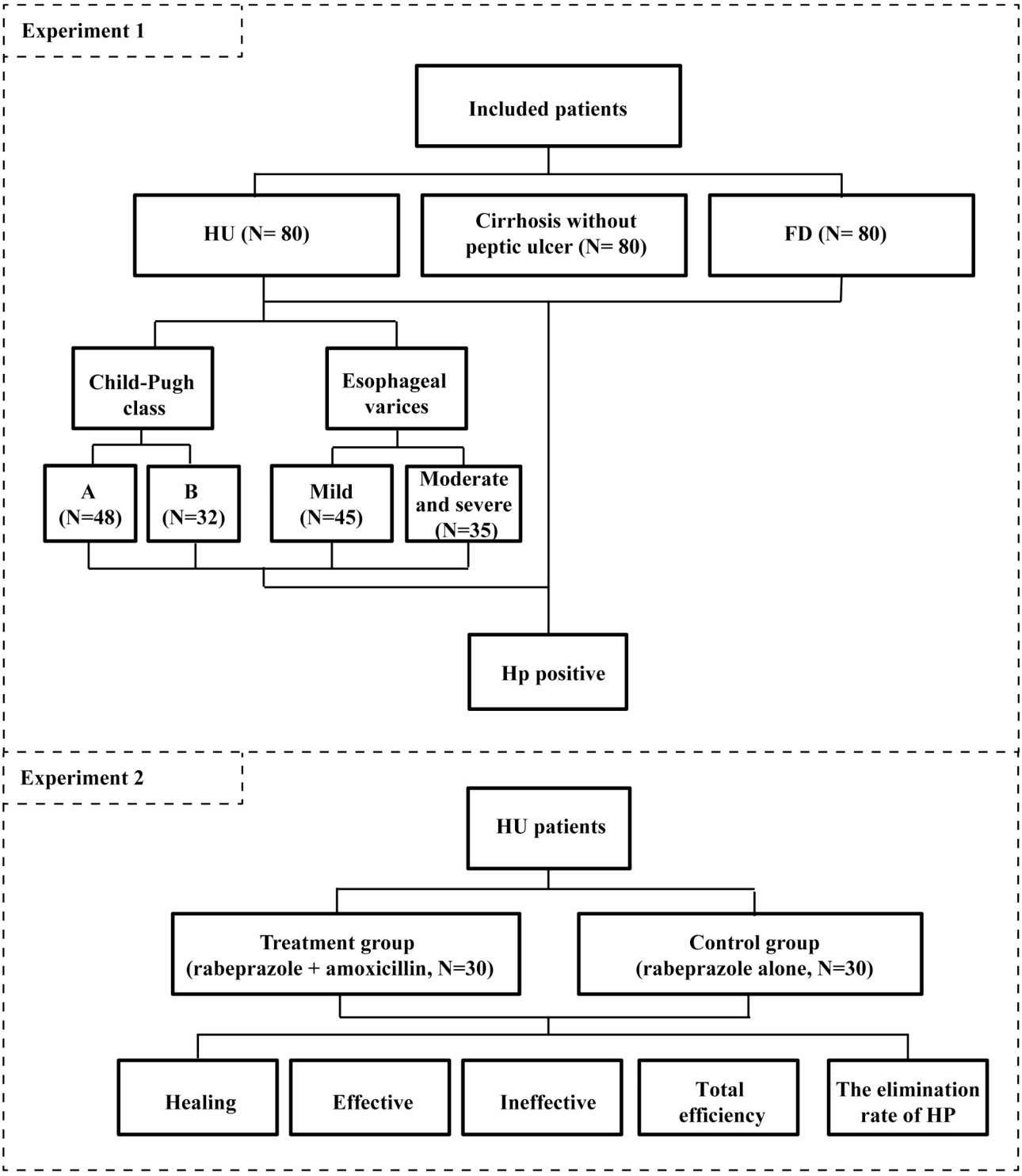

Fig. 1 Flow chart of this research program

observations and evaluations made in the course of the study, it was suggested that the remission time of ulcer-related symptoms in the treatment group was 4.2 ± 1.9 days and that in the control group was 7.8 ± 3.6 days, the difference was statistically significant ($P < 0.05$). As shown in Table 2, it was observed that the number of healing, effective, and ineffective patients in the treatment group were 18, 10, and 2, respectively; while the number of healing, effective, and ineffective patients in the control group were 14, 8, 8, respectively. Statistical analysis

