

Prealbumin is predictive for postoperative liver insufficiency in patients undergoing liver resection

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Abstract

AIM: To investigate the risk factors for postoperative liver insufficiency in patients with Child-Pugh class A liver function undergoing liver resection.

METHODS: A total of 427 consecutive patients undergoing partial hepatectomy from October 2007 to April 2011 at a single center (Department of Hepatic Surgery I, Eastern Hepatobiliary Surgery Hospital, Shanghai, China) were included in the study. All the patients had preoperative liver function of Child-Pugh class A and were diagnosed as having primary liver cancer by postoperative histopathology. Surgery was performed by the same team and hepatic resection was carried out by a clamp crushing method. A clamp/unclamp time of 15 min/5 min was adopted for hepatic inflow occlusion. Patients' records of demographic variables, intraoperative parameters, pathological findings and laboratory test results were reviewed. Postoperative

liver insufficiency and failure were defined as prolonged hyperbilirubinemia unrelated to biliary obstruction or leak, clinically apparent ascites, prolonged coagulopathy requiring frozen fresh plasma, and/or hepatic encephalopathy. The incidence of postoperative liver insufficiency or liver failure was observed and the attributing risk factors were analyzed. A multivariate analysis was conducted to determine the independent predictive factors.

RESULTS: Among the 427 patients, there were 362 males and 65 females, with a mean age of 51.1 ± 10.4 years. Most patients (86.4%) had a background of viral hepatitis and 234 (54.8%) patients had liver cirrhosis. Indications for partial hepatectomy included hepatocellular carcinoma (391 patients), intrahepatic cholangiocarcinoma (31 patients) and a combination of both (5 patients). Hepatic resections of ≤ 3 and ≥ 4 liver segments were performed in 358 (83.8%) and 69 (16.2%) patients, respectively. Seventeen (4.0%) patients developed liver insufficiency after hepatectomy, of whom 10 patients manifested as prolonged hyperbilirubinemia unrelated to biliary obstruction or leak, 6 patients had clinically apparent ascites and prolonged coagulopathy, 1 patient had hepatic encephalopathy and died on day 21 after surgery. On univariate analysis, age ≥ 60 years and prealbumin < 170 mg/dL were found to be significantly correlated with postoperative liver insufficiency ($P = 0.045$ and $P = 0.009$, respectively). There was no statistical difference in postoperative liver insufficiency between patients with or without hepatitis, liver cirrhosis and esophago-gastric varices. Intraoperative parameters (type of resection, inflow blood occlusion time, blood loss and blood transfusion) and laboratory test results were not associated with postoperative liver insufficiency either. Age ≥ 60 years and prealbumin < 170 mg/dL were selected on multivariate analysis, and only prealbumin < 170 mg/dL remained predictive (hazard ratio, 3.192; 95%CI: 1.185-8.601, $P = 0.022$).

CONCLUSION: Prealbumin serum level is a predictive factor for postoperative liver insufficiency in patients with liver function of Child-Pugh class A undergoing hepatectomy. Since prealbumin is a good marker of nutritional status, the improved nutritional status may decrease the incidence of liver insufficiency.

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Key words: Prealbumin; Hepatectomy; Liver insufficiency; Child-Pugh class A; Primary liver cancer

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INTRODUCTION

In spite of techniques such as local ablation, liver resection is still the accepted gold standard treatment for liver tumors. The aim of liver resection is to remove all macroscopic diseases (with negative resection margins), retain sufficient functioning liver^[1] and preserve vascular inflow and outflow. If too much healthy liver parenchyma is removed, patients may develop postoperative liver insufficiency or liver failure, which is a complication dreaded by surgeons.

