ORIGINAL ARTICLE

Venous outflow congestion is related to poor recurrence-free survival of living donor liver transplantation recipients with hepatocellular carcinoma – a retrospective study

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SUMMARY

This study analyzed the impact of venous outflow congestion in the liver graft on hepatocellular carcinoma recurrence in liver transplantation recipients. Hepatocellular carcinoma patients who underwent living donor liver transplantation at Samsung Medical Center between 2007 and 2018 were included. The congested volume was calculated based on 2-week post-transplantation computed tomography. Recurrence-free survival and overall survival were analyzed using the multivariable Cox proportional hazard model including the degree of venous congestion. A total of 582 patients were included. There were 232 patients (39.9%) with certain degree of congestion volume. Kaplan–Meier survival analyses showed 1-, 5-, and 10-year recurrence-free survivals of 86.0%, 72.2%, and 70.7%, respectively, and overall survivals of 91.5%, 73.4%, and 68.9%, respectively. While congestion volume per 10 cm^3 was a significant risk factor for recurrence-free survival (HR = 1.024, CI: 1.002–1.047, $P = 0.034$), there was no significant relationship with overall survival. (HR = 1.015, CI: 0.992–1.039, $P = 0.213$). Venous outflow congestion in the liver after living donor liver transplantation was related to the poor recurrence-free survival of hepatocellular carcinoma patients.

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Key words
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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies, with a high recurrence rate [1–3]. Although there have been improvements in locoregional therapies, including surgical resection, liver transplantation (LT) can offer the best patient outcome by removing the cirrhotic liver containing the malignancy. However, due to the shortage of donated organs, LT is not a universal option but living donor liver transplantation (LDLT) can be an alternative for those patients who seek LT as a treatment strategy for HCC. Since LT for HCC targets two goals, treating the cirrhotic liver and HCC, the management for those patients should also focus on the oncological perspective.

Recently, Yamashita *et al.* [4] reported that remnant liver ischemia was a prognostic factor for the cancer-specific survival of patients with colorectal liver

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metastasis after liver resection. In 2014, Suh *et al.* [5] also reported a study showing that more than 10% hepatic venous congestion of the LDLT allograft was related to increased HCC recurrence.

Living donor liver transplantation using right hemiliver without the middle hepatic vein (MHV) can be compromised by venous congestion if the outflow is not reconstructed. To avoid this, hepatic venous branches draining into the MHV can be reconstructed using various surgical methods. In some cases of reconstructed MHV, venous congestion can still occur, whether or not the MHV graft is occluded. The cutoff point of 10% suggested by Suh *et al.* is quite low and the proportion of congestion is not representative of the actual congestion volume due to the variation in total graft volume. Therefore, we designed this study to reveal the impact of venous outflow congestion on HCC in LDLT patients using the congestion volume as an indicator that can be a guide for transplantation surgeons.

Methods

The studied population consisted of adult patients who underwent their first LDLT for HCC at Samsung Medical Center between 2007 and 2018. The exclusion criteria were (i) patients who expired or experienced graft failure within 1-month post-LT and (ii) patients who did not undergo 2-week post-LT computed tomography (CT) scans.

Methods of venous reconstruction

The surgical methods and decision for reconstructing the venous outflow are illustrated in Fig. 1. Preoperatively, proportion of volumes of each hepatic veins are measured using the Volume viewer application in the AW server 3.2 (GE Healthcare, Chicago, IL, USA). When the venous territories were expected to exceed 10% of the graft volume, reconstruction was considered and the graft was anastomosed to the inferior vena cava. Venous reconstruction was performed based on the estimated proportion of the venous territory along with the width of the venous branch openings. Our center used cryopreserved iliac veins or arteries for the reconstructions but not artificial grafts. Iliac vein grafts were preferred more than those using arteries. Graft was selected by measuring the diameter of venous openings and the distance to the inferior vena cava ligament. When the reconstructed venous outflow was obstructed based on Doppler ultrasonography or CT scan, whether to perform thrombectomy or thrombolysis was decided by the clinical condition of the recipient.

