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Mortality and associated factors among patients who underwent liver transplantation in South Korea from 2017 to 2021: a retrospective observational study

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Purpose: Liver transplantation (LT) in South Korea dates back to 1988. However, Asians may be reluctant to donate their organs because of the influence of their traditional religious and philosophical beliefs. We aimed to investigate the mortality and associated factors among patients admitted after LT in South Korea.
Methods: The South Korean National Health Insurance Service database was used as a data source. All adult patients who underwent LT between January 1, 2017 and December 31, 2021 (5 years) were included in the study.
Results: A total of 7,316 patients were included in the analysis (living donor LT [LDLT], 5,412; deceased donor LT [DDLT], 1,904). The 1-year mortality rate was 12.8% (LDLT, 8.2%; DDLT, 25.9%; P < 0.001), and the postoperative complication rate was 26.8% (LDLT, 16.7%; DDLT, 55.6%; P < 0.001). The average length of hospital stay was 30.8 days, and that in the intensive care unit was 6.1 days. The total mean cost was 69,954 US dollars, and the self-cost was 6,008 US dollars. After adjusting confounders, DDLT (hazard ratio [HR], 2.10; 95% confidence interval [CI], 1.79–5.20; P < 0.001), re-LDLT (HR, 4.82; 95% CI, 3.10–7.40; P < 0.001), re-DDLT (HR, 4.65; 95% CI, 3.55–7.12; P < 0.001), and postoperative complications (HR, 1.72; 95% CI, 1.39–2.12; P < 0.001) were potential risk factors for higher 1-year mortality after transplantation.
Conclusion: LDLT was performed at a higher rate in South Korea and was associated with lower mortality and fewer postoperative complications than DDLT. Redo LT led to higher mortality rates.
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Key Words: Liver transplantation, Living donors, Mortality, Republic of Korea

INTRODUCTION

Liver transplantation (LT) in South Korea dates back to 1988 when a child with Wilson's disease underwent a successful LT from a deceased donor (DDLT) [1]. Living donor LT (LDLT) was performed for the first time in 1994 [2].

Asians may be reluctant to donate their organs or those of their families when deceased because of the influence of their traditional religious and philosophical beliefs [3,4]. Unlike other Asian countries, South Korea has experienced a rapid increase in the DDLT rate relative to the legislation on organ transplant acts and the launch of the Center for the Korean Network for Organ Sharing (KONOS) in 2000 [5,6]. Since 2008, the DDLT rate has increased and remained at 20%–30% of the total liver transplants. Although South Korea's rate of brain-dead organ donors (7.9 per million population [PMP]) was higher than that of other Asian countries, it was still far lower than that of Spain (46.0 PMP), the United States (44.5 PMP), France (21.1 PMP), Australia, and other countries [7-10].

The number of living donors was 51.1 PMP compared to 19.2

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PMP in the USA, and 6–7 PMP in Spain, Italy, and Germany in 2021. While there is great cultural resistance to donating organs of the deceased, donating organs to one's family or relatives is relatively proactive [1,11]. Due to the shortage of deceased donors, the number of LDLTs in South Korea has increased. South Korea has been at the forefront of LDLT technology advancement, with an impressive 1-year survival rate of 89.9% [2,8,9,12].

Accordingly, we aimed to analyze recent trends and risk factors for mortality and postoperative complications of LT in South Korea using the National Health Insurance Service (NHIS) data.

METHODS

Study design, setting, and ethical statements

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations were adhered to in this population-based, retrospective cohort study. The need for a review of the study protocol was waived by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital due to the use of publicly available data (No. X-2304-825-901). The requirement for informed consent was also waived by the IRB due to the retrospective and anonymous nature of the data analysis.

Data source

South Korea's NHIS database was used as the data source. The NHIS is the sole public health insurance system in South Korea and encompasses comprehensive information regarding disease diagnoses and prescriptions for all drugs and procedures in accordance with the codes of the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Access to the data was granted by the NHIS after approval of the study protocol (NHIS-2023-1-566).

Patient population

All adult patients (aged 18 years or older) who underwent LT between January 1, 2017 and December 31, 2021 were included. Children under 18 years of age were excluded from the analysis.

Endpoint

The primary endpoint was 1-year mortality, defined as any death occurring within 1 year of transplantation surgery. The secondary outcomes included 30-day and 90-day mortality and postoperative complications. Complications that occurred following surgery and during the hospitalization period were considered postoperative complications. The hospitalization period also encompassed the time when the patient was transferred to another medical facility for the purpose of receiving rehabilitation and postoperative care. Postoperative conditions were extracted using the ICD-10 codes, such as cerebral infarction or hemorrhage (I60–I64), acute coronary events (I21, I22, and I252), heart failure (I50), pulmonary embolism (I26), biliary tract complications (K83), acute renal failure (N17), sepsis (A40 and A41), wound infection (T793 and T814), pneumonia (J12–J18 and J69), or urinary tract infection (N390, T835, and N30).

