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Small-for-Size Syndrome After Living Donor Liver Transplantation

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1. Introduction

Patients scheduled for liver transplantation frequently have portal hypertension and consequently they are likely to have a high portal blood flow in the transplanted graft. When the graft volume is small in adult living donor liver transplantation with partial liver transplantation, various problems that may affect the prognosis often occur because the partial graft cannot sustain excessive portal blood perfusion. It is widely known that liver transplant recipients can potentially develop a specific syndrome known as “small-for-size syndrome”, when a small for size graft causes size mismatch in the presence of portal hypertension. The small-for-size syndrome can result in large-volume ascites, hyperbilirubinemia, and coagulopathy. The pathologic mechanism of small-for-size syndrome includes graft failure caused by excessive and destructive portal inflow into the small for size graft. The small-for-size syndrome is widely recognized by transplant surgeon as one of the important post-transplant events. Thus, sufficient graft volume is one of the important determinants of successful transplant and clinically satisfactory outcome. Particularly in the case of living donor liver transplantation, there is the added problem of insufficient donor pool and donor safety, but it is essential to maintain graft function under the given circumstances. The decision on the type of liver graft depends on various factors, such as recipients’ status and donor safety: a small for size graft tends to be selected due to problems related to donor selection and to ensure the safety of the donor. In this regard, many centers stipulate the absolute lack of various pre-transplant risk factors and a minimal graft size in order to prevent the development of this syndrome and good outcome.

2. Pathophysiological mechanisms of small-for-size syndrome

Small-for-size syndrome can occur in the special situation of partial liver graft transplantation, especially in adult living donor liver transplantation, with resultant size mismatching between graft size and recipient hepato-portal circulation. Once the partial liver volume graft is subjected to excessive portal inflow, portal hyperperfusion results in the development of the small-for-size syndrome. The basic pathophysiology in this syndrome relates to graft injury after transplantation, which is caused by graft size mismatch and portal hypertension, followed by the appearance of various clinical

abnormalities such as excessive ascites, hyperbilirubinemia, coagulopathy, encephalopathy, and renal dysfunction. Transplant recipients develop symptoms related to the above abnormalities after transplantation and post-transplant prognosis is reported to be less than ideal.

To understand the pathophysiological mechanism of the small-for-size syndrome, several studies examined post-transplant biopsies. These studies reported histopathological evidence of mechanical injury and graft failure caused by destructive portal hyperperfusion. The main histopathological findings are: (1) Portal vein and periportal sinusoidal endothelial denudation and focal hemorrhage into the portal tract connective tissue; and (2) poor arterial flow and vasospasm, resulting in ischemic cholangitis and parenchymal infarct. Furthermore, electron microscopic examination showed sinusoidal congestion, excessive swelling of the mitochondria in hepatocytes, irregular large gaps of sinusoidal lining cells, and collapse of the space of Disse. These findings are considered to represent progressive damage of the graft resulting from microcirculatory failure due to irreversible endothelial injury after reperfusion. On the other hand, other studies examined the molecular basis of graft damage by analyzing intra-graft gene expression. The results of these studies provided evidence for sinusoidal damage. Cases of small-for-size syndrome and associated graft dysfunction due to portal hyperperfusion, showed intra-graft upregulation of endothelin-1 and down regulation of heme-oxygenase-1 and heat shock protein-70. Others showed low portal venous plasma nitric oxide levels. In addition, experimental studies using animal models of the small-for-size syndrome showed intra-graft over-expression of endothelin-1, early growth response -1 (Egr-1) and endotherin-1A receptor and significant changes in intra-graft mRNA levels as well as plasma levels of inflammatory cytokines (interleukin [IL]-6, IL-15, tumor necrosis factor [TNF]-alpha). Furthermore, the small for size isografts and allografts, with volumes measuring 50% or 30% of the liver graft volume, demonstrated higher expression levels of vascular endothelial growth factor (VEGF) and fetal liver kinase (Flk)-1 than the whole isograft and allograft. In addition, Flk-1-positive activated macrophages were also detected in small for size isografts and allografts, which were probably induced by VEGF. In this regard, the expression of VEGF and its interaction with Flk-1 could mediate the inflammatory response, early activation of macrophages. Thus, the above changes in the small for size graft injury likely play important roles in the accelerated acute rejection process of the small for size allograft.

Previous studies indicated that liver regeneration begins in the early period after partial liver transplantation. Although the detailed mechanism remains unknown at present, the high portal flow rate and high portal pressure are considered important triggers of liver regeneration. In partial liver transplantation, a high level of liver regeneration is observed when the graft size is small, or when portal pressure is high in cirrhotic patients. On the other hand, liver tissue damage and ischemic reperfusion injury caused by high portal pressure in small-for-size syndrome result in serious interference with the process of liver regeneration. Interestingly, IL-6 and TNF-alpha play key roles in liver regeneration, though they are also considered to represent markers of acute-phase tissue damage. Local activation and excessive production of these cytokines is associated with poor liver regeneration, since they can act as negative regulators of cell proliferation. In fact, TNF-alpha could trigger the cell death pathway after binding to the TNF-receptor. Thus, although the role of these cytokines remains controversial, they are considered to function as inflammatory cytokines, rather than as liver regenerative factors, in patients with small-for-size syndrome.

