Impact of Graft Size on Postoperative Thrombocytopenia in Living Donor Liver Transplant

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Hypothesis: Perioperative variables, including portal venous pressure (PVP) and graft size, can predict thrombocytopenia after living donor liver transplant (LDLT).

Design: Retrospective analysis.

Setting: University hospital.

Patients: Forty-five adult patients with liver cirrhosis who underwent LDLT without splenectomy (n=38) or with simultaneous splenectomy (n=7).

Main Outcome Measures: Preoperative and postoperative platelet counts and perioperative variables of recipient age, preoperative Model for End-Stage Liver Disease score, donor age, graft volume to standard liver volume ratio, PVP, cold and warm ischemia times, blood loss, and surgical complications.

Results: In the 38 recipients who did not undergo splenectomy, there was a strong correlation between PVP at the completion of the transplant and the platelet count (at 14 and 28 days and at 3 months). A high PVP (≥25 mm Hg) correlated with posttransplant thrombocytopenia, as did a small graft. Patients undergoing a simultaneous splenectomy had sufficient platelet levels at each measurement, irrespective of the graft volume.

Conclusions: Portal venous pressure and graft size were associated with posttransplant thrombocytopenia. Splenectomy is an option in cases with a high PVP or a small graft, especially for patients receiving postoperative interferon therapy for hepatitis C virus.

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Liver cirrhosis with portal hypertension is often accompanied by thrombocytopenia of various causes. Thrombocytopenia complicates the postoperative course by causing an increased bleeding tendency, infection, and a higher incidence of morbidity after liver transplant. Furthermore, the platelet count is one of the crucial determinants for discontinuation of interferon therapy used preemptively or as treatment for recurrent hepatitis C virus. In living donor liver transplant (LDLT), the graft size is sometimes inadequate, causing elevated portal venous pressure (PVP) and the small-for-size syndrome, which may result in thrombocytopenia. Splenectomy at the time of transplant is one of the definitive procedures for avoiding postoperative thrombocytopenia and the small-for-size syndrome in LDLT, although its protective mechanism has not been fully understood.

In this study, we aimed to clarify the relationship between perioperative variables, including PVP, graft size, and thrombocytopenia, after LDLT. We hypothesized that perioperative variables, including PVP and graft size, would predict thrombocytopenia after LDLT.

See Invited Critique at end of article
to acute heart failure (n=1), sepsis (n=1), portal venous thrombosis (n=1), and persistent acute cellular rejection (n=1). These patients were excluded from the analysis.

In the remaining 38 recipients without splenectomy and the 7 recipients with splenectomy, the following items were evaluated and noted: preoperative platelet counts at 7, 14, and 28 days, 3 and 6 months, and 1 year after the transplant (until prophylactic interferon therapy was started in recipients with hepatitis C virus); recipient age; preoperative Model for End-Stage Liver Disease score; donor age; graft volume to standard liver volume ratio (GV:SLV ratio); PVP at the completion of the procedure; cold and warm ischemic times; blood loss; and surgical complications.

Portal venous pressure was obtained via an intravenous catheter placed in a tributary of the superior mesenteric vein during the transplant in 21 recipients. We divided patients into the high PVP group (> 25 mm Hg) (n=8) and the low PVP group (< 25 mm Hg) (n=13), according to their PVP at the completion of the procedure.

A standard immunosuppressive regimen consisted of a calcineurin inhibitor, with or without a corticosteroid, with or without mycophenolate mofetil, and with or without anti-interleukin 2 receptor antibody. Platelets were not transfused until the platelet count had dropped to less than 20 x 10^9/L (the conversion to cells/µL is a 1-to-1 conversion). In 2 patients, preemptive interferon therapy was initiated by 3 months after the transplant, and data collected at that time were not counted for either patient.

Ganciclovir sodium and a combination of trimethoprim and sulfamethoxazole were administered routinely for 10 days and 6 months, respectively, after LDLT in each patient.

The statistical analysis used the Mann-Whitney test for nonparametric data and the Pearson correlation test to examine the correlations among the variables. A P < .05 value was considered significant.

## RESULTS

The demographic characteristics of the recipients are shown in the Table. A comparison between the high and low PVP groups showed that the GV:SLV ratio was smaller and donors were older in the high PVP group, although these differences did not reach statistical significance. The patients experienced stable allograft function, without any surgical complications or recurrence of primary disease.

