Tohoku J. Exp. Med., 2016, **239**, 47-55

# Postoperative Decrease in Platelet Counts Is Associated with Delayed Liver Function Recovery and Complications after Partial Hepatectomy

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Peripheral platelet counts decrease after partial hepatectomy; however, the implications of this phenomenon are unclear. We assessed if the observed decrease in platelet counts was associated with postoperative liver function and morbidity (complications grade ≤ II according to the Clavien-Dindo classification). We enrolled 216 consecutive patients who underwent partial hepatectomy for primary liver cancers, metastatic liver cancers, benign tumors, and donor hepatectomy. We classified patients as either low or high platelet percentage (postoperative platelet count/preoperative platelet count) using the optimal cutoff value calculated by a receiver operating characteristic (ROC) curve analysis, and analyzed risk factors for delayed liver functional recovery and morbidity after hepatectomy. Delayed liver function recovery and morbidity were significantly correlated with the lowest value of platelet percentage based on ROC analysis. Using a cutoff value of 60% acquired by ROC analysis, univariate and multivariate analysis determined that postoperative lowest platelet percentage ≤ 60% was identified as an independent risk factor of delayed liver function recovery (odds ratio (OR) 6.85; $P < 0.01$) and morbidity (OR, 4.90; $P < 0.01$). Furthermore, patients with the lowest platelet percentage ≤ 60% had decreased postoperative prothrombin time ratio and serum albumin level and increased serum bilirubin level when compared with patients with platelet percentage ≥ 61%. A greater than 40% decrease in platelet count after partial hepatectomy was an independent risk factor for delayed liver function recovery and postoperative morbidity. In conclusion, the decrease in platelet counts is an early marker to predict the liver function recovery and complications after hepatectomy.

**Keywords:** delayed liver function recovery; liver regeneration; morbidity; partial hepatectomy; platelet
Tohoku J. Exp. Med., 2016 May, **239** (1), 47-55. 

## Introduction

Technical improvements in liver surgery have resulted in an expansion of the indications for hepatectomies, especially in high-risk patients with underlying conditions including liver fibrosis, steatosis, and chemotherapy-induced injury (Belghiti et al. 2000). However, the risks of postoperative liver failure and grim outcomes remain an important concern. Although the Child-Pugh score is a useful clinical criterion for evaluating preoperative liver function, it often does not accurately predict the postoperative outcome (Nagashima et al. 2005). Balzan et al. (2005) described the "50-50 criteria," namely a serum bilirubin (Bil) > 50 $\mu$mol/L and a prothrombin time ratio (PTR) < 50% on postoperative day (POD) 5. Those criteria predict nearly 100% of morbidity and 50% of mortality after cases of liver resection. The criteria were mainly based on the results of major hepatectomies that involved resection of more than three segments. On the other hand, some centers, especially in Asia, have placed a greater level of importance on minor hepatectomies in order to preserve the remnant liver volume in cases of poor liver function reserve. Examples include subsegmentectomy for hepatocellular carcinoma (HCC) and partial hepatectomy for metastatic liver cancers.

Surgeons have reported decreased peripheral platelet counts after liver surgery (McCaughan et al. 1992; Kaneko et al. 2005). However, the implications of this phenomenon have been documented only recently (Alkozai et al. 2010; Lesurtel et al. 2014; Starlinger et al. 2014). Starlinger et al. (2014) demonstrated that reduced intra-platelet serotonin levels together with decreased platelet counts are associated

Received February 1, 2016; revised and accepted April 19, 2016. Published online May 13, 2016; doi: 10.1620/tjem.239.47.
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with an increased morbidity and liver dysfunction after hepatectomy. Alkozai et al. (2010) reported that immediate postoperative platelet counts below $100 \times 10^3/\mu L$ were associated with delayed liver function recovery after hepatectomy. These studies focused on platelets as a promoter of liver regeneration. Accordingly, a decrease in platelet counts was identified as a delay in postoperative liver function recovery. However, in the study by Alkozai et al. (2010), hepatectomy was only performed on patients with colorectal metastatic liver tumors who did not have preexisting liver diseases. It is difficult to use their indicators in patients with complicated backgrounds such as liver cirrhosis, a condition in which preoperative platelet counts can be below $100 \times 10^3/\mu L$. Therefore, it is desirable to find an indicator that can predict postoperative liver failure and morbidity in patients with a variety of backgrounds.

In this clinical study, we assessed the relationship between decreases in platelet count and post-hepatectomy outcomes. The primary outcomes included postoperative delayed liver function recovery and morbidity. We classified patients as having either a low or a high postoperative lowest platelet percentage (postoperative platelet count/preoperative platelet count) using the optimal cutoff value calculated using a receiver operating characteristic (ROC) curve analysis. In addition, postoperative serum parameters were compared between the two groups.

## Materials and Methods

*Study population*

A total of 293 consecutive hepatectomies without biliary reconstruction were performed at the Department of Surgery in the University of Tsukuba between June 2006 and March 2014. Two patients received platelet transfusions after hepatectomy and were excluded from the analysis. A total of 63 patients, including the above-mentioned one patient who received a platelet transfusion, were excluded because postoperative laboratory data were not fully documented. Furthermore, 13 patients who received fresh frozen plasma (FFP) perioperatively were excluded because FFP use could complicate postoperative outcomes in our study. Thus, the final study population consisted of 216 patients. Patient characteristics are presented in Table 1. Informed consent was obtained from all individual participants included in the study. The study was reviewed and approved by the University of Tsukuba Institutional Review Board.

*Outcome parameters and laboratory variables*

CT scans are not routinely performed after hepatectomy at our institution. Thus, delayed liver function recovery was used as a surrogate marker for poor liver regeneration. We defined a delayed liver function recovery according to the definition of post-hepatectomy liver failure by the International Study Group of Liver Surgery (ISGLS), characterized by an increased international normalized ratio (decreased PTR) and concomitant hyperbilirubinemia on or after POD 5 (Rahbari et al. 2011a).