Furthermore, accumulation of oxygen free radicals in the graft could possibly contribute to graft dysfunction.

3. Treatment strategy for small-for-size syndrome

The most important step is prevention of small-for-size syndrome through perioperative treatment strategies that include approaches aimed at reducing excessive portal inflow as the major cause of small-for-size syndrome, and lowering the graft perfusion pressure. Furthermore, efforts should be made to prevent hepatic venous congestion due to insufficient vascular orifices or mechanical stenosis and kinking.

An important factor in determining portal inflow volume and pressure is the blood perfusion level in the spleen, thus highlighting the benefits of splenectomy and ligation of the splenic artery. However, patients with end-stage hepatic failure exhibit a hyperdynamic state of splanchnic blood flow, compared with normal state, and are at increased risk of hemorrhage associated with seriously invasive surgical procedures. Thus, careful attention should be paid to the expansion of the dissection area during surgery, especially in patients with collateral circulation around the splenic artery, such as gastric coronary vein and spleno-renal shunt. However, the development of new surgical technique and advances in medical devices have allowed a reduction in blood loss during surgical dissection procedures and splenectomy. Although the invasiveness of surgical procedure such as splenectomy and splenic artery ligation could be diminished further, adverse events such as increased susceptibility to infection caused by low immunity and portal vein thrombosis, may occur after splenectomy. Thus, patients should be carefully selected for splenectomy and splenic artery ligation.

Portosystemic shunt is currently considered an efficacious procedure in the treatment of portal hypertension. Especially adequate portosystemic shunt, which achieves favorable portal decompression to below 15 mmHg, could dramatically improve the post-transplant prognosis of patients with small for size graft. The procedure has allowed lowering the cut-off value for graft weight-to-recipient body weight ratio from 0.8% to 0.6%. This procedure is anticipated to become the main strategy in the future to prevent the development of the small-for-size syndrome. However, the separation of the graft portal route, as seen in portosystemic shunt, may result in portal steal to the extrahepatic route, which sometimes leads to fatal events especially in cases with decreased graft portal vascular compliance, such as the case of steatotic liver graft or acute cellular rejection. Based on this potential complication, some centers have adopted certain precautionary measures against such complications using modifications of the shunt closing technique.

The recently introduced approach of splenic artery embolization could be an effective procedure for portal decompression instead of the conventional treatment. Splenic artery embolization is described by some investigators as a rescue treatment for post-transplant small-for-size syndrome. In this regard, we previously reported that preoperative portal decompression by splenic artery embolization efficaciously reduced blood loss during operation and shortened the operating time, and that it contributed to favorable prognosis without serious complications related to the procedure itself. In our institution, preoperative embolization is selected for patients considered at risk of development of shunt in the peri-celiac trunk. The risk assessment is based on preoperative radiography showing possible problems with safety of splenic artery ligation. In each patient scheduled

for preoperative splenic artery embolization, abdominal angiography was performed 12 to 18 hours before transplantation. As a rule, a metallic coil was placed in the area adjacent to the root of the splenic artery and proximal to the bifurcation of the major pancreatic artery, to produce total embolization of the splenic artery trunk (Figure 1). Evaluation of post-transplantation graft hemodynamics by Doppler ultrasonography showed a significant reduction in the level of graft portal perfusion following splenic artery ligation and splenic artery embolization in the portal modulation group, compared with the non-portal modulation group (Figure 2). In the portal modulation group, the efficacy of portal decompression following splenic artery embolization was equivalent to that after splenic artery ligation. Furthermore, hepatic arterial flow was significantly higher during the postoperative phase in the portal modulation group, reflecting arterial flow shift from the spleen to the hepatic artery or hepatic arterial buffer response (Figure. 1).

