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Original Article

Clinical characteristics and risk factors of patients with flupirtine-induced liver cirrhosis complicated with upper gastrointestinal bleeding

Mengjun Zhang[1*], Si Huang[2*], Na Ye[3], Xuehong Wang[1]

[1]Department of Gastroenterology, Qinghai University Affiliated Hospital, Qinghai, China; [2]The First People's Hospital of Changde City, Changde, China; [3]People's Hospital of WuLan County, Wulan, Hainan, China. [*]Equal contributors.

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Abstract: Objective: To investigate clinical characteristics and risk factors of patients with Flupirtine-induced liver cirrhosis complicated with upper gastrointestinal bleeding. Methods: A total of 116 patients with liver cirrhosis admitted to our hospital from July 2018 to July 2019 were selected and divided into bleeding group (liver cirrhosis complicated with upper gastrointestinal bleeding, n = 71) and non-bleeding group (liver cirrhosis, n = 45). The clinical data of patients in the two groups were collected, including general data, liver function, urinalysis, coagulation function and imaging data. Univariate analysis and multivariate logistic regression analysis were utilized to find the influencing factors of liver cirrhosis complicated with upper gastrointestinal bleeding. Results: Of the 116 patients, 45 patients had upper gastrointestinal bleeding, with an incidence rate of 38.79%, including 18 patients (40.00%) with rupture of esophageal varices, 9 (20.00%) with rupture of gastric varices, 9 (20.00%) of portal hypertensive gastropathy, 8 (17.78%) with peptic ulcer, 1 (2.22%) with acute erosive hemorrhagic gastritis; 14 (31.11%) experienced recurrent hemorrhage within 72 hours after treatment, but no death occurred. There were 45 cases (38.79%) in the bleeding group, and 71 (61.21%) in the non-bleeding group, and the differences in the course of liver cirrhosis, the degree of esophageal varices, peptic ulcer, portal hypertension, non-steroidal drug medication and TP between the bleeding group and non-bleeding group were significant ($P < 0.05$). Severe esophageal varices, liver cirrhosis, peptic ulcer, portal hypertension, non-steroidal drug medication, and TP ≥ 16 s were found to be risk factors of liver cirrhosis complicated with upper gastrointestinal bleeding by logistic regression analysis. Conclusion: Clinically, it is necessary to take corresponding intervention measures to reduce the incidence of upper gastrointestinal bleeding in patients with liver cirrhosis and improve the prognosis of patients with liver cirrhosis.

Keywords: Liver cirrhosis, upper gastrointestinal bleeding, clinical characteristics, risk factors

Introduction

Liver cirrhosis is a common liver disease in clinical practice, which is characterized by chronic, progressive and diffuse development [1]. It is usually presented with diffuse liver injury caused by long-term action of diverse etiologies, clinically manifested as liver function damage and portal hypertension. Flupirtine is a non-opioid analgesic used to treat acute or chronic pain, such as pain of muscle tension, cancer related pain, menstrual pain, and pain caused by orthopedic surgery or injury. Flupirtine-induced liver cirrhosis causes damage ranging from the elevation of liver enzyme to liver failure, and results in death or liver transplantation of some cases eventually. The length of time in Flupirtine treatment is associated with the occurrence of liver damage, but patients who take less than or equal to 2 weeks will not develop liver failure or liver transplantation.

Upper gastrointestinal bleeding and hepatic encephalopathy often take place in the late stage. Moreover, upper gastrointestinal bleeding, the most common complication of liver cirrhosis, is mostly caused by esophageal and gastric varices, and the rupture of gastric varices. The main clinical symptoms include

hematemesis, melena, etc., with rapid condition, which can lead to acute peripheral circulatory failure in a short period [2, 3]. According to recent studies [4], the mortality rate of liver cirrhosis complicated with upper gastrointestinal bleeding is more than 40.0%, which poses a great threat to the life and safety of patients. Therefore, it is required to analyze the clinical characteristics and identify the factors of liver cirrhosis complicated with upper gastrointestinal bleeding, which are of great clinical significance to take early prevention and treatment measures, reduce the number of bleeding and improve the treatment rate. In this study, 116 patients with liver cirrhosis admitted to our hospital from July 2018 to July 2019 were selected for the study with the purpose to find the clinical characteristics and risk factors of liver cirrhosis complicated with upper gastrointestinal bleeding.

