Low immediate postoperative platelet count is associated with hepatic insufficiency after hepatectomy

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Abstract

AIM: To investigate the relationship between low immediate postoperative platelet count and perioperative outcome after liver resection in patients with hepatocellular carcinoma (HCC).

METHODS: In a cohort of 565 consecutive hepatitis B-related HCC patients who underwent major liver resection, the characteristics and clinical outcomes after liver resection were compared between patients with immediate postoperative platelet count < 100 × 10^9/L and patients with platelet count ≥ 100 × 10^9/L. Risk factors for postoperative hepatic insufficiency were evaluated by multivariate analysis.

RESULTS: Patients with a low immediate postoperative platelet count (< 100 × 10^9/L) had more grade III-V complications (20.5% vs 12.4%, P = 0.016), and higher rates of postoperative liver failure (6.8% vs 2.6%, P = 0.02), hepatic insufficiency (31.5% vs 21.2%, P < 0.001) and mortality (6.8% vs 0.5%, P < 0.001), compared to patients with a platelet count ≥ 100 × 10^9/L. The alanine aminotransferase levels on postoperative days 3 and 5, and bilirubin on postoperative days 1, 3 and 5 were higher in patients with immediate postoperative low platelet count. Multivariate analysis revealed that immediate postoperative low platelet count, rather than preoperative low platelet count, was a significant independent risk factor for hepatic insufficiency.

CONCLUSION: A low immediate postoperative platelet count is an independent risk factor for hepatic insufficiency. Platelets can mediate liver regeneration in the cirrhotic liver.

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Key words: Thrombocytopenia; Hepatic insufficiency; Hepatocellular carcinoma; Hepatectomy; Hepatitis B

Core tip: Recent animal experiments suggested that platelets not only have a role in hemostasis and thrombogenesis, but can also improve liver function by mediating liver regeneration. Our study found that patients with a low immediate postoperative platelet count < 100 × 10^9/L had more grade III-V complications, and higher rates of postoperative liver failure, hepatic insufficiency and mortality. In addition, these patients had worse liver function after liver resection, with higher alanine aminotransferase and bilirubin and lower albumin levels. This indicated that platelets could mediate liver regeneration in cirrhotic liver.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common global cause of cancer-related deaths[1]. Liver resection is performed as first-line treatment in almost all HCC patients[2]. With the refinement of surgical techniques and perioperative management in liver surgery during the last few decades, outcomes after liver resection have improved substantially in recent years, with the operative mortality less than 5% in high-volume centers[3]. However, liver failure or hepatic insufficiency, which usually results in severe outcomes, is more common after liver resection, with an incidence ranging from 1.2% to 32%[4,5]. In Asia, about 80% of HCC cases occur in patients with cirrhosis derived from hepatitis B virus (HBV) infection[6]. Concurrent portal hypertension and thrombocytopenia usually increase the risk of postoperative liver failure and hepatic insufficiency[6,7]. Recent studies on animals demonstrated that platelets had a role not only in blood coagulation[8], but also in liver regeneration[9-11], tissue repair[12] and ischemia/reperfusion injury[13]. Several clinical studies[14-18] have also indicated that preoperative thrombocytopenia is a risk factor associated with postoperative complications and mortality. In addition, immediate postoperative low platelet count has recently been proved to be associated with delayed liver function recovery after partial liver resection for colorectal liver metastases, which indicated that platelets play a critical role in liver regeneration after liver resection[19]. However, the role of immediate postoperative low platelet count in underlying liver damage derived from HBV infection has not been investigated. Here, we report a cohort study to determine the relationship between immediate postoperative platelet count and outcome after partial liver resection in patients with HBV-related HCC.

