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***Retrospective Study***

**Immune function, gastrointestinal hormone levels, and their clinical significance in patients with gastric ulcers complicated with depression**

Yang YH *et al.* Patients with GU complicated with depression

## **Abstract**

### **BACKGROUND**

Gastric ulcer (GU) is a common digestive tract disease, and medical records of GU combined with depression are increasingly common. Currently, the risk factors and pathogenesis of GU complicated with depression remain unclear. Low immune function and gastrointestinal hormone levels may also be significant risk factors. Therefore, this study explored the immune function and gastrointestinal hormone levels in patients with GU combined with depression.

### **AIM**

To explore the immune function, gastrointestinal hormone level, and clinical significance of patients with GU combined with depression.

### **METHODS**

A retrospective analysis was conducted on 300 patients with GU combined with depression admitted to Guizhou Provincial People's Hospital from January 2021 to June 2022 as the study subjects. According to the Hamilton Depression Scale (HAMD) score, patients were divided into mild-to-moderate ( $n = 210$ ) and heavy ( $n = 90$ ) groups. Basic data, immune function indices [immunoglobulin A (IgA), IgM, IgG, serum CD4<sup>+</sup> and CD8<sup>+</sup> percentage, and CD4<sup>+</sup>/CD8<sup>+</sup> ratio], and gastrointestinal hormone indices [serum gastrin (GAS), cholecystokinin (CCK), and motilin (MTL) levels] were collected. The basic data of the two groups were compared, and the immune function and gastrointestinal hormone indices were analyzed. Multivariate logistic regression was used to analyze the factors influencing the severity of GU complicated with depression. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to analyze the value of

the immune function index, gastrointestinal hormone index, and combined index in predicting the severity of GU complicated with depression.

## RESULTS

There were no marked differences in sex, age, body mass index, abdominal distension, abdominal pain, belching, nausea, vomiting, or sleep disorders between the heavy and mild-to-moderate groups ( $P > 0.05$ ). There was a marked difference in the family history of depression between the heavy and mild-to-moderate groups ( $P < 0.05$ ). There were significant differences in serum IgA and IgM levels and serum CD4<sup>+</sup>, CD8<sup>+</sup>, and CD4<sup>+</sup>/CD8<sup>+</sup> ratios between the heavy and mild-to-moderate groups ( $P < 0.05$ ). Multivariate analysis showed that IgA, IgM, GAS, and CCK serum levels influenced the severity of GU with depression ( $P < 0.05$ ). The AUC of the ROC curve for serum IgA level predicting GU with depression severity was 0.808 [95% confidence interval (CI): 0.760-0.857], the AUC of the serum IgM level was 0.757 (95%CI: 0.700-0.814), the AUC of the serum GAS level was 0.853 (95%CI: 0.810-0.897), the AUC of the serum CCK level was 0.762 (95%CI: 0.709-0.822), the AUC of immune function (IgA, IgM) and gastrointestinal hormone levels (GAS, CCK) for the prediction of GU with depression severity was 0.958 (95%CI: 0.933-0.976).

## CONCLUSION

Important factors influencing GU complicated with depression are serum IgA, IgM, GAS, and CCK indicators. They can be used as indicators to predict the severity of GU complicated with depression.

**Key Words:** Gastric ulcer combined with depression; Immune function; Gastrointestinal hormones

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**Core Tip:** The occurrence and severity of gastric ulcer (GU) combined with depression may be related to autoimmune dysfunction and gastrointestinal hormone levels. In this study, multivariate logistic regression analysis was used to influence the severity of concurrent depression in GU. The results suggest that impaired T cell function and gastrointestinal hormone disorders may directly affect the development and development of depression. In addition, the immune function indicators combined with gastrointestinal hormone levels predict high AUC, specificity and sensitivity, which has a very good reference value.

## **INTRODUCTION**

With the continuous development of living standards, people's eating and living habits have changed to varying degrees; however, poor living habits have had a greater impact on people's health. Gastric ulcers (GU) are common digestive system diseases. The occurrence and continuous progression of the disease are related to the dynamic balance between gastric mucosal defense and invasion factors. *Helicobacter pylori* (*H. pylori*) infection, excessive gastric acid secretion, and adverse drug factors are all influencing factors that cause GU<sup>[1,2]</sup>. Gastric juice concentration in patients with GU stimulates the gastric mucosa, promotes changes in the gastric structure and environment, causes serious damage to the gastric mucosa, and causes long-term stay of pathogenic factors, resulting in the long-term treatment of the disease<sup>[3]</sup>. Clinical manifestations of GU include stomach and abdominal pain, heartburn, acid reflux, among others. The symptoms worsen after eating irritating foods or foods that are hard to digest. Smoking and alcohol

consumption can also cause GU. Patients with severe GU often experience gastric perforation and gastric bleeding<sup>[4]</sup>.

