Original Article

DOI: 10.5582/bst.2020.03230

# High platelet count as a poor prognostic factor for liver cancer patients without cirrhosis

**Yutaka Midorikawa[1,*], Tadatoshi Takayama[1], Tokio Higaki[1], Osamu Aramaki[1], Kenichi Teramoto[1], Nao Yoshida[1], Shingo Tsuji[2], Tatsuo Kanda[3], Mitsuhiko Moriyama[3]**

[1] Department of Digestive Surgery, Nihon University School of Medicine, Tokyo, Japan;
[2] Genome Science Division, Research Center for Advanced Science and Technology, University of Tokyo, Tokyo, Japan;
[3] Department of Gastroenterology and Hepatology, Nihon University School of Medicine, Tokyo, Japan.

**SUMMARY** A low platelet count, one of parameters of portal hypertension, is clinically a predictor of postoperative mortality, while platelets induce tumor development during growth factor secretion. In this study, we retrospectively investigated whether high platelet count negatively affects the survival of patients with hepatocellular carcinoma (HCC). Patients undergoing initial and curative resection for HCC were included. Surgical outcomes were compared between the high platelet (platelet count $\geq 20 \times 10^4/\mu L$) and control ($< 20 \times 10^4/\mu L$) groups in patients without cirrhosis and between the low platelet ($< 10 \times 10^4/\mu L$) and control ($\geq 10 \times 10^4/\mu L$) groups in patients with cirrhosis. Among patients without cirrhosis, tumor was larger ($P < 0.001$) and tumor thrombus was more frequent ($P < 0.001$) in the high-platelet group than in the control group. After a median follow-up period of 3.1 years (range 0.2-16.2), median overall survival was 6.3 years (95% confidence interval [CI], 5.3-7.8) and 7.6 years (6.6-10.9) in the high-platelet ($n = 273$) and control ($n = 562$) groups, respectively ($P = 0.027$). Among patients with cirrhosis, liver function was worse ($P < 0.001$) and varices were more frequent ($P < 0.001$) in the low-platelet group. The median overall survival of patients in the low-platelet group ($n = 172$) was significantly shorter than that of patients in the control group ($n = 275$) (4.5 years [95% CI, 3.7–6.0] *vs.* 5.9 years [4.5-7.5], $P = 0.038$). Taken together, thrombocytopenia indicates poor prognosis in HCC patients with cirrhosis, while thrombocytosis is a poor prognostic predictor for those without cirrhosis.

***Keywords*** growth factor, hepatocellular carcinoma, platelet, portal hypertension, prognostic predictor

## 1. Introduction

Portal hypertension is clinically defined based on the presence of esophageal varices or splenomegaly and is associated with a platelet count of less than $10 \times 10^4/\mu L$ (*1*). Therefore, a low platelet count due to portal hypertension is one of the risk factors for patients undergoing resection for hepatocellular carcinoma (HCC). The surgical outcomes for these patients are worse, although these outcomes do not contradict with the postoperative outcomes for patients with cirrhosis (*2-4*). In addition to the cessation of bleeding and thrombosis induction, platelets play a direct role in hepatocyte proliferation by triggering the secretion of several growth factors such as platelet-derived growth factor, serotonin, transforming growth factor-ß, and hepatocyte growth factor (*5-7*). Clinically, platelets have been reported to support the regeneration of remnant liver after resection (*8,9*). A low platelet count has served as a predictor of postoperative dysfunction and postoperative mortality (*10,11*).

However, *in vitro* studies have shown that platelets also induce tumor growth, migration, and invasion through the secretion of growth factors (*12,13*) and could antagonize sorafenib- or regorafenib-mediated tumor growth suppression and apoptosis in HCC cells through epidermal growth factor and insulin-like growth factor 1 release (*14*). Clinically, early tumor recurrence and shorter survival of patients with HCC are associated with a high platelet count and serotonin level (*15,16*). Patients with a high platelet count or pretreatment platelet count are also at risk of extrahepatic recurrence of HCC after resection (*17,18*) or recurrence after living donor liver transplantation (*19*).

Given that platelet has multiple contrasting functions in patients with HCC and that portal hypertension negatively affects the platelet count, the clinical significance of the platelet count in HCC patients with

and without liver cirrhosis should be investigated in great detail. In this study, we focused on the clinical significance of platelet count in HCC patients undergoing liver resection. To avoid the strong effect of portal hypertension on the survival rate, patients with and without liver cirrhosis were analyzed separately in this series. We further compared surgical outcomes and tumor progression in patients with HCC on the basis of platelet count.

