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Receiving Hypertensive Donor Grafts Is Associated with Inferior Prognosis in Simultaneous Liver-Kidney Transplantation Recipients

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Background: The impact of hypertensive (HTN) donor grafts on the prognosis of simultaneous liver-kidney transplantation (SLKT) patient is not known, and an applicable risk scoring system for SLKT patient survival is lacking. This study aimed to evaluate the impact of donor HTN on patient survival of SLKT recipients and to identify independent risk factors.

Material/Methods: Data from 3844 adult SLKT recipients receiving deceased donor grafts from March 2002 to December 2014 in the Scientific Registry of Transplant Recipients (SRTR) database were retrospectively analyzed. Kaplan-Meier analysis was used to compare patient and graft survival. Multivariate Cox proportional hazard models were built to identify independent risk factors associated with patient and graft survival.





Results: SLKT patients receiving HTN donor grafts had significantly shorter 5-year patient survival and kidney graft survival rates than did those receiving non-HTN donor grafts (50.1% vs. 63.2%, $p < 0.0001$ and 45.4% vs. 67.8%, $p < 0.0001$, respectively). Multivariate analysis identified HTN donor, donor age, donation after cardiac death, cold ischemia time, recipient age, recipient condition at transplant, recipient hepatitis C infection, need for life support, and recipient pre-transplant albumin level as independent risk factors associated with inferior patient survival in SLKT recipients. A risk scoring model that predicted excellent stratification of prognostic subgroups was established (AUC, 0.762; 95% CI, 0.739–0.785).

Conclusions: An SLKT patient receiving a graft from an HTN donor has an inferior prognosis. A risk scoring system applicable to patient survival in SLKT recipients was developed.

MeSH Keywords: **Donor Selection • Graft Survival • Hypertension • Kidney Transplantation • Liver Transplantation • Survival**

Abbreviations: **HTN** – hypertensive; **SLKT** – simultaneous liver-kidney transplantation; **SRTR** – Scientific Registry of Transplant Recipients; **DCD** – donation after cardiac death; **DBD** – donation after brain death; **CIT** – cold ischemia time; **MELD** – model for end-stage liver disease; **UNOS** – United Network for Organ Sharing; **PH** – potential of hydrogen; **ICU** – intensive care unit; **HCV** – hepatitis C virus; **BMI** – body mass index; **HCC** – hepatocellular carcinoma; **ROC** – receiver operating characteristic; **AUC** – area under curve; **HR** – hazard ratio; **CI** – confidence interval

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Background

Simultaneous liver-kidney transplantation (SLKT) is effective for treating patients with end-stage liver disease combined with acute or chronic renal insufficiency [1,2]. During the past 15 years, the use of SLKT has obviously increased with the utilization of the model for end-stage liver disease (MELD) scoring system [3–5]. Because the number of patients needing to be transplanted far exceeds the availability of donor organs [6], reasonable use of scarce organs and evaluating donor-associated risk indexes of patient prognosis post-transplantation become quite important in clinical practice. It is well known that hypertension is a common chronic disease worldwide; previous reports suggested a 28–30% percent prevalence of hypertension in the 18-year-old and older population of the United States [7–9]. Therefore, some organ donors have had a history of hypertension. In addition, in recent years, researchers have noticed the impact of using grafts from hypertensive (HTN) donors on patient outcomes in liver transplantation and kidney transplantation.

Several studies have evaluated the effect of HTN donors on the outcomes of kidney transplantation. It has been demonstrated that a history of donor hypertension was associated with an increased risk of poor survival in kidney transplantation recipients [10,11]. In parallel with these findings, there are also studies [12,13] reporting that having a donor with hypertension is a poor prognostic factor for survival of liver transplantation recipients. However, the effects of HTN donors on the survival outcomes of SLKT patients are not known to date. Given that the number of SLKT procedures is increasing and 5-year patient survival is not high, there has been great interest in identifying factors that predict poor outcome. Prior studies [14–16] utilizing the United Network for Organ Sharing (UNOS) database have reported some independent risk factors associated with patient survival after SLKT, but they concluded that the risk factors were inconsistent. Evaluating patient prognosis before SLKT is meaningful to surgeons as well as patients. However, an applicable risk scoring system for SLKT patient survival is currently lacking in clinical practice.

In the present study, we analyzed the SLKT data from March 2002 to December 2014 from the Scientific Registry of Transplant Recipients (SRTR) database. This large organ transplantation registry in the United States was used to compare the patient survival outcomes for SLKT using HTN donors vs. survival in patients with non-HTN donors. Additionally, we sought to find factors associated with poor outcomes after SLKT, and we attempted to develop a clinical risk scoring system applicable for SLKT patient survival.

Material and Methods

Patient population

This study was a retrospective analysis of data from the SRTR database. The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere [17]. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors. The present study was reviewed and approved by the Ethics Committee of Sun Yat-sen University. Adult patients (18 years and older) who underwent SLKT with grafts from deceased donors between March 2002 and December 2014 in the United States were evaluated in this study. Patients undergoing a previous transplant or being transplanted with other organs were excluded. Finally, 3844 SLKT adult patients were enrolled in the analysis. The process of study cohort selection is shown in Supplementary Figure 1. Pre-transplant variables of the 3844 SLKT patients were evaluated in this study. The variables for which missing data were >10% (such as donor PH missing 11.2% and warm ischemia time for the liver missing 22.3%) were excluded from the analysis.

