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# Long-Term Outcomes of Simultaneous Liver-Kidney Transplant Patients with Hepatitis B Compared to with Liver Transplant Alone

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**Background:** The number and survival rate of simultaneous liver-kidney transplant (SLKT) recipients have increased dramatically since 2002. However, the long-term effectiveness of SLKT in patients with hepatitis B is unknown.





**Material/Methods:** Forty-six patients who visited the Organ Transplant Center of the Shanghai First People's Hospital between January 2001 and May 2005 had hepatitis B virus infection and renal failure (any degree), and underwent organ transplantation: 21 patients underwent SLKT and 25 patients underwent liver transplant (LT) alone.

**Results:** The 1-, 3-, and 5-year survival rates of SLKT recipients were 90.5%, 81.0%, and 81.0%, respectively. Incidence of acute hepatic allograft rejection between SLKT recipients and LT recipients (33% vs. 16%) did not reach significance ( $P=0.170$ ). Despite higher infection rate, more prevalent hepatitis B relapse, and longer stay in the intensive care unit, SLKT recipients experienced significantly higher 1-year survival rate (90.5%) compared with LT recipients (60%,  $P=0.019$ ). Multivariate regression analysis revealed that postoperative renal failure (odds ratio (OR)=48,  $P=0.003$ ) and Risk/Injury/Failure/Loss/End-stage (RIFLE) stage (OR=8,  $P=0.012$ ) were independent risk factors for postoperative death after LT.

**Conclusions:** SLKT in patients with hepatitis B had higher early-stage infection rate, but had a higher long-term survival rate compared with the LT group. Although the incidence of postoperative hepatitis B relapse in SLKT recipients was higher, timely and reasonable treatment can ensure long-term survival of patients. Worsening RIFLE stage of recipients can predict high mortality when only given LT. SLKT might be a better choice for RIFLE stage 2 or 3 patients than LT alone.

**MeSH Keywords:** **Hepatitis B • Kidney Transplantation • Liver Transplantation**

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## Background

Since Margreiter et al. [1] successfully conducted the first simultaneous liver-kidney transplant (SLKT) in 1983 on a patient with chronic kidney allograft rejection and liver cirrhosis, this procedure has become the most effective method for the treatment of combined end-stage liver disease and renal failure. The number of patients with end-stage liver disease and renal insufficiency receiving SLKT has increased remarkably, particularly since the introduction of the model for end-stage liver disease (MELD) scoring system by the United Network for Organ Sharing (UNOS) in 2002 [2]. Statistics showed that the number of SLKT recipients in the United States has quadrupled from 1998 to 2006 [3]. In addition, the survival rate of SLKT recipients has significantly increased following the adoption of MELD [4,5].

The primary causes of end-stage liver disease are cirrhosis caused by viral hepatitis, alcoholic cirrhosis, liver cancer, and congenital liver diseases. While hepatitis C is the leading cause in Western countries, hepatitis B is the most prevalent type in China [6,7]. Epidemiological studies have shown that more than 800 million people have been infected with hepatitis B in China. Up to 10.31% of the Chinese population is hepatitis B surface antigen (HBsAg)-positive [6]. In China, up to 80% of patients with liver failure requiring liver transplant are due to hepatitis B-associated causes [8]. Relapse of hepatitis B after liver transplant can reduce the patient's probability of survival by inducing graft dysfunction, recurrence of liver cancer, and lymphatic proliferation [9,10]. A previous study reported that SLKT for hepatitis C, non-alcoholic steatosis and hepatocellular cancer could be associated with worst outcomes compared with other SLKT indications [11]. However, few studies have reported the effectiveness of SLKT and hepatitis B recurrence in hepatitis B carriers receiving SLKT. Little is known about the influence of relapse of hepatitis B on transplantation outcome.

Previous studies have compared the outcome of SLKT mainly to outcomes of liver transplant (LT) patients with normal renal function as controls [12–16], while comparison to LT patients with renal insufficiency has been largely ignored [17,18]. A comparison between SLKT recipients with hepatitis B infection and LT recipients with renal insufficiency and hepatitis B infection could provide a more objective assessment of the outcome of SLKT associated with hepatitis B. In addition, which indicators can predict the long-term outcomes of liver transplant patients still need to be assessed.