Protocol of computed tomography

Computed tomography scans were obtained using one of multidetector CTs in our center (Discovery CT750 HD; GE Healthcare, Waukesha, WI, USA; Lightspeed VCT, GE Healthcare; Revolution frontier, GE Healthcare; Aquilion ONE, Canon Medical System; Somatom Definition Flash; Siemens Healthineers, Erlangen, Germany; Somatom Force; Siemens Healthineers) with the following scan parameters: slice thickness/slice interval of 1–1.25 mm for arterial and 2.5–3 mm for portal phase, 5 mm for delayed phase, 80–120 kV, rotation time of 0.5–0.6 s, and applying automatic tube current modulation. Routine quadruple phase liver CT at our institution is performed.

Enhanced scans were taken after administrating 120 mL iobitridol (Xenetic, Guerbet, Germany) or iomeprol (Iomeron, Bracco, Italy) as a contrast agent. Arterial phase was obtained with a delay of 12 s after aortal bolus tracking, with the threshold at 100 HU. Subsequent scanning was performed at 60 s for hepatic portal phase and at 80 s for delayed phase.

Data collection

The recipient data, including demographics, the underlying cause of liver disease, the model for end-stage liver disease (MELD) scores, the type and numbers of pre-LT locoregional therapies, and alpha-fetoprotein (AFP) level at the time of LT, were collected. Surgical data regarding the reconstruction of venous outflow were collected. Pathological data, including microvascular invasion, portal invasion, tumor size and number, and the Edmonson–Steiner grade were collected. The post-LT follow-up data included 30-day complications, HCC recurrence, death and date of the last follow-up, recurrence or death. The data were collected by independent investigators blinded to the final database and statistical analysis.

Venous congestion volume measurement

For evaluating whether venous outflow congestion was present in the 2-week post-LT liver graft, CTs were reviewed by a radiologist and surgeon experienced in LT. Three different phases, namely, the arterial, portal, and delayed phases, were reviewed and Hounsfield