Morbidities associated with platelet counts or splenectomy are shown in the Table. Bleeding episodes tended to be more frequent in the high PVP group, although this difference did not reach statistical significance. Two patients with splenectomy developed retroperitoneal hematoma within 3 days after the transplant, when their platelet counts were less than 30 x 10^9/L. Sepsis was not observed in recipients with splenectomy.

Possible causes of drug-induced thrombocytopenia were similar between the low and high PVP groups. No drug therapy was discontinued because of drug-induced thrombocytopenia during the study. Mycophenolate was used in 39 patients (87%) (including all of

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### Table. Patient Characteristics (Platelet Counts and Variables)a

<table>
<thead>
<tr>
<th></th>
<th>Recipients Without SPN</th>
<th>P Value (High vs Low PVP)</th>
<th>Recipients With SPN</th>
<th>P Value (High vs Without SPN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=38)</td>
<td>High PVP Group (n=8)</td>
<td>Low PVP Group (n=13)</td>
<td></td>
</tr>
<tr>
<td>Recipient age, y</td>
<td>50.3±10.3</td>
<td>56.2±6.1</td>
<td>49.0±10.9</td>
<td>.11</td>
</tr>
<tr>
<td>Course of disease: Hepatitis C virus with cirrhosis</td>
<td>22</td>
<td>4</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Donor age, y</td>
<td>35.0±12.2</td>
<td>41.9±10.5</td>
<td>32.4±12.1</td>
<td>.08</td>
</tr>
<tr>
<td>MELD score</td>
<td>20±8.2</td>
<td>19.0±5.0</td>
<td>15.7±4.4</td>
<td>.27</td>
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<tr>
<td>Cold ischemia time, min</td>
<td>73.0±30.5</td>
<td>74.6±26.2</td>
<td>67.0±19.5</td>
<td>.64</td>
</tr>
<tr>
<td>Warm ischemia time, min</td>
<td>43.2±13.6</td>
<td>43.1±13.0</td>
<td>39.8±8.3</td>
<td>.61</td>
</tr>
<tr>
<td>Graft, left/right/RL</td>
<td>12/24/2</td>
<td>4/4</td>
<td>5/8/0</td>
<td></td>
</tr>
<tr>
<td>GV:SLV ratio (range)</td>
<td>50.4±10.9 (28.3-80.0)</td>
<td>41.5±9.1 (28.3-51.5)</td>
<td>51.5±11.9 (34.2-70.1)</td>
<td>.09</td>
</tr>
<tr>
<td>PVP, mm Hg</td>
<td>23.1±4.8</td>
<td>28.4±2.4</td>
<td>20.2±2.8</td>
<td>&lt;.001</td>
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<tr>
<td>Blood loss, mL</td>
<td>10678±12 822</td>
<td>14 803±15 980</td>
<td>5272±5702</td>
<td>.08</td>
</tr>
<tr>
<td>Platelet count, x 10^9/µL</td>
<td>9.6±10.8</td>
<td>5.6±3.6</td>
<td>6.9±4.3</td>
<td>.90</td>
</tr>
<tr>
<td>Before transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 14</td>
<td>14.3±3.4</td>
<td>8.4±2.3</td>
<td>17.9±7.4</td>
<td>.006</td>
</tr>
<tr>
<td>Day 28</td>
<td>14.2±2.6</td>
<td>8.2±2.5</td>
<td>16.1±7.8</td>
<td>.01</td>
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<tr>
<td>Day 90</td>
<td>12.3±4.8</td>
<td>8.7±3.2</td>
<td>14.1±3.6</td>
<td>.009</td>
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<tr>
<td>Morbidity, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding or hematoma b</td>
<td>5 (13.2)</td>
<td>2 (25.0)</td>
<td>2 (15.4)</td>
<td>.66</td>
</tr>
<tr>
<td>Graft dysfunction without surgical complication</td>
<td>4 (10.5)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>.22</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (5.3)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>.22</td>
</tr>
</tbody>
</table>

Abbreviations: GV:SLV, graft volume to standard liver volume; left, left lobe with or without caudate; MELD, Model for End-Stage Liver Disease; PVP, portal venous pressure; right, right lobe; RL, right lateral sector; SPN, splenectomy.

a Unless otherwise indicated, data are expressed as mean ± SD. The PVP groups are described in the “Methods” section.

b Includes intra-abdominal or retroperitoneal bleeding/hematoma, gastrointestinal tract bleeding, and intrathoracic bleeding.
the patients in the high and low PVP groups). The mean duration of mycophenolate administration was 3.6 months in the low PVP group and 1.7 months in the high PVP group (P=.17). Cytomegalovirus infection was observed in 3 patients (1 in the low PVP group and 2 in the high PVP group), and was treated with ganciclovir for 15 days in the patient in the low PVP group and 17 days in the patients in the high PVP group.