Materials and methods

General data

A total of 116 patients who took Flupirtine for a long time and ended with hepatotoxicity and liver cirrhosis admitted to our hospital from July 2018 to July 2019 were recruited. Inclusion criteria: (1) clinically diagnosed as liver cirrhosis; (2) the absence of obvious contraindications to medication; (3) complete data available; (4) signed informed consent forms. Exclusion criteria: (1) complicated with coronary heart disease, hypertension and diabetes and other cardiovascular and cerebrovascular diseases; (2) the presence of heart, brain, kidney and lung and other vital organ dysfunction or malignant lesions; (3) intolerance to gastroscopy; (4) the presence of speech disorders and mental illness. The patients were divided into bleeding group (liver cirrhosis complicated with upper gastrointestinal bleeding, n = 45) and non-bleeding group (liver cirrhosis, n = 71) according to whether they were complicated with upper gastrointestinal bleeding. This study has been approved by the ethics committee of our hospital.

Methods

Patient-related data

By referring to the electronic medical records of 116 patients with liver cirrhosis, the clinical information of the patients was obtained, including gender, age, course of liver cirrhosis, type of liver cirrhosis (hepatitis B, hepatitis C, alcoholic hepatitis), degree of esophageal varices (severe: esophageal varices showed serpentine tortuous bulge and red sign, or esophageal varices showed beading, nodule or tumor; severe and mild: esophageal varices showed linear or slightly tortuous, with red sign or without red sign), peptic ulcer, portal hypertensive gastropathy, ascites, liver function grade (grade A, B and C), history of gastrointestinal bleeding, non-steroidal drug medication, alcohol history, etc. Meanwhile, it is necessary to assess their urinalysis [blood platelet count (BPC), albumin (ALB), and hemoglobin (Hb)], coagulation function [prothrombin time (PT)], liver function indicators [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL)].

Treatment methods

All patients underwent gastroscopy after admission, and patients with severe bleeding such as massive hemorrhage and shock were first treated with blood transfusion, blood volume supplementation, and anti-shock. Grading of bleeding degree [5]: ① Severe: bleeding volume ≥ 1.5 L, Hb < 70 g/L; ② Moderate: bleeding volume 0.5-1.5 L, Hb 70-100 g/L; ③ Mild: bleeding volume < 0.5 L, Hb at normal level; there was no hematemesis and melena within 1 week of treatment, negative for fecal occult blood and stable HGB level and no active bleeding by gastroscopy and imaging, indicating that it was valid; if the patient still had symptoms of hematemesis and melena, no improvement in signs and symptoms, or even aggravation and death after 1 week of treatment, it was considered as ineffective.

Statistical analysis

SPSS22.0 software was used to analyze and process the study data. Count data were expressed as rate (%) and analyzed by Chi-square test. Measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd) and analyzed by t-test. The risk factors of liver cirrhosis complicated with upper gastrointestinal bleeding were analyzed by binary logistic regression. $P < 0.05$ was considered to be statistically significant. GraphPad prism 8 software was used to plot graphics.

Table 1. Clinical manifestations of liver cirrhosis complicated with upper gastrointestinal bleeding

Clinical manifestation	N	Percentage (%)
Hematemesis	28	62.22
Melena	16	35.56
Dizziness, fatigue	20	44.44
Abdominal pain, fullness	11	24.44
Syncope	15	33.33

Table 2. Etiologies of liver cirrhosis complicated with upper gastrointestinal bleeding

Profile	N	Incidence (%)
Rupture of esophageal varices	32	45.07
Rupture of gastric varices	15	21.13
Portal hypertensive gastropathy	12	16.90
Peptic ulcer	10	14.08
Acute erosive hemorrhagic gastritis	2	2.82

Results

Clinical manifestations of liver cirrhosis complicated with upper gastrointestinal bleeding

The clinical manifestations of liver cirrhosis complicated with upper gastrointestinal bleeding included hematemesis, melena, dizziness, fatigue, abdominal pain, fullness and syncope, etc. (**Table 1**).

