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Evaluation of safety of concomitant splenectomy in living donor liver transplantation: a retrospective study

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SUMMARY

In Asian countries, concomitant splenectomy in living donor liver transplantation (LDLT) is indicated to modulate the portal vein pressure in the small-sized graft to protect against small for size syndrome. While concomitant splenectomy in deceased donor liver transplantation is almost contraindicated based on Western Reports of increased mortality and morbidity rate due to septic complications, there are few studies about that in LDLT. So, we retrospectively investigated the clinical outcome of adult LDLT at Kyoto University Hospital from July 2010 to July 2016. We divided the patients ($n = 164$) into those with concomitant splenectomy ($n = 88$) and those without ($n = 76$). The splenectomy group showed significantly increased operative time and intraoperative blood loss ($P = 0.008$, $P = 0.0007$, respectively), and significantly higher rate of postoperative splenic vein thrombosis and cytomegalovirus infection ($P = 0.03$, $P = 0.016$, respectively). However, there were no significant differences between the two groups regarding the incidence of postoperative hemorrhage ($P = 0.06$), post-transplant bacteremia ($P = 0.38$), infection-related mortality rates ($P = 0.8$), acute rejection ($P = 0.87$), and patient and graft survival ($P = 0.66$, $P = 0.67$ respectively); finally, model for end-stage liver disease score above 30 was an independent predictor for infection-related mortality post-transplant (HR = 5.99, 95% CI = 2.15–16.67, $P = 0.001$). In conclusion, concomitant splenectomy in LDLT can be safely performed when indicated.

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Key words
concomitant splenectomy, infection, living donor liver transplantation, postoperative complications, vascular thrombosis

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Introduction

Living donor liver transplantation (LDLT) was first started in pediatric patients in 1989 in response to a severe organ shortage from deceased donor livers [1,2], then extended to adults after the first successful adult-to-adult LDLT performed in Japan in 1994 [3]. Since that time, many techniques were developed particularly in Asian countries to enable transplant surgeons to use smaller liver graft and decrease the risk to the donors. One of these techniques is the portal vein pressure (PVP) modulation through portosystemic shunts, splenic artery ligation, or splenectomy [4].

The indications of concomitant splenectomy in LDLT include severe thrombocytopenia, ABO-incompatible liver transplantation, associated splenic artery aneurysm,

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to improve the tolerance to interferon therapy for hepatitis C virus (HCV) positive recipients [5] and PVP modulation in small-sized liver graft.

The major impacts of splenectomy are the increased susceptibility to postoperative infections especially overwhelming postsplenectomy sepsis (OPSS) caused by encapsulated bacteria, vascular thrombosis, and postoperative bleeding [6,7].

Several research reports studied the risk of concomitant splenectomy in deceased donor liver transplantation (DDLT), and most of them confirmed the increased mortality and morbidity rates due to the septic complications [8–11]. While in LDLT, most of the studies reported the beneficial role of concomitant splenectomy in the small liver grafts [4,5]. So, this study aimed to re-evaluate the safety of concomitant splenectomy in LDLT.

Patients and methods

Patients

Between July 2010 and July 2016, 182 adult patients underwent LDLT at Kyoto University Hospital. We excluded 18 patients who had undergone previous splenectomy or splenic artery embolization, so a total number of 164 patients were enrolled in the study. We divided them into two groups: those with splenectomy (Sp group, $n = 88$) and those without splenectomy (Nsp group, $n = 76$). The study was approved by the ethics committee of Kyoto University and conducted in accordance with the Declaration of Helsinki.

We retrospectively reviewed the patient characteristics, the intraoperative parameters, and the postoperative outcome of all cases. The main indication for splenectomy during LDLT was to modulate the portal pressure, and other indications of splenectomy included severe thrombocytopenia, associated splenic artery aneurysm, to excise a large splenorenal shunt and HCV-positive recipients. We did not perform splenectomy for ABO-incompatible cases.