Postoperative morbidity was defined as a complication of grade II or higher using the Clavien-Dindo classification system (Clavien et al. 2009). In our study, only one patient died within the 30-day observation period after surgery. Postoperative mortality was not used as a primary outcome because of the small number of cases.

Table 1. Patient demographics (n = 216).

| | |
|---|---|
| Age, median | 66 (17-82) |
| Sex, male | 141 (65%) |
| Type of tumor | |
| Primary liver cancer | 127 (59%) |
| HCC | 112 (88%) |
| CCC | 10 (8%) |
| Combination | 5 (4%) |
| Metastasis | 70 (32%) |
| Colon/Rectum cancer | 50 (71%) |
| Ovary/testicle cancer | 5 (7%) |
| Uterus cancer | 4 (6%) |
| Neuroendocrine tumor | 3 (4%) |
| Stomach caner | 2 (3%) |
| Brest cancer | 2 (3%) |
| Kidney caner | 2 (3%) |
| Lung cancer | 1 (1%) |
| CCC | 1 (1%) |
| Benign and donor | 19 (9%) |
| Benign tumors | 6 (32%) |
| Donor | 13 (68%) |
| Child-Pugh score | |
| A | 206 (95%) |
| B | 10 (5%) |
| Cirrhotic liver (F4) | 26 (12%) |
| Liver segments removed | |
| ≤ 2 segments | 151 (70%) |
| 3.4 segments | 54 (25%) |
| > 4 segments | 11 (5%) |
| Complication (Grade 2 ≤) | 58 (27%) |
| 30 days mortality | 1 (0.5%) |
| Hospital stay (days), median | 11 (6-100) |

HCC, Hepatocellular carcinoma; CCC, Cholangiocellular carcinoma.

We classified patients as having either a low or a high postoperative lowest platelet percentage using the cutoff value calculated by ROC curve analysis. We analyzed risk factors for postoperative delayed liver function recovery and morbidity. Furthermore, postoperative serum parameters were compared between the two groups. The analyzed postoperative laboratory variables included PTR, serum Bil, and albumin (Alb). Laboratory data were obtained on POD 1, POD 3, between POD 4 and 7, between POD 8 and 14, between POD 15 and 21, and between POD 22 and 30.

*Statistical analysis*

Results are presented as numbers and percentages, and groups were compared using the chi-squared test or Fisher's exact test. Continuous variables are expressed as the median, minimum, and maximum and were compared using *t*-tests. Pearson's correlations, univariate and multivariate logistic regression analyses, and ROC analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL). The predictive ability was considered poor if an area under the receiver operating characteristic (AUROC) curve was < 0.7. All variables that had $P < 0.05$ in the univariate analysis were included in the

multivariate logistic regression analysis. Values of $P < 0.05$ were considered statistically significant.

## Results

*Postoperative platelet variables*

Of the 216 patients, 31 (14.4%) were deemed to have a delayed liver function recovery, while 185 were considered to have an adequate liver function recovery. A total of 58 patients (26.9%) experienced morbidity, while 158 patients recovered without morbidity. Postoperative platelet percentages are presented in Fig. 1a, b. Platelet percentages for both liver function recovery groups reached a minimum on POD 3 ($P = 0.22$). Platelet percentage returned to preoperative levels significantly faster in the adequate recovery group than in the delayed group (POD 6 vs. POD 11, $P < 0.01$) (Fig. 1a). Platelet percentages in both postoperative morbidity groups reached a minimum on POD 3 ($P = 0.26$). Platelet percentage returned to preoperative levels significantly faster in the group without morbidity than in the group suffering morbidity (POD 6 vs. POD 8, $P < 0.01$) (Fig. 1b). There was no difference in postoperative platelet percentage between patients with and without liver cirrhosis (Fig. 1c). Furthermore, postoperative platelet percentage was independent of the underlying primary disease (Fig. 1d).

*Prediction of postoperative complications*

An independent *t*-test showed that the lowest postoperative platelet count ($\times 10^3/\mu$l), lowest postoperative platelet percentage (%), intraoperative blood loss (ml), and preoperative serum Alb (mg/dl), and total Pringle maneuver time (min) were significantly correlated with delayed liver function recovery and postoperative morbidity. The AUROCs are shown in Table 2. Only the lowest postoperative platelet percentage had an AUROC > 0.7 in both the delayed liver function recovery and the postoperative morbidity groups. The AUROCs for this parameter were higher when compared with the other four factors. The calculated cutoff value for the lowest platelet percentage was 60% with a sensitivity of 67.7% and a specificity of 78.9% for