Etiologies of liver cirrhosis complicated with upper gastrointestinal bleeding

Among the 116 patients, 45 patients had upper gastrointestinal bleeding, with an incidence of 38.79%, including 18 patients (40.00%) with rupture of esophageal varices, 9 patients (20.00%) with rupture of gastric varices, 9 patients (20.00%) with portal hypertensive gastropathy, 8 patients (17.78%) with peptic ulcer, 1 patient (2.22%) with acute erosive hemorrhagic gastritis (**Table 2**). The constituent ratio of bleeding etiology is detailed in **Figure 1**. 6-aminoacetic acid + 10% glucose solution was dripped intravenously, and octreotide was administered subcutaneously at a dose of 0.1 mg/time q8h. 24 units of pituitrin were infused, glucose was added, and the source of the bleeding was stopped. Furthermore, 14 patients (31.11%) experienced recurrent hemorrhage within 72 h post-dose, without deaths.

Univariate analysis of liver cirrhosis complicated with upper gastrointestinal bleeding

There were 45 cases (38.79%) in bleeding group and 71 cases (61.21%) in non-bleeding group. Moreover, there were statistically significant differences in the course of liver cirrhosis, degree of esophageal varices, peptic ulcer, portal hypertension, non-steroidal drug medication, and TP between bleeding group and non-bleeding group ($P < 0.05$); and there were no statistically significant differences in gender, age, type of liver cirrhosis, ascites, liver function grade, history of gastrointestinal bleeding, alcohol history, BPC, ALB, Hb, ALT, AST and TBIL between bleeding group and non-bleeding group ($P > 0.05$) (**Table 3**).

Multivariate logistic regression analysis of liver cirrhosis complicated with upper gastrointestinal bleeding

Taking the program with statistical significance in univariate analysis (degree of esophageal varices, course of liver cirrhosis, peptic ulcer, portal hypertension, non-steroidal drug medication, and TP) as independent variables, independent variables and value assignment were presented in **Table 2**. It was revealed by logistic regression analysis that severe esophageal varices, course of liver cirrhosis, peptic ulcer, portal hypertension, non-steroidal drug medication and TP ≥ 16 s were considered to be risk factors for liver cirrhosis complicated with upper gastrointestinal bleeding (**Tables 4**, **5**).

Discussion

Liver cirrhosis is a common chronic liver disease that manifests clinically as hepatic impairment, portal hypertension, and even serious complications such as secondary infections, hepatic coma and gastrointestinal bleeding in the advanced stage. Upper gastrointestinal bleeding is the most common complication in the middle and late stages of liver cirrhosis, with the incidence rising in recent years [6, 7]. The liver cirrhosis complicated with upper gastrointestinal bleeding is a manifestation of decompensated liver cirrhosis. Relevant reports [8, 9] showed that approximately 1/3 of patients with liver cirrhosis will be complicated with upper gastrointestinal bleeding in the process of the disease, of which about 25.0% of patients with bleeding may die in the early

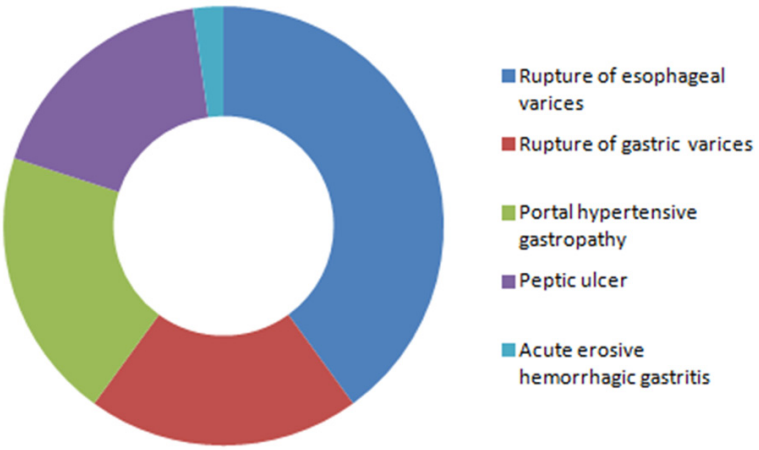

Figure 1. Analysis of the cause of bleeding.

stage of bleeding. Upper gastrointestinal bleeding is more common in the late stage of liver cirrhosis, most patients get severe hemorrhage, while certain patients experience a small amount of bleeding due to concurrent acute erosive gastritis, peptic ulcer and other gastric mucosal lesions [10]. Patients with massive bleeding are clinically presented as hematemesis and melena, which have the potential to cause shock and death if not rescued promptly [11]. Therefore, it is necessary to analyze the clinical characteristics of patients with liver cirrhosis complicated with gastrointestinal bleeding and confirm their causes of the disease timely, which are of great significance to improve the clinical therapeutic effect and save their lives.

