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Analysis of the related influencing factors of hepatic abscess associated with hepatobiliary ischemic necrosis after cholangiocarcinoma operation

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ABSTRACT

To investigate related factors of liver abscess associated with hepatobiliary ischemic necrosis after cholangiocarcinoma surgery, 100 patients with cholangiocarcinoma requiring surgical resection were collected and divided into a test group (53 patients with liver abscess) and a control group (47 patients without liver abscess) according to presence or absence of liver abscess. Related factors were compared: gender, age, body mass index (BMI), body temperature at admission, duration of medical history, presence or absence of a history of diabetes, time of medical history, presence or absence of hepatolithiasis, absolute neutrophil count, absolute lymphocyte count (ALC), C-reactive protein, serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), direct bilirubin (DBIL), serum creatine, and presence or absence of anemia. Univariate analysis showed that BMI, age, gender, absolute lymphocyte count, serum ALB, AST, and time of medical history were significantly different between the two (P<0.05). Multivariate logistic regression analysis of the above influencing factors showed that independent influencing factors of postoperative liver abscess formation were: ALC<1.1*10^9/L (P<0.001, OR=23.459, 95% CI=8.529-64.576), AST≥40 U/L (P=0.012, OR=3.946, 95% CI=1.355-11.487), time of medical history≥21 days (P=0.010, OR=4.028, 95% CI=1.389-11.681). Decreased ALC, increased AST, and occurrence of acute biliary tract infection were independent factors for hepatobiliary ischemic necrosis-related liver abscess. Abnormal nutritional status, age, and gender were also the influencing factors of liver abscess.

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Introduction

Cholangiocarcinoma is a type of malignant tumor produced by the occurrence of lesions in the bile duct (1-3), which is rare in clinical practice, and the role of the bile duct in the human body is to be responsible for transporting bile to the digestive system so that food is better digested. There is no clear conclusion about the mechanism by which lesions occur in the bile duct to produce cancer cells, and it is generally accepted in the medical community that there is some correlation with the effects of factors such as hepatitis B, hepatitis C, and cirrhosis (4,5). Patients with cholangiocarcinoma usually have common symptoms such as abdominal discomfort and jaundice. With the aggravation of the lesion site, patients may have elevated body temperature, nausea, vomiting, weakness, etc. (6). The late stage of the disease may lead to liver and kidney failure and metastasis of malignant tumors, posing a great threat to the life safety of patients (7).

At present, the most effective clinical treatment for patients with cholangiocarcinoma is surgical resection (8). There has also been some progress in the treatment of cholangiocarcinoma using liver transplantation. However, there is great controversy in this therapy (9). If patients can't receive surgical resection due to some reasons, adjuvant radiotherapy, chemotherapy, and radiotherapy can also be used to help patients reduce tumor compression and relieve the degree of pain (10). Cholangiocarcinoma itself has the possibility of leading to liver abscess. Cholangiocarcinoma is a very serious malignant tumor, which is mainly characterized by a rapid growth rate and insufficient blood supply, thus causing liver tumor necrosis (11). Liver tumor necrosis, liquefaction combined with infection, there will be tumor suppuration, infection, local liver tumor, and liver abscess formed (12,13). When patients with cholangiocarcinoma are treated with surgical resection, hepatic artery involvement may occur, and timely resection is required at this time (14). In order to further prevent ischemic hepatic necrosis after surgery, physicians should fully assess the possibility of vascular reconstruction. If there are some difficulties in hepatic artery reconstruction, it should be ensured that the normal flow of venous blood flow is not affected during surgery (15). In addition, attention should be paid to adjacent arteries in time to prevent the possibility of collateral circulation. After the completion of the surgery, it should prevent the occurrence of liver abscesses caused by hepatobiliary ischemic necrosis (16,17).

A total of 100 adult patients diagnosed with cholangiocarcinoma in Xinchang People's Hospital from December 2020 to December 2021 were retrospectively analyzed to investigate the independent influencing factors of hepatobiliary ischemic necrosis-related liver abscess after cholangiocarcinoma surgery. It provides the basis for predicting

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the possibility of hepatobiliary ischemic necrosis-related liver abscess after cholangiocarcinoma surgery in clinical practice, so as to develop a more reasonable and effective treatment plan for patients who may have postoperative symptoms during clinical diagnosis and treatment. Then, the patients can obtain the best therapeutic effect.