MATERIALS AND METHODS

Study population

Between January 2009 and March 2013, 574 consecutive HBV-related HCC patients who underwent major liver resection were included in this study. All included patients were diagnosed with HCC by histology and with HBV infection (or a history of HBV infection). All patients underwent surgery when Child-Turcotte-Pugh (CTP) class did not exceed 7, or a history of HBV-related HCC. Patients with comorbid conditions, laboratory values, intraoperative parameters and postoperative outcomes were obtained from the West China Hospital of Liver Cancer Registry Database. The protocol was approved by the West China Hospital Ethics Committee and written informed consent was obtained from all patients before inclusion. We excluded 9 patients due to synchronous biliary obstruction, splenectomy or platelet transfusion. This resulted in a total of 565 patients included in the study. All patients had major liver resection which was defined as the resection of more than three liver segments. The platelet count was obtained immediately after surgery (usually upon arrival at the intensive care unit or liver department after surgery, and referred to as the immediate postoperative platelet count), and the patients were stratified into the Low Platelet Group (platelet count < 100 × 10³/L) and High Platelet Group (platelet count ≥ 100 × 10³/L). The aim of this study was to evaluate whether immediate postoperative platelet count was associated with hepatic insufficiency and mortality.

Perioperative management

All patients were managed by the same surgical team. The 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 on under general anesthesia and were explored through an extended right subcostal incision, and intraoperative ultrasonography was used routinely. Hemispheric vascular inflow occlusion[20], or the Pringle maneuver[21] was used according to the surgeon’s preference in most patients. Liver parenchymal transection was performed using the Hooking ligation method[22] or an ultrasonic dissector with coagulator. Based on preoperative and intraoperative condition, patients were transferred to the intensive care unit for treatment if necessary.

Definition of the parameters measured

The 50-50 criteria defined as prothrombin time < 50% and serum bilirubin level > 50 µmol/L on day 5 after liver resection, were used to define liver failure. Based on the 50-50 criteria, hepatic insufficiency[23] was defined as bilirubin > 50 µmol/L or prothrombin time < 50% at any time point between postoperative day 1 and postoperative day 5. Hepatic insufficiency was used as a surrogate marker for poor liver regeneration[24]. The liver volume removed was calculated as follows: segment I = 2%, segment II = 8%, segment III = 8%, segment IV = 17%, segment V = 17.5%, segment VI = 15%, segment VII = 15%, segment VIII = 17.5%. Immediate postoperative platelet count indicated the platelet count obtained on the day of surgery. Mortality was defined as death within 30 d after surgery or death before discharge involving a hospital stay of more than 30 d. The Clavien-Dindo complication classification system was used for postoperative complication grading, and grade III-V complications were defined as severe complications. Extrabiliary procedures included all other operations, except liver resection, such as bowel resection, adrenalectomy, diaphragm resection and adhesion separation due to reoperation.

Statistical analysis

All statistical analyses were performed using SPSS v17 software (SPSS Inc., Chicago, IL, United States), and statistical significance was set at P < 0.05. Continuous
two groups had similar operative procedures (Table 2), except that the Low Platelet Group required more packed red blood cell transfusion ($P = 0.001$) because of greater blood loss ($P = 0.036$). There were no significant differences between the groups regarding the other analyzed parameters (Tables 1 and 2).

### Postoperative outcomes in the low platelet group and high platelet group

No significant differences were found in total complications between the two groups. However, compared with the High Platelet Group, the Low Platelet Group had more grade III-V complications (20.5% vs 12.4%, $P = 0.016$) and longer hospital stay (14 d vs 13 d, $P = 0.011$). In the whole study group of 565 patients, 21 (3.7%) patients developed irreversible postoperative liver failure and 135 (23.9%) had hepatic insufficiency. Postoperative liver failure (6.8% vs 2.6%, $P = 0.02$) and hepatic insufficiency (31.5% vs 21.2%, $P < 0.001$) occurred more frequently in the Low Platelet Group. Postoperative mortality within 30 d was 2.1% (12 patients). Mortality in the Low Platelet Group was 6.8%, which was almost 14 times higher than that in the High Platelet Group with a mortality rate of 0.5% ($P < 0.001$). In addition, more patients in the Low Platelet Group had delayed recovery of liver function. Statistically significant differences were noted in alanine aminotransferase (ALT) levels on postoperative day 3 and day 5 (Figure 1), albumin level on postoperative day 5 (Figure 2) and total bilirubin on postoperative day 1, day 3 and day 5 (Figures 3 and 4). No significant differences were found in the other perioperative parameters.

