CASE REPORT

Postoperative neutrophil-to-lymphocyte ratio of living-donor liver transplant: Association with graft size

Hironori Hayashi*, Hiroyuki Takamura, Yoshinao Ohbatake, Shinichi Nakanuma, Isamu Makino, Hisatoshi Nakagawara, Tomoharu Miyashita, Hidehiro Tajima, Sachio Fushida, Tetsuo Ohta

Department of Gastroenterologic Surgery, Division of Cancer Medicine, Graduate School of Medical Science, Kanazawa University, 13-1, Takara-machi, Kanazawa, Ishikawa 920-8641, Japan

Received 4 August 2015; received in revised form 30 September 2015; accepted 21 October 2015
Available online 14 December 2015

KEYWORDS
complete blood count; endothelial injury; small-for-size graft

Summary
Issues related to small-for-size grafts in living donor liver transplantation (LDLT) are highly important. The neutrophil lymphocyte ratio (NLR) has been reported to be an inexpensive index of systemic inflammation for various diseases. We retrospectively evaluated the relationship between NLR and clinical course of 61 adult LDLT recipients in our institute until post-operative day 14. Patients were classified into two groups based on the graft volume divided by standard liver volume, as over 35% of graft volume divided by standard liver volume (GV/SLV) (Group L; n = 55) and under 35% of GV/SLV (Group S; n = 6). No differences were seen in background of the patients between the two groups. Also, absolute neutrophil, lymphocyte and platelet counts in both the groups showed no significant differences. In contrast, the NLR between the groups differed significantly from post-operative day 3 to 10, being higher in the Group S. In addition, the incidence of prolonged hyperbilirubinemia and small for size graft syndrome differed significantly between the two groups. Therefore, the elevation of post-operative NLR in the smaller graft group reflect suggestive pathophysiology of endothelial injuries that related to small for size graft syndrome in LDLT.

Copyright © 2015, Asian Surgical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Conflicts of interest: The authors declare no conflicts of interest.

* Corresponding author. Department of Gastroenterologic Surgery, Division of Cancer Medicine, Graduate School of Medical Science, Kanazawa University, 13-1, Takara-machi, Kanazawa, Ishikawa 920-8641, Japan.
E-mail address: pwrofdrms2000@staff.kanazawa-u.ac.jp (H. Hayashi).

http://dx.doi.org/10.1016/j.asjsur.2015.10.005
1015-9584/ Copyright © 2015, Asian Surgical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
1. Introduction

Many reports have described issues associated with graft size in living-donor liver transplantation (LDLT). Graft size affects the small-for-size (SFS) graft syndrome, which is often catastrophic and needs to be avoided. The principal pathogenesis of the SFS syndrome is thought to be excessively increased portal flow and the subsequent induction of graft sinusoidal endothelial injury. However, the symptoms of the SFS syndrome cannot be completely avoided, even when an appropriate ratio of graft size to portal inflow is obtained. Therefore, a greater understanding of the underlying pathophysiology is important for overcoming the SFS syndrome.

Complete blood count is an inexpensive and indispensable test following major surgeries, including LDLT. Thus far, the platelet count and its time-serial changes have been the focus of attention, given its reported relationship with postoperative morbidity and mortality. Similarly, the neutrophil-to-lymphocyte ratio (NLR) is an inexpensive index of systemic inflammation. Preoperative NLR has been investigated as a prognostic factor of hepatocellular carcinoma (HCC) in LDLT recipients. In addition, a relationship between prognosis and NLR has been reported in patients with colorectal, lung, and ovarian cancers, as well as in HCC patients. Further, NLR can predict the survival in patients with acute coronary syndrome treated by percutaneous coronary intervention and coronary artery bypass grafting. However, to date, no reports have analyzed the postoperative NLR in LDLT recipients. Here, we describe a retrospective pilot study to evaluate the relationship between NLR and adult SFS grafts, along with an analysis of other clinical factors.

2. Methods

Between January 1999 and December 2013, 61 patients underwent their first adult LDLT at Kanazawa University Hospital, Kanazawa, Japan. These patients were included in the present study after obtaining an approval from the Institutional Review Board of Kanazawa University Hospital. All living donors were evaluated by contrast-enhanced abdominal computed tomography with using three-dimensional image-analyzing system (SYNAPSE VINCENT; Fuji Film, Tokyo, Japan). The results of the computed tomography were used to calculate whole-liver volumetry, liver graft volume, and residual liver in the donor. The standard liver volume was calculated using the formula developed by Urata et al. The actual graft weight of the procured graft was measured on the back table in the operating room and was defined as graft volume (GV). Then, the graft size was evaluated as the GV/standard liver volume (GV/SLV) ratio and the graft-to-recipient body-weight ratio.

