

## Clinical outcome of 1,000 consecutive cases of liver transplantation: a single center experience

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**Purpose:** The aim of this study was to analyze survival outcomes in 1,000 consecutive liver transplantations (LTs) performed at a single institution from 1993 to April 2017.

**Methods:** The study population was divided into 2 groups based on donor type: deceased donor LT (DDLT; n = 181; 18.1%) and living donor LT (LDLT; n = 819; 81.9%), and into 3 periods based on the number of cases (first 300 cases, middle 300 cases, last 400 cases).

**Results:** Infection was the most common cause of death, accounting for 34.8% (95 of 273). Mortality due to hepatocellular carcinoma recurrence occurred most frequently between 1 and 5 years after transplantation. Mortality rate by graft rejection was highest between 5 and 10 years after transplantation. And mortality by *de novo* malignancy occurred most frequently after 10 years after transplantation. The patient survival rates for the entire population at 5 and 10 years were 74.7%, and 68.6%, respectively. There was no difference in survival rate between the LDLT and DDLT groups (P = 0.188). Cause of disease, disease severity, case period, and retransplantation had a significant association with patient survival (P = 0.002, P = 0.031, P = 0.003, and P = 0.024, respectively).

**Conclusion:** Surgical techniques and perioperative management for transplant patients have improved and undergone standardization. Controlling perioperative infection and managing patients with HCC as LT candidates will result in better outcomes.

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**Key Words:** Liver transplantation, Cause of death, Survival, Risk factors

### INTRODUCTION

Liver transplantation (LT) is the most effective treatment for patients with end stage liver disease, acute liver failure, and some metabolic liver diseases, including hepatocellular carcinoma (HCC). The first case of LT in humans was performed in Denver, by Starzl et al. [1] in 1967. LT in Asia, including South Korea, was started in the late 1980s [2]. The first LT from a living

donor was accomplished in 1989. This has made it possible to drastically reduce graft ischemia time, although there is a risk to the donor [3]. Since the late 1980s, the number of LTs in Korea has been increasing steadily. According to statistics from the Korean Network of Organ Sharing (KONOS), there were 1,471 LTs in South Korea in 2016. Among them, there were 963 living donor LTs (LDLTs; 65.5%) and 508 deceased donor LTs (DDLTs; 34.5%). The Pittsburgh Health Center reported that the 1-year

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recipient survival rate in 1985 was approximately 30% and the 5-year survival rate was approximately 20% [4]. In 2008, the US Department of Health and Human Services reported patient and graft survival rates, at 1, 5, and 10 years after DDLT, of 87%, 73%, and 59%, and 83%, 68%, and 53%, respectively [5]. Five-year survival rates > 90% have been reported in LDLT using a right liver graft [6]. These remarkably improved outcomes are due not only to the continued development of surgical techniques, but also to improvements in perioperative medical care.

The first DDLT was performed in our institution on a 30-year-old male patient, who had hepatitis B-related cirrhosis, in June 1993. The first LDLT was performed in May 1996 at our institution. The patient was a 2-year-old female who suffered from biliary atresia. She received a left lateral segment of liver from her mother. There has been a sharp increase in the number of LTs, especially LDLTs, since 2000. From June 1993 to April 2017, 1,000 LTs were performed for various types of liver diseases, including HCC. The aim of this study was to analyze the survival outcomes and causes of mortality of 1,000 LTs performed at a single institution.

## METHODS

### Patient status

Data on 1,000 LTs, performed in 969 patients who underwent LT from June 1993 to April 2017, were reviewed and analyzed retrospectively. Among them, there were 819 LDLTs (81.9%) and 181 DDLTs (18.1%). Fourteen pediatric recipients were <18 years of age (1.4%). Among them, primary transplantation was performed in 969 cases (96.9%) and a retransplantation was performed in 31 cases (3.1%). The study population was divided into 2 groups based on donor type (DDLT vs. LDLT), and into 3 periods based on the number of cases (period 1: first 300 cases, period 2: middle 300 cases, period 3: last 400 cases). The period 1 cases were from June 1993 to May 2006, the period 2 cases were from May 2006 to April 2011, and the period 3 cases were from April 2011 to April 2017. In DDLT, there was an event switching of venous flow reconstruction technique from classic method to Piggyback method. But there was no definite change of operative techniques and perioperative care in LDLT. Therefore we divided the periods evenly according to case numbers.

The causes of mortality according to donor type and case period were evaluated. A survival analysis was performed according to donor type, cause of disease, disease severity, case period, and retransplantation. Operative mortality was defined as death within 30 days after surgery. The mean follow-up was  $71.8 \pm 59.1$  months. Survival of 2 patients could not be evaluated because they were lost to follow-up. The study was reviewed and approved by the Ethics Committee of Seoul St. Mary's Hospital, the Catholic University of Korea