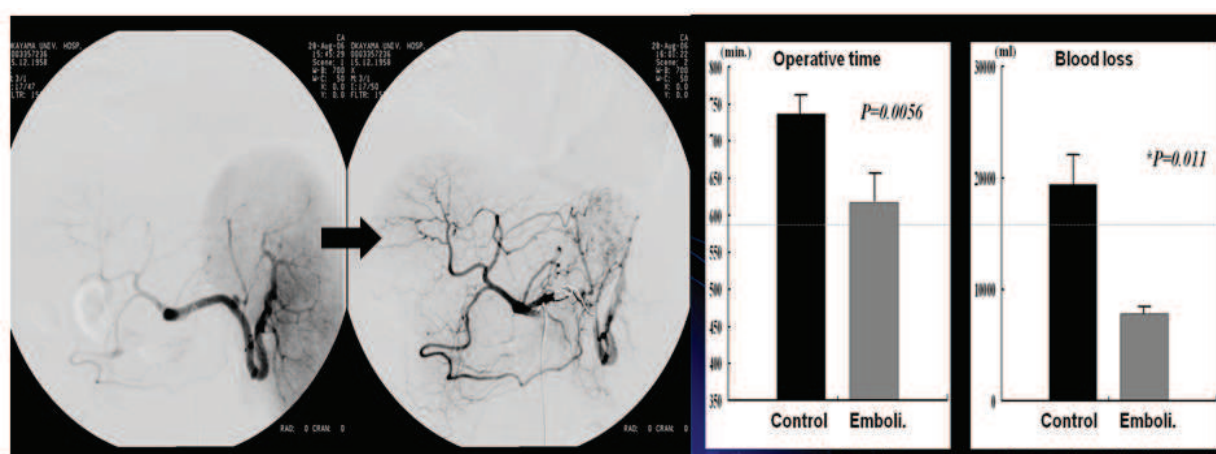


Fig. 1. Preoperative splenic artery embolization as a prophylactic procedure for the prevention of small-for-size syndrome. Splenic artery was totally embolized adjacent to the root of celiac artery, 12-18 hours before liver transplantation. Splenic artery embolization reduced portal flow and increased hepatic arterial flow. Preoperative portal decompression also decreased blood loss and shortened operative time

As a result, such change in arterial blood flow could also contribute to the prevention of splenic artery steal syndrome, which causes poor arterial blood supply. Based on this procedure, none of the patients developed portal vein thrombosis or septicemia, which are sometimes observed after splenectomy.

Another issue related to liver transplantation is the post-transplant course. In this regard, high level liver regeneration is observed when the graft size is small, or when portal pressure is high in cirrhotic patients. Importantly, high serum IL-6 concentrations are considered to reflect high hemodynamic shear stress, which could lead to regenerative signaling pathway. However, in patients with extra small for size graft, regeneration of the graft liver does not occur sometimes, and liver tissue damage and ischemic reperfusion injury could result in increased release of inflammatory cytokines, such as IL-6 and TNF-alpha, which lead to poor liver regeneration, i.e., these cytokines act as negative regulators of cell proliferation. Thus, although the role of these cytokines remains controversial, they are considered to function as inflammatory cytokines, rather than as liver regenerative factors, in patients with small-for-size syndrome, and thus, are considered as markers of

graft injury. The postoperative outcome depends on the extent of graft injury immediately after the transplantation and portal decompression can protect the liver graft from destructive portal hyperperfusion and reduce the levels of these inflammatory cytokines. Our previous study reported that prophylactic splenic artery embolization and ligation decreased serum IL-6 and TNF-alpha after graft reperfusion and resulted in certain graft liver regeneration and favorable outcome. Based on these new findings, in terms of treatment strategy in small-for-size syndrome, prophylactic treatment would be favorable compared with rescue therapy.

