Incidence and risk factors for hypoglycemia in patients with hepatocellular carcinoma

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Abstract

Aim

To evaluate the incidence and risk factors for hypoglycemia in patients with hepatocellular carcinoma (HCC).

Methods

We collected and analyzed the clinical data of patients with HCC in our cancer center between April 2020 and June 2021. Univariate and multivariate logistic regression analyses were performed to identify the risk factors associated with hypoglycemia.

Results

The incidence rate of hypoglycemia in patients with HCC was 28.9% (67/232). Multivariate logistic regression analysis showed a significant association between hypoglycemia and Child-Pugh grade C (odds ratio [OR]=7.3, 95% confidence interval [CI] 2.28–23.31, p=0.001), alpha-fetoprotein (AFP) level (OR=1.000035, 95% CI 1.000007–1.000063, p=0.015), and glycated hemoglobin (HbA1c) level (OR=0.46, 95% CI 0.29–0.73, p=0.001).

Conclusion

Child-Pugh stage and HbA1c and AFP levels were associated with hypoglycemia in patients with HCC. Our study suggests that these three factors should be comprehensively considered when estimating the risk of hypoglycemia in these patients, and the diagnosis, treatment, and nursing plan should be adjusted in time to reduce the incidence of hypoglycemia.

Introduction

Hepatocellular carcinoma (HCC) with hypoglycemia is one of the clinical features of primary liver cancer with paraneoplastic syndrome, with an incidence rate of 4–27%.[1] There are several mechanisms by which this occurs, including the following[2–6]: (1) tumor cells' production of insulin-like substance growth factor 2, (2) inhibition of hormones that antagonize insulin, (3) consumption of a significant number of glucose by a tumor, (4) hepatic glycogen production disorder, (5) reduced inactivation of insulin and increased insulin level in the blood, and (6) patients having poor appetite, dyspepsia, and decreased intake and absorption capacity. The symptoms of hypoglycemia in patients with hepatocellular carcinoma are easily concealed and ignored by the symptoms of liver cancer and confused with hepatic coma when consciousness disorder occurs, which leads to misdiagnosis or missed diagnosis, thus missing the best treatment opportunity. Reducing the incidence of hypoglycemia in patients with HCC and avoiding hypoglycemia-induced impairment of the heart, brain, and other organs are important issues for healthcare personnel. At present, there are few studies on the assessment of the risk of

hypoglycemia in patients with HCC according to clinical characteristics. This study aimed to explore the incidence and risk factors for hypoglycemia in patients with HCC.

Methods

Participants

This study collected the clinical data of patients with HCC at the Cancer Center, Guangdong Provincial People's Hospital from April 2020 to June 2021. The collected data included demographic characteristics, clinical symptoms, previous history of disease, medication history, laboratory test data, and dietary conditions. Hypoglycemia was defined as blood glucose < 3.9 mmol/L[7]. The patients were divided into a hypoglycemia group and a non-hypoglycemia group according to whether there was two or more hypoglycemia in the 3 months before enrollment. The inclusion criteria were as follows: patients (1) diagnosed with primary hepatocellular carcinoma by histology or cytology and with at least one episode of hypoglycemia in the past 3 months; (2) with an estimated survival period of not less than 3 months; (3) with no past and current serious mental disorders (brain organic mental disorder, schizophrenia, bipolar disorder, severe depression, mental disorder caused by psychoactive substances, hysteria), central nervous system diseases, primary or metastatic brain tumors, and unconscious disorder; and (4) who voluntarily participated in the study and an signed informed consent form. The exclusion criteria were as follows: (1) patients who declined to participate and (2) patients with hypoglycemia caused by using hypoglycemic drugs. The study protocol was approved by the ethics committee of the hospital (KY-Z-2020-615-02), and written informed consent was obtained from all patients.

Statistical analyses

The Statistical Package for the Social Sciences software (version 25.0, International Business Machines Corporation; Armonk, NY, USA) was used for the statistical analysis. Continuous variables were statistically described by observed number, mean, standard deviation, median, minimum, maximum, and quartile. Frequencies and percentages were used as categorical variables. Student's t-test or rank sum test was used to compare continuous variables between the two groups. Chi-squared test or Fisher's exact test was used to compare categorical variables between the two groups. Multivariate analyses were performed using logistic regression (stepwise forward selection) to determine the significant factors for hypoglycemia in patients with HCC. The p value was set at two sides with a significance level of 0.05.

