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Risk Factors for Hepatic Venous Outflow Obstruction in Piggyback Liver Transplantation: The Role of Recipient's Pattern of Hepatic Veins Drainage into the Inferior Vena Cava

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The recipient's pattern of hepatic veins (HVs) drainage into the inferior vena cava (IVC) (drainage pattern, for short) may influence outflow reconstruction and thus hepatic venous outflow obstruction (HVOO) in piggyback liver transplantation (PBLT). However, no previous study has investigated this association.

Material/Methods: A retrospective analysis of 202 PBLT (2000–2016) was conducted. Based on drainage patterns, the patients were divided into Group A (common trunk of left and middle HVs), Group B (common trunk of right and middle HVs), and Group C (common trunk of 3 HVs). Patients' demographic and surgical data were compared within the 3 groups, and risk factors for HVOO were tested using a multiple logistic regression model.

Results: A chi-square test revealed a significantly higher HVOO incidence in Group 1 compared with the other groups (23.5% *vs.* 9.6% *vs.* 7.1%, p=0.047). The demographics and surgical data except angle∠AOB between the reconstructed outflow and IVC in cross-section of 3D image (∠AOB), ratio of the length of reconstructed outflow and ∠AOB (LRO/∠AOB ratio), and types of HV ligation did not differ significantly within the 3 groups. ∠AOB and LRO/∠AOB ratio were used to assess the level of anastomosis twisting and compression, respectively. Among the 3 groups, the largest ∠AOB and highest LRO/∠AOB ratio were observed in Group A and B, respectively. In addition, multivariate analysis indicated that the ∠AOB (OR=1.016, 95%CI: 1.006–1.027) and LRO/∠AOB ratio (OR=2.254, 95% CI: 1.041–5.519) were risk factors for HVOO.

Conclusions: This study demonstrated that drainage patterns were associated with HVOO. The best choice for outflow reconstruction is Group C. The patients in Group A and B were likely to develop HVOO due to anastomosis twisting and compression, respectively.

MeSH Keywords: **Hepatic Veins • Hepatic Veno-Occlusive Disease • Liver Transplantation**

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Background

The technique of orthotopic liver transplantation often has physiologic disturbance associated with the hepatectomy of the recipient's inferior vena cava (IVC). To overcome this problem, "piggyback liver transplantation" (PBLT), a technique involving the direct anastomosis of the recipient's hepatic veins with the donor's IVC without the removal of the recipient's IVC, was described by Calne in 1968 and Tzakis in 1989 [1,2].

In orthotopic liver transplantation, hepatic venous outflow obstruction (HVOO) is uncommon, as a suprahepatic cava-caval anastomosis was performed. With the use of PBLT, however, the occurrence of HVOO has increased. HVOO is a rare but lethal complication related with PBLT, and the reported that the incidences range between 1.5% and 4.6%, leading to a mortality rate of up to 23% [3–5].

In standard PBLT, to fashion an orifice for the direct anastomosis with the suprahepatic vena cava of the graft, the venoplasty of the recipient's major hepatic veins (HVs) is performed based on the patterns of hepatic veins (HVs) drainage into the IVC (drainage pattern) [2]. Different types of venoplasty may influence the anatomical relationship between the venous outflow and graft location within the recipient liver fossa, leading to the twisting or compression of the anastomosis, which are considered as major factors for HVOO [6-8]. Thus, we speculated that the recipient's drainage pattern affects the venous outflow reconstruction; therefore, hepatic venous outflow obstruction (HVOO) in standard in PBLT. The aim of this retrospective study was to evaluate the role of drainage pattern in HVOO.

Material and Methods

Study design

A retrospective multicenter study of 202 patients who received PBLT from 2000 to 2016 was conducted. None of the patients had thrombotic tendencies, such as Budd-Chiari syndrome. The indications for PBLT in these patients included hepatocellular diseases such as hepatitis B or C virus-associated liver cirrhosis in 125 cases, hepatocellular carcinoma in 65 cases, and liver metabolic disease in 12 cases. Based on the experience of Tzakis [2], all of the patients had favorable circumstances in which the large HVs are relatively normal and accessible, or at least have small cirrhotic livers.