## 2. Materials and Methods

### 2.1. Patients

Patients who underwent initial and curative resection for HCC between 2000 and 2018 at Nihon University Itabashi Hospital (Tokyo, Japan) were included in this study. Each participant provided written informed consent, and this study was approved by the institutional review board of Nihon University (RK-200512-4). All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

### 2.2. Indications for liver resection

The indications for liver resection and other treatments for patients with HCC were determined by assessing their liver functional reserve according to Guidelines on Liver Cancer Examination and Treatment in Japan (*20*). Briefly, patients with Child-Pugh A or B with up to three viable lesions were candidates for liver resection.

### 2.3. Patient groups

Among the patients who were histologically diagnosed as not having liver cirrhosis after the operation, those with a platelet count of $\geq 20 \times 10^4/\mu L$ were included in the high-platelet group. Among the patients with cirrhosis, those with a platelet count of $< 10 \times 10^4/\mu L$ were included in the low-platelet group. Clinical characteristics and surgical outcomes were compared between the high-platelet and control (platelet count $< 20 \times 10^4/\mu L$) groups in patients without cirrhosis and between the low-platelet and control (platelet count $\geq 10 \times 10^4/\mu L$) groups in patients with cirrhosis.

### 2.4. Surgical procedures

Open liver resection was performed in all patients according to the criteria based on the liver function (*21*). Patients with a preoperative platelet count of $< 10 \times 10^4/\mu L$ had platelet transfusion on the day of operation. Anatomical resection was the first-line treatment. Major resection included segmentectomy, hemihepatectomy, and trisegmentectomy, while anatomic resection was defined as liver resection over subsegmentectomy. The liver was transected under ultrasonographic guidance using the clamp-crushing method with the inflow-blood-occlusion technique (*22*). Curative resection was defined as the complete removal of recognizable viable HCC diagnosed preoperatively or intraoperatively with macroscopically tumor-free surgical margins. Postoperative complications were stratified according to the Clavien-Dindo classification (*23*), which defines morbidities as complications with a score of ≥ 3a. Complications specific to liver resection were defined as described previously (*24*).

### 2.5. Follow-up after operation

All patients were followed up for postoperative recurrence as described previously (*25*). Briefly, the levels of tumor markers including alpha-fetoprotein and des-gamma-carboxy prothrombin were measured, and imaging studies including computed tomography and ultrasonography were performed every three months in all patients. Tumor recurrence was diagnosed by dynamic computed tomography and/or magnetic resonance imaging. The date of recurrence was defined as the date of examination when the recurrent HCC was noted.

### 2.6. Statistical analysis

Data collected from each group were statistically analyzed with Fisher's exact test and Wilcoxon rank-sum test. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Prognostic factors for overall survival were identified with the Cox proportional hazards regression model. Statistical analyses were performed using JMP 12.0.1 statistical software (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered to indicate significance.

## 3. Results

### 3.1. Patients

The 1,282 patients who underwent initial and curative resection for HCC were included (Figure 1). The median platelet count for 835 patients (65.1%) without cirrhosis was $18.6 \times 10^4/\mu L$ (range; 2.4-68.6). Two hundred seventy-three patients (32.6%) with a platelet count of $\geq 20 \times 10^4/\mu L$ were included into the high-platelet group. By contrast, among the 447 patients (34.8%) who were histologically diagnosed as having cirrhosis, the median platelet count was $11.1 \times 10^4/\mu L$ (range 3.2-66.0) and 172 patients (38.4%) with a platelet count of $< 10 \times 10^4/\mu L$ were included in the low-platelet group.

For patients without cirrhosis, hepatitis C virus infection ($P < 0.001$) and varices ($P = 0.011$) were less frequent, liver functions such as Child-Pugh classification ($P = 0.013$) and indocyanine green clearance rate at 15 minutes ($P < 0.001$) were better, and des-gamma-carboxy prothrombin was higher ($P < 0.001$) in the high-platelet

group than in the control group (Table 1). By contrast, for patients with cirrhosis, hepatitis C virus infection ($P < 0.001$) and varices ($P < 0.001$) were more frequent and liver function parameters were worse ($P < 0.001$) in the low-platelet group than in the control group (Table 2).

### 3.2. Operative data

For patients without cirrhosis, operation time was longer ($P < 0.001$), the amount of blood loss was higher ($P = 0.013$), and major resection ($P < 0.001$) and anatomic resection ($P < 0.001$) were more frequent in the high-platelet group than in the control group (Table 3), but complication rates except for bile leakage ($P = 0.014$) and respiratory complications ($P = 0.005$) were not significantly different between the two groups (Table 4). Histological findings showed that the tumor was in a more advanced stage in the high-platelet group than in the control group; the tumor was larger ($P < 0.001$) and the tumor thrombus was more frequent ($P < 0.001$).