The selection criteria for the donors and recipients and the surgical procedures including the method of measurement of PVP, the splenectomy procedure, and our strategy for intentional portal pressure control have been described before [4,12–15]. Briefly, we performed splenectomy if the PVP was more than 15 mmHg after reperfusion of the liver graft regardless of what the GRWR was, as we believe that portal pressure <15 mmHg is a key for successful adult LDLT [4]. After splenectomy, all large spontaneous portosystemic shunts should be ligated to prevent the portal venous steal phenomenon unless the portal pressure became more than 15 mmHg after collateral test clamping.

The immunosuppressive regimens and management of ABO-incompatible cases have been described before [16,17]. The immunosuppressive regimen usually consisted of tacrolimus or cyclosporine and mycophenolate mofetil (MMF). ABO-incompatible cases usually received rituximab more than 2 weeks before LDLT and MMF preoperatively. If the titer of anti-A or anti-B was high (>eightfold) after rituximab administration, plasma exchange was performed.

Definition of infections

Infections were defined as proposed by the Centers for Disease Control and Prevention, and previous reports for liver transplant patients [18].

Diagnosis of bacteremia was performed by the isolation of bacteria other than the common skin commensals from a single blood culture in the presence of clinical symptoms or signs of infection, and if any common skin commensal was identified, it was considered significant only if the organism was isolated from two blood cultures and associated with clinical signs of infection.

Surgical site infections included cholangitis, peritonitis, intra-abdominal abscess, and wound infections. An abscess was defined as an infected fluid collection that was drained surgically or aspirated under ultrasound guidance, with positive bacterial culture.

Cholangitis was considered when there were one or more clinical signs of infection as fever with otherwise unexplained elevation of liver function tests associated with repeated positive bacterial culture from bile obtained by T-tube [19].

The antibacterial prophylaxis protocol involved giving ampicillin and cefotaxime for 72 h before the operation. Trimethoprim and sulfamethoxazole were administered once daily as a prophylaxis against Pneumocystis during immunosuppressant use [20]. All patients with splenectomy received Pneumococcal vaccine after the operation.

Postoperative cytomegalovirus (CMV) infection was diagnosed by the presence of postoperative cytomegalovirus pp65 antigenemia, regardless of preoperative CMV antibody-positive donors and recipients. Antiviral prophylaxis including Ganciclovir was not given except if the recipient was CMV seronegative and the donor was CMV seropositive.

Thrombotic complications

Postoperative thrombotic complications included hepatic artery, portal vein, hepatic veins, and splenic vein thrombosis. Doppler US was performed to check the blood flow in these vessels twice a day for the first 2 weeks and once a day for the next 2 weeks following liver transplant. When any suspicious findings of thrombosis or stenosis emerged, enhanced CT was performed to confirm the diagnosis.

Postoperative hemorrhage

Postoperative hemorrhage was confirmed when the patient required re-laparotomy or radiological intervention to stop bleeding, which was defined as grade C by the International Study group of liver surgery [21].

Acute rejection

Rejection was diagnosed by a liver biopsy or the clinical judgment if the biopsy was contraindicated. We graded the acute cellular rejection (ACR) according to the Banff criteria into indeterminate, mild, moderate, and severe. Recipients with ACR were treated by steroid pulse therapy which was described before [22].

Small for size syndrome

Small for size syndrome (SFSS) was defined according to Dahm *et al.* [23], which is the presence of two of the followings on three consecutive days: (bilirubin >100 μmol/l, INR >2, and encephalopathy grade 3 or 4) in a small partial liver graft [the graft recipient weight ratio (GRWR) <0.8] during the first postoperative week, after the exclusion of other causes.

Statistical analysis

Continuous variables were often non-normally distributed and expressed as medians and interquartile ranges (IQR) or as means and standard deviations. Categorical data were compared between groups using the chi-square or Fisher's exact test or while continuous data were compared using Mann–Whitney *U*-tests or Student's *t*-tests.