The search for a method to categorically quantify the functional reserve of the liver and tailor surgical intervention has resulted in the development of a range of methods. These methods range from clinical scores such as the Child-Pugh classification, tests assessing complex hepatic metabolic pathways and radiological methods assessing functional reserve. Child-Pugh classification, a convenient and practical scoring system, has proven to be a useful tool in estimating the risks for both hepatic and nonhepatic surgery in patients with liver diseases^[2-4]. Liver resection is generally safe for patients with preoperative liver function of Child-Pugh class A, even for patients with cirrhosis. However, a minority of patients undergoing apparently safe resection still inexplicably develop postoperative liver insufficiency or liver failure despite seemingly sufficient liver remained preoperatively^[5].

The objective of this study is to determine the incidence of postoperative liver insufficiency in patients with preoperative liver function of Child-Pugh class A who underwent liver resection, and to clarify the risk factors for postoperative liver insufficiency in those patients.

MATERIALS AND METHODS

We reviewed the data of a single center database (De-

partment of Hepatic Surgery I, Eastern Hepatobiliary Surgery Hospital, Shanghai, China). This database comprises 427 patients undergoing partial hepatectomy with liver function of Child-Pugh class A observed during the period from October 2007 to April 2011. All the patients were diagnosed as having primary liver cancer by postoperative histopathology.

Before surgery, all patients had a chest X-ray, ultrasonography, esophagogastric endoscopy, and contrast computed tomography scan or magnetic resonance imaging of the abdomen. Laboratory blood tests included count of white blood cell and platelet, hepatitis B surface antigen, antibodies to hepatitis C, serum alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19 to 9, serum albumin, serum prealbumin, serum total bilirubin, alanine aminotransferase (ALT) and prothrombin time (PT).

Surgery was performed through a right subcostal incision with a midline extension. As for hepatic inflow occlusion, normothermic intermittent interruption of the porta hepatis, with a clamp/unclamp time of 15 min/5 min, was adopted. Hepatic resection was carried out by a clamp crushing method, which has been reported previously^[6]. Blood loss was accurately recorded and blood transfusion was given when necessary. Serum albumin, serum prealbumin, serum total bilirubin, ALT, PT and ascites were monitored after surgery. Patients were discharged when the liver function was recovered (total bilirubin ≤ 34 $\mu\text{mol/L}$, ALT ≤ 40 IU/L, PT ≤ 15 s, no ascites on abdominal ultrasound and no appearance of hepatic encephalopathy).

We reviewed patients' records for demographic variables (age, gender, hepatitis background, liver cirrhosis and esophagogastric endoscopic findings), intraoperative parameters (type of resection, inflow blood occlusion time, blood loss and blood transfusion), pathological diagnosis and laboratory test results. Postoperative liver insufficiency and failure were defined as "prolonged hyperbilirubinemia unrelated to biliary obstruction or leak, clinically apparent ascites, prolonged coagulopathy requiring frozen fresh plasma, and/or hepatic encephalopathy"^[7], which was recommended by Mullin *et al.*^[5].

Statistical analysis

Data were collected and analyzed with the SPSS statistical software (SPSS version 16.0, Chicago, IL, United States). The variable data were expressed as means and SDs or median and range. Categorical variables were compared using χ^2 or Fisher's exact test when appropriate, and continuous variables were compared using the independent sample *t* test. A multiple logistic regression analysis was used to determine predictors of postoperative liver insufficiency.

Variables with a $P < 0.05$ in the univariable analysis were added to the multi-variable model. In the multivariate analysis, a stepwise method was used to select variables for the final model: the conditional probabilities for stepwise entry and stepwise removal of a factor were 0.05 and 0.20, respectively.