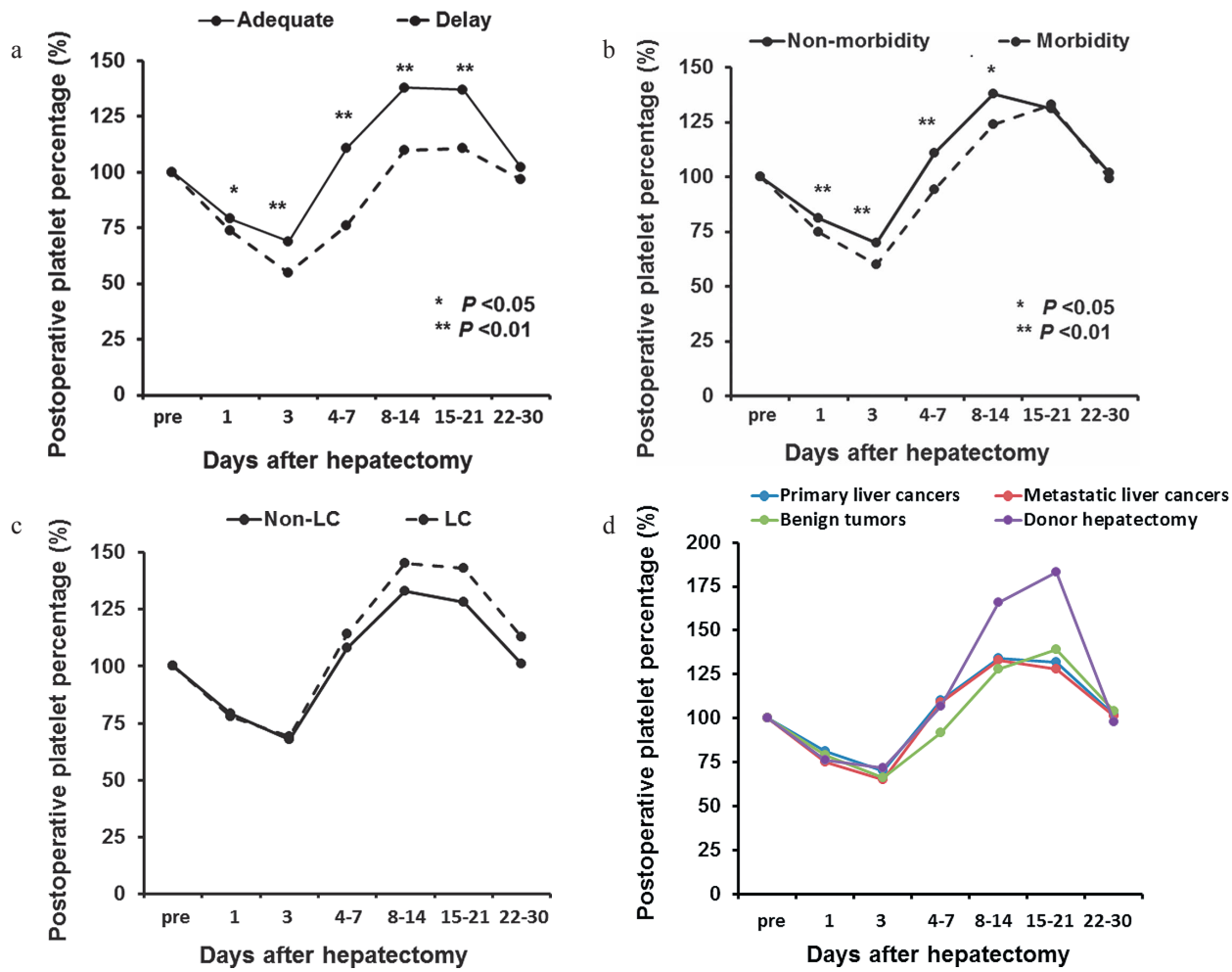


Fig. 1. Dynamics of postoperative platelet percentage (postoperative platelet count/preoperative platelet count) (%). a. Platelet percentages of patients with delayed and adequate liver function recovery. b. Platelet percentages in patients with and without morbidity. c. Platelet percentages in patients with and without liver cirrhosis (LC). d. Platelet percentages of the patients classified by the underlying primary disease. Median values are shown.

Table 2. Area under the receiver operating characteristic curves (AUROC) for delayed postoperative liver function recovery and postoperative morbidity.

| | AUROC | 95% CI | *P* value |
|---|---|---|---|
| **Delayed postoperative liver function recovery** | | | |
| Lowest platelet count (× $10^3$/μl) | 0.63 | 0.52-0.75 | 0.02 |
| Lowest platelet percentage (%) | 0.77 | 0.68-0.87 | < 0.01 |
| Blood loss (ml) | 0.65 | 0.54-0.76 | < 0.01 |
| Preoperative albumin level (mg/dl) | 0.62 | 0.51-0.74 | 0.03 |
| Total Pringle maneuver time (min) | 0.56 | 0.44-0.67 | 0.30 |
| **Postoperative morbidity (Grade2 ≤)** | | | |
| Lowest platelet count (× $10^3$/μl) | 0.57 | 0.49-0.66 | 0.11 |
| Lowest platelet percentage (%) | 0.72 | 0.64-0.80 | < 0.01 |
| Blood loss (ml) | 0.71 | 0.63-0.80 | < 0.01 |
| Preoperative albumin level (mg/dl) | 0.68 | 0.60-0.76 | < 0.01 |
| Total Pringle maneuver time (min) | 0.58 | 0.50-0.67 | 0.07 |

CI, confidence interval.