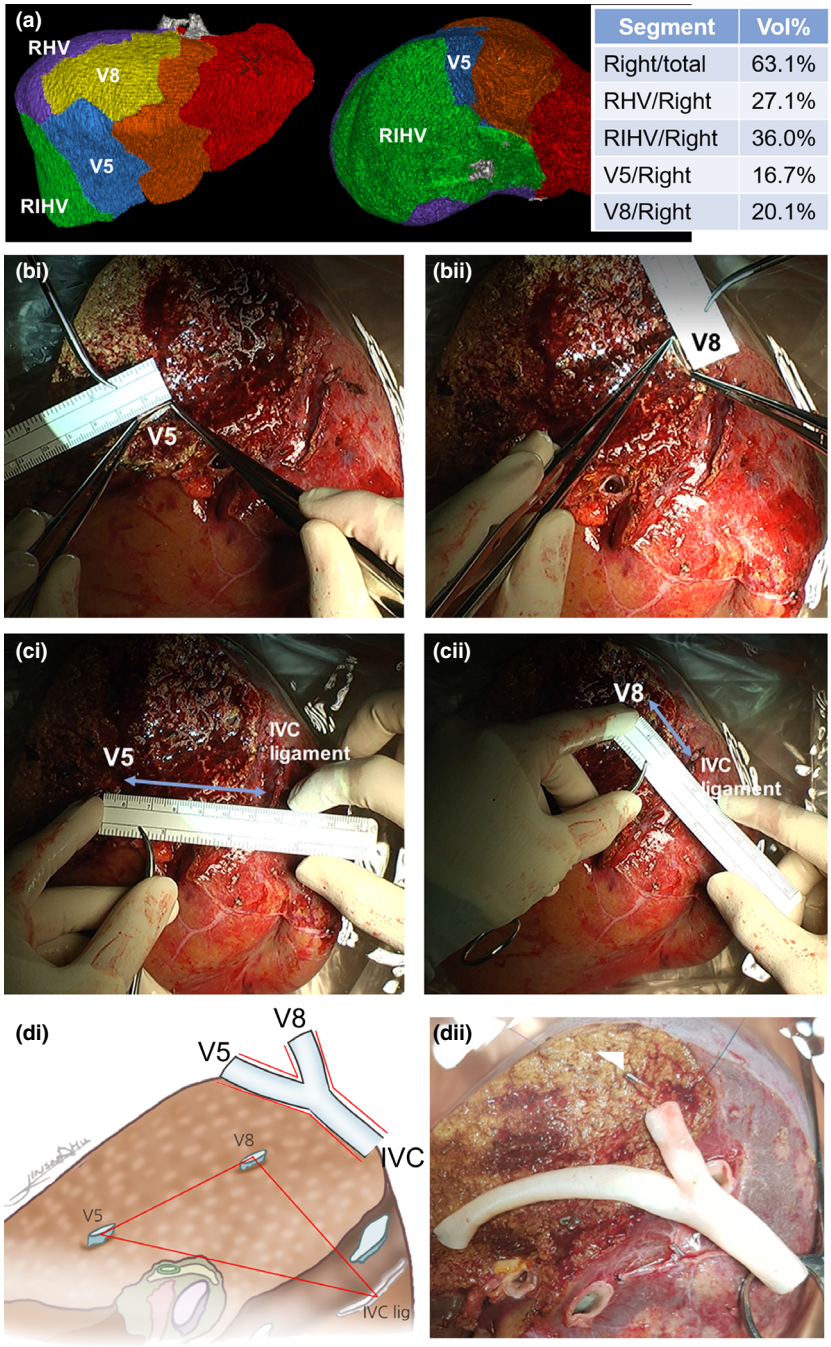

Figure 1 Venous outflow reconstruction of right hemi-liver graft. (a) The venous territories of right hemi-liver graft are calculated, preoperatively. (b) Opening of venous branches of the middle hepatic vein, namely, from segment 5 (V5) and 8 (V8) are measure. (c) The distance from the venous opening to the inferior vena cava ligament is measured. (d) By measuring the widths and lengths, cryopreserved iliac vessel grafts are anastomosed to the venous openings.

units (HU) were measured when there was a difference in enhancement between the different segments. When there was evident venous outflow congestion, the volume of the congested segments was calculated using the Centricity PACS system (GE Healthcare) and Excel (Microsoft, Redmond, WA, USA; Fig. 2).

Statistical analysis

Kaplan–Meier survival was performed for analyzing the recurrence-free survival and overall survival. Multivariable Cox proportional hazard ratio was performed for analyzing the risk factors of recurrence-free survival and