(KC17RCSI0689). Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

### Surgical technique

A bilateral subcostal incision with upper midline extension was used in LDLT recipients. The donor and recipient surgery were performed concurrently, to minimize cold ischemic time of the graft, and the graft vessels were not divided until the recipient was ready to receive the graft. The right lobe, without the middle hepatic vein, was resected from most donors. The procured graft was flushed with 2 L of cold (4°C) histidine-tryptophan-ketoglutarate (HTK) solution (HTK-Custodiol, Koehler Chemi, Alsbach-Haenli, Germany) through the portal vein and hepatic artery at the back table. After all procedures were completed on the back table, the recipient portal vein and hepatic veins were resected, and the total hepatectomy was completed. The vascular anastomosis was started after controlling bleeding in the recipient operative field. End-to-side anastomosis was performed between the right hepatic vein of the donor and the right hepatic vein of the recipient in transplantations that used the modified right lobe. An end-to-end anastomosis was performed in the order of portal vein and hepatic artery. The hepatic arterial anastomosis was performed under a microscope ( $\times 10$ ). The middle hepatic vein tributaries from segments 5 and 8 were reconstructed using an interpositioned prosthetic graft to the middle hepatic vein of the recipient. All accessory right hepatic veins over 5 mm were reconstructed to the inferior vena cava (IVC) to prevent venous congestion of the graft. Finally, duct-to-duct anastomosis was performed at the bile duct reconstruction. Otherwise, Roux-en-Y hepaticojejunostomy was performed only for patients who cannot be anastomosed by duct-to-duct method ( $n = 20/819$ , 2.4% in LDLT;  $n = 3/181$ , 1.7% in DDLT).

Most of the DDLT procedures were similar to those used for LDLT, although one difference was in the venous flow reconstruction method. Initially, the recipient IVC, from above the renal veins to the diaphragm, was totally removed. The excised retrohepatic vena cava was replaced with a donor vena caval segment using end-to-end anastomosis between the graft IVC and the recipient IVC. During the procedure, veno-venous bypass was used to decompress the splanchnic circulation and reduce bowel edema during the anhepatic phase. Since March 2008 (54th DDLT), we started hepatic venous flow reconstruction using the Piggyback technique, which was made popular in 1989 by Tzakis et al. [7]. A side-to-side anastomosis was routinely performed between the IVC segment of the graft and the IVC of the recipient.

## Immune suppression

Immunosuppressive treatment included a regimen featuring a calcineurin inhibitor, cyclosporine (Sandimmun, Novartis Pharmaceuticals, Basel, Switzerland) or tacrolimus (Prograf, Astellas Pharma Inc., Tokyo, Japan) as a component of a double- or triple-drug cocktail (the other 2 drugs were prednisone and mycophenolate mofetil [Myrept, Chong Kun Dang Pharmaceutical Corp., Seoul, Korea]). An interleukin-2 receptor blocker (Simulect, Novartis Pharmaceuticals) was administered on the day of the operation and on postoperative day 4. Steroids were withdrawn 1 month after surgery, and mycophenolate mofetil was withdrawn 6 months after surgery. Only a low-dose calcineurin inhibitor was given after this time. The immunosuppressive protocol in the patients who underwent LT due to HCC did not differ from those used to treat benign diseases. When recurrence was detected during follow-up, the immunosuppressive agent was switched to everolimus (Certican, Novartis Pharmaceuticals), or a low trough level of the immunosuppressant was maintained.

## Statistical analysis

Numerical data are presented as means and standard deviations. Continuous variables were analyzed using the independent t-test, one way analysis of variance, or the Kruskal-Wallis test, as appropriate. Proportions were tested using Pearson chi-square test or the Fisher exact test. A Kaplan-Meier analysis was used to calculate survival curves. Differences in survival curves were compared using log-rank statistics. Cox proportional hazards model was used to identify factors that were independently associated with overall survival. The statistical analysis was performed using IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA). A P-value of <0.05 was considered significant.

## RESULTS

### Demographic changes

The mean age of the 969 total patients was  $49.9 \pm 10.3$  years (range, 1–75 years), and there were 695 male patients (69.5%). Cause of disease was hepatitis B in 652 patients (65.2%), hepatitis C in 60 patients (6%), alcohol use in 124 patients (12.4%), acute hepatic failure in 56 patients (5.6%), and autoimmune disease in 57 patients (5.7%). A total of 412 patients (41.2%) underwent transplantation due to a hepatic tumor. In DDLT group (n = 181), 25 patients (13%) were classified to transplantation due to other causes. The most of them (21 of 25, 84%) were retransplantation due to graft failure of primary transplanted liver. And the 2 patients underwent LT due to non-A, non-B hepatitis, 1 patient due to nonalcoholic steatohepatitis, and 1 patient due to unknown cause. Thirty-one patients underwent retransplantation. The most common cause

of retransplantation was rejection (14 of 31, 45.2%), followed by graft failure due to vascular complications (9 of 31, 29.0%) and graft failure due to biliary complications (5 of 31, 16.1%). And other causes included primary non function and small for size syndrome. The mean Child-Turcotte-Pugh (CTP) score was  $9.4 \pm 2.7$ . The mean model for end-stage liver disease (MELD) score was  $17.5 \pm 10.2$ . The mean operation time and volume of transfusion were  $562.1 \pm 140.4$  minutes and  $12.3 \pm 9.4$  units, respectively. The surgical complication rate was 29.4%, and the perioperative mortality rate was 9.0%.