For patients with cirrhosis, the amount of blood loss was higher ($P = 0.015$) and both major resection and anatomic resection were less frequent ($P < 0.001$) in the low-platelet group than in the control group (Table 5). Complication rates were not different between the two groups (Table 6). Histological findings were not significantly different between the low-platelet and control groups.

Coefficients of determination ($R^2$) between platelet count and tumor size were 0.164 and 0.015 in patients without cirrhosis ($P < 0.001$) and those with cirrhosis ($P = 0.008$), respectively (Figure 2).

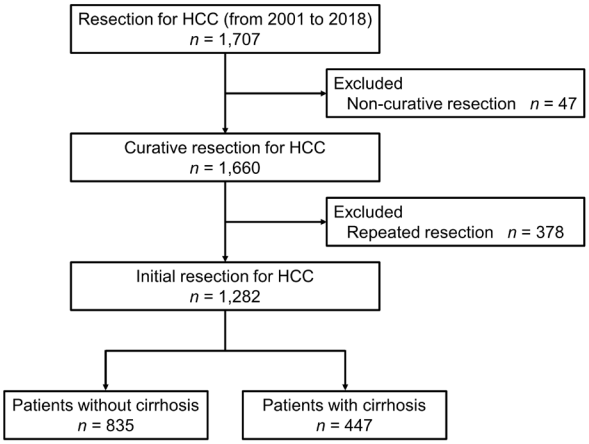


**Figure 1. Flowchart for patient selection.**

### 3.3. Survivals

For patients without cirrhosis, the median overall

**Table 1. Patient background (without cirrhosis)**

| Items | High platelet ($n = 273$) | Control ($n = 562$) | $P$ value |
|---|---|---|---|
| Age, years | 69 (35-84) | 70 (33-86) | 0.314 |
| Sex, male (%) | 226 (82.7) | 456 (81.1) | 0.633 |
| Alcoholic, $n$ (%) | 70 (25.6) | 177 (31.4) | 0.089 |
| Diabetes mellitus, $n$ (%) | 90 (32.9) | 190 (33.8) | 0.875 |
| HBV, $n$ (%) | 39 (14.2) | 102 (18.1) | 0.169 |
| HCV, $n$ (%) | 77 (28.2) | 267 (47.5) | < 0.001 |
| Varices, $n$ (%) | 18 (6.5) | 70 (12.4) | 0.011 |
| Child-Pugh, A (%) | 256 (93.7) | 496 (88.2) | 0.013 |
| ICGR15, % | 9.4 (1.9-35.5) | 12.4 (1.3-48.0) | < 0.001 |
| Alpha-fetoprotein, ng/mL | 8 (1-541,432) | 11 (1-449,211) | 0.725 |
| DCP, mAU/mL | 214 (9-75,000) | 75 (1-75,000) | < 0.001 |

Data are presented as median with range, if not specified. HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, indocyanine green clearance rate at 15 minutes; DCP, des-gamma carboxyprothrombin.

**Table 2. Patient background (with cirrhosis)**

| Items | Low platelet ($n = 172$) | Control ($n = 275$) | $P$ value |
|---|---|---|---|
| Age, years | 68 (32-81) | 68 (40-85) | 0.783 |
| Sex, male (%) | 108 (62.7) | 193 (70.1) | 0.120 |
| Alcoholic, $n$ (%) | 36 (20.9) | 69 (25.0) | 0.359 |
| Diabetes mellitus, $n$ (%) | 55 (48.6) | 96 (45.0) | 0.560 |
| HBV, $n$ (%) | 20 (11.6) | 51 (18.5) | 0.062 |
| HCV, $n$ (%) | 130 (75.5) | 161 (65.1) | < 0.001 |
| Varices, $n$ (%) | 96 (55.8) | 92 (33.4) | < 0.001 |
| Child-Pugh, A (%) | 99 (57.5) | 228 (82.9) | < 0.001 |
| ICGR15, % | 19.4 (2.0-48.4) | 14.4 (2.0-49.8) | < 0.001 |
| Alpha-fetoprotein, ng/mL | 32 (1-17,853) | 18 (1-53,460) | 0.182 |
| DCP, mAU/mL | 39 (7-35,203) | 42 (1-60,300) | 0.187 |

Data are presented as median with range, if not specified. HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, indocyanine green clearance rate at 15 minutes; DCP, des-gamma carboxyprothrombin.

