Original Article

Hypoglycemia on admission in patients with acute on chronic liver failure: a retrospective cohort analyzing the current situation, risk factors, and associations with prognosis

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Background: Hypoglycemia is a common phenomenon in patients with various severe liver diseases. However, its implications for the prognosis of patients with acute on chronic liver failure remains largely unknown. This study investigated the status of hypoglycemia in patients with acute on chronic liver failure, as well as its risk factors and correlation with 90-day patient outcomes.

Methods: A total of 218 patients with acute on chronic liver failure diagnosed and treated in our hospital from January 2019 to August 2021 were enrolled. Hypoglycemia is defined as a fasting blood glucose level ≤2.8 mmol/L. Baseline data on the patients' clinical characteristics and laboratory examinations were collected. Patients were followed-up with a primary outcome of 90-day mortality. The risk factors for hypoglycemia were identified by univariate and multivariate logistic regression.

Results: A total of 99 cases (45.41%) had hypoglycemia. Liver cirrhosis [odds ratio (OR) =5.16, P<0.001] and a higher model for end-stage liver disease (MELD) score (OR =1.29, P<0.001) were risk factors for hypoglycemia in acute on chronic liver failure, while higher fibrinogen (FIB) was a protective factor for hypoglycemia (OR =0.17, P=0.001). The 90-day mortality rate in the hypoglycemia group was significantly higher than that in the non-hypoglycemia group (72.73% *vs.* 48.74%, P<0.001). After adjusting for hepatic encephalopathy, cirrhosis, and MELD scores, hypoglycemia (OR =8.72, P=0.01) was still an independent risk factor for 90-day mortality in patients with acute on chronic liver failure.

Conclusions: Hypoglycemia is common in patients with acute on chronic liver failure and is related to poor prognosis. Patients with cirrhosis, a higher MELD score, and a significant decrease in FIB are more likely to develop hypoglycemia. Thus whether ameliorating hypoglycemia could improve patient outcomes deserves additional investigations.

Keywords: Acute on chronic liver failure; hypoglycemia; risk factors; prognosis

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Introduction

Acute on chronic liver failure is a serious clinical syndrome characterized by acute liver dysfunction in patients with chronic liver disease, which has a high mortality rate and poor prognosis (1). In China, hepatitis B virus infection is the leading cause of acute on chronic liver failure. Since the liver is the most important organ for the synthesis, storage, decomposition, and release of glycogen in the body, it plays a vital role in maintaining and regulating the stability of blood glucose levels. Patients with acute on chronic liver

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failure are more likely to develop hypoglycemia in the presence of massive hepatocyte necrosis, which seriously affects the synthesis, storage, and release of glycogen and weakens the inactivation of hypoglycemic hormones such as insulin by the liver (2). Previous studies (3-5) have shown that abnormal glucose metabolism is extremely common in patients with liver disease, and the incidence of hypoglycemia in patients with severe liver disease is as high as 56%. Hypoglycemia can not only increase the incidence of adverse events in patients but also exerts adverse effects on long-term prognosis. There are few studies on hypoglycemia in patients with acute on chronic liver failure, and most of the available studies focused on the mechanism of gluconeogenesis. There is also a lack of research on blood glucose management, risk factors, and prognosis in these patient populations. To the best of our knowledge, studies that explored the predictive role of hypoglycemia in acute on chronic liver failure remain scarce. Therefore, to bridge this gap, this study aims to clarify the risk factors of hypoglycemia and explore its impact on the outcome of patients with acute on chronic liver failure. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1422/rc).

Highlight box

Key findings

- This study found that hypoglycemia is common in patients with acute on chronic liver failure, which is related to poor patient prognosis. Patients with cirrhosis, a high MELD score, and a significant decrease in fibrinogen are more likely to suffer from hypoglycemia.

What is known and what is new?

- A hypoglycemic attack can increase the incidence of adverse events in patients with acute on chronic liver failure.
- This study confirmed that the prognosis of acute on chronic liver failure patients with hypoglycemia was poor, providing a theoretical basis and reference for the follow-up blood glucose management and intervention of such patients.

What is the implication, and what should change now?

- This study suggests that medical staff should pay attention to the blood glucose management of such patients, and avoid hypoglycemia by strengthening blood glucose monitoring, adjusting diet structure, and adding meals before sleep.

