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ORIGINAL RESEARCH

Analysis of Factors Influencing Prognosis and Assessment of 60 Cases of Decompensated Cirrhotic Patients with Portal Hypertension

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Objective: To investigate the risk factors for the development of portal hypertension in patients with decompensated cirrhosis and analyze their prognosis.

Methods: Patients with decompensated cirrhosis who were admitted to our hospital and Qu fu People's Hospital from June 2022 to June 2023 were included in this study. Among them, there were 45 male and 15 female patients, with a median age of 56 (range: 35–77) years. A comparative analysis was performed between Group A (hepatic venous pressure gradient, HVPG <16 mmHg) and Group B (HVPG ≥16 mmHg) patients, along with various clinical outcomes. Multivariate analysis was conducted to explore the risk factors influencing the occurrence of portal hypertension and adverse prognosis in patients with cirrhosis.

Results: In Group A patients with portal hypertension, we observed lower levels of aspartate aminotransferase, laminin, serum hyaluronic acid, type III procollagen N-terminal peptide, total bile acids, and cholylglycine acid compared to Group B. On the other hand, levels of alanine aminotransferase, white blood cells, and serum albumin were higher in Group A than in Group B. These differences between the groups were statistically significant ($P < 0.05$). Multivariate analysis of the aforementioned risk factors indicated that low white blood cell count, high cholylglycine acid levels, and high serum hyaluronic acid levels were identified as independent risk factors for the occurrence of difficult-to-control complications in decompensated portal hypertension among patients with liver cirrhosis ($P < 0.05$).

Conclusion: Liver cirrhosis patients with portal hypertension and multiple risk factors like low white blood cell count and high liver transaminase levels should be cautious regarding the progression of portal hypertension when combined with splenomegaly, liver fibrosis, and bile stasis, as it often indicates a poor prognosis.

Keywords: portal hypertension, white blood cells, glycine cholate, serum hyaluronic acid

Introduction

According to statistics, the number of patients with chronic liver diseases in China, including chronic hepatitis, fatty liver, and cirrhosis, may exceed 447 million in 2020. Cirrhosis, as a major cause of morbidity and mortality in hepatic diseases, affects over 120 million people worldwide.[1] Decompensated cirrhosis serves as a turning point in the prognosis, primarily manifested by complications such as ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or variceal bleeding. Accurate staging of decompensated cirrhosis can significantly reduce the risk of mortality.[2] Measurement of HVPG is considered the gold standard for assessing portal hypertension, with HVPG ≥ 16 mm Hg indicating a higher likelihood of refractory complications.[3] Although there have been numerous studies on the risk factors for decompensated cirrhosis in patients with liver cirrhosis, there is a paucity of research focused on the risk

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factors for decompensated cirrhosis with concomitant portal hypertension. In this study, we conducted a retrospective analysis of clinical data from 60 patients with decompensated cirrhosis from our hospital and People's Hospital of Qu fu City. By employing univariate and multivariate logistic regression analysis, we aimed to identify the risk factors for rebleeding in these patients.

Materials and Methods

Clinical Data

In this retrospective analysis, we selected patient records meeting our study criteria from the inpatient electronic case systems at Qingdao Sixth People's Hospital and Qu fu Municipal Hospital. All participant data and relevant measurement outcomes were directly derived from the electronic health records of these two medical centers. To assure data quality, we performed an exhaustive check and validation of these records to ensure the accuracy and completeness of the data for analysis. The inclusion and exclusion criteria, as well as the data validation process, are described in detail in the Methods section of our research. Ultimately, we collected a total of 60 cases of patients suffering from decompensated liver cirrhosis with concomitant portal hypertension as subjects for our study.

Inclusion and exclusion criteria: Diagnosis of cirrhosis was established based on the diagnostic criteria of the revised "Guidelines for the Diagnosis and Treatment of Cirrhosis" in 2019.[4] The diagnosis of portal hypertension was made according to the diagnostic criteria outlined in the "Expert Consensus on the Clinical Application of Hepatic Venous Pressure Gradient in China"[3] All patients with cirrhosis presented with varying degrees of decompensated manifestations upon admission and were clinically diagnosed with decompensation. All patients underwent measurement of hepatic venous pressure gradient. Exclusion criteria included concomitant liver cancer or other malignant tumors, hematologic disorders, previous treatment for decompensation events, and incomplete data.