Patient survival was defined as the time from transplantation to death. Liver allograft survival was considered as being from the time of primary transplantation to graft loss. Kidney allograft survival was considered as being from the time of primary transplantation to the initiation of dialysis or re-transplantation. An HTN donor was identified in the SRTR data set by the code “donor history of hypertension=yes”. Patients in the HTN donor group and non-HTN donor group were compared for the following donor characteristics: age, cause of death, history of diabetes, donor type (DBD or DCD), highest creatinine level pre-transplant, expanded criteria donor kidney, cold ischemia time (CIT) for the liver, and CIT for the kidney. They were also compared for the following recipient characteristics: age, sex, medical condition before transplantation (not in hospital, in hospital, or in ICU), HCV status, need for life support, level of albumin before transplantation, diagnosis (HCC or no HCC), ascites, hepatic encephalopathy, dialysis, race, and MELD score.

Statistical analysis

The clinical and demographic characteristics of the 2 groups are presented as frequencies and proportions (categorical variables) or as the mean \pm standard deviation (continuous variables). Chi-square test or *t* test was used to compare the difference between the HTN donor group and non-HTN donor group. Transforming from continuous variables (donor age,

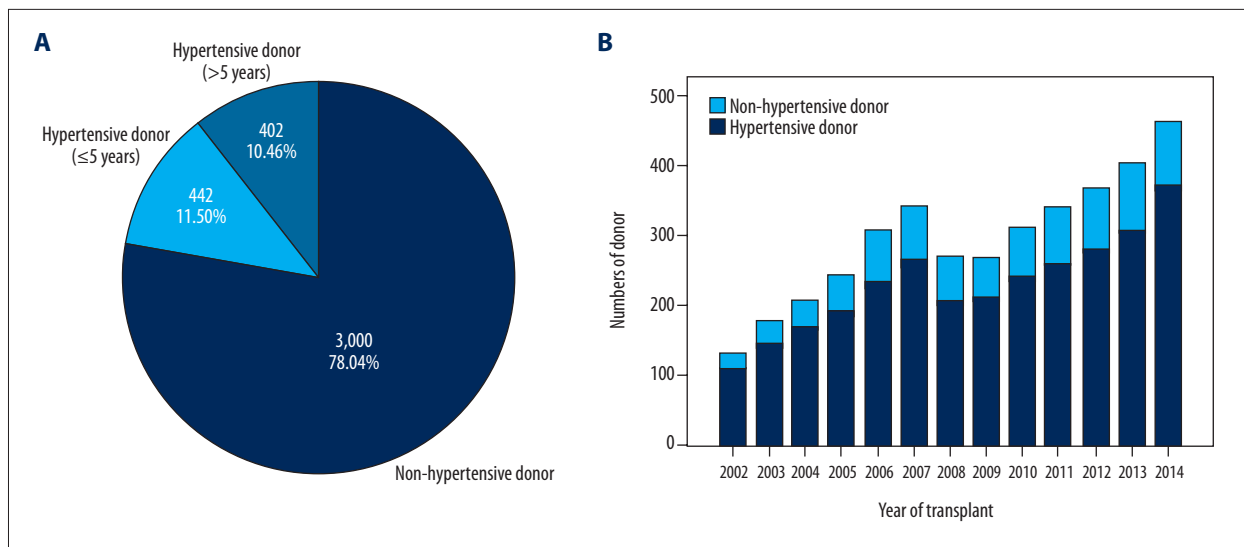


Figure 1. The numbers of simultaneous liver-kidney transplantation (SLKT) procedures from hypertensive (HTN) donors and non-HTN donors in the Scientific Registry of Transplant Recipients (SRTR) database between March 2002 and December 2014. (A) Proportion of different lengths of donor history of hypertension. (B) Total number of SLKT using grafts from HTN donors and non-HTN donors by year.

recipient age, recipient serum albumin level before transplant) to categorical variables was based on the methods of a previous study [18]. Cox proportional hazard regression models with stepwise methods were built to identify independent risk factors associated with patient and graft survival. Variables demonstrating significance in the univariate regression model ($p < 0.05$) were included in the multivariate regression model. Multivariable Cox regression was used to test for differences in patient and graft survival between the HTN donor group and the non-HTN donor group; the covariates adjusted included donor age, donor sex, donor race, cause of donor death, donor history of diabetes, deceased donor type (DCD and DBD), expanded criteria donor kidney, recipient age, recipient serum albumin level pre-transplant, liver CIT, recipient HCV status, need for life support, and recipient condition at transplant. The results are presented as hazard ratio (HR) with 95% confidence interval (CI). A receiver operating characteristic (ROC) analysis was conducted to assess the performance of the prognosis model. All statistical analyses were performed using Statistical Package for the Social Science (SPSS) for Windows, version 22.0 (IBM, USA). Results were considered significant when a p value was less than 0.05.

Results

Overview

The study identified 3844 SLKT adult patients from 1 March 2002 to 31 December 2014 in the SRTR database. The median follow-up period was 6.3 years. The corresponding 3844

donors included 3000 non-HTN donors (78.04%) and 844 HTN donors (21.96%) (Figure 1A). Among the 844 HTN donors, there were 442 (52.37%) donors with a 0–5-year history of hypertension and 402 (47.63%) with a >5-year history of hypertension (Figure 1A). The number of SLKT transplants showed an initial rising trend from 2002 to 2007, after reaching the first peak of 343 transplants in 2007 followed by a second rising trend. In addition, in 2014, the number of SLKT transplants reached 464 (Figure 1B).