Materials and Methods

Study subjects and grouping

100 patients with cholangiocarcinoma requiring surgical resection admitted to the Department of Hepatobiliary Surgery of Xinchang People's Hospital from December 2020 to December 2021 were collected. The age, gender, and other relevant data of the patients were recorded. The results of chest radiography and CT scan imaging were observed. All study subjects underwent MRI plain + enhanced + MRCP or CT plain + enhanced to determine whether there was a postoperative hepatobiliary ischemic necrosis-related liver abscess (18-20). According to the results of abdominal CT and MRI plain + enhanced + MRCP and other imaging examinations, all patients with cholangiocarcinoma were divided into a test group (53 with liver abscess) and a control group (47 without liver abscess) according to whether liver abscess occurred after cholangiocarcinoma surgery. The experiment was approved by the ethics committee of Xinchang People's Hospital, and the patients and their families understood the content and method and agreed to sign the corresponding informed consent form.

Inclusion criteria: after admission, the imaging findings of B ultrasound and CT scan were consistent with cholangiocarcinoma or liver abscess; the abscess disappeared after the use of a certain amount of antibiotics; amoebic or tuberculous liver abscess was excluded (21,22).

Exclusion criteria: imperfect registration of general data; imaging findings showed benign and malignant tumors; severe heart, brain, liver, lung, and kidney failure.

Outcome measures

(I) Basic data: gender, age, body mass index (BMI), time of medical history, body temperature measured at admission, whether there had been diabetes, whether there were bile duct stones.

(II) Laboratory parameters: absolute neutrophil count, absolute lymphocyte count (ALC), C-reactive protein, serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), direct bilirubin (DBIL), serum creatinine, urinary bilirubin, and the presence or absence of anemia.

BMI calculation equation and classification criteria for laboratory data

BMI = body weight (kg)/height (m^2). BMI < 18.5 kg/m^2 was considered lean, 18.5 ≤ BMI < 24 kg/m^2 was considered normal weight, 24 kg/m^2 ≤ BMI < 28 kg/m^2 was considered overweight, and BMI ≥ 28 kg/m^2 was considered obese (23,24).

Hemoglobin < 120 g/L was diagnosed as anemia, and 90-120 g/L, 60-90 g/L, 30-60 g/L, and 30 g/L were diagnosed as mild anemia, moderate anemia, severe anemia, and very severe anemia, respectively.

Normal range of ALC: 1.1-3.2*10^9/L; AST: 0-40 U/L; the normal value of serum ALB: 40-55 g/L.

Couinaud segmentation method: bounded by the middle hepatic vein, the liver can be divided into the left lobe and the right lobe, which passes from the valvular vein to the gallbladder fossa; bounded by the right hepatic vein, the liver can be divided into the right anterior segment and the right posterior segment; bounded by the left hepatic vein, the left lobe can be divided into the medial segment and the lateral segment; bounded by the portal vein, the liver can be divided into the upper and lower segments (25).

Statistical processing

SPSS 24.0 statistical software was used for data processing. In univariate analysis, if the data comparison conformed to a normal distribution and the variance was homogeneous, a pairwise independent sample *t*-test was used. If the data comparison did not meet normal distribution or the variance was uneven, a rank sum test was used; measurement data were expressed as ($\bar{x}\pm s$) or median (interquartile range), enumeration data were expressed as frequency and percentage, and the χ^2 test was used for comparison. The related influencing factors of hepatobiliary ischemic necrosis-related liver abscess after cholangiocarcinoma surgery were preliminarily screened. The statistically different parameters were included in a binary logistic regression analysis to determine the independent influencing factors of hepatobiliary ischemic necrosis-related liver abscess after cholangiocarcinoma surgery. The above analysis was performed at the test level of α=0.05, and P<0.05 was considered statistically significant.

Results

Basic information about patients

A total of 100 patients with cholangiocarcinoma were collected, including 45 male patients (45 %) and 55 female patients (55 %); the average age was 43.9 ± 9.8 years, the youngest was 15 years old and the oldest was 79 years old, including 4 patients aged < 30 years, 88 patients aged 30 to 70 years, and 8 patients aged ≥ 70 years; 63 patients (63 %) had high fever as the first symptom, 38 patients (38 %) had chills, 79 patients (79 %) had right upper abdominal pain, 8 patients (8 %) had diarrhea, and 73 patients (73 %) had percussion pain in the liver area (Figure 1, Figure 2,