Therefore, this comparative study analyzed rates of postoperative infection, rejection, long-term survival, and relapse of hepatitis B in hepatitis B carriers receiving SLKT at the Organ Transplant Center of the Shanghai First People's Hospital.

## Material and Methods

### Patients

This was a retrospective analyses in 21 patients (male: 19, female: 2) who underwent SLKT at the Organ Transplant Center of Shanghai First People's Hospital, Shanghai Jiaotong University, between January 2001 and May 2005. Recipients of SLKT were selected based on the following criteria: 1) irreversibly compromised renal function confirmed by preoperative examination, including serum creatinine levels  $>133 \mu\text{mol/L}$  lasting for 1 month continuously; 2) high-risk factors for kidney diseases, such as diabetes and hypertension; and 3) massive proteinuria and/or requiring renal replacement therapy for more than 3 weeks. Major reasons for SLKT are presented in Table 1. Liver and kidney allografts for the same patient came from the same donor, whom was not necessarily a relative [19,20]. Donors and recipients were matched by ABO blood types according to transfusion principles. Panel reactive antibody (PRA) class I of recipients was 0–28%, and class II was 0–17%. Lymphocytotoxicity cross-match value was  $<10\%$ .

The study period also included 25 patients who underwent LT alone with renal insufficiency (preoperative serum creatinine levels  $>133 \mu\text{mol/L}$ ). Twenty-five recipients developed renal insufficiency due to hepatorenal syndrome without acute tubular necrosis and renal parenchymal disease.

This study was approved by the ethical committee of the Shanghai First People's Hospital, and written informed consent was obtained from each patient. Written consent has been obtained from all donors at the time of their donation. No donor livers were from executed prisoners. Subjects were divided into 2 groups: SLKT and LT.

### Operative indication

Criteria for SLKT: 1) end-stage liver disease and irreversible kidney failure; 2) congenital diseases involving the liver and kidney; 3) liver failure and chronic kidney disease (CKD) with  $\text{GFR} \leq 30 \text{ ml/min}$ ; 4) acute kidney injury (AKI) with creatinine levels  $\geq 176.8 \mu\text{mol/L}$  and dialysis  $\geq 8$  weeks; or 5) liver failure and CKD and biopsy demonstrating  $>30\%$  glomerulosclerosis or fibrosis [21,22].

Liver transplant indications: 1) irreversible hepatic failure or liver cancer. If there was no evidence to prove irreversible renal damage, liver transplantation alone was preferred. Whether patients with hepatorenal syndrome should undergo SLKT was controversial, and each patient was discussed. When patients with hepatorenal syndrome were on dialysis for  $<4$  weeks, liver transplant alone was performed.

**Table 1.** Causes of kidney and liver failure in 21 patients who underwent SLKT.

Causes of kidney failure	Causes of liver failure	N
Chronic glomerulonephritis	HBV/end-stage liver disease	10
Interstitial nephritis	HBV/end-stage liver disease	4
Bilateral kidney deformity	HBV/acute liver failure	1
Progressive renal fibrosis	HBV/chronic liver diseases	2
Chronic renal insufficiency (uremia stage)	HBV/post-hepatitis cirrhosis	2
Acute tubular necrosis	HBV/acute liver failure	2

SLKT – simultaneous liver-kidney transplant; HBV – hepatitis B virus.

### Observation indicators

Biochemical indicators (including serum creatinine, total bilirubin, and aspartate aminotransferase (AST) levels) were followed up for 5 years in all transplant recipients. LT patients were stratified according to the severity of AKI as described by the Risk, Injury, Failure, Loss and Endstage kidney disease (RIFLE) classification: risk, injury or failure [23]. Early- and late-stage postoperative complications, postoperative infections, rejection, and long-term survival were also recorded. Comparative analyses were conducted between SLKT and LT recipients.

### Diagnosis and treatment of acute allograft rejection

The diagnosis of acute renal allograft rejection was primarily based on recipients' clinical presentation, biochemical indicators (a 25% increase of serum creatinine levels or more), and histopathological biopsy. The diagnosis of acute hepatic allograft rejection required increases in serum AST levels and/or in total bile acids, and was confirmed by liver biopsy. Treatment of acute allograft rejection mainly relied on methylprednisolone sodium succinate pulse therapy, an increase in the dose of immunosuppressants, and/or change of types of immunosuppressive agent.