**Table 3. Operative data (without cirrhosis)**

| Items | High platelet (*n* = 273) | Control (*n* = 562) | *P* value |
|---|---|---|---|
| Operation data | | | |
| Operation time, min | 360 (107-855) | 310 (97-1,004) | < 0.001 |
| Bleeding, mL | 298 (5-7,066) | 252 (10-3,777) | 0.013 |
| Pringle time, min | 80 (0-274) | 68 (0-304) | < 0.001 |
| Transfusion, *n* (%) | 23 (8.4) | 32 (5.6) | 0.139 |
| Major resection, *n* (%) | 99 (36.2) | 83 (14.7) | < 0.001 |
| Anatomic resection, *n* (%) | 149 (54.5) | 224 (39.8) | < 0.001 |
| Pathology | | | |
| Multiple, *n* (%) | 61 (22.3) | 134 (23.8) | 0.663 |
| Size, cm (range) | 5.0 (0.8-21.0) | 3.2 (0.5-20.0) | < 0.001 |
| Differentiation grade, well, (%) | 33 (12.0) | 105 (18.6) | 0.017 |
| Vascular invasion, *n* (%) | 105 (38.4) | 147 (26.1) | < 0.001 |
| Tumor exposure, *n* (%) | 23 (8.4) | 43 (8.2) | 0.683 |

Data are presented as median, if not specified.

**Table 4. Complications (without cirrhosis)**

| Items | High platelet (*n* = 273) | Control (*n* = 562) | *P* value |
|---|---|---|---|
| Overall, *n* (%) | 84 (30.7) | 194 (34.5) | 0.309 |
| Morbidity, *n* (%) | 59 (21.6) | 140 (24.9) | 0.300 |
| Intraperitoneal hemorrhage | 1 (0.3) | 5 (0.8) | 0.669 |
| Intraperitoneal abscess | 8 (2.9) | 13 (2.3) | 0.639 |
| Bile leakage | 18 (6.5) | 16 (2.8) | 0.014 |
| Ascites | 2 (0.7) | 3 (0.5) | 0.664 |
| Portal thrombus | 1 (0.3) | 1 (0.1) | 0.547 |
| Wound infection | 11 (4.0) | 23 (4.0) | 1 |
| Respiratory | 13 (4.7) | 55 (9.7) | 0.005 |
| Cardiovascular | 1 (0.3) | 2 (0.3) | 1 |
| Stroke | 0 | 1 (0.1) | 1 |
| Liver failure | 0 | 0 | 1 |
| Variceal rapture | 0 | 1 (0.1) | 1 |
| Ileus | 0 | 4 (0.7) | 0.309 |
| Perforation | 1 (0.3) | 1 (0.1) | 0.547 |
| Others | 3 (1.0) | 15 (2.6) | 0.203 |
| Re-operation, *n* (%) | 8 (2.9) | 13 (2.3) | 0.639 |
| Mortality, *n* (%) | 0 (0) | 2 (0.3) | 1.000 |

Morbidity was defined as complication with score of ≥ 3a.

**Table 5. Operative data (with cirrhosis)**

| Items | Low platelet (*n* = 172) | Control (*n* = 275) | *P* value |
|---|---|---|---|
| Operation data | | | |
| Operation time, min | 316 (130-705) | 305 (113-655) | 0.884 |
| Bleeding, mL | 315 (20-4,530) | 275 (5-2,988) | 0.015 |
| Pringle time, min | 64 (0-266) | 69 (0-230) | 0.824 |
| Transfusion, *n* (%) | 15 (8.7) | 18 (6.5) | 0.392 |
| Major resection, *n* (%) | 2 (1.1) | 17 (6.1) | 0.013 |
| Anatomic resection, *n* (%) | 33 (19.1) | 88 (32) | 0.003 |
| Pathology | | | |
| Multiple, *n* (%) | 55 (31.9) | 75 (27.2) | 0.287 |
| Size, cm (range) | 2.6 (0.7-10.5) | 2.5 (0.7-18.0) | 0.781 |
| Differentiation grade, well (%) | 38 (22.0) | 56 (20.3) | 0.720 |
| Vascular invasion, *n* (%) | 30 (17.4) | 56 (20.3) | 0.462 |
| Tumor exposure, *n* (%) | 21 (12.2) | 19 (86.9) | 0.062 |

Data are presented as median, if not specified.

survival of patients in the high-platelet group was 6.3 years (95% confidence interval [CI], 5.3-7.8), which was significantly shorter than that of patients in the control group (7.6 years; 95% CI, 6.6-10.9; $P = 0.027$) after a median follow-up period of 3.1 years (range 0.2-16.2) (Figure 3A). By contrast, there was no significant difference in the median recurrence-free survival between the two groups (1.9 years, [95% CI, 1.5-2.2]

*vs.* 2.1 years, [95% CI, 1.9-2.3]; $P = 0.904$) (Figure 3B). The overall survival and recurrence-free survival rates at five years were 60.5% and 30.6% in the high-platelet group, respectively, and 66.9% and 27.5% in the control group, respectively.