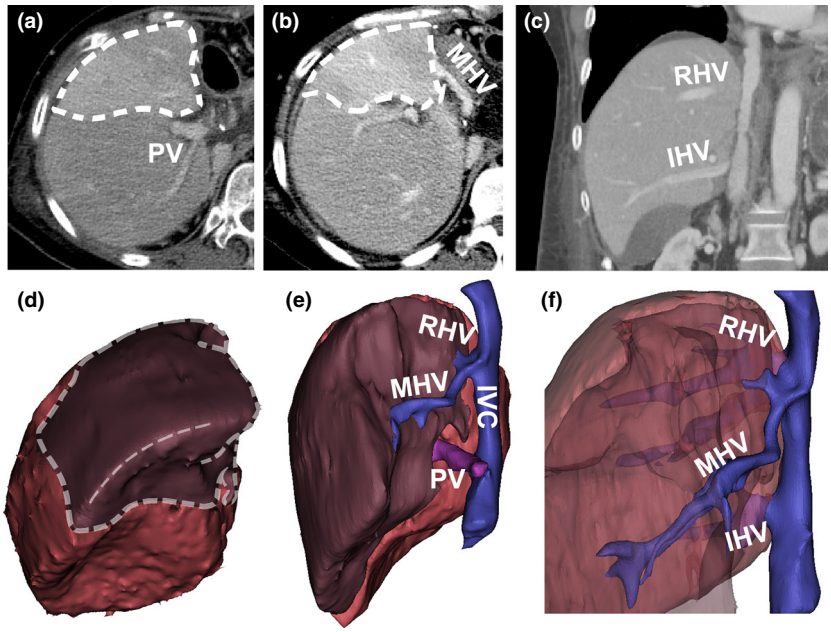

Figure 2 Two-week post-transplantation CT showing the congested area of the anterior section (a, b) with a patent portal vein and reconstructed middle hepatic vein graft. (c) The right hepatic vein and inferior hepatic vein also show patency without occlusion. (d) 3D model of the liver graft shows the congested area with significant volume (e) while the vascular structures are all patent without thrombosis. (f) The right hepatic vein and inferior hepatic vein also show patency inside the liver parenchyma.

overall survival including the volume of venous outflow congestion as continuous variable and the presence of congestion as a binary variable. The unit for congestion volume was set as 10 cm^3 as a continuous variable. The durations for recurrence and death were calculated between the date of LT to the date of specific endpoints. Variables that were clinically relevant as potential risk factor for HCC recurrence and survival after LT were included in the multivariable analysis using backward likelihood ratio. Hazard ratio curves for the association between congestion volume and both recurrence-free survival and overall survival were demonstrated.

The statistical analyses were performed using SPSS 20.0 (IBM, Chicago, IL, USA). This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2019-10-106).

Results

A total of 597 adult patients underwent LDLTs for HCC during the study period. After excluding 11 patients who expired and two patients who had deceased donor LTs for graft failure within 1-month after LT and two patients who did not have 2-week post-LT CT scans, 582 patients were finally included in the study. Except for two cases with an extended left graft with no congestion, every case was performed with a right (n = 562) or extended right graft (n = 18).

The demographical characteristics of the study patients are summarized in Table 1. Mean age and mean body weight were 54.5 ± 7.8 years and 69.0 ± 0.7 kg, respectively. Median size of the largest tumor was 2.2 cm (IQR 1.2–3.5). Median number of locoregional therapies before LT was two times (IQR 0–5) and median number of tumor on the extracted liver was 1 (IQR 1–3). There was no viable tumor on the extracted liver in 12.7% (n = 74) of patients. Microvascular invasion in portal invasion of present on histology in 45.4% (n = 264) and 6.7% (n = 39) of patients. Median graft weight was 693 g (IQR 614–785) and median graft-recipient weight ratio was 1.02% (IQR 0.87–1.19).

There were 350 patients (60.1%) with no congestion, whereas congestion volumes <100 cm^3, between 100 and 200 cm^3, between 200 and 300 cm^3, and ≥300 cm^3 were present in 58 (10.0%), 109 (18.7%), 40 (6.9%), and 25 (4.3%) patients, respectively.

Middle hepatic vein branch reconstruction and inferior hepatic vein (IHV) reconstruction were performed in 428 patients (73.5%) and 173 patients (29.7%), respectively. Regarding MHV reconstruction, both V5 and V8 were reconstructed in 194 patients (33.3%),

Table 1. Baseline characteristics of the patients included to the study

Variables	Number of patients	%
Sex (male/female)	496/86	85.2
Mean age (years)	54.5 ± 7.8	
Mean body weight (kg)	69.0 ± 10.7	
Median MELD score	11 (8–15)	
Median alpha-fetoprotein	10.5 (4.1–62.4)	
Median number of locoregional therapies	2 (0–5)	
Median size of largest tumor	2.2 (1.2–3.5)	
Median number of tumor	1 (1–3)	
No viable tumor on extracted liver	74	12.7
1	224	38.5
2	108	18.6
≥3	176	30.2
Edmonson grade		
1	47	8.1
2	368	63.2
3	73	12.5
4	2	0.3
Microvascular invasion on histology	264	45.4
Portal invasion on histology	39	6.7
Donor sex (male/female)	386/196	66.3
Median donor age (years)	29 (24–40)	
ABO incompatible	107	18.4
Median graft weight (g)	693 (614–785)	
Median graft-recipient weight ratio (%)	1.02 (0.87–1.19)	
Median warm ischemic time	83.5 (70–100)	
Median cold ischemic time	34.0 (26–44)	
Degree of congestion (cm^3)		
None	350	60.1
<100	58	10.0
100–200	109	18.7
200–300	40	6.9
≥300	25	4.3
Median	0 (0–133)	
Middle hepatic vein reconstruction	428	73.5
Occlusion of reconstructed vein	149/428	34.8
Inferior hepatic vein reconstruction	173	29.7
Occlusion of reconstructed vein	19/173	11.0
Laboratory values during 2 weeks, median		
Mean aspartate aminotransferase (U/l)	94.8 (71–135)	
Maximum aspartate aminotransferase (U/l)	308 (220–484)	
Mean alanine aminotransferase (U/l)	186 (131–301)	
Maximum alanine aminotransferase (U/l)	381.5 (248–659)	
Mean total bilirubin (mg/dl)	1.8 (1.3–2.8)	
Maximum total bilirubin (mg/dl)	4.4 (2.8–6.5)	

