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Immediate postoperative Fibrosis-4 predicts postoperative liver failure for patients with hepatocellular carcinoma undergoing curative surgery

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ABSTRACT

Background: Postoperative liver failure remains the main complication and predominant cause of hepatectomy-related mortality for patients undergoing liver resection.
Aim: Our aim is to investigate whether immediate postoperative Fibrosis-4 could predict postoperative liver failure.
Methods: We retrospectively enrolled 1353 consecutive hepatocellular carcinoma patients undergoing radical resection. The characteristics and clinical outcomes were compared between patients with high and low immediate postoperative Fibrosis-4. Risk factors for hepatic failure were evaluated by univariate and multivariate analysis.
Results: Using a receiver operating characteristic curve, immediate postoperative Fibrosis-4 showed good prediction ability for postoperative liver failure (AUROC = 0.647, $P < 0.001$). With the optimal cut-off value of 5.9, the high postoperative Fibrosis-4 group (Fibrosis-4 < 5.9) had higher postoperative complication (39.1% *vs* 28.6%, $P < 0.001$), mortality (2.8% *vs* 0.6%, $P < 0.001$) and liver failure (13.9% *vs* 6.2%, $P < 0.001$). In addition, patients with high Fibrosis-4 had worse and delayed recovery of liver function. By univariate and multivariate analysis, Fibrosis-4, as well as liver removed volume, total bilirubin and albumin was identified as independent risk factor for postoperative liver failure.
Conclusions: Immediate postoperative Fibrosis-4 showed good prediction ability for postoperative liver failure, and required measure should be taken to prevent liver failure when high postoperative Fibrosis-4 appeared.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death worldwide [1]. Radical liver resection and liver transplantation are the most effective methods of treatment for HCC. Liver transplantation has been limited because of the worldwide organ shortage, so liver resection is the first treatment option for patients with well-selected candidates with HCC of early stage [2]. But patients selected for liver resection usually are always on risk of postoperative liver failure because HCC patients usually have underlying liver damage, especially in Asia where approximately 80% of HCC cases are associated with hepatitis B virus (HBV) or C virus (HCV) infection, with varying degrees of liver fibrosis or cirrhosis [3]. In addition, the increasing extended liver resections results in smaller functional remnant liver volumes, thus increases the risk for the development of liver failure, though theses patients usually have clinically well-preserved liver function [4]. In the past decades, the refinement of surgical techniques and perioperative management in liver surgery has resulted in marked reduction of mortality and morbidity for HCC patients undergoing hepatectomy [5]. Postoperative liver failure remains as high as 11% and has been shown to be a predominant cause of hepatectomy-related mortality [4]. Many studies have

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identified the risk factors for postoperative liver failure, these risk factors include smaller remnant liver volume, impaired functional capacity, transfusion, poor indocyanine green clearance rate, portal hypertension, cirrhosis, preoperative thrombocytopenia and so on [6–10]. Recently, several studies focused on the preoperative chronic disease score (such as Fibrosis-4, APRI) and found that they could predict the postoperative liver failure [7,11–13]. However, whether the immediate postoperative Fibrosis-4(FIB-4) could influence the postoperative liver function has not been investigated. Here, we reported a cohort study to discuss the relationship between immediate postoperative FIB-4 and liver failure after partial liver resection in patients with HCC.

2. Materials and methods

2.1. Study population

All the included patients were from Sichuan Cancer Hospital and West China Hospital. 788 consecutive HCC patients who underwent radical liver resection Between January 2009 and January 2016 were from Sichuan Cancer Hospital, and 565 consecutive patients who underwent radical liver resection came from West China Hospital Between January 2009 and March 2013. HCC patients with obstructive jaundice and patients with metastatic hepatic carcinoma and intrahepatic cholangiocarcinoma were excluded in our study. The study protocol was approved by the Clinical Research Ethics Committee of the two hospitals conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written Informed consent was obtained from all patients according to the policies of the committee. Medical records containing patient demographics, laboratory values, intraoperative parameters and postoperative outcomes were obtained from a prospectively maintained database. All patients underwent liver resection by two surgery teams.