Measurement of Hepatic Venous Pressure Gradient

Hepatic venous pressure gradient (HVPG) measurement was performed using the balloon catheter occlusion technique. Under monitored conscious sedation with electrocardiogram monitoring, the internal jugular vein was punctured, and a catheter with a balloon at the tip was advanced through the brachial vein into the hepatic vein or right hepatic vein. A Swan-Ganz catheter was floated into the right or middle hepatic vein along the catheter sheath. After inflation of the balloon to block the blood flow, wedged hepatic venous pressure (WHVP) was measured. The balloon was then deflated to measure free hepatic venous pressure (FHVP) and inferior vena cava pressure. The hepatic venous pressure gradient was calculated as WHVP minus FHVP. WHVP and FHVP were measured three times and the average values were obtained.

Observation Indicators and Follow-Up

Clinical data of all patients were collected, including gender, age, etiology, and medical history. Upon admission, the following measurements were recorded: peripheral blood routine, liver function, coagulation function, liver fibrosis four indicators, serum bile acids, transient elastography of the liver (Fibroscan), and HVPG measurement. Follow-up and readmission were used to gather information on previous decompensation events. Based on the HVPG measurement, severe decompensation events were evaluated and classified into Group A (HVPG < 16 mmHg, 24cases) and Group B (HVPG ≥ 16 mmHg, 36cases).

Treatment Methods

During the study period, all patients received routine hepatoprotective, anti-fibrotic, etiological, and no previous treatment for reducing portal hypertension.

Statistical Methods

SPSS 27.0 statistical analysis software was used to analyze the data of the two groups Normally distributed continuous variables were presented as mean ± standard deviation ($\bar{x} \pm s$) and were compared between groups using *t*-test Non

normally distributed variables were presented as media (interquartile range) Categorical variables were presented as counts (%) and were compared using *t*-test or Z-test for univariate analysis, and multiple factor logistic regression analysis was performed A P value<0.05 was considered statistically significant.

Ethical Considerations

This study strictly adheres to the guidelines set out in the Declaration of Helsinki. The retrospective analysis of clinical data was accomplished with utmost measures taken for de-identification of personal information during the data collection process. Because this study is in retrospective nature, there was no requirement of informed consent from the patients. We had extensive consultations with the Ethics Committee of Qingdao Sixth People's Hospital and Qu fu People's Hospital, and it was collectively determined that our study does not require formal ethical approval. The study protocol as well as data handling procedures were designed to uphold patient confidentiality and privacy, aligning with the principles outlined in the Declaration of Helsinki.

Results

Among the 60 included patients, there were 45 males and 15 females, with an age range of 35–77 years and a mean age of (51.33 ± 16.45) years. The reasons for liver cirrhosis included 7 cases of self-limited cirrhosis, 39 cases of hepatitis B related cirrhosis, 8 cases of alcohol related cirrhosis, 4 cases of cirrhosis of unknown etiology, and 1 case each of hepatitis C related cirrhosis and Hepatic venous occlusive disease leading to liver cirrhosis. In Group A, there were 14 cases classified as Child Pugh grade A, 8 cases as grade B, and 2 cases as grade C, with 1 death during follow-up. In Group B, there were 12 cases classified as Child Pugh grade A, 19 cases as grade B, and 5 cases as grade C, with 2 deaths during follow-up.

Univariate Analysis of Portal Hypertension in Compensated Cirrhosis

Significant differences (P<0.05) were observed between the two groups in terms of alanine aminotransferase (ALT), aspartate aminotransferase (AST), laminin (LN), hyaluronic acid (HA), type III collagen amino-terminal peptide (PCIII), total bile acid (TBA), Cholylglycine (CG), white blood cell count (WBC), and albumin (ALB). Refer to attached Table 1.

Multivariate Analysis of Portal Hypertension in Compensated Cirrhosis

Multivariate logistic regression analysis was conducted on the variables with P<0.05 in the univariate analysis. The results indicated that low white blood cell count, high Cholylglycine, and high hyaluronic acid were associated as independent risk factors with the development of portal hypertension in decompensated patients (P<0.05). Refer to attached Table 2.

Discussion

Portal hypertension (PH) is a progressive complication of liver cirrhosis, and problems resulting from PH are the leading cause of death in patients with compensated cirrhosis.[5] Therefore, early identification of portal hypertension, regular monitoring of portal vein pressure, and timely intervention are of paramount importance. As research progresses, several non-invasive markers have been proposed. However, none of these non-invasive markers have yet been applied in clinical practice.[6–9] During the decompensated phase, due to limitations in patient conditions, some patients may not receive accurate assessment of HVPG (hepatic venous pressure gradient) in a timely manner, resulting in missed opportunities for optimal intervention and treatment.