Variables

Demographic information including age and sex was also obtained. Data on occupation, dwelling type, and household income level were gathered to determine the patients' socioeconomic status.

The habitat at the time of transplantation was classified as urban (Seoul and other metropolitan cities) or rural (all other locations). The NHIS uses patients' family income levels to calculate insurance premiums in a given year, and the government subsidizes approximately 67% of their medical expenses. Individuals who cannot afford insurance premiums or struggle to sustain themselves are eligible for the medical aid program. The government pays almost all medical expenses, thereby reducing the financial burden of medical treatment for such patients. The patients were divided into 5 groups based on their income levels, with 4 groups established using quartiles and the medical aid program group.

The Charlson Comorbidity Index score was derived using codes from the ICD-10 (Supplementary Fig. 1), which were entered into the NHIS database within 1 year of transplantation. People must declare all disabilities in the NHIS database in order to be eligible for social welfare benefits in South Korea. As a result, data about underlying disabilities was acquired. In South Korea, disability evaluations are carried out by experts in the relevant professions. The degree to which the illness interferes with day-to-day functioning was assessed by a trained medical professional, and underlying disability were classified as mild-to-moderate or severe. The main diagnosis at the time of LT was also collected and classified into 4 groups as follows; liver cancer (C22.0), liver cirrhosis (K74.6), liver cancer with liver cirrhosis, and others. The hospital levels were divided into 3 categories: A, B, and C. Hospital levels were determined using a hierarchical technique and were included as covariates. Hierarchical cluster analysis was used to evaluate hospital-related variables along with agglomerative clustering. These factors were hospital type (tertiary general hospital, general hospital, or other types of hospital), total number of physicians, specialized physicians, nurses, pharmacists, operating room beds, emergency room beds, and operating room beds. The findings of the hierarchical clustering analysis led to the definition of 3 hospital levels. Supplementary Table 1 contains detailed information on the attributes at each hospital level.

Statistical analysis

Categorical data are presented as frequencies with percentages, while continuous variables are presented as means with standard deviations (SDs). To compare clinical outcomes between 2 groups (LDLT *vs.* DDLT), the chi-square test was employed for categorical variables, respectively. We conducted a multivariable Cox regression analysis to identify factors related to 1-year mortality, and the results are presented as hazard ratios (HRs) with 95% confidence interval (CIs). All covariates were included in the adjustment model, and log-log plots were used to ensure that the central assumption of the Cox proportional hazards model was met. Statistical analyses were conducted using R software (ver. 4.0.3; R Foundation for Statistical Computing).

RESULTS

From January 1, 2017, to December 31, 2021, 7,316 individuals received LT in South Korea. Of these instances, 5,412 underwent LDLT, while 1,904 underwent DDLT. The average age was 54.2 years (SD, ±13.0 years), and 31.4% (2,297/7,316) were females. The average lengths of hospital and intensive care unit (ICU) stays were 30.8 days (SD, ±15.8 days) and 6.1 days (SD, ±7.1 days), respectively. The average total cost of hospitalization was 69,953.6 US dollars (SD, ±26,178.6 US dollars) (Table 1). Table 2 shows that the age and total medical costs of patients who underwent LT tended to increase, whereas the length of stay in the hospital and ICU did not change during the 5 years.

Fig. 1 presents the 30-day, 90-day, and 1-year mortality rates after LT. As shown in Table 3, the LDLT group showed lower 30-day (1.7% *vs.* 10.9%; P < 0.001), 90-day (3.6% *vs.* 18.4%; P < 0.001), and 1-year mortality (8.2% *vs.* 25.9%; P < 0.001), and lower postoperative complications (19.4% *vs.* 54.7%; P < 0.001) than the DDLT group. Moreover, as a result of the multivariable Cox regression model for 1-year all-cause mortality after LT, the first DDLT showed an association with higher mortality than the first LDLT (HR, 2.10; 95% CI, 1.79–5.20; P < 0.001), as shown in Table 4. Additionally, re-LDLT (HR, 4.82; 95% CI, 3.10–7.75; P < 0.001) and re-DDLT (HR, 4.65; 95% CI, 3.55–7.12; P < 0.001) were associated with higher 1-year mortality compared to the first LDLT, respectively. The occurrence of postoperative complications was associated with higher mortality after LT (HR, 1.72; 95% CI, 1.39–2.12; P < 0.001). Particularly, cerebral infarction or hemorrhage, pulmonary embolism, acute kidney injury, sepsis, and pneumonia were associated with increased 1-year mortality as described in Table 4.

