

# A correlation between gastrointestinal dysfunction and cirrhosis severity

Ping Wang, MD<sup>a,\*</sup>, Ying-Jian Zhang, MD<sup>b</sup>, Yi-Ran Li, MD<sup>b</sup>, Xiao-Min Liu, MD<sup>b</sup>, Shu-Yan Lv, MD<sup>a</sup>, Xiao-Yan Xia, MD<sup>a</sup>

## Abstract

This study aims to investigate the relationship between gastrointestinal dysfunction (GD) and cirrhosis severity in cirrhotic patients, to provide evidences for the prevention and treatment of GD in cirrhotic patients.

A total of 95 cirrhotic inpatients and outpatients, who were treated in the Department of Gastroenterology of Xinqu Hospital of the First Affiliated Hospital of Henan University of Science and Technology, were enrolled in the present study, and assigned as the experimental group (cirrhosis group). According to Child–Pugh classification, these patients were divided into 3 groups: group A ( $n = 45$ ), group B ( $n = 23$ ), and group C ( $n = 27$ ). Forty healthy adults who received health check-ups during the same period served as the control group. The gastrointestinal (GI) symptoms of cirrhotic patients were scored, and the fasting serum gastrin (GAS), motilin (MTL), and vasoactive intestinal peptide (VIP) levels were measured in all subjects.

The potential correlations of GI symptom scores of patients in these cirrhosis groups with GI hormone levels and cirrhosis severity were analyzed. In cirrhotic patients, the GI symptom scores significantly increased. Furthermore, the symptom scores gradually increased along with the aggravation of liver damage. Moreover, serum GAS and VIP levels were significantly higher in the cirrhosis groups than in the control group, whereas MTL levels were significantly lower. These changes were significantly correlated with cirrhosis severity. The linear correlation analysis revealed that the GI symptom score was positively correlated with GAS and VIP levels, and negatively correlated with MTL level. In addition, the linear correlation analysis revealed that GI symptom score and GAS and VIP levels were positively correlated with cirrhosis severity, whereas MTL level was negatively correlated with cirrhosis severity.

Cirrhotic patients have more obvious GI symptoms and higher GI hormone levels, which are closely correlated with the progression of liver cirrhosis and the degree of liver function damage.

**Abbreviations:** CHB = chronic hepatitis B, ELISA = enzyme-linked immunosorbent assay, GAS = gastrin, GD = gastrointestinal dysfunction, GI = gastrointestinal, LES = lower esophageal sphincter, LIFE = lausanne intestinal failure estimation, MMC = migrating motor complex, MTL = motilin, VIP = vasoactive intestinal peptide.

**Keywords:** gastrin, gastrointestinal dysfunction, liver cirrhosis, motilin, vasoactive intestinal peptide

## 1. Introduction

Cirrhosis is the end stage of many chronic, progressive and diffuse liver diseases that occur after long-term effects on the liver by a variety of etiologies.<sup>[1]</sup> Cirrhosis is clinically divided into 2 stages: compensated and decompensated.<sup>[2]</sup> Most cirrhotic patients have no specific clinical manifestations at the early stage. However, as cirrhosis progresses to a decompensated stage, in addition to severe liver function damage, patients frequently suffer from ascites, esophageal varices rupture and bleeding,

hepatorenal syndrome, spontaneous bacterial peritonitis, and splenomegaly.<sup>[3]</sup> In severe cases, this can be life-threatening.