Age, sex, body mass index (BMI), and mean follow-up duration were not different between the LDLT and DDLT groups. Significantly more patients were diagnosed with a tumor in the LDLT group than in the DDLT group ( $P < 0.001$ ). The CTP score and MELD score were significantly higher in the DDLT versus LDLT group (both  $P < 0.001$ ). Operation time was shorter in the DDLT versus LDLT group ( $P = 0.008$ ). Otherwise, more perioperative transfusions were needed in the DDLT versus LDLT group ( $P < 0.001$ ). Significantly more surgical complications occurred in the LDLT group than in the DDLT group ( $P < 0.001$ ). Surgical mortality was higher in the DDLT versus LDLT group ( $P = 0.027$ ) (Table 1).

Demographics according to case period were compared. Age and BMI increased significantly over time (both  $P < 0.001$ ). The rate of hepatitis B decreased, while alcohol use increased, over time (both  $P < 0.001$ ); the CTP score also decreased over time ( $P = 0.063$ ). The MELD score was higher in periods 2 and 3 than in period 1 ( $P = 0.031$ ). The proportion of LDLTs decreased significantly over time ( $P < 0.001$ ). Operative time and volume of perioperative transfusion decreased over time (both  $P < 0.001$ ). The surgical complication rate (37.3%) and operative mortality were higher (12.0%) during period 1 than during the other periods. Abrupt decrease in surgical complications and operative mortality occurred during period 2 (22.3%,  $P < 0.001$  and 7.0%,  $P = 0.081$ , respectively). The surgical complication and operative mortality rates were similar between periods 2 and 3 (Table 2).

### Operative methods

The DDLT (n = 181) group was further subdivided into 2 groups according to the venous outflow anastomosis technique. The classic technique was used on the initial cases, up to February 2008 (n = 53); the Piggyback technique was used thereafter (n = 128). The Piggyback technique group showed significantly shorter operative times than the classic technique group ( $P < 0.001$ ). Transfusions during the operation, the surgical complication rate, and the operative mortality rate were not different between the groups ( $P = 0.890$ ,  $P = 0.206$  and  $P = 0.621$ , respectively). In this study, surgical complication included events occurred only in hospital period from operation to discharge. The most common surgical complication in

**Table 1.** Demographics according to graft type

Variable	Total (n = 1,000)	LDLT (n = 819)	DDLT (n = 181)	P-value
Age (yr)	49.9 ± 10.3	49.9 ± 10.3	50.1 ± 10.6	0.869
Male sex	695 (69.5)	570 (69.6)	125 (69.1)	0.887
BMI (kg/m <sup>2</sup> )	24.2 ± 3.7	24.1 ± 3.5	24.8 ± 4.3	0.088
Cause of disease				<0.001
Hepatitis B	652 (65.2)	550 (67.2)	102 (56.4)	
Hepatitis C	60 (6.0)	48 (5.9)	12 (6.6)	
Alcohol	124 (12.4)	98 (12.0)	26 (14.4)	
Acute hepatic failure	56 (5.6)	51 (6.2)	5 (2.8)	
Autoimmune	57 (5.7)	46 (5.6)	11 (6.1)	
Others	51 (5.1)	26 (3.2)	25 (13.8)	
Tumor	412 (41.2)	362 (44.2)	50 (27.6)	<0.001
CTP score	9.4 ± 2.7	9.1 ± 2.7	11.0 ± 2.0	<0.001
MELD score	17.5 ± 10.2	16.5 ± 9.9	23.7 ± 10.0	<0.001
Operation time (min)	562.1 ± 140.4	567.6 ± 135.3	537.1 ± 156.1	0.008
Transfusion (unit)	12.3 ± 9.4	11.6 ± 8.4	15.6 ± 12.7	<0.001
Surgical complications	294 (29.4)	266 (32.5)	28 (15.5)	<0.001
Operation mortality	90 (9.0)	66 (8.1)	24 (13.3)	0.027
Follow-up (mo)	71.8 ± 59.1	72.5 ± 56.1	68.6 ± 71.2	0.487

Values are presented as mean ± standard deviation or number (%).

LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; BMI, body mass index; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.

**Table 2.** Demographics according to case period

Variable	Period 1 (n = 300)	Period 2 (n = 300)	Period 3 (n = 400)	P-value
Age (yr)	47.9 ± 10.1	48.9 ± 11.5	52.3 ± 9.0	<0.001
Male sex	222 (74.0)	197 (65.7)	276 (69.0)	0.082
BMI (kg/m <sup>2</sup> )	23.5 ± 3.4	23.9 ± 3.3	24.8 ± 4.0	<0.001
Cause of disease				<0.001
Hepatitis B	243 (81.0)	182 (60.7)	227 (56.8)	
Hepatitis C	16 (5.3)	14 (4.7)	30 (7.5)	
Alcohol	17 (5.7)	38 (12.7)	69 (17.3)	
Acute hepatic failure	6 (2.0)	30 (10.0)	20 (5.0)	
Autoimmune	13 (4.3)	21 (7.0)	23 (5.8)	
others	5 (1.7)	15 (5.0)	31 (7.8)	
CTP score	9.6 ± 2.3	9.4 ± 2.6	9.2 ± 2.9	0.063
MELD score	16.1 ± 8.4	18.3 ± 10.6	17.9 ± 10.9	0.031
LDLT	250 (83.3)	273 (91.0)	296 (74.0)	<0.001
Operation time (min)	651.62 ± 123.2	590.2 ± 124.3	473.8 ± 107.0	<0.001
Transfusion (unit)	14.1 ± 8.5	12.7 ± 8.8	10.6 ± 10.2	<0.001
Surgical complications	112 (37.3)	67 (22.3)	115 (28.8)	<0.001
Operation mortality	36 (12.0)	21 (7.0)	33 (8.3)	0.081

Values are presented as mean ± standard deviation or number (%).

LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; BMI, body mass index; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.

Period 1: from June 1993 to May 2006; period 2: from May 2006 to April 2011; period 3: from April 2011 to April 2017.

the DDLT group was bleeding (11 of 28, 39.3%), and the most common cause of surgical mortality was infection (17 of 24, 70.8%). biliary complications occurred in 7 patients (3.9%).

Among them, 3 patients had bile leakage, another 3 patients had biliary stricture, and 1 patient had both. In all 7 patients, 1 patient was treated by intervention with endoscopic retrograde

cholangio-pancreatography (ERCP), and 3 patients were treated by intervention with percutaneous transhepatic biliary drainage (PTBD). Two patients were treated by conservative care. And 1 patient underwent reoperation by bile peritonitis (Table 3).

The LDLT (n = 819) group was further subdivided into 3 groups according to the time intervals previously described in Table 2. Operative time and volume of perioperative transfusion decreased over time (both P < 0.001). The surgical complication rate in period 1 (40.8%) was higher than that in the other periods (P < 0.001). Among the surgical complications, bleeding decreased over time (P < 0.001). No significant differences were observed in any other complications

according to period. Operative mortality in period 1 (12.0%) was highest among the three periods (P = 0.023). Mortality due to vascular complications tended to decrease over time. No significant differences in mortality were observed due to other causes according to the period. The most common surgical complication in the LDLT group was a biliary complication (149 of 819, 56.0%). Among them, 116 patients (77.9%) had bile leakage, another 23 patients (15.4%) had biliary stricture, and 10 patients (6.7%) had both. In all 149 patients, 51 patients were treated by intervention with ERCP, and 26 patients were treated by intervention with PTBD. Drain catheter insertion was done in 5 patients. And 67 patients were treated by conservative care.

**Table 3.** Demographics according to operative methods: DDLT

Variable	DDLT (n = 181)	Classic (n = 53)	Piggyback (n = 128)	P-value
Operation time (min)	537.1 ± 156.1	626.0 ± 146.4	500.3 ± 145.2	<0.001
Transfusion (unit)	15.6 ± 12.7	15.4 ± 12.4	15.7 ± 12.8	0.890
Surgical complication	28 (15.5)	11 (20.8)	17 (13.3)	0.206
Bleeding	11 (39.3)	4 (36.4)	7 (41.2)	
Vascular	7 (25.0)	3 (27.3)	4 (23.5)	
Biliary	7 (25.0)	4 (36.4)	3 (17.6)	
Bile leak	3 (42.9)	1 (25.0)	2 (66.6)	
Stricture	3 (42.9)	2 (50.0)	1 (33.3)	
Both	1 (14.3)	1 (25.0)	0 (0)	
Operation mortality	24 (13.3)	6 (11.3)	18 (14.1)	0.621
Infection	17 (70.8)	6 (100)	11 (61.1)	
Vascular complication	3 (12.5)	0 (0)	3 (16.7)	
Graft failure, rejection	2 (8.3)	0 (0)	2 (11.1)	

Values are presented as mean ± standard deviation or number (%).

DDLT, deceased donor liver transplantation.

Classic: up to February 2008; Piggyback: from March 2008.

**Table 4.** Demographics according to case period: LDLT

Variable	LDLT (n = 819)	Period 1 (n = 250)	Period 2 (n = 273)	Period 3 (n = 296)	P-value
Operation time (min)	567.6 ± 135.3	658.7 ± 117.8	591.1 ± 116.2	468.9 ± 96.1	<0.001
Transfusion (unit)	11.6 ± 8.4	14.0 ± 7.5	12.4 ± 8.7	8.9 ± 8.1	<0.001
Surgical complication	266 (32.5)	102 (40.8)	65 (23.8)	99 (33.4)	<0.001
Bleeding	76 (28.6)	44 (43.1)	16 (24.6)	16 (16.1)	
Vascular	38 (14.3)	14 (13.7)	8 (12.3)	16 (16.1)	
Biliary	149 (56.0)	44 (43.1)	39 (60.0)	66 (66.7)	
Bile leak	116 (77.9)	29 (65.9)	30 (76.9)	57 (86.4)	
Stricture	23 (15.4)	8 (18.2)	7 (17.9)	8 (12.1)	
Both	10 (6.7)	7 (15.9)	2 (5.1)	1 (1.5)	
Operation mortality	66 (8.1)	30 (12.0)	18 (6.6)	18 (6.1)	0.023
Infection	32 (48.5)	13 (43.3)	9 (50.0)	10 (55.6)	
Vascular complication	16 (24.2)	10 (33.3)	5 (27.8)	1 (5.6)	
Graft failure, rejection	8 (12.1)	4 (13.3)	1 (5.6)	3 (16.7)	

Values are presented as mean ± standard deviation or number (%).

LDLT, living donor liver transplantation.

