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ORIGINAL ARTICLE

Low Platelet Counts After Liver Transplantation Predict Early Posttransplant Survival: The 60-5 Criterion

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Platelets play a critical role in liver injury and regeneration. Thrombocytopenia is associated with increases in postoperative complications after partial hepatectomy, but it is unknown whether platelet counts could also predict outcomes after transplantation, a procedure that is often performed in thrombocytopenic patients. Therefore, the aim of this study was to evaluate whether platelet counts could be indicators of short- and long-term outcomes after liver transplantation (LT). Two hundred fifty-seven consecutive LT recipients (January 2003-December 2011) from our prospective database were analyzed. Preoperative and daily postoperative platelet counts were recorded until postoperative day 7 (POD7). Univariate and multivariate analyses were performed to assess whether low perioperative platelet counts were a risk factor for postoperative complications and graft and patient survival. The median pretransplant platelet count was 88 $\times$ 10^9/L [interquartile range (IQR) = 58-127 $\times$ 10^9/L]. The lowest platelet counts occurred on POD3: the median was 56 $\times$ 10^9/L (IQR = 41-86 $\times$ 10^9/L). Patients with low platelet counts on POD5 had higher rates of severe (grade IIIb/IV) complications [39% versus 29%, odds ratio (OR) = 1.09 (95% CI = 1.1-3.3), $P = 0.02$] and 90-day mortality [16% versus 8%, OR = 2.25 (95% CI = 1.0-5.0), $P = 0.05$]. In the multivariate analysis, POD5 platelet counts $< 60 \times 10^9$/L were identified as an independent risk factor for grade IIIb/IV complications [OR = 1.96 (95% CI = 1.07-3.56), $P = 0.03$)], graft survival [hazard ratio (HR) = 2.0 (95% CI = 1.1-3.6), $P = 0.03$)], and patient survival [HR = 2.2 (95% CI = 1.1-4.6), $P = 0.03$)]. The predictive value of platelet counts for graft and patient survival was lost in patients who survived 90 days. In conclusion, after LT, platelet counts $< 60 \times 10^9$/L on POD5 (the 60-5 criterion) are an independent factor associated with severe complications and early graft and patient survival. These findings may help us to develop protective strategies or specific interventions for high-risk patients. ***Liver Transpl 20:147-155, 2014.*** **© 2013 AASLD.**

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Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; OR, odds ratio; POD, postoperative day.

The ClinicalTrials.gov registration number for this study is NCT01711957.

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Please See Editorial on Page 127

Besides the well-known properties of platelets in primary hemostasis, platelets participate in many other conditions such as inflammation,[1] atherosclerosis,[2] antimicrobial defense,[3] angiogenesis,[4] ischemia/reperfusion injury,[5] and tissue repair and regeneration.[6,7] Most of these conditions contribute to the physiopathology of liver transplantation (LT), but it is unclear whether platelet counts have beneficial or detrimental effects on the outcomes of patients undergoing LT.[8] For example, platelets are a key factor in efficient hemostasis in the perioperative period, and they may contribute to liver regeneration through a platelet-derived serotonin/vascular endothelial growth factor mechanism.[6,9] Platelets may also promote liver tissue repair after hepatic ischemic injury.[7] In contrast, platelets may cause injury through participation in reperfusion injury after cold ischemia[10] or contribute to thrombosis of the hepatic artery, a feared complication after LT.[11] Finally, platelet transfusions may also be associated with poorer survival after LT.[12]

Platelet counts and function are typically impaired in many candidates for LT, and this is often attributed to passive platelet sequestration in the spleen due to portal hypertension. Recent data also suggest increased platelet breakdown and, to a lesser extent, decreased platelet production related to bone marrow depression and reduced thrombopoietin production.[13] Functional defects such as hypo-aggregability have also been observed in some candidates with liver diseases.[14]

Low postoperative platelet counts have been found to be associated with higher morbidity rates and poorer liver function after hepatectomy.[15] The authors postulated that a critical number of platelets are required for the recovery of liver function, possibly through the effect of platelets on liver regeneration.[6]

In this study, we aimed to determine the predictive value of perioperative platelet counts for various parameters of short- and long-term outcomes after LT.