### Immunosuppressive regimen and treatment of hepatitis B relapse

The induction regimen of anti-CD25 monoclonal antibody (daclizumab or basiliximab) was prescribed to all patients. SLKT recipients received a triple maintenance therapy of calcineurin inhibitor (CNI; cyclosporine and tacrolimus), mycophenolate mofetil (MMF) and prednisolone (Pred), while LT recipients received the steroid-free regimen of CNI + MMF.

Nucleoside analogues coupled with low-dose hepatitis B immunoglobulin (HBIG) were given to prevent hepatitis B relapse. Preoperative nucleoside analogue therapy was followed by intraoperative HBIG 2000 U. Postoperative combined therapy was administered with maintenance HBIG twice per week.

Within 6 months of transplantation, hepatitis B antibody titer was maintained above 100 U/L.

### Statistical analysis

SPSS 11.5 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Survival rates of recipients and allografts were analyzed using the Kaplan-Meier and log-rank methods. Continuous data were analyzed using the Student's *t*-test, and categorical variables using the chi-square test. Multivariate analysis was conducted using logistic regression. Statistical significance was set at  $P < 0.05$ .

## Results

### Baseline characteristics

MELD scores, Child-Pugh scores, and incidence of preoperative dialysis were not significantly different between SLKT and LT recipients. However, SLKT recipients had lower eGFR ( $P=0.003$ ) and higher preoperative serum creatinine levels ( $P=0.004$ ), lower serum AST levels, and lower total serum bilirubin levels than LT recipients (Table 2).

### Survival

The average follow-up duration among the 21 SLKT recipients was 66 months. Four SLKT recipients died: 2 died due to hepatitis B relapse and graft-versus-host disease within 2 months of surgery; 1 discontinued lamivudine against medical advice and died due to hepatitis B relapse and subsequent acute liver failure 14 months after surgery; and 1 died due to systemic infection 24 months after surgery. The 17 surviving recipients demonstrated good physical conditions and graft function. Recipients had a 1-year survival rate of 90.5%, a 3-year survival rate of 81.0%, and a 5-year survival rate of 81.0% (Table 2).

The average follow-up duration among the 25 LT recipients was 46 months. Eleven recipients died (Table 3): 6 died due to

**Table 2.** Comparisons of preoperative and postoperative data between SLKT recipients and LT recipients.

	SLKT	LT	P
Age	44.6±13.5	40.8±11.9	0.334
Gender (male), n (%)	20 (95.2%)	22 (88.0%)	0.614
MELD score	30.8±7.2	29.4±8.5	0.542
Child-Pugh score	10.8±2.5	11.3±2.6	0.538
Preoperative dialysis, n (%)	4 (19.0%)	3 (12.0%)	0.686
Preoperative serum creatinine (μmol/L)	370.6±310.4	174.4±76.2	0.004
eGFR (mL/min/1.73 m <sup>2</sup> )	28.5±16.9	41.9±12.5	0.003
Preoperative total bilirubin (μmol/L)	111.6±156.6	238.3±242.6	0.039
Preoperative AST (U/L)	43.0±26.6	117.2±121.9	0.006
Immunosuppressive maintenance regimen			
CNI+MMF+Steroid, n (%)	21	0	<0.001
CNI+MMF, n (%)	0	25	<0.001
Immunosuppressant induction regimen			
Daclizumab, n (%)	10 (47.6%)	10 (40.0%)	0.604
Basiliximab, n (%)	6 (28.6%)	11 (44.0%)	0.280
Postoperative dialysis, n (%)	2 (9.5%)	1 (4.0%)	0.585
ICU stay (h)	741.5±595.0	320.7±192.8	0.005
Hospital stay (d)	68.9±34.3	31.1±25.9	<0.001
Hepatitis B relapse, n (%)*	8 (38.1%)*	1 (4.0%)*	0.007
Postoperative renal failure, n (%)	2 (9.5%)	7 (28.0%)	0.151
Early-stage infection, n (%)	8 (38.1%)	5 (20.0%)	0.175
Late-stage infection, n (%)**	4 (19.0%)	2 (11.8%)	0.672
Early-stage death, n (%)	0	8 (32.0%)	0.005
Hepatic allograft rejection, n (%)	7 (33.3%)	4 (16.0%)	0.170
Early-stage hepatic allograft rejection, n (%)	4 (19.0%)	2 (8.0%)	0.390
Late-stage hepatic allograft rejection, n (%)#	3 (14.3%)	2 (8.0%)	0.648
Hepatic allograft dysfunction, n (%)	1 (4.8%)	2 (8.0%)	1.000
Survival			
1-year survival, n (%)	19 (90.5%)	16 (64.0%)	0.036
3-year survival, n (%)	17 (81.0%)	15 (60.0%)	0.124
5-year survival, n (%)	17 (81.0%)	15 (60.0%)	0.124