Methods

Subjects

In this retrospective study spanning from January 2019 to August 2021, 218 patients with acute on chronic liver failure were selected (*Figure 1*). Assuming that a 5% difference in hypoglycemia rate is clinically significant, 201 patients were estimated to be needed to achieve 80% power with a two-sided significance level of 0.05 based on the sample size calculation for retrospective cohort study. The inclusion criteria were as follows: (I) patients aged ≥18 years old; and (II) patients who met the diagnostic criteria of chronic and acute liver failure in the *Guidelines for the Diagnosis and Treatment of Liver Failure* (2018 edition). The exclusion criteria were as follows: (I) patients with abnormal glucose metabolism (such as diabetes) and impaired fasting glucose diagnosed before the presence of liver disease; (II) those with malignant liver tumors or severe renal insufficiency; (III) patients taking medications that disrupt blood glucose, such as insulin, oral hypoglycemic medications, glucocorticoids, and others; (IV) special patient populations, such as pregnant women, alcohol-dependent patients, and others; and (V) patients with incomplete clinical and laboratory examination data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2018LSK-217) and informed consent was obtained from all patients.

Research methods

The patients' general clinical characteristics and laboratory examination data on admission were collected through the electronic medical record. General clinical characteristics collected included patient age, gender, body mass index (BMI), co-morbidities (hypertension, chronic heart failure), Child-Pugh score, hepatic encephalopathy, liver cirrhosis, gastrointestinal bleeding, hepatic ascites, and hepatorenal syndrome. Laboratory tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), serum albumin (Alb) and prealbumin, serum creatinine (Scr), international normalized ratio (INR), white blood cell count (WBC), fibrinogen (FIB), and model for end-stage liver disease (MELD) score (6).

According to the diagnostic criteria of hypoglycemia in

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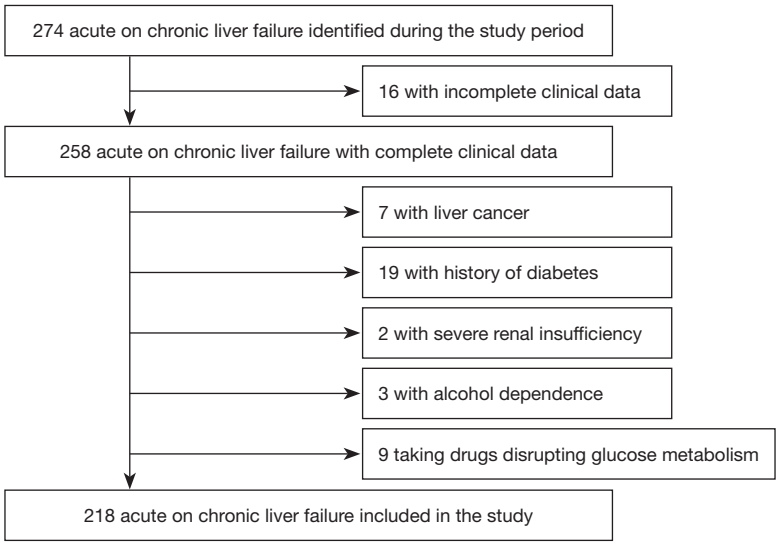

Figure 1 Study flow chart.

the *2013 China Guidelines for the Prevention and Treatment of Type 2 Diabetes*, a fasting blood glucose ≤2.8 mmol/L during hospitalization is characteristic of hypoglycemia. The prognosis of patients was defined as the survival state at 90 days from the onset of acute on chronic liver failure, as the majority of the mortalities occurred within 3 months after disease onset. The patients were divided into the deceased group and the survival group.

Statistical analysis

SPSS 25.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis. The enumeration data were expressed as numbers and percentages and compared with the chi-square test. The measurement data were expressed as the mean ± standard deviation or median with interquartile range and compared using the independent sample *t*-test or the non-parametric Mann-Whitney U test, as appropriate. The risk factors for hypoglycemia were first screened by univariate analysis, and the significant factors were further subject to multivariate binary logistic regression. A two-sided P<0.05 denoted statistical significance.