PATIENTS AND METHODS

Study Population

In all, 257 consecutive LT procedures performed at the University Hospital of Zurich from January 2003 to December 2011 were included in this study. Living donor LT (n = 28) and split LT cases (n = 1) were excluded to reduce confounding variables. No patient received any graft from a deceased cardiac donor during this period of time. During the study period, all demographic, radiological, and laboratory data were prospectively entered into a database after approval by the local ethics committee. This study follows the guidelines for reporting observational studies (the Strengthening the Reporting of Observational Studies in Epidemiology statement[16]) and is registered at ClinicalTrials.gov (identification number NCT01711957). Patient characteristics and surgical variables collected for the entire series are presented in Table 1.

Operative Procedure

Organ procurement was performed via aortic and portal perfusion in a consistent manner with the exception of the choice of the preservation solution. As part of a national agreement, we used University of Wisconsin solution until 2006, and we switched to Celsior solution thereafter. All patients underwent transplantation according to the classic implantation technique using cava resection or preservation without the use of venovenous bypass, as previously described.[17] Because there is no benefit from antiplatelet therapy after LT (including aspirin), none of the patients received any antiplatelet therapy after LT, even when there was a risk of hepatic artery thrombosis.

Laboratory Variables

Preoperative and postoperative platelet counts were prospectively recorded daily from admission until postoperative day 7 (POD7). In addition, the following laboratory variables were recorded daily before and after LT: international normalized ratio, factor V, serum creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase.

Outcome Parameters

The median follow-up was 35 months [interquartile range (IQR) = 20-65 months]. The primary outcome measured for the regression analysis was severe complications after LT. Severe complications were defined as grade IIIb/IV complications according to the Clavien-Dindo classification.[18] Mortality was defined as any death occurring from the time of surgery up to 90 days after transplantation.

Primary graft nonfunction was defined as death or retransplantation within the first postoperative week after the exclusion of technical, immunological, and infectious causes.[19-21] Delayed graft function was defined as the presence of at least 1 of the following parameters 7 days after LT: a serum bilirubin level $\geq$ 10 mg/dL and an international normalized ratio $\geq$ 1.6 or an alanine aminotransferase level > 2000 IU/L.[20,22]

A number of pre-LT parameters based on the survival outcomes following LT score[23] were recorded: the Model for End-Stage Liver Disease (MELD) score, the Child-Pugh stage, the use of renal replacement therapy, hepatorenal syndrome, and the use of life support (mechanical support) corresponding to ventilator dependence. Finally, preoperative and postoperative blood, platelet, and fresh frozen plasma transfusions were recorded until POD10.

Statistical Analysis

Statistical analyses were performed with SPSS Statistics 21 for Mac (IBM). Continuous variables were expressed as medians and IQRs. Continuous variables were compared with the Mann-Whitney U test. Differences between proportions derived from categorical data were compared with Fisher's exact test. A

TABLE 1. Comparison of Patient Characteristics and Perioperative Variables for Patients With Low and High Platelet Counts After LT