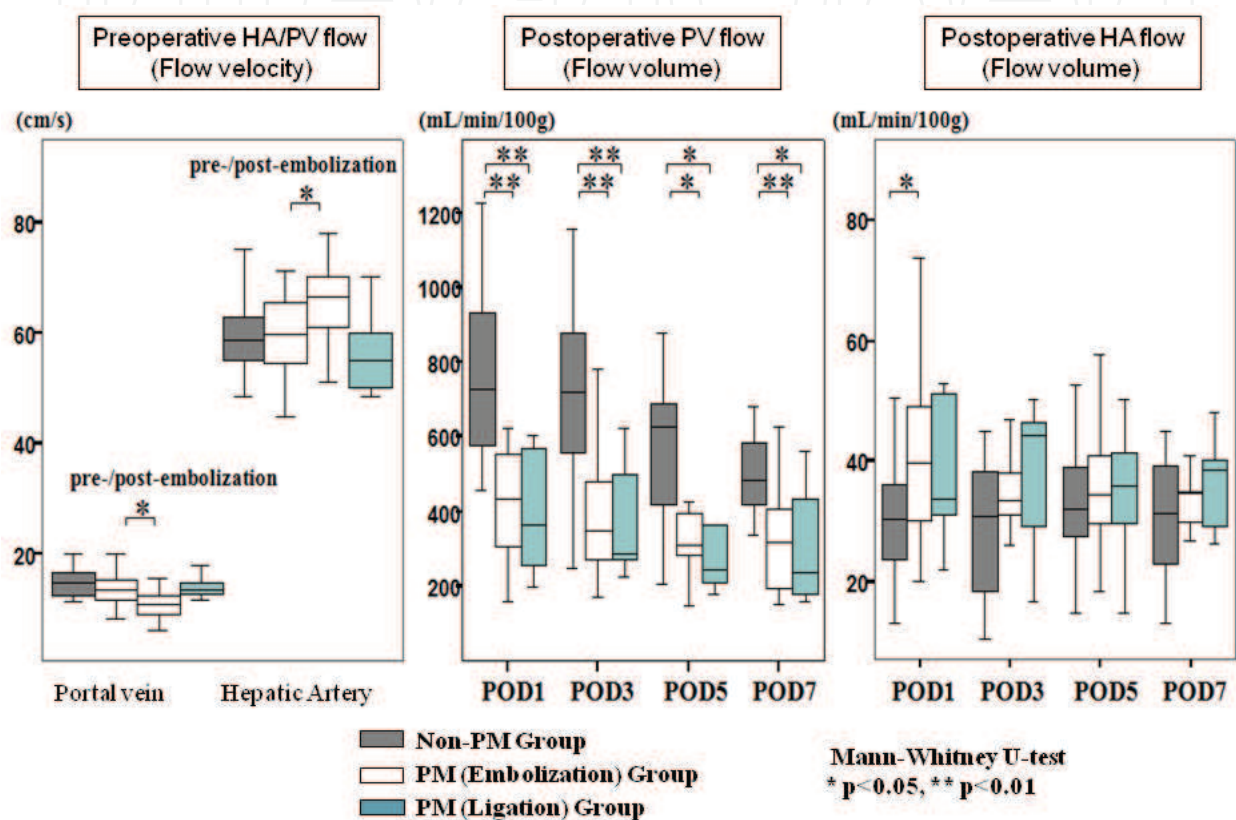


Fig. 2. Box-and-whisker plots of portal vein flow and hepatic artery flow in patients of the non-portal modulation (PM) and PM groups during postoperative days (POD) 1, 3, 5 and 7

Any decision regarding the treatment strategy for small-for-size syndrome, flexible stance is often needed. Among the various approaches, either decision could be suitable depending on the individual patient. For example, the patient characteristics and institutional operative policies could influence the final decision. While portosystemic shunt is widely used for the prevention of small-for-size syndrome, there is no doubt that splenectomy and splenic artery ligation are also suitable and effective techniques to produce portal decompression. Furthermore, splenic artery embolization prior to transplantation could be an alternative effective treatment modality especially in patients with severe portal hypertension, and with established collateral circulation in the peri-celiac trunk, which makes it difficult to perform splenic artery ligation or splenectomy. In this regard, when sufficient portal decompression cannot be achieved through a single technique, a combination of two or more procedures should be applied. In essence, a proper portal decompression therapy can inhibit portal overperfusion injury and prevent small-for-size syndrome and also have beneficial effects

on liver generation as well as improvement of post-transplantation prognosis. In addition to the reduction in the mortality rate after the development of the technique of living donor liver transplantation, from medical and economic standpoints, the cost benefits of liver transplantation can be fully expected based on the reduced use of blood products, and shorter hospitalization through improvement of perioperative clinical condition.

4. Prediction of small-for-size syndrome and hospital mortality

Theoretically, small-for-size syndrome is expected in cases of small for size graft with high portal inflow. However, several studies have demonstrated that small-for-size syndrome does not necessarily occur even in such situations. In other words, the development of small for size syndrome and post-transplant graft function could not be predicted from the graft size only. We hypothesized that early graft function does not only depend on graft size, but also on portal hypertension, donor age and recipient status. To test our hypothesis, we determined the perioperative risk factors in small-for-size syndrome and post-transplant hospital death. In this regard, there are only a few studies that have dealt with the prediction of small-for-size syndrome in living donor liver transplantation.

We analyzed retrospectively 200 consecutive adult patients who underwent living donor liver transplantation in our hospital during the period from August 1998 to January 2010. We used multivariate analysis of hospital deaths for this purpose and various clinical, pathological and surgical parameters, after employment of cut-off values for these parameters using ROC analysis. Patients were divided into two groups according to the treatment protocol for the prevention of small-for-size syndrome. The first 50 patients had not received any prophylactic portal decompression. There were significant differences in the clinical parameters based on the time trend between the groups with and without prophylactic portal decompression. Interestingly, an aggressive operative stance was identified in the late time group and this correlated with the recipient age, donor age, MELD, and graft volume. Meanwhile, there was a significant learning curve, which seemed to reflect the development of the operative procedure, including the cold ischemic time, blood loss, and operative time (Figure 3). In the first 50 cases, the in-hospital mortality rate and 1-year survival rates of patients with a graft weight (GW)/recipient body weight (RBW) rate less than 0.8% were 27.3% and 63.6%, respectively (Figure 4). Multivariate analysis identified a single factor, which was a graft weight (GW)/recipient body weight (RBW) rate less than 0.8%, as a significant determinant of post-transplant hospital death (Table 1). From the 51st patients onward, prophylactic portal decompression was used in 70 of the 150 patients in order to prevent small-for-size syndrome. The prophylactic portal decompression consisted of splenic artery embolization in 50 patients, splenic arterial ligation in 14, splenectomy in 5, and portocaval shunt in 1 patient. After the introduction of the prophylactic portal decompression in the later 150 cases, the hospital mortality rate and 1-year survival rate of patients with GW/RBW less than 0.8% were 7.2% and 86%, respectively. After the introduction of prophylactic portal decompression, post-transplant prognosis did not correlate with a cut-off value of 0.8% for the GW/RBW ratio (Figure 4). Multivariate analysis of post-transplant hospital mortality rate in the later 150 cases identified donor age more than 54 years and MELD score more than 23, but not the GW/RBW, as significant perioperative risk factors (Table 2). In other words, the minimum GW/RBW ratio could be safely lowered to 0.68% with adequate portal modulation.