Our study demonstrated that of the 116 patients, 45 patients had upper gastrointestinal bleeding with an incidence rate of 38.79%, including 18 patients (40.00%) with rupture of esophageal varices, 9 (20.00%) with rupture of gastric varices, 9 (20.00%) with portal hypertensive gastropathy, 8 (17.78%) with peptic ulcer, and 1 (2.22%) with acute erosive hemorrhagic gastritis. The course of liver cirrhosis, the degree of esophageal varices, peptic ulcer, portal hypertension, non-steroidal drug medication and TP between the bleeding group and non-bleeding group were markedly different ($P < 0.05$). Through standard operation of multivariate logistic regression analysis, it can be inferred that the course of liver cirrhosis, severe esophageal varices, peptic ulcer, portal hypertension, non-steroidal drug medication and TP ≥ 16 s were likely to be risk factors of liver cirrhosis complicated with upper gastrointestinal bleeding. The causes of disease were as follows: (1) The longer course of the disease leads to a higher incidence, which is the same as the result of some studies [11, 12]. In the view of long course of liver cirrhosis, complicated with upper gastrointestinal bleeding, much less economic burden and other conditions, patients tend to experience anxiety, tension, restlessness and other emotions, which may affect or even aggravate their conditions [13]. (2) There is a correlation between esophageal varices and upper gastrointestinal bleeding, which is basically consistent with the relevant reports [14]. The occurrence of gastrointestinal bleeding is affected by the tension and thickness of variceal wall. With the decrease in vascular wall tolerance and the increase in varicosity, the supporting effect of peripheral tissues is weakened, thereby contributing to the increase in upper gastrointestinal bleeding rate. Therefore, the key to preventing the ruptures of esophageal and gastric varices lies in lowering the pressure. The more serious varicosity will lead to more severe injury caused by direct food irritation. The great pressure is associated with the high risk of esophageal and gastric variceal bleeding [15]. (3) Peptic ulcer is mainly attributed to excessive secretion of acidic gastric juice, leading to a certain erosion of the gastric mucosa. Clinical symptoms include periodic epigastric stomach pain, nausea, loss of appetite, etc. Upper gastrointestinal bleeding is closely related to peptic ulcer, whereas peptic ulcer may cause hemorrhage due to corrosion of the surrounding blood vessels, and hemorrhagic shock if left untreated, greatly endangering the safety of patients [16]. (4) Portal venous blood reflux is blocked by liver cirrhosis and portal hypertension, gastric mucosal capillary distension and blood stasis result in gastric mucosal hypoxia, erosion and necrosis, lower barrier function, decreased liver function, reduced inactivation of gastrin and histamine, increased acid secretion of parietal cell and gastric mucosal damage [17]. The rupture of gastric varices is a

Table 3. Univariate analysis of liver cirrhosis complicated with upper gastrointestinal bleeding

Factor	Bleeding group (n = 45)	Non-bleeding group (n = 71)	t/χ^2	*P*
Gender			0.042	0.838
Male	24 (39.34)	37 (60.66)		
Female	21 (37.5)	35 (62.5)		
Age (year)	55.78±11.32	54.58±11.45	0.552	0.581
Course of liver cirrhosis			4.146	0.042
≥ 40	29 (47.54)	32 (52.46)		
< 40	16 (29.09)	39 (70.91)		
Type of liver cirrhosis			2.111	0.348
Hepatitis B	29 (44.62)	36 (55.38)		
Hepatitis C	11 (31.43)	24 (68.57)		
Alcoholic hepatitis	5 (31.25)	11 (68.75)		
Degree of esophageal varices			7.348	0.007
Severe	30 (50.85)	29 (49.15)		
Moderate and mild	15 (26.32)	42 (73.68)		
Peptic ulcer			4.764	0.029
Yes	29 (48.33)	31 (51.67)		
No	16 (28.57)	40 (71.43)		
Portal hypertension			5.373	0.020
Yes	32 (47.76)	35 (52.24)		
No	13 (26.53)	36 (73.47)		
Ascites			0.011	0.916
Yes	30 (38.46)	48 (61.54)		
No	15 (39.47)	23 (60.53)		
Liver function grade			4.757	0.093
Grade A	7 (15.91)	37 (84.09)		
Grade B	24 (51.06)	23 (48.94)		
Grade C	12 (52.17)	11 (47.83)		
History of gastrointestinal bleeding			1.119	0.290
Yes	14 (32.56)	29 (67.44)		
No	31 (42.47)	42 (57.53)		
Non-steroidal drug medication			7.348	0.007
Yes	30 (49.18)	31 (50.82)		
No	15 (27.27)	40 (72.73)		
Alcohol history			0.004	0.952
Yes	18 (39.13)	28 (60.87)		
No	27 (38.57)	43 (61.43)		
TP (s)			13.599	< 0.001
< 16	31 (56.36)	24 (43.64)		
≥ 16	14 (22.95)	47 (77.06)		
BPC (10^9/L)	84.85±9.32	85.02±9.30	0.923	0.095
ALB (g/L)	33.03±3.40	31.98±3.10	0.289	1.172
Hb (g/L)	83.44±9.10	82.10±9.22	0.444	0.766
ALT (U/L)	163.85±14.56	164.20±14.11	0.897	0.128
AST (U/L)	172.25±16.87	171.66±17.10	0.855	0.182
TBIL (μmol/L)	16.90±2.56	17.01±2.77	0.830	0.214