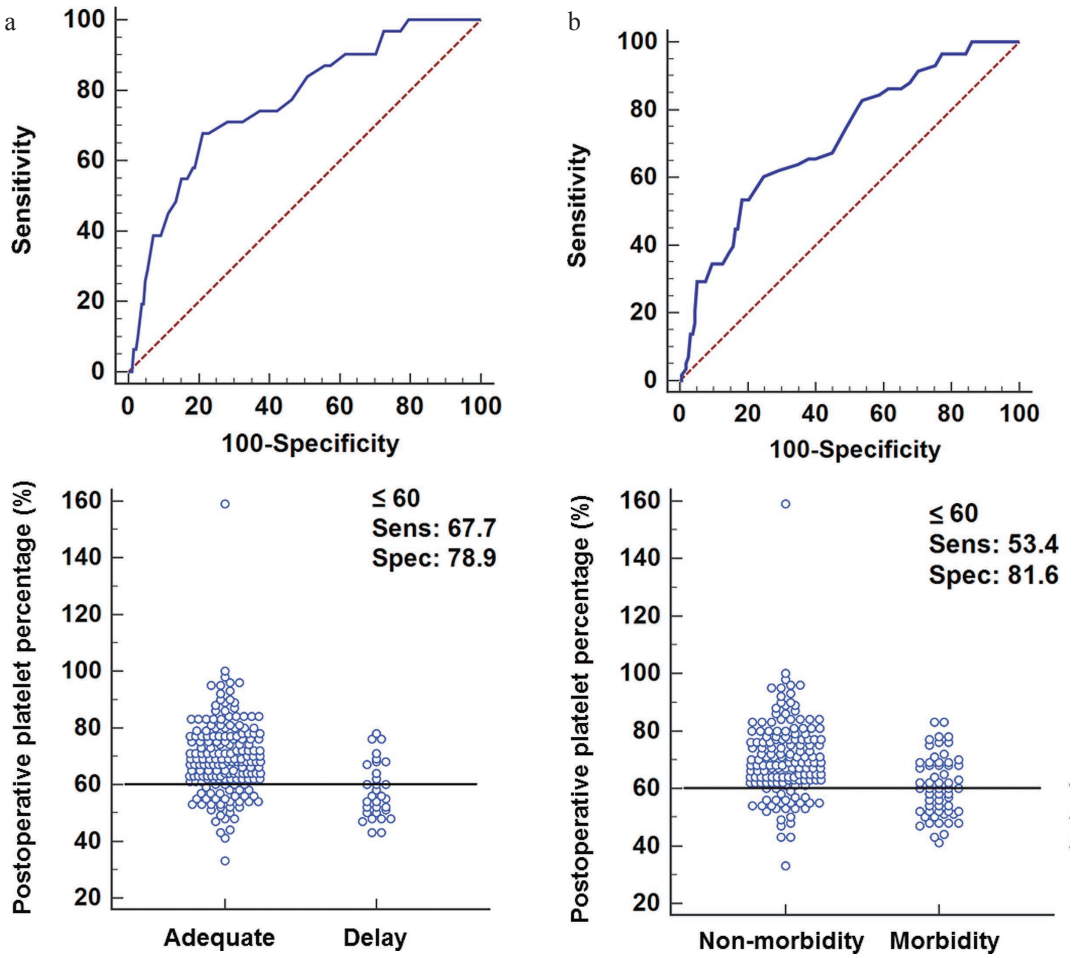


Fig. 2. Receiver operating characteristic curves and interactive dot diagrams for postoperative platelet percentage in relation to delayed liver function recovery and postoperative morbidity.
a. Relationship between postoperative platelet percentage and delayed liver function recovery. b. Relationship between postoperative platelet percentage and postoperative morbidity.

the prediction of delayed liver function recovery (Fig. 2a). The sensitivity was 53.4% and specificity was 81.6% for the prediction of postoperative morbidity (Fig. 2b).

*Univariate and multivariate analyses of risk factors for delayed liver function recovery and postoperative morbidity*

We performed univariate and multivariate analyses to

examine the possible relationship between a low platelet percentage and a delayed liver function recovery or postoperative morbidity. A univariate analysis revealed that six variables, blood loss, operation time, total Pringle maneuver time, red blood cell (RBC) transfusion, preoperative serum Alb < 3.5 mg/dl, and lowest platelet percentage ≤ 60%, were risk factors for delayed liver function recovery (Table 3). Blood loss showed significant correlation with operation time (R = 0.56) and RBC transfusion (R = 0.48) as calculated by Pearson's correlation analysis. Four variables, namely blood loss, total Pringle maneuver time, preoperative serum Alb < 3.5 mg/dl, and platelet percentage ≤ 60%, were used for a multivariate analysis. Postoperative platelet percentage ≤ 60% (the odds ratio (OR) 6.85; 95% confidence interval (CI) 2.82-16.70; $P < 0.01$) and blood loss (OR, 1.00; 95% CI, 1.00-1.01; $P = 0.04$) were found to be independent risk factors for delayed liver function recovery (Table 4). A univariate analysis revealed that eight variables, namely, age > 60, removed liver segments, blood loss, operation time, total Pringle maneuver time, RBC transfusion, preoperative serum Alb < 3.5 mg/dl, and platelet percentage ≤ 60%, were risk factors for postoperative morbidity (Table 3). Because blood loss showed a significant correlation with operation time and RBC transfusion, six variables (age > 60, removed liver segments, blood loss, total Pringle maneuver time, preoperative serum Alb < 3.5 mg/dl, and platelet percentage ≤ 60%) were used for a multivariate analysis. Age > 60 (OR, 3.98; 95% CI, 1.60-9.88; $P < 0.01$), Postoperative platelet percentage ≤ 60% (OR, 4.90; 95% CI, 2.29-10.50; $P < 0.01$), and blood loss (OR, 1.01; 95% CI, 1.00-1.02; $P = 0.01$) were found to be independent risk factors for postoperative morbidity (Table 4). Notably, preoperative platelet counts were not associated with either delayed liver function recovery or postoperative morbidity. Furthermore, there was no correlation with the POD in which platelet counts reached a minimum value.

*Postoperative laboratory variables between low and high platelet percentage groups*

Based on a cutoff value of 60% obtained from analysis of ROC curves, patients were stratified into two groups: high platelet percentage (156 patients) and low platelet percentage (60 patients). Postoperative variables for both groups were evaluated (Fig. 3). Peak level of serum Bil was significantly higher in the low platelet percentage group than in the high platelet percentage group. Patients in the low group had prolonged liver dysfunction, as indicated by a significantly lower PTR almost until POD 21. Furthermore, serum Alb was significantly decreased in the low group on POD 30. Until September 2008, the majority of patients received purified Alb preparations within a few days following hepatectomy. However, the half-life of these preparations is nine to ten days under invasive conditions such as surgery (Spiess et al. 1996), and their administration had no influence on serum Alb on POD 30. These data also suggest that a postoperative platelet percentage of ≤ 60% is associated with liver dysfunction immediately after hepatectomy.