	All Patients (n = 257)	Patients With POD5 Platelet Counts $< 60 \times 10^9$/L (n = 130)	Patients With POD5 Platelet Counts $\geq 60 \times 10^9$/L (n = 127)	*P* Value
Patient variables				
Age (years)*	52 (46-61)	50 (47-60)	55 (45-62)	0.50
Sex: male [n (%)]	189 (74)	97 (75)	92 (72)	0.69
Body mass index (kg/m^2)*	25 (22-28)	26 (23-29)	24 (22-27)	<0.001
Hepatitis C [n (%)]	97 (38)	55 (42)	42 (33)	0.21
Hepatitis B [n (%)]	33 (13)	16 (12)	17 (17)	0.67
Acute liver failure [n (%)]	7 (2.7)	3 (2.3)	4 (3.1)	0.72
MELD score*	18 (10-26)	20 (14-28)	12 (8-22)	<0.001
Child stage [n (%)]				
A	52 (29)	13 (14)	39 (45)	<0.001
B	65 (36)	34 (37)	31 (36)	
C	63 (35)	46 (49)	17 (20)	
American Society of Anesthesiologists score [n (%)]				
II	20 (8)	4 (3)	16 (13)	0.008
III	134 (53)	65 (50)	69 (54)	
IV	99 (39)	57 (43)	42 (33)	
Previous LT [n (%)]	13 (5.1)	7 (5.3)	6 (4.7)	>0.99
Life support before LT [n (%)]	30 (12)	16 (12)	14 (11)	0.73
Renal replacement therapy before LT [n (%)]	31 (12)	21 (16)	10 (8)	0.05
Hepatorenal syndrome before LT [n (%)]	54 (21)	36 (28)	18 (14)	0.009
Donor variables				
Age > 40 years [n (%)]	187 (73)	97 (75)	90 (71)	0.71
Cold ischemia time > 12 hours [n (%)]	27 (11)	16 (12)	11 (9)	0.41
Perioperative variables				
Intraoperative blood loss (mL)*	1250 (800-2500)	1500 (1000-3500)	1000 (700-1600)	0.001
Intraoperative red blood cell transfusion (U)*	2 (0-79)	3 (0-10)	1 (0-4)	0.008
Intraoperative platelet transfusion (U)*	0 (0-1)	1 (0-2)	0 (0-4)	0.001
Intraoperative fresh frozen plasma transfusion (U)*	5 (0-14)	7 (0-14)	4 (0-12)	0.16

*The data are presented as medians and IQRs.

receiver operating characteristic curve analysis and Youden's index,[24,25] which gives equal weight to sensitivity and specificity, were used to identify ideal cutoff values for platelet counts to detect grade IIIb/IV complications after LT. The Kaplan-Meier method was used to generate survival curves, and the log-rank test was used to assess differences in survival between different groups. Multivariate logistic regression analysis was used to identify independent risk factors for severe complications, and odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were calculated. Cox regression analysis was used for the multivariate survival analysis. In addition to the perioperative platelet counts and transfusions, significant variables of current prediction models were included in these analyses: a donor age > 40 years and a cold ischemia time > 12 hours (based on the donor risk index[26]) and a MELD score > 25, a recipient age > 60 years, previous transplantation, and life support (mechanical support; based on the survival outcomes following LT score[23]). Notably, the cutoff value for the MELD score (>25) corresponded to the 75th percentile value in our population and was validated in the balance of risk scoring system as a cutoff value for discriminating patients at risk after LT.[27] $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of Patients With Low Postoperative Platelet Counts and Patients with High Postoperative Platelet Counts

The median pretransplant platelet count was 88 $\times$ 10^9/L (IQR = 58-127 $\times$ 10^9/L). The lowest median

platelet counts after LT were observed on POD3: the median was 56 $\times$ 10^9/L (IQR = 41-86 $\times$ 10^9/L). The platelet count on POD5 was the most accurate cutoff value for predicting the risk of grade IIIb/IV complications after LT (Supporting Table 1), with the patients divided into 2 groups: patients with platelet counts $<$ 60 $\times$ 10^9/L (n = 130) and patients with platelet counts $\geq$ 60 $\times$ 10^9/L (n = 127; Fig. 1 and Table 1). Pretransplant platelet counts were not associated with the risk of complications after LT (data not shown).

In the group of patients with low platelet counts on POD5, there were more patients with severe chronic liver disease and higher MELD scores and Child stages (Table 1). These patients more frequently presented with signs of renal failure and often had a need for renal replacement therapy (hepatorenal syndrome). This population also experienced higher intraoperative blood loss and received more intraoperative red blood cell and platelet transfusions, although the median numbers of platelet units transfused during LT were only 1 (IQR = 0-2) and 0 (IQR = 0-4) for patients with low and high platelet counts, respectively, on POD5 (P = 0.001).