The patients were divided into 3 groups based on the drainage patterns by preoperative 3D reconstruction. In Group A (n=136), the left and middle HVs formed a common trunk before draining into the IVC; in Group B (n=52), the right and middle HVs formed a common trunk before draining into the IVC; and in Group C (n=14), the left, middle and right HVs formed a common trunk before draining into the IVC. Table 1 compares demographic and surgical data from the groups: sex, age, angle ∠AOB between the reconstructed outflow and IVC in cross-section of 3D image (∠AOB), graft-to-recipient weight ratio (GRWR), with or without HV ligation, caliber of HV anastomosis, length of reconstructed outflow (LRO), ratio between LRO and ∠AOB (LRO/∠AOB ratio), and HVOO incidence. The measurement for ∠AOB and LRO is described in this article's section "Evaluation for the level of twisting or compression of the reconstructed outflow". The risk factors of HVOO were analyzed using multivariate analyses. All of the donors had experienced either brain death or cardiac death. The main causes of donor death were head trauma, intracerebral hemorrhage, and cerebral thrombosis. The study was conducted according to the Helsinki Declaration

Table 1. Comparison of patients' characteristics within the 3 groups.

Variable	Group A (n=136)	Group B (n=52)	Group C (n=14)	*p*
Sex, male/female	97/39	44/8	8/6	0.342
Age (years)	40.5±0.59	40.3±1.08	39.5±1.66	0.877
GRWR(%)	1.50±0.03	1.48±0.04	1.42±0.09	0.571
Caliber of HV anastomosis (mm)	35±0.76	35±1.16	38±1.67	0.520
Size of ∠AOB (°)	159.9±0.5	50.4±0.9*#	93.2±0.8*	0.000
LRO (cm)	4.4±0.29	2.9±0.18*#	3.6±0.69	0.008
LRO/∠AOB ratio	0.03±0.002	0.06±0.003*#	0.04±0.007	0.000
Ligation of HV (%)	100#	100#	0	0.000
HVOO (%)	23.5#	9.6*	7.1	0.047

* $p<0.05$ *vs.* group A; # $p<0.05$ *vs.* group C.

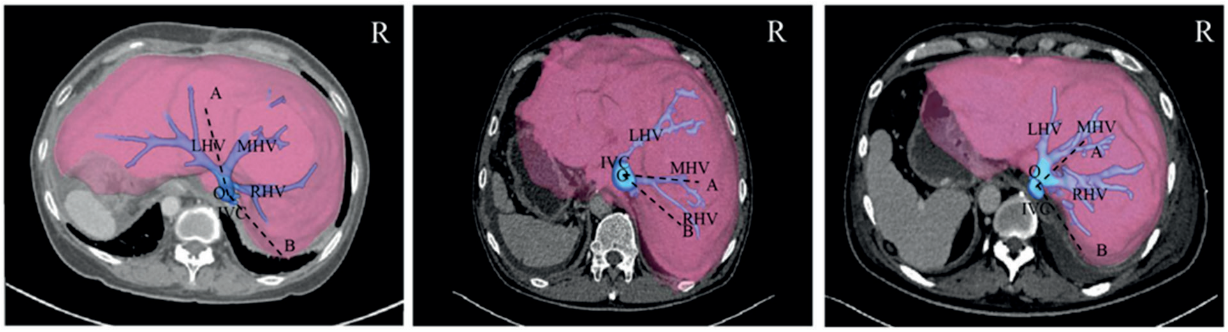

Figure 1. The measurement of the angle ∠AOB between the recipient's HVs common trunk and IVC in cross-section. LHV – the left hepatic vein of recipient; MHV – the middle hepatic vein of recipient; RHV – the right hepatic vein of recipient; IVC – the inferior vena cava of recipient; R – the right side of recipient.

of 1975 and was approved by our Institutional Review Board. All patients provided written the informed consent for use of clinical data collected from their medical records.

Evaluation for level of twisting or compression of the reconstructed venous outflow

The twisting or compression of the reconstructed venous outflow due to graft location within the recipient's liver fossa were considered as 2 major reasons for HVOO [6–8]. ∠AOB, a plane angle between the recipient's common trunk of HVs and IVC in cross-section, was drawn using a three-dimensional reconstruction of the recipient's liver, created using the IQQA®-Liver analysis system (EDDA Technology, NJ). We placed the vertex "O" on the center of the IVC, the side "OA" in the direction of common trunk of the recipient's HVs and the side "OB" in the direction of largest transverse diameter of IVC. In our study, the venous outflow reconstruction was performed by the end-to-end anastomosis of the common trunk formed by the recipient's HVs and the graft's IVC according to Tzakis's description [2], Therefore, the angle ∠AOB was used to assess the level of the venous outflow twisting (Figure 1). During the operation, LRO was the distance between the 2 confluences of recipient and graft's suprahepatic veins. Patients with longer LRO but smaller size of ∠AOB were more likely to have HVOO due to venous outflow compression. Thus, LRO/∠AOB ratio was used to assess the level of the venous outflow compression.

