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The correlation between intestinal mucosal lesions and hepatic dysfunction in patients without chronic liver disease

Li-Hao Wu, BD, Mei-Hui Chen, MM, Jie-Yi Cai, BD, Yu Yuan, BD, Li-Quan Wu, MD, Hui-Min Zhou, MD, Lan Li, MD, Kayiu Wan, PhD, Xing-Xiang He, MD*

Abstract

Patients with cirrhosis are known to develop small bowel mucosal lesions. However, the occurrence of mucosal lesions in patients with abnormal liver function test results in the absence of chronic liver disease has not been fully evaluated. This study aims to examine the association between small bowel endoscopic lesions and liver dysfunction in patients without confirmed chronic liver disease.

Two hundred ninety six consecutive patients who met the selection criteria underwent capsule endoscopy. The severity of the small intestinal mucosal lesions was evaluated quantitatively using the Lewis scoring system, and hepatic dysfunction was evaluated using an algorithm-based combination scoring system with 8 individual serological markers.

Small bowel lesions were observed in 121 patients (40.88%). Hepatic dysfunction was significantly more prevalent in patients with small bowel lesions than in those without lesions (33.1%; 40/121 and 5.7%; 10/175, respectively; $P < .001$). The mean serum ALT and AST levels were significantly higher in patients with small bowel lesions than in those without lesions ($P = .007$ and $P = .004$, respectively). The mean scores for AST to Platelet Ratio Index, Forns Index, S-Index, Fibrosis-4 Index and BARD were significantly higher in patients with small bowel lesions than those without lesions. The Lewis score significantly and positively correlated with the Forns Index ($P = .008$) and the FIB-4 Index ($P = .006$).

There is a close correlation between small intestinal mucosal lesions and hepatic dysfunction. The severity of hepatic dysfunction is directly proportional to the severity of the small intestinal mucosal lesions in patients without confirmed chronic liver disease.

Abbreviations: ALB = albumin, ALT = alanine aminotransferase, AST = aspartate transaminase, BMI = body mass index, BT = bacterial translocation, CE = capsule endoscopy, CT = computed tomography, GGT = gamma-glutamyl transpeptidase, HCC = hepatocellular cancer, PH = portal hypertension, PHE = portal hypertensive enteropathy, PLT = platelets, PT = prothrombin time, SIBO = small intestinal bacterial overgrowth, TBIL = total bilirubin, TC = total cholesterol.

Keywords: algorithm-based combination scoring system, hepatic abnormalities, Lewis scoring system, small intestinal bacterial overgrowth, Small intestinal mucosal lesions

1. Introduction

The small bowel was previously considered to be the most difficult segment of the gut to evaluate due to its long length. Furthermore, the diagnosis of small bowel lesions has been challenging due to its inaccessibility with conventional endoscopy. However, with the development of capsule endoscopy (CE), which is superior to other modalities including small bowel barium studies and push enteroscopy,[1–3] visualization of the whole small bowel has become safe and feasible. It is currently possible to obtain clear CE images with the proper preparation.[4] Mucosal lesions of the small bowel are clinically associated with hepatic dysfunction in patients with cirrhosis and portal hypertension (PH).[5] The pathogenesis of mucosal lesions in the small intestine that are associated with chronic liver damage is still not completely understood. The observation of liver dysfunction in patients without a previously diagnosed chronic liver disease and unexplained chronic recurrent gastrointestinal symptoms represents a true diagnostic challenge to gastroenterologists. For this reason, a considerable amount of work has been performed to investigate the intestinal microbiota and the gut-liver axis. The liver interacts with the gut through the gut-liver axis.[6,7] It is well documented that liver diseases, such as alcoholic liver disease and primary sclerosing cholangitis are associated with qualitative and quantitative changes in the intestinal microbiota.[8,9] Moreover, recent studies have demonstrated that intestinal mucosal lesions are significantly more frequent in cirrhotic patients than in control patients.[5,10,11] However, whether impaired hepatic function is associated with the presence of intestinal mucosal lesions is not known. The

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Department of Gastroenterology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, Guangdong Province, China.

* Correspondence: Xing-Xiang He, Department of Gastroenterology, The First Affiliated Hospital of Guangdong Pharmaceutical University, 19 Nonglin Road, Yuexiu District, Guangzhou 510080, Guangdong Province, China (e-mail: hexingxiang@gdpu.edu.cn).

