Am J Transl Res 2024;16(8):4011-4019
www.ajtr.org /ISSN:1943-8141/AJTR0156876

Original Article

Analysis of factors associated with Helicobacter pylori infection in severe pancreatitis patients and its effect on patient's prognosis

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Received March 28, 2024; Accepted July 6, 2024; Epub August 15, 2024; Published August 30, 2024

Abstract: Objective: To analyze the factors related to Helicobacter pylori (Hp) infection in patients with severe acute pancreatitis (SAP) and to observe the effect of Hp on SAP, and to provide a reference for future clinical prevention and treatment of Hp infection in SAP. Methods: A retrospective analysis was performed on 77 SAP patients admitted to Pingxiang People's Hospital between January 2020 and February 2022, with 33 Hp-infected individuals as the Hp-positive group and the other 44 patients being without Hp infection served as the Hp-negative group. First, the related factors of Hp infection in SAP patients were analyzed with multiple Logistic regression. Subsequently, the Acute Physiology and Chronic Health Evaluation II (APACHE II), Bedside Index for Severity in Acute Pancreatitis (BISAP) and Modified CT Severity Index (MCTSI) scores, as well as the levels of C-reactive protein (CRP), white blood cell (WBC), procalcitonin (PCT) and immunoglobulins A/M/G (IgA, IgM, and IgG) were recorded for inter-group comparisons. The adverse reactions and hospitalization time were also recorded. Besides, a six-month follow-up was carried out after discharge, and patients' quality of life was evaluated using the Short-Form 36 Item Health Survey (SF-36). Results: Logistic regression analysis identified that history of Hp infection, long-term drinking, eating habits and history of biliary tract diseases were independent risk factors for Hp infection (all $P<0.05$). At 2 weeks after admission, higher APACHE II, BISAP and MCTSI scores were observed in Hp-positive group compared with Hp-negative group (all $P<0.05$). The Hp-positive group exhibited higher CRP, WBC and PCT levels while lower IgA, IgM and IgG levels during treatment compared to the Hp-negative group (all $P<0.05$). No difference was found in the incidence of adverse reactions between the two groups ($P>0.05$), but the hospitalization time of the Hp-positive group was significantly prolonged ($P<0.05$). The follow-up results determined better quality of life in the Hp-negative group, which resulted in higher SF-36 scores in various dimensions ($P<0.05$). Conclusion: The history of Hp infection, long-term drinking, eating habits, and history of biliary tract diseases are all independent risk factors for Hp infection. Hp infection exacerbates disease progression of SAP, adversely influences patients' recovery, impairs their immune function, and compromises their prognoses.

Keywords: Severe acute pancreatitis, Helicobacter pylori, disease progression, ICU, prognosis

Introduction

The incidence of acute pancreatitis (AP) has shown a rising trend, reaching 5-30 people out of every 100,000 in 2020, approximately 4 times that in 2010 [1]. Severe acute pancreatitis (SAP), characterized by rapid disease progression, multiple complications, complicated treatment, high cost and high mortality rate, accounts for about 15% of all AP with a mortality rate as high as 50% [2, 3]. SAP is also one of the primary conditions necessitating intensive care unit (ICU) admission, posing an enormous potential threat [4]. Realizing how to delay SAP progression and improve patients' prognosis is a major clinical focus [5].

Helicobacter pylori (Hp) is a Gram-negative, micro-aerobic bacterium characterized by its unipolar, multi-flagellated, and spirally curved shape, with bluntly rounded ends. It primarily resides in the stomach and duodenum. By synthesizing virulence factors such as adhesin and urease, it can overcome various factors unfa-