whereas only V5 or V8 were reconstructed in 182 patients (31.3%) and 52 patients (8.9%), respectively. In the 2-week post-LT CTs, the patency rate was 65.2% (279 out of 428) in the MHV and 89.0% (154 out of 173) in the IHV reconstructions.

There were significant differences between the normal and congested segments in different phases. The median HUs in the arterial phase were 76.4 (IQR 44.2–120.9) and 58.8 (IQR 23.5–132.4, $P < 0.001$) in normal and congested segments, respectively. The median HUs in the portal phase were 107.4 (IQR 71.5–167.3) and 92.6 (23.6–171.9, $P < 0.001$) in normal and congested segments, respectively. The median HUs in the delayed phase were 89.1 (IQR 52.3–120.1) and 104.3 (IQR 18.6–152.0, $P < 0.001$) in normal and congested segments, respectively.

Table 2. Characteristics of congested segments within the liver and pattern of recurrence

Variables	Number of patients	%
Congested segments		
Segment 5	144/232	62.1
Segment 6	8/232	3.4
Segment 7	15/232	6.5
Segment 8	194/232	83.6
Segments with recurrence		
Segment 5	27/58	46.6
Segment 6	24/58	41.4
Segment 7	26/58	44.8
Segment 8	30/58	51.7
Organ involvement of recurrence		
Single organ	112/134	83.6
Multiple organ	22/134	16.4
Recurred site		
Liver	58/134	43.3
Lung	48/134	35.8
Peritoneum	9/134	6.7
Lymph node	20/134	14.9
Bone	23/134	17.2
Mediastinum	1/134	0.7
Adrenal	4/134	3.0
Treatment for recurrence		
Surgery	30/134	22.4
Radiofrequency ablation	12/134	9.0
Transarterial chemoembolization	47/134	35.1
Radiotherapy	45/134	33.6
Sorefenib	41/134	30.6
Doxorubicin	2/134	1.5
Regorafenib	1/134	0.7
Nivolumab	1/134	0.7

Whereas the normal enhancing segments showed the highest enhancement in the portal phase with decreased enhancement in the delayed phase, the congested segments showed the highest enhancement in the delayed phase with gradually increasing patterns suggesting outflow congestion.

Table 2 shows the characteristics of the congested segments as well as the patterns of recurrence. Most of the congestion occurred in segment 5 (n = 144/232, 62.1%) or segment 8 (n = 194/232, 83.6%), and only a few patients showed congestion in segment 6 (n = 8/232, 3.4%) or segment 7 (n = 15/232, 6.5%). In contrast, recurrence within the liver showed a similar distribution between the segments. Initial recurrences mostly involved single organs (n = 112/134, 83.6%) while the liver (n = 58/134, 43.4%) was the most common organ involved in patients with recurrences.