Cirrhotic patients often have GI symptoms, including early satiety, belching, nausea, and vomiting, which are similar to those of weakened gastric motor activity.<sup>[4]</sup> Furthermore, the proximal gastric smooth muscle maintains tetanic contractions during the fasting state. However, during or after a meal, the proximal gastric smooth muscle is relaxed, allowing a large amount of food into the stomach without markedly changing intragastric pressure (i.e., gastric receptive relaxation).<sup>[5]</sup> Impaired gastric accommodation mainly causes upper GI symptoms such as early satiety, bloating and abdominal pain, and it is more likely to occur in patients with functional dyspepsia, diabetes mellitus, and those who have undergone fundoplication, vagotomy, or subtotal gastrectomy.<sup>[6]</sup> It has been found that the change in gastric receptivity during a meal was more prominent in cirrhotic patients than in healthy controls.<sup>[7]</sup> However, gastrointestinal (GI) stimulation, especially gastric dilation following food intake, may also cause corresponding GI symptoms.<sup>[8]</sup> In the experiment on the sensory threshold of gastric dilation conducted by Kalaitzakis,<sup>[4]</sup> it was found that the sensory threshold was not significantly different between cirrhotic patients and healthy controls. However, the sensory threshold values were significantly correlated with the severity of GI symptoms and liver function damage. That is, the gastric sensory threshold progressively decreases along with the increase in the severity of GI symptoms and liver function damage.

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<sup>a</sup> Department of Preventive Medicine, Henan University of Science and Technology, <sup>b</sup> Department of Gastroenterology, First Affiliated Hospital Henan University of Science and Technology, Luoyang, China.

\* Correspondence: Ping Wang, Department of Preventive Medicine, Henan University of Science and Technology, Medical College, No 263, Kaiyuan Street, Luolong District, LuoYang 471023, China (e-mail: wangp012357@163.com).

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An increasing number of studies have explored the relationship between cirrhosis and GI hormones.<sup>[9]</sup> Vasoactive intestinal peptide (VIP) is one of the major transmitters that mediate lower esophageal sphincter (LES) relaxation. It can relax LES smooth muscle by directly acting on LES. Thus, the increase in VIP in blood can lead to the relaxation of LES smooth muscles, which may cause gastroesophageal reflux. VIP also has a relaxing effect on intestinal smooth muscles. Abnormal VIP levels can weaken colonic motility, and even cause constipation.<sup>[4]</sup> Somatostatin is secreted by D cells in the enteric plexus, stomach and pancreas. As an inhibitory GI hormone, it can suppress GI motor neurons.<sup>[10]</sup>

## 2. Materials and methods

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Xinqu Hospital of the First Affiliated Hospital of Henan University of Science and Technology. Written informed consent was obtained from all participants.

### 2.1. Data source

Cirrhotic inpatients and outpatients, who were treated in the Department of Gastroenterology of Xinqu Hospital of the First Affiliated Hospital of Henan University of Science and Technology from October 2014 to August 2015, were randomly enrolled in the present study. A total of 95 patients with different types of cirrhosis (76 patients with hepatitis B-associated cirrhosis and 19 patients with other types of cirrhosis; 66 males and 29 females) entered the final analysis. According to Child–Pugh classification, these patients were divided into 3 groups: grade A group ( $n=45$ ), grade B group ( $n=23$ ), and grade C group ( $n=27$ ). The age of these patients ranged within 20 to 75 years old (mean:  $53.31 \pm 12.76$  years old).

The diagnosis of cirrhosis was based on the following guidelines: *Guidelines on the Prevention and Treatment of Chronic Hepatitis B* (revised in 2012 by Chinese Society of Hepatology and Chinese Society of Infectious Diseases),<sup>[11]</sup> *Multidisciplinary Diagnosis, Evaluation, and Antiviral Treatment of Hepatitis B Virus-associated Cirrhosis* (2014 edition, released by the “12th 5-year” Major and Special Project Joint Research Group of the Ministry of Science and Technology of China and published in the Chinese Journal of Gastroenterology),<sup>[12]</sup> *Guidelines on the Prevention and Treatment of Hepatitis C* (revised by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases in 2004),<sup>[13]</sup> and *Guidelines on the Diagnosis and Treatment of Alcoholic Liver Disease* (established by the Chinese Society of Hepatology in 2010).<sup>[14]</sup>

All patients completed the demographic data form. Informed consent was obtained from patients and their families. The study was approved by the Ethics Committee of Henan University of Science and Technology. Subjects in all the cirrhosis groups had not been administered with any drug that could affect GI motility or gastric acid secretion within the past 7 days. Forty normal subjects (25 males and 15 females), who received health check-ups in our center during the same period, were assigned as the control group. The age of these healthy subjects ranged within 23 to 70 years old (mean:  $50.58 \pm 11.41$  years old). Subjects in the control group had not taken any drug that could affect GI motility or gastric acid secretion within the past 7 days.