In the 38 recipients without splenectomy, there was a strong correlation between PVP at completion of the transplant and the platelet count (at 14 days, 28 days, and 3 months; r = −0.728, −0.627, and −0.620, respectively) (Figure 1). The GV:SLV ratio, preoperative Model for End-Stage Liver Disease score, and warm ischemia time also had some correlation with postoperative platelet counts, although these associations were much weaker than that of PVP. We found no association between preoperative and postoperative platelet counts.

The platelet counts for LDLT recipients in the low and high PVP groups without and with splenectomy are shown in Figure 2A. The platelet count in the low PVP group increased to greater than $100 \times 10^3/\mu L$ by 14 days after the transplant, whereas it remained as low as less than $100 \times 10^3/\mu L$ in the high PVP group, a difference that was significant.

The GV-SLV ratio in the high PVP group differed by less than 0.55 (Table); therefore, we compared the time course of platelet counts between recipients with a large graft (GV:SLV ratio > 0.55) and those with a small graft (GV:SLV ratio < 0.55). The platelet counts of all recipients without splenectomy (n = 38) showed increased platelet levels in recipients with large grafts, whereas it remained suppressed in recipients with small grafts (Figure 2B), although the difference was not statistically significant.

Patients with splenectomy had sufficient platelet levels at each measurement, irrespective of the graft volume (Figure 2A). Portal venous pressure at the end of surgery ranged from 18 to 23 mm Hg. Morbidity associated with splenectomy was observed in only 1 recipient (14%), who underwent reoperation for a retroperitoneal hematoma on postoperative day 10.

**COMMENT**

Liver cirrhosis with portal hypertension often accompanies thrombocytopenia of various causes. Advanced hepatic fibrosis or augmented splanchnic flow to the portal venous system under cirrhotic conditions results in hypersplenism and thrombocytopenia. A low thrombopoietin level in the blood, which is regulated by portal venous hemodynamics, causes thrombocytopenia in cirrhotic patients. Posttransplant thrombocytopenia can be induced by decreased thrombopoietin levels. Platelets are also absorbed in grafts and destroyed by platelet-associated IgG in patients with hepatitis C virus. Although thrombocytopenia is one of the risk factors...
for morbidity after LDLT, we are aware of no report about the influence of portal venous hemodynamics and graft size on postoperative platelet counts. Among the perioperative clinical factors, PVP was the most significant determinant of platelet counts after LDLT. This is reasonable because PVP, which is influenced by the graft portal venous vascular resistance and the recipient’s splanchinic flow to the portal vein, is closely related to splenomegaly and hypersplenism. The GV:SLV ratio is related to PVP and is therefore indirectly related to platelet counts after LDLT. A GV:SLV ratio of less than 0.55 corresponded to the high PVP group without splenectomy in our cohort, in whom postoperative platelet counts remained low.

Platelet counts in each group after LDLT were stable for as long as 12 months, despite liver regeneration and improvement of graft function (Figure 2A). We previously reported that PVP remained almost unchanged during the first 3 weeks after right-lobe adult-to-adult LDLT. The present results suggest that PVP remained unchanged (high in the high PVP group) for a long time, and even the liver regeneration and graft function were stabilized after LDLT.

Our data demonstrate that intervention with splenectomy or partial splenic embolization were necessary for patients with a high PVP (>25 mm Hg) or a small graft (<55% of the SLV) to maintain platelet counts greater than 100 × 10^9/L. Adequate platelet counts are also required for postoperative interferon and ribavirin antiviral therapy for hepatitis C virus infection.

Because of these results, we now perform a splenectomy in patients in the group at high risk for thrombocytopenia after LDLT. The feasibility and usefulness of increasing platelet counts after LDLT with simultaneous splenectomy were reported by Cescon et al and Kishi et al. Potential morbidities associated with splenectomy include bleeding, hematoma, leakage of pancreatic juice, and infection. Kishi et al reported that splenectomy was performed concurrently with LDLT in 21 patients, 6 (29%) of whom had morbidities of infectious diseases, a finding similar to that of the control group without splenectomy. Among 7 splenectomy recipients in our series, only 1 developed a retroperitoneal hematoma and required reoperation. Another patient in the splenectomy group developed thrombosis of the splenic vein, which was uneventfully reduced with anticoagulant therapy. Careful surgical procedure could minimize the morbidity associated with splenectomy.