For patients with cirrhosis, the median overall survival of patients in the low-platelet group and the control group was 4.5 years (95% CI, 3.7-6.0) and 5.9 years (95% CI, 4.5-7.5; $P = 0.038$), respectively (Figure 4A). Recurrence-free survival was 1.8 years (95% CI, 1.5-2.0) and 2.0 years (95% CI, 1.6-2.4; $P = 0.268$), respectively (Figure 4B). The 5-year overall survival rates were 46.6% and 54.3%, and 5-year recurrence-free survival rates were 15.7% and 21.4% in the two groups, respectively.

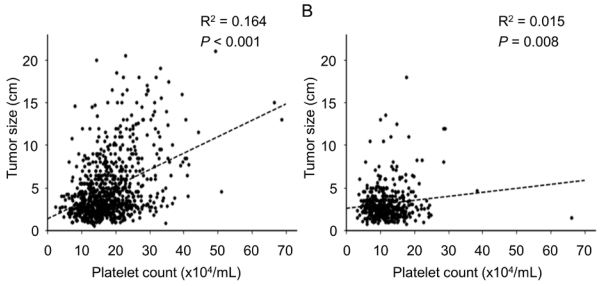


**Figure 2. Scatter plots showing the correlation between tumor size and platelet count. (A)** Tumor size weakly correlated with platelet count in patients without cirrhosis. **(B)** There was no correlation between tumor size and platelet count in patients with cirrhosis.

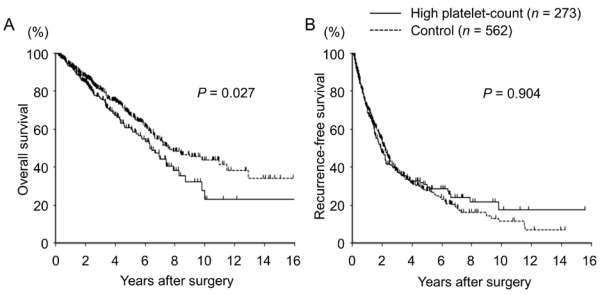


**Figure 3. Survival outcomes following liver resection in patients without cirrhosis. (A)** Overall survival of patients in the high-platelet count group was significantly shorter than that of patients in the control group ($P = 0.027$). **(B)** Recurrence-free survival was not significantly different between the two groups ($P = 0.904$). Study group sizes are indicated ($n$).

## 4. Discussion

Our data showed that a high platelet count was associated with liver cancer progression and, consequently, shorter survival and early recurrence in patients without cirrhosis who underwent resection for HCC. By contrast, a low platelet count indicated poorer prognosis due to the worse liver function in patients with cirrhosis. Thus, according to the background chronic liver disease status, platelet count harbored different predictive values for patients with HCC.

Both experimental and clinical studies demonstrated

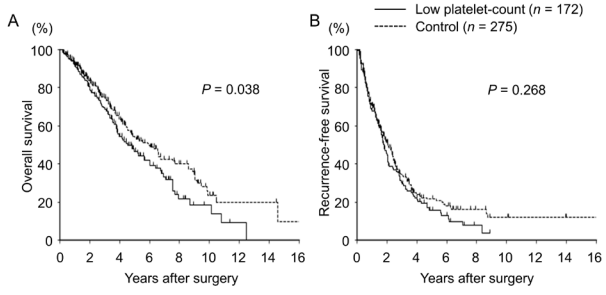


**Figure 4. Survival outcomes following liver resection in patients with cirrhosis. (A)** Overall survival of patients in the low-platelet count group was significantly shorter than that of patients in the control group ($P = 0.038$). **(B)** Recurrence-free survival was not significantly different between the two groups ($P = 0.268$). Study group sizes are indicated ($n$).