Variables	n	Odds ratio	P-Value
Recipient factors			
Age ≥ 50 (vs < 50 years)	22 / 28	23.4	0.99
MELD ≥ 20 (vs < 20)	2 / 48	6.29	0.23
Disease			
Cholestatic disease vs PLC	22 / 19	0.34	0.21
Acute liver failure vs PLC	9 / 19	1.39	-
Donor factors			
Age ≥ 53 (vs < 53 years)	10 / 40	1.15	0.92
Graft type (right lobe vs left lobe graft)	38 / 12	0.29	0.46
GW/RBW < 0.8% (vs ≥ 0.8%)	12 / 38	8.44	0.02
Treatment and Operative factors			
Blood loss ≥ 50 (vs < 50ml/kg)	39 / 11	3.59	0.99
CIT ≥ 80 (vs < 80min)	16 / 34	1.16	0.91
WIT ≥ 50 (vs < 50min)	14 / 36	1.92	0.40
Operating time ≥10 (vs <10 hrs)	38 / 12	4.56	0.74

Table 1. Logistic regression analysis of post-transplant hospital mortality (the first 50 cases). PLC, Post-necrotic Liver cirrhosis; MELD, Model for End-stage Liver Disease; GW/RBW, Graft weight to recipient body weight ratio; CIT, Cold ischemic time; WIT, Warm ischemic time

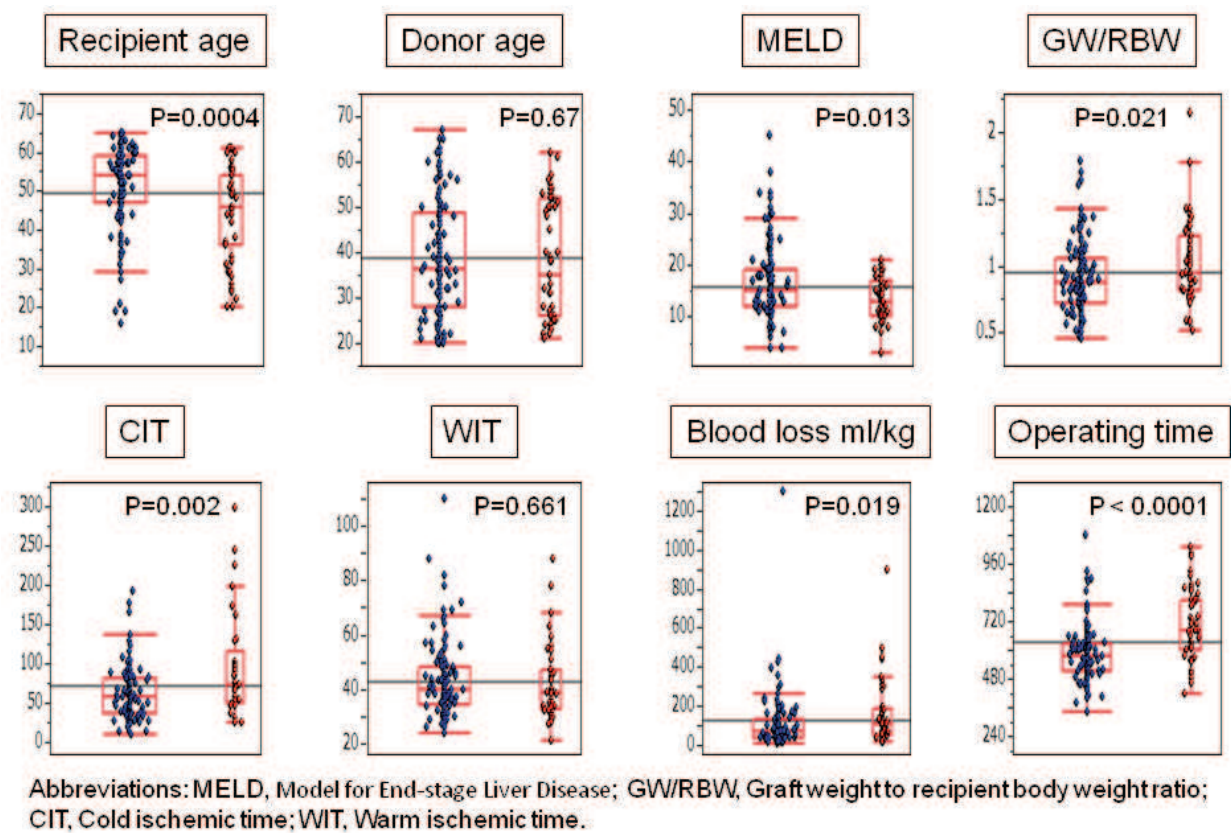


Fig. 3. Box-and-whisker plots of clinical factors in the first 50 cases (right side) and the later 150 cases (left side)