Donor and recipient characteristics between the HTN donor group and the non-HTN donor group

The clinical and demographic characteristics of the 2 groups are compared in Table 1 (donor characteristics) and Table 2 (recipient characteristics). The non-HTN donor group and the HTN donor group were quite similar for 3 donor characteristics (highest creatinine level, liver graft CIT, and kidney graft CIT) and characteristics for all recipients (sex, age, race, BMI, medical condition pre-transplant, HCV status, need for life support, MELD scores, albumin, ascites, hepatic encephalopathy, HCC, and dialysis status before transplant). The proportion of females was much higher in the HTN donors than in the non-HTN donors (51.2% vs. 34.7%, $p < 0.0001$). The non-HTN donors were younger than the HTN donors (32.6 ± 13.7 years vs. 48.7 ± 10.4 years, $p < 0.0001$). The proportion of white race was much higher in the non-HTN donors than in the HTN donors (83.2% vs. 73.4%, $p < 0.0001$). The most common cause of death was head trauma followed by stroke in non-HTN donors, while the most common cause of death was stroke followed by anoxia in HTN donors, and the difference was significant

Table 1. Donor characteristics among HTN and Non-HTN donor (n=3844).

Characteristics		Non-HTN (3000)	HTN (844)	p Value
Gender (Female)	n (%)	1041 (34.7)	432 (51.2)	<0.0001
Age (years)	Mean ±SD	32.6±13.7	48.7±10.4	<0.0001
Race	n (%)			<0.0001
White		2496 (83.2)	619 (73.4)	
Black		408 (13.6)	185 (21.9)	
Other*		96 (3.2)	40 (4.7)	
Cause of death	n (%)			<0.0001
Anoxia		608 (20.3)	136 (16.1)	
Stroke		707 (23.6)	559 (66.2)	
Head trauma		1595 (53.2)	127 (15.0)	
Other**		90 (3.0)	22 (2.6)	
History of diabetes (Yes)	n (%)	66 (2.1)	110 (13.0)	<0.0001
Donor type (DCD)	n (%)	132 (4.4)	22 (2.6)	0.019
Donor highest creatinine (>1.5 mg/dL)	n (%)	379 (12.7)	126 (14.9)	0.084
Expanded donor kidney (Yes)	n (%)	122 (4.1)	336 (39.8)	<0.0001
Kidney CIT (hours)	Mean ±SD	11.5±7.4	11.4±7.0	0.345
Liver CIT (hours)	Mean ±SD	6.9±3.3	7.1±4.6	0.125

HTN – hypertensive; DCD – donation after cardiac death; CIT – cold ischemia time; SD – standard deviation. Other* contains Native American, Asian, Pacific Islander and multiracial; Other ** contains central nervous system tumor and other specify.

($p < 0.0001$). Compared to the non-HTN donors, the HTN donors were more likely to have diabetes (13.0% vs. 2.1%, $p < 0.0001$). The non-HTN donors had slightly higher rates of DCD than did the HTN donors (4.4% vs. 2.6%, $p = 0.019$), while the HTN donors were much more likely to have expanded criteria donor kidneys (39.8% vs. 4.1%, $p < 0.0001$).

Outcomes in HTN donors compared with non-HTN donors

SLKT patients receiving grafts from HTN donors had significantly shorter 5-year survival rates than did SLKT patients receiving grafts from non-HTN donors, according to Kaplan-Meier survival analysis (50.1% vs. 63.2%, $p < 0.0001$, Figure 2A). Furthermore, in the subgroup analysis based on duration of HTN history, recipients receiving grafts from donors with >5 years of HTN history had a significantly shorter 5-year survival than did recipients receiving grafts from non-HTN donors (43.8% vs. 63.2%, $p < 0.0001$). Recipients receiving grafts from donors with >5 years of HTN history also had a shorter 5-year survival than did recipients receiving grafts from donors with ≤5 years HTN history (43.8% vs. 56.3%, $p < 0.0001$). The 5-year patient survival rates in SLKT patients receiving grafts from non-HTN donors and in recipients receiving grafts from donors

with ≤5 years HTN history were 63.2% and 56.3%, respectively. However, the difference was not significant ($p = 0.168$, Figure 3A).

The 5-year liver graft survival rates in SLKT patients receiving grafts from HTN donors and from non-HTN donors were 54.7% and 58.4%, respectively. The difference was not significant ($p = 0.586$, Figure 2B). In the subgroup analysis, the 5-year liver graft survival rates in SLKT patients receiving grafts from non-HTN donors, donors with ≤5 years HTN history and donors with >5 years HTN history were 58.4%, 55.8% and 52.2%, respectively. The difference between each of the 2 groups was not significant (donors with ≤5 years HTN history vs. non-HTN, $p = 0.267$; donors with >5 years HTN history vs. non-HTN, $p = 0.109$; donors with >5 years HTN history vs. donors with ≤5 years HTN history, $p = 0.185$, Figure 3B).

SLKT patients receiving grafts from HTN donors had significantly shorter 5-year kidney graft survival rates than did those receiving grafts from non-HTN donors (45.4% vs. 67.8%, $p < 0.0001$, Figure 2C). In the subgroup analysis, SLKT patients receiving grafts from HTN donors (HTN history ≤5 years) had significantly shorter 5-year kidney graft survival rates than those receiving grafts from non-HTN donors (48.5% vs. 67.8%,

Table 2. Recipient characteristics among HTN and Non-HTN donor (n=3844).