Cox regression analysis was performed to determine the predictive factors for the infection-related mortality post-transplant. Factors with $P < 0.2$ in the univariate analysis were further analyzed using a multivariate analysis. Hazard ratio and 95% confidence intervals (CI) were calculated for each factor.

Survival was calculated by the Kaplan–Meier method, and the difference in survival between the two groups was compared using the log-rank test. A two-sided *P* value of less than 0.05 was considered statistically significant.

All statistical analyses were performed using PRISM 7.02 (GraphPad Software Inc., La Jolla, CA, USA) and STATA 14 (Stata Corp, College Station, TX, USA).

Results

The characteristics of the recipients and donors of Sp group and Nsp group were summarized in Table 1. The median follow-up period of patients of both groups was 33 months (range between 1 and 76 months). There were no significant differences between the two groups as regards the recipient age, gender, body mass index (BMI), preoperative PT-INR, Child–Pugh score, and model for end-stage liver disease (MELD) score, history of portal vein thrombosis, donor age, gender and CMV serology, ABO blood type incompatibility, and the incidence of positive lymphocyte cross-match, except the preoperative platelet count was significantly lower in the Sp group compared to the Nsp group ($P = 0.008$), and the percentage of CMV seropositive recipients in the Sp group was significantly higher than that in the Nsp group ($P = 0.001$).

The main indication for liver transplant in the Sp group was hepatocellular carcinoma (HCC) on top of viral cirrhosis (33%), while in the Nsp groups was cholestatic diseases (37%). Concomitant splenectomy performed mainly for PVP modulation ($n = 60$), excision of splenic artery aneurysm ($n = 11$), improve tolerance to IFN therapy ($n = 8$), excision of a large splenorenal shunt ($n = 5$), and severe thrombocytopenia ($n = 4$).

Intraoperative parameters

The type of graft and graft weight were comparable in both groups, but the GRWR was lower in the Sp group than in the Nsp group but not statistically significant ($P = 0.22$). Also, the GRWR was less than 0.8 in 43% of LDLT procedures in the Sp group and in 32% in the Nsp group. The operative time, the intraoperative blood loss, and intraoperative packed RBCs transfusion were significantly higher in the splenectomy group ($P = 0.008$, $P = 0.0007$, $P = 0.01$, respectively) as shown in Table 2. There was no significant difference in the initial PVP between the two groups and the mean initial PVP was

Table 1. Patient characteristics and perioperative variables of both groups.

Variables	(Sp) Group (n = 88)	(Nsp) Group (n = 76)	P value
Recipient parameters			
Gender, n (%)			
Male	49 (56)	34 (45)	0.2
Female	39 (44)	42 (55)	
Age (year)*	56 (47–59)	53 (39–61)	0.35
BMI*	22.8 (20.68–25.15)	22.6 (20.22–24.29)	0.63
MELD score*	17 (14–20)	18.5 (13–23)	0.49
Child–Pugh score*	10 (9–12)	10 (9–12)	0.63
History of PVT	11	13	0.50
Platelet count ($\times 10^3$ μl)*	61.5 (38–83.75)	78.3 (54–104.5)	0.008
INR*	1.56 (1.28–1.76)	1.58 (1.27–1.89)	0.87
CMV seropositive (yes/no/unknown)	41/23/24	11/65/0	0.001
ABO incompatibility, n (%)			
Identical/compatible	66 (75)	55 (72)	0.65
Incompatible	22 (25)	21 (28)	
Positive LCM (n, %)	20 (23)	12 (16)	0.325
Donor parameters			
Age (year)*	45 (31–56)	47 (34–56)	0.81
Gender, (n, %)			
Male	48 (55)	38 (50)	0.639
Female	40 (45)	38 (50)	
CMV seropositive (yes/no/unknown)	55/16/17	53/11/12	0.676
Indication of LDLT			
Viral cirrhosis	22 (25%)	4 (5%)	0.001
HCC	29 (33%)	20 (26%)	
Alcohol	2 (2%)	6 (8%)	
Biliary	24 (27%)	27 (36%)	
Others	11 (13%)	19 (25%)	
Indications of splenectomy			
PVP modulation	60		
Excision of splenic artery aneurysm	11		
Improve tolerance to IFN therapy	8		
Excision of large splenorenal shunts	5		
Severe thrombocytopenia	4		
Immunosuppressive therapy (FK based/CsA based)	86/2	69/7	0.083