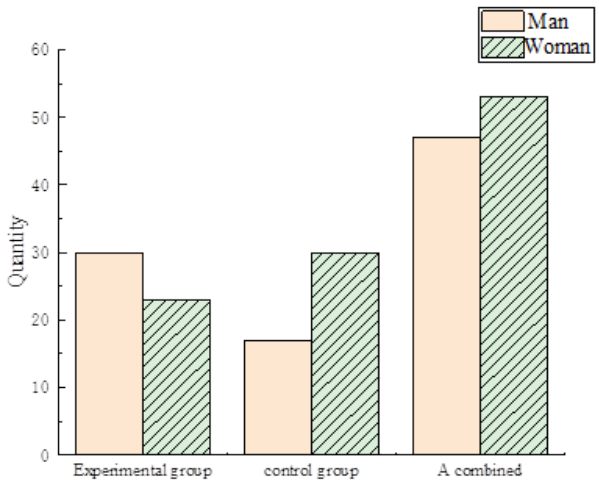

Figure 1. Gender distribution of 100 patients with cholangiocarcinoma.

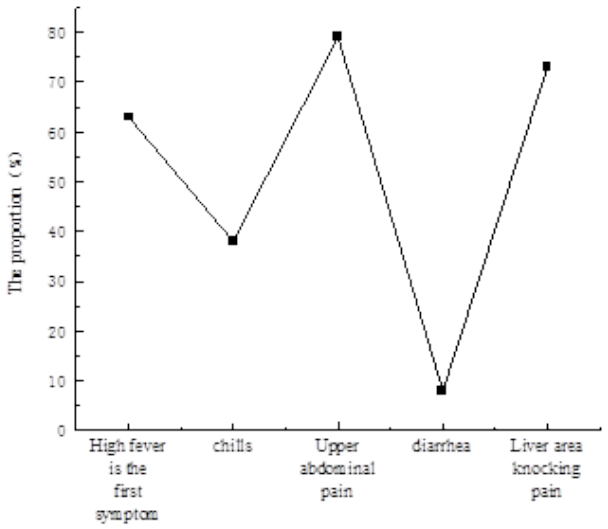

Figure 2. Different symptoms after operation in 100 cholangiocarcinoma patients.

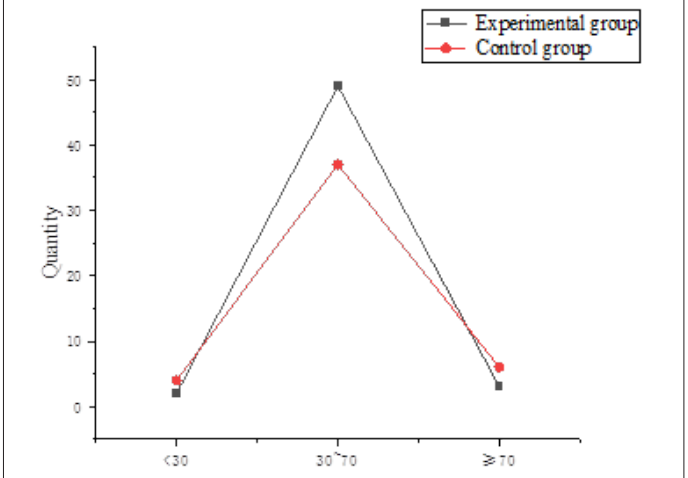

Figure 3. Age distribution of 100 patients with cholangiocarcinoma.

and Figure 3).

Univariate analysis of related factors of hepatobiliary ischemic necrosis-related liver abscess after cholangiocarcinoma surgery

Univariate analysis of basic data

General data such as gender, age, BMI, whether they had diabetes, whether they had pneumonia, as well as the presence or absence of bile duct stones, and whether they had anemia were compared in the test group and the control group, and the χ^2 test was used. Among them, the age of the patients was divided into three intervals, and the patients were divided into ages< 30 years, 30 ~ 70 years, and age ≥ 70 years; BMI was based on 18.5-24 kg/m^2, and the patients were divided into the normal and abnormal weight of 18.5 kg/m^2 ≤ BMI < 24 kg/m^2; hemoglobin < 120 g/L was considered anemia, and the body temperature at admission was divided into two groups according to 37°C; no statistical analysis was performed because only 3 diabetic patients were collected. The results showed that there were significant differences in BMI (P<0.001), gender (P<0.001), and age (P<0.001) between the two groups, but there was no significant difference in the presence or absence of bile duct stones (P = 0.107), anemia (P = 0.270), pulmonary infection (P = 0.115), and body temperature at admission (P = 0.204) between the two groups (Table 1).