This study includes 60 patients with cirrhosis who have underlying HVPG measures, of which 39 were assigned to hepatitis B virus (HBV) infection as the etiology of their liver cirrhosis. HVPG serves as a direct index of portal hypertension, an essential reflection of circulatory dynamics, thereby rendering it as an indicator of the severity of liver circulation. Specifically, an increase in HVPG indicates an aggravation of liver cirrhosis and a poorer liver functional reserve. Elevated portal vein pressure correlates with a greater degree of esophageal varices.[10–12] The Child-Pugh score is commonly used in clinical practice to assess liver function,[13,14] with higher scores indicating worse liver function. Research by Zheng Jin Liu[15] has shown that HVPG values in patients classified as Child-Pugh C are higher than those in

Table 1 Comparison of General Information Between Two Groups

Item	Group A (24 Cases)	Group B (36 Cases)	Significance	P-value
Age (*years*)	55.67±10.724	54.97±9.557	t=0.263	0.794
Gender Male (%)	16 (66.667%)	29 (80.556%)	χ^2=1.481	0.224
WBC (×*10^9/L*)	4.445±1.944	3.653±2.185	t=1.437	0.007
PT (*s*)	14.183±2.099	15.036±2.477	t=−1.386	0.171
APTT (*s*)	34.158±6.427	36.031±5.637	t=−1.192	0.238
INR	1.232±0.183	1.314±0.213	t=−1.552	0.126
TBIL (*μmol/L*)	28.055±16.1	28.993±18.539	t=−0.202	0.841
ALT (*U/L*)	27.714±20.418	19.0 (34.5)	Z=−0.498	0.009
AST (*U/L*)	26.0 (14.0)	31.0 (19.5)	Z=1.087	0.007
ALP (*U/L*)	86.692±42.26	104.709±56.983	t=−1.314	0.194
GGT (*U/L*)	39.0 (81.0)	40.0 (53.3)	Z=0.196	0.844
PA (*mg/L*)	0.146±0.058	0.09 (0.06)	Z=−1.005	0.315
ALB (*g/L*)	35.588±6.819	32.753±5.554	t=1.696	0.097
TBA (*μmol/L*)	12.329±8.249	38.2 (57.6)	Z =3.006	0.003
LN (*μg/mL*)	55.4±24.1	53.7 (71.4)	Z=0.628	0.006
HA (*μg/mL*)	113.286±57.573	397.362±22.13	t=−2.53	0.018
PCIII (*μg/mL*)	52.5±32.417	101.897±91.227	t=−1.719	0.031
IV-C (*μg/mL*)	86.95±52.03	269.247±198.198	t=−1.521	0.137
CG (*μg/mL*)	4.456±3.143	10.847±5.33	t=−3.315	0.003
LSM (*kPa*)	40.214±24.793	19.2 (36.8)	Z=0.978	0.344

Notes: Parentheses indicate median values, while the values outside the parentheses represent the interquartile range. "t" denotes the *t*-test, "z" denotes the z-test, and "p < 0.05" indicates statistical significance.
Abbreviations: WBC, white blood cell count; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AKP, Alkaline Phosphatase; GGT, Gamma-Glutamyl Transferase; PA, Pyruvate Dehydrogenase; TBA, total bile acid, CG, Cholylglycine, ALB, albumin; LN, laminin; HA, hyaluronic acid; PCIII, type III collagen amino-terminal peptide; IV-C, Type IV Collagen Amino-Terminal Peptide; LSM, liver stiffness measurement.

Table 2 Multifactorial Regression Analysis of Factors Influencing the Occurrence of Difficult-to-Control Complications in Decompensated Cirrhosis with Portal Hypertension

Factors	Regression Coefficient	Standard Deviation	X^2	P	OR	95% CI
WBC	−0.741	0.532	1.941	0.009	0.477	0.168~1.351
TBA	0.119	0.076	2.46	0.004	1.126	0.971~1.307
HA	0.009	0.007	1.498	0.027	1.009	0.995~1.024

Abbreviations: WBC, white blood cell count; TBA, total bile acid; HA, hyaluronic acid, PCIII, type III collagen amino-terminal peptide.

class B. Our study suggests that within the compensated phase of cirrhosis, a significant number of patients still maintain a Child-Pugh classification of A. However, as HVPG increases, the Child-Pugh classification worsens consistently. The indications of poor liver function and more severe portal hypertension in patients with decompensated cirrhosis are becoming more evident.