### Results

#### Patient characteristics and operative details in the low platelet group and high platelet group

In our cohort, 146 (25.8%) patients had immediate low postoperative platelet count (platelet count < 100 x 10^9/L) (Table 1), of whom 79 (54.1%) had low preoperative platelet count. A total of 419 patients had postoperative platelet count > 100 x 10^9/L immediately after surgery. All these patients were in CTP class A when surgery was performed. Patients in the Low Platelet Group had a significantly increased rate of preoperative thrombocytopenia ($P < 0.001$) and diabetes mellitus ($P = 0.001$). The

### Table 1 Patient characteristics in patients with low or high platelet count after major liver resection $n$ (%)

| Clinical characteristics | Low platelet group ($n = 146$) | High platelet group ($n = 419$) | P value |
|--------------------------|-------------------------------|--------------------------------|---------|
| Male                     | 131 (89.7)                    | 335 (84.2)                     | 0.104   |
| Age > 65 yr              | 23 (15.8)                     | 51 (12.2)                      | 0.269   |
| Preoperative platelet    | 79 (54.1)                     | 28 (6.7)                       | < 0.001 |
| < 100 x 10^9/L           |                               |                                |         |
| ASA grade                |                               |                                |         |
| I - II                   | 117 (80.1)                    | 369 (88.1)                     |         |
| III                      | 24 (16.4)                     | 42 (10.0)                      |         |
| IV                       | 5 (3.4)                       | 8 (1.9)                        |         |
| BMI (kg/m^2), mean (SD)  | 22.9 (2.80)                   | 22.90 (2.83)                   | 0.941   |
| Esophageal varices        | 22 (15.1)                     | 47 (11.2)                      | 0.221   |
| Hypertension             | 30 (20.5)                     | 66 (15.8)                      | 0.184   |
| Cardiovascular disease   | 3 (2.1)                       | 12 (2.9)                       | 0.822   |
| Pulmonary disease        | 3 (2.1)                       | 9 (2.1)                        | 1.000   |
| Diabetes mellitus        | 22 (15.1)                     | 26 (7.6)                       | 0.001   |
| HBsAg                    | 124 (84.9)                    | 330 (78.8)                     | 0.106   |
| HBeAg                    | 22 (15.1)                     | 58 (13.8)                      | 0.714   |
| HBV DNA > 2000 U/mL      | 51 (34.9)                     | 135 (32.2)                     | 0.548   |
| AST (U/L) > ULN           | 68 (46.6)                     | 194 (46.3)                     | 0.954   |
| ALT (U/L) > ULN           | 49 (33.6)                     | 133 (31.7)                     | 0.685   |
| Total bilirubin (µmol/L), median (IQR) | 145.0 (103.3-184.6) | 129.0 (90.9-184.0) | 0.145   |
| Albumin (g/L), median (IQR) | 40.9 (43.1-37.6) | 40.5 (37.6-43.2) | 0.538   |
| Hemoglobin (g/L), median (IQR) | 141 (129-150) | 140 (127-152) | 0.913   |

BMI: Body mass index; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; SD: Standard deviation; ULN: Upper limit of normal; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ASA: American Society of Anesthesiologists category; IQR: Interquartile range.