Characteristics		Non-HTN (3000)	HTN (844)	p Value
Gender (Female)	n (%)	1040 (34.7)	269 (31.9)	0.130
Age (years)	Mean ±SD	55.7±9.4	56.4±9.2	0.051
Race	n (%)			0.523
White		2402 (80.1)	661 (78.3)	
Black		446 (14.9)	135 (16.0)	
Other*		152 (5.1)	48 (5.7)	
BMI (kg/m ²)	Mean ±SD	27.6±5.8	28.0±5.8	0.120
Medical condition	n (%)			0.135
In ICU		537 (17.9)	174 (20.6)	
Hospitalized		728 (24.3)	210 (24.9)	
Not hospitalized		1735 (57.8)	460 (54.5)	
HCV (Positive)	n (%)	1107 (39.0)	310 (38.4)	0.745
Need for life support (Yes)	n (%)	341 (11.4)	110 (13.0)	0.184
MELD score	Mean ±SD	28.8±7.4	29.2±7.4	0.127
Serum albumin level (g/dL)	Mean ±SD	3.0±0.8	3.0±0.8	0.565
Ascites (Yes)	n (%)	2554 (85.1)	715 (84.7)	0.764
Hepatic encephalopathy (Yes)	n (%)	2128 (70.9)	598 (70.9)	0.964
Diagnosis (HCC)	n (%)	85 (2.8)	35 (4.1)	0.053
Dialysis (Yes)	n (%)	1633 (54.5)	466 (55.4)	0.648

HTN – hypertensive; ICU – intensive care unit; MELD – model for end stage liver disease; BMI – body mass index; HCV – hepatitis C virus; HCC – hepatocellular carcinoma; SD – standard deviation. Other * contains Native American, Asian, Pacific Islander and multiracial.

$p=0.004$). SLKT patients receiving grafts from donors with >5 years HTN history had significantly shorter 5-year kidney graft survival rates than those receiving grafts from non-HTN donors (33.9% vs. 67.8%, $p<0.0001$). Additionally, the difference in 5-year kidney graft survival rates between SLKT patients receiving grafts from donors with ≤5 years HTN history and from donors with >5 years HTN history was significant (33.9% vs. 48.5%, $p=0.017$) (Figure 3C).

Risk factors of patient and graft survival in adult SLKT

The univariate analysis identified 16 potential risk factors (Supplementary Table 1) for 5-year patient survival as follows: HTN donor, donor age, donor cause of death, donor history of diabetes, DCD, expanded criteria donor kidney, liver graft CIT, recipient age, recipient medical condition before transplantation, HCV status, need for life support, level of albumin before transplantation, ascites, hepatic encephalopathy, dialysis, and MELD score.

Multivariable Cox regression analysis was performed to examine the independent risk factors for SLKT patient survival (Table 3). The adjusted HR showed that SLKT patients receiving grafts from HTN donors had an inferior 5-year survival (HR=1.236, 95% CI: 1.035–1.476; $p=0.019$) compared with patients receiving grafts from non-HTN donors. In the multivariable Cox regression model, there were 8 other variables involved in the poor survival of SLKT patients. Patients receiving DCD allografts had inferior survival (HR=1.716, 95% CI: 1.249–2.358; $p=0.001$) compared with those receiving DBD allografts. In addition, lower post-SLKT survival was noted among patients with HCV infection (HR=1.355, 95% CI: 1.166–1.574; $p<0.0001$), ICU stay (HR=1.412, 95% CI: 1.132–1.761; $p=0.002$), increased liver CIT (HR=1.207, 95% CI: 1.042–1.400; $p=0.012$), increased donor age (HR=1.998, 95% CI: 1.490–2.680; $p<0.0001$) and recipient age (HR=2.470, 95% CI: 1.332–4.582; $p=0.004$), need for life support (HR=1.318, 95% CI: 1.037–1.675; $p=0.024$), and decreased recipient albumin level pre-transplant (HR=1.664, 95% CI: 1.310–2.114; $p<0.0001$). To evaluate the accuracy of the Cox

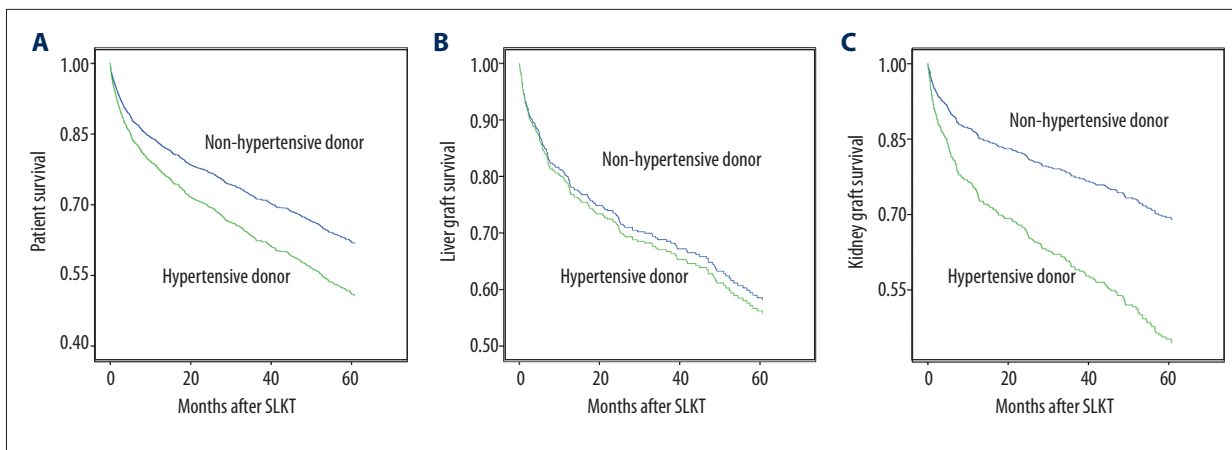


Figure 2. The adjusted 5-year graft and patient survival for SLKT recipients with HTN donors vs. non-HTN donors. **(A)** The adjusted 5-year patient survival curves for SLKT recipients with HTN donors vs. non-HTN donors. **(B)** Adjusted 5-year liver graft survival curves for SLKT recipients with HTN donors vs. non-HTN donors. **(C)** Adjusted 5-year kidney graft survival curves for SLKT recipients with HTN donors vs. non-HTN donors.