Table 1 Baseline characteristics of all 427 patients

Variables	<i>n</i> = 427
Sex (male/female)	362/65
Age (yr)	51.1 ± 10.4
Surgical indications	
HCC	391
ICC	31
HCC-ICC ¹	5
Tumor size (cm)	6.2 ± 4.0
WBC (× 10 ⁹ /L)	5.5 ± 1.8
PLT (× 10 ⁹ /L)	160.5 ± 66.4
PT (s)	12.2 ± 4.8
Total bilirubin (μmol/L)	14.6 ± 5.8
Albumin (g/L)	42.0 ± 4.0
Prealbumin (mg/dL)	217.6 ± 61.0
ALT (IU/L)	47.4 ± 43.7
Hepatitis virus background	
HBV	362
HCV	4
HBV-HCV ²	3
None	58
Liver cirrhosis	
Yes	234
No	193
Ascites	
Little	48
No	378
Esophageal varices	
Present	60
Absent	367
Types of liver resection	
Minor ≤ 3 liver segments	358
Major ≥ 4 liver segments	69
Inflow blood occlusion time (min)	15.8 ± 8.0
Blood loss (mL)	200 (50, 5500)
Blood transfusion (yes/no)	43/384

¹Concurrence of HCC and ICC; ²Concurrence of HBV and HCV. HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma; WBC: White blood cell; PLT: Platelet; PT: Prothrombin time; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

RESULTS

Baseline data

The clinical features of the 427 patients included in the study are reported in Table 1. There were 362 males and 65 females, with a mean age of 51.1 ± 10.4 years. Most patients (86.4%) had a background of viral hepatitis (hepatitis B and/or hepatitis C), 234 (54.8%) patients suffered from liver cirrhosis, and 48 (11.2%) patients had controlled ascites before surgery. Indications for partial hepatectomy included hepatocellular carcinoma (391 patients), intrahepatic cholangiocarcinoma (31 patients) and combination of hepatocellular carcinoma and intrahepatic cholangiocarcinoma (5 patients). Hepatic resection of ≤ 3 and ≥ 4 liver segments was performed in 358 (83.8%) and 69 (16.2%) patients, respectively.

Liver insufficiency and its risk factors

There were 17 (4.0%) patients who had liver insufficiency after hepatectomy, of whom 10 patients presented with prolonged hyperbilirubinemia unrelated to biliary

Table 2 Univariate analysis of factors related to postoperative liver insufficiency

Variables	Patients with liver insufficiency (<i>n</i> = 17)	Patients without liver insufficiency (<i>n</i> = 410)	<i>P</i> value
Sex (male/female)	17/0	345/65	0.075
Age (yr)	57.6 ± 7.1	50.8 ± 10.4	0.008
< 60	10	325	
≥ 60	7	85	
Tumor size (cm)	6.6 ± 5.0	6.2 ± 3.9	0.664
≥ 10	4	79	
< 10	13	331	
WBC (× 10 ⁹ /L)	5.2 ± 1.9	5.5 ± 1.8	0.581
PLT(× 10 ⁹ /L)	146.0 ± 88.2	161.1 ± 65.4	0.357
PT (s)	12.5 ± 1.3	12.2 ± 4.9	0.816
Total bilirubin (μmol/L)	16.3 ± 5.7	14.5 ± 5.8	0.205
Albumin (g/L)	40.2 ± 4.3	42.0 ± 4.3	0.074
Prealbumin (mg/dL)	191.4 ± 59.6	217.9 ± 61.1	0.049
< 170	8	84	
≥ 170	9	326	
ALT (IU/L)	52.2 ± 38.0	47.2 ± 43.9	0.647
≥ 100	3	29	
< 100	14	381	
Viral background			0.222
HBV and/or HCV	4	54	
None	13	356	
Liver cirrhosis			0.182
No	5	188	
Yes	12	222	
Ascites			0.415
Little	3	46	
No	14	364	
Esophageal varices			0.251
Present	4	56	
Absent	13	354	
Types of liver resection			0.130
Minor ≤ 3 liver segments	12	346	
Major ≥ 4 liver segments	5	64	
Inflow blood occlusion time (min)	17.2 ± 6.2	15.7 ± 8.0	0.438
> 20	4	102	
≤ 20	13	308	
Blood loss (mL)	200 (50-5500)	200 (50-2800)	0.362
≥ 800	1	36	
< 800	16	374	
Blood transfusion			0.558
Yes	1	42	
No	16	368	

WBC: White blood cell; PLT: Platelet; PT: Prothrombin time; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

obstruction or leak, 6 patients had clinically apparent ascites and prolonged coagulopathy requiring frozen fresh plasma, and 1 patient had hepatic encephalopathy and died on day 21 after surgery.