Technical procedure of venous outflow reconstruction in different groups

All of the recipients received end-to-end anastomosis of the recipient's venoplasty of the HVs' common trunk and the graft's suprahepatic IVC for venous outflow reconstruction in standard PBLT [2]. In Group A, we ligated the right HV and performed venoplasty comprising the left and middle HVs before the end-to-end anastomosis. In Group B, patients received ligation of the left HV and venoplasty comprising the left and middle HVs followed by end-to-end anastomosis. Group C patients received venoplasty comprising the right, middle, and left HVs with end-to-end anastomosed with the donor's IVC (Figure 2).

The classification and diagnosis of HVOO

HVOO was classified into 3 types (intraoperative, postoperative acute, and chronic HVOO).

When the blood supply of the graft was recovered during the operation, the intraoperative HVOO should show signs of liver swelling, portal hypertension, and even hypotension resulting from insufficient venous return. If these signs were relieved by adjusting the position of the graft, intraoperative HVOO was diagnosed.

For the early diagnosis of postoperative HVOO, venous outflow was regularly examined by ultrasound twice per day from PBLT to postoperative day (POD) 14, and then once per day until POD 28, and then once or twice per week during the remaining hospitalization time.

Although Doppler ultrasound is considered more sensitive and accurate than computed tomography (CT) [5], CT has some value for detection of hyperplasia and/or fibrotic changes around the anastomoses resulting in HVOO, as well as avoiding unnecessary invasive venographies, particularly when the patient's condition was suggestive for chronic HVOO.

Hepatic venography and manometry are the criterion standard for diagnosis of HVOO and are performed when HVOO is suspected according to these findings mentioned above. Finally, HVOO was confirmed if the venous outflow had a pressure gradient >3 mm Hg and/or the anastomotic stricture was >50%.

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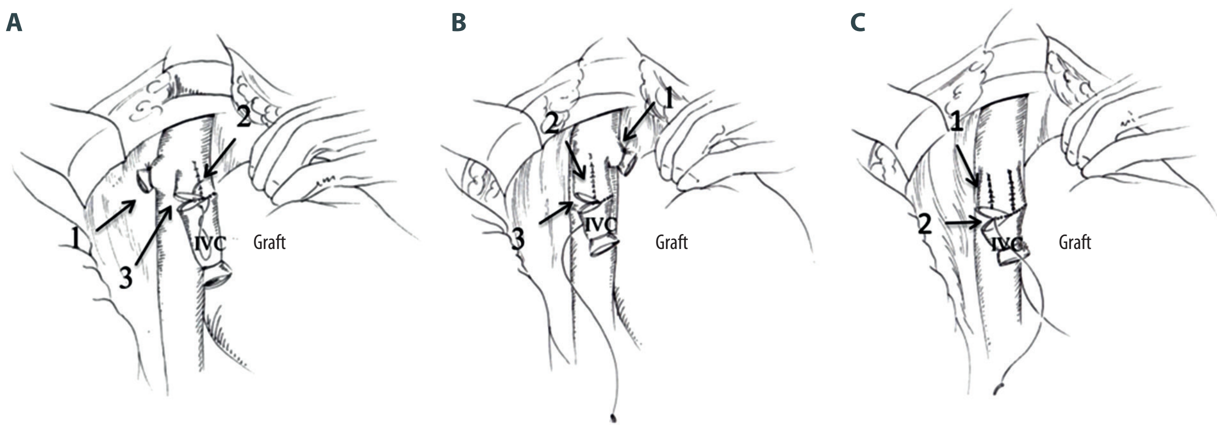

Figure 2. Scheme of venous outflow reconstruction in different drainage patterns. (**A**) the scheme in Group A: 1. ligation of right HV; 2. venoplasty comprising the left and middle HVs; 3. end-to-end anastomosis for outflow reconstruction; (**B**) the scheme in Group B: 1. ligation of left HV; 2. venoplasty comprising the right and middle HVs; 3. end-to-end anastomosis for outflow reconstruction; (**C**) the scheme in Group C: 1. venoplasty comprising the right, left and middle HVs; 2. end-to-end anastomosis for outflow reconstruction.

The postoperative acute HVOO was defined as occurrence within 1 month after the initial PBLT, and chronic HVOO was defined as that at 1 month or later after the initial PBLT.