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present study was conducted to identify suspected small bowel disease in patients with liver dysfunction that did not have confirmed chronic liver disease. Additionally, we aimed to evaluate whether the small bowel endoscopic findings correlated with the severity of the liver dysfunction.

2. Methods

2.1. Study design and patient selection

This single-center retrospective study included consecutive patients who underwent CE between August 2011 and August 2015 in the Department of Gastroenterology at the First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China. The study protocol was approved by the Institutional Review Board of Guangdong Pharmaceutical University (approval no. 201601). A retrospective analysis of the prospectively maintained clinical data of 296 patients with and without small intestinal mucosal lesions and hepatic abnormalities was performed. All of the patients that were included in the present study underwent a basic diagnostic workup, including upper endoscopy, colonoscopy, abdominal ultrasound, and upper gastrointestinal series with small-bowel follow-through (UGI/SBFT) prior to CE, which showed no evidence of portal hypertension. Computed tomography (CT) was performed to rule out complete mechanical intestinal obstruction and detect hepatocellular cancer (HCC) if clinically suspected.

2.2. Inclusion criteria

Patients aged between 18 and 90 years who underwent CE for various complaints during the study period were included after written informed consent was provided. The majority of the patients had gastrointestinal symptoms such as undiagnosed recurrent melena and/or hematochezia, chronic abdominal pain, weight loss, chronic diarrhea, and/or chronic constipation.

2.3. Exclusion criteria

Patients with the following conditions were excluded:

1. confirmed chronic liver diseases, such as liver cirrhosis, non-alcoholic steatohepatitis, alcoholic liver disease, and chronic hepatitis;
2. confirmed hepatitis virus carriers;
3. previously diagnosed liver malignancy;
4. severe heart, pulmonary, or kidney diseases;
5. patients using non-steroidal anti-inflammatory drugs;
6. previously diagnosed patients with complete mechanical intestinal obstruction;
7. patients with implanted cardiac devices;
8. pregnancy; and
9. patients with missing data.

2.4. Clinical data collection

The following patient information was collected: age, gender, body mass index (BMI), smoking and drinking status, the presence of diabetes, *Helicobacter pylori* (*H. pylori*) infection, hepatic encephalopathy, ascites, and serum levels of alanine aminotransferase (ALT), aspartate transaminase (AST), platelets (PLT), gamma-glutamyl transpeptidase (GGT), albumin (ALB), total bilirubin (TBIL), total cholesterol (TC), and prothrombin time (PT).

2.5. Capsule endoscopy

All patients were given standardized instructions before the CE procedure. Patients voluntarily signed the informed consent after the gastroenterologists briefly explained the CE procedure and the potential risks to patients. Patients were instructed to have a semi-liquid diet for 2 days followed by a liquid diet for 1 day prior to the CE. Patients were asked to fast for 8 to 12 h prior to the procedure. At 8 P.M. the night before the procedure, patients were told to drink 1 L of a polyethylene glycol electrolyte solution mixed with 1 L of water. At 6 A.M. the following day, the patients drank an additional 1 L of the polyethylene glycol electrolyte solution and 1 L of water. Two hours before swallowing the capsule endoscope, patients were given 2 doses of tetracaine hydrochloride-endoscope lubricant ("Wei Lang", Fuzhou Seekya Bio-Sci & Tech Co. Ltd., China), and then the capsule (PillCam^{TM}, Medtronic Inc., Minneapolis, MN, USA) was swallowed. A sensor array was applied to the patient's abdomen and connected to the data recorder. All CE examinations were interpreted by 3 gastroenterologists who were unaware of the patients' clinical data. All the gastroenterologists had more than 5 years of experience of interpreting capsule endoscopic findings.

Controversial findings were discussed, and a consensus was reached to make the final diagnosis.

2.6. Evaluation of small intestinal mucosal lesions

The characteristics of small intestinal mucosal abnormalities were assessed using the Lewis scoring system, which was validated for use in the measurement of mucosal inflammatory activity as detected by small-bowel capsule endoscopy (SBCE).[12] The severity of the small intestinal mucosal lesions was quantitatively evaluated by this score. A score less than 135 represented normal or clinically insignificant mucosal lesions; a score between 135 and 790 represented mild mucosal lesions; and a score greater than 790 represented moderate to severe mucosal lesions.