Period 1: from June 1993 to May 2006; Period 2: from May 2006 to April 2011; Period 3: from April 2011 to April 2017.

The most common cause of surgical mortality was infection (32 of 66, 48.5%) (Table 4).

### Causes of mortality

A total of 273 patients (27.3%) died during the follow-up period. The causes of mortality according to various factors are

**Table 5.** Cause of mortality according to graft type

Cause of mortality	Total (n = 273)	LDLT (n = 218)	DDLT (n = 55)	P-value
Infection	95 (34.8)	66 (30.3)	29 (52.7)	0.002
Peumonia	44 (46.3)	29 (43.9)	15 (51.7)	
Biliary sepsis	9 (9.5)	7 (10.6)	2 (6.9)	
Others	42 (44.2)	30 (45.5)	12 (41.4)	
HCC recurrence	50 (18.3)	49 (22.5)	1 (1.8)	<0.001
Graft failure, rejection	41 (15.0)	34 (15.6)	7 (12.7)	0.595
Vascular complication	36 (13.2)	29 (13.3)	7 (12.7)	0.910
<i>De novo</i> malignancy	14 (5.1)	9 (4.1)	5 (9.1)	0.136
Others	37 (13.6)	31 (14.2)	6 (10.9)	0.521

Values are presented as number (%).

LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma.

**Table 6.** Cause of mortality according to survival period

Cause of mortality	OP mortality	<1 Yr	1–5 Yr	5–10 Yr	≥10 Yr
Total (n = 273)	63 (23.1)	90 (32.9)	85 (31.1)	28 (10.3)	7 (2.6)
Infection	34 (54.0)	29 (32.2)	24 (28.2)	6 (21.4)	2 (28.6)
Peumonia	16 (47.1)	10 (34.5)	12 (50.0)	5 (83.3)	1 (50.0)
Biliary sepsis	0 (0)	4 (13.8)	5 (20.8)	0 (0)	0 (0)
Others	18 (52.9)	15 (21.7)	7 (29.2)	1 (16.7)	1 (50.0)
HCC recurrence	1 (1.6)	20 (22.2)	26 (30.6)	2 (7.1)	1 (14.3)
Graft failure, rejection	6 (9.5)	15 (16.7)	12 (14.1)	7 (25.0)	1 (14.3)
Vascular complication	15 (23.8)	15 (16.7)	5 (5.9)	1 (3.6)	0 (0)
<i>De novo</i> malignancy	0 (0)	1 (1.1)	5 (5.9)	5 (17.9)	3 (42.9)
Others	7 (11.1)	10 (11.1)	13 (15.3)	7 (25.0)	0 (0)
P-value					<0.001

Values are presented as number (%).

OP, operation; HCC, hepatocellular carcinoma.

**Table 7.** Cause of mortality according to case period

Cause of mortality	Period 1 (n = 300)	Period 2 (n = 300)	Period 3 (n = 400)	P-value
Total (n = 273)	115 (42.1)	71 (26.0)	87 (31.9)	<0.001
Infection	37 (32.2)	23 (32.4)	35 (40.2)	0.437
Peumonia	16 (43.2)	11 (47.8)	17 (48.6)	
Biliary sepsis	8 (21.6)	1 (4.3)	0 (0)	
Others	13 (35.1)	11 (47.8)	18 (51.4)	
HCC recurrence	22 (19.1)	7 (9.9)	21 (24.1)	0.067
Graft failure, rejection	17 (14.8)	14 (19.7)	10 (11.5)	0.355
Vascular complication	20 (17.4)	9 (12.7)	7 (8.0)	0.151
<i>De novo</i> malignancy	7 (6.1)	5 (7.0)	2 (2.3)	0.337
Others	12 (10.4)	13 (18.3)	12 (13.8)	0.313

Values are presented as number (%).

HCC, hepatocellular carcinoma.

Period 1: from June 1993 to May 2006; period 2: from May 2006 to April 2011; period 3: from April 2011 to April 2017.

shown in Tables 5–7. Infection was the most common cause of death, representing 34.8% (95 of 273) of all deaths. This was followed by recurrent HCC (18.3%), graft failure (15.0%), and vascular complications (13.2%). Among all infection related deaths, pneumonia was most common (44 of 95, 46.3%). Deaths by biliary sepsis occurred only in 9 patients (9 of 95, 9.5%). Significantly more infection-related deaths occurred in the DDLT group than in the LDLT group ( $P = 0.002$ ). Most deaths related to HCC recurrence occurred in the LDLT group ( $P < 0.001$ ) (Table 5). Among all deaths ( $n = 273$ ), 56.0% (153 of 273) occurred within 1 year after transplantation, and 87.1% (238 of 273) occurred within 5 years after transplantation. Infection was the most common cause of death within 1 year after transplantation. Mortality due to a vascular complications occurred mainly during the perioperative period. Mortality due to HCC recurrence occurred most frequently between 1 and 5 years after transplantation. The rate of mortality due to graft failure was highest between 5 and 10 years after transplantation. Mortality due to *de novo* malignancy occurred most frequently 10 years after transplantation (Table 6). Causes of death according to case period were also evaluated. Infection was the most common cause of death during all case periods (Table 7).