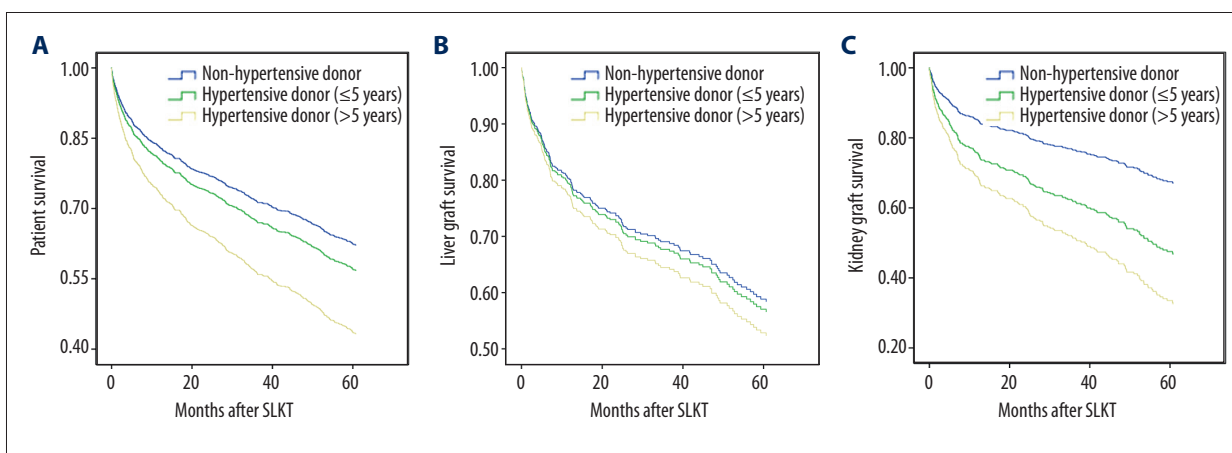


Figure 3. Comparison of adjusted 5-year grafts and patient survival between subgroups with different lengths of donor history of hypertension and non-HTN donors. **(A)** Comparison of adjusted 5-year patient survival between subgroups with different lengths of donor history of hypertension and non-HTN donors. **(B)** Comparison of adjusted 5-year liver graft survival between subgroups with different lengths of donor history of hypertension and non-HTN donors. **(C)** Comparison of adjusted 5-year kidney graft survival between subgroups of different durations of donor history of hypertension and non-HTN donors.

regression model, an ROC analysis was conducted. The AUC value of the present model was 0.752 (95% CI: 0.730-0.775).

Multivariable Cox regression analysis also revealed that having an HTN donor was a risk factor for kidney graft survival (HR=1.379, 95% CI: 1.098-1.787; $p=0.034$). Other risk factors were increased donor age, donor diabetes, increased donor high creatinine, black race, intensive care unit (ICU) stay, recipient HCV, and dialysis pre-transplant (Supplementary Table 2). For liver graft survival, multivariable analysis did not demonstrate having an HTN donor was a risk factor. Other risk factors for 5-year liver graft survival are listed in Supplementary Table 2.

Risk score stratification

Based on the analysis of the multivariate Cox proportional hazard regression model, a clinical risk scoring system applicable to SLKT patient survival was established. Risk score points were assigned to the 9 factors associated with poor outcomes after SLKT (Table 3). Total risk scores were calculated by summing all points of the 9 independent predictors for each patient (Table 4). The range of the total risk scores were from 0 to 30 points. Next, according to the inter-quartile range of the total risk scores, the whole cohort was stratified into the following 4 groups: a low-risk group (score 0–11 points, 957 patients, 24.9%), an intermediate-risk group (score 12–14 points, 992 patients, 25.8%), a high-risk group (score 15–16 points,

Table 3. Multivariate analysis of 5-year patient survival.

Characteristics	B	SE	p	HR (95% CI)
Donor age (years): Mean ±SD				
41–60 vs. 0–40	0.308	0.085	<0.0001	1.360 (1.152–1.607)
≥61 vs. 0–40	0.692	0.149	<0.0001	1.998 (1.490–2.680)
Donor type (DCD vs. DBD)				
HTN donor	0.540	0.162	0.001	1.716 (1.249–2.358)
Recipient condition at transplant				
In ICU vs. not hospitalized	0.345	0.113	0.002	1.412 (1.132–1.761)
Hospitalized vs. not hospitalized	0.183	0.091	0.044	1.201 (1.005–1.434)
Recipient HCV (+)	0.304	0.077	<0.0001	1.355 (1.166–1.574)
Need for life support (+)	0.276	0.122	0.024	1.318 (1.037–1.675)
Liver graft CIT (hours, ≥6.1 vs. 0–6)	0.189	0.075	0.012	1.207 (1.042–1.400)
Recipient serum albumin level (g/dL)				
≤1.9 vs. ≥2.6	0.509	0.122	<0.000	1.664 (1.310–2.114)
2.0–2.5 vs. ≥2.6	0.306	0.090	0.001	1.359 (1.140–1.619)
Recipient age (years)				
35–49 vs. 18–34	0.648	0.316	0.040	1.912 (1.029–3.552)
50–64 vs. 18–34	0.730	0.307	0.018	2.074 (1.136–3.787)
≥65 vs. 18–34	0.904	0.315	0.004	2.470 (1.332–4.582)

HTN – hypertensive; ICU – intensive care unit; HCV – hepatitis C virus; CIT – cold ischemia time; DBD – donation after brain death; DCD – donation after cardiac death; HR – hazard ratio; CI – confidence interval.

Table 4. Independent predictors and assigned risk score points.