2.7. Evaluation of hepatic function

Eight individual serological markers (ALT, AST, PLT, GGT, ALB, TBIL, TC, and PT) were used to assess hepatic function. In addition, other indices in an algorithm-based combination scoring system, including the AST to Platelet Ratio Index (APRI),[13] Forns Index,[14] S-Index,[15] Fibrosis-4 (FIB-4) index,[16] BARD Score,[17] and Child-Pugh score,[18] were used for qualitative and quantitative analysis of hepatic function. Although the majority of the scoring systems were validated to be applied in cases of specific hepatic diseases,[13–18] in the present study, they were used to further identify our outcomes in an ambitious way. For the clinical applicability, patients with the following scores were identified as having hepatic dysfunction: APRI ≥ 0.95, Forns Index > 6.9, S-Index ≥ 0.5, FIB-4 Index > 2, BARD Score > 2 and/or Child-Pugh ≥ 5.

2.8. Statistical analysis

The analysis was performed using IBM SPSS Statistics v23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were

presented as frequency, ratio, or proportion. Continuous variables with a normal distribution were presented as mean ± standard deviation (SD). Categorical variables were compared using the Chi-Squared or Fisher exact test. Two-group comparisons of continuous variables were performed using the Student *t* test. For multiple-group comparisons, one-way analysis of variance (ANOVA) was used to compare the differences following a test for equal variances. Correlations between continuous variables were studied using Pearson correlation coefficient. Two-sided *P* values less than .05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 296 consecutive patients were included in the study. In all 296 cases, capsules were spontaneously excreted, including 1 case of mucosal edema accompanied by erosion with inflammatory luminal narrowing (mild to moderate; Fig. 1). Of the 296 patients, small intestinal mucosal lesions were detected in 121 patients (40.88%; 121/296), while 175 patients (59.12%; 175/296) did not show any significant mucosal damage (Table 1). Representative images of normal small intestinal mucosa and mucosal abnormalities are shown in Figure 1. The endoscopic appearance of small intestinal mucosal lesions included villous edema, friable/necrotic erosion, mucosal ulcers, mucosal edema accompanied by erosion, and inflammatory strictures.

3.2. Association between liver function tests and intestinal mucosal lesions

The mean serum ALT and AST levels were significantly higher in patients with small intestinal mucosal lesions (20.6 ± 13.9 μ/L

Table 1

Clinical characteristics.

Characteristics	With mucosal lesions (n = 121)	Without mucosal lesions (n = 175)	*P* value
Age (yrs)			
Minimum	22	22	
Maximum	84	89	
Median	61	57	
Mean ± SD	59.7 ± 13.8	57.2 ± 13.9	.117
Gender			
male, n (%)	61 (50.4)	77 (44.0)	.277
BMI, mean ± SD	22.1 ± 3.6	21.8 ± 2.8	.505
Smoking status			
Yes, *n* (%)	24 (19.8)	32 (18.3)	.738
Drinking status	11/110	26/149	
Yes, *n* (%)	11 (9.1)	26 (14.9)	.140
H. pylori infection			
Yes, *n* (%)	70 (57.9)	98 (81.0)	.752
Hepatic encephalopathy			
Yes, *n* (%)	0 (0.0)	0 (0.0)	–
Ascites			
Yes, *n* (%)	0 (0.0)	0 (0.0)	–
Laboratory tests, mean ± SD			
ALT (μ/L)	20.6 ± 13.9	17.0 ± 8.9	.007*
AST (μ/L)	22.8 ± 9.6	20.0 ± 7.1	.004*
PLT ($x10^3$/ml),	217.1 ± 65.8	250.8 ± 82.0	<.001*
GGT (μ/l)	23.6 ± 31.3	18.3 ± 21.4	.103
ALB (g/dl)	40.6 ± 4.3	42.2 ± 4.4	.002*
TBIL (mg/dl)	18.1 ± 63.3	12.1 ± 5.9	.304
TC (mg/dl)	4.5 ± 1.0	4.9 ± 1.0	.004*
PT (s)	13.2 ± 1.1	13.1 ± 1.0	.413
Lewis Score, mean ± SD	153.1 ± 177.3	0.0	<.001*

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate transaminase, BMI = body mass index, GGT = gamma-glutamyl transpeptidase, PLT = platelets, PT = prothrombin time, SD = standard deviation, TBIL = total bilirubin, TC = total cholesterol.