### Table 2 Intraoperative and postoperative parameters in patients with low or high platelet count after major liver resection $n$ (%)

| Intraoperative parameters | Low platelet group ($n = 146$) | High platelet group ($n = 419$) | P value |
|---------------------------|-------------------------------|--------------------------------|---------|
| Liver volume removed      |                               |                                | 0.140   |
| < 35%                     | 61 (41.8)                     | 215 (51.3)                     |         |
| 35%-65%                   | 38 (26.0)                     | 91 (21.7)                      |         |
| > 65%                     | 47 (32.2)                     | 113 (27.0)                     |         |
| Extrahepatic procedures   | 33 (22.6)                     | 90 (21.5)                      | 0.777   |
| Liver resection with       |                               |                                | 0.083   |
| Hooking with ligation      | 35 (24.0)                     | 103 (24.6)                     |         |
| Ultrasonic dissection      | 111 (76.0)                    | 316 (75.4)                     |         |
| Inflow occlusion           | 60 (41.4)                     | 191 (45.6)                     | 0.347   |
| Anatomic resection         | 94 (64.4)                     | 263 (69.9)                     | 0.214   |
| Blood loss (mL), mean (SD) | 765 (1011)                    | 583 (436)                      | 0.036   |
| PRBCs transfusion          | 58 (39.7)                     | 105 (25.1)                     | 0.001   |
| Total complication         | 63 (43.2)                     | 150 (35.8)                     | 0.114   |
| III-V grade complication   | 30 (20.5)                     | 52 (12.4)                      | 0.016   |
| Mortality                  | 10 (6.8)                      | 2 (0.5)                        | < 0.001 |
| Liver failure              | 10 (6.8)                      | 11 (2.6)                       | 0.020   |
| Hepatic insufficiency      | 46 (31.5)                     | 89 (21.2)                      | 0.012   |
| ICU stay (d), median (IQR) | 0 (0-1)                       | 0 (0-1)                        | 0.129   |
| Hospital stay (d), median (IQR) | 14 (12-18) | 13 (11-16) | 0.011   |

PRBC: Packed red blood cell; IQR: Interquartile range; SD: Standard deviation; ICU: Intensive care unit.
DISCUSSION

The perioperative outcomes after liver resection such as liver failure, hemorrhage and mortality are major concerns in hepatobiliary surgery, especially in HCC patients who usually have underlying liver diseases due to HBV infection. Many preoperative and intraoperative parameters affecting morbidity and mortality after hepatectomy have been evaluated, however, the effect of low postoperative platelet count on postoperative morbidity and mortality is not well known. We carried out a cohort study of 565 HCC patients undergoing major liver resection to assess whether immediate low postoperative platelet count affected postoperative outcomes. In our study, a low immediate postoperative platelet count was associated with liver failure, hepatic insufficiency and mortality in univariate and multivariate analyses. This demonstrated that low platelet count is an independent predictor of postoperative hepatic insufficiency.

To date, several studies have evaluated the role of platelets on morbidity and mortality. In addition, their short-term importance and positive significance have been confirmed. Three large high-volume studies indicated that preoperative thrombocytopenia was as-

Risk factors for delayed postoperative recovery of liver function

In order to identify the risk factors for postoperative hepatic insufficiency, a univariate analysis of patients with and without hepatic insufficiency was carried out. Univariate analysis (Table 3) showed that 11 variables were significantly associated with the occurrence of hepatic insufficiency. Both low preoperative platelet count and low postoperative platelet count were significant risk factors. The other 9 variables were male sex, esophageal varices, HBsAg, aspartate aminotransferase, ALT, total bilirubin, hemoglobin concentration, liver volume removed, and blood loss. These significantly different variables were included in a multivariate logistic regression model to identify whether low postoperative platelet count was an independent risk factor for hepatic insufficiency. The logistic regression analysis (Table 4) indicated that male sex, low postoperative platelet count, esophageal varices, total bilirubin, and liver volume removed were independent risk factors for hepatic insufficiency. Low platelet count remained a strong and independent risk factor for hepatic insufficiency, rather than low preoperative platelet count.
associated with increased mortality or morbidity. Ishizawa et al. found that low platelet count was an independent risk factor for postoperative ascites. A study by Maithel et al. suggested that low preoperative platelet count may better serve with liver resection as a modified Child score which incorporates preoperative platelet count as a substitute for encephalopathy. However, with regard to the long-term effects of low platelet count, only one study has been carried out which suggested that the 3-year cumulative survival rate of HCC patients was comparable to those without thrombocytopenia. Many studies have proved that a low preoperative platelet count was related to portal hypertension and its resulting hyperplenism and hepatic fibrosis. Portal hypertension is considered a contraindication for liver resection because it significantly impairs liver function. The underlying mechanisms involved in the postoperative platelet count affecting postoperative liver function are not well understood. However, accumulating evidence from experimental and clinical studies indicated that platelets do not only have a role in hemostasis and thrombogenesis, but can also improve liver function by mediating liver regeneration via the portal vein. Recent animal experiments suggested that platelets, or rather platelet-derived serotonin, contribute to cell cycle progression and metabolic pathways to prevent acute liver failure. Other studies also proved that thrombopoietin or platelets infused via the portal vein can stimulate regeneration after hepatectomy in rats. This phenomenon in animal experiments was also confirmed in clinical practice. A retrospective study showed that transfused platelets were significantly associated with graft regeneration in liver donors.