Recently, psychophysiological factors have been significant in the pathogenesis of gastrointestinal illnesses. GU are characterized by repeated attacks that can easily cause adverse severe psychological states. Some patients also experience anxiety and depression due to a lack of timely and effective treatment for physical illness, which makes depression increasingly prominent in GU patients<sup>[5]</sup>. Anti-*H. pylori* therapy, drugs controlling excessive gastric acid secretion, and protecting gastric mucosa are primarily used for the clinical treatment of GU. The impact of psychological factors on disease occurrence and progression in clinical practice is often overlooked, which makes it difficult to treat patients comprehensively<sup>[6]</sup>. Relevant data show that poor psychological status may increase the risk of digestive disorders<sup>[7]</sup>; however, there are few studies on patients with GU associated with depression. Exploring the factors influencing GU combined with depression is important for clinical treatment and the improvement of patients' quality of life. Studies have shown that the occurrence of GU combined with depression may be related to abnormal autoimmune function and disorders of gastrointestinal hormone levels<sup>[8]</sup>; however, the specific mechanism is not clear. Due to the decrease in gastrointestinal function and food intake, GU complicated with depression is often accompanied by a decline in immune function, and the adverse psychological state aggravates the risk of malnutrition. The intestinal mucosal barrier and immune function are extremely poor, which increases the risk of depression. Therefore, 300 patients with GU and depression were included in this study to explore their immune function, gastrointestinal hormone levels, and clinical significance, to provide a reference for reducing the incidence of GU complicated by depression.

## **MATERIALS AND METHODS**

### ***Patient characteristics***

A retrospective analysis was conducted to select 300 patients with GU complicated with depression admitted to Guizhou Provincial People's Hospital from January 2021 to June 2022 as the study subjects. Inclusion criteria: (1) Age  $\geq$  18 years old; (2) All patients have nausea, stomach pain, and acid reflux symptoms; and (3) The basic information and laboratory indicators of all patients are complete. The exclusion criteria were as follows: (1) Patients with malignant tumors or chronic atrophic gastritis and other gastrointestinal illnesses; (2) Patients who had undergone gastrointestinal surgery in the past 3 mo; (3) Patients with organic disorders; and (4) Patients with autoimmune diseases and systemic inflammatory diseases.

Diagnostic criteria for GU<sup>[9]</sup>: GU was confirmed by endoscopy, and the pathological diagnosis of *H. pylori* infection was positive. Diagnostic criteria for depression<sup>[10]</sup>: Diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders were employed. The diagnosis was based on the patient's low mood, slow thinking, reduced language, movements, suspected illness, insomnia, loss of interest, and related symptoms lasting more than 2 wk. The severity of the disease and the degree of social function impairment increase with the number of symptoms.

### ***Grouping method***

All patients on the day of admission, patients were routinely assessed using the Hamilton Depression Scale (HAMD)<sup>[11]</sup>, And were graded according to the HAMD scale: A score of 7 points indicates no depression, > 8-19 points indicates depression, > 20-34 points indicates mild to moderate depression, and > 35 points indicates major depression. All enrolled patients with GU and depression were divided into mild-to-moderate ( $n = 210$ ) and heavy ( $n = 90$ ) groups.

### ***Clinical data collection***

Clinical data collection: (1) Basic information: Sex, age, body mass index (BMI), abdominal distension, abdominal pain, belching, nausea, vomiting, sleep disorders, and family history of depression; (2) Immune function index: The levels of serum immunoglobulin A (IgA), IgM, and IgG were detected by immunoturbidimetry (the kit was purchased from LIFOTRONIC TECHNOLOGY CO., LTD.). The percentages of serum CD4<sup>+</sup> and CD8<sup>+</sup> cells were detected using a Beckman CytoFLEX flow cytometer and a supporting kit (BECKMAN COULTER), and the ratio of CD4<sup>+</sup>/CD8<sup>+</sup> cells was calculated; (3) Gastrointestinal hormone indices: The levels of serum gastrin (GAS), cholecystokinin (CCK), and motilin (MTL) were detected by ELISA (the kit was purchased from MLBIO Enzyme Linked Biology).