Variables	Risk score points
Donor age (years)	
≥61	7
41–60	3
Donor type (DCD)	5
HTN donor	4
Liver CIT (≥6.1 hours)	2
Recipient age (years)	
≥65	9
50–64	7
35–49	6

Variables	Risk score points
Recipient condition at transplant	
In ICU	3
Hospitalized not In ICU	2
Recipient HCV (Positive)	3
Need for life support	3
Recipient serum albumin level (g/dL)	
<2.0	5
2.0–2.5	3

HTN – hypertensive; ICU – intensive care unit; HCV – hepatitis C virus; CIT – cold ischemia time; DCD – donation after cardiac death.

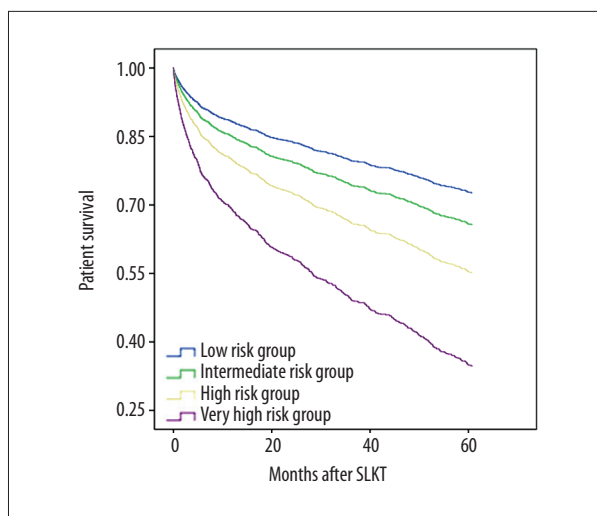


Figure 4. Five-year patient survival after SLKT by risk score stratification based on multivariate predictors.

973 patients, 25.3%), and a very high-risk group (score ≥ 17 points, 962 patients, 25.0%). The 1-, 3-, and 5-year patient survival rates were: 89.7%, 81.5%, and 73.7% in the low risk group; 86.5%, 75.2%, and 65.4% in the intermediate risk group; 81.3%, 71.5%, and 55.8% in the high-risk group; and 79.1%, 50.5%, 36.3% in very high-risk group, respectively. The intermediate-risk group, high-risk group, and very high-risk group had significantly lower 5-year survival rates than the low-risk group when utilizing Kaplan-Meier survival analysis ($p < 0.05$ for all, Figure 4). The AUC value of the ROC analysis in this model was 0.762 (95% CI: 0.739–0.785).

Discussion

Hypertension is an important component of the expanded criteria donor definition [19], and it has been reported that donor hypertension is associated with increased risk of poor survival outcomes in kidney transplantation recipients and in liver transplantation recipients. However, the effects of HTN donors on the survival outcomes of SLKT patients are not known. Furthermore, the risk factors associated with the survival outcomes of SLKT patients are unclear, and an applicable risk scoring system is lacking in clinical practice. In the present study, we found, first, that having an HTN donor was an independent risk factor associated with SLKT patient survival by Kaplan-Meier and multivariate regression analysis. SLKT patients with grafts from HTN donors had a significantly lower 5-year survival rates than did those receiving grafts from non-HTN donors. Additionally, we established a clinically applicable risk-scoring system for SLKT patient survival based on the analysis of the multivariate Cox regression model. To the best of our knowledge, our study is the first to show that having an HTN donor is an independent risk factor of adult SLKT

survival, with concurrent development of a clinical risk scoring system suitable for SLKT patient survival.

Hypertension is a common chronic disease worldwide. HTN donors account for a certain proportion of all donors, both in liver transplantation and kidney transplantation. In this study, the proportion of HTN donors was approximately 22.0% (844/3844). Several studies have demonstrated that having an HTN donor a poor prognostic factor in the survival of kidney transplantation recipients. Watson et al. [10] showed that a history of donor hypertension was associated with increased risk of poor survival outcome in kidney transplantation recipients. A previous study has shown that duration of donor hypertension was an independent risk factor for graft survival in deceased renal transplant recipients [20]. Fraser et al. [21] found that donor hypertension was an independent predictor of poor kidney graft survival. In a retrospective single-center study, Singh et al. [19] showed that history of donor hypertension is associated with worse graft function and an increased risk of graft loss in recipients of kidney transplantation. The reason why donor hypertension induces lower survival in transplanted recipients is probably the inferior function of the organs from HTN donors. Early graft function is associated with donor hypertension after renal transplantation [22]. A previous study [23] documented that donor hypertension is associated with low estimated glomerular filtration rate in kidney transplantation recipients. In an animal model of allogeneic kidney transplantation, Pratschke et al. [24] revealed that donor hypertension can intensify the chronic injury of the allografts in recipients. After transplantation, kidney allografts from HTN animals showed accelerated deterioration in structure and function. Recently, Li et al. [11] proposed that the risk of post-transplantation death was increased with donor hypertension. Similarly, in the present study, we also found that donor hypertension was an independent risk factor associated with patient survival and kidney graft survival in SLKT recipients. In our subgroup analysis of patient survival in those having HTN donors compared with non-HTN donors, recipients receiving grafts from donors with >5 years HTN history had a significantly shorter 5-year survival than recipients receiving grafts from non-HTN donors (43.8% vs. 63.2%, $p < 0.0001$) and recipients receiving grafts from donors with ≤ 5 years HTN history (43.8% vs. 56.3%, $p < 0.0001$). In terms of kidney graft survival, patients who received transplanted grafts from donors with ≤ 5 years HTN history or from donors with >5 years HTN history had significantly shorter 5-year kidney graft survival rates than receiving transplanted grafts from non-HTN donors (48.5% vs. 67.8%, $p = 0.004$; 33.9% vs. 67.8%, $p < 0.0001$). These results imply that the increased duration of donor HTN history is associated with poorer prognosis in SLKT. For future allocation of donor organs to SLKT recipients, using the grafts from donors with >5 years HTN history should not be considered, but grafts from donors with ≤ 5 years HTN history

should be used cautiously. In terms of improving the prognosis of SLKT recipients, donors with >5 years HTN history could be excluded from the donor list but donors with ≤5 years HTN history should not.