Student *t* tests or Chi-Squared tests were used to compare the 2 groups. $P < .05$ was considered statistically significant.

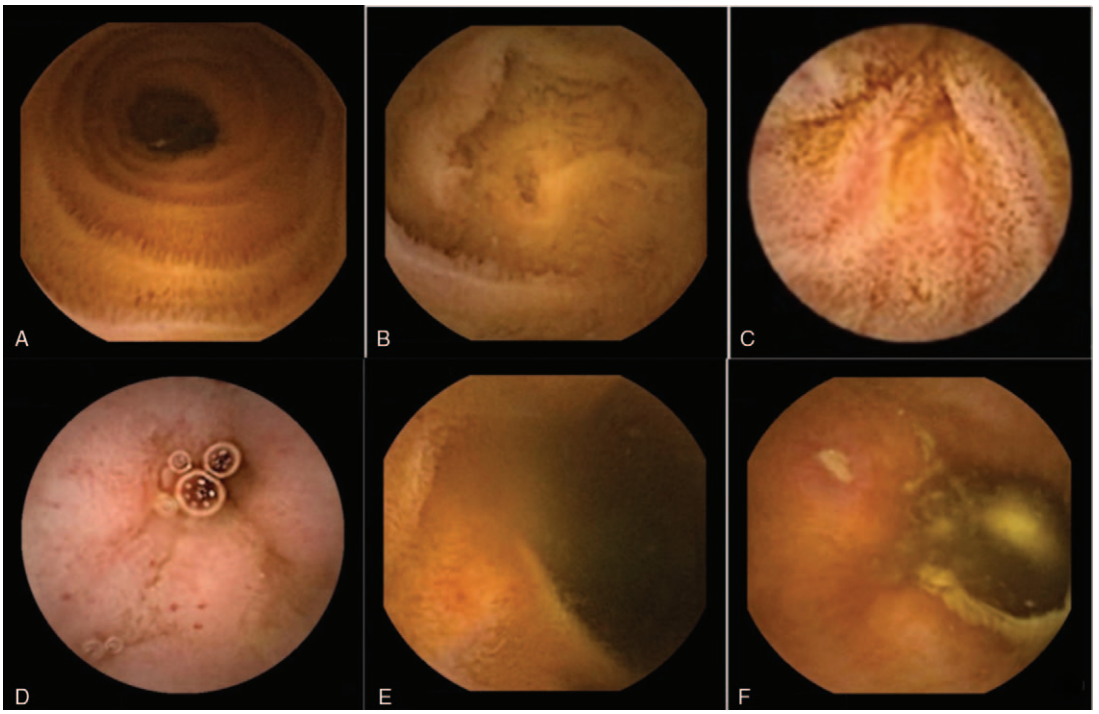

Figure 1. Representative images of normal small intestinal mucosa and mucosal abnormalities. A. Normal mucosa. B. Mucosal edema (mild to moderate). C. Mucosal edema (moderate). D. Mucosal edema accompanied by erosion and inflammatory stricture (mild to moderate). E. Mucosal erosion. F. Mucosal ulcer.

Table 2

Algorithm-based scoring system in patients with mucosal lesions compared with patients without mucosal lesions.

Scoring systems	Mucosal lesions present (n = 121)	Mucosal lesions absent (n = 175)	*P* value
APRI	0.351 ± 0.578	0.222 ± 0.106	.017*
Forns Index	7.543 ± 1.544	6.454 ± 1.393	<.001*
S-Index	0.079 ± 0.125	0.045 ± 0.063	.006*
FIB-4 Index	1.803 ± 1.287	1.181 ± 0.566	<.001*
BARD	2.050 ± 0.729	1.874 ± 0.708	.039*
Child-Pugh	4.17 (4.165) ± 0.489	4.091 ± 0.376	.163

APRI = AST to Platelet Ratio Index, FIB-4 = Fibrosis-4.
Student *t* test was used to compare the 2 groups.
* $P < .05$ was considered statistically significant.

and 22.8 ± 9.6 μ/L, respectively) than those without lesions (17.0 ± 8.9 μ/L and 20.0 ± 7.1 μ/L, respectively; $P = .007$ and $P = .004$, respectively, Table 1). Conversely, the patients without small intestinal mucosal lesions had significantly higher serum levels of PLT, ALB, and TC than in those with mucosal lesions (all $P < .05$, Table 1).