https://doi.org/10.62347/JKEF1700

vorable to settlement and parasitize on the gastric mucosal surface for a long time [6, 7]. In addition, Hp can directly cause gastric mucosal damage by secreting vacuolating toxins, heat-shock proteins, urease and other toxins, leading to inflammation and immune responses [8]. Recent research has increasingly demonstrated that Hp is not only closely related to the occurrence and development of gastrointestinal diseases, but also has a potential link with a variety of parenteral diseases (cardiovascular diseases, hematological diseases, nervous system diseases, etc.) [9, 10]. Moreover, Hp is considered to have an important influence on AP progression. For instance, Fox JG et al. found the presence of Hp in the bile and gallbladder tissue of patients with chronic pancreatitis [11], while Hori Y et al. indicated that vacuolating toxins secreted by Hp can inhibit pancreatic acinar synthesis and amylase secretion [12]. Hp infection is not rare in SAP patients, but there are few studies summarizing the factors associated with the development of Hp infection in SAP patients, and clinical references to develop preventive measures are still lacking. Meanwhile, the exact impact of Hp on the progression of SAP is still unclear, necessitating an in-depth study on the relationship between the two.

Therefore, the present study analyzed the factors related to Hp infection in SAP as well as the impact of Hp infection on disease progression of SAP patients, which will provide a reference for future clinical practice in the prevention and treatment of Hp infection in SAP.

Data and methods

Sample size calculation

The required number of cases for this study was calculated according to the formula sample size (N) = $Z^2 \times [P \times (1\text{-}P)]/E^2$. In this case, we set the statistic (Z) to 1.64, the probability value (P) to 0.5, and the error value (E) to 10%. Using this formula, the calculated sample size (N) was 67, indicating that the study required a minimum of 67 cases.

Study participants

Seventy-seven SAP patients admitted to the our hospital from January 2020 to February 2022 were selected for this retrospective study. After admission, Hp antigen in feces was detected by anti-Hp antibody enzyme-linked immunosorbent assay (ELISA), returning 33 positives (Hp-positive group) and 44 negatives (Hp-negative group). This study strictly followed the Declaration of Helsinki, and this study was approved by the ethical committee of Pingxiang People's Hospital institution.

Eligibility criteria

Inclusion criteria: 1) Patients with an age >18; 2) Patients who conformed to the diagnostic guidelines for SAP [13] and were diagnosed with SAP after examination; 3) Patients with complete medical records. Exclusion criteria: 1) Presence of other cardio-cerebrovascular diseases, immune deficiency, tumor, or mental illness; 2) Those with severe trauma; 3) Pregnant or lactating patients; 4) Referrals from other hospitals; 5) False or incomplete information.

Methods of treatment

Upon admission, all patients were fasted and received rehydration, psychological counseling, and medication, including growth inhibitors, antibiotics, and analgesics. For Hp-infected patients, proton pump inhibitors and antibiotics based on the results of drug sensitivity tests were given for 4-6 weeks.

Research data collection

The relevant case data of patients (age, sex, history of Hp infection, smoking, alcohol consumption, etc.) were collected to analyze the relevant factors affecting the occurrence of Hp infection in SAP. In addition, the Acute Physiology and Chronic Health Evaluation II (APACHE II) [14] and the Bedside Index for Severity in Acute Pancreatitis (BISAP) [15] at the time of admission (T0), 96 h (T1) and 2 weeks (T2) after admission were recorded. The APACHE II includes acute physiology score, age and chronic health subscales, with higher scores representing worse prognoses. The BISAP score includes blood urea nitrogen, disturbance of consciousness, systemic inflammatory response syndrome, age and pleural effusion, with a full score of 5. Higher scores indicate more severe SAP. Additionally, CT examination was performed, and the pancreatic inflammatory reaction, pancreatic necrosis and extrapancreatic complications were evaluated by referring to the modified CT Severity

Index (MCTSI; score range: 0-10) [16]. The score is proportional to the malignancy of SAP. Furthermore, fasting venous peripheral blood samples were collected from patients at the above-mentioned time points, for the detection of white blood cells (WBC) and C-reactive protein (CRP) by an automatic biochemical analyzer (Myriad BS-1000M), procalcitonin (PCT) by the immunoluminescence method (Roche Cobas e411), and immunoglobulin (IgA, IgM, IgG) levels by immunoturbidimetry (Tnano 700). Moreover, the adverse reactions (ARs; pancreatic infection etc.), mortality and hospitalization time (length of ICU stay and total hospitalization time) of the two groups were recoreded.