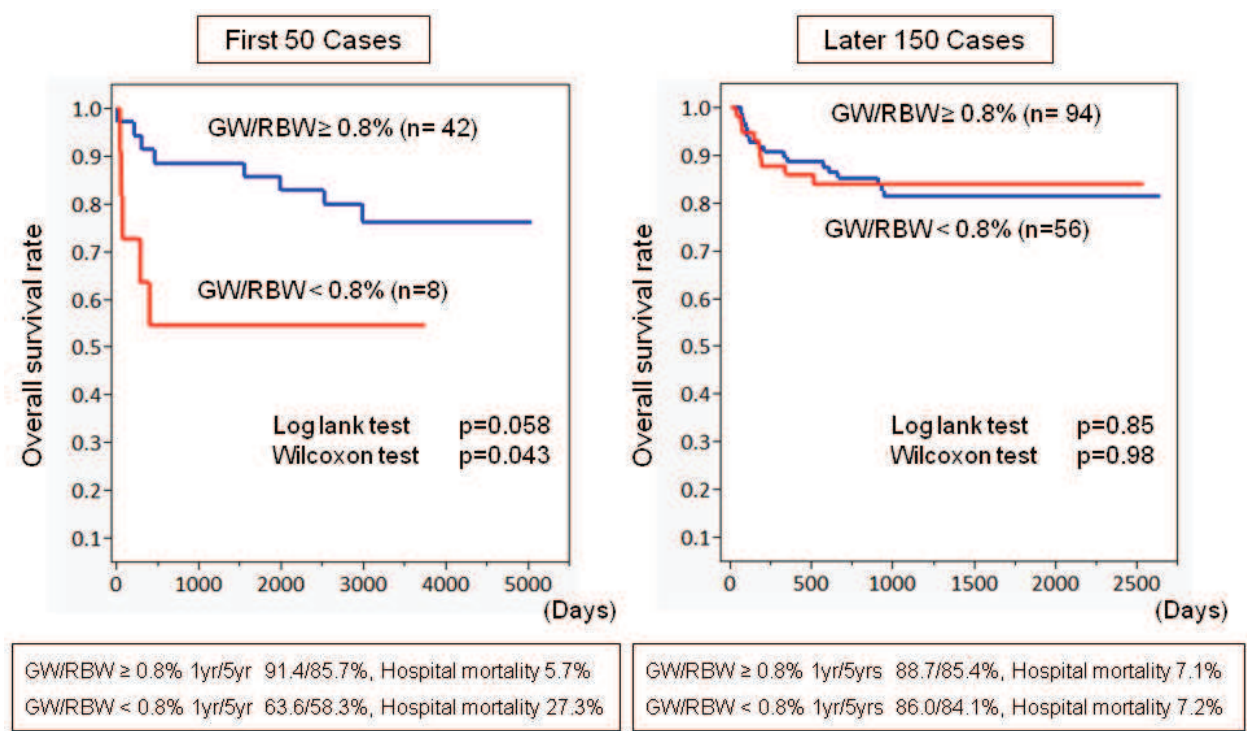


Fig. 4. Overall survival curves and hospital mortality before and after the introduction of portal modulation