The mean Lewis score of patients with small intestinal mucosal lesions was significantly higher than that of patients without mucosal lesions ($P < .001$, Table 1). Hepatic dysfunction was assessed quantitatively using the algorithm-based combination scoring system. The mean APRI, Forns Index, S-Index, FIB-4 Index, and BARD scores were significantly higher in the group with small intestinal mucosal lesions than the group without mucosal lesions (all $P < .05$, Table 2). In contrast, the mean Child-Pugh score was not significantly different between the 2 groups (Table 2). Hepatic dysfunction was significantly more prevalent in patients with small intestinal mucosal lesions (33.1%; 40/121) than in those without mucosal lesions (5.7%; 10/175; $P < .001$, Table 3).

3.3. Correlation between Lewis score and hepatic dysfunction assessed by algorithm-based combination scoring system

To further investigate the correlation between small intestinal mucosal lesions and the severity of hepatic dysfunction, the correlation between the Lewis scoring system and the algorithm-based combination scoring system was analyzed using Pearson correlation coefficient. It was revealed that the Lewis score significantly and positively correlated with the Forns Index and the FIB-4 Index scores ($P = .008$ and $P = .006$ respectively, Table 4, Fig. 2). However, there was no correlation between the Lewis scoring system and the APRI, S-Index, BARD, and Child-Pugh scores ($P = .308$, $P = .778$, $P = .079$, and $P = .507$ respectively, Table 4, Fig. 2).

Table 3

Comparison between patients with small intestinal mucosal lesions and patients with hepatic impairment.

	Mucosal lesions present (Total n = 121)	Mucosal lesions absent (Total n = 175)	*P* value
With hepatic impairment *n* (%)	40 (33.1%)	10 (5.7%)	<.001*
Without hepatic impairment *n* (%)	81 (66.9%)	165 (94.3%)	

Chi-Squared test was used to compare the 2 groups.
* $P < .05$ was considered statistically significant.

4. Discussion

In the present study, we found that patients without chronic liver disease that had small intestinal mucosal lesions on CE were more likely to have impaired liver function test results than those with normal mucosa. The most common intestinal lesion observed through CE in this study was an ulcer. Moreover, the severity scoring system of the intestinal lesions that were observed through CE had a positive correlation with the Forns Index and the FIB-4 Index scores. However, the etiologies of the endoscopic and serological manifestations of these patients could not be ascertained. It is possible that the etiologies may include inflammatory bowel disease, small bowel vascular diseases, gastrointestinal malignancies, celiac disease,[2] and/or SIBO.[19–25]

In healthy individuals, the intestinal epithelial barrier is pivotal in preventing the translocation of orally taken toxic substances as well as microbes and/or their products into the portal circulation.[26] However, the integrity of the intestinal epithelial barrier requires a maintenance of a balance between diet, gastrointestinal (GI) microbiome, hormones, and the systemic immune status. If the integrity of the intestinal barrier is disrupted, by either the external factors or the gut dysbiosis,[19] intestinal lesions and hepatic impairment could develop. Additionally, there have been various reports suggesting a role of gut microbiota and bacterial translocation (BT) in the pathogenesis of chronic liver disease and PH.[5,8–11,27–32] Conversely, overproduction of nitric oxide is constantly present in PH, leading to the disruption of intestinal epithelial integrity.[28] One possible explanation for the coexistence of small intestinal mucosal lesions and hepatic impairment may be related to the "henhouse" hypothesis. The qualitative and/or quantitative changes in the gut microbiota that result in bacterial translocation can lead to the development of hepatic

Table 4

Correlation between Lewis score and algorithm-based scoring system.

	Lewis scores	
Scoring systems	γ value	*P* value
APRI	0.06	.308
Forns Index	0.155	.008*
S-Index	0.016	.778
FIB-4 Index	0.161	.006*
BARD	0.103	.079
Child-Pugh	0.039	.507

Correlations were analyzed using Pearson correlation coefficient.
* $P < .05$ was considered statistically significant.
APRI = AST to Platelet Ratio Index, FIB-4 = Fibrosis-4.