The transplant procedures for both donors and recipients have previously been reported. Hepatic arterial reconstruction was performed using a surgical microscopic procedure. Biliary reconstruction was routinely conducted in a duct-to-duct fashion. Portal vein pressure during surgery was not measured, and concomitant splenectomy for inflow modulation was not performed during this period.

Table 1 Baseline characteristics of the recipients, donors, grafts, and operations.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Group L (n = 55)</th>
<th>Group S (n = 6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.9 ± 9.7</td>
<td>50.7 ± 8.7</td>
<td>0.58</td>
</tr>
<tr>
<td>Male/female</td>
<td>33/22</td>
<td>3/3</td>
<td>0.68</td>
</tr>
<tr>
<td>MELD score</td>
<td>19.1 ± 12.3</td>
<td>20.2 ± 3.7</td>
<td>0.83</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestatic diseases</td>
<td>13</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>27</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Donor and graft</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>46.5 ± 6.9</td>
<td>40.2 ± 13.0</td>
<td>0.25</td>
</tr>
<tr>
<td>Male/female</td>
<td>32/23</td>
<td>4/2</td>
<td>0.70</td>
</tr>
<tr>
<td>GV/SLV (%)</td>
<td>48.8 ± 9.9</td>
<td>32.5 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GRWR (%)</td>
<td>0.98 ± 0.26</td>
<td>0.62 ± 0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left lobe/right lobe/others</td>
<td>38/16/1</td>
<td>4/0/2</td>
<td>0.56</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>947 ± 252</td>
<td>1078 ± 233</td>
<td>0.23</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>6836 ± 12,023</td>
<td>10,885 ± 9918</td>
<td>0.36</td>
</tr>
</tbody>
</table>

GRWR = graft-to-recipient body-weight ratio; GV/SLV = graft volume divided by standard liver volume; HCC = hepatocellular carcinoma; MELD = model for end-stage liver disease.
Acute cellular rejection included clinically suspected and steroid-treated cases, as well as histologically proven ones. The SFS syndrome is defined as the criteria of the report from Soejima et al.\(^3\)

To analyze the relationship between SFS graft and other clinical factors, the patients were divided into two groups according to the GV/SLV, as over 35% GV/SLV (Group L) and under 35% GV/SLV (Group S). The parametric variables were compared using unpaired Student \(t\) test, while the nonparametric variables were compared using Chi-square analysis. The survival probability of the recipients was determined by the Kaplan–Meier method. A \(p\) value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

The baseline characteristics of the recipients, donors, grafts, and operations are listed in Table 1. No differences were seen with respect to age, gender, or MELD scores between the two groups. The indications of liver transplantation differed significantly between the two groups. Further, the mean GV/SLV and graft-to-recipient body-weight ratio between the two groups showed significant differences, being 48.8 ± 9.9% and 0.98 ± 0.26% in Group L, and 32.5 ± 2.0% (\(p < 0.001\)) and 0.62 ± 0.06% (\(p < 0.01\)) in Group S, respectively.

The neutrophil and lymphocyte absolute counts in Groups L and S did not differ significantly (Figures 1A and 1B); further, the platelet counts also showed no significant differences (Figure 1C). However, the NLR showed significant differences between the two groups from POD 3 to POD 10 (Figure 1D). The post-transplantation prothrombin time—international normalized ratio was not significantly different between the two groups, except on POD 1 (Figure 2A). By contrast, the total bilirubin levels differed significantly between the two groups from POD 3 to POD 14 (Figure 2B). The C-reactive protein in Groups L and S did not differ significantly (Figure 2C).

According to the postoperative clinical course, the incidence of post-transplantation complications (i.e., prolonged hyperbilirubinemia and SFS graft syndrome) differed significantly between the two groups. However, the incidence of other postoperative complications, including acute cellular rejection, infection, graft loss, and relaparotomy because of postoperative bleeding, bowel perforation, or vascular complication, was not statistically different between the groups (Table 2).