Statistics

All data were processed by SPSS 16.0. Results are expressed as mean ± standard error or percentages. Continuous variables were tested using one-way analysis of variance followed by least significant difference *t* test within groups. Categorical variables were compared by chi-square test followed by Bonferroni post hoc test within the 3 groups. Any variable that was observed as significant ($p<0.05$) by univariate analysis was considered as a candidate for multivariate analysis by multiple logistic regression models. Differences were considered statistically significant at $p<0.05$.

Results

Patient characteristics

All of the patients were divided into 3 groups based on the recipient drainage pattern. The comparisons of patient demographics and surgical data within the 3 groups are summarized in Table1. Overall, while it remained comparatively low in Group B (9.6%) and Group C (7.1%), the incidence of HVOO increased significantly in Group A (23.5%).

Among the 136 patients in Group A, HVOO occurred in 32 cases, including 28 cases with intraoperative HVOO and 4 cases with postoperative acute HVOO. In Group B, the overall occurrence of HVOO was 9.6% (5 of 52 patients). Among the 5 cases with HVOO, 2 cases were diagnosed as intraoperative HVOO and the others were postoperative HVOO. Group C had 14 patients in total, among who only 1 had postoperative chronic HVOO after PBLT.

No significant differences were observed within the 3 groups in the comparisons of sex ratio, age, GRWR, or caliber of HV anastomosis. Unlike Group C, all of the patients in Group A and B had right or left HV ligation. In Group A, the patients had a significantly larger size of ∠AOB (159.9±0.5°) than in the other groups (Group B 50.4±0.9°, Group C 93.2±0.8°, $p=0.000$). The LRO/∠AOB ratio in Group B (0.06±0.003) significantly increased compared with Group A (0.03±0.002) and Group B (0.04±0.007) (Table1).

Risk factors for HVOO

Based on comparisons of patient characteristics, size of ∠AOB, LRO/∠AOB ratio, and with or without HV ligation, produced significant results and were considered for multivariate analysis. In multiple logistic regression models, size of ∠AOB and LRO/∠AOB ratio were both risk factors for HVOO (Table 2).

Discussion

HVOO is a type of vascular complication related to PBLT and often causes inferior outcomes of recipients. According to the drainage patterns, the patients were divided 3 groups. The overall incidence of HVOO of 18.8% in a series of 202 PBLT patients in our study was observed (Table 1). Compared with

Table 2. Multivariate Analysis of Risk Factors for HVOO.

Variable	OR	95% CI	*p*
Size of ∠AOB	1.016	1.006–1.027	0.003
LRO/∠AOB ratio	2.254	1.041–5.519	0.018

previous reports (1.5–4.6%) [3–5], the incidence in our study was much higher due to the diagnosis of intraoperative HVOO, which was ignored by the other investigators. However, we also observed a significantly higher HVOO incidence in Group A than in the other 2 groups, which was consistent with a previous study [4]. We demonstrated that drainage patterns were associated with HVOO via affecting the ∠AOB and LRO/∠AOB ratio, which has been identified by multivariate analysis as a risk factor for HVOO.

Among the 3 groups, the highest HVOO incidence occurred in Group A. The largest size of ∠AOB, one of the risk factors, was responsible for the highest HVOO incidence in this group. According to the description above (see "Material and Methods"), ∠AOB reflected the anatomical relationship between the venous outflow and IVC in the cross-section. If the size of ∠AOB was larger, the venous outflow was more likely to locate at the recipient's left side. However, the graft's center of gravity was located at the recipient's right side after transplantation. Therefore, the risk of HVOO rapidly increased with larger ∠AOB due to anastomosis twisting.

LRO/∠AOB ratio was another risk factor for HVOO, indicating that patients with longer venous outflow and smaller ∠AOB were more likely to have HVOO due to anastomosis compression. Based on the comparison of ∠AOB, the smallest ∠AOB was observed in Group B, indicating the reconstructed outflow was likely to located at the patient's right side, and in line with the graft's center of gravity. However, the highest LRO/∠AOB ratio in Group B suggested the relatively over-length venous outflow was more likely to lead to anastomosis compression for HVOO.

In addition, only 1 patient in Group C was diagnosed with postoperative chronic HVOO, with CT evidence of the associated pathological changes (hyperplasia and fibrotic changes around the anastomoses). The reasonable size of ∠AOB and LRO/∠AOB ratio was responsible for the lowest HVOO incidence in Group C.