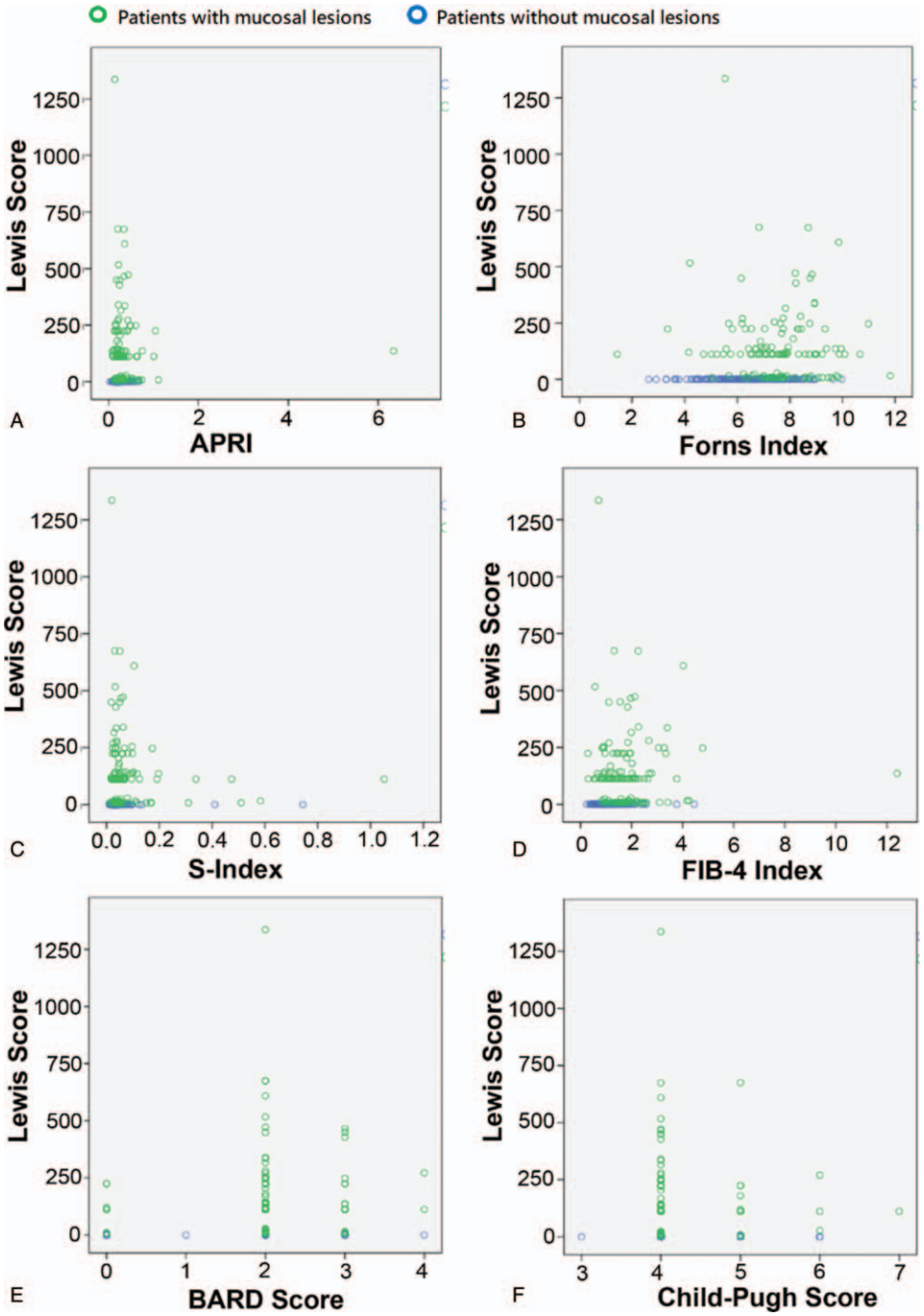

Figure 2. Correlation between the Lewis scoring system and the algorithm-based scoring system. The correlation between the Lewis scoring system and the algorithm-based combination scoring system was analyzed using Pearson correlation coefficient. A. APRI score, AST to Platelet Ratio Index. B. Forns Index. C. S-Index. D. FIB-4 Index, Fibrosis-4 Index. E. BARD score. F. Child-Pugh score.