Results

Comparison of the patients' general characteristics and laboratory test results

Among the 218 cases included, 99 cases (45.41%) had hypoglycemia. As shown in *Table 1*, compared with the non-hypoglycemic group, the proportion of liver cirrhosis and ascites, AST, TBIL, and MELD in the hypoglycemic group were significantly higher, whereas FIB was significantly lower. The 90-day mortality rate in the hypoglycemia group was markedly higher than that in the non-hypoglycemia group (72.73% *vs.* 48.74%, P<0.001).

Analysis of the risk factors for hypoglycemia

The multivariate binary logistic regression (*Table 2*) results showed that liver cirrhosis [odds ratio (OR) =5.16] and a higher MELD score (OR =1.29) were risk factors for hypoglycemia in patients with acute on chronic liver failure, whereas FIB was a protective factor for hypoglycemia (OR =0.17).

Univariate analysis of the risk factors for 90-day mortality

A total of 130 (59.63%) of the 218 included patients died within 90 days of onset (*Table 3*). Compared with the patients in the survival group, the deceased group had a significantly higher proportion of patients with liver cirrhosis, hepatic encephalopathy, gastrointestinal bleeding, hepatic ascites, higher MELD scores, and hypoglycemia.

Multivariate analysis of 90-day mortality

Binary logistic regression analysis (*Table 4*) showed that hepatic encephalopathy, cirrhosis, a higher MELD score,

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Table 1 Comparison of the general characteristics and laboratory test results between the hypoglycemia and non-hypoglycemia groups

Variables	Hypoglycemia group (n=99)	Non-hypoglycemia group (n=119)	t/χ^2/Z value	P value
Age (years)	69.67±5.85	70.34±5.65	–0.86	0.39
Gender, n (%)			0.55	0.46
Male	67 (67.68)	86 (72.27)		
Female	32 (32.32)	33 (27.73)		
Body mass index (kg/m^2)	22.57±2.91	22.16±3.07	1.02	0.31
Hypertension, n (%)	11 (11.11)	23 (19.33)	2.77	0.10
Chronic heart failure, n (%)	15 (15.15)	20 (16.81)	0.11	0.74
Child-Pugh score, n (%)			1.61	0.45
A	4 (4.05)	7 (5.88)		
B	49 (49.49)	67 (56.30)		
C	46 (46.46)	46 (38.66)		
Hepatic encephalopathy, n (%)	23 (23.23)	25 (21.01)	0.16	0.69
Liver cirrhosis, n (%)	64 (64.65)	49 (41.18)	11.92	<0.001
Gastrointestinal bleeding, n (%)	6 (6.06)	8 (6.72)	0.04	0.84
Hepatic ascites, n (%)	78 (78.79)	68 (57.14)	11.45	<0.001
Hepatorenal syndrome, n (%)	5 (5.05)	4 (3.36)	0.39	0.53
ALT (U/L)	335 [276, 437]	314 [243, 400]	–1.66	0.10
AST (U/L)	264 [207, 308]	216 [161, 276]	–3.85	<0.001
TBil (μmol/L)	379 [317, 424]	308 [260, 370]	–4.99	<0.001
Alb (g/L)	32.9 [30.0, 36.2]	33.4 [31.0, 35.7]	–0.91	0.36
Prealbumin (mg/L)	36.4 [30.0, 42.8]	35.7 [30.8, 42.2]	–0.36	0.72
Scr (μmol/L)	71 [58, 82]	67 [58, 78]	–1.15	0.25
INR	2.50 [2.21, 2.81]	2.53 [2.23, 2.76]	–0.43	0.67
WBC (×10^9/L)	7.10 [5.40, 8.80]	6.80 [5.10, 8.61]	–0.91	0.36
FIB (g/L)	1.30 [1.11, 1.60]	1.60 [1.21, 1.80]	–3.71	<0.001
MELD score (points)	31 [27, 33]	25 [20, 29]	–7.10	<0.001
90-day mortality, n (%)	72 (72.73)	58 (48.74)	12.92	<0.001

Data are expressed as n (%), median [interquartile range] or mean ± standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; Alb, serum albumin; Scr, serum creatinine; INR, international normalized ratio, WBC, white blood cell count; FIB, fibrinogen; MELD, model for end-stage liver disease.