### ***Statistical analysis***

Data analysis was performed using SPSS statistical software 24.0. The measurement data conforming to the normal distribution were expressed as mean  $\pm$  SD and analyzed by *t*-test. Count data is expressed as frequency percentage (*n*%) by the  $\chi^2$  test. Multivariate logistic regression analysis was used to explore factors influencing the severity of GU complicated with depression. The receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) were used to analyze the value of the immune function index, gastrointestinal hormone index, and combined index in predicting the severity of GU complicated with depression, and the specificity and sensitivity were calculated. Test level:  $\alpha = 0.05$ .

## **RESULTS**

### ***Basic data analysis***



Figure 1 shows the number of patients, the number of patient inclusion, and the flow chart of the analysis method. There was no significant difference in gender, age, BMI, abdominal distension, abdominal pain, belching, nausea, vomiting, and sleep disorders between the heavy group and the mild to moderate group ( $P > 0.05$ ). There was statistically significant difference in family history of depression between severe group and mild to moderate group ( $P < 0.05$ ) (Table 1).

#### ***Comparison of the immune function indicators between the two groups***

There were significant differences in serum IgA and IgM levels and serum CD4<sup>+</sup>, CD8<sup>+</sup>, and CD4<sup>+</sup>/CD8<sup>+</sup> ratios between the heavy and mild-to-moderate groups ( $P < 0.05$ ). There was no significant difference in serum IgG level between the two groups ( $P > 0.05$ ) (Table 2).

#### ***Comparison of the gastrointestinal hormone indexes***

Serum GAS and CCK levels were compared between the severe and mild-to-moderate groups ( $P < 0.05$ ), and there was no difference in serum MTL levels between the two groups ( $P > 0.05$ ) (Table 3).

#### ***Multivariate analysis affecting the severity of GU combined with depression***

The above statistically significant indicators (family history of depression, IgA, IgM, CD4<sup>+</sup>, CD8<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup> ratio, GAS, and CCK) were used as independent variables, and GU combined with depression severity as the dependent variable (see Table 4). Multivariate analysis showed that serum IgA, IgM, GAS, and CCK levels influenced the severity of GU complicated with depression ( $P < 0.05$ ) (Table 5).

#### ***ROC curve of immune function predicting GU with depression severity***

The AUC of the ROC curve of serum IgA level for predicting GU with depression severity was 0.808 [95% confidence interval (CI): 0.760-0.857], sensitivity was 0.738, and specificity was 0.778, The AUC of the serum IgM level was 0.757 (95%CI: 0.700-0.814), with a sensitivity of 0.748 and a specificity of 0.700 (Figure 2A).

***The ROC curve of gastrointestinal hormones in predicting GU combined with depression severity***

The AUC of the ROC curve of serum GAS level predicting GU with depression severity was 0.853 (95%CI: 0.810-0.897), sensitivity was 0.814, and specificity was 0.767, The AUC of serum CCK level was 0.762 (95%CI: 0.709-0.822), with a sensitivity of 0.590 and a specificity of 0.844 (Figure 2B).

***ROC curve of immune function combined with gastrointestinal hormone levels in predicting GU combined with depression severity***

The AUC of immune function (IgA, IgM) combined with gastrointestinal hormone levels (GAS, CCK) predicting GU with depression severity was 0.958 (95%CI: 0.933-0.976), sensitivity was 0.967, and specificity was 0.829 (Figure 2C).

**DISCUSSION**

GU refers to the ulcer formed in the gastric angle, gastric antrum, cardia, and hiatal hernia. It is a gastric mucosal injury that is caused by various factors. It can be caused by *H. pylori* infection, drugs, heredity, diet, and other factors and is often accompanied by acid reflux, belching, abdominal distension, and upper abdominal pain symptoms<sup>[12]</sup>. The related study showed that the occurrence of GU is caused by the process of 'attack factor' or the weakening of 'defense factor'; the "attack factor" includes gastric acid, pepsin, *H. pylori*, among others, and the "defense factor" includes gastric mucosa, gastric

mucus, bicarbonate, among others<sup>[13]</sup>. It has been found that *H. pylori* infection is the most common cause of GU. *H. pylori* can damage the protective layer of the gastric mucosa, thus accelerating the occurrence of gastric mucosal lesions, easily causing various complications, and threatening the physical and mental health of patients<sup>[14]</sup>. GU combined with depression is a typical digestive tract illness in clinical medicine, and gastric acid secretion in the human body is associated with psychological pressure. Patients are affected by psychological and physiological factors, and inner tension and nervous system pressure can cause GUs. The incidence of psychosocial abnormalities has increased in recent years and exists as a comorbidity of other basic and chronic diseases, with these two factors influencing each other<sup>[15]</sup>.