Follow-up for prognosis

A six-month follow-up was performed on patients via regular hospital review after discharge, with the interval between each review not exceeding one month. At the end of the follow-up, patients were scored by the Short-Form 36 Item Health Survey (SF-36) [17] for quality of life (QOL) assessment. The SF-36 includes eight dimensions, namely, physical functioning (PF), role-physical function (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). For each dimension, as well as the total QOL score, higher scores indicate better QOL.

Statistics and methods

Statistical analyses were made by SPSS 22.0 software. Count data, denoted by percentage (%), were compared using Chi-square test. Measurement data, expressed as mean ± standard deviation, were compared using independent sample t-test between two groups, while comparison among multiple time points was conducted using analysis of variance followed with Bonferroni post-hoc test. Logistic regression analysis was performed to analyze the related factors. Differences were considered statistically significant when $P<0.05$.

Results

Comparison of general information

Upon comparing the case data between the Hp-positive group and the Hp-negative group, no significant differences were found in age, body mass index (BMI) and gender composition (all $P>0.05$). However, statistical differences were identified in terms of the history of Hp infection, spouse's history of Hp infection, long-term drinking, halitosis, eating habits, and biliary tract diseases (all $P<0.05$, **Table 1**).

Multivariate analysis of Hp infection

Then, the above-mentioned single factors with statistical differences were assigned (**Table 2**) and input into SPSS as covariates, and the occurrence of Hp infection (with vs. without) was used as the dependent variate, for multiple Logistic regression analysis. The output results revealed that halitosis and spouse's history of Hp infection were not independent risk factors for Hp infection (all $P>0.05$), while Hp infection history, long-term drinking, eating habits and biliary tract disease history were (all $P<0.05$, **Table 3**).

Comparison of APACHE II, BISAP score and MCTSI

At T0 (baseline), the two groups had no significant difference in APACHE II, BISAP I and MCTSI scores (all $P>0.05$). Increases in the above scores were observed at T1 ($P<0.05$). The Hp-positive group had a higher APACHE II score ($P<0.05$), and similar BISAP scores and MCTSI ($P>0.05$) compared to Hp-negative group. At T2, those scores of both groups were lower than those at T1, but still higher than the baseline ($P<0.05$); at this time, all the three scores were higher in the Hp-positive group compared to Hp-negative group (all $P<0.05$, **Figure 1**).

Comparison of inflammatory factors

At T0, there were no significant differences between the two groups in WBC, CRP and PCT levels (all $P>0.05$). However, at T1 and T2, the Hp-positive group showed higher levels of WBC, CRP and PCT than the Hp-negative group (all $P<0.05$). In both groups, WBC, CRP and PCT increased at T1 compared with the baseline, but decreased at T2 (all $P<0.05$, **Figure 2**).

Comparison of immune function

Immunoglobulin (IgA, IgM and IgG) levels in both groups were found to be decreased at T1, and increased at T2, although they remained lower than baseline levels (T0) ($P<0.05$). Immunoglobulin (IgA, IgM and IgG) levels were similar in the two cohorts at T0 ($P>0.05$) but

Table 1. Univariate analysis of risk factors for Hp infection in SAP patients

	Hp-positive group (n=33)	Hp-negative group (n=44)	t or χ^2	P
Age	64.52±6.29	65.09±6.25	0.694	0.395
BMI (kg/m^2)	23.49±2.62	22.50±2.30	1.761	0.082
Gender			0.020	0.888
Male/Female	22/11	30/14		
Long-term Smoking			0.558	0.455
Yes/No	14/19	15/29		
Long-term drinking			8.250	0.004
Yes/No	18/15	10/34		
History of Hp infection			7.955	0.005
Yes/No	9/24	2/42		
Spouse's history of Hp infection			7.412	0.007
Yes/No	10/23	3/41		
Halitosis			25.880	<0.001
Yes/No	26/7	9/35		
Eating habits			7.130	0.008
Light foods/Greasy foods	8/25	24/20		
Biliary tract diseases			5.075	0.024
Yes/No	7/26	2/42		
Place of residence			0.873	0.350
Urban/Rural	25/8	29/15		

Note: Body mass index, BMI.