\* Hepatitis B relapse: There were 18 hepatitis B surface antigen (HBsAg)-positive patients who underwent SLKT. There were 22 HBsAg-positive patients who underwent LT. Among them, 8 patients died at an early stage after operation and were excluded, and 14 were included in our analysis; \*\* late-stage infection: cases of infection, excluding patients who died within 1 month of operation.  
 # Late-stage rejection: cases of rejection, excluding patients who died within 1 month of operation. SLKT – simultaneous liver-kidney transplant; LT – liver transplant; CNI – calcineurin inhibitor; MMF – mycophenolate mofetil; ICU – intensive care unit; eGFR – estimated glomerular filtration rate; MELD – model for end-stage liver disease; AST – aspartate transaminase.

**Table 3.** Causes of death in LT recipients (n=11).

Causes	N
Fulminant hepatic failure/ renal failure	6
Primary graft dysfunction	1
Portal vein thrombosis	1
Bleeding of the inferior vena cava aneurysm	1
Tumor recurrence	2

LT – liver transplant.

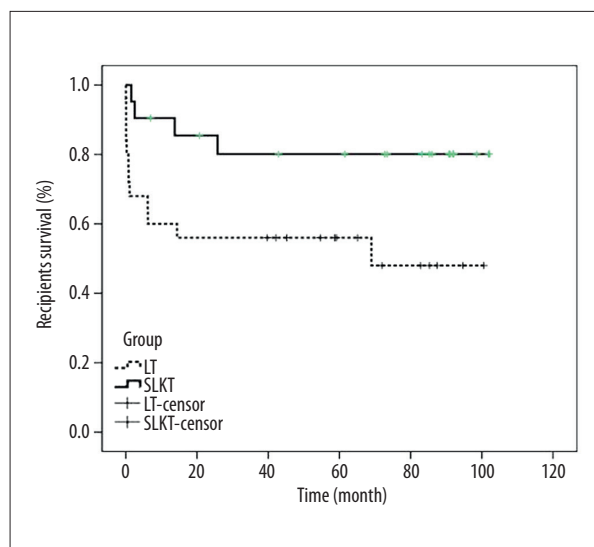
fulminant hepatic failure and subsequent renal failure within 1 month of surgery, which is defined as a clinical syndrome developing as a result of massive necrosis of liver cells or following any other cause of sudden and severe impairment of hepatic function occurring in patients without pre-existing or at least well-compensated liver disease [24]; 1 died due to primary graft dysfunction; 1 died due to portal vein thrombosis; and 1 died due to bleeding of an inferior vena cava aneurysm. Another 2 patients died due to tumor recurrence during long-term follow-up. The 14 surviving recipients demonstrated good physical conditions. Recipients had a 1-year survival rate of 60.0%, a 3-year survival rate of 56.0%, and a 5-year survival rate of 56.0% (Table 2).

Kaplan-Meier survival analysis showed that SLKT recipients had a higher survival rate than that of LT recipients ( $P=0.025$ ), particularly at 1 year post-transplant (Figure 1).

### Postoperative rejection, infection, and other complications

Seven cases of hepatic allograft rejection occurred among the SLKT recipients; 4 developed rejection within 1 month of surgery, and the others developed rejection at 12 months, 18 months, and 37 months after surgery, respectively. Liver function in all patients was restored after steroid pulse therapy. Four LT recipients developed allograft rejection (Table 2): 2 cases of allograft rejection occurred within 1 month of surgery, while the other 2 cases occurred at 6 months and 12 months of surgery, respectively.