Table 1 Comparison of Hp infection, liver function and esophagogastric varices grading (n, %)

Group	Hp positive	Child-Pugh class A	Child-Pugh class B	Mild esophageal varices	Moderate and severe esophageal varices
HU	64/80 (80.00%)	38/48 (79.17%)	(26/32)81.25%	40/45 (88.89%)	24/35 (68.57%)
Cirrhosis without ulceration	48/80 (60.00%)	-	-	-	-
FD	35/80 (43.75%)	-	-	-	-
Comparisons	HU vs. Cirrhosis without ulceration	HU vs. FD	Child-Pugh (A vs. B)	Mild vs. Moderate and severe	-
P values	0.009	0.000	0.955	0.049	-

Table 2 Comparison of efficacy between two groups

Group	Healing	Effective	Ineffective	Total efficiency	The elimination rate of HP	*P*
Treatment group (*N* = 30)	18 (60%)	10 (33.33%)	2 (6.66%)	93.3%	26 (86.67%)	$P < 0.05$
Control group (*N* = 30)	14 (46.67%)	8 (26.67%)	8 (26.67%)	73.3%	5 (16.67%)	

exhibited that the total efficiency in the treatment group (93.3%) was higher compared with that in the control group (73.3%). In addition, the elimination of the treatment group (86.67%) was more effective than in the control group (16.67%). These results sustained the concept that the therapeutic effect of the treatment group with rabeprazole plus amoxicillin was better than that of the control group with rabeprazole alone.

Hp treatment of HU does not increase the incidence of abnormal adverse reactions

After clarifying the difference in treatment between the two groups, we also analyzed the adverse reactions of these groups. In the treatment group, nausea occurred in 3 cases, dry stool in 3 cases, rash in 1 case and fatigue in 1 case. The incidence of adverse reactions was 20.0%. In the control group, nausea occurred in 3 cases, dry stool in 2 cases, fatigue in 1 case, and leukocyte decline in 1 case. The incidence of adverse reactions was 17.5%. There was no statistical significance between the two groups. To recapitulate briefly, anti-Hp treatment for HU does not increase the risk of abnormal adverse effects.

Discussion

HU is a common complication of liver cirrhosis, which is a major global health care challenge with poor long-term clinical outcomes. Unfortunately, about 65% of patients lack typical clinical symptoms [13, 14], giving rise to untimely treatment intervention. At present, the exact mechanism of HU has not been fully clarified, which is considered to be related to multiple factors, including portal hypertension, the Child-Pugh class of liver function and endotoxemia [15–19]. In addition, the pathogenesis of HU is also considered to be related to Hp infection, immune complex deposition of hepatitis virus and other factors [15, 20]. Studies conducted in the 1960s demonstrated that severe liver disease could result in the development of fatal ulcers [21]. Thiel (1978) elaborates on the theories and evidence concerning HU, emphasizing the intricate relationship between liver pathology and gastrointestinal ulcer formation [22]. Hp infection is associated with a spectrum of digestive diseases, including chronic gastritis, PU, and gastric cancer. Infection of 8-month-old C57BL/6 mice with Hp resulted in severe gastric mucosal inflammation, and the Hp was reaching to the hepatobiliary system, leading to hepatitis [23]. Patients with cirrhosis exhibit a markedly higher prevalence of Hp infection compared to the general population [24]. Moreover, the virulence of Hp in cirrhotic patients is enhanced, causing more substantial damage to the gastric mucosa and potentially exacerbating ulcer formation [25]. In the present study, our results demonstrate for the first time that the Hp-positive infection rate in the HU group was significantly higher than that in the cirrhosis without ulceration group or the FU group. Furthermore, the treatment effect of Hp eradication and ulcer healing in the group of rabeprazole combined with amoxicillin and levofloxacin was significantly better than that in the group of rabeprazole alone.

Furthermore, our results suggest a higher proportion of Hp infection in patients with mild esophageal varices compared to moderate and severe cases. Esophageal varices are caused by hypertension (portal hypertension) of the blood vessels in and around the liver. Gastric mucosal atrophy caused by Hp is accompanied by decreased gastric acid secretion, and its infection also appears to prevent bleeding, as is the clinical practice of acid suppression in patients with upper gastrointestinal bleeding to maintain platelet aggregation and coagulation. The results of a Japanese study have shown that Hp infection

has a certain protective effect on esophagogastric variceal bleeding by inducing atrophic gastritis and accompanying low acidity in patients with cirrhosis and portal hypertension [26]. However, this effect has not been consistent in other studies, so further clinical research and exploration are needed.