Table 2. Assignment table

Factors	Assignment
Long-term drinking	"Yes" =0, "No" =1
History of Hp infection	"Yes" =0, "No" =1
Spouse's history of Hp infection	"Yes" =0, "No" =1
Halitosis	"Yes" =0, "No" =1
Eating habits	"Light foods" =0, "Greasy foods" =1
Biliary tract diseases	"Yes" =0, "No" =1

were lower in the Hp-positive group compared to the Hp-negative group at T1 and T2 (all P<0.05, **Figure 3**).

Comparison of adverse reactions (ARs)

During treatment, both groups experienced pancreatic infection, nausea and vomiting, severe abdominal pain, fever and other ARs. The inter-group comparison showed no evident difference in the incidence of overall ARs (P>0.05, **Table 4**).

Comparison of survival and hospitalization time

Four patients died in the Hp-positive group and one in the Hp-negative group, with no statistical difference between groups (P> 0.05). The length of ICU stay and total hospitalization time of the Hp-positive group were (12.39± 3.90) d and (27.91±6.26) d, respectively, which were significantly longer compared with the Hp-negative group (all P<0.05, **Figure 4**).

Comparison of prognosis

The prognostic survival rate was 87.88% (29/33) in the Hp-positive group and 97.73% (43/44) in the Hp-negative group (P>0.05). However, the SF-36 score showed that all dimensions were lower in the Hp-positive group compared to the Hp-negative group, indicating better quality of life in patients of Hp-negative group (all P<0.05, **Figure 5**).

Discussion

The incidence of severe acute pancreatitis (SAP) is increasing with the continuous improvement in living standards, making it a common and frequently-occurring disease in critical care medicine [18]. Clinically, the progression of SAP is believed to be the result of various

Table 3. Multivariate analysis of risk factors for Hp infection in SAP patients

Factors	B	S.E.	Wald	P	OR	95% CI
Long-term drinking	-0.342	0.052	16.224	<0.001	1.624	0.624-2.733
History of Hp infection	0.184	0.045	15.634	<0.001	1.324	0.941-1.964
Spouse's history of Hp infection	0.054	0.086	0.492	0.581	1.421	0.742-1.669
Halitosis	0.096	0.057	3.254	0.076	1.091	0.841-1.262
Eating habits	0.642	0.364	10.542	<0.001	1.226	0.906-4.061
Biliary tract diseases	0.342	0.762	26.642	<0.001	1.707	1.224-3.667

Note: regression coefficient, β; standard error, S.E.; odds ratio, OR; 95% confidence interval, 95% CI.

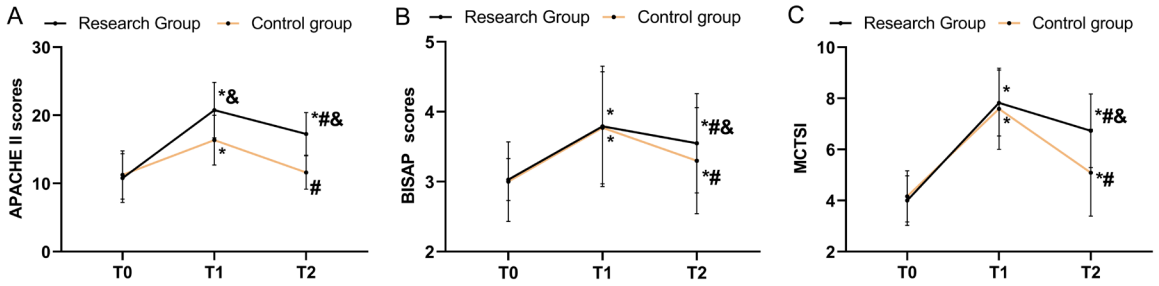

Figure 1. Comparison of APACHE II, BISAP and MCTSI scores between the two groups. A. Comparison of APACHE II scores between the two groups during treatment. B. Comparison of BISAP scores between the two groups during treatment. C. Comparison of MCTSI between the two groups during treatment. *P<0.05, compared with T0; #P<0.05, compared with T1; &P<0.05, compared with the Hp-negative group at the same time point. Acute Physiology and Chronic Health Evaluation II, APACHE II; Bedside Index for Severity in Acute Pancreatitis, BISAP; Modified CT Severity Index, MCTSI.