## Discussion

Surgeons frequently observe a decrease in peripheral platelet counts after hepatectomy (Kaneko et al. 2005; Okano et al. 2010). This phenomenon is more pronounced after a major hepatectomy, but it usually resolves within the first week after surgery (Kaneko et al. 2005). Several factors are thought to underlie this process, including sequestration of platelets in the remnant liver, impaired production of thrombopoietin due to reduction in hepatocyte volume, increased consumption of circulating platelets due to intrahepatic and splenic congestion, hypersplenism, and hemodilution (Chatzipetrou et al. 1999; Kaneko et al. 2005; Okano et al. 2010). In recent years, experimental studies have demonstrated that platelets play an important role in promoting liver regeneration after hepatectomy. Platelet-derived serotonin was demonstrated to be involved in initiating liver regeneration (Lesurtel et al. 2006). It was also determined that platelets accumulate in the liver immediately after hepatectomy (Matsuo et al. 2011), and promote liver regeneration by interactions with parenchymal cells and non-parenchymal cells (Murata et al. 2007; Kawasaki et al. 2010; Takahashi et al. 2013). In our study, a postoperative platelet percentage of ≤ 60% after hepatectomy was associated with delayed liver function recovery and postoperative morbidity. Although platelet counts reached a minimum on POD 3 for patients in both the delayed and adequate liver function recovery groups, platelet counts returned to preoperative levels significantly earlier in the adequate liver function recovery group than in the delayed liver function recovery group. Based on these results, we consider that although platelets accumulated in the liver early after hepatectomy, more platelets were consumed to promote liver regeneration in the delayed liver function recovery group, thus resulting in delayed restoration of peripheral platelet counts. This hypothesis is supported by the work of Takahashi et al. (2013) showing that inhibition of platelet accumulation in the liver by Kupffer cell depletion attenuated decreases in peripheral platelet counts and impaired liver regeneration within 96 hours after hepatectomy.

Improvements in liver surgery have increased the ability to resect larger parenchymal volumes and leave smaller liver remnants (Belghiti et al. 2000; Golse et al. 2013). It is now possible to perform hepatectomies in patients with underlying liver dysfunction, as in liver cirrhosis, severe steatosis, or chemotherapy-related liver lesions (Belghiti et al. 2000; Golse et al. 2013). These conditions can impair postoperative liver regeneration and increase the likelihood of postoperative liver failure. The Child-Pugh score, which accurately evaluates preoperative liver function, is likely to be biased and is usually inappropriate for postoperative use (Nagashima et al. 2005). The 50-50 criteria were developed to evaluate postoperative liver failure (Balzan et al.

Table 3. Univariate analysis of risk factors for delayed liver function recovery and postoperative morbidity.

| Variables | Delayed liver function recovery Yes (n = 31) | No (n = 185) | *P* value | Morbidity (Grade 2 ≤) Yes (n = 58) | No (n = 158) | *P* value |
|---|---|---|---|---|---|---|
| **Patient variables** | | | | | | |
| Age > 60 | 25 (81%) | 116 (63%) | 0.06 | 46 (79 %) | 95 (60 %) | < 0.01 |
| Sex, male | 25 (81%) | 116 (63%) | 0.06 | 40 (69 %) | 101 (64 %) | 0.49 |
| Type of tumor | | | 0.48 | | | 0.45 |
| HCC, CCC, combination | 20 (65%) | 107 (58%) | - | 37 (64 %) | 90 (57 %) | - |
| Metastasis | 10 (32%) | 60 (32%) | - | 15 (26 %) | 55 (35 %) | - |
| Benign and donor | 1 (3%) | 18 (10%) | - | 6 (10 %) | 13 (8 %) | - |
| Comorbidity | | | | | | |
| Diabetes mellitus | 9 (29%) | 52 (28%) | 0.92 | 16 (28 %) | 45 (29 %) | 0.90 |
| Hypertension | 9 (29%) | 42 (23%) | 0.44 | 17 (29 %) | 34 (22 %) | 0.23 |
| Respiratory complication | 2 (6%) | 3 (2%) | 0.10 | 2 (3 %) | 3 (2 %) | 0.50 |
| Renal complication | 0 (0%) | 7 (4%) | 0.27 | 2 (3 %) | 5 (3 %) | 0.92 |
| Preoperative chemotherapy | 2 (6%) | 21 (11%) | 0.41 | 3 (5 %) | 20 (13 %) | 0.11 |
| Simultaneous resection | 4 (13%) | 15 (8%) | 0.38 | 5 (9 %) | 14 (9 %) | 0.96 |
| Child-Pugh score | | | 0.60 | | | 0.09 |
| A | 29 (94%) | 177 (96%) | - | 53 (91 %) | 153 (97 %) | - |
| B | 2 (6%) | 8 (4%) | - | 5 (9 %) | 5 (3 %) | - |
| Cirrhotic liver (F4) | 5 (16%) | 21 (11%) | 0.50 | 10 (17 %) | 16 (10 %) | 0.15 |
| MELD score, median | 7 (6-12) | 7 (6-20) | 0.78 | 7 (6-20) | 7 (6-20) | 0.45 |
| ICG 15 min (%), median, n = 201 | 13.0 (3.7-44.0) | 10.9 (1.0-40.8) | 0.17 | 12.7 (3.0-44.0) | 11.0 (1.0-44.0) | 0.37 |
| **Surgical variables** | | | | | | |
| Liver segments removed | | | 0.23 | | | < 0.01 |
| ≤ 2 segments | 18 (58 %) | 133 (72 %) | - | 32 (55 %) | 119 (75 %) | - |
| 3.4 segments | 10 (32%) | 44 (24%) | - | 19 (33 %) | 35 (22 %) | - |
| > 4 segments | 3 (10%) | 8 (4%) | - | 7 (12 %) | 4 (3 %) | - |
| Blood loss (ml), median | 665 (90-3,630) | 420 (0-2,680) | < 0.01 | 770 (80-3,630) | 370 (0-2,700) | < 0.01 |
| Operation time (min), median | 384 (195-695) | 306 (92-691) | < 0.01 | 408 (92-695) | 297 (125-691) | < 0.01 |
| Total Pringle maneuver time (min), median | 45 (0-149) | 34 (0-227) | 0.04 | 47 (0-277) | 31 (0-149) | 0.02 |
| RBC transfusion, yes | 5 (16%) | 10 (5 %) | 0.03 | 9 (16 %) | 6 (4 %) | < 0.01 |
| **Preoperative laboratory variables** | | | | | | |
| Platelet count ($\times 10^3/\mu l$), median | 186 (81-433) | 178 (34-504) | 0.55 | 179 (81-504) | 181 (34-433) | 0.45 |
| AST (U/L), median | 34 (17-101) | 27 (11-176) | 0.14 | 31 (12-147) | 26 (11-175) | 0.15 |
| ALT (U/L), median | 27 (14-126) | 26 (5-128) | 0.33 | 25 (5-94) | 27 (6-128) | 0.78 |
| Bil (mg/L), median | 0.7 (0.2-2.1) | 0.7 (0.4-1.9) | 0.63 | 0.7 (0.2-1.9) | 0.7 (0.3-2.1) | 0.47 |
| PTR (%), median | 90 (75-107) | 94 (58-164) | 0.20 | 94 (73-120) | 94 (58-164) | 0.40 |
| Alb < 3.5 mg/dl | 7 (23%) | 15 (8%) | 0.01 | 10 (17%) | 12 (6%) | 0.04 |
| CRP > 3.0 mg/dl | 2 (6%) | 6 (3%) | 0.37 | 4 (7%) | 4 (3%) | 0.13 |
| **Postoperative platelet variables** | | | | | | |
| Postoperative lowest platelet day (day), median | 3 (1-18) | 3 (1-6) | 0.32 | 3 (1-18) | 3 (1-13) | 0.26 |
| Lowest platelet percentage ≤ 60%* | 21 (68%) | 39 (21%) | < 0.01 | 31 (53%) | 29 (18%) | < 0.01 |