Anastomosis stricture was reported to be a risk factor for HVOO in a previous study [6]. However, it was reported that a transversal incision (>1 cm) of the recipient HVs common trunk could provide an adequate width for venous outflow reconstruction [5]. In our study, the caliber of HV anastomosis in the 3 groups met this demand and was not considered as a risk factor for HVOO by logistic regression analysis. Theoretically, the retardation of the venous outflow from the graft would be deteriorated due to HV ligation in venoplasty. However, although HV ligation was performed in Groups A and B, we did not find this factor contributed to HVOO, using logistic regression analyzing. The communicating branches within the graft's HVs may help overcome the problem to some extent. Hyperplasia and fibrotic changes around the anastomoses were considered as risk factors for HVOO; however, it is hard to state that HVOO resulted from these pathological changes, because of the relatively small sample size of Group C.

As HVOO is likely to present with subtle clinical signs, misdiagnoses and delays in treatment often lead to deterioration in hepatic function. In addition, because of the difficulty in this anastomosis, re-operation often leads to inferior outcomes [8]. Therefore, effective prevention is needed to avoid complications. According to our findings, HVOO is of much greater concern in patterns of HVs into IVC in Groups A and B, in which the outflow tract is threatened by the possibility of anastomosis twisting or compression with graft. In our experience, techniques including the design of the anastomosis angle based on the graft's gravity center and the anterior suturing of the falciform ligament to the diaphragm in Group A would be beneficial in preventing HVOO by stabilization of graft position and orientation. Compared to the first 3 years, the incidence of HVOO in Group A decreased from 66.7% (20/30) to 11.3% (12/106) after these intraoperative preventive actions were employed. Additionally, suitable minimization of hepatic vein length in Group B was also effective in preventing HVOO, due to the comparatively low incidence of HVOO compared with Group C.

Successful treatment of recipients with HVOO depends on timely diagnosis and treatment. Based on the findings mentioned above, HVOO, particularly intraoperative type, should be alert in Group A. Once suggestive signs of intraoperative HVOO were observed, especially in Group A, adjusting the position of the graft toward the recipient's left side should be the first option. The symptomatic relief would be helpful to diagnose intraoperative HVOO and avoid delays in treatment. Postoperative HVOO can be classified into postoperative acute onset (≤1 month after surgery) and chronic postoperative onset (>1 month after transplantation) according to its onset time. Consistent with a previous study [5], we found advantages of Doppler ultrasound for detection of HVOO; however, CT has some value for chronic HVOO. Currently, interventional therapy, which allows diagnosis and therapeutic intervention in the same procedure, has been considered as a more efficient way to resolve HVOO compared with drug therapy and re-operation [9,10]. However, many previous reports showed that the patients often needed more than 1 session of interventional therapy [6,8]. Based on the relationship between the drainage patterns and HVOO, all of the patients with postoperative acute HVOO in Groups A and B received drug therapy (heparin, coumadin, and urokinase) in left recumbent position. These procedures proved successful in resolving HVOO after 1 session of interventional therapy.

Limitations

Results of our study and some previous studies are not consistent with regard to the association between HVOO and the hyperplasia and/or fibrotic changes around the anastomoses [3,7,11,12]. However, we cannot conclude that these pathologic changes were not risk factors for HVOO, due to the retrospective nature of our study and the relatively small sample size of Group C. Although conflicting results were reported on cavo-caval side-to-side or end-to-side anastomosis for outflow reconstruction, it is clear that the best-performing techniques are using the stumps of the 3 major hepatic veins to avoid HVOO in PBLT [3,13–15]. In our study, we had the same opinion on the use of the stumps of the 3 major HVs. However, we cannot state that cavo-caval side-to-side or end-to-side anastomosis technique is more effective than the other 2 types of venoplasty for outflow reconstruction, due to the lack of comparative analysis. Cavo-caval side-to-side or end-to-side anastomosis needs a complete or partial clamp of IVC temporarily and cannot completely avoid the complications related to vascular anastomosis [14]. In fact, the relatively simpler intraoperative preventions described above in Groups A and B also contributed to reduced incidence of HVOO, particularly in Group B, whose HVOO incidence did not differ significantly from Group 3.

Conclusions

Our findings demonstrate a strong association between the drainage patterns and HVOO. The best choice for outflow reconstruction is Group C. The patients in Group A and B were likely to develop HVOO due to anastomosis twisting and compression, respectively. Prevention and treatment based on the patients' drainage patterns were helpful for prevention and treatment of HVOO.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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