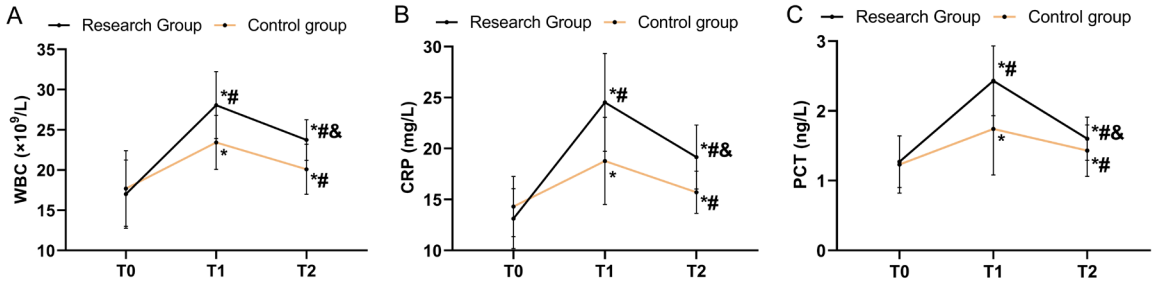

Figure 2. Comparison of inflammatory factors. A. Comparison of WBC between the two groups during treatment. B. Comparison of CRP between the two groups during treatment. C. Comparison of PCT between the two groups during treatment. *P<0.05, compared with T0; #P<0.05, compared with T1; &P<0.05, compared with the Hp-negative group at the same time point. White blood cell, WBC; C-reactive protein, CRP; procalcitonin, PCT.

comprehensive factors. Identifying these factors to delay or even block disease progression is an ongoing area of exploration in clinical practice [19].

First, through Logistic regression analysis, we found that the history of Hp infection, long-term drinking, eating habits, and history of biliary tract diseases were all independent risk factors for Hp infection in SAP patients, which is consistent with previous studies [20-22]. Based on these findings, clinical practitioners should pay more attentions to patients with a history of Hp infection and biliary tract diseases. Besides, a good diet plan should be developed for these patients, and alcohol consumption should be strictly prohibited, which will provide a solid foundation for patients' rehabilitation treatment, thus reducing the risk of Hp infection and improving overall outcomes of SAP patient.

Subsequently, we found that the Hp-positive group had statistically higher APACHE II scores than the Hp-negative group at 96 hours after

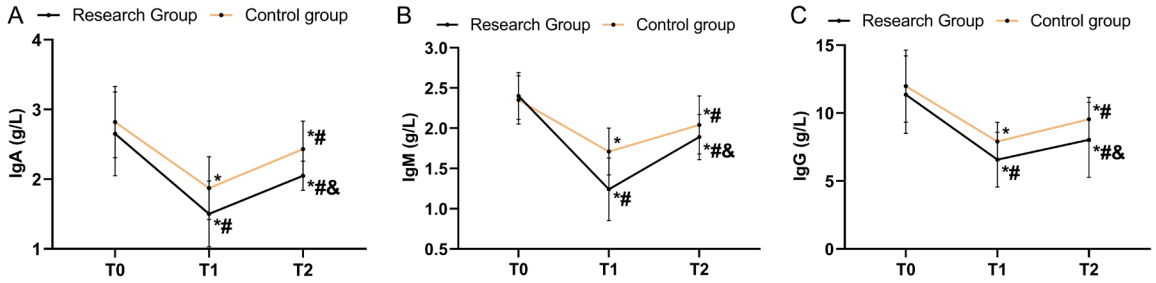

Figure 3. Comparison of immune function. A. Comparison of IgA between the two groups during treatment. B. Comparison of IgM between the two groups during treatment. C. Comparison of IgG between the two groups during treatment. Compared with T0, *P<0.05; compared with T1, #P<0.05; compared with the Hp-negative group at the same time point, &P<0.05. Immunoglobulin A/M/G, IgA/M/G.