The incidence of infection may increase after splenectomy. Streptococcus pneumoniae is the most prevalent causative organism of severe infection after splenectomy in children not undergoing transplantation, and vaccination is recommended, but vaccination is unnecessary in adult patients. The risk of infection in the liver transplant population has not yet been clarified. Neumann et al reported that simultaneous splenectomy increased the risk for opportunistic pneumonia, but none of our recipients with splenectomy developed any clinically obvious infection. Therefore, prophylaxis, such as preemptive vaccination, and careful monitoring for infection after LDLT are recommended.

Splenic artery ligation at the time of surgery is another option for preventing hypersplenism. Several reports have described how splenic artery ligation decreased portal venous flow and prevented small-for-size syndrome in partial liver transplant. However, one report stated that thrombocytopenia failed to improve in patients with splenic artery ligation after liver transplant, suggesting that splenic artery ligation may be inadequate to avoid thrombocytopenia after liver transplant.

Partial splenic embolization is another alternative. This procedure is less invasive and effectively increases the platelet count in cirrhotic patients. It is possible to perform partial splenic embolization before scheduled LDLT. One should consider performing partial splenic embolization during surgery for LDLT, but always be aware that there is a risk of life-threatening adverse effects in patients with end-stage liver disease.

In conclusion, PVP and graft size were associated with posttransplant thrombocytopenia in this study. Splenectomy is an option in cases with a PVP greater than 25 mm Hg after reperfusion or a GV:SLV ratio of less than 0.55, especially for patients receiving postoperative interferon therapy for hepatitis C virus infection.

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Statistical analysis: Dono. Administrative, technical, and material support: Miyamoto and Monden. Study supervision: Dono and Monden.

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REFERENCES


Marubashi et al have presented their data regarding the effect of allograft size on thrombocytopenia after living donor liver transplant. The authors note that posttransplant thrombocytopenia contributes to bleeding, infection, and “a higher incidence of morbidity” and, for those with recurrent hepatitis C virus infection, it can be a contraindication to interferon therapy. The results of the study are based on the posttransplant portal venous pressure (PVP) measurements from a subset of patients. A separate smaller group underwent splenectomy, but their selection for splenectomy apparently was not based on PVP measurements. The authors found that recipients of smaller grafts tended to have higher PVPs after transplant and a persistence of relative thrombocytopenia. Among those undergoing splenectomy, platelet counts were consistently higher, regardless of the graft volume. The authors conclude that splenectomy at the time of living donor liver transplant is indicated in those recipients with relatively low graft volumes or high measured PVP.

Although posttransplant thrombocytopenia can certainly contribute to bleeding, in almost all cases such problems are transient and confined to the first few hours or days after surgery. The contribution of thrombocytopenia to an increased incidence of infection or other morbidity would also need to be weighed against obvious similar concerns presented by the splenectomy itself, especially in the immunosuppressed patient. Indeed, in a comparable setting, Cescon et al described a rather high incidence of bacterial infection among their subgroup of patients who underwent splenectomy. Even in the present study, 2 of 7 patients who underwent splenectomy developed retroperitoneal hematoma. Finally, it should be noted that protocols for the treatment of recurrent hepatitis C virus infection generally initiate therapy many weeks or months after transplant, making the short-term issues of thrombocytopenia of less general concern than perhaps implied.

The importance of this study is the apparent strong correlation among small graft volumes, high measured PVP, and the findings of protracted thrombocytopenia. What is intriguing is the authors’ suggestion that PVPs may remain persistently elevated despite allograft regeneration with stable function. It is implied, if not demonstrated, that splenectomy will effectively lower PVPs and reliably improve this condition. As mentioned in the “Comment” section, others have found that a simple splenic artery ligation or postoperative splenic arterial embolization can be effective in analogous circumstances. A logical proposition would be selective intervention based on measurements of posttransplant PVPs. If elevated beyond the 25–mm Hg threshold observed by Marubashi and colleagues, then splenic artery ligation could easily be performed. If PVPs were persistently elevated, then a splenectomy would be more completely justified. Although the patients in this study had good graft function, as alluded to by the authors, such a strategy is also of relevance to the portal hyperperfusion that likely contributes to the small-for-size syndrome. It is hoped that this group will give us more insights into these important issues in the near future.

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