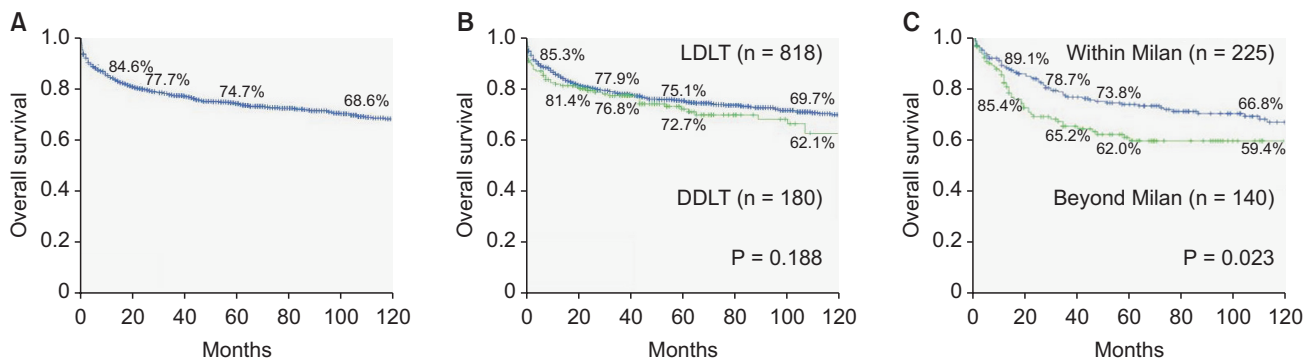
### Survival analysis

The patient survival rates for the entire population ( $n = 998$ ) at 1, 3, 5, and 10 years were 84.6%, 77.7%, 74.7%, and 68.6%, respectively (Fig. 1A). Little difference was found in the survival rate between the LDLT and DDLT groups ( $P = 0.188$ ). The 1-, 3-, 5-, and 10-year survival rates were 85.3%, 77.9%, 75.1%, and 69.7% for the LDLT group and 81.4%, 76.8%, 72.7%, and 62.1% for the DDLT group (Fig. 1B). LTs due to tumor were 411 cases. Among them, we could find reports of exact size and numbers of HCC in 365 patients by pathologic review. 225 patients (61.6%) were within Milan criteria, and 140 patients (38.4%) were beyond Milan criteria. We analyzed overall survival according to Milan

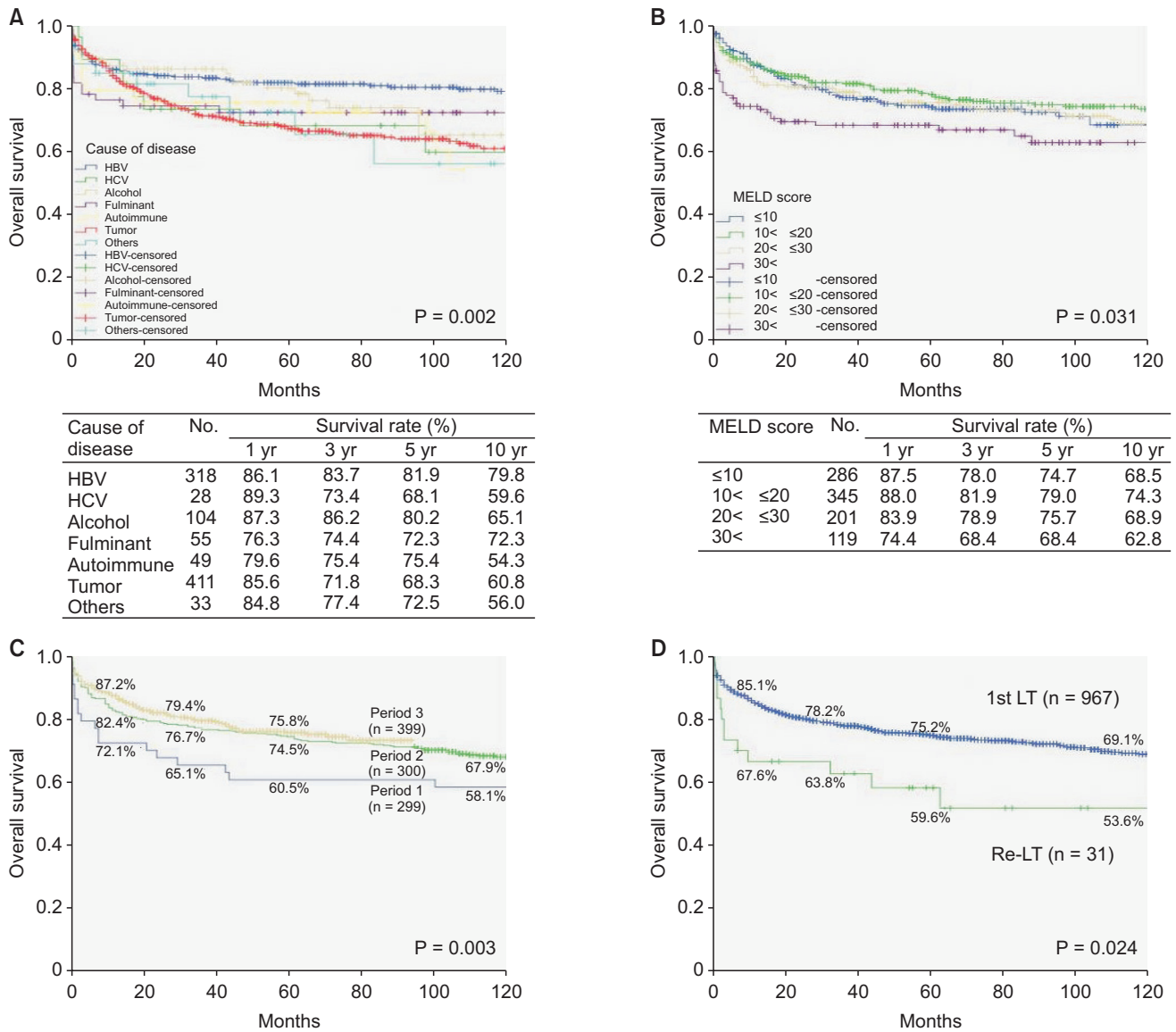
criteria. The patients within Milan criteria showed significant better survival rate than patients beyond Milan criteria ( $P = 0.023$ ) (Fig. 1C).