Table 4. Comparison of adverse reactions

Group	Pancreatic infection	Frequent vomiting	Severe abdominal pain	Fever
Hp-positive group (n=33)	5 (15.15)	3 (9.09)	2 (6.06)	7 (21.21)
Hp-negative group (n=44)	2 (4.55)	1 (2.27)	1 (2.27)	3 (6.81)
χ^2	2.567	1.780	0.723	3.457
P	0.109	0.182	0.395	0.063

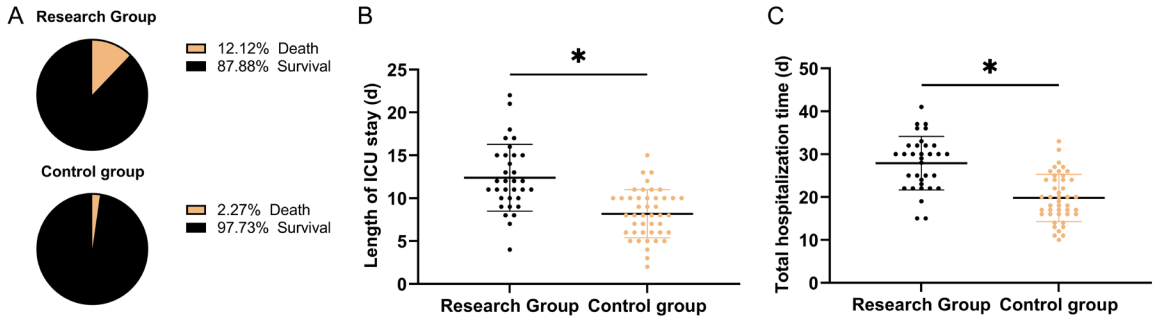

Figure 4. Comparison of survival and hospitalization time. A. Comparison of mortality between the two groups. B. Comparison of the length of ICU stay between the two groups. C. Comparison of total hospitalization time between the two groups. *P<0.05.

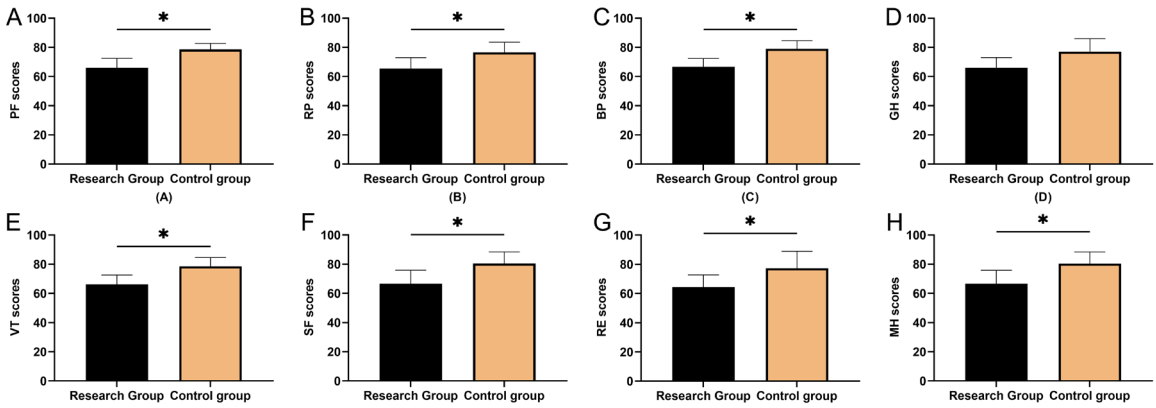

Figure 5. Comparison of prognosis. A. Comparison of PF scores. B. Comparison of RP scores. C. Comparison of BP scores. D. Comparison of GH scores. E. Comparison of VT scores. F. Comparison of SF scores. G. Comparison of RE scores. H. Comparison of MH scores. *P<0.05. Physical functioning, PF; role-physical function, RP; bodily pain, BP; general health, GH; vitality, VT; social functioning, SF; role-emotional, RE; mental health, MH.