Univariate analysis of laboratory parameters

Univariate analysis was performed for serum ALB, absolute neutrophil count, medical history time, C-reactive protein, ALC, alkaline phosphatase, serum creatinine, total bilirubin, ALT, AST, and other laboratory indicators in the two groups. The results showed that there were significant differences in ALC (< 0.001), serum ALB (P = 0.002), AST (P = 0.024), and medical history time (P = 0.001) between the two groups, but there was no significant difference in absolute neutrophil count, C-reactive protein,

Table 1. Univariate analysis of basic data of patients in the two groups.

Item	Type	Proportion of patients (%)		χ^2	P
		Test Group (n, %)	Control Group (n, %)		
Gender	Male	30 (56.6)	17 (36.2)	1.028	<0.001
	Female	23 (43.4)	30 (69.8)		
Age	<30 years old	2 (3.7)	4 (8.5)	1.028	<0.001
	30~70years old	48 (90.6)	37 (78.7)		
	≥70years old	3 (5.7)	6 (12.8)		
Pulmonary infection	Presence	5 (9.4)	5 (10.6)	2.364	0.119
	Absence	48 (90.6)	42 (89.4)		
BMI	Normal	27 (50.9)	37 (78.7)	13.875	<0.001
	Abnormal	26 (49.1)	10 (21.3)		
Bile duct stones	Presence	15 (28.3)	12 (25.5)	3.107	0.102
	Absence	38 (71.7)	35 (74.5)		
Anemia	Presence	4 (7.5)	5 (10.6)	1.306	0.310
	Absence	49 (92.5)	42 (89.4)		
Body temperature at admission	≥37°C	5 (9.4)	4 (8.5)	1.542	0.198
	<37°C	48 (90.6)	43 (91.5)		

Table 2. Univariate analysis of laboratory parameters.

Group	Absolute white blood cells (10^9/L)	ALC (10^9/L)	AST (U/L)	Serum ALB (g/L)	Serum creatinine (μmol/L)
Test	9.8±7.9	0.93±0.51	29.8±11.8	32.9±3.8	69.8±21.3
Control	7.1±1.9	1.65±0.32	25.7±13.9	41.8±3.2	51.8±14.1
t	1.189	-4.892	3.122	-4.012	1.192
P	0.301	<0.001	0.019	0.127	0.003

Group	ALT (U/L)	AKP (U/L)	DBIL (μmol/L)	C-reactive protein (mg/L)	Medical history time (days)
Test	29.8 (21.7,69.1)	151.3 (79.8,319.4)	7.9 (6.1,71.9)	19.8 (17.9,63.2)	25.2 (6.9,31.2)
Control	21.4 (13.2,51.7)	90.1 (59.1,245.3)	6.9 (2.9,32.6)	17.5 (23.4,55.9)	16.8 (4.3,32.1)
t	-1.321	-1.423	-1.501	-1.598	-3.421
P	0.189	0.172	0.178	0.099	0.001

Table 3. Multivariate analysis of related factors of liver abscess associated with hepatobiliary ischemic necrosis after cholangiocarcinoma surgery.

Indicators	ALC < 1.1*10^9/L	AST ≥ 40 U/L	Serum ALB < 40 g/L	Normal BMI	Medical history time ≤ 21 days
Regression coefficient (B)	3.089	1.421	0.978	-0.492	1.421
The standard error (SE)	0.502	0.561	0.554	0.531	0.547
X statistic (Wald)	35.678	5.998	2.989	1.210	7.001
P	<0.001	0.013	0.069	0.301	0.010
Relative impact (OR)	25.765	4.021	2.782	0.632	4.632
95 % confidence interval (95 % CI)	7.996-59.875	1.545-12.784	0.899-7.324	0.302-1.732	1.419-12.016

alkaline phosphatase, serum creatinine, DBIL, and ALT indicators between the two groups ($P>0.05$) (Table 2).

Multivariate analysis of related factors of liver abscess associated with hepatobiliary ischemic necrosis after cholangiocarcinoma surgery

Binary logistic regression analysis was performed on factors with statistical significance in univariate analysis (BMI, ALC, serum ALB, AST, medical history time). It showed that the independent influencing factors for hepatobiliary ischemic necrosis-related liver abscess after cholangiocarcinoma surgery: ALC < 1.1*10^9/L ($P < 0.001$, OR = 23.459, 95 % CI = 8.529-64.576), AST ≥ 40 U/L ($P = 0.012$, OR = 3.946, 95 % CI = 1.355-11.487), time of medical history ≤ 21 days ($P = 0.010$, OR = 4.028, 95 % CI = 1.389-11.681). Serum ALB < 40 g/L ($P = 0.075$, OR = 2.686, 95 % CI = 0.903-7.992) and normal BMI ($P = 0.294$, OR = 0.576, 95 % CI = 0.206-1.613) were not independent factors for the occurrence of hepatobiliary ischemic necrosis-related liver abscess after cholangiocarcinoma surgery (Table 3).