We analyzed patient survival according to various factors. Cause of disease ( $P = 0.002$ ) (Fig. 2A), disease severity according to the MELD score ( $P = 0.031$ ) (Fig. 2B), case period ( $P = 0.003$ ) (Fig. 2C), and retransplantation ( $P = 0.024$ ) (Fig. 2D) were significantly associated with patient survival. Survival rate by cause of disease is shown in Fig. 2A. Cause of disease was classified into 6 categories: hepatitis B; hepatitis C; alcohol; fulminant hepatitis; autoimmune liver diseases, including primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis; and tumors; a significant difference in survival rate was noted by category ( $P = 0.002$ ): patients with hepatitis B showed the best survival rate among all cause of disease categories. Patients with tumors showed relatively poorer survival than those with other kinds of disease. Among 998 cases, survival rates at 1, 5, and 10 years of patients with tumors ( $n = 411$ ) were significantly worse than those of patients without tumors ( $n = 587$ ) (84.1%, 68.4%, and 60.9% vs. 84.9%, 79.1%, and 73.8%, respectively) ( $P < 0.001$ ) (Fig. 2A). In the survival analysis according to disease severity, patients were split into 4 groups: MELD score of  $\leq 10$  ( $n = 287$ ), 10–20 ( $n = 346$ ), 20–30 ( $n = 201$ ), or  $>30$  ( $n = 119$ ). Patients with MELD scores  $> 30$  demonstrated significantly worse survival than those with a MELD score of  $\leq 10$  ( $P = 0.032$ ) or 10–20 ( $P = 0.004$ ) (Fig. 2B). Case period showed a significant association with overall survival ( $P = 0.003$ ). The survival rate between periods 2 and 3 was similar. However, the survival rate during period 3 was significantly better than that during period 1 (period 1 vs. period 2,  $P = 0.086$ ; period 1 vs. period 3,  $P = 0.034$ ; period 2 vs. period 3,  $P = 0.454$ ) (Fig. 2C). The survival rate of re-transplantation at 1, 5, and 10 years was significantly worse than that of patients who underwent primary transplantation ( $P = 0.024$ ) (Fig. 2D).

We performed multivariate analysis using the Cox regression



**Fig. 1.** Overall survival analysis of 1,000 liver transplantations; overall survival in all cases (A), overall survival according to graft type (B) and overall survival in patients with hepatocellular carcinoma according to Milan criteria (C). LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation.



**Fig. 2.** Overall survival analysis of the 1,000 liver transplantations (LTs); causes of diseases (A), disease severity (B), case period (C), and primary versus retransplantation (D). Period 1: from June 1993 to May 2006; period 2: from May 2006 to April 2011; period 3: from April 2011 to April 2017.

proportional hazard model to identify risk factors for overall survival in the 1,000 LTs. In multivariate analysis, cause of disease ( $P < 0.001$ ), MELD score ( $P < 0.001$ ), case period ( $P = 0.004$ ) were independent prognostic factors in the 1,000 LTs. Otherwise re-LT was not ( $P = 0.221$ ) (Table 8).

## DISCUSSION

We analyzed the survival outcomes of 1,000 LTs performed at a single institution. The results illustrate the evolution of the LT program at our center over the 24 years since its inception in 1993. Although the number of LTs performed annually was nearly 10 in the 1990s, there was an abrupt increase in

the number of LTs, and especially LDLTs, since 2000; we reached a total of 1,000 cases in 2017. Similar to the situation in other Asian countries, LDLTs have been more frequently performed than DDLTs. Continued efforts have been made to improve social awareness regarding organ donation. As a result, according to statistics from the KONOS, the proportion of DDLTs has increased gradually, reaching 34% in 2016 [8]. In our institution, the proportion of DDLTs has also increased over the past several years.