Results

Demographic and clinical characteristics

The study enrolled 232 patients with HCC, of which 67 (28.9%) were in the hypoglycemia group and 165 (71.1%) in the non-hypoglycemia group. The median age was 56 (range: 28–84) years. Most of the patients were men (207 [89.2%]). In total, 54 (23.3%), 143 (61.6%), and 35 (15.1%) patients had educational levels of primary, secondary, and university education, respectively. There was no significant

difference between the two groups in terms of sex and age ($p>0.05$), but the difference in the composition ratio of educational level was statistically significant ($\chi^2=7.22$, $p=0.027$). The proportion of patients in the hypoglycemia group with secondary education was higher than that of patients in the non-hypoglycemia group. The proportion of patients with Child-Pugh grades A, B, and C in the hypoglycemia group were 20.9%, 26.9%, and 50.7%, respectively. In the non-hypoglycemia group, the proportions were 32.1%, 28.5%, and 39.4%, respectively. There was a significant difference in the Child-Pugh stage between the two groups ($\chi^2=35.93$, $p<0.001$). The incidence rates of mild, moderate, and severe ascites in the two groups were 14.9%, 20.9%, 17.9% and 7.3%, 10.9%, and 9.7%, respectively, and the difference was statistically significant. In addition, the incidence rates of diarrhea (17.9% and 7.3%, $\chi^2=5.82$, $p=0.016$) and lower extremity edema (34.3% and 13.9%, $\chi^2= 12.46$, $p<0.001$) and the patient's diet ($\chi^2=19.20$, $p<0.001$) were significantly different between the two groups. However, there were no significant differences in diabetes history, Barcelona staging, hepatic encephalopathy, persistent vomiting, or use of somatostatin between the two groups ($p>0.05$). Detailed information is shown in Table1.

Table 1 Demographic and clinical characteristics of patients with hepatocellular carcinoma

	Hypoglycemia group (n=67)	Non-hypoglycemia group (n=165)	x^2/Z	P
Sex				
Male	60 (89.6%)	147 (89.1%)	0.01	0.918
Female	7 (10.4%)	18 (10.9%)		
Age (year, median [min–max])	55 (31–76)	57 (28–84)	1.60	0.110
Educational levels				
Primary school education	8 (11.9%)	46 (27.9%)	7.22	0.027
High school education	49 (73.1%)	94 (57.0%)		
College degree	10 (14.9%)	25 (15.2%)		
Diabetes history				
No	60 (89.6%)	132 (80.0%)	3.05	0.081
Yes	7 (10.4%)	33 (20.0%)		
Barcelona staging				
A	14 (20.9%)	53 (32.1%)	5.76	0.098
B	18 (26.9%)	47 (28.5%)		
C	34 (50.7%)	65 (39.4%)		
D	1 (1.5%)	0 (0)		
Child-Pugh grades				
A	25 (37.3%)	113 (68.5%)	35.93	<0.001
B	24 (35.8%)	47 (28.5%)		
C	18 (26.9%)	5 (3.0%)		
Hepatic encephalopathy*				
No	64 (95.5%)	163 (98.8%)	-	0.146
Yes	3 (4.5%)	2 (1.2%)		
Ascites				
No	31 (46.3%)	119 (72.1%)	13.98	0.003
Mild	10 (14.9%)	12 (7.3%)		
Moderate	14 (20.9%)	18 (10.9%)		
Severe	12 (17.9%)	16 (9.7%)		
Diarrhea				
No	55 (82.1%)	153 (92.7%)	5.82	0.016
Yes	12 (17.9%)	12 (7.3%)		
Persistent vomiting*				
No	64 (95.5%)	163 (98.8%)	-	0.146
Yes	3 (4.5%)	2 (1.2%)		
Lower extremity edema				
No	44 (65.7%)	142 (86.1%)	12.46	<0.001
Yes	23 (34.3%)	23 (13.9%)		

Whether to use somatostatin*				
No	64 (95.5%)	163 (98.8%)	-	0.146
Yes	3 (4.5%)	2 (1.2%)		
The patient’s diet				
Fasting	3 (4.5%)	2 (1.2%)	19.20	<0.001
Poor	3 (4.5%)	1 (0.6%)		
General	24 (35.8%)	26 (15.8%)		
Good	37 (55.2%)	136 (82.4%)		

*Fisher’s exact probability method.