Table 2 Analysis of the risk factors for hypoglycemia in patients with acute on chronic liver failure

Variables	β	Standard error	Wald value	OR (95% CI)	P value
Liver cirrhosis	1.64	0.46	12.99	5.16 (2.11–12.60)	<0.001
Hepatic ascites	0.81	0.4	3.07	2.24 (0.23–4.89)	0.94
AST (U/L)	0.01	0.003	0.29	1.01 (0.54–2.00)	0.76
TBil (μmol/L)	0.01	0.002	0.28	1.00 (0.87–1.23)	0.44
FIB (g/L)	–1.77	0.53	11.12	0.17 (0.06–0.48)	0.001
MELD score (points)	0.26	0.04	36.28	1.29 (1.19–1.41)	<0.001

AST, aspartate aminotransferase; TBil, total bilirubin; FIB, fibrinogen; MELD, model for end-stage liver disease; OR, odds ratio; CI, confidence interval.

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Table 3 Univariate analysis results of the risk factors for 90-day mortality in patients with acute on chronic liver failure

Variables	Deceased group (n=130)	Survival group (n=88)	t/χ^2/Z value	P value
Age (years)	69.94±5.54	70.17±6.05	−0.29	0.77
Gender, n (%)			0.46	0.50
Male	89 (68.46)	64 (72.73)		
Female	41 (31.54)	24 (27.27)		
Body mass index (kg/m^2)	22.26±3.03	22.47±2.97	−0.50	0.62
Hypertension, n (%)	19 (14.62)	15 (17.05)	0.24	0.63
Chronic heart failure, n (%)	24 (18.46)	11 (12.50)	1.38	0.24
Child-Pugh score, n (%)			2.94	0.23
A	7 (5.38)	4 (4.55)		
B	63 (48.46)	53 (60.23)		
C	60 (46.15)	31 (35.23)		
Hepatic encephalopathy, n (%)	39 (30.00)	9 (10.23)	11.95	<0.001
Liver cirrhosis, n (%)	82 (63.08)	31 (35.23)	16.30	<0.001
Gastrointestinal bleeding, n (%)	12 (9.23)	2 (2.27)	4.23	0.04
Hepatic ascites, n (%)	95 (73.08)	51 (57.95)	5.43	0.02
Hepatorenal syndrome, n (%)	5 (3.85)	4 (4.55)	0.07	0.80
ALT (U/L)	328 [252, 404]	331 [267, 406]	−0.30	0.76
AST (U/L)	253 [188, 300]	225 [172, 286]	−1.49	0.14
TBil (μmol/L)	342 [288, 398]	342 [279, 386]	−0.52	0.60
Alb (g/L)	33.0 [30.4, 35.9]	33.4 [30.9, 35.6]	−0.36	0.72
Prealbumin (mg/L)	35.8 [30.0, 42.1]	36.1 [31.3, 43.2]	−0.72	0.47
Scr (μmol/L)	68 [57, 80]	70 [63, 81]	−0.95	0.34
INR	2.52 [2.22, 2.76]	2.52 [2.24, 2.83]	−0.07	0.94
WBC (×10^9/L)	7.05 [5.10, 8.48]	6.71 [5.40, 8.60]	−0.29	0.77
FIB (g/L)	1.51 [1.10, 1.80]	1.55 [1.20, 1.77]	−0.10	0.92
MELD score (points)	30 [26, 33]	25 [22, 29]	5.21	<0.001
Hypoglycemia, n (%)	72 (55.38)	27 (30.68)	12.92	<0.001

Data are expressed as n (%), median [interquartile range] or mean ± standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; Alb, serum albumin; Scr, serum creatinine; INR, international normalized ratio, WBC, white blood cell count; FIB, fibrinogen; MELD, model for end-stage liver disease.

Table 4 Multivariable analysis of 90-day mortality in patients with acute on chronic liver failure

Variables	β	Standard error	Wald value	OR (95% CI)	P value
Hepatic encephalopathy	1.80	0.46	15.09	6.02 (2.43–14.89)	<0.001
Cirrhosis	1.17	0.33	12.17	3.21 (1.67–6.17)	<0.001
Gastrointestinal bleeding	0.10	0.38	0.07	1.10 (0.53–2.32)	0.80
Hepatic ascites	0.61	0.35	2.98	1.83 (0.92–3.65)	0.09
MELD score (points)	0.14	0.03	17.80	1.16 (1.08–1.24)	<0.001
Hypoglycemia	2.17	0.86	6.28	8.72 (1.60–7.42)	0.01

OR, odds ratio; CI, confidence interval; MELD, model for end-stage liver disease.