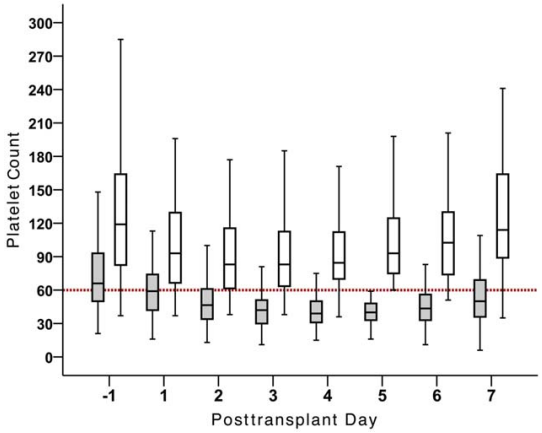

Figure 1. Dynamics of platelet counts in patients with platelet counts $<$ 60 $\times$ 10^9/L (gray bars) or $\geq$ 60 $\times$ 10^9/L (white bars) on day 5 after LT.

Multivariate Analysis of Platelet Counts and Other Factors Affecting Outcomes

Overall, the rate of severe postoperative complications (grade IIIb/IV) was 34%, and the mortality rate after LT was 12%. As shown in Table 2, patients with low platelet counts on POD5 had a significantly increased rate of postoperative severe complications in comparison with patients with high platelet count (39% versus 29%, P = 0.02). The mortality rate was also significantly higher for patients with low platelet counts on POD5 versus the group with high platelet counts (16% versus 8%, P = 0.05). In the multivariate analysis (Fig. 2), independent predictors of the development of grade IIIb/IV complications were a preoperative MELD score $>$ 25 and a platelet count $<$ 60 $\times$ 10^9/L on POD5 (P = 0.02 and P = 0.03, respectively), even when adjustments were made for low preoperative platelet counts and perioperative platelet and red blood cell transfusions. Patients with low postoperative platelet counts stayed longer both in the intensive care unit and in the hospital after LT.

Rates of delayed graft function and a need for retransplantation within 3 months after LT were higher for patients with low platelet counts on POD5, but this difference failed to reach statistical significance. A formal multivariate analysis of these 2 outcome parameters could not be performed because of the low number of events.

Impact of Low Platelet Counts on POD5 on Graft and Patient Survival After LT

There were 58 patients with a graft loss during follow-up. Forty-seven cases (81%) were related to patient

TABLE 2. Univariate Analysis of Postoperative Outcomes for Patients With Low and High Platelet Counts After LT

Variable	Patients With POD5 Platelet Counts $<$ 60 $\times$ 10^9/L (n = 130)	Patients With POD5 Platelet Counts $\geq$ 60 $\times$ 10^9/L (n = 127)	OR (95% CI)	P Value
Grade IIIb/IV complications [n (%)]*	51 (39)	37 (29)	1.09 (1.1-3.3)†	0.02†
Mortality: grade V [n (%)]*	21 (16)	10 (8)	2.25 (1.0-5.0)	0.05
Total intensive care unit stay (days)‡	6 (3-11)	3 (1-6)	Not available	0.001
Hospital stay (days)‡	24 (17-37)	18 (13-26)	Not available	0.005
Primary graft nonfunction [n (%)]	6 (5)	1 (1)	6.10 (0.72-51.40)	0.12
Delayed graft function [n (%)]	13 (10)	6 (5)	2.41 (0.88-6.59)	0.09
Retransplantation within 3 months [n (%)]	7 (5)	1 (1)	7.17 (0.87-59.16)	0.06

*According to the Clavien-Dindo classification.
†The analysis was performed with 226 patients. Patients classified as grade V (in-hospital deaths; n = 31) were excluded from the analysis so that mortality could be reported alone.
‡The data are presented as medians and IQRs.