According to the consensus recommendations, an HVPG level ≥ 16 mmHg indicates a significant risk of complications related to portal hypertension3. In this study, compensated cirrhotic patients with portal hypertension were divided into two groups: those with HVPG < 16 mmHg and those with HVPG ≥ 16 mmHg. The analysis of non-invasive indicators revealed differences between these two groups. With the elevation of HVPG, AST, LN, HA, PC III, TBA, and CG demonstrated an increasing trend, while ALT, WBC, and ALB demonstrated a decreasing trend. This suggests that higher HVPG levels correspond to more severe portal hypertension, impaired liver and coagulation function, and increased severity of liver fibrosis and splenic hyperfunction, which aligns with the clinical progression of liver disease. Further diversified analysis of these factors indicated that low WBC, high CG, and high HA serve as independent risk factors for the development of complications related to portal hypertension in patients with decompensated cirrhosis.

Furthermore, this also implies that during the progression of decompensated cirrhosis, when splenic hyperfunction occurs, attention should be paid to the progression of portal hypertension caused by liver fibrosis activity and bile stasis, often indicating a poor prognosis.

Laminin, a unique non-cohesive structure protein found in the cellular basement membrane, serves as a sensitive indicator for early detection of liver fibrosis. It is closely associated with the degree of liver fibrosis and portal pressure, playing a significant role in the formation of liver fibrosis and the capillarization of liver sinusoids. In patients with liver fibrosis, serum laminin can combine with type IV collagen protein to form the fibrous septum of the liver basement membrane, which plays a critical role in hepatic sinusoidal capillarization.[12,13] Hyaluronic acid, a glycoprotein composed of proteins and glycosaminoglycans, can be synthesized by normal cells and efficiently degraded in liver epithelial cells. It is widely present in the extracellular matrix and is absorbed and degraded in liver epithelial cells.[14,15] With progressive liver fibrosis, endothelial cells cannot perform normal physiological activities, and their ability to degrade hyaluronic acid correspondingly decreases. Thus, an increase in its concentration can be observed in peripheral blood. The extent of liver damage also significantly increases, leading to a series of changes like liver fibrosis and inflammatory changes. Therefore, the detection of hyaluronic acid in peripheral blood can serve as an indicator for assessment and diagnosing portal hypertension.[16,17]

Cholylglycine is the most abundant organic acid secreted into bile by the liver, aiding in fat digestion and absorption in the intestinal tract. The majority of CG is absorbed in the ileum and colon and enters the liver via the portal vein. Liver cells effectively uptake a significant amount of CG from the portal vein, maintaining serum CG concentrations within the normal range. Absorbed CG can rejoin the enterohepatic circulation, and in cases of hepatic disease, the concentration of CG will elevate accordingly. Compared to other indicators, the occurrence of CG is relatively early, its duration is long, and its recovery time is late, making it superior in assessing liver cell damage. Levels of CG can mildly elevate in acute and chronic diseases and significantly rise during cirrhosis. Although CG has been recognized as a sensitive and reliable indicator reflecting liver damage, it lacks specificity when tested alone. In this study, we conducted tests on liver function indicators in patients with decompensated cirrhosis. By comparing the group with HVPG < 16mmHg and the group with HVPG ≥ 16mmHg, we discovered that the serum CG level in the HVPG ≥ 16mmHg group was higher than that in the HVPG < 16mmHg group. This suggests not only can the expression of serum CG detect liver episodes, but it also has the potential to predict portal pressure in cirrhotic patients.

There are several limitations to this study. Firstly, research has shown that non-invasive markers may have varying performance in predicting HVPG in liver cirrhosis of different etiologies. This study did not differentiate between liver cirrhosis of various causes, which could potentially impact the results. Moreover, the study had a small sample size, which led to the lack of validation of the discovered risk factors. Thus, it is unclear whether WBC, CG, and HA still exhibit good predictive value in other populations. FibroScan measurements of liver stiffness measurement (LSM) have been demonstrated to have value for predicting portal hypertension in several studies as an early assessment method for cirrhosis. Unfortunately, in this study, accurate LSM measurements could not be obtained for decompensated patients due to the presence of ascites, which might introduce errors in the statistical results. In addition, we also overlooked the significant presence of sarcopenia in decompensated liver cirrhosis, primarily due to the lack of a universally accepted definition and common diagnostic criteria for assessing sarcopenia. Consequently, we did not investigate sarcopenia as a risk factor in our study. In future investigations, we intend to expand our study population to encompass a broader range of individuals, conducting more comprehensive research on decompensated liver cirrhosis and its accuracy. We will aim to incorporate the assessment of sarcopenia into our subsequent studies, recognizing its importance in this patient population.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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