**Table 6. Complications (with cirrhosis)**

| Items | Low platelet ($n$ = 172) | Control ($n$ = 275) | $P$ value |
|---|---|---|---|
| Overall, $n$ (%) | 79 (45.9) | 120 (43.6) | 0.695 |
| Morbidity, $n$ (%) | 61 (35.4) | 92 (33.4) | 0.682 |
| Intraperitoneal hemorrhage | 4 (2.3) | 6 (2.1) | 1 |
| Intraperitoneal abscess | 13 (7.5) | 15 (5.4) | 0.423 |
| Bile leakage | 3 (1.7) | 8 (2.9) | 0.542 |
| Ascites | 2 (1.1) | 3 (1.0) | 1 |
| Portal thrombus | 0 | 1 (0.3) | 1 |
| Wound infection | 6 (3.4) | 9 (3.2) | 1 |
| Respiratory | 26 (15.1) | 40 (14.5) | 0.891 |
| Cardiovascular | 0 | 1 (0.3) | 1 |
| Stroke | 0 | 0 | 1 |
| Liver failure | 3 (1.7) | 1 (0.3) | 0.161 |
| Variceal rapture | 0 | 0 | 0 |
| Ileus | 1 (0.5) | 1 (0.3) | 1 |
| Perforation | 1 (0.5) | 0 | 0.384 |
| Others | 2 (1.1) | 7 (2.5) | 0.492 |
| Re-operation, $n$ (%) | 9 (5.2) | 7 (2.5) | 0.187 |
| Mortality, $n$ (%) | 0 | 0 | 1.000 |

Morbidity was defined as complication with score of ≥ 3a.

that platelets promoted HCC proliferation by secreting several types of growth factors (*12,13*). Therefore, platelets had positive induction of further tumor progression in patients with HCC, and a high platelet count in patients with HCC was associated with shorter overall survival (*26,27*). Consistent with the previous data, tumor size weakly correlated with platelet count in patients without cirrhosis, while there was no correlation between the two variables in patients with cirrhosis. Taken together, in the patients without cirrhosis, tumors were more advanced at the time of operation, and consequently, overall survival was shorter despite better parameters of liver function in the high-platelet group.

Recurrence-free survival was not significantly different in both cohorts, but the recurrence rates in the low-platelet group were relatively longer in patients with cirrhosis, although the differences between the low-platelet and control groups were not significant. By contrast, for patients without cirrhosis, recurrence-free survival curves in the high-platelet and control groups crossed at approximately three years, and recurrence rates at two years were higher in the high-platelet group (46.0%) than in the control group (52.3%), while those at five years were lower in the high-platelet group. The characteristics of HCC recurrence are generally understood as follows: most cases of tumor recurrence by metachronous intrahepatic metastasis occurred within two years (*28*), while most cases of recurrence two years after operation were due to multicentric origin, which was more remarkable in patients with poor liver function (*29,30*). Therefore, we assumed that platelets could contribute to the early recurrence by stimulating liver cancer cells through the secretion of growth factors, while low platelet count, both in patients with and without cirrhosis, indicated the possibility of the late-term recurrence. On the other hand, there was no significance of the recurrence-free survival rates between the low-platelet count and the control groups. However the recurrence-free survival tended to be shorter especially two years after surgery, which did not conflict the results of overall survival.

Thrombocytopenia is also one of the most important indicators of portal hypertension. Consistent with a previous report (*31*), liver function was worse and varices were more frequent in the low-platelet group, and therefore, a low preoperative platelet count was associated with poor survival after operation in patients with liver cirrhosis in this study.

Moreover, platelets play a pivotal role in the initiation of the coagulation cascade and reduce the amount of blood loss through bleeding during liver transection, leading to the low rate of postoperative complications (*32*). Platelets also have a strong proliferative effect on hepatocytes and induce liver regeneration by secreting growth factors (*5-7*). Consequently, a decrease in platelet counts was associated with morbidity such as postoperative liver dysfunction and rupture of varices after operation (*33,34*). To avoid massive bleeding during operation, patients with a preoperative platelet count of $< 10 \times 10^4/\mu L$ routinely had platelet transfusion on the day of operation in our institute. Consequently, there was no significant difference in postoperative complications between the low-platelet and control groups observed in this study.

In the previous reports, the cut-off value for platelet counts ranged from 6.8 to $10 \times 10^4/\mu L$, especially, $10 \times 10^4/\mu L$ seemed be the most frequent (*10,11,17,19,30*). Given that platelet counts were strongly affected by the liver status, the cut-off value should be separately determined according to whether the patients have liver cirrhosis or not. Therefore, we defined the cut-off value of the platelet counts ($20 \times 10^4/\mu L$ in the patients without cirrhosis and $10 \times 10^4/\mu L$ in those with cirrhosis) based on the median value ($18.6 \times 10^4/\mu L$ and $11.1 \times 10^4/\mu L$), which could be considered to be adequate.

This study had several limitations. First, concentrations of serotonin or other growth factors were not measured, and therefore, it is not clear whether the advanced stage of tumors in the high-platelet group was actually caused specifically by the growth factors secreted by platelets. If that is the case, we should observe the correlation between patient survival and the presence of growth factors in the serum with the expression of their respective receptors in tumors in future studies. Second, platelet count is easily affected by liver function. However, despite better liver function in the high-platelet group in patients without cirrhosis, survival time in these patients was shorter, and therefore, we assumed that a high platelet count could have negatively affected the survival of patients with HCC. Finally, it is clinically difficult to fully predict whether a patient has cirrhosis before operation. In this situation, it needs more consideration to apply these findings to clinical practice.