BMI, body mass index; MELD, model for end-stage liver disease; PVT, portal vein thrombosis; INR, international normalized ratio; CMV, cytomegalovirus; PVP, portal vein pressure; GRWR, graft recipient weight ratio; HCC, hepatocellular carcinoma; LCM, lymphocyte cross-match; FK, tacrolimus; CsA, cyclosporine.

*The data are presented as medians and interquartile ranges.

close to 20 mmHg, while the mean final PVP was below 15 mmHg in the Sp group and in the Nsp group. The effect of splenectomy in reducing the final PVP below 15 mmHg in the Sp group is illustrated in Fig 1.

Postoperative parameters

The incidence of postoperative thrombotic complications was higher in the Sp group (P = 0.03), but after we had compared each vessel individually, we noticed that the incidence of portal vein or hepatic artery thrombosis alone was not statistically different between both groups (P = 0.45, P = 0.65, respectively), while the incidence of isolated splenic vein thrombosis was significantly higher in the Sp group than in the Nsp group (P = 0.03) as shown in Table 3.

The incidence of postoperative hemorrhage was higher in the splenectomy group but not statistically significant (P = 0.06), and in only two patients in the Sp group, the source of bleeding was from the splenic bed.

There was no significant difference in both groups with regard to the incidence of acute rejection. Two patients in the Nsp group developed SFSS, while in the

Table 2. Intra-operative parameters of patients of both groups.

	(Sp) Group (n = 88)	(Nsp) Group (n = 76)	P value
Operative time (min)*	905 (786–1034)	834 (723–945)	0.008
Intra-operative blood loss (ml)*	6600 (4171–10942)	4255 (2717–7215)	0.0007
Graft weight (g)*	547 (441–650)	533 (410–711)	0.79
GRWR (%)*	0.84 (0.73–1)	0.91 (0.75–1.08)	0.22
GRWR (<0.8) (n, %)	38 (43)	24 (32)	0.15
GRWR (≥0.8) (n, %)	50 (57)	52 (68)	
Type of graft, n (%)			
Right	49 (56)	43 (57)	>0.99
Left	39 (44)	33 (43)	
Warm ischemia time (min)*	45 (37–560)	41 (35–50)	0.017
Cold ischemia time (min)*	108 (64–163)	101 (59–181)	0.81
Intra-operative PRBCs transfusion(units)*	12 (8–22)	8 (4–16)	0.014
Initial portal vein pressure (mmHg)	18.91 ± 5.44	18.57 ± 6.92	0.68
Final portal vein pressure (mmHg)	12.74 ± 3.3	12.18 ± 2.36	0.18

GRWR, graft recipient weight ratio; PRBCs, packed red blood cells.

*The data are presented as medians and interquartile ranges.

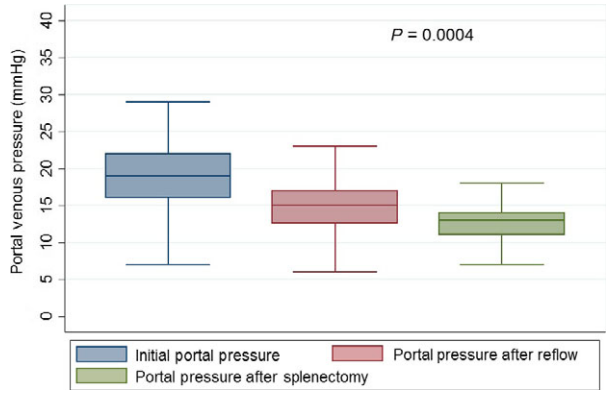

Figure 1 Portal venous pressure decreased significantly from 14.9 ± 4.42 mmHg after reflow and before splenectomy to 12.8 ± 3.29 mmHg after splenectomy (P = 0.0004).