Univariate analyses revealed that SLKT recipients had a higher but insignificant incidence of infection at an early postoperative stage, compared with LT recipients. SLKT recipients had significantly longer stay in the intensive care unit (ICU) and longer total length of hospital stay, compared with LT recipients. On the other hand, LT recipients demonstrated higher incidence of renal failure and higher mortality at an early postoperative stage compared to SLKT recipients ( $P=0.005$ ) (Table 2).



**Figure 1.** Survival curves of SLKT and LT recipients ( $P=0.025$ ).

### Postoperative hepatitis B relapse

SLKT recipients and LT recipients demonstrated sero-clearance of HBsAg within 3 months after surgery. However, SLKT recipients experienced a significantly higher rate of hepatitis B relapse (38.1%,  $P=0.007$ ) compared with LT recipients. Two patients died due to hepatitis B relapse. Steroid therapy for other subjects was discontinued, and nucleoside analogues coupled with high-dose HBIG (HBIG 20 000 U/d $\times$ 14d) were given. Following the treatment, the patients had serologic hepatitis B virus (HBV) DNA test results that showed undetectable levels of HBV (Table 4).

### Risk factors for mortality

Risk factors for high mortality (32%) at an early stage after LT were analyzed using univariate and multivariate analyses. According to univariate analyses (Table 5), patients who died at an early stage after surgery had significantly higher preoperative serum creatinine levels ( $239.5\pm 107.7$   $\mu\text{mol/L}$ ) than survivors ( $146.0\pm 21.6$   $\mu\text{mol/L}$ ), and had significantly lower eGFR levels ( $30.8\pm 12.7$  mL/min/1.73  $\text{m}^2$ ) than survivors ( $47.1\pm 8.7$  mL/min/1.73  $\text{m}^2$ ). The early death recipients after LT had higher RIFLE stage than survivors (75% vs. 11.8,  $P=0.004$ ). Compared with survivors, patients who died during the study had significantly higher preoperative MELD scores and Child-Pugh scores. In addition, a higher incidence rate of postoperative renal failure (24%) was associated with mortality compared with that of survivors (4%,  $P=0.001$ ). Multivariate analysis revealed that postoperative renal failure ( $P=0.003$ ; OR 48; 95%CI: 3.65–631.76) and higher RIFLE stage ( $P=0.012$ , OR 8; 95%CI: 1.56–38.22) were independent risk factors for mortality after liver transplant (Table 6).

**Table 4.** Characteristics of HBV relapse and prognosis.

N	Age	Sex	Date of surgery	Date of relapse	Causes of relapse	Treatment	Prognosis
1	58	M	2002-6-24	2005-1-31	YMDD mutation	Discontinued steroid; HBIG+ Adefovir + Lamivudine	HBVDNA(-) HBSAg(-)
2	48	M	2003-4-20	2004-10-22	YMDD mutation	Discontinued steroid; HBIG+Adefovir + Lamivudine	HBVDNA(-) HBSAg(-)
3	57	M	2003-7-2	2004-2-9	YMDD/YVDD mutation	Discontinued steroid; HBIG + Adefovir + Lamivudine	HBVDNA(-) HBSAg(+)
4	49	M	2003-6-25	2004-8-9	YMDD mutation	Discontinued steroid; HBIG+ Adefovir + Lamivudine	HBVDNA(-) HBSAg(-)
5	57	M	2002-12-24	2004-2-9	Self-discontinued medicine	Discontinued steroid; HBIG + Lamivudine	Death HBVDNA(+)
6	26	M	2003-12-24	2004-2-1	YMDD mutation	Discontinued steroid; HBIG+ Adefovir + Lamivudine	HBVDNA(-) HBSAg(-)
7	39	M	2001-2-16	2003-4-17	Self-discontinued medicine	Discontinued steroid; HBIG+Lamivudine	Death HBVDNA(+)
8	35	M	2003-12-15	2005-6-25	YMDD/YVDD mutation	Discontinued steroid; HBIG + Adefovir + Lamivudine	HBVDNA(-) HBSAg(+)

M – male; HBVDNA – hepatitis B virus DNA; HBSAg – hepatitis B surface antigen; HBIG – hepatitis B immunoglobulins; YMDD – lamivudine-resistant mutant; YVDD – lamivudine-resistant mutant.