Discussion

Extrahepatic cholangiocarcinoma is a type of malignant tumor with a gradually increasing incidence in recent years. It is classified into two parts by the American Joint Committee on Cancer (AJCC): hilar cholangiocarcinoma and distal cholangiocarcinoma (26). Partial hepatectomy or bile duct resection is a routine surgical treatment modality for hilar cholangiocarcinoma. However, biliary tract surgery will lead to an increased incidence of bile duct stones and liver abscesses. Surgical treatment to destroy the normal structure of the bile duct can lead to biliary stricture, so that the biliary tract is prone to infection, and thus the formation of stones and abscesses (27). In recent years, the incidence of extrahepatic cholangiocarcinoma has gradually increased, and the prognosis is poor. The limitations of surgical resection in the treatment are gradually reflected, such as easy recurrence after the operation, poor efficacy, and great possibility of hepatobiliary ischemic necrosis-related liver abscess after the operation. Some studies suggest that surgical exploration of the biliary tract leads to damage to the integrity of the bile duct mucosa, decreased immunity, and intestinal bacteria can enter the liver through the biliary system, which leads to cholangitis, peri-cholangitis, and liver abscess in severe cases. Czerwonko et al. (2016) (28) confirmed that biliary surgery is a factor influencing liver abscess, and found that serum bilirubin was correlated with the prognosis of patients. Mittelstaedt et al. (2018) (29) confirmed diabetes and pneumonia were found to be independent factors for bacterial liver abscesses.

The patients were divided into a test group and a control group according to whether a hepatobiliary ischemic necrosis-related liver abscess occurred after cholangiocarcinoma surgery, and whether the patients were infected with a liver abscess in the test group and uninfected in the control group. The general data of the two groups were compared. The results showed that the incidence of liver abscess associated with hepatobiliary ischemic necrosis after cholangiocarcinoma surgery was higher in males than in females. Right upper abdominal pain was the common first symptom, followed by liver percussion pain, high fever, and chills. The incidence of the single liver abscess was high. In addition, the infection of liver abscess associated with hepatobiliary ischemic necrosis after cholangiocarcinoma surgery was also related to the age of the patients. The age group of 30 to 70 years was the age group more likely to be infected. BMI was considered normal according to 18.5 kg/m^2 ≤ BMI < 24 kg/m^2, and cases were classified as normal and abnormal. Previous

studies have suggested that obesity can produce chronic and systemic low-grade inflammation in the body. Generally, this inflammation is controllable and is very important for the homeostasis and balance of the body. However, when invaded by pathogens and externally stimulated, the inflammation can be excessively activated, thus aggravating exogenous or endogenous inflammation, and causing damage to the body. Domestic studies have confirmed that obese patients are more likely to have the infection than patients with normal weight, and the surgical incision infection rate in obese patients is 3.22 times that in patients with normal weight. Malnutrition decreases the body's immunity, which leads to an increased chance of infection. Numerous foreign studies have also confirmed a "U"-shaped relationship between BMI and infectious diseases. The proportion of abnormal BMI in cholangiocarcinoma patients with postoperative infection of liver abscess (49.1 %) was higher than that in patients without liver abscess (21.3 %). However, the multivariate analysis suggested that BMI had no statistical significance for cholangiocarcinoma hepatobiliary ischemic necrosis-related liver abscess. Therefore, BMI is not an independent factor for liver abscess associated with hepatobiliary ischemic necrosis in cholangiocarcinoma.

Serum ALB is mainly synthesized by the liver, has a half-life of 20 days, and can represent visceral proteins in body composition (30). It is not regulated when protein intake is insufficient or too much is consumed in a short period of time. The concentration in serum can remain normal, and the concentration can be reduced in impaired liver function or long-term chronic disease. It has been confirmed that patients with hypoproteinemia are more likely to suffer from liver abscess, which may be due to the reduction of immunoglobulin, complement, and antibody production by hypoproteinemia, which predisposes to liver abscess. The mean value of serum ALB in the test group was 32.9 g/L, which was significantly lower than 41.8 g/L in the control group, and there was a difference between the test group and the control group, but serum ALB < 40 g/L was not an independent factor for liver abscess associated with hepatobiliary ischemic necrosis in cholangiocarcinoma in multivariate analysis.