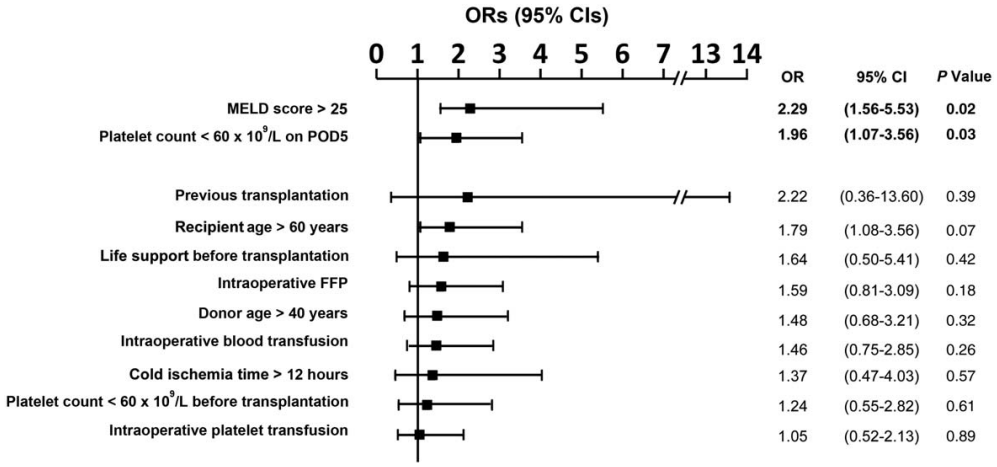

Figure 2. Independent risk factors for grade IIIb/IV complications in the multivariate analysis. Error bars indicate 95% CIs, and squares indicate ORs.

death. For the 11 remaining patients who survived (19%), graft loss was due to primary graft nonfunction (n = 4), ischemic cholangiopathy (n = 4), or recurrent hepatitis C cirrhosis (n = 3).

The 1-, 3-, and 5-year graft survival rates were significantly worse for patients with low platelet counts on POD5 versus patients with high platelet counts (81.5%, 77.2%, and 72.1% versus 90.8%, 83.1%, and 80.1%, respectively; $P = 0.02$). Similarly, the 1-, 3-, and 5-year patient survival rates were significantly worse for patients with low platelet counts on POD5 versus patients with high platelet count (82.2%, 78.9%, and 73.8% versus 96%, 86.5%, and 81.7%, respectively; $P = 0.03$; Fig. 3). Because most of the difference in survival occurred early, subgroup survival analyses were repeated, and patients who died within 90 days of LT (n = 24) were excluded. The predictive value of platelet counts for graft and patient survival was then lost, and this confirmed that low platelet counts after LT were associated with early complications and mortality (Supporting Fig. 1).

The multivariate analysis showed that low platelet counts on POD5 [hazard ratio (HR) = 2.0, 95% CI = 1.1-3.6, $P = 0.03$] and previous transplantation (HR = 3.09, 95% CI = 1.12-7.88, $P = 0.02$) were the only 2 independent predicting factors associated with impaired graft survival after LT (Fig. 4), and this finding was independent of the intraoperative administration of platelet or blood transfusions. Patients with low postoperative platelet counts had a significantly higher risk of graft failure than patients whose platelet counts were normalized within a few days after LT. Similarly, only low platelet counts on POD5 (HR = 2.2, 95% CI = 1.1-4.6, $P = 0.03$) were independently associated with impaired patient survival after LT (Fig. 5).