Table 3  Patient parameters in patients with or without liver dysfunction after major liver resection

| Parameters                              | Liver dysfunction (n = 135) | No Liver dysfunction (n = 430) | OR (95% CI) | P value |
|-----------------------------------------|-----------------------------|--------------------------------|-------------|---------|
| Male                                    | 127 (94.1)                  | 357 (83.0)                     | 2.87 (1.42-5.79) | 0.001   |
| Age > 65 yr                             | 12 (8.9)                    | 62 (14.4)                      | 0.58 (0.30-1.11) | 0.097   |
| Preoperative platelet < 100 × 10⁹/L    | 37 (27.4)                   | 70 (16.3)                      | 1.94 (1.23-3.07) | 0.004   |
| Postoperative platelet < 100 × 10⁹/L   | 46 (34.1)                   | 100 (23.3)                     | 1.71 (1.12-2.60) | 0.012   |
| BMI (kg/m²), mean (SD)                  | 22.9 (21.2-25.0)            | 22.5 (20.9-24.5)               | Not available | 0.147   |
| Esophageal varices                      | 36 (26.7)                   | 33 (7.7)                       | 4.38 (2.60-7.37) | 0.001   |
| Hypertension                            | 22 (16.3)                   | 74 (17.2)                      | 0.94 (0.56-1.58) | 0.805   |
| Cardiovascular disease                  | 11 (8.3)                    | 11 (2.6)                       | 1.16 (0.36-3.71) | 0.799   |
| Pulmonary disease                       | 2 (1.5)                     | 10 (2.3)                       | 0.63 (0.14-2.92) | 0.802   |
| Diabetes mellitus                       | 10 (7.4)                    | 3 (1.7)                        | 0.83 (0.4-1.70)  | 0.603   |
| ASA III-IV                              | 17 (12.6)                   | 62 (14.4)                      | 0.86 (0.48-1.52) | 0.594   |
| HBsAg                                   | 119 (88.1)                  | 335 (77.9)                     | 2.11 (1.19-3.73) | 0.009   |
| HBeAg                                   | 24 (17.8)                   | 56 (13.0)                      | 1.44 (0.86-2.44) | 0.167   |
| HBV DNA > 2000 U/mL                     | 47 (34.8)                   | 139 (32.3)                     | 1.12 (0.74-1.68) | 0.591   |
| AST (U/L) > ULN                         | 75 (55.6)                   | 187 (43.5)                     | 1.62 (1.12-2.40) | 0.014   |
| ALT (U/L) > ULN                         | 55 (40.7)                   | 127 (29.5)                     | 1.64 (1.05-2.50) | 0.015   |
| Total bilirubin (µmol/L), median (IQR)  | 16.1 (11.4-20.5)            | 12.5 (9.6-17.4)                | Not available | < 0.001 |
| Hemoglobin (g/L), median (IQR)          | 146 (131-157)               | 139 (127-150)                  | Not available | 0.001   |
| Liver volume removed                    | < 0.001                     |                                |             |         |
| < 35%                                   | 15 (11.1)                   | 145 (33.7)                     | 1 (reference) |         |
| 35%-65%                                 | 32 (23.7)                   | 97 (22.6)                      | 3.19 (1.64-6.20) |         |
| > 65%                                   | 88 (65.2)                   | 188 (43.7)                     | 4.53 (2.51-8.15) |         |
| Extrahepatic procedures                | 37 (27.4)                   | 86 (20.0)                      | 1.51 (0.97-2.36) | 0.069   |
| Liver resection with                    |                            |                                | 0.248       |         |
| Hooking with ligation                   |                            |                                |             |         |
| Ultrasonic dissection                   |                            |                                |             |         |
| Inflow occlusion                        |                            |                                |             |         |
| Anatomic resection                      |                            |                                |             |         |
| Blood loss (mL), mean (SD)              |                            |                                |             |         |
| PRBCs transfusion                       |                            |                                |             |         |
| Hospital stay (d), median (IQR)         |                            |                                |             |         |