**Table 5.** Risk factor for deaths in LT recipients (univariate analysis).

	Early-stage deaths (8)	Survivors (17)	P
Age	48.3±8.0	50.0±13.0	0.730
Gender (male), n (%)	7 (28.0%*)	15 (60.0%*)	1.000
MELD score	37.3±4.5	25.6±7.4	<0.001
Child-pugh score	13.6±1.5	10.2±2.2	0.001
eGFR	30.8±12.7	47.1±8.7	0.001
RIFLE stage 2 or 3, n (%)	6 (75.0%)	2 (11.8%)	0.004
Preoperative serum creatinine	239.5±107.7	146.0±21.6	0.044
Postoperative renal failure, n (%)	6 (24.0%*)	1 (4.0%*)	0.001

\* Percentage among all LT recipients. LT – liver transplant; eGFR – estimated glomerular filtration rate; MELD – model for end-stage liver disease; RIFLE – risk/injury/failure/loss/end-stage.

## Discussion

The effectiveness of SLKT in patients with hepatitis viral infection had not been thoroughly examined previously. In Western countries, hepatitis C virus is the primary cause of end-stage liver disease and subsequently renal impairment. Hepatitis C

carriers who received SLKT have demonstrated a 5-year survival rate of 68% [9]. However, in Asian countries, including China, most liver transplant recipients are hepatitis B virus carriers, in whom the outcome of SLKT is less understood. This study reported the largest number of hepatitis B patients receiving SLKT, in which the 1-, 3-, and 5-year survival rates were

**Table 6.** Multivariate analysis of mortality in LT recipients.

	<i>P</i>	OR (95%CI)
Postoperative renal failure	0.003	48 (3.647–631.76)
RIFLE 2 stage or 3 stage	0.012	8 (1.557–38.221)

LT – liver transplant; OR – odds ratio; 95%CI – 95% confidence interval; RIFLE – risk, injury, failure, loss of kidney function and end-stage kidney disease.

90.5%, 81.0%, and 81.0%, respectively. Our results revealed good prognosis of SLKT in hepatitis B carriers. Singal et al. have reported that SLKT for hepatitis C, non-alcoholic steatosis and hepatocellular cancer could be associated with worst outcomes compared with other SLKT indications [11]; however, they did not include patients with hepatitis B, which is the most common indication for liver transplantation due to liver failure in China [8].

SLKT recipients had significantly higher 1-year survival rate (90.5%), compared with LT recipients with hepatitis B infection and renal failure. This finding suggested that SLKT was effective in improving the survival rate of transplant recipients with renal insufficiency. Compared with LT alone, SLKT was associated with significantly longer ICU stay, longer total hospital stay, and higher incidence of postoperative early-stage infection (38.1% vs. 20%), which might be related to the greater surgical trauma and higher incidence of complications. In addition, the healthcare system in China requires that the patients are completely symptom-free at discharge, which could explain, at least in part, this longer hospital stay. The incidence of acute allograft rejection between SLKT recipients (33.3%) and LT recipients (16%) did not reach statistical significance, suggesting that SLKT failed to decrease the incidence of acute hepatic allograft rejection. These results are comparable with previous studies, but this comparison should be made with caution since these previous studies evaluated patients without hepatitis B virus infection [12,14–16]. High mortality was observed in the LT group, which could be attributable to the fact that these patients were with kidney dysfunction, as shown by the multivariate analysis. In addition, even if the MELD score was similar between the 2 groups, creatinine and bilirubin levels were higher in the LT group, which could be another part of the reason for the high mortality observed in this group. Six patients in the LT group died from fulminant hepatic failure. HBV relapse might be a cause of fulminant hepatic failure [25]. In addition, some other articles have reported a mortality rate from fulminant hepatic failure as high as 90% after transplantation [26,27]. A number of factors may also be associated with death after liver transplantation, including infections and rejection [28]. A previous study

showed that primary liver graft dysfunction could predict kidney failure [29], but the present study was not designed to address this relationship.