Of all the treatments of HU, it is well-accepted that based on the recovery of liver function, measures such as acid-suppressant medication therapy, gastric mucosal protective agent and reducing portal pulse pressure. However, there is still controversy about whether Hp-positive patients need eradication treatment. Villalan R et al. [27] insists that the eradication of Hp could not reduce the residual rate of ulcers in patients with liver cirrhosis, suggesting that Hp infection may not be an important risk factor for ulcer in patients with liver cirrhosis. It is considered that routine eradication of Hp may not be necessary for patients with HU; Tzathas C et al. [28] identify that the eradication of Hp could not protect all patients with liver cirrhosis from ulcer recurrence and most HP negative ulcer recurrence. However, Shen et al. [29] believe that early eradication of Hp in patients with liver cirrhosis can reduce the risk of recurrent PU, and eradication of Hp is the main method to treat patients with liver cirrhosis with infectious PU; Furthermore, Raffaele et al. [30] considers that Hp is the cause of PU and should be eliminated in patients with liver cirrhosis to reduce the risk of hemorrhagic anemia. Our previous research identified Hp infection can significantly reduce the level of EGF in gastric mucosa in patients with liver cirrhosis, and increase the level of PGE2 and TNF-α, but there is no significant change in IL-8, indicating that the infection of Hp in patients with liver cirrhosis not only weakens the defense function of gastric mucosa but also increases the factors affecting gastric mucosa. The combination of the two aspects makes the gastric mucosa of liver cirrhosis more fragile and prone to complications such as ulcers and bleeding. In this research, we found that HU patients exhibited a higher Hp infection rate, which highlighted the importance of Hp function as a high-risk factor that leads to the development of HU.

As a second-generation proton pump inhibitor, rabeprazole whose metabolism does not depend on cytochrome P450 and has little impact on liver function blocks gastric acid secretion by specifically inhibiting the H^+/K^+- ATPase proton pump of gastric parietal cells, which makes it suitable for the treatment of patients with liver disease [31]. Amoxicillin and levofloxacin are common anti-Hp drugs. Their combination with rabeprazole in the treatment of HP-positive common PU has achieved a good curative effect [32], but their treatment of HU has not been reported yet. The results of this study showed that the effective rate of ulcer healing and HP eradication rate of the observation group with anti-Hp treatment drugs in the treatment of HU are significantly higher than those of the control group without anti-Hp treatment drugs, indicating that anti-Hp treatment is beneficial to Hp eradication and the healing of HU. In addition, during the treatment of the two groups, no serious adverse reactions were found except that some cases had symptoms such as nausea and fatigue. Similarly, Li et al. [33] found that rabeprazole, levofloxacin and amoxicillin combined with Hp infection in gastric ulcer could effectively eradicate Hp, regulate the levels of inflammatory factors and improve clinical symptoms. Another study also showed that triple therapy had high clinical application value [34]. Taken together, based on protecting liver function and inhibiting gastric acid secretion, adding anti-Hp measures to treat HU has good curative effects and mild adverse reactions, which is worthy of further popularization and application.

Briefly, the present study suggests that Hp infection is an increased risk that brought about HU. Furthermore, our results indicate that an integrated strategy consisting of rabeprazole, amoxicillin and levofloxacin is effective in the treatment of HU, and the eradication of Hp is beneficial to the healing of HU, in which the novel analyses performed could potentially offer insights for the study of HU as well as the development of beneficial clinical treatments. Nevertheless, there are still some shortcomings, the most notable limitation of which is that the patients included are single-center samples, and more samples from different hospitals are needed to further validate these findings in the future.

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Author contributions
G. Q. designed the protocol and wrote the manuscript. L. F and M. W: edited and revised the manuscript. C. W., C. L. and S. H. analyzed and interpreted the data. Y. W. and S. L. rigorously revised for intellectual content. S. X. guided the methodology. All authors approved the final version.

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Data availability
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval
All participants were collected from the Handan First Hospital. This study was approved by the Ethics Committee of Handan First Hospital (2022-017) and was performed in accordance with the Declaration of Helsinki.

Patient anonymity and informed consent
This study was registered at Chinese Clinical Trial Registry (Chictr.org.cn, ChiCTR2200061355, 2022/06/21), which waived the need for consent forms because this was a retrospective study and has been approved by the Ethics Committee of Handan First Hospital.

Competing interests
The authors declare no competing interests.

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