BMI: Body mass index; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; SD: Standard deviation; ULN: Upper limit of normal; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IQR: Interquartile range.
The role of platelets in the promotion of liver regeneration has been clinically confirmed in patients undergoing liver resection for colorectal liver metastases. In Asia, in contrast to the liver with metastatic tumors, the liver with HCC usually has cirrhosis or fibrosis and secondary hypersplenism due to HBV infection. There is not only the well-known feature of thrombocytopenia, but also decreased platelet function in chronic HBV liver diseases and cirrhosis. It is not known whether postoperative thrombocytopenia also has an effect on liver function recovery after liver resection for HBV-related HCC. Therefore, in the present study, we selected low immediate postoperative platelet count instead of preoperative platelet count as the criterion for thrombocytopenia, as platelet count usually changes due to intraoperative blood loss or platelet transfusion. In addition, preoperative platelet count appeared to be a surrogate for the preoperative severity of a patient's liver disease. In our study, low immediate postoperative platelet count was associated with a greater likelihood of liver failure, hepatic insufficiency and mortality. Compared with patients with a high platelet count, the mortality rate was almost 14 times higher in patients with a low postoperative platelet count, and the rate of liver failure was 2.6 times higher. As there were a few cases involved, independent risk factors for liver failure and mortality were not analyzed by multivariate analysis. For hepatic insufficiency, multivariate analysis showed that liver volume removed was the strongest independent risk factor, followed by esophageal varices and platelet count. This differed from a previous study which found that low immediate postoperative platelet count was the strongest independent risk factor. A possible reason for this difference was that patients in our study also had esophageal varices and underwent major liver resection. Portal hypertension (represented by esophageal varices) and major liver resection mainly contribute to hepatic insufficiency.

Our findings are instructive for surgeons to ensure that they take positive measures to increase platelet count to prevent hepatic insufficiency. These treatments should include platelet transfusion and administration of thrombopoietin and serotonin. One study showed that administration of thrombopoietin reduces liver fibrosis and stimulates regeneration in the cirrhotic liver. This is suitable for HCC patients as most have different degrees of liver fibrosis which has a strong impact on morbidity. However, further research is needed before this treatment can be considered for use in the clinic.

Our study has several limitations mainly due to the retrospective analysis. It is important to point out that some of the patients in our study were highly selected for surgical safety. Secondly, the immediate postoperative platelet count may not be as exact as it may have been affected by hemodilution or hemoconcentration after surgery. In addition, increased consumption of circulating platelets occurred due to subsequent bleeding and hemostasis after surgery. This was different in each patient and was not considered in our study.

In conclusion, our study found that a low immediate postoperative platelet count was associated with postoperative hepatic insufficiency, liver failure and mortality. A low immediate postoperative platelet count is an independent risk factor for hepatic insufficiency. These findings indicated that platelets can mediate liver regeneration in the cirrhotic liver.

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