2.2. Perioperative management

All patients were managed by the two surgical teams. These patients underwent a thorough history, physical examination and routine preoperative laboratory measurements. Routine preoperative imaging examination to evaluate the tumor included contrast computed tomography or magnetic resonance imaging of the abdomen. Echocardiography, chest radiography or computed tomography and pulmonary function tests were carried out if necessary. Patients were operated under general anesthesia and intraoperative ultrasonography was used routinely. Hemihepatic vascular inflow occlusion or the Pringle maneuver was used according to the surgeon's preference in most patients as those previously described [14]. Liver parenchymal transection was performed using the Hooking with ligation method or an ultrasonic dissector with coagulator [15]. Based on preoperative and intraoperative condition, patients were transferred to the intensive care unit for treatment if necessary.

2.3. Outcome parameters

The platelet count, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) obtained immediately after surgery (usually upon arrival at the intensive care unit or liver department after surgery), it was referred to as the immediate postoperative index and were prospectively recorded daily from admission until postoperative day 14 after liver resection. The Clavien–Dindo complication classification system was used for postoperative complication grading [16]. Liver resection with more than 3 segments was defined as major resection, or as minor resection. Mortality was defined as any death occurring from the time of surgery up to 90 days after hepatectomy. Postoperative liver failure was defined according to the criterion of International Study Group of Liver Surgery, Grade A liver failure required no change of the patient's clinical management. The clinical management of patients with grade B postoperative liver failure deviated from the regular course but does not require invasive therapy. The need for invasive treatment defined grade C postoperative liver failure [4]. FIB-4 was calculated as: age × AST/[platelet × $(ALT)^{1/2}$]. The liver volume removed [17] was calculated as follows: segment I: 2%, segment II2: 8%, segment III: 8%, segment IV: 17%, segment V: 17.5%, segment VI: 15%, segment VII: 15%, segment VIII: 17.5%. Extrahepatic procedures included all other operations, except liver resection, such as splenectomy, adrenalectomy, diaphragm resection and so on.

2.4. Statistical analysis

Continuous variables were reported as mean (SD) or median (range), and were compared using the Student *t* test for continuous variables with parametric distribution, Mann–Whitney U test or Kruskal–Wallis H test for those with nonparametric distribution. Categorical variables were reported as numbers and percentages, and compared using Pearson x^2 analysis or Fisher exact test. The predictive ability of FIB-4 for postoperative liver failure was assessed by the receiver operating characteristic (ROC) curve and corresponding area under the ROC (AUROC) curve. The optimal cutoff value was set as the value maximizing the sum of sensitivity and specificity, namely Youden index. To identify risk factors for postoperative liver failure, only significant factors associated with liver failure in the univariate analysis were entered into the forward stepwise logistic regression analysis. All statistical analyses were performed using SPSS Version 17 statistical software, and statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient characteristics in the low postoperative FIB-4 group and high postoperative FIB-4 group

A total of 1353 patients undergoing liver resection for HCC were included in this study. 885 (65.4%) patients underwent major liver resection and 845 (62.3%) of them had anatomic hepatectomy. Only 88 (6.5%) patients were operated by laparoscope. The operative procedures displayed in Table 1. The average of preoperative platelet was 152 (10^9/L), but the average of immediate postoperative platelet reduced to 133 (10^9/L). The immediate postoperative ALT and AST levels got at least 7 times increase than preoperative levels. The average of preoperative FIB-4 was 3.38 and it increased to 8.65 after liver resection. Based on AUROC curve, preoperative FIB-4 showed a good prediction ability for postoperative liver failure (Fig. 1) (AUROC = 0.629, P = 0.024), but immediate postoperative FIB-4 showed the best prediction ability for postoperative liver failure (Fig. 1) (AUROC = 0.647, P < 0.001) than Child–Pugh score (AUROC = 0.568, P = 0.009), preoperative platelet, postoperative platelet and the preoperative FIB-4. The optimal cutoff value for prediction postoperative liver failure was 5.9 for immediate postoperative FIB-4 with the maximizing Youden index of 0.223 (sensitivity = 0.711, specificity = 0.488). With this cut-off value, patients were stratified into the low postoperative FIB-4 group (postoperative FIB-4 < 5.9) with 663 patients and the high postoperative FIB-4 group with 690 patients (postoperative FIB-4 ≥ 5.9). The patient characteristics of the two groups are shown in Table 1. The high postoperative FIB-4 group had a median age of 56, which obviously older than the low postoperative FIB-4 group. Although the two groups had similar Child Pugh score, the high postoperative FIB-4 group had higher preoperative AST, platelet

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