Sp group, three patients had pancreatic leakage and they were treated conservatively.

Postoperative infections

The incidence of bacteremia within the first year post-transplant was comparable in both groups (P = 0.38), and the most common organism isolated from the Sp group was *Klebsiella pneumoniae* while in the Nsp group was *Escherichia coli*. There were no significant differences between the two groups in the incidence of intra-abdominal or liver abscess, Pneumonia, or cholangitis (P = 0.59, P = 0.66, P = 0.61, respectively) while the incidence of CMV infection was higher in the Sp group (P = 0.01) and more severe with two cases had CMV enteritis, one case had CMV hepatitis, and one case had a refractory CMV infection. Infection-related mortality within the first year post-transplant in the Sp group was 13%, while in the Nsp group was 11% and it was also not significantly different between the two groups (P = 0.8) as shown in Table 4.

Univariate and multivariate regression analyses were performed to determine the independent predictors of infection-related mortality post-transplant, and we found that MELD score above 30 was an independent predictive factor of infection-related mortality (HR = 5.99, 95% CI = 2.15–16.67, P = 0.001) as shown in Table 5.

Survival

Fourteen patients (16%) in the Sp group died within the first 3 months, 9 of them from sepsis, three from graft failure, and two patients died from intracerebral hemorrhage, while in the Nsp group six patients (8%) died, four of them due to sepsis, one patient from graft failure, and one patient died from intracerebral hemorrhage, and the difference was not statistically different between the two groups (P = 0.15) as shown in Table 3. The 1- and 3-year patient and graft survival rates were in the Sp group (79%, 73%), (78%, 72%) and in the Nsp group (82%, 79%), (85%, 77%), respectively, and the overall patient and graft survival were not significantly different between both groups (P = 0.66, P = 0.67, respectively) as shown in Figs 2 and 3.

Table 3. Postoperative outcome of patients of both groups.

Variables	(Sp) Group (n = 88)	(Nsp) Group (n = 76)	P value
Postoperative hemorrhage, n (%)	12 (14)	3 (4)	0.06
Splenic bed	2	0	0.5
Hepatic a. or portal v.	3	0	0.25
Diaphragm	2	0	0.5
Abdominal wall	3	0	0.12
Thoracic cavity	1	0	>0.9
Small bowel	1	2	0.6
Right adrenal gland	0	1	>0.9
Postoperative thrombosis, n (%)			
All	13 (15)	3 (4)	0.03
Splenic v. thrombosis	6	0	0.03
Portal v. thrombosis	5	2	0.45
Hepatic a. thrombosis	2	1	0.65
Acute rejection, n (%)	48 (55)	40 (53)	0.87
ACR	45	36	
AMR	3	4	
Graft loss within the follow-up period, n (%)	24 (27)	19 (25)	0.85
Pancreatic leak	3	0	0.24
Small for size syndrome	0	2	0.21
Hospital mortality within the first 3 months, n (%)	14 (16)	6 (8)	0.15
Sepsis	9	4	
Graft failure	3	1	
Intracerebral hemorrhage	2	1	
Hospital stay in days*	60 (47–97)	61 (44–100)	0.73

ACR, acute cellular rejection; AMR, antibody-mediated rejection.

*The data are presented as medians and interquartile ranges.

Table 4. Summary of the infectious complications.