The differences in albumin (t = 3.38, p = 0.001), total bilirubin (TBIL) (Z = 4.44, p < 0.001), and direct bilirubin (DBIL) levels (Z = 4.89, p < 0.001), prothrombin time (PT) (Z = 3.26, p = 0.001), glycated hemoglobin (HbA1c) level (Z = 5.28, p < 0.001), body weight loss index (Z = 2.71, p = 0.007), and alpha-fetoprotein (AFP) (Z = 2.50, p = 0.012) and aspartate transaminase (AST) levels (Z = 3.69, p < 0.001) were statistically significant, but those in platelet count and alanine aminotransferase level were not (p > 0.05) (Table 2). The TBIL, DBIL, PT, AFP, and AST levels of patients in the hypoglycemia group were higher than those in the non-hypoglycemia group.

Table 2
The difference of hematology test indexes between the hypoglycemia and non-hypoglycemia groups

	Hypoglycemia group (n = 67)	Non-hypoglycemia group (n = 165)	*t/Z*	P
Albumin	32.4 ± 5.3	35.0 ± 5.3	3.38	0.001
TBIL	22.5 (14.3–48.1)	15.0 (10.1–20.8)	4.44	< 0.001
DBIL	6.9 (4.1–24.1)	3.6 (2.4–6.3)	4.89	< 0.001
Plasma prothrombin time	14.6 (13.4–17.0)	13.8 (13.2–14.6)	3.26	0.001
PLT	138.0(93.0–199.0)	133.0 (88.0–188.0)	0.75	0.451
HbA1c	4.9 (4.2–5.4)	5.4 (5.0–6.1)	5.28	< 0.001
AFP	64.8 (6.1–913.7)	12.0 (3.2–318.6)	2.50	0.012
ALT	26.0 (16.0–59.0)	25.0 (17.0–40.5)	0.75	0.456
AST	52.0 (32.0–103.0)	38.0 (26.0–54.0)	3.69	< 0.001
Body weight loss index	−0.02 (− 0.08–0)	0 (− 0.04–0.02)	2.71	0.007
*				
TBIL, total bilirubin; DBIL, direct bilirubin; PLT, platelet; HbA1c, glycated hemoglobin; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase				

Multivariate regression analysis to determine the factors for hypoglycemia in hepatocellular carcinoma

We further performed a multivariate logistic regression analysis on the statistically significant variables in the univariate analysis. The specific variable assignments are listed in Table 3. The regression analysis results showed that Child-Pugh grade C (odds ratio [OR] = 7.3, 95% confidence interval [CI] 2.28–23.31, p = 0.008), HbA1c level (OR = 0.46, 95% CI 0.29–0.73, p = 0.001), and AFP level (OR = 1.000035, 95% CI 1.000007–1.000063, p = 0.015) were significantly associated with hypoglycemia in patients with HCC. Patients with Child-Pugh grade C had a 7.3 times higher risk of hypoglycemia than grade A. Every percent increase in HbA1c was associated with a 0.56 decrease in the risk of hypoglycemia.

Table 3
Multivariate logistic regression model odds ratios (95% confidence interval [CI], p-value) analysis of the hypoglycemia versus non-hypoglycemia group

Variables	B coefficient	Standard error	Wald	P	Odds ratio (OR) (95% CI)
Child-Pugh grades			11.247	0.004	
A	-	-	-	-	1.00
B	0.42	0.36	1.34	0.246	1.52 (0.75–3.09)
C	1.99	0.59	11.23	0.008	7.3 (2.28–23.31)
HbA1c	−0.77	0.23	10.81	0.001	0.46 (0.29–0.73)
AFP	0.4×10^{-4}	0.2×10^{-4}	5.91	0.015	1.35×10^{-4} (1.7×10^{-5}–1.63×10^{-4})
Constant	4.67	1.21	14.74	0.000	106.96

HbA1c, glycated hemoglobin; AFP, alpha-fetoprotein

Discussion

Since Nadcer et al. first reported on primary liver cancer combined with spontaneous hypoglycemia in 1929, hypoglycemia caused by HCC has gradually entered the vision of healthcare providers. In recent years, individualized nursing programs have gradually emerged in terms of nursing care, such as the symptomatic care model for HCC hypoglycemia, and preventive care for patients who may develop hypoglycemia.[8, 9] However, existing clinical nursing measures lack initiative and pertinence. Therefore, by exploring the factors related to hypoglycemia in HCC, we clarified the risk and protective factors for hypoglycemia. This was conducive to preventive care, reducing the occurrence of hypoglycemia events in patients with hepatocellular carcinoma, thereby reducing rescue and death events caused by hypoglycemia events and improving the quality of life of patients. At the same time, it provides data support for the formulation of interventional nursing measures, specialized nursing measures, and continuous nursing measures, which have important clinical significance.