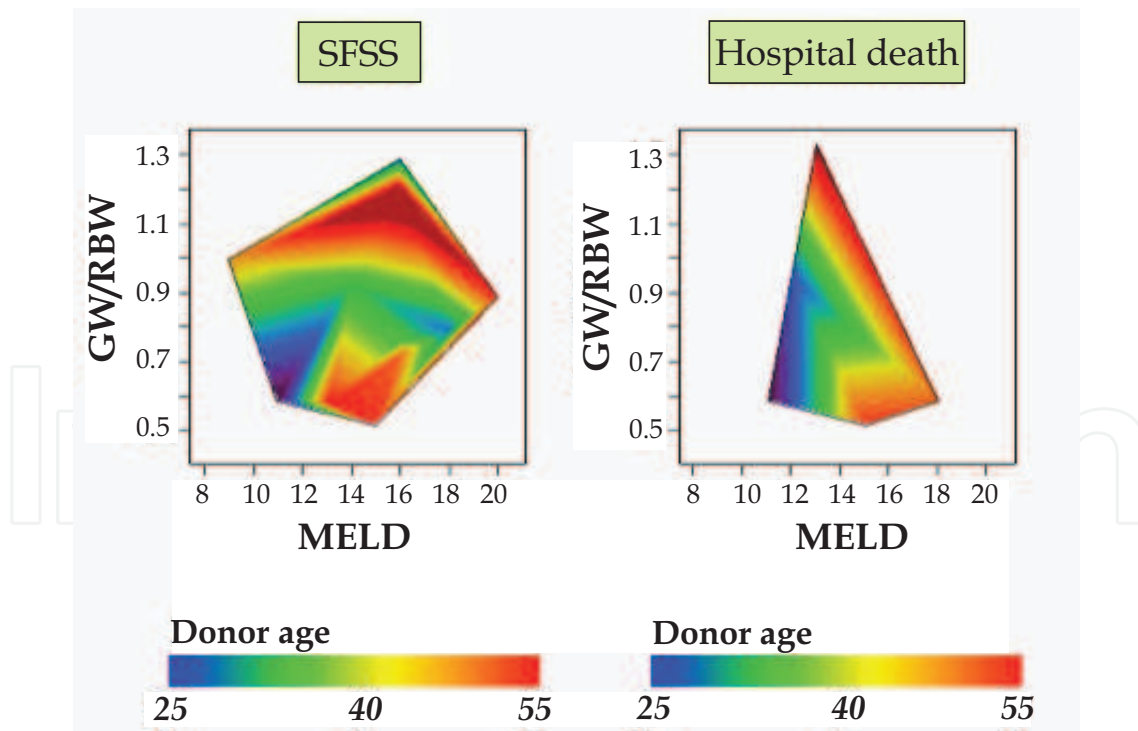


Fig. 5. Correlation between graft size, MELD, and donor age in cases of small-for-size syndrome and hospital death

To evaluate the impact of small for size graft on the outcome, we defined small-for-size syndrome as both prolonged functional cholestasis and intractable ascites. Prolonged

functional cholestasis was defined as total bilirubin >10 mg/dL at postoperative day 14, without any other cause of cholestasis. Intractable ascites was defined as daily production of ascites of more than one liter at postoperative day 14 or >500 mL at postoperative day 28. Production of ascites represented the daily volume of ascites estimated by discharge from the abdominal drain. According to this diagnostic criterion, small-for-size syndrome occurred in 21 of 200 cases (10.5%) and 5 cases had fatal outcome. Patients with the small-for-size syndrome consisted of 11 cases (22%) in the first 50 cases and 10 cases (6.7%) in the later 150 cases, respectively. Furthermore, early hospital death was noted in 16 of 200 cases (8%).

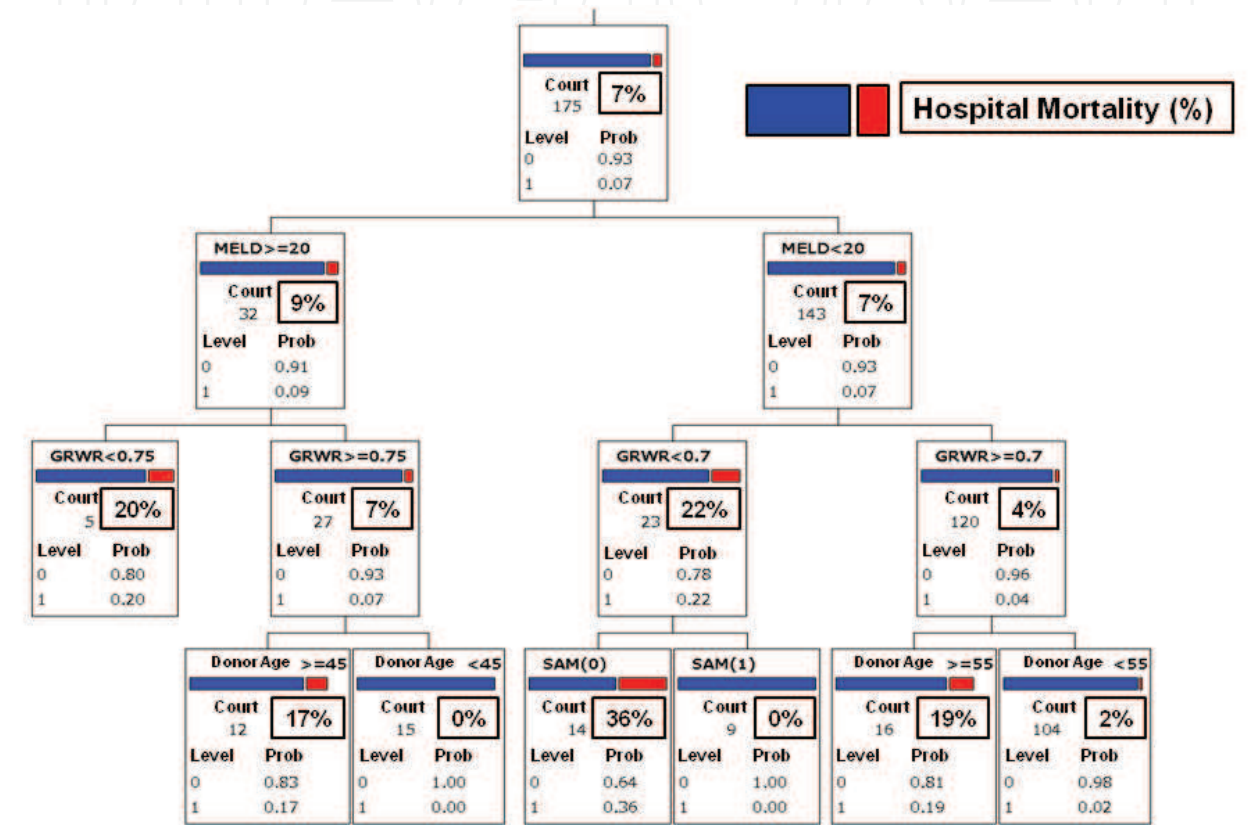


Fig. 6. Decision tree analysis of post-transplant hospital mortality (175 cases). MELD, model for end-stage liver disease; GRWR, graft weight to recipient body weight ratio; SAM, splenic artery embolization as portal modulation