Variables			(Sp) Group (n = 88)	(Nsp) Group (n = 76)	P value
Bacteremia within 1 year, n (%)			21 (24)	26 (34)	0.17
Intra-abdominal abscess or liver abscess, n (%)			10 (11)	6 (7)	0.59
Cholangitis, n (%)			30 (34)	23 (30)	0.61
Pneumonia, n (%)			14 (16)	10 (13)	0.66
CMV infection, n (%)			27 (31)	11 (14)	0.016
Infection-related deaths within the follow-up period, n (%)			12 (14)	8 (11)	0.64
Causative pathogens of infection-related mortality	Gram +ve	MRCNS	2	3	
		MRSA	1	1	
		Enterococcus sp.	2	0	
		Streptococcus sp.	0	0	
		Others	0	0	
	Gram −ve	*Escherichia coli*	1	1	
		Klebsiella pneumoniae	2	1	
		Pseudomonas aeruginosa	0	1	
		Enterobacter sp.	1	1	
		Others	3	0	

MRCNS, methicillin-resistant coagulase negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; CMV, cytomegalovirus.

Table 5. Univariate and multivariate Cox regression analysis for infection-related mortality

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Recipient parameters				
Age (year)	1.02 (0.98–1.06)	0.199	1.03 (0.99–1.07)	0.094
Male gender	0.83 (0.34–2.05)	0.69		
BMI (kg/m^2)	0.94 (0.83–1.07)	0.36		
MELD score ≥30	5.08 (1.87–13.87)	0.001	5.99 (2.15–16.67)	0.001
Child–Pugh Score ≥10	1.33 (0.5–3.57)	0.57		
Preoperative PLC ($\times 10^3$ µl)	0.99 (0.99–1)	0.58		
Preoperative INR	0.89 (0.48–1.67)	0.74		
Donor parameters				
Age (year)	1.01 (0.98–1.04)	0.61		
Male gender	0.46 (0.18–1.17)	0.102	0.37 (0.14–0.96)	0.042
GRWR	0.36 (0.04–3.55)	0.38		
Operative time (min)	0.99 (0.99–1.002)	0.408		
Intra-operative blood loss (l)	0.98 (0.895–1.07)	0.68		
Intra-operative blood transfusion (unit)	1.01 (0.98–1.04)	0.405		
WIT (min)	0.97 (0.93–1.014)	0.196	0.97 (0.92–1.015)	0.181
CIT (min)	0.99 (0.98–1.001)	0.112	0.99 (0.98–1.001)	0.119
Concomitant splenectomy	1.024 (0.41–2.57)	0.96		

BMI, body mass index; MELD, model for end-stage liver disease; INR, international normalized ratio; GRWR, graft recipient weight ratio; PLC, platelets count; WIT, warm ischemia time; CIT, cold ischemia time.

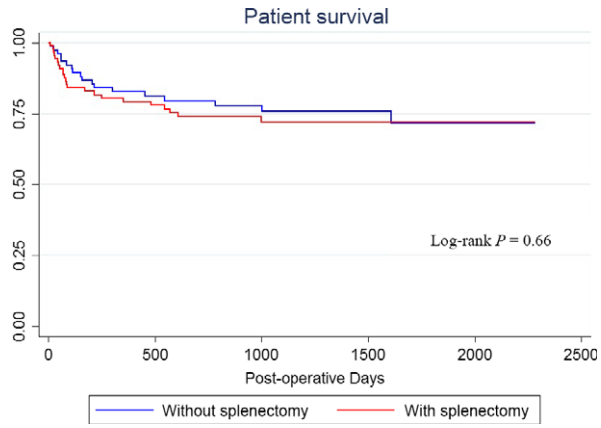

Figure 2 Patient survival based on splenectomy: with splenectomy (n = 88) and without splenectomy (n = 76). There was no statistically significant difference between both groups (P = 0.66).