HCC, hepatocellular carcinoma; CCC, cholangocellular carcinoma; MELD, Model for End-Stage Liver Disease; ICG, indocyanine green; RBC, red blood cell; AST, Aspartate transaminase; ALT, alanine aminotransferase; Bil, bilirubin; PTR, prothrombin time ratio; Alb, albumin; CRP, C-reactive protein.

*Platelet percentage = Postoperative count/preoperative platelet count.

2005). These criteria include two components of the Child-Pugh score that are unlikely to be biased, namely PTR < 50% and Bil levels of > 50 $\mu$mol/L (3 mg/dl). Previous studies determined that the 50-50 criteria from POD 5 provided an accurate and early indicator of postoperative liver failure, predicting nearly 100% of morbidity and 50% of

Table 4. Multivariate analysis for delayed liver function recovery and postoperative morbidity.

| Variables | Delayed liver function recovery | | Morbidity (Grade 2 ≤) | |
|---|---|---|---|---|
| | **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** |
| Age > 60 | - | - | 3.98 (1.60-9.88) | < 0.01 |
| Liver segments removed | | | | |
| ≤ 2 segments | - | - | | 0.19 |
| 3.4 segments | - | - | 1.30 (0.534-3.17) | 0.56 |
| > 4 segments | - | - | 4.77 (0.89-25.71) | 0.07 |
| Blood loss (ml) | 1.00 (1.00-1.01) | 0.04 | 1.01 (1.00-1.02) | < 0.01 |
| Total Pringle maneuver time (min) | 1.03 (0.99-1.01) | 0.57 | 1.00 (0.99-1.01) | 0.68 |
| Preoperative Alb < 3.5 mg/dl | 2.47 (0.76-7.97) | 0.13 | 1.64 (0.54-5.02) | 0.39 |
| Postoperative lowest platelet percentage ≤ 60% * | 6.85 (2.82-16.70) | < 0.01 | 4.90 (2.29-10.50) | < 0.01 |

OR, odds ratio; CI, confidence interval; Alb, albumin.
*Platelet percentage = Postoperative count/preoperative platelet count.

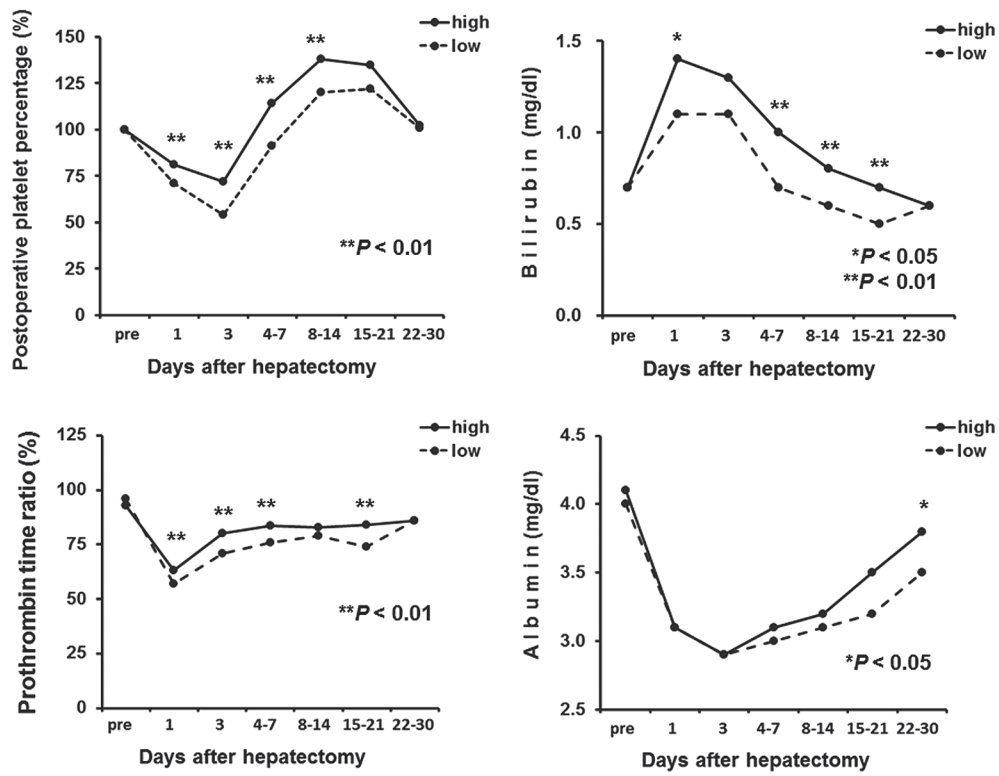


Fig. 3. Postoperative platelet percentage and laboratory variables in the low and high platelet percentage groups. Postoperative platelet percentage, prothrombin time ratio, serum bilirubin, and albumin concentrations of the patients in the low platelet percentage (n = 60) and high platelet percentage groups (n = 156). Median values are shown. *$P$ < 0.05, **$P$ < 0.01.