### 2.2. Biochemistry, blood coagulation analysis, and other relevant examinations

All the examinations and tests were performed in the Clinical Laboratory and in the Department of Radiology of the First Affiliated Hospital of Henan University of Science and Technology.

### 2.3. Child–Pugh classification of liver function

In all cirrhotic patients, liver function was scored using the Child–Pugh classification (Table 1).

### 2.4. GI symptom scoring

GI symptoms were scored in all eligible cirrhotic patients following the modified Lausanne Intestinal Failure Estimation (LIFE) proposed by Berger et al in 2008. Eleven GI symptoms, including anorexia, early satiety, belching, acid regurgitation, heartburn, nausea, vomiting, postprandial bloating, abdominal pain or discomfort, diarrhea and constipation, were scored as 0, 1, 2, and 3 for no symptom (asymptomatic), mild symptom (the patient can identify the presence of a specific symptom after being reminded), moderate symptom (the patient can identify the presence of a specific symptom, but the symptom did not affect daily life), and severe symptom (the patient had obvious symptoms that affected daily life), respectively. The GI symptom score was the sum of the scores of various symptoms. The highest score of a specific symptom was 3 points, and the highest total score of all symptoms was 33 points.

### 2.5. Determination of GI hormone levels

Serum GAS, MTL, and VIP levels in all subjects were determined using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). All the determinations were performed in strict accordance with the manufacturer’s instructions of the ELISA kit.

**Table 1**

#### Child–Pugh scoring.

Clinical biochemical indicators	1	2	3
Hepatic encephalopathy (grade)	None	1–2 (mild)	3–4 (moderate or higher)
Ascites	None	Small, easy to control	Moderate, difficult to control
Serum total bilirubin, $\mu\text{mol/L}$	<34.2	34.2–51.3	>51.3
Plasma albumin, g/L	>35	28–35	<28
Prothrombin time, s	1–3	4–6	>6
Prothrombin ratio, %	>50	30–50	<30

In primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC): total bilirubin ( $\mu\text{mol/L}$ ): 17–68  $\mu\text{mol/L}$ , 1 point; 68–170  $\mu\text{mol/L}$ , 1 point; >170  $\mu\text{mol/L}$ , 1 point. Classification criteria: class A, 5–6 points; class B, 7–9 points; and class C,  $\geq 10$  points.

## 2.6. Statistical analysis

All the experimental data were analyzed using the SPSS 16.0 software package. Measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{X} \pm SD$ ), and numeration data were compared using Chi-squared test. The comparison of the means of 2 independent samples was performed using *t* test. The inspection level was  $\alpha = 0.05$ . A *P*-value  $< .05$  was regarded as statistically significant. Multiple-sample means were compared using 1-way ANOVA (when the variables were homogeneously distributed). Paired comparisons were performed using SNK test. The inspection level was  $\alpha = 0.05$ . A *P*-value  $< .05$  was considered statistically significant. Pearson correlation analyses were used to analyze the correlation of 2 indicators. A scatter plot was drawn, followed by Pearson linear correlation analysis, when 2 indicators exhibited a linear trend. The inspection level was  $\alpha = 0.05$ . A *P*-value  $< .05$  was considered statistically significant.

## 3. Results

### 3.1. General data

A total of 95 patients with different types of cirrhosis (76 patients with hepatitis B-associated cirrhosis and 19 patients with other types of cirrhosis; 66 males and 29 females) entered the final analysis. There were 33 males and 12 females in group A ( $n = 45$ ), 15 males and 8 females in group B ( $n = 23$ ), and 18 males and 9 females in group C ( $n = 27$ ). The age of these patients ranged within 20 to 75 years old (mean:  $53.31 \pm 12.76$  years old). A total of 40 healthy controls (25 men and 15 women) were enrolled in the present study. The age of these subjects ranged within 23 to 70 years old (mean:  $50.58 \pm 11.41$  years old) (Table 2).