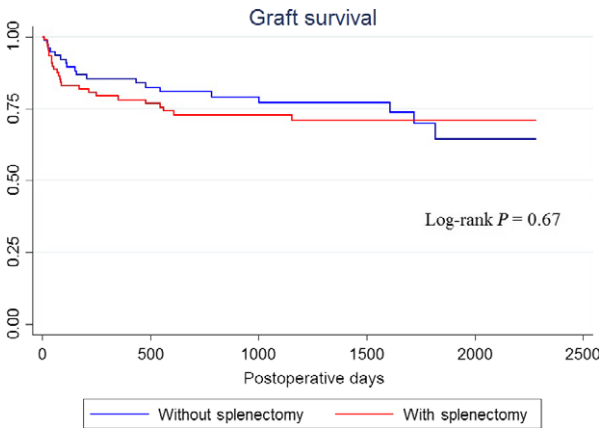

Figure 3 Graft survival based on splenectomy: with splenectomy (n = 88) and without splenectomy (n = 76). There was no statistically significant difference between both groups (P = 0.67).

Discussion

The spleen is the only organ that acts as a phagocytic filter that removes particulate antigens from the blood (innate immunity) and as a lymphoid organ that can trigger an immune response against these antigens (acquired immunity). Splenic phagocytosis particularly is more effective than the liver in removing the poorly opsonized organisms from the blood, in an antigen-nonspecific process. So, The spleen likely plays a role in the clearance of encapsulated bacteria regardless of the immune status, but it appears that the absence of the spleen is not of clinical significance in patients immunized for encapsulated bacteria prior to splenectomy [24,25].

The major postoperative complications of splenectomy include infection, thrombosis, and hemorrhage. Overwhelming postsplenectomy sepsis is the most severe

infectious complication after splenectomy that can progress from mild flulike disease to fulminant sepsis in a short time and associated with high mortality. It is usually caused by encapsulated organisms such as *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Hemophilus influenzae* type B, and the risk is highest in the first 2 years after splenectomy and with the younger age at the time of splenectomy. Different prophylactic modalities have been proved to be effective in preventing overwhelming postsplenectomy infection, such as prophylactic antibiotics and vaccination against encapsulated bacteria [7].

In case of simultaneous splenectomy in liver transplant, some reports found that it has increased the risk of septic complications and the infection-related mortality rate in DDLT [8–10], while others reported that simultaneous splenectomy in LDLT did not increase the incidence of bacterial infection, bacteremia, or infection-related mortality rate [17,26–28]. On the contrary, Wang *et al.* [29] found that simultaneous splenectomy in LDLT decreased the septic complications, but not statistically significant, and they recommended the administration of the pneumococcal vaccine to help to prevent OPSS. In our series, we did not notice any significant differences between both groups as regard the incidence of bacteremia or bacterial infection, and the infection-related mortality rates.

This difference between LDLT and DDLT as regards the incidence of septic complications after splenectomy was explained by Yoshizumi *et al.* [26] as they found that simultaneous splenectomy, in the case of whole graft, may result in insufficient portal flow, which induces liver atrophy, liver failure, and septic complications.

We noticed that the most common organism isolated from the blood cultures in the splenectomy group was encapsulated bacteria "*Klebsiella pneumoniae*", and no bacterial infection was caused by *S. pneumoniae*. While Yamashita *et al.* [30] reported the occurrence of OPSI post-LDLT caused by *S. pneumoniae* in a patient who was not vaccinated by pneumococcal vaccine either before or after the operation, this confirms the importance of prophylactic vaccination against encapsulated bacteria and the need for vaccination against *K. pneumoniae* due to the emergence of multidrug-resistant species. A recent study by Lee *et al.* [31] found that *K. pneumoniae*-derived extracellular vesicles vaccination could protect against infection by that organism through both humoral and cellular immunity. The timing of vaccination should be pretransplant or 2–6 months after LDLT if not administered before the procedure, with the timing based on the patient's degree of immunosuppression [32].