common complication of collateral circulation. Elevated portal venous pressure is of certain value in predicting the occurrence of liver cirrhosis complicated with upper gastrointestinal

Table 4. Potential risk factors and value assignment for liver cirrhosis complicated with upper gastrointestinal bleeding

Factor	Code	Value assignment
Course of liver cirrhosis	X1	0 = ≥ 40, 1 = < 40
Degree of esophageal varices	X2	0 = severe, 1 = moderate and mild
Peptic ulcer	X3	0 = Yes, 2 = No
Portal hypertension	X4	0 = Yes, 2 = No
Non-steroidal drug medication	X5	0 = Yes, 2 = No
TP (s)	X6	0 = ≥ 16, 1 = < 16

Table 5. Multivariate logistic regression analysis of liver cirrhosis complicated with upper gastrointestinal bleeding

Independent variable	β	Wald χ^2	*P* value	OR (95% CI)
Liver cirrhosis for the duration of ≥ 40 months	0.792	4.673	0.032	2.209 (1.201, 3.420)
Severe esophageal varices	1.064	7.908	0.001	2.898 (1.276, 3.651)
Peptic ulcer	0.849	4.725	0.029	2.339 (1.089, 3.290)
Portal hypertension	0.929	5.706	0.006	2.532 (1.582, 3.923)
Non-steroidal drug medication	0.947	5.672	0.012	2.580 (1.816, 4.019)
TP ≥ 16 s	1.468	7.940	0.000	4.341 (2.206, 5.177)

bleeding, and has a better effect on diagnosis and judgment [18]. (5) Non-steroidal drugs show an inhibitory effect on prostaglandin secretion and mucus and bicarbonate secretion, and can reduce mucosal permeability and blood flow. Thus, non-steroidal drugs should be contraindicated, but administered prophylactically for those patients who have to take medication [19]. (6) The long PT time will be more likely to cause gastrointestinal bleeding. Liver injury will not merely reduce the production of immunoglobulins and coagulation factors, but also cause hypersplenism, thereby activating the mononuclear macrophage system and destroying platelets. With the aggravation of liver cirrhosis, hepatic reserve function will decrease, patients can develop prothrombin synthesis disorders, resulting in decreased whole blood cell count and platelet function, and increased risk of bleeding [20].

The course of liver cirrhosis, severe esophageal varices, peptic ulcer, portal hypertension, non-steroidal drug medication and TP ≥ 16 s are thought to be risk factors for liver cirrhosis complicated with upper gastrointestinal bleeding. Clinically, it is necessary to take corresponding intervention measures to reduce the incidence of upper gastrointestinal bleeding in patients with liver cirrhosis and ameliorate the prognosis of patients with liver cirrhosis. However, due to the small sample size, numerous analytical factors, and potentially mutual effects of this study, it is required to expand the sample size and source in the subsequent studies.

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Disclosure of conflict of interest

None.

Address correspondence to: Xuehong Wang, Department of Gastroenterology, Qinghai University Affiliated Hospital, Chengxi District, Xining, Qinghai, China. Tel: +86-13639718580; E-mail: xuehong__wang@126.com

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