### 3.2. Comparisons of the fasting serum levels of GAS, MTL, and VIP between the cirrhotic group and control group

Comparisons of the fasting serum levels of GAS, MTL, and VIP between the cirrhotic groups and control group are presented in Tables 3 and 4.

### 3.3. GI symptom scores in patients with different Child–Pugh classifications

The GI symptom scores of patients with different Child–Pugh classifications are presented in Table 5.

### 3.4. Relationship between GI symptom scores and GI hormone levels in the cirrhosis groups

Linear correlation analysis revealed that the GI symptom score had a moderate positive correlation with fasting serum GAS level in the cirrhosis groups ( $P < .05$ ,  $r = 0.614$ ). That is, cirrhotic

**Table 2**  
Comparison of general data among different groups.

Group	n	Gender, n (%)		Age, y ( $\bar{X} \pm SD$ )
		Male	Female	
Group A	45	33 (73.33)	12 (26.67)	$51.87 \pm 13.21$
Group B	23	15 (65.22)	8 (34.78)	$57.65 \pm 11.14$
Group C	27	18 (66.67)	9 (33.33)	$52.00 \pm 12.90$
Control group	40	25 (62.50)	15 (37.50)	$50.58 \pm 11.41$
$\chi^2/F$ value		1.215		1.727
<i>P</i> -value		.749		.165

**Table 3**

Comparison of GAS, MTL, and VIP levels between cirrhosis group and control group.

Group	n	GAS, pg/mL	MTL, pg/mL	VIP, ng/L
Control group	40	$83.46 \pm 22.50$	$194.87 \pm 25.19$	$56.86 \pm 26.89$
Cirrhosis groups	95	$129.86 \pm 32.29^*$	$151.25 \pm 38.03^*$	$89.16 \pm 42.51^*$

GAS = gastrin, MTL = motilin, VIP = vasoactive intestinal peptide.  
\* *P* < .05, compared with control group.

**Table 4**

Comparison of GAS, MTL, and VIP levels among different groups.

Group	n	GAS, pg/mL	MTL, pg/mL	VIP, ng/L
Control group	40	$83.46 \pm 22.50^{*,\dagger}$	$194.87 \pm 25.19^{*,\dagger}$	$56.86 \pm 26.89^*$
Group A	45	$108.56 \pm 21.58^{*,\ddagger}$	$175.29 \pm 34.45^{*,\ddagger}$	$56.58 \pm 20.64^*$
Group B	23	$131.15 \pm 24.14^{*,\ddagger}$	$129.08 \pm 25.69^{\ddagger}$	$96.54 \pm 27.14^{*,\ddagger}$
Group C	27	$164.26 \pm 21.72^{\ddagger}$	$130.05 \pm 27.59^{\ddagger}$	$137.17 \pm 30.15^{\ddagger}$

GAS = gastrin, MTL = motilin, VIP = vasoactive intestinal peptide.  
\* *P* < .05, compared with group C.  
 $\dagger$  *P* < .05, compared with group A.  
 $\ddagger$  *P* < .05, compared with control group.

**Table 5**

Comparison of GI symptom scores among different Child–Pugh classes.

Group	n	GI symptom score (points)
Class A	45	$1.71 \pm 1.41^*$
Class B	23	$3.13 \pm 1.71^{*,\dagger}$
Class C	27	$7.96 \pm 1.89^{\dagger}$

GI = gastrointestinal.  
\* *P* < .05, compared with group C.  
 $\dagger$  *P* < .05, compared with group A.

patients with higher fasting serum GAS levels had more obvious GI symptoms. Furthermore, the GI symptom score had a higher negative correlation with fasting serum MTL level ( $P < .05$ ,  $r = -0.634$ ). That is, when fasting serum MTL level increased, the GI symptoms became less obvious in cirrhotic patients. However, the GI symptom score had a high positive correlation with fasting serum VIP level ( $P < .05$ ,  $r = 0.820$ ). That is, along with the increase in fasting serum MTL levels, GI symptoms became more obvious in cirrhotic patients (Fig. 1).