mortality after liver resection (Balzan et al. 2005). Considering the lack of a standardized definition of posthepatectomy liver failure, the ISGLS recently proposed to define posthepatectomy liver failure, characterized by an increased INR (decreased PT) and concomitant hyperbilirubinemia on or after POD 5, together with a grading system of severity considering the impact on patients` clinical management (Rahbari et al. 2011a). It was reported that the sensitivity and specificity of the ISGLS definition for detection of overall mortality were 65% and 91%, respectively (Rahbari et al. 2011b). On the other hand, liver regeneration early after hepatectomy is largely mediated by hepatocyte mitosis (Michalopoulos and DeFrances 1997). Greater than 95% of quiescent hepatocytes enter the cell cycle, with DNA synthesis peaking at 24 hours and mitosis peaking at 48 hours after hepatectomy (Michalopoulos and DeFrances 1997; Garcea and Maddern 2009). Therefore, it is essential to find the earliest possible indicator of liver failure after hepatectomy in order to establish effective interventions for promoting liver regeneration and avoiding liver failure. In the present study, a postoperative lowest platelet percentage of ≤ 60% was a strong and independent risk factor for delayed liver function recovery and postoperative morbidity. Postoperative platelet counts and percentages reached a

minimum on POD 3, a time when the majority of hepatocytes are undergoing active mitosis. Based on this indicator, effective hepatocyte-targeted treatments such as prostaglandin (Togo et al. 2008), cytokine therapy (Zhang et al. 2016) and HGF gene therapy (Xue et al. 2003) could potentially be used during the optimal period for liver regeneration. Furthermore, our results suggest that maintaining platelet counts above 61% with platelet transfusion, thrombopoietin, or thrombopoietin-receptor agonist administration may prevent delayed liver function recovery and postoperative complications. This hypothesis is supported by a report from Kim et al. (2010) showing that platelet transfusion volume after liver transplantation from living related donors was positively correlated with graft regeneration. However, there are several critical obstacles that need to be overcome before exploiting platelets in clinical practice, including the production of anti-platelet antibodies following platelet transfusion (Howard and Perkins 1978), the production of anti-thrombopoietin antibodies after thrombopoietin administration (Wormann 2013), and the several-day delay between thrombopoietin-receptor agonist administration and increases in platelet counts (Schipperus and Fijnheer 2011). Further research is necessary to determine the optimal treatment methods and time intervals for increasing postoperative platelet counts.

Our study has several limitations. First, the retrospective study used a small patient population, conducted in a single center. Furthermore, we cannot ignore the heterogeneity of the patient backgrounds in terms of the type of tumor and the volume of liver removed. Second, we failed to determine if the low platelet count was the cause of poor outcomes or a result of the worse postoperative liver function. At this moment, we advocate that postoperative platelet percentage of ≤ 60% is an independent predictor of the delayed liver function recovery and postoperative morbidity. Third, the sensitivity of our indicator for detecting postoperative morbidity is low (53%). However, the specificity is relatively high (82%). Based on the lack of other indicators that can be applied as quickly as our criterion of a low platelet percentage, we believe that our finding can serve as the earliest marker for delayed liver function recovery and postoperative morbidity.

## Conclusion

We demonstrated that a postoperative platelet percentage of ≤ 60%, or a greater than 40% decrease in platelets, after hepatectomy was associated with delayed liver function recovery and postoperative morbidity. These results are in accordance with experimental data showing that platelets play an important role in liver regeneration. Because platelet counts reached a minimum on POD 3, we suggest that a decrease of greater than 40% in postoperative platelet count is a potential early marker for delayed liver function recovery and morbidity after partial hepatectomy.

## Conflict of Interest

The authors declare no conflict of interest.

## References

Alkozai, E.M., Nijsten, M.W., de Jong, K.P., de Boer, M.T., Peeters, P.M., Slooff, M.J., Porte, R.J. & Lisman, T. (2010) Immediate postoperative low platelet count is associated with delayed liver function recovery after partial liver resection. *Ann. Surg.*, **251**, 300-306.

Balzan, S., Belghiti, J., Farges, O., Ogata, S., Sauvanet, A., Delefosse, D. & Durand, F. (2005) The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann. Surg.*, **242**, 824-828.

Belghiti, J., Hiramatsu, K., Benoist, S., Massault, P., Sauvanet, A. & Farges, O. (2000) Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J. Am. Coll. Surg.*, **191**, 38-46.

Chatzipetrou, M.A., Tsaroucha, A.K., Weppler, D., Pappas, P.A., Kenyon, N.S., Nery, J.R., Khan, M.F., Kato, T., Pinna, A.D., O'Brien, C., Viciana, A., Ricordi, C. & Tzakis, A.G. (1999) Thrombocytopenia after liver transplantation. *Transplantation*, **67**, 702-706.

Clavien, P.A., Barkun, J., de Oliveira, M.L., Vauthey, J.N., Dindo, D., Schulick, R.D., de Santibanes, E., Pekolj, J., Slankamenac, K., Bassi, C., Graf, R., Vonlanthen, R., Padbury, R., Cameron, J.L. & Makuuchi, M. (2009) The Clavien-Dindo classification of surgical complications: five-year experience. *Ann. Surg.*, **250**, 187-196.

Garcea, G. & Maddern, G.J. (2009) Liver failure after major hepatic resection. *J. Hepatobiliary Pancreat. Surg.*, **16**, 145-155.

Golse, N., Bucur, P.O., Adam, R., Castaing, D., Sa Cunha, A. & Vibert, E. (2013) New paradigms in post-hepatectomy liver failure. *J. Gastrointest. Surg.*, **17**, 593-605.