admission, as well as higher APACHE II score, BISAP and MCTSI scores at 2 weeks after admission, indicating that SAP patients with Hp infection experienced a significantly aggravated condition as their illness progressed. Meanwhile, the Hp-positive group patients exhibited higher PCT, WBC and CRP levels and lower levels of IgA, IgM and IgG compared to the Hp-negative group, supporting the viewpoint that Hp infection can worsen the SAP by aggravating the inflammatory reaction and immune dysfunction of patients. Previous studies have also shown that Hp infection can promote the malignant development of gastric ulcers, colorectal adenocarcinoma and other diseases [23, 24], which is basically consistent with our views. In reviewing the relevant literature, we found that Warzecha Z et al. established an acute pancreatitis (AP) animal model induced by ischemia-reperfusion injury and infected animal gastric mucosa with Hp. They found a marked reduction in pancreatic blood flow and aggravated pancreatic injury and ischemia. They suggest that Hp infection can release lipopolysaccharides, which leads to leukocyte activation that triggers a cascade of pancreatic and systemic inflammation, aggravating pancreatic damage [25]. In this experiment, the WBC count of patients in the Hp-positive group also increased significantly, which also supported this view. Besides, some studies have shown that reactive oxygen metabolites are released after infection with Hp, and the activated granulocytes and macrophages can release inflammatory cytokines, which participate in the changes of pancreatic microcirculation and increase vascular permeability, forming thrombosis and hemorrhage and finally leading to pancreatic necrosis [26]. This further highlights the potential impact of Hp infection on SAP. However, pathological studies of Hp-infected autoimmune pancreatitis mainly show fibrosis or lymphocyte infiltration, with abnormalities occurring with T cell apoptosis [27]. In the pathological examination of patients with autoimmune pancreatitis, significant lymphocyte infiltration can also be observed, and the epithelial tissue around the pancreatic duct and the pancreatic islet cells inside the duct are destroyed, leading to further serious local pancreatic inflammation and impairment of both exocrine and endocrine functions [28]. The decrease in immunoglobulin levels observed in the Hp-positive group is also consistent with this view.

In addition, significantly longer hospitalization time was observed in the Hp-positive group in this study. This suggests that Hp infection can prolong the pathological process of SAP patients, which not only causes greater pain to patients, but also imposes a greater economic burden to patients and their families. The absence of a statistical difference in the incidence of ARs and mortality between the two groups may be due to chance, caused by the small number of cases included in this study. It is believed that a difference can be found through a multicenter study with larger samples. In the prognostic follow-up, the SF-36 scores of patients in the Hp-positive group were lower in all dimensions, indicating the reduction of their QOL, which confirmed the negative impact of Hp infection on the prognosis of SAP patients. This further emphasizes that in future diagnosis and treatment of SAP, clinical attention should be paid to the occurrence of Hp infection, so as to provide a more reliable prognosis guarantee for patients.

This study has several limitations. The limited number of cases included and the short follow-up time due to constrained conditions may lead to some bias in results and statistical calculation contingency. To address these limitations, it is essential to conduct a randomized controlled trial with a larger sample size and extended follow-up period to confirm our findings. In addition, the specific mechanism through which Hp infection promotes the malignant development of SAP will also be the focus of our follow-up research. We plant to conduct a more rigorous experimental analysis on the relationship between Hp infection and SAP to provide more reliable reference opinions for clinical practice.

In summary, a history of Hp infection, long-term drinking, bad eating habits, and history of biliary tract diseases are all independent risk factors for Hp infection in SAP patients. After Hp infection, the recovery of SAP patients will be severely compromised, their immune function will be disrupted, and the quality of life will be reduced; thus, these patients require special attention.

Acknowledgements

This work was supported by the Science and Technology Plan of Jiangxi Provincial Health Commission (20204373).

Disclosure of conflict of interest

None.

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