### 3.5. Relationship between Child–Pugh class and GI hormone levels in cirrhotic patients

Linear correlation analysis revealed that the Child–Pugh class had a high positive correlation with fasting serum GAS level ( $P < .05$ ,  $r = 0.655$ ). That is, cirrhotic patients with a high Child–Pugh class tended to have high fasting serum GAS levels. In addition, the Child–Pugh class had a moderate negative correlation with fasting serum MTL levels ( $P < .05$ ,  $r = -0.567$ ). That is, cirrhotic patients with a high Child–Pugh class had lower fasting serum MTL levels. Finally, the Child–Pugh class had a high positive correlation with fasting serum VIP levels ( $P < .05$ ,  $r = 0.814$ ). That is, cirrhotic patients with a high Child–Pugh class had high fasting serum VIP levels (Fig. 2).

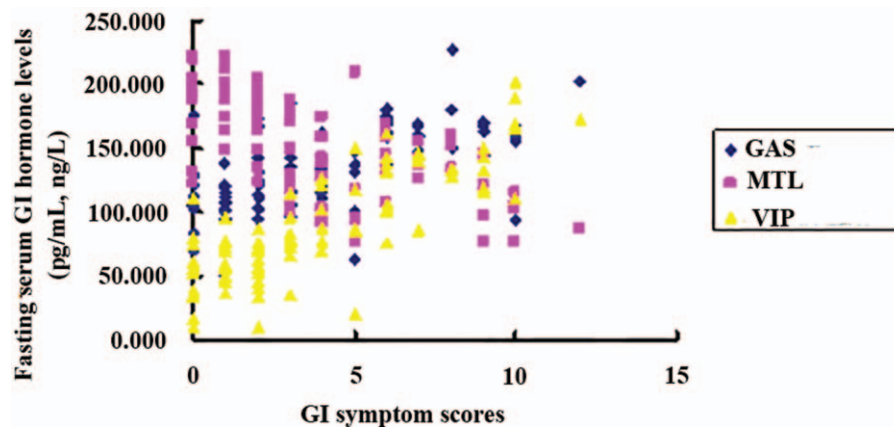


Figure 1. The scatter plot of correlation of symptoms score and gastrointestinal hormone levels in cirrhosis group.

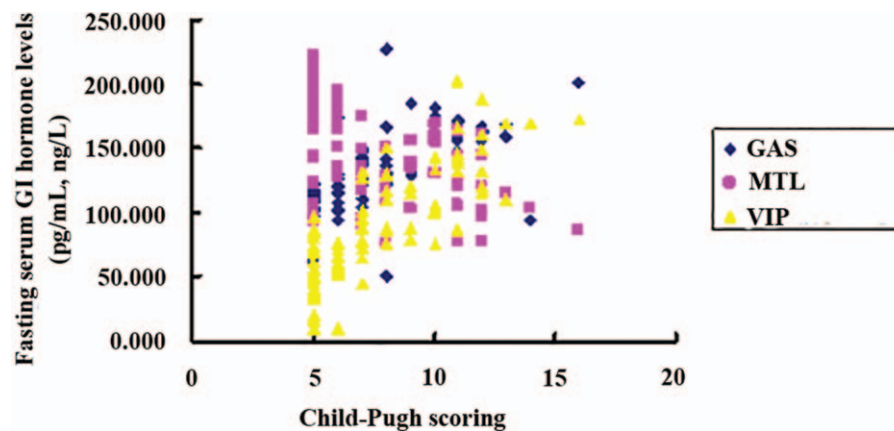


Figure 2. The scatter plot of correlation of Child-Pugh class with gastrointestinal hormone levels in liver cirrhosis group.

### 3.6. Relationship between Child-Pugh class and GI symptom scores in cirrhotic patients

Linear correlation analysis revealed that the Child-Pugh class had a high positive correlation with GI symptom scores in cirrhotic patients ( $P < .05$ ,  $r = 0.837$ ). That is, cirrhotic patients with a high Child-Pugh class tended to have more obvious GI symptoms (Fig. 3).