Risk factors related to recurrence-free survival

Kaplan–Meier survival analyses showed 1-, 5-, and 10-year recurrence-free survivals of 86.0% (CI: 83.4–89.2, 459 at risk), 72.2% (CI: 68.1–76.7, 167 at risk), and 70.7% (CI: 66.4–75.7, 37 at risk), respectively, and overall survivals of 91.5% (CI: 89.5–94.1, 513 at risk), 73.4% (CI: 69.4–78.0, 190 at risk), and 68.9% (CI: 64.4–73.9, 41 at risk), respectively.

Table 3 summarizes the multivariable Cox proportional hazard model analyzing the potential risk factors for recurrence-free survival. While presence of congestion as a binary variable was not a significant factor related to recurrence-free survival (HR = 0.991, CI: 0.582–1.690, P = 0.975), congestion volume as a linear variable with a unit of 10 cm^3 (HR = 1.021, CI: 1.024–1.047, P = 0.034) was a significant risk factor along with AFP ≥ 100 ng/ml (HR = 1.555, CI: 1.071–2.256, P = 0.020), five or more locoregional therapies (HR = 1.858, CI: 1.283–2.691, P = 0.001), size of the biggest tumor ≥5 cm (HR = 2.545, CI: 1.703–3.805, P < 0.001) microvascular invasion (HR = 2.535, CI: 1.643–3.911, P = 0.001), and portal invasion (HR = 2.524, CI: 1.540–4.137, P < 0.001). Figure 3a shows the hazard ratio curve for the association between congestion volume (cm^3) and recurrence-free survival.

Risk factors related to overall survival

Table 4 shows the multivariable Cox proportional hazard model analyzing the potential risk factors for overall survival. Presence of venous outflow congestion as a binary variable (HR = 0.922, CI: 0.537–1.583, P = 0.769) as well as linear variable (HR = 1.015, CI: 0.992–1.039, P = 0.213) were not significant risk factors, whereas AFP ≥ 100 ng/mL (HR = 1.653, CI: 1.147–2.410, P = 0.007), five or more locoregional therapies (HR = 1.594, CI: 1.097–2.317, P = 0.014), size of the biggest tumor ≥5 cm (HR = 2.038, CI: 1.319–3.150, P = 0.001), and portal invasion (HR = 2.263, CI: 1.338–3.826, P = 0.002) were significant risk factors related to overall survival. Figure 3b shows the hazard ratio curve for the association between congestion volume (cm^3) and overall survival.

Discussion

Ischemia-reperfusion injury is the most studied subject in the field of transplantation. Since organs from both living donors and deceased donors face ischemic damage, ischemia-reperfusion injury is important for graft

Table 3. Multivariable Cox analyses on potential risk factors for recurrence-free survival

		Univariable			Multivariable		
Factor	No	HR	95% CI	*P*	HR	95% CI	*P*
Congestion volume (10 cm^3)		1.024	1.010–1.037	<0.001	1.024	1.002–1.047	0.034
Presence of graft congestion	232	1.871	1.330–2.631	<0.001	0.991	0.582–1.690	0.975
Male (vs. female)	496	1.917	1.059–3.469	0.032			
Age ≥50 years	459	0.646	0.445–0.938	0.022			
AFP ≥100	120	2.705	1.903–3.846	<0.001	1.555	1.071–2.256	0.020
Locoregional therapy ≥5	153	2.454	1.736–3.470	<0.001	1.858	1.283–2.691	0.001
Number of tumor ≥3	176	1.755	1.235–2.495	0.002			
Size of biggest tumor ≥5 cm	60	5.035	3.461–7.324	<0.001	2.545	1.703–3.805	<0.001
Edmonson grade ≥3	75	1.672	1.059–2.641	0.027			
Microvascular invasion	263	4.403	2.999–6.464	<0.001	2.535	1.643–3.911	0.001
Portal invasion	39	5.644	3.637–8.757	<0.001	2.524	1.540–4.137	<0.001
Warm ischemic time ≥80 min	317	1.124	0.786–1.608	0.523			
Cold ischemic time ≥35 min	269	0.780	0.546–1.114	0.172			

function and survival. Moreover, recent studies reported that the ischemic damage of organs can not only compromise the quality of the organ but can also impact cancer progression.