The occurrence of small-for-size syndrome and hospital death depends on the specific combination of graft size, donor age, and MELD. Even using large-size graft, the use of grafts with high MELD and from old-age donors tended to result in the development of small-for-size syndrome and hospital mortality (Figure 5). These results indicated that the use if sufficient graft volume does not prevent the development of small-for-size syndrome graft, and that the incidence of this syndrome depends on other risk factors, which affect the post-transplant prognosis. Concerning the prediction of small-for-size syndrome or post-transplant prognosis, none of the analyses used could find significant risk factors. The decision tree analysis for hospital mortality indicated that the value of any one risk factor should affect the cut-off values of other risk factors (Figure 6). Thus, early graft function and hospital mortality are determined not only by graft size, but also by donor age and recipient status. Donor age and graft size should be matched to the recipient status when possible,

and when not possible, portal modulation should be considered. Splenic artery embolization could help reduce the morbidity and mortality rates, as well as increase the survival rates, and should be considered along with the other perioperative risk factors.

Variable	n	Odds ratio	P-Value
Recipient factors			
Age ≥ 54 (vs < 54 years)	78 / 72	1.54	0.59
MELD ≥ 23 (vs < 23)	24 / 126	3.66	0.001
Disease			
Cholestatic disease vs PLC	21 / 115	0.61	0.73
Acute liver failure vs PLC	14 / 115	1.39	
Donor factors			
Age ≥ 53 (vs < 53 years)	33 / 117	6.84	0.03
Graft type (Right lobe vs Left lobe graft)	80 / 70	0.47	0.44
GW/RBW < 0.68% (vs ≥ 0.68%)	26 / 124	1.41	0.72
Treatment and Operative factor			
Portal modulation	70 / 80	0.61	0.54
Blood loss ≥ 50 (vs < 50ml/kg)	101 / 49	1.90	0.61
CIT ≥ 80 (vs < 80min)	35 / 115	1.91	0.40
WIT ≥ 50 (vs < 50min)	42 / 108	1.87	0.74
Operating time ≥ 10 (vs < 10hrs)	59 / 91	3.98	0.39

Table 2. Logistic regression analysis of post-transplant hospital mortality (the later 150 cases). LC, post-necrotic liver cirrhosis; MELD, model for end-stage liver disease; GW/RBW, graft weight to recipient body weight ratio; CIT, cold ischemic time; WIT, warm ischemic time

5. Conclusion

Recently published clinical trials and basic research conducted by several groups have uncovered the mechanism of small-for-size syndrome, allowing the design and implementation of new treatment strategies. These advances have resulted in significant improvement in prognosis after living donor transplantation. Further improvement of liver transplantation and liver surgery techniques should result in better outcome of patients with small for size syndrome.

6. Acknowledgement

This work was supported by a Grant-in-Aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan

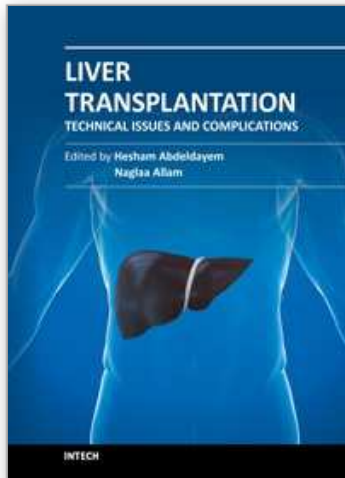
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Liver Transplantation - Technical Issues and Complications

Edited by Prof. Hesham Abdeldayem

ISBN 978-953-51-0015-7

Hard cover, 454 pages

Publisher InTech

Published online 10, February, 2012

Published in print edition February, 2012

This book covers a wide spectrum of topics including, but not limited to, the technical issues in living and deceased donor liver transplant procedures, cell and experimental liver transplantation, and the complications of liver transplantation. Some of the very important topics, such as the arterial reconstruction in living donor liver transplantation, biliary complications, and the post-transplant-lymphoproliferative disorders (PTLD), have been covered in more than one chapter.

How to reference

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Yuzo Umeda (2012). Small-for-Size Syndrome After Living Donor Liver Transplantation, Liver Transplantation - Technical Issues and Complications, Prof. Hesham Abdeldayem (Ed.), ISBN: 978-953-51-0015-7, InTech, Available from: <http://www.intechopen.com/books/liver-transplantation-technical-issues-and-complications/small-for-size-syndrome-after-living-donor-liver-transplantation>

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