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and hypoglycemia were associated with an increased risk of 90-day mortality in patients with acute on chronic liver failure.

Discussion

This study examined the incidence, risk factors, and impact of hypoglycemia on the short-term prognosis in patients with acute on chronic liver failure. We found that the incidence of hypoglycemia in the present study was 45.41%, which was similar to those reported previously (7). The specific mechanism of hypoglycemia in patients with acute on chronic liver failure remains unclear. It is speculated that factors such as reduced food intake, compromised liver metabolic capacity, glycogen depletion and gluconeogenesis disorders, and disruption of the inactivation of hypoglycemic hormones (8,9) may account for the occurrence of hypoglycemia in patients with severe liver dysfunction. At present, the research on hypoglycemia in patients with liver failure (10-12) is mostly limited to animal experiments, primarily discussing the related molecular regulation mechanism, and there is still a lack of research on the clinically significant topic of risk factors and prognosis of hypoglycemia in patients with acute on chronic liver failure.

The present study confirmed that hypoglycemia was related to liver cirrhosis, a higher MELD score, and lower FIB. Patients with liver cirrhosis often have portal hypertension, which leads to gastrointestinal congestion and decreased appetite. In addition, patients often need to avoid consuming foods rich in protein to prevent hepatic encephalopathy, resulting in a negative nitrogen balance in energy metabolism. The MELD score has been widely used to evaluate liver function and prognosis. A higher MELD score directly reflects poor liver function, in which the inactivation of insulin is substantially compromised (13,14). Honda *et al.* (15) found that with the deterioration of liver function, the proportion of patients with fasting hypoglycemia and postprandial hyperglycemia increased significantly, reflecting the failure of the liver to regulate insulin hormones. FIB is one of many coagulation factors synthesized by the liver, and it has been demonstrated to be decreased in acute liver failure (16). In this study, FIB reduction was found to significantly increase the risk of hypoglycemia, which is consistent with previous relevant reports (17).

Univariate and multivariate analysis showed that the short-term prognosis of patients with hypoglycemia was significantly worse than that of patients without hypoglycemia. A study of 636 patients with decompensated cirrhosis without diabetes by Hung *et al.* (18) found that the 30-day mortality of patients with hypoglycemia was as high as 30.2%. In contrast, the 30-day mortality of patients without hypoglycemia was only 7.4%, which was similar to the results of this study. The 2020 guidelines of the American Society of Critical Care Medicine also suggested that preventing and improving hypoglycemia in patients with severe liver disease helps to improve patient outcomes (19). In a meta-analysis comprising eight previous clinical trials, Chen *et al.* (20) found that adding meals before bedtime for patients with severe liver disease reduced the risk of fasting hypoglycemia the next day and helped to improve liver function. Currently, the American Society for Parenteral and Enteral Nutrition (21) and the European Society for Clinical Nutrition and Metabolism (22) recommend that patients with severe liver dysfunction should consume extra night-time meals to improve their nutritional metabolism and prevent the adverse effects of hypoglycemia.

This study is the first to systematically investigate the incidence, risk factors, and prognosis of hypoglycemia in patients with acute on chronic liver failure. However, this study also had several limitations, including its retrospective nature, single-center design, and small sample size. Therefore, it is necessary to carry out prospective, multi-center studies with larger sample sizes in the future to validate and generalize the results of this study.

Conclusions

In conclusion, this study found that hypoglycemia was common in patients with acute on chronic liver failure, and is related to poor prognosis. Patients with cirrhosis, a higher MELD score, and a significant decrease in FIB were more likely to develop hypoglycemia. Therefore, medical staff should pay attention to blood glucose management and avoid hypoglycemia by enhancing blood glucose monitoring, adjusting diet structure, and adding meals before bed. However, given that this study is a single-center, retrospective analysis, future prospective, multi-center research is needed.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1422/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1422/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1422/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2018LSK-217) and informed consent was obtained from all patients.

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