In some previous studies, having a donor with hypertension was related to poor outcomes for liver transplantation recipients. Campos-Varela et al. [12] found donor hypertension was significantly associated with graft loss among liver transplant recipients with human immunodeficiency virus in a univariate analysis. Alamo et al. [13] found donor hypertension was suggestive of poor prognostic factors in liver transplant recipient survival. Recently, in an analysis of the SRTR database, Hu et al. [25] found that liver transplant recipients of HTN donor grafts have poorer graft and patient survival than those of non-HTN donor grafts. However, in the present study, we found that having a donor with hypertension is not a poor prognostic factor for patient survival and liver graft survival in SLKT recipients. The 5-year liver graft survival rates in SLKT patients receiving grafts from HTN donors were similar to those for SLKT patients receiving grafts from non-HTN donors. In the subgroup analysis, the differences in 5-year liver graft survival rates in SLKT patients receiving grafts from non-HTN donors, from donors of ≤5 years HTN history, and from donors of >5 years HTN history were not significant.

Analysis of the UNOS database from 2002 to 2011 by Alhamad et al. [14] revealed DCD, increased recipient BMI, white race, recipient diabetes, decreased recipient albumin, longer ICU stay, delayed graft function, increased donor age, and HCC were associated with worse SLKT patient survival. Later, another study [15] reported lower post-SLKT survival among patients with HCV infection, HCC, and diabetes in an analysis of the UNOS database from 2003 to 2012. Recently, in a study of adult SLKT between 2002 and 2013 from the UNOS registry, increased donor risk index, recipient diabetes, HCV, increased MELD, regional differences, and the need for liver re-transplantation were factors associated with higher post-SLKT mortality [16]. Although the above analyses were from the same database (UNOS), the risk factors of SLKT survival remain controversial. In addition, to the best of our knowledge, an applicable risk scoring system for SLKT patient survival is lacking in clinical practice. In the present study, we also identified donor age, DCD, liver graft CIT, recipient age, recipient condition at transplant, recipient HCV infection, need for life support, and recipient pre-transplant albumin level as independent risk factors associated with inferior patient survival in SLKT recipients. It is widely regarded that DCD, recipient condition at transplant (hospitalization), decreased recipient pre-transplant albumin level, and older donor age are associated

with worse allograft and patient outcomes in SLKT [14,26]. Previous reports [15,16,26] demonstrated that patients infected with HCV had significantly lower survival following SLKT than patients with non-HCV disease. Prolonged CIT, increased recipient age, and need for life support were associated with inferior outcomes in liver transplantation [27–29]. In our study, we found 9 independent risk factors of adult SLKT survival. Furthermore, we established a clinically applicable risk scoring system for SLKT patient survival based on an analysis of the multivariate Cox regression model. Patients in the low-risk group had significantly superior survival compared with those in the intermediate-risk group, high-risk group, and very high-risk group. According to the risk scoring model, we should be able to evaluate patient prognosis before SLKT in the clinic.

Based on an analysis of the SRTR database, we found SLKT patient with grafts from HTN donors had inferior patient and kidney graft survival; furthermore, we developed a clinically applicable risk scoring system for SLKT patient survival. Nevertheless, there are some limitations in our study. One limitation is that in the SRTR database some variables have certain missing values; these variables were excluded from the analysis. Moreover, the accuracy of the risk scoring system was not verified in another SLKT cohort. Before broad application of this system in the clinic, it should be verified in different SLKT cohorts.

Conclusions

In conclusion, based on a large cohort, we found that SLKT patients with grafts from HTN donors have an inferior prognosis compared with SLKT patients with grafts from non-HTN donors. A clinically applicable risk scoring system for SLKT patient survival initially has been developed, and it could provide a practical guide for better utilization of the scarce organs in SLKT.

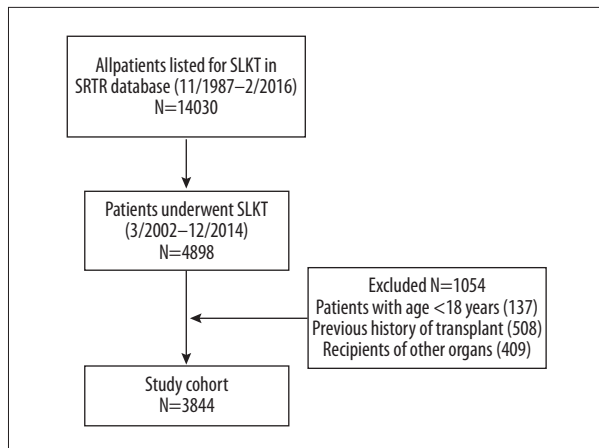
Acknowledgement

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Conflict of interest

None.

Supplementary Files



Supplementary Figure 1. Strobe flow chart showing study cohort selection.

Supplementary Table 1. Univariate analysis of 5-year patient survival.