The incidence rate of hepatocellular carcinoma with hypoglycemia ranges from 4–27%[1]. This study showed that the incidence rate of hypoglycemia in patients with HCC was 28.9%, which is consistent with those of previous reports. Among them, 25 (25/138, 18.11%), 24 (24/71, 33.80%), and 18 (18/23, 78.26%) patients had Child-Pugh grades A, B, and C, respectively. The higher the Child-Pugh classification, the higher the incidence of hypoglycemia. It is well known that the liver is an important organ for the body to maintain a relatively stable blood sugar level and has the ability to synthesize and decompose glycogen. Liver diseases, such as liver cirrhosis, liver flukes, and liver malignant tumors, can lead to impaired liver cell function and abnormal glycogen synthesis and decomposition capabilities, which are also known as

abnormal glucose metabolism. Previous studies have shown that the worse the liver function of patients with liver diseases, the more severe the abnormal glucose metabolism.[10] Patients with Child-Pugh grade A had the lowest probability of hypoglycemia, and patients with Child-Pugh grade C had the highest probability of hypoglycemia.[11, 12] The results of this study suggest that clinical nurses need to pay attention to the liver function of patients with HCC, especially when the patient's liver function is abnormal. To prevent hypoglycemia and reduce the incidence of hypoglycemia strengthening blood glucose management and observation of patients, intervening in potential hypoglycemia-prone behaviors, and implementing relevant care for patients are considered beneficial.

HbA1c is the product of a combination of hemoglobin and glucose in human red blood cells. Its synthesis process is slow and irreversible and directly proportional to the blood glucose concentration and can be used to monitor the overall blood glucose level of patients in the past 120 days.[13–15] This study found that a high HbA1c level (OR = 0.46, 95% CI 0.29–0.73, p = 0.001) was a protective factor for HCC hypoglycemia. Numerous large-scale clinical studies have shown that HbA1c can reflect the risk of hypoglycemia, but the law of its occurrence has not yet formed a unified argument.

AFP can reflect liver damage and prognosis, which is closely associated with liver function.[16–18] The level of AFP in patients with abnormal liver function is significantly higher than that in patients with normal liver function. The results of this study show that AFP level is a risk factor for hepatocellular carcinoma with hypoglycemia. However, the range of AFP in this study was 0.9–54000, resulting in only a little increase in the risk of hypoglycemia for every 1 ng/ml increase in AFP.

A previous study has found that the risk of hypoglycemia increases when the HbA1c level is < 7%. Although controlling HbA1c level to < 6.0%, the incidence rate of hypoglycemia did not increase significantly. Therefore, lower or higher HbA1c levels are associated with an increased risk of hypoglycemia. The more drastic the fluctuation of blood glucose, the greater the risk of hypoglycemia.[19–21] The results of this study were different from those of previous studies, which may be caused by individual differences in the study population enrolled in each study. The association between HbA1c level and the risk of hypoglycemia in patients with HCC requires further study.

This study showed that Child-Pugh stage and HbA1c and AFP levels were associated with the incidence of hypoglycemia in patients with HCC. Therefore, when medical workers provide nursing services to such patients, they need to be alert to the occurrence of hypoglycemia and adjust the diagnosis and treatment and care plan according to the situation to reduce the occurrence of hypoglycemia.

Declarations

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Declaration of conflict of interest

The authors declare that they have no competing interests.

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Data Availability Statement

All necessary data have been presented as tables and figures in the manuscript. Relate information is accessible under request to the corresponding author.

Authors' contributions

X-J.Z., H-H.Y., B.G., contributed equally to this article,They designed the study ,analyzed and interpreted the data, generated the figures and tables, and wrote the manuscript draft.X-T.Q. and J.Q. conceived the study, collected the data. J.Z., X-M.C., X-M.C. and C-J.H. conceived the study and critically reviewed and gave approval of the manuscript.

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