Impact of Previous LT on Outcomes

Thirteen patients had previously undergone LT more than 3 months before re-LT. The indications for re-LT were recurrent hepatitis C cirrhosis (n = 5), ischemic cholangiopathy (n = 4), hepatitis C–related ischemic type biliary lesions (n = 3), and recurrent primary biliary cirrhosis (n = 1). Because re-LT may have influenced the outcomes, a sensitivity analysis (receiver operating characteristic curves) and a survival analysis were performed, and these patients who had previously undergone LT were excluded. The sensitivity, the specificity, and Youden's index used to determine the ideal platelet count cutoff for predicting complications remained unchanged with or without these 13 patients (Supporting Table 2). Similarly, graft and patient survival analyses remained unchanged after the exclusion of these 13 patients who had previously undergone LT in comparison with the analyses of all patients (Supporting Fig. 2).

DISCUSSION

In this study, we provide evidence showing that platelet counts $< 60.10^9$/L on POD5 after LT (which we have nicknamed the 60-5 criterion) are associated with a higher risk of severe complications and graft loss and a 2-fold decreased chance of patient survival.

Most of the large prospective LT databases, such as those of the United Network for Organ Sharing[28] and the European Liver Transplant Registry,[29] do not include postoperative laboratory values, and this precludes their use in any predictive score derived from those sources. Clinical research about postoperative laboratory variables is, therefore, scarce.[30-32] Thrombocytopenia is common in the early postoperative period after LT because of consumption in hemostatic processes and platelet sequestration in the reperfused liver graft.[33,34] In old reports, persistent thrombocytopenia after LT was found to be associated with poor outcomes, including severe postoperative infections, increased allograft dysfunction, and decreased patient

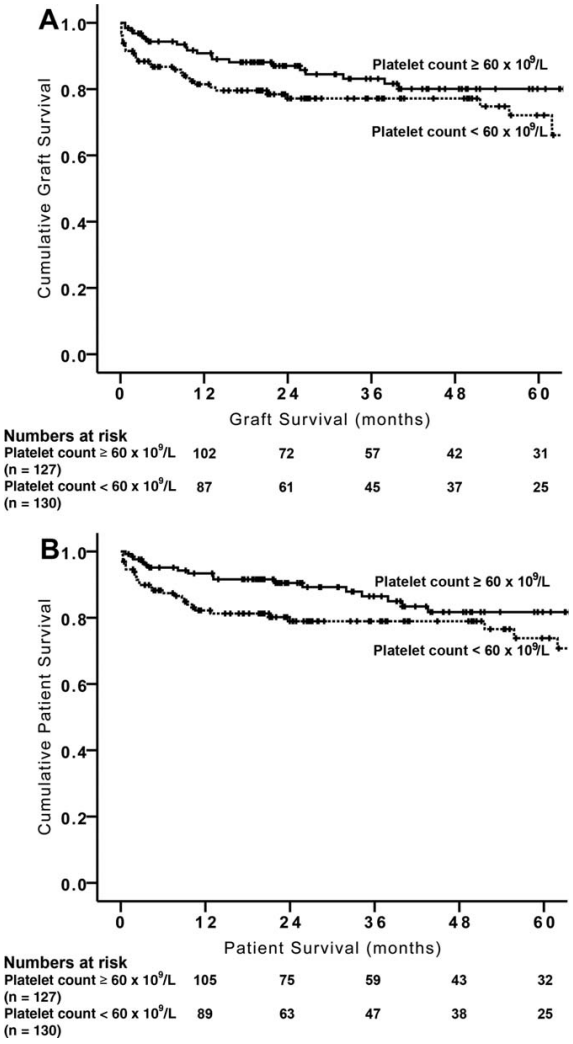

Figure 3. (A) Graft survival of patients with platelet counts $< 60 \times 10^9$/L or $\geq 60 \times 10^9$/L on day 5 after LT ($P = 0.02$). (B) Overall survival of patients with platelet counts $< 60 \times 10^9$/L or $\geq 60 \times 10^9$/L on day 5 after LT ($P = 0.03$).

survival.[30-32] These studies were, however, limited by small sample sizes, arbitrary determinations of low platelet cutoffs, and the use of azathioprine or massive perioperative platelet transfusions.