Characteristics	B	SE	p	HR (95% CI)
Donor gender (Female)	0.111	0.071	0.121	1.117 (0.971–1.285)
Donor age (years)				
41–60 vs. 0–40	0.428	0.073	<0.0001	1.535 (1.329–1.772)
≥61 vs. 0–40	0.899	0.132	<0.0001	2.457 (1.976–3.036) (1.897–3.184)
Donor BMI (≥30 vs. <30 kg/m ²)	0.153	0.083	0.065	1.165 (0.991–1.370)
Donor race				
Black vs. White	0.036	0.097	0.708	1.037 (0.858–1.253)
Other* vs. White	–0.010	0.193	0.958	0.990 (0.678–1.445)
Donor death cause				
Anoxia vs. Head trauma	0.198	0.102	0.051	1.219 (0.999–1.487)
Stroke vs. Head trauma	0.485	0.079	<0.0001	1.624 (1.391–1.897)
Other** vs. Head trauma	0.412	0.194	0.034	1.510 (1.032–2.210)
Donor diabetes	0.479	0.140	0.001	1.614 (1.228–2.123)
Donor type (DCD)	0.259	0.168	0.123	1.296 (0.932–1.803)
Donor HTN	0.487	0.078	<0.0001	1.472 (1.263–1.715)
Donor highest creatinine (>1.5 mg/dL)	0.160	0.099	0.105	1.174 (0.967–1.425)
Expanded donor kidney (Yes)	0.492	0.094	<0.0001	1.635 (1.360–1.966)
Liver CIT (>6 vs. ≤6 h)	0.087	0.073	0.235	1.091 (0.945–1.259)
Kidney CIT (h)				
6–12 vs. 0–6	–0.065	0.129	0.616	0.937 (0.728–1.207)
>12 vs. 0–6	0.025	0.138	0.853	1.026 (0.783–1.343)

Characteristics	B	SE	p	HR (95% CI)
Recipient gender (Femal)	-0.077	0.074	0.299	0.926 (0.800–1.071)
Recipient age (years)				
35–49 vs. 18–34	0.327	0.239	0.171	1.387 (0.868–2.217)
50–64 vs. 18–34	0.471	0.228	0.039	1.602 (1.025–2.504)
≥65 vs. 18–34	0.603	0.240	0.012	1.827 (1.143–2.922)
Recipient BMI (≥30 vs. <30 kg/m ²)	0.011	0.077	0.891	1.011 (0.869–1.176)
Recipient race				
Black vs. White	0.247	0.091	0.007	1.280 (1.070–1.530)
Other* vs. White	-0.108	0.167	0.519	0.898 (0.647–1.246)
Recipient condition at transplant				
In ICU vs. not hospitalized	0.356	0.090	<0.0001	1.427 (1.196–1.704)
Hospitalized vs. not hospitalized	0.230	0.084	0.006	1.259 (1.068–1.483)
Recipient HCV (+)	0.453	0.072	<0.0001	1.573 (1.366–1.811)
Need for life support (+)	0.316	0.101	0.002	1.372 (1.124–1.673)
MELD score				
25–34 vs. ≤24	0.145	0.084	0.086	1.156 (0.980–1.364)
≥35 vs. ≤24	0.269	0.089	0.002	1.309 (1.100–1.557)
Recipient albumin level (g/dL)				
≤1.9 vs. ≥2.6	0.416	0.119	<0.0001	1.516 (1.202–1.913)
2.0–2.5 vs. ≥2.6	0.222	0.084	0.008	1.249 (1.059–1.473)
Ascites	0.290	0.109	0.008	1.336 (1.079–1.655)
Hepatic encephalopathy	0.239	0.081	0.003	1.270 (1.083–1.489)
HCC	0.412	0.128	0.001	1.510 (1.174–1.942)
Dialysis	0.129	0.071	0.070	1.138 (0.990–1.308)

HTN – hypertensive; ICU – intensive care unit; MELD – model for end stage liver disease; BMI – body mass index; HCV – hepatitis C virus; HCC – hepatocellular carcinoma; CIT – cold ischemia time; DCD – donation after cardiac death; HR – hazard ratio; CI – confidence interval. Other * contains Native American, Asian, Pacific Islander and multiracial; Other ** contains central nervous system tumor and other specify.

Supplementary Table 2. Multivariate analysis of 5-year kidney and liver graft survival.

Characteristics	Kidney graft		Liver graft	
	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)
Donor age (years)				
41–60 vs. 0–40	0.011	1.492 (1.095–2.035)	0.031	1.528 (1.192–2.014)
≥61 vs. 0–40	<0.0001	1.998 (1.490–2.680)	0.008	1.962 (1.210–2.746)
Donor diabetes	0.002	1.926 (1.260–2.946)	0.003	2.167 (1.305–3.599)
HTN donor	0.034	1.379 (1.098–1.787)	–	–
Donor highest creatinine (>1.5 mg/dL)	0.004	1.608 (1.164–2.221)	–	–
Recipient BMI (kg/m ² , ≥30 vs. <30)	0.046	1.302 (1.005–1.686)	–	–
Recipient race				
Black vs. White	0.018	1.463 (1.066–2.009)	–	–
Other* vs. White	0.914	0.967 (0.523–1.786)	–	–
Recipient condition at transplant				
In ICU vs. not hospitalized	0.029	1.416 (1.036–1.938)	–	–
Hospitalized vs. not hospitalized	0.201	1.264 (0.883–1.812)	–	–
Recipient HCV (+)	0.010	1.407 (1.087–1.823)	<0.0001	2.412 (1.787–3.254)
Dialysis	<0.0001	1.916 (1.460–2.516)	0.004	2.470 (1.332–4.582)
Donor death cause				
Anoxia vs. Head trauma	–	–	0.272	1.270 (0.829–1.948)
Stroke vs. Head trauma	–	–	0.002	1.718 (1.222–2.416)
Other** vs. Head trauma	–	–	0.346	1.498 (0.646–3.470)

HTN – hypertensive; ICU – intensive care unit; BMI – body mass index; HCV – hepatitis C virus; HR – hazard ratio; CI – confidence interval. Other * contains Native American, Asian, Pacific Islander and multiracial; Other ** contains central nervous system tumor and other specify.

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