A study published by Suh *et al.* [5] reported increased HCC recurrence in recipients of a liver graft with a congested area of more than 10%. In 2015, Nagai *et al.* [6] reported increased HCC recurrence in patients with prolonged cold and warm ischemia time, suggesting the impact of ischemia-reperfusion injury on cancer progression. In 2018, Grat *et al.* [7] also reported increased HCC recurrence in patients with higher post-LT liver function tests. Several studies have proposed the mechanisms of hepatic ischemia-reperfusion injury promoting tumor recurrence [8–11]. The inflammatory response derived from ischemia of the liver induces a microenvironment favorable for tumor cells. Microvascular dysfunction, induction of hypoxia and the activation of pro-inflammatory networking can influence the organ microenvironment to provide an environment favorable for tumor growth and metastasis through sinusoidal damage, parenchymal necrosis, and apoptosis. Furthermore, inflammatory cascades can promote tumor cell adhesion, migration, and invasion, and tumor angiogenesis can be induced by certain signaling molecules [12].

Therefore, it is best to avoid congested or ischemic segments of the grafted liver not only for graft function but also for tumor recurrence. However, since inflow-outflow mismatch can commonly occur, especially in the anterior section of the right hemi-liver, we tried to analyze whether different degrees of congestion affected the risk of recurrence. Based on our data, congested volume of the graft were related to increased risks of recurrence with an HR of 1.024 (CI = 1.002–1.047) per 10 cm^3. The result implicates that it is always better to avoid ischemia-reperfusion injury caused by venous outflow congestion (Fig. 3a).

Recurrence in the liver occurred randomly within the liver. This finding suggests that recurrence after LT is a systemic disease and the inflammatory cytokines from ischemia-reperfusion injury were not restricted to the surrounding liver parenchyma but have a systemic impact.

A limitation of this study was that this was a retrospective study. Although we demonstrated that congestion volume had proportional relationship to the risk of recurrence, direct evidence of a provoked inflammatory cascade originating from the ischemic injury was not presented.

Nevertheless, even with some limitations, the data of our study can provide good guidance in the clinical practice of transplantation surgeons. Our study included 582 HCC patients with LDLTs. Every CT scan was reviewed and the amount of venous congestion was thoroughly calculated. Most of the variables known to be related to the prognosis of HCC, including AFP level, microvascular invasion, portal invasion, size and number of tumors, the number of locoregional therapies, and histological grades, were adjusted in a multivariable analysis [13,14]. Even after adjusting for these well-known risk factors, congestion of the liver graft showed significant relationship to recurrence.

Our study suggests the need for transplantation surgeons to perform LTs with more precision in every step of the procedure. Venous outflow congestion in the CT scan could even be observed in the graft without an

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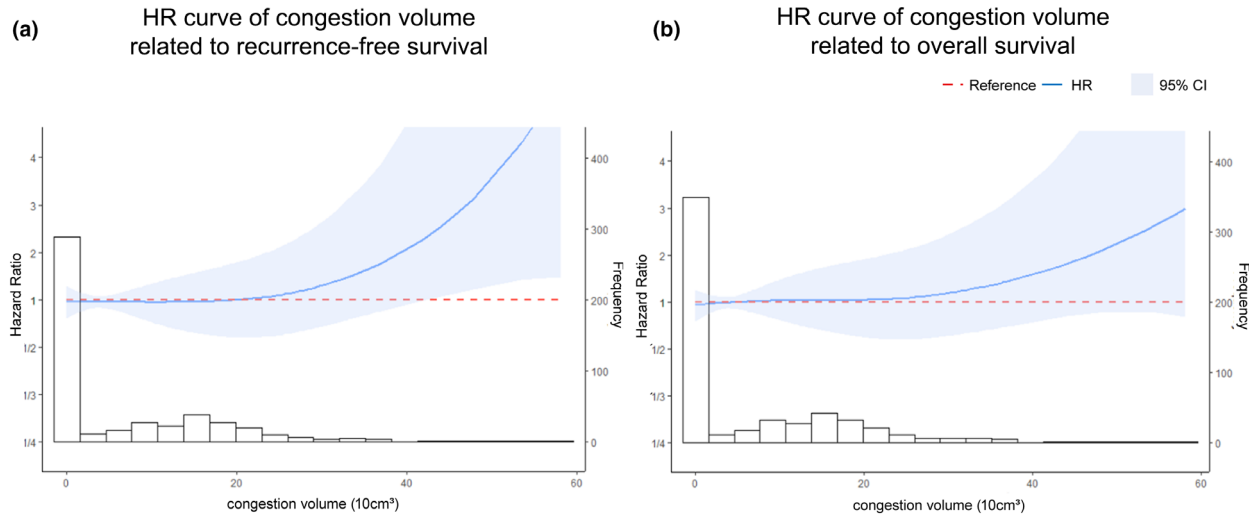