Howard, J.E. & Perkins, H.A. (1978) The natural history of alloimmunization to platelets. *Transfusion*, **18**, 496-503.

Kaneko, K., Shirai, Y., Wakai, T., Yokoyama, N., Akazawa, K. & Hatakeyama, K. (2005) Low preoperative platelet counts predict a high mortality after partial hepatectomy in patients with hepatocellular carcinoma. *World J. Gastroenterol.*, **11**, 5888-5892.

Kawasaki, T., Murata, S., Takahashi, K., Nozaki, R., Ohshiro, Y., Ikeda, N., Pak, S., Myronovych, A., Hisakura, K., Fukunaga, K., Oda, T., Sasaki, R. & Ohkohchi, N. (2010) Activation of human liver sinusoidal endothelial cell by human platelets induces hepatocyte proliferation. *J. Hepatol.*, **53**, 648-654.

Kim, J., Yi, N.J., Shin, W.Y., Kim, T., Lee, K.U. & Suh, K.S. (2010) Platelet transfusion can be related to liver regeneration after living donor liver transplantation. *World J. Surg.*, **34**, 1052-1058.

Lesurtel, M., Graf, R., Aleil, B., Walther, D.J., Tian, Y., Jochum, W., Gachet, C., Bader, M. & Clavien, P.A. (2006) Platelet-derived serotonin mediates liver regeneration. *Science*, **312**, 104-107.

Lesurtel, M., Raptis, D.A., Melloul, E., Schlegel, A., Oberkofler, C., El-Badry, A.M., Weber, A., Mueller, N., Dutkowski, P. & Clavien, P.A. (2014) Low platelet counts after liver transplantation predict early posttransplant survival: the 60-5 criterion. *Liver Transpl.*, **20**, 147-155.

Matsuo, R., Nakano, Y. & Ohkohchi, N. (2011) Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy. *Ann. Surg.*, **253**, 759-763.

McCaughan, G.W., Herkes, R., Powers, B., Rickard, K., Gallagher, N.D., Thompson, J.F. & Sheil, A.G. (1992) Thrombocytopenia post liver transplantation: correlations with pre-operative platelet count, blood transfusion requirements, allograft func-

tion and outcome. *J. Hepatol.*, **16**, 16-22.
Michalopoulos, G.K. & DeFrances, M.C. (1997) Liver regeneration. *Science*, **276**, 60-66.
Murata, S., Ohkohchi, N., Matsuo, R., Ikeda, O., Myronovych, A. & Hoshi, R. (2007) Platelets promote liver regeneration in early period after hepatectomy in mice. *World J. Surg.*, **31**, 808-816.
Nagashima, I., Takada, T., Okinaga, K. & Nagawa, H. (2005) A scoring system for the assessment of the risk of mortality after partial hepatectomy in patients with chronic liver dysfunction. *J. Hepatobiliary Pancreat. Surg.*, **12**, 44-48.
Okano, E., Ko, S., Kanehiro, H., Matsumoto, M., Fujimura, Y. & Nakajima, Y. (2010) ADAMTS13 activity decreases after hepatectomy, reflecting a postoperative liver dysfunction. *Hepatogastroenterology*, **57**, 316-320.
Rahbari, N.N., Garden, O.J., Padbury, R., Brooke-Smith, M., Crawford, M., Adam, R., Koch, M., Makuuchi, M., Dematteo, R.P., Christophi, C., Banting, S., Usatoff, V., Nagino, M., Maddern, G., Hugh, T.J., et al. (2011a) Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*, **149**, 713-724.
Rahbari, N.N., Reissfelder, C., Koch, M., Elbers, H., Striebel, F., Buchler, M.W. & Weitz, J. (2011b) The predictive value of postoperative clinical risk scores for outcome after hepatic resection: a validation analysis in 807 patients. *Ann. Surg. Oncol.*, **18**, 3640-3649.
Schipperus, M. & Fijnheer, R. (2011) New therapeutic options for immune thrombocytopenia. *Neth. J. Med.*, **69**, 480-485.
Spiess, A., Mikalunas, V., Carlson, S., Zimmer, M. & Craig, R.M. (1996) Albumin kinetics in hypoalbuminemic patients receiving total parenteral nutrition. *JPEN J. Parenter. Enteral. Nutr.*, **20**, 424-428.
Starlinger, P., Assinger, A., Haegele, S., Wanek, D., Zikeli, S., Schauer, D., Birner, P., Fleischmann, E., Gruenberger, B., Brostjan, C. & Gruenberger, T. (2014) Evidence for serotonin as a relevant inducer of liver regeneration after liver resection in humans. *Hepatology*, **60**, 257-266.
Takahashi, K., Kozuma, Y., Suzuki, H., Tamura, T., Maruyama, T., Fukunaga, K., Murata, S. & Ohkohchi, N. (2013) Human platelets promote liver regeneration with Kupffer cells in SCID mice. *J. Surg. Res.*, **180**, 62-72.
Togo, S., Chen, H., Takahashi, T., Kubota, T., Matsuo, K., Morioka, D., Watanabe, K., Yamamoto, H., Nagashima, Y. & Shimada, H. (2008) Prostaglandin E1 improves survival rate after 95% hepatectomy in rats. *J. Surg. Res.*, **146**, 66-72.
Wormann, B. (2013) Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists. *Transfus. Med. Hemother.*, **40**, 319-325.
Xue, F., Takahara, T., Yata, Y., Kuwabara, Y., Shinno, E., Nonome, K., Minemura, M., Takahara, S., Li, X., Yamato, E. & Watanabe, A. (2003) Hepatocyte growth factor gene therapy accelerates regeneration in cirrhotic mouse livers after hepatectomy. *Gut*, **52**, 694-700.
Zhang, Y.M., Liu, Z.R., Cui, Z.L., Yang, C., Yang, L., Li, Y. & Shen, Z.Y. (2016) Interleukin-22 contributes to liver regeneration in mice with concanavalin A-induced hepatitis after hepatectomy. *World J. Gastroenterol.*, **22**, 2081-2091.