## 4. Discussion

Cirrhosis is a common liver disease that has an annual incidence of 17/100,000. This disease is mainly found in 20- to 50-year-old males, and the mortality rate of elderly patients with cirrhosis in urban areas can reach 112/100,000. In China, the majority of cirrhosis cases developed from chronic hepatitis B, although chronic alcoholic liver disease, nonalcoholic fatty liver disease, and cholestasis can also be the etiologies.<sup>[11]</sup>

In the present study, the GI symptom score markedly increased in cirrhotic patients. Furthermore, this gradually increased in patients with a Child-Pugh class of A, B, and C, and this increase was more obvious in group C than in groups A and B. Linear correlation analysis revealed that the Child-Pugh class had positive correlation with GI symptom scores. That is, patients

with a high Child-Pugh class tended to have more obvious GI symptoms. Therefore, the occurrence of GI symptoms is parallel to liver function damage in cirrhotic patients, and the GI symptom score increases along with the aggravation of liver function damage. This further demonstrates that the manifestations of GI dysfunction are associated with liver function damage in cirrhotic patients. These symptoms may also be associated with disordered gastric electrical rhythm, autonomic dysfunction, and the decreased inactivation of some GI hormones.<sup>[15]</sup>

Many studies have explored the relationship between cirrhosis and changes in GI hormones, among which quite a few GI hormones are involved in regulating GI activities. In the present study, the relationships of fasting serum GAS, MTL, and VIP with cirrhosis were explored. It was found that fasting serum GAS level was significantly higher in cirrhotic patients than in control group, indicating that cirrhotic patients have high GAS levels. In addition, GAS levels also increase along with the aggravation of liver function damage. These findings are consistent with most previous studies.<sup>[15]</sup> Therefore, serum GAS level is positively correlated with the severity of liver disease. GAS is mainly metabolized in the liver, but it may also be partially metabolized in the capillary bed throughout the body. In cirrhotic

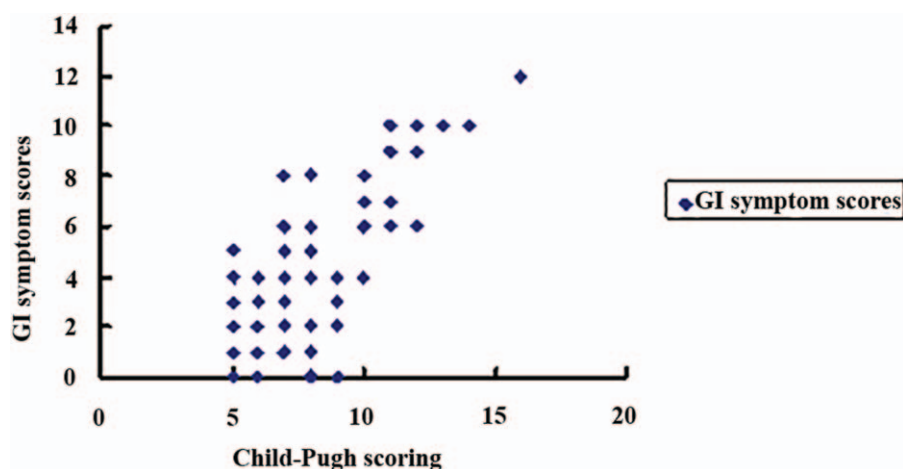


Figure 3. The scatter plot of correlation of Child–Pugh grades with symptoms score in cirrhosis group.

patients, damaged hepatocytes result in the decreased inactivation capability of GAS in the liver, leading to increased GAS levels in blood. Furthermore, portosystemic shunt and portal hypertensive gastropathy caused by portal hypertension can lead to the degeneration and necrosis of gastric parietal cells, which would thereby seriously affect gastric acid secretion and its reactivity to GAS. In the present study, GI symptom scores increased along with the increase in fasting serum GAS levels, and there was a moderate positive correlation between serum GAS levels and GI symptom scores in cirrhotic patients. Various studies have demonstrated that symptoms of GI motility disorder (mainly delayed gastric emptying) are common in most cirrhotic patients.<sup>[16]</sup> The results of the present study are consistent with the hypothesis that the mechanism of GI dysfunction is closely correlated to the abnormal secretion of GI hormones.