These results are in line with recent experimental studies suggesting that platelets play a critical role in outcomes after liver surgery. In rodents, thrombocytopenia impaired liver regeneration after partial hepatectomy,[6,35,36] whereas thrombocytosis or platelet injections into the portal vein improved liver regeneration.[37,38] Platelets and platelet-derived serotonin are key mediators of liver regeneration, and they may mediate tissue repair and liver regeneration in the postischemic liver, which is paramount after LT.[6,7] Additionally, in a mouse model of marginal (30%) graft transplantation, serotonin agonism substantially reduced the incidence of small-for-size syndrome and, consequently, improve animal survival.[39]

Several clinical studies have suggested that low platelet counts before an operation[40-44] or immediately after an operation[15] are associated with postoperative liver failure and complications after liver resection. After living donor LT, the amount of platelets transfused during the first postoperative week has been shown to be an independent positive factor for graft regeneration.[45]

Thrombocytopenia is also associated with increased morbidity, mortality, and hospital resource utilization in patients admitted to the intensive care unit for any disease.[46,47] As a result, platelet counts have been introduced into scoring systems for critically ill patients such as the Sequential Organ Failure Assessment score and the multiorgan dysfunction score.[48,49] It is, therefore, intuitively logical to consider platelet counts as a marker of outcomes after LT.

Although platelet cutoffs were arbitrarily chosen in most of the previous studies, we used a validated statistical model (receiver operating characteristic curve and Youden's index) to determine the best platelet cutoff (60×10^9/L) for detecting severe (grade IIIb/IV) complications and mortality after LT. Although our study is a retrospective analysis of a prospective database including a relatively small sample of patients, the 60-5 criterion was a strong predictor of poorer outcomes after LT. It remained the most significant prognostic factor of outcomes after LT after the implementation of a multivariate logistic regression analysis that considered the MELD score, the cold ischemia time, previous transplantation, the recipient and donor ages, and the need for pretransplant life support. Other potential confounders such as blood and platelet transfusions were also included in the multivariate analysis.

The survival analysis was also adjusted for the same relevant prognostic factors.[27] Furthermore, when patients surviving less than 90 days after LT were excluded from the Kaplan-Meier graft and patient survival analysis, the predictive value of platelet counts on POD5 for complications was lost. This emphasizes that low platelet counts are associated with early complications and mortality that may be handled during hospitalization, and they are strong enough to affect the overall median and 5-year graft and patient survival rates. Although significantly different between patients with low and high platelet counts, the 5-year graft and patient survival rates remained better than 70%. These high survival rates can probably be explained by the fact that we excluded from the analysis the patients who underwent retransplantation within 3 months to avoid confounding factors.

Despite the low level of evidence, platelet transfusions have been claimed to be associated with an increased risk of postoperative morbidity and mortality after LT.[8,12,50] However, because of the current refinement of anesthetic and surgical strategies, perioperative platelet transfusions are seldom used. Thus,