To determine the risk factors for postoperative liver insufficiency, 427 patients were classified into two groups: patients with liver insufficiency (17 patients) and patients without liver insufficiency (410 patients). Eighteen variables as listed in Table 2 were analyzed. On univariate analysis, age ≥ 60 years and prealbumin serum level < 170 mg/dL were found to be significantly correlated with the postoperative liver insufficiency (*P* = 0.045 and *P* = 0.009, respectively). On multivariate analysis using

a logistic regression, only prealbumin serum level < 170 mg/dL remained predictive (hazard ratio, 3.192; 95%CI: 1.185-8.601, $P = 0.022$).

Other complications

Twenty-five patients had one or more complications, one (0.2%) them died in the hospital because of multiple organ failure including liver failure, the other patients recovered after a longer hospital stay. These complications included pleural effusion (15 patients), abdominal hemorrhage (3 patients), wound infection (2 patients), acute renal failure (2 patients) and bile leakage (1 patient).

DISCUSSION

Child score, first proposed in 1964^[8] and modified as Child-Pugh score thereafter, was originally developed to predict the risk of mortality in patients undergoing shunting procedures for portal hypertension. Its role has been expanded to predict risk for a range of procedures, including hepatectomy, and liver resection is generally safe in patients with class A liver function^[9]. However, in the present study, the minority of patients (4.0%) with good liver function (Child-Pugh class A) still had postoperative liver insufficiency, one of them even developed undesirable liver failure.

Because of several apparent limitations in the assessment of risk of liver failure following hepatectomy, to improve the Child-Pugh classification system, many quantitative techniques have been developed to assess postoperative risk of liver failure in patients undergoing hepatectomy. Indocyanine green (ICG) elimination is the most widely used assessment for liver function and a number of retrospective studies have found some efficacy in predicting liver dysfunction and mortality following hepatectomy^[10-13]. Unfortunately, ICG elimination is not a routine test in our hospital and we could not present such data in this study. However, with the finite data in our study, we found that patients with postoperative liver insufficiency were correlated with elder age and lower serum level of prealbumin, and prealbumin serum level < 170 mg/dL remained predictive for liver insufficiency after hepatectomy.

Prealbumin, also known as transthyretin, is synthesized in the liver and serves as a transport protein throughout the body. Serum prealbumin differs from albumin, which has a relatively short half-life of 48 h and does not accumulate in the body to undergo redistribution^[14-17]. Therefore, it might be a better indicator to assess nutritional status than the widely used albumin serum level, and any fluctuations in nutritional status can be detected rapidly^[18,19]. Prealbumin has been considered an effective indicator of malnutrition in cancer patients^[15,16]. Nutrition is an important part of the management of surgical patients, and poor nutritional status in patients undergoing surgery is well known to increase postoperative morbidity and mortality by deteriorating various organ functions and the immune system of the host^[14,20-23]. Thus, we could infer that it was the poor nutritional status that caused the postoperative liver insufficiency, and prealbumin serum

level < 170 mg/dL was an indicator of malnutrition.

With regard to the Child-Pugh score, we noticed that the initial version of Child or Child-Turcotte score^[8], included nutritional status which was classified as good, fair and poor. One of the limitations which is argued by studies reported thereafter was that some values (ascites, encephalopathy and nutritional status) were determined subjectively by clinicians^[24,25]. There was no quantitative index for clinicians to give the substantial score. Due to its good representation of nutritional status, we think that prealbumin could be a quantitative variable to evaluate the patient's nutritional status, and possibly as a modification to the Child-Pugh classification system, which will make the score system more objective to assess the liver function.