Depression is a primary emotional and common mood disorder. Its incidence ranks second in the incidence of various diseases worldwide. Furthermore, it is found that patients with various chronic diseases have anxiety and depression, and the mortality rate of patients with heart disease complicated with depression is higher than that of patients with simple depression, so the treatment of patients with depression is necessary<sup>[16]</sup>. The National Institute of Mental Health showed that the prevalence of mental disorders in patients with somatic diseases is as high as 41%<sup>[17]</sup>. Therefore, while paying clinical attention to the diagnosis and treatment of physical diseases, we should also pay attention to mental and psychological interventions, as the number of patients with GU complicated with depression in China has increased annually<sup>[18]</sup>. Several factors affect the pathogenesis of GU, which is complicated with depression. Autoimmune dysfunction and gastrointestinal hormone disorders may be important factors affecting disease severity; however, this hypothesis remains controversial. Therefore, it is necessary to explore the importance of immune function and gastrointestinal hormone indices in patients with GU or depression.

In this study, all selected patients were scored using the HAMD. Among them, 210 patients with mild to moderate GU complicated with depression, accounting for 70%, and 90 patients in the heavy group, accounting for 30%. Studies have shown that disease characteristics and severity of depression are influenced by a family history of affective disorder<sup>[19]</sup>. In this study, the mild-to-moderate and heavy groups had a family history of depression. This indicates that patients with a family history of depression may have more severe anhedonia and anxiety symptoms and that these mood disorders can potentially affect immune function and gastrointestinal hormone levels. The pathogenesis of GU is closely associated with immune deficiency<sup>[20]</sup>. Depression and anxiety can cause digestive system diseases. Long-term mental disorders overstretch the nervous system, leading to gastrointestinal hormone secretion disorders and excessive sensitivity to food stimulation. Patients with GU and depression have weakened gastrointestinal motility, delayed gastric emptying, and uncoordinated gastrointestinal motility, causing a series of complex syndromes such as fullness, belching, and abdominal pain<sup>[21]</sup>. There was no significant difference in gender, age, BMI, abdominal distension, abdominal pain, belching, nausea, vomiting and sleep disorders between the moderate-to-severe group and the mild-to-moderate group in this study, this result may be related to the sample size included in this study. However, these syndromes must be considered clinically.

Immunoglobulin is produced by B lymphocytes as long as it is a specific binding antigen. Serum IgA, IgM, and IgG are important components of the body's immune cell molecules, which can be consumed in large amounts in consumptive diseases, acute inflammation, and malignant tumors, resulting in a decline in immune function<sup>[22]</sup>. In this study, serum IgA and IgM levels in the moderate and heavy groups were lower than those in the mild and moderate groups, indicating that impaired B cell function and low immune function could aggravate the risk of infection, GU progression, and

depression status. According to modern immunology, the clinical manifestations and prognosis of diseases are closely related to the functional status of T lymphocytes<sup>[23]</sup>. The percentage of serum CD4<sup>+</sup> and CD8<sup>+</sup> cells and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio reflect the cellular immune function of the body. The percentage of serum CD4<sup>+</sup> cells are helper T lymphocytes, the percentage of serum CD8<sup>+</sup> cells are inhibitory T lymphocytes, and the CD4<sup>+</sup>/CD8<sup>+</sup> ratio is an index to assess immunity, which can reflect the immune status of the body. When the body is stimulated or damaged by stress, the percentage of CD4<sup>+</sup> cells decreased rapidly, the percentage of CD8<sup>+</sup> cells increased rapidly, the CD4<sup>+</sup>/CD8<sup>+</sup> cell ratio increased significantly, and the immune function of the body decreases<sup>[24]</sup>. In this study, serum CD4<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup> ratios were significantly decreased in the moderate-to-heavy group, and serum CD8<sup>+</sup> levels were markedly increased. This indicates that impaired T-cell function may directly lead to the development of depression. Therefore, enhancing immune cell function is of great clinical value for controlling illness progression in patients with GU and depression.