Both MTL and GAS are excitatory GI hormones. The main physiologic function of MTL is to affect GI motility. It can promote gastric emptying by regulating the cyclic activity of the migrating motor complex. Studies have shown that the injection of MTL into the lateral ventricle of the brain could increase food intake, and MTL had an anti-anxiety effect on experimental animals. However, these above effects disappeared after the application of a MTL receptor. Thus, the authors consider that MTL might be involved in the regulation of animal feeding and related emotions. In the central nervous system, it might be involved in regulating GI motility by adjusting blood MTL levels.<sup>[17]</sup> Therefore, the central nervous system is closely correlated to the regulation of MTL concentration. In the present study, fasting serum MTL levels were significantly lower in cirrhotic patients, compared with healthy controls. The paired comparison of MTL levels between groups B and C exhibited no significant difference, and this might be explained by the differences in sample size and individual variations. The comparison of group C with group A and the control group revealed that the decrease in serum MTL level was significantly more prominent in patients with more severe liver function damage. Moreover, the present study also found that there was a high correlation between changes in MTL levels and GI symptom scores. Cirrhotic patients often suffer from delayed gastric emptying-related symptoms including anorexia, nausea, and vomiting. Since MTL can stimulate gastric acid secretion, it has an obvious function in promoting gastric emptying. Therefore, the symptoms of GI motility disorder in cirrhotic patients may be

associated with decreased MTL levels, although it can also be caused by disorders of other GI hormones.

In the present study, the fasting serum VIP levels of 95 cirrhotic patients and 40 healthy controls were determined. Compared with healthy controls, cirrhotic patients had significantly elevated fasting serum VIP levels. In addition, cirrhotic patients with different Child–Pugh classes (A, B, and C) also had different VIP levels, when compared with the control group. Although the VIP levels exhibited no significant differences between group A and the control group, group C had a significantly higher VIP level than groups A and B. Therefore, it can be speculated that there is a close relationship between serum VIP levels and liver function damage. VIP is an inhibitory GI hormone that can directly cause LES relaxation, which is the main cause of gastroesophageal reflux disease. Studies have shown that the incidence of gastroesophageal reflux in patients with liver cirrhosis was higher than that in normal subjects, and blood VIP levels in cirrhotic patients with gastroesophageal reflux are significantly higher than in subjects without gastroesophageal reflux.<sup>[18]</sup>

Abnormal secretion of other GI hormones may also occur in cirrhotic patients. Studies have shown that changes in SS, GLU, insulin, substance P, and pancreatic polypeptide levels (increase or decrease, or even no obvious change) in blood were found in cirrhotic patients. These can jointly influence the function and motility of the GI tract.

### Author contributions

**Conceptualization:** Ping Wang.

**Data curation:** Ping Wang, Ying-Jian Zhang, Yi-Ran Li, Xiao-Min Liu, Shu-Yan Lv, Xiao-Yan Xia.

**Formal analysis:** Ping Wang, Ying-Jian Zhang, Yi-Ran Li, Xiao-Min Liu, Shu-Yan Lv, Xiao-Yan Xia.

**Funding acquisition:** Ping Wang.

**Investigation:** Ping Wang, Ying-Jian Zhang, Yi-Ran Li, Xiao-Min Liu, Xiao-Yan Xia.

**Methodology:** Ping Wang.

**Project administration:** Ping Wang.

**Resources:** Ying-Jian Zhang, Yi-Ran Li, Xiao-Min Liu, Shu-Yan Lv, Xiao-Yan Xia.

**Software:** Ying-Jian Zhang, Yi-Ran Li, Xiao-Min Liu, Shu-Yan Lv, Xiao-Yan Xia.

**Supervision:** Ping Wang.

**Writing – original draft:** Ping Wang.

**Writing – review & editing:** Ying-Jian Zhang, Yi-Ran Li, Xiao-Min Liu, Shu-Yan Lv, Xiao-Yan Xia.

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