In conclusion, a high platelet count was an unfavorable prognostic factor and it negatively impacted the survival of HCC patients without cirrhosis because a high platelet count promoted liver cancer progression. By contrast, low platelet count negatively affected the surgical outcomes of patients with cirrhosis. Therefore, our findings suggest that platelet count has different implications for predicting patient survival based on the chronic liver disease status background.

**Acknowledgements**

This research was supported by AMED under Grant Number JP20hk0102049s0303 and a grants-in-aid of The 106th Annual Congress of JSS Memorial Surgical Research Fund, Tokyo, Japan. The funding body supported the data collection used in this study. The funding body has no role in the design of the study and analysis and interpretation of data and in writing the manuscript.

## References


1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012; 379:1245-1255.
2. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, Grazi GL, Pinna AD. Is portal hypertension a contraindication to hepatic resection? Ann Surg. 2009; 250:922-928.
3. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008; 134:1908-1916.
4. Ohkubo T, Midorikawa Y, Nakayama H, Moriguchi M, Aramaki O, Yamazaki S, Higaki T, Takayama T. Liver resection of hepatocellular carcinoma in patients with portal hypertension and multiple tumors. Hepatol Res. 2018; 48:433-441.
5. Lesurtel M, Clavien PA. Platelet-derived serotonin: translational implications for liver regeneration. Hepatology. 2014; 60:30-33.
6. Padickakudy R, Pereyra D, Offensperger F, Jonas P, Oehlberger L, Schwarz C, Haegele S, Assinger A, Brostjan C, Gruenberger T, Starlinger P. Bivalent role of intra-platelet serotonin in liver regeneration and tumor recurrence in humans. J Hepatol. 2017; 67:1243-1252.
7. Lisman T, Porte RJ. Mechanisms of platelet-mediated liver regeneration. Blood. 2016; 128:625-629.
8. Han S, Park HW, Song JH, Gwak MS, Lee WJ, Kim G, Lee SK, Ko JS. Association Between Intraoperative Platelet Transfusion and Early Graft Regeneration in Living Donor Liver Transplantation. Ann Surg. 2016; 264:1065-1072.
9. Yamazaki S, Takayama T, Mitsuka Y, Aoki M, Midorikawa Y, Moriguchi M, Higaki T. Platelet recovery correlates parenchymal volume recovery after liver resection. Hepatol Res. 2020; 50:620-628.
10. Alkozai EM, Nijsten MW, de Jong KP, de Boer MT, Peeters PM, Slooff MJ, Porte RJ, Lisman T. Immediate postoperative low platelet count is associated with delayed liver function recovery after partial liver resection. Ann Surg. 2010; 251:300-306.
11. Li L, Wang H, Yang J, Jiang L, Yang J, Wang W, Yan L, Wen T, Li B, Xu M. Immediate Postoperative Low Platelet Counts After Living Donor Liver Transplantation Predict Early Allograft Dysfunction. Medicine (Baltimore). 2015; 94:e1373.
12. Carr BI, Cavallini A, D'Alessandro R, Refolo MG, Lippolis C, Mazzocca A, Messa C. Platelet extracts induce growth, migration and invasion in human hepatocellular carcinoma *in vitro*. BMC Cancer. 2014; 14:43.
13. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell. 2011; 20:576-590.
14. D'Alessandro R, Refolo MG, Lippolis C, Giannuzzi G, Carella N, Messa C, Cavallini A, Carr BI. Antagonism of sorafenib and regorafenib actions by platelet factors in hepatocellular carcinoma cell lines. BMC Cancer. 2014; 14:351.
15. Shu B, Wang S, Deng Y, Zhai M, Liu S. Intra-platelet serotonin in prognosis of tumorigenesis: Friend or foe? J Hepatol. 2018; 68:1333-1334.
16. Liu PH, Hsu CY, Su CW, Huang YH, Hou MC, Rich NE, Fujiwara N, Hoshida Y, Singal AG, Huo TI. Thrombocytosis is associated with worse survival in patients with hepatocellular carcinoma. Liver Int. 2020 (*in press*)
17. Morimoto Y, Nouso K, Wada N, Takeuchi Y, Kinugasa H, Miyahara K, Yasunaka T, Kuwaki K, Onishi H, Ikeda F, Miyake Y, Nakamura S, Shiraha H, Takaki A, Yamamoto K. Involvement of platelets in extrahepatic metastasis of hepatocellular carcinoma. Hepatol Res. 2014; 44:E353-359.
18. Lee CH, Lin YJ, Lin CC, Yen CL, Shen CH, Chang CJ, Hsieh SY. Pretreatment platelet count early predicts extrahepatic metastasis of human hepatoma. Liver Int. 2015; 35:2327-2336.
19. Han S, Lee S, Yang JD, Leise MD, Ahn JH, Kim S, Jung K, Gwak MS, Kim GS, Ko KJS. Risk of posttransplant hepatocellular carcinoma recurrence is greater in recipients with higher platelet counts in living donor liver transplantation. Liver Transpl. 2018; 24:44-55.
20. Kokudo N, Hasegawa K, Akahane M, *et al.* Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res. 2015; 45:123-127.
21. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, Kawasaki S. Surgery for small liver cancers. Semin Surg Oncol. 1993; 9:298-304.
22. Takayama T, Makuuchi M, Kubota K, Harihara Y, Hui AM, Sano K, Ijichi M, Hasegawa K. Randomized comparison of ultrasonic *vs.* clamp transection of the liver. Arch Surg. 2001; 136:922-928.
23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240:205-213.
24. Midorikawa Y, Kubota K, Takayama T, Toyoda H, Ijichi M, Torzilli G, Mori M, Makuuchi M. A comparative study of postoperative complications after hepatectomy in patients with and without chronic liver disease. Surgery. 1999; 126:484-491.
25. Midorikawa Y, Takayama T, Shimada K, Nakayama H, Higaki T, Moriguchi M, Nara S, Tsuji S, Tanaka M. Marginal survival benefit in the treatment of early hepatocellular carcinoma. J Hepatol. 2013; 58:306-311.
26. Nouso K, Ito Y, Kuwaki K, Kobayashi Y, Nakamura S, Ohashi Y, Yamamoto K. Prognostic factors and treatment effects for hepatocellular carcinoma in Child C cirrhosis. Br J Cancer. 2008; 98:1161-1165.
27. Scheiner B, Kirstein M, Popp S, Hucke F, Bota S, Rohr-Udilova N, Reiberger T, Müller C, Trauner M, Peck-Radosavljevic M, Vogel A, Sieghart W, Pinter M. Association of Platelet Count and Mean Platelet Volume with Overall Survival in Patients with Cirrhosis and Unresectable Hepatocellular Carcinoma. Liver Cancer. 2019; 8:203-217.
28. Yamamoto S, Midorikawa Y, Nagae G, Tatsuno K, Ueda H, Moriyama M, Takayama T, Aburatani H. Spatial and temporal expansion of intrahepatic metastasis by molecularly-defined clonality in multiple liver cancers. Cancer Sci. 2020; 111:601-609.
29. Cucchetti A, Piscaglia F, Caturelli E, Benvegnù L, Vivarelli M, Ercolani G, Cescon M, Ravaioli M, Grazi GL, Bolondi L, Pinna AD. Comparison of recurrence of hepatocellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic

population. Ann Surg Oncol. 2009; 16:413-422.
30. Sasaki K, Shindoh J, Margonis GA, Nishioka Y, Andreatos N, Sekine A, Hashimoto M, Pawlik TM. Effect of Background Liver Cirrhosis on Outcomes of Hepatectomy for Hepatocellular Carcinoma. JAMA Surg. 2017; 152:e165059.
31. Pang Q, Qu K, Zhang JY, Song SD, Liu SS, Tai MH, Liu HC, Liu C. The Prognostic Value of Platelet Count in Patients With Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2015;94:e1431.
32. Aramaki O, Takayama T, Higaki T, Nakayama H, Ohkubo T, Midorikawa Y, Moriguchi M, Matsuyama Y. Decreased blood loss reduces postoperative complications in resection for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2014;21:585-591.
33. Takahashi K, Liang C, Oda T, Ohkohchi N. Platelet and liver regeneration after liver surgery. Surg Today. DOI: 10.1007/s00595-019-01890-x.
34. Nathan H, Herlong HF, Gurakar A, Li Z, Koteish AA, Bridges JF, Pawlik TM. Clinical decision-making by gastroenterologists and hepatologists for patients with early hepatocellular carcinoma. Ann Surg Oncol. 2014;21:1844-1851.

Received June 18, 2020; Revised July14, 2020; Accepted July 20, 2020.

*Address correspondence to:
Yutaka Midorikawa, Department of Digestive Surgery, Nihon University School of Medicine, 30-1 Oyaguchi Kami-machi, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail: mido-tky@umin.ac.jp

Released online in J-STAGE as advance publication July 25, 2020.