The gastrointestinal hormone level is a sensitive index that reflects the function of the gastric mucosa. It plays an important role in regulating the function of the digestive system and is closely related to digestive system dysfunction<sup>[25]</sup>. GAS is the main hormone of the digestive tract that affects gastrointestinal transitional compound movement, prolongs gastric emptying time, stimulates the vagus nerve inhibitory fiber, promotes gastric fundus relaxation, and inhibits reflux of bile discharge<sup>[26]</sup>. When patients with GU are complicated with depression, the patient's body is in an emergency state, and the levels of stress hormones, such as hypothalamus-pituitary-adrenaline, increase, which affects the interaction between the gastrointestinal flora and gastrointestinal mucosa and the shedding of mucosal mast cells, resulting in dyspepsia<sup>[27]</sup>. In this study, the levels of serum GAS and CCK were markedly increased in the severe group. This shows that increased secretion or

synthesis of gastrointestinal hormones occurs in GU patients with severe depression, leading to an imbalance in the gastrointestinal hormone balance. The low levels of GAS and CCK in plasma affect the normal functioning of their physiological functions and slow down gastrointestinal motility, thus affecting the digestive tract symptoms of patients with depression. CCK is an important hormone that regulates the gallbladder function. Its main functions include promoting bile secretion, destroying the mucosa lining of the digestive tract, preventing gastrointestinal peristalsis, and prolonging gastric emptying<sup>[28]</sup>. The increase in CCK levels stimulates the hypothalamus and acts on the central nervous system to inhibit appetite, which is also the reason for the loss of appetite in patients with GU and depression.

In this study, the ROC curves of immune function, gastrointestinal hormone levels, and the combined prediction curve of GU and depression severity were drawn. The results showed that the immune function and gastrointestinal hormone indices alone predicted low AUC, specificity, and sensitivity, and the combined prediction had the highest efficacy, indicating that the immune function indices (IgA and IgM) combined with gastrointestinal hormone levels (GAS and CCK) have good efficacy and significance in predicting the severity of GU and depression. Serum IgA, IgM, GAS, and CCK indicators are simple, convenient, economical, effective, and have strong applicability and operability, which is conducive to the development of primary medical institutions.

Limitations of this study: All the selected participants were admitted to our hospital, the reliability may be affected by the limitation of sample size. In the later stages, the sample size can be expanded clinically, a multicenter study can be conducted, and the mechanism of immune function and gastrointestinal hormone levels in GU complicated with depression can be analyzed in depth.

## **CONCLUSION**

In summary, the important influencing factors of GU with depression were serum IgA, IgM, GAS, and CCK indices. Immune function and gastrointestinal hormone levels can be used as effective indicators to predict the severity of GU combined with depression. Clinically, targeted measures should be taken to address these causes and reduce the risk of GU concomitant with depression.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Psychophysiological factors play a significant role in the pathogenesis of gastrointestinal illnesses. Gastric ulcers (GU) are characterized by repeated attacks that can cause adverse severe psychological states. Some patients also experience anxiety and depression due to a lack of timely and effective treatment for physical diseases, which makes depression increasingly prominent in patients with GU.

### ***Research motivation***

The relevant risk factors and pathogenesis of GU concomitant with depression have not yet been fully elucidated. The occurrence and severity of GU complicated with depression may be related to autoimmune dysfunction and gastrointestinal hormonal disorders.

### ***Research objectives***

This study aimed to investigate the immune function, gastrointestinal hormone levels, and clinical significance of patients with GU combined with depression and to control disease progression in patients with GU complicated with depression.

### ***Research methods***

This study used a retrospective approach to analyze two indexes of immune function and gastrointestinal hormones. Furthermore, it explored the factors influencing the severity of GU concurrent depression using multivariate logistic regression analysis.

### ***Research results***

Serum immunoglobulin A (IgA), IgM, gastrin (GAS), and cholecystokinin (CCK) levels were the influencing factors affecting the severity of GU combined with depression; the area under the receiver operating characteristic curve of immune function (IgA, IgM) and gastrointestinal hormone levels (GAS, CCK) for the prediction of GU with depression severity was 0.958 (95% confidence interval: 0.933-0.976).

### ***Research conclusions***

The occurrence of GU complicated with depression is related to autoimmune dysfunction and disorders of gastrointestinal hormone levels. Immune function and gastrointestinal hormone levels can be used as effective indicators to predict the severity of GU complicated with depression.

### ***Research perspectives***

Using a retrospective analysis approach, patients were divided into severe and mild-moderate groups according to the Hamilton Depression Scale. Basic data from both groups, including immune function and gastrointestinal hormone markers, were used to analyze the factors affecting the severity of GU and concurrent depression. To explore the value of immune function indices, gastrointestinal hormone indices and a combination of indices were used to predict the severity of GU and depression.



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