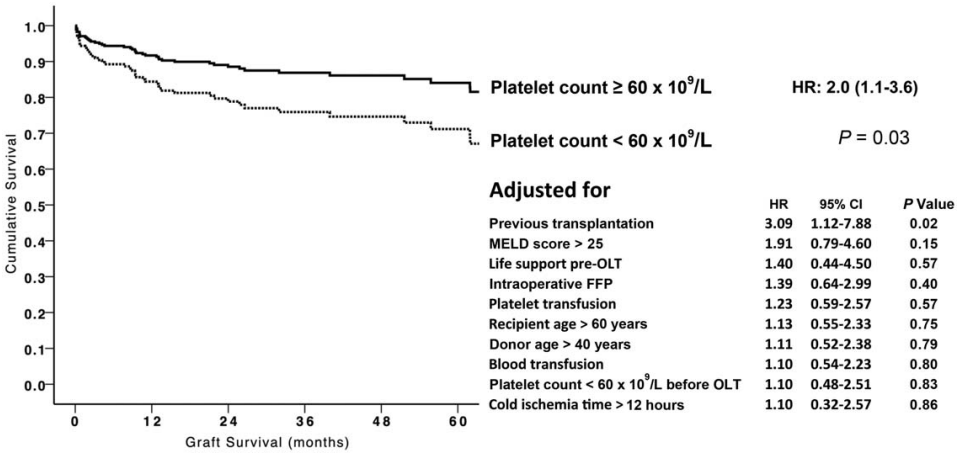

Figure 4. Adjusted cumulative graft survival rates for patients with platelet counts $< 60 \times 10^9$/L or $\geq 60 \times 10^9$/L on day 5 after LT.

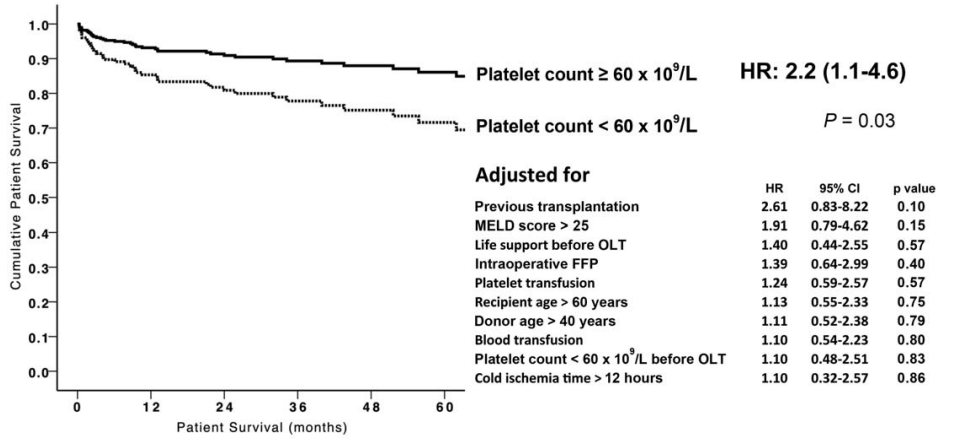

Figure 5. Adjusted cumulative patient survival rates for patients with platelet counts $< 60 \times 10^9$/L or $\geq 60 \times 10^9$/L on day 5 after LT.

the median number of platelet units transfused during LT was less than 1 in our series, and the amount of transfused platelets was not an independent factor for worse outcomes after LT. Similarly, preoperative platelet counts, although different for the 2 groups, were neither an independent factor for negative outcomes after LT nor a predictive factor for low postoperative platelet counts on POD5. In our series, preoperative platelet counts appeared to be more a surrogate of the preoperative severity of a patient's liver disease rather than a predictive factor of negative outcomes after LT.

This study has several limitations mainly due to the retrospective analysis and the relatively small sample of patients. The multivariate models suffer from a low event rate and a high need to control for confounders, and this means a high risk of overfitting. The timing of the platelet cutoff comes late after LT for predicting any complications. However, as confirmed in other studies,[32,33] thrombocytopenia was common in the early postoperative period, regardless of the outcomes of LT, and it was not discriminative before POD4. We also failed to determine whether thrombocytopenia was the cause of bad outcomes or a result of complications. At this stage, we advocate using the 60-5 criterion as an alert signal that should prompt us to perform aggressive investigations in order to look for undetected complications such as infections.[30]

In conclusion, although these results need to be confirmed in a prospective cohort of patients, this study suggests that the 60-5 criterion (a postoperative platelet count $< 60 \times 10^9$/L on POD5) after LT is an independent and strong predictor of severe

postoperative complications and is associated with worse graft and patient survival. These results are in accordance with recent data showing the pivotal role of platelets in liver regeneration and postischemic liver repair mechanisms. This study should enable a new focus on the dynamics of postoperative platelet counts after LT for anticipating complications. However, whether maintaining high platelet counts after LT is protective could not be determined in this study.

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