Figure 3 Hazard ratio curves for (a) the association between congestion volume (cm^3) and recurrence-free survival and (b) the association between congestion volume (cm^3) and overall survival.

Table 4. Multivariable Cox analyses on potential risk factors for overall survival

		Univariable			Multivariable		
Factor	No.	HR	95% CI	*P*	HR	95% CI	*P*
Congestion volume (10 cm^3)		1.015	1.001–1.030	0.035	1.015	0.992–1.039	0.213
Presence of graft congestion	232	1.402	0.998–1.970	0.052	0.922	0.537–1.583	0.769
Male (vs. female)	496	1.473	0.860–2.521	0.158			
Age ≥50 years	459	0.847	0.573–1.250	0.403			
AFP ≥100	120	2.065	1.439–2.963	<0.001	1.653	1.147–2.410	0.007
Locoregional therapy ≥5	153	1.788	1.246–2.565	0.002	1.594	1.097–2.317	0.014
Number of tumor ≥3	176	1.358	0.937–1.968	0.106			
Size of biggest tumor ≥5 cm	60	2.929	1.949–4.402	<0.001	2.038	1.319–3.150	0.001
Edmonson grade ≥3	75	1.560	0.938–2.595	0.087			
Microvascular invasion	263	1.870	1.326–2.637	<0.001			
Portal invasion	39	3.203	1.966–5.216	<0.001	2.263	1.338–3.826	0.002
Warm ischemic time ≥80 min	317	1.052	0.741–1.493	0.779			
Cold ischemic time ≥35 min	269	0.736	0.515–1.052	0.093			

obstruction of the reconstructed venous outflow. Although we could not analyze whether minor disturbances in the outflow were as hazardous as totally occluded outflow, the results of our study can warn surgeons not to make any disturbances in the outflow. To achieve this, proper decisions are required to select the venous branches for reconstruction. After the decision, the selection of a vascular graft with a proper width and length is required along with a proper landing site and expert surgical skills to construct a natural outflow.

Some concerns have been raised for using a right liver graft without the MHV. Evidently, an extended right hemi-liver with an MHV can be more advantageous regarding the congestion of the anterior section. However, donor safety should be prioritized in LDLT and taking the MHV to the recipient can only be considered in a limited number of cases. To overcome this problem, more effort should be made to reconstruct the outflow.

Ischemia-reperfusion injury of the liver and its impact on cancer requires more investigation. Even with the surgeon's best effort, an ischemic or congested portion of the hepatic parenchyma can occur. If therapeutic agents that can improve the negative impact of the inflammatory cascade are developed, they will not only extend the organ donation pool

but also help suppress the tumor-friendly microenvironment.

In conclusion, based on our study, venous outflow congestion in the LDLT liver graft was related to poor recurrence-free survival. Therefore, venous reconstruction of the MHV should be made with the surgeon's best effort when a significant amount of venous congestion is predicted without a reconstructed outflow.

Authorship

JR: research design, writing paper, performance of research, data analysis. JMK: research design, writing paper, performance of research, data analysis. WKJ: research design, performance of research, data analysis. G-SC: research design, performance of research, data analysis. J-WJ: research design, writing paper, performance of research.

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Conflict of interest

There are no conflicts of interest related to this study.

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