4. Discussion

LDLT is an important therapeutic modality for patients suffering from end-stage liver disease. However, following LDLT, problems related to the SFS graft syndrome remain unresolved. Many reports have described various issues...
related to graft size in LDLT, although elucidating these specific postoperative findings has been still difficult. One of the most important factors related to the SFS graft-associated symptoms has been reported to be sinusoidal endothelial injury due to various reasons, such as ischemia/reperfusion, usage of immunosuppressant agents, and excessive portal vein pressure. Coagulopathies cause microcirculatory disturbances in the graft and impaired graft function. In this report, we used NLR to evaluate the severity of inflammation in LDLT recipients, demonstrating statistically significant differences in the early postoperative period in the small graft group. NLR has been reported to have a relationship with the clinical course in various diseases, such as solid tumors (including HCC before liver transplantation) and acute coronary syndrome. Coagulopathies cause microcirculatory disturbances in the graft and impaired graft function. In this report, we used NLR to evaluate the severity of inflammation in LDLT recipients, demonstrating statistically significant differences in the early postoperative period in the small graft group. NLR has been reported to have a relationship with the clinical course in various diseases, such as solid tumors (including HCC before liver transplantation) and acute coronary syndrome. Coagulopathies cause microcirculatory disturbances in the graft and impaired graft function. In this report, we used NLR to evaluate the severity of inflammation in LDLT recipients, demonstrating statistically significant differences in the early postoperative period in the small graft group. NLR has been reported to have a relationship with the clinical course in various diseases, such as solid tumors (including HCC before liver transplantation) and acute coronary syndrome. In our study, pathophysiological changes concerning post-transplantation NLR are suggested to have a resemblance to these vascular injuries, because the graft is exposed to similar ischemia/reperfusion injuries to acute coronary syndrome, and also, excessive shear stress for sinusoidal endothelial cell, which is unavoidable in LDLT using SFS graft. Thus, we speculate that the mechanism of NLR elevation is due to the induction of strong inflammatory changes by these vascular injuries.

In the domain of vascular diseases, neutrophilia is itself a prognostic factor. Therefore, neutrophil counts are suggested to have a strong relationship with vascular endothelial cell injury. We have previously reported that the neutrophil elastase inhibitor (sivelestat) has a suppressive effect on hepatic ischemia/reperfusion injury, suggesting the effectiveness and importance of suppressing neutrophil activation. By contrast, excessive and persistent suppression of neutrophils can lead to infections; thus, appropriate suppression is considered important in the clinical setting.

The relationship between inflammatory changes of the endothelium and activation of neutrophils and platelets is very important. As suggested in the present study, neutrophil activation is an important pathophysiology of graft sinusoidal endothelial injury in LDLT. In damaged sinusoids, activated neutrophils and platelets migrate to the space of Disse. Moreover, platelet aggregation is observed in this condition; we named this phenomenon “extravasated platelet aggregation.” As mentioned previously, various transplant-related pathophysologies can cause
incompatible transplantation has been reported. PGE1 infusion of prostaglandin E1 (PGE1) therapy applied in ABO-incompatible transplantaion, beneficial immunological modulation by portal venous ligation of lymphocytic functionality and differentiation. In addition, beneficial immunological modulation by portal venous pressure decompression, but also by immunological modulatory functions. Further, PGE1 is suggested to protect graft microcirculation via endothelial cytoprotection by cyclic adenosine monophosphate. Thus, our present results support speculations about relationships between graft size, sinusoidal endothelial injury, immunological reaction, graft microcirculation, and postoperative clinical course.

The effects of small intestinal congestion induced by portal venous hypertension should not be ignored in the pathophysiology of the SFS graft syndrome. Congestion of the small intestine has been reported to induce mucosal apoptosis in an experimental model. Such intestinal injury via tumor necrosis factor-alpha leads to inflammation and immunological activation, which affect the neutrophil activation and lymphocyte interactions. Further, preserving the small intestinal immunity is important in the setting of portal venous congestion induced by SFS grafts in LDLT.

The small number of presented cases is a limitation of this retrospective study. The small sample size affected statistical power of this study, because postoperative outcomes were considered mostly to be due to reduced portal venous pressure decompression, but also by immunological modulatory functions. Further, PGE1 is suggested to protect graft microcirculation via endothelial cytoprotection by cyclic adenosine monophosphate. Thus, our present results support speculations about relationships between graft size, sinusoidal endothelial injury, immunological reaction, graft microcirculation, and postoperative clinical course.

The small number of presented cases is a limitation of this retrospective study. The small sample size affected statistical power of this study, because postoperative outcomes were considered mostly to be due to reduced portal venous pressure decompression, but also by immunological modulatory functions. Further, PGE1 is suggested to protect graft microcirculation via endothelial cytoprotection by cyclic adenosine monophosphate. Thus, our present results support speculations about relationships between graft size, sinusoidal endothelial injury, immunological reaction, graft microcirculation, and postoperative clinical course.

The authors would like to express the deepest appreciation to Dr Takashi Tani (Public Central Hospital of Matto Ishikawa) and Dr Koichi Shimizu (Toyama Prefectural Central Hospital) for their sincere encouragement and insightful support to our transplant program team.

References