There have been few reports on hepatitis B relapse in SLKT recipients. Our study revealed that SLKT was associated with a higher rate of hepatitis B recurrence than LT (38.1% vs. 4%). This finding might be due to the stronger and longer immunosuppressive therapy, particularly long-term steroids, administered to SLKT recipients compared with steroid-free treatment for LT recipients. The use of steroids has been reported as a risk factor for hepatitis B relapse [10] and for poor survival and hepatitis C relapse [30]. Glucocorticoids can directly stimulate an enhancer region and a glucocorticoid response element in hepatitis B virus DNA, thereby inducing viral transcription. Glucocorticoid administration also suppresses the immune response by reducing the HBV-specific cytotoxic T cell response, and therefore HBV-DNA titer increases during glucocorticoid treatment [31]. Alternatively, SLKT recipients' higher hepatitis B relapse rate might be related to the effect of double transplantation on recipients' immune function. Several previous studies have indicated that HBV can influence the survival of hepatic and renal allografts and lead to fulminant hepatic failure and renal allograft dysfunction [32,33]. However, 2 subjects in our study died due to hepatic failure; they discontinued anti-HBV medicine against medical advice and died due to fulminant hepatic failure. Renal allograft rejection or dysfunction did not increase in the remaining patients. For the 6 SLKT recipients with hepatitis B relapse, hormone therapy was discontinued and replaced by nucleoside analogues and high-dose HBIG (20 000 U/d×14d) immediately after the relapse. Therefore, SLKT recipients with HBV infection should be advised of the risks for hepatitis B relapse. Reasonable treatment can achieve HBV-DNA sero-clearance in patients with hepatitis B relapse without affecting long-term survival.

Criteria for SLKT for potential LT recipients with renal insufficiency are still unclear [17,18]. According to the study by Hanish et al. [5] on transplant recipients with dialysis history, SLKT generates better outcome than single kidney transplantation, liver transplantation followed by dialysis, or staged liver and kidney transplantation. Haad et al. [34] and Xing et al. [35] reached similar conclusions. In the present study, LT recipients with renal insufficiency had higher mortality at an early stage after surgery than SLKT recipients (LT vs. SLKT: 32% vs. 0%). Risk factors for death in LT recipients included lower eGFR and higher RIFLE stage, preoperative serum creatinine levels, MELD score, Child-Pugh score, and postoperative renal failure. Although GFR is considered the best estimate of renal function than serum creatinine levels, GFR was not an independent risk factor for postoperative deaths. Therefore, a GFR less than 30 ml/min is not enough to qualify for SLKT. Postoperative renal failure (OR=48) and RIFLE stage (OR=8) among LT recipients

were an independent risk factor for postoperative deaths. It is reported that RIFLE criteria has been shown to predict clinical outcomes with a progressive increase in mortality with worsening RIFLE class [36,37]. Therefore, patients who might inevitably develop postoperative renal failure or be in need of dialysis should opt for SLKT when possible. It is essential that patients with liver failure with worsening RIFLE class should be considered for SLKT.

The present study has some limitations. Indeed, this was a retrospective study that suffers from all the limitations inherent to this type of study. Furthermore, these patients were from a single center, and the sample size was relatively small. The small number of death events in the SLKT group (4/21) prevented a multivariate analysis in this group. Larger multi-center studies should be performed to improve the conclusions of the present study.

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## Conclusions

Despite longer hospital stay and higher infection rate at an early stage after surgery, SLKT demonstrated satisfactory long-term survival rates in patients with hepatitis B infection. Despite a higher rate of hepatitis B relapse following SLKT, timely and reasonable treatments were able to prevent hepatitis B relapse from affecting long-term prognosis. Therefore, SLKT can achieve good long-term outcomes in patients with hepatitis B, end-stage liver disease, and renal insufficiency. For LT recipients with renal failure, postoperative renal failure and RIFLE stage were independent risk factors for postoperative deaths. Worsening RIFLE stage of recipients can predict high mortality in LT alone.

## Conflict of interest

The authors declare that they have no conflict of interests.



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