C-reactive protein is a protein that can bind to C-polysaccharide in the cell wall of *Streptococcus pneumoniae* and is synthesized by liver cells stimulated by interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor. It is commonly used in clinical practice for the diagnosis of infectious diseases and the prediction of cardiovascular diseases (31,32). The serum content of healthy people is very small, and its increased concentration is a sensitive indicator of inflammation and tissue damage caused by various causes. C-reactive protein concentrations increased in both the test and control groups, but there was no statistically significant difference in the increased values between the two groups. C-reactive protein can be elevated once combined with inflammation or infection after cholangiocarcinoma surgery, which is independent of the type of inflammation infected. Therefore, C-reactive protein can be used as an indicator of postoperative infection in cholangiocarcinoma, but it can't be used as an influencing factor of liver abscess associated with hepatobiliary ischemic necrosis in cholangiocarcinoma.

Studies have confirmed that diabetes can increase the risk of liver abscess, systemic metabolic disorders, decreased immunity, and direct damage caused by diabetes to the liver weaken the clearance of bacteria by the liver, and bacteria are easy to colonize and multiply to form abscesses. Diabetes leads to abnormal glucose metabolism and insufficient energy supply of white blood cells (33), thereby reducing humoral immunity and cellular immunity. Moreover, hyperglycemia is conducive to the reproduction of pathogens while leading to increased blood osmotic pressure, so that the chemotaxis, phagocytosis, and sterilization of neutrophils are reduced. Diabetes is often accompanied by water loss, dehydration, acidosis, and poor blood glucose control, which can make the body in a state of low immunity due to a variety of defense defects. In this experiment, only three diabetic patients were collected and none of them had a concurrent liver abscess, which was of no research value and did not do much analysis.

Lymphocytes are an important part of the immune system. According to their different cell surface markers and functions, they are divided into T lymphocytes, B lymphocytes, and natural killer (NK) cells. T lymphocytes mainly mediate specific cellular immunity, B lymphocytes mediate major humoral immunity, and cellular immunity and humoral immunity complement each other. Studies in patients with pneumonia have shown that patients with lymphopenia have more severe pneumonia and a worse prognosis. Studies suggest that the reduction of lymphocyte levels in peripheral blood can be used as an indicator to predict the risk of severe infection during treatment in patients with infection. In this experiment, ALC < 1.1*10^9/L was an independent factor for liver abscess associated with hepatobiliary ischemic necrosis in cholangiocarcinoma.

ALT and AST are the most used indicators to determine liver function in clinical practice. AST is present in tissues such as the myocardium, liver, skeletal muscle, and kidney; ALT is mainly distributed in the liver, followed by skeletal muscle, kidney, and myocardium. The content of transaminases in the entire liver is about 100 times that in the blood. Under normal conditions, the contents of ALT and AST in serum are low, the permeability of cell membrane is increased when the cells are damaged, and the concentrations of ALT and AST in serum are increased. ALT and AST mainly reflect the presence or absence and severity of hepatocyte damage. When a liver abscess occurs in the liver, hepatocytes are damaged, and the corresponding increases in ALT and AST occur, but the increases in the two are not parallel. In this experiment, ALT was not an independent factor for hepatobiliary ischemic necrosis-related liver abscess in cholangiocarcinoma. AST ≥ 40 U/L is an independent factor for the association of hepatobiliary ischemic necrosis in cholangiocarcinoma.

In conclusion, for poor nutritional status, abnormal body weight is associated with a hepatobiliary ischemic necrosis-related liver abscess in cholangiocarcinoma, in addition, gender and age are also associated with the occurrence of liver abscess. C-reactive protein can reflect the severity of inflammation, but it does not diagnose hepatobiliary ischemic necrosis-related liver abscess in cholangiocarcinoma. ALC < 1.1*10^9/L, medical history time ≤ 21 days, and AST > 40 U/L were independent factors for hepatolithiasis with liver abscess. Therefore, attention should be paid to patients with cholangiocarcinoma who have the above factors. It is necessary to improve the relevant imaging examination before surgery to determine

whether there is liver abscess formation. If there is abscess formation, the size, number, and liquefaction degree of abscess should be timely identified. The treatment plan should be adjusted according to the judgment results to improve the prognosis of patients.

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