The relation between splenectomy and increased incidence of vascular thrombosis is not clear, but splenectomy may result in both thrombocytosis and an increased number of damaged circulating red cells, leading to hypercoagulability. Also blood stasis in the stump of the splenic vein results in the development of thrombosis which subsequently extends to the portal and superior mesenteric vein [33–35]. In our study, the incidence of portal vein thrombosis did not differ significantly between both groups, while the incidence of isolated splenic vein thrombosis was more in the splenectomy group which required only short-term anticoagulant therapy. We noticed that the early diagnosis and management of splenic vein thrombosis had prevented the extension of thrombosis to the portal vein. Furthermore, Wu *et al.* [36] observed that ligating the splenic vein close to the portal vein to shorten the stump may reduce the incidence of portal vein thrombosis.

Ito *et al.* [6] reported that simultaneous splenectomy increased the incidence of postoperative hemorrhage, and the most common site of bleeding was the splenectomy stump, but we did not observe increased incidence of postoperative hemorrhage significantly after splenectomy, and only in two patients, the source of bleeding was from the splenic bed. This could be explained by the fact that our technique of using vessel sealing systems and endo-stapling devices during splenectomy has been proved to be safer and associated with less bleeding [37].

Many studies found that splenectomy has decreased the incidence of acute rejection, and this may be attributed to the reduction in the antibody production [6,8,27,29], but we did not notice a statistically significant difference between both groups as regards the incidence of ACR or antibody-mediated rejection (AMR), and this is similar to what was reported by Lüsebrink *et al.* [38].

It has been reported that cytomegalovirus mononucleosis after splenectomy is a unique clinicopathological syndrome with prolonged fever and marked lymphocytosis and this is due to impaired IgM response as the spleen has a major role in producing IgM antibodies [39]. Ljungman [40] found that the CMV seropositivity of patients was a major risk for CMV infection after transplant. In our study, we noticed increased incidence and severity of CMV infection (mainly reactivation of dormant CMV infections) in the splenectomy group, and this might be attributed to either the effect of

splenectomy or the higher percentage of CMV seropositive recipients in the Sp group or both.

On the other hand, concomitant splenectomy has a beneficial role in small liver graft as it decreases the portal hyperperfusion which is one of the major causative factors of SFSS [41,42], and increases the hepatic arterial blood flow to the graft with increased oxygen supply which has a positive impact on liver regeneration [43,44]. Besides, splenectomy causes a significant increase in hepatic serotonin which plays an important role in liver regeneration as reported by Tian *et al.* [45] and Furrer *et al.* [46].

In our study, we observed that SFSS occurred only in Nsp group, and the difference was not statistically significant between both groups, while Yoshizumi *et al.* [26] found that simultaneous splenectomy decreased the risk of SFSS for transplant patients with GW-SLW ratio of 40% or less.

We found that the overall patient and graft survival were comparable between both groups, the infectious complications did not increase significantly except for CMV infection and the thrombotic complications if diagnosed early and managed properly, would not increase the patient morbidity and mortality.

IFN-free direct antiviral therapy for HCV eradication post-transplant has been proved to be safe and effective, and so splenectomy is no longer indicated in HCV recipients [47], and in ABO-incompatible liver transplant, it is not indicated at our institutions depending on previous study which reported that splenectomy does not alter the outcome of ABO-incompatible liver transplant with preoperative rituximab prophylaxis [17].

So, the main indications of concomitant splenectomy in LDLT at our institution include PVP modulation, severe thrombocytopenia, associated splenic artery aneurysm, and radical removal of a large splenorenal shunt to avoid portal flow steal phenomenon.

Unfortunately, this study has some limitations, as it is a retrospective study with a relatively small number of patients, medium-term follow-up and it reflects observation from a single center. So, a large multicenter study with long-term follow-up is needed to evaluate the safety of concomitant splenectomy in LDLT. In conclusion, concomitant splenectomy in LDLT can be safely performed when indicated, but we recommend the administration of polysaccharide vaccines for prevention of encapsulated bacterial infections prior to transplantation and short-term anticoagulant therapy post-transplant.

Authorship

AB: participated in research design, paper writing, and data analysis. YH and TK: participated in research review and in performance of research. SS, HO and SU: participated in performance of research.

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Conflict of interest

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