The longer operation time and 2 fold higher surgical complication rate for LDLT versus DDLT may be related to anatomical characteristics, whereby the diameters of vessels and biliary structure at the anastomosis site were smaller in



**Table 8.** Risk factors for overall survival (OS) in the 1,000 liver transplantations by multivariate analysis using the Cox regression proportional hazard model

Risk factor	Univariate analysis of OS			Multivariate analysis of OS		
	HR	95% CI	P-value	HR	95% CI	P-value
Cause of disease			0.003			<0.001
HBV	1			1		
HCV	1.921	0.984–3.749	0.056	3.002	1.507–5.982	0.002
Alcohol	1.294	0.803–2.087	0.290	1.422	0.844–2.398	0.186
Fulminant	1.644	0.936–2.886	0.083	1.627	0.901–2.938	0.107
Autoimmune	1.838	1.062–3.180	0.030	2.015	1.088–3.732	0.026
Tumor	1.855	1.376–2.500	<0.001	2.622	1.853–3.710	<0.001
Others	1.853	0.951–3.610	0.070	2.017	0.985–4.129	0.055
MELD score			0.048			<0.001
Case period			0.013			0.004
Period 1	1			1		
Period 2	0.640	0.473–0.865	0.004	0.578	0.417–0.801	0.001
Period 3	0.823	0.614–1.103	0.192	0.738	0.536–1.017	0.064
Retransplantation			0.040			0.221

HR, Hazard ratio; CI, confidence interval; MELD, model for end-stage liver disease.

living versus deceased donor grafts, so more meticulous and advanced surgical skills are needed for LDLT. The greater number of perioperative transfusions and higher operative mortality rate in the DDLT group may be associated with higher disease severity (higher CTP and MELD scores) versus the LDLT group. As the number of cases increased, age and BMI also increased, showing that the number of LT candidates has been increasing. The volume of transfusion, surgical complications, and operative mortality rates have decreased as the number of cases has increased, likely due to advances in surgical skill and perioperative management [9].

The DDLT Piggyback technique was associated with a significantly shorter operation time than that of classic anastomosis, because of the lack of a veno-venous bypass procedure and improvements in surgical skill over time. Operation time tended to decrease over time in both the DDLT and LDLT groups. Transfusions, surgical complications, and operative mortality tended to improve more significantly over time in the LDLT versus DDLT group, supporting the notion that technical improvements were apparently more pronounced for LDLT. It has also been proposed that LDLT requires a more sophisticated technique due to the anatomical characteristics [10,11].

In this study, 273 of the 969 total patients died during the follow-up period. Survival data of only 2 patients could not be evaluated because of loss to follow-up due to emigration. The most common cause of mortality was infection. Other large studies with long-term follow-up also reported that infection was a major cause of death [12,13]. Infection was the major cause of death in all survival periods after transplant (21.4%–

54.0%) in our study. Furthermore, it was the most common cause of death in all case periods (26.0%–42.1%). Therefore, controlling infection is an important challenge to improve survival in LT, especially DDLT [14]. In addition, over half of the cases of operative mortality (54.0%) were due to infection. Therefore, infection control has a more important role during perioperative period than during other periods. Mortality rate due to recurrence of HCC was significantly higher for patients who underwent LDLT versus those who underwent DDLT, which may be related to a higher proportion of tumors in the LDLT versus DDLT group.

The patient survival rates for the entire population at 5 and 10 years were 74.7% and 68.6%, respectively. These results are comparable with those reported by the largest volume LT centers, although the study populations differed [9,15]. Patients with hepatitis B had the best survival rates among all causes of disease, which can be explained by the effective antiviral agents used for hepatitis B prophylaxis. Combining prophylaxis with antiviral agent and hepatitis B immune globulins can prevent recurrence of hepatitis B following LT [16]. In the present study, the 5-year survival rate for patients who underwent LT due to a tumor was 68.3%, which was comparable with outcomes at other institutions [17-19]. Otherwise, patients with tumors showed relatively poorer survival than those with other kinds of disease in this study. The most common cause of mortality in this group was tumor recurrence (n = 49, 36.6%). This may be the result of applying expanded criteria beyond the Milan criteria in our center, as in many other institutions. Among our cases, 35% of our patients underwent LT due to a tumor, which was beyond the Milan criteria. Applying expanded

criteria, especially for LDLT, has been widely performed [18-20]. Otherwise, some studies reported unsatisfactory results [21,22]. Therefore, the optimal criteria for LT in patients with HCC are still uncertain; more studies and discussion are needed. Disease severity according to the MELD score was associated with long-term survival. In particular, patients with a MELD score > 30 showed significantly poorer survival than other patients. The relationship between pretransplant MELD score and posttransplant patient survival is controversial. However, many studies have reported poorer survival with a higher MELD score [23-25]. Survival during period 3 was significantly better than that during period 1 in this study ( $P = 0.034$ ). Perioperative mortality, defined as death within 30 days after surgery, also tended to be lower in period 3 than period 1 ( $P = 0.100$ ), indicating that surgical techniques and perioperative management for transplant patients have improved and undergone standardization since 1993. As a result, the learning curve for LT has been overcome and survival has

been improved. Survival of retransplant patients showed a steep decrease within 1 year. This result was associated with emergent transplants due to sudden deterioration, such as vascular complications or acute rejection after primary transplantation. It may also be related to the technical difficulty of retransplantation compared to primary transplantation.

In conclusion, surgical techniques and perioperative management for transplant patients have improved and become standardized. As a result, the learning curve for LT has been overcome and survival rates have improved. Perioperative infection control and management of patients with HCC will continue to play important roles in improving outcomes.

## CONFLICTS OF INTEREST

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

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