Almost all the serum prealbumin is synthesized in the liver, thus, its level can be influenced by the liver condition. It has been reported that the prealbumin level could be lowered in patients with acute or chronic liver diseases and alcoholism^[16]. We think that the decreased prealbumin level may reflect the damage of liver function, which also indicates the risk of liver insufficiency after hepatectomy. More importantly, oral and parenteral steroids can falsely elevate the prealbumin levels. This elevation can make patients on steroids appear to be at a lower risk for surgery than they really are^[26]. For those patients, more attention should be paid and other variables can be taken into account to justify the liver function.

In summary, the present study exhibited that the minority of patients (4.0%) with good liver function (Child-Pugh class A) still had postoperative liver insufficiency, one of them even developed undesirable liver failure. Patients' age ≥ 60 years and serum level of prealbumin serum level < 170 mg/dL were found to be significantly correlated with the postoperative liver insufficiency, and prealbumin serum level < 170 mg/dL remained predictive for liver insufficiency after liver resection. Considering prealbumin has served as a good marker of nutritional status in cancer patients, the improved nutritional status may decrease the incidence of liver insufficiency. However, further studies with a larger number of patients are needed to confirm this hypothesis.

COMMENTS

Background

In spite of techniques such as local ablation, liver resection is still the accepted gold standard treatment for liver tumors. The aim of liver resection is to remove all macroscopic diseases (with negative resection margins) and retain sufficient functioning liver with preservation of vascular inflow and outflow. If too much healthy liver parenchyma is removed, patients may develop postoperative liver insufficiency or liver failure, which is a complication dreaded by surgeons. Liver resection is generally safe in patients with preoperative liver function of Child-Pugh class A, even in patients with cirrhosis. However, a small number of patients undergoing apparently safe resection still inexplicably develop postoperative liver insufficiency or liver failure although seemingly sufficient liver remained preoperatively.

Research frontiers

The search for a method to categorically quantify the functional reserve of the liver and tailor surgical intervention has resulted in the development of a range of methods. These methods include clinical scores such as the Child-Pugh clas-

sification, tests assessing complex hepatic metabolic pathways and radiological methods assessing functional reserve. Child-Pugh classification, a convenient and practical scoring system, has proven to be a useful tool in estimating the risks for both hepatic and nonhepatic surgery for patients with liver diseases.

Innovations and breakthroughs

In this study, the authors exhibited that a small number of patients (4.0%) with good liver function (Child-Pugh class A) still had postoperative liver insufficiency, one of them even developed undesirable liver failure. Patients' age \geq 60 years and serum level of prealbumin serum level $<$ 170 mg/dL were found to be significantly correlated with the postoperative liver insufficiency, and prealbumin serum level $<$ 170 mg/dL remained predictive for liver insufficiency after liver resection. Prealbumin has been considered an effective indicator of malnutrition in cancer patients. Nutrition is an important part of the management of surgical patients, and poor nutritional status in patients undergoing surgery is well known to increase postoperative morbidity and mortality by deteriorating various organ functions and the immune system of the host. Thus, the authors inferred that it was the poor nutritional status that caused the postoperative liver insufficiency, and prealbumin serum level $<$ 170 mg/dL was an indicator of malnutrition.

Applications

One of the limitations which is argued by previous studies was that some values (ascites, encephalopathy and nutritional status) were determined subjectively by clinicians. There was no quantitative index for clinicians to give the substantial score. Due to its good representation of nutritional status, the authors think that prealbumin could be a quantitative variable to evaluate the patient's nutritional status, and possibly as a modification to the Child-Pugh classification system, which will make the score system more objective to assess the liver function.

Peer review

This manuscript demonstrates that preoperative serum level of prealbumin is a predictor of postoperative liver insufficiency in patients with Child-Pugh class A. This manuscript is well written and attractive.

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