impairment and chronic liver diseases.[6–9,27–32] However, hepatocellular injury, liver fibrosis, cirrhosis, and portal hypertension can affect the intestinal microbiota and increase bacterial translocation. This leads to a "chicken or the egg" phenomenon, where bacterial translocation increases portal pressure, and vice versa. Thus, intestinal lesions and hepatic impairment may worsen one another, creating a vicious cycle. Regardless of the origin of the initial insult in the gut-liver axis, changes to the gut microbiome may contribute to the development of both intestinal lesions and hepatic dysfunction. Researchers have also indicated that mucosal abnormalities of the GI tract that are secondary to PH can be attributed to an increase in the mucosal permeability.[33] The presence of mucosal inflammatory changes and vascular lesions have been reported to be the manifestations of portal hypertensive enteropathy (PHE).[5,34] We believe that an impairment of the integrity of the intestinal mucosa could be the main reason for the relationship between intestinal mucosal lesions and hepatic dysfunction.

The patterns and types of mucosal lesions in the patients included in this study were distinctly different from those described by De Palma et al.[5] and Figueiredo et al[34] The representative images of mucosal abnormalities in this study are shown in Figure 1. Mucosal vascular lesions observed in patients with cirrhosis and portal hypertension, such as telangiectasias, angiodysplastic-like lesions, varices, areas of mucosa with a reticulate pattern, and active bleeding, were not seen in this study as cirrhotic patients were excluded from this study. However, the most common intestinal lesions that were observed were ulcers, edema, stricture, and erosion. We speculate that small intestinal bacterial overgrowth (SIBO) syndrome could be 1 of the factors responsible for the small bowel ulcers that were observed in this study. A lot of the patients that were enrolled in our study had chronic diarrhea, which can be caused by dysbiosis. Moreover, intestinal dysbiosis plays a vital role in the generation of chronic liver diseases.[35]

The present study used various hepatic scoring systems to assess the relationship between intestinal lesions and the severity of hepatic function. Only the Forns Index and FIB-4 Index scores were positively correlated with the Lewis score. The probable reason for this could be that the accuracy of the different algorithm-based scoring system appears to vary widely, depending on the etiologies underlying the liver disease. Although there is an association between mucosal lesions and hepatic dysfunction, this does not suggest causality. Clinically, it is easy to observe hepatic dysfunction in the absence of chronic liver diseases. However, understanding the clinical interpretation of this dysfunction is difficult. For clinical practice, in patients with severe mucosal lesions, 1 may perform liver function tests to rule out hepatic dysfunction. Additionally, if dysfunction is detected, 1 should individualize the treatment accordingly. However, future prospective studies are required to validate our findings before any clinical recommendations are made.

The present study has some limitations, which should be kept in mind while interpreting the results. First, this is a single-center retrospective study. Second, the sample size was relatively small. Third, we could not prove that small bowel mucosal lesions resulted from intestinal dysbiosis, as this study was not designed to determine SIBO by CE. Nevertheless, our findings indicate that there is a correlation between the presence of small intestinal mucosal lesions and impaired hepatic function. In this regard, a proof-of-concept study, as an extension of the current work, needs to be performed. An ongoing study to evaluate the frequency of SIBO in patients with coexisting small intestinal mucosal lesions and impaired hepatic function is under way at our institute.

In conclusion, our findings indicate that there is a strong correlation between small intestinal mucosal lesions and hepatic dysfunction in patients with no confirmed chronic liver disease. The severity of the hepatic function impairment correlates with the severity of the small intestinal mucosal lesions in such patients.

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Author contributions

All authors read and approved the final manuscript.
Conceived and designed research: Lihao Wu and Xingxiang He.
Collected data and conducted research: Meihui Chen, Huimin Zhou and Lan Li.
Analyzed and interpreted data: Jieyi Cai, Yu Yuan, Liquan Wu and Lihao Wu.
Wrote the initial paper: Lihao Wu.
Revised the paper: Kayiu Wan and Xingxiang He.
Supervision had primary responsibility for final content: Xingxiang He.

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