DISCUSSION

A total of 7, 316 adult patients with LT in South Korea were classified as LDLT, and more than twice as many as DDLT. The postoperative complication rate and the 1-year mortality rate were higher in the DDLT group than in the LDLT group. The 1-year survival rate of adults with LT in the recent 5 years in this study was higher than the average 1-year survival rate of LT in the annual report of South Korea (LDLT, 90.5%; DDLT, 76.4%)

Table 1. Clinicopathologic characteristics

Characteristic	Data
No. of patients	7,316
Age (yr)	54.2 ± 13.0
Female sex	2,297 (31.4)
Having a job	5,717 (78.1)
Household income level	
Q1 (lowest)	978 (13.4)
Q2	1,049 (14.3)
Q3	1,342 (18.3)
Q4 (highest)	1,894 (25.9)
Medical aid program group	316 (4.3)
Unknown	1,737 (23.7)
Residence	
Urban area	2,437 (33.3)
Rural area	4,879 (66.7)
Underlying disability	
Mild-to-moderate	3,226 (44.1)
Severe	222 (3.0)
Hospital level	
A	2,941 (40.2)
B	79 (1.1)
C	4,296 (58.7)
CCI score	3.9 ± 2.1
Type of LT	
First LDLT	5,345 (73.1)
First DDLT	1,738 (23.8)
Re-LDLT	67 (0.9)
Re-DDLT	166 (2.3)
Main diagnosis at LT	
Liver cancer	2,286 (31.2)
Liver cirrhosis	1,561 (21.3)
Liver cancer with liver cirrhosis	927 (12.7)
Others	2,542 (34.7)
LOS (day)	30.8 ± 15.8
ICU stay (day)	6.1 ± 7.1
Total cost for hospitalization (US dollar)	69,953.6 ± 26,178.6
Self-cost for hospitalization (US dollar)	6,007.5 ± 3,498.4
Year of LT	
2017	1,425 (19.5)
2018	1,408 (19.2)
2019	1,515 (20.7)
2020	1,492 (20.4)
2021	1,476 (20.2)

Values are presented as number only, mean ± standard deviation, or number (%).
CCI, Charlson Comorbidity Index; LT, liver transplantation; LDLT, living donor LT; DDLT, DDLT, deceased donor LT; LOS, length of hospital stay; ICU, intensive care unit.

[10]. The first DDLT was associated with higher mortality than the first LDLT. Redo operations of LDLT and DDLT were higher than the first LT, respectively. The average duration of stay in the ICU was 6.1 days, whereas the overall hospital stay was 30.8 days. The self-cost was 6,008 US dollars, while the overall mean cost was 69,954 US dollars.

With the exception of nations like China and South Korea, attempts to promote DDLT in Asia have not been very successful [12]. According to research, Asians are less likely than Caucasians to donate their organs [12]. It has been demonstrated that Confucian principles and, to a lesser extent, Buddhist and Daoist beliefs—which link an undamaged body to reverence for one's ancestors or the natural world—have a detrimental impact on people's general willingness to donate [4]. Unlike most other Asian countries, DDLT has grown dramatically in South Korea, accounting for 20%–30% of LT with the legislation of related acts and KONOS [10]. KONOS was founded in 1999 as the national organization responsible for managing transplant-

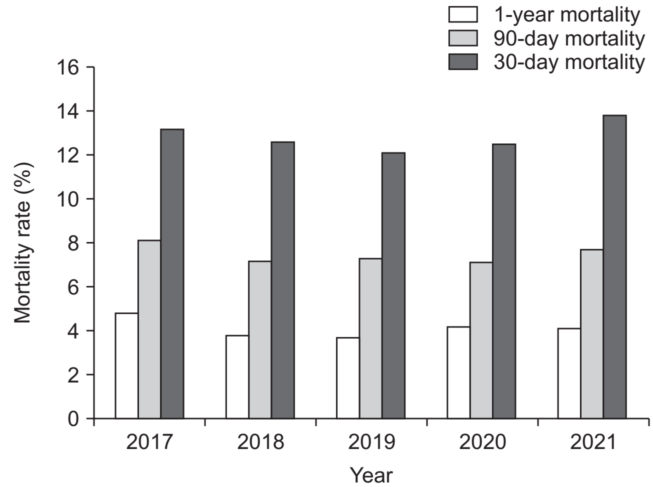

Fig. 1. The 30-day, 90-day, and 1-year mortality rates after liver transplantation.

Table 2. Age and total medical costs of patients who underwent liver transplantation

Variable	Year				
	2017	2018	2019	2020	2021
Age (yr)	53.1 ± 13.6	54.1 ± 12.4	54.0 ± 13.3	54.8 ± 12.6	55.1 ± 13.0
LOS (day)	30.0 ± 15.3	31.6 ± 15.6	31.1 ± 16.0	30.8 ± 16.6	30.6 ± 15.5
ICU LOS (day)	6.0 ± 6.9	5.7 ± 5.6	6.3 ± 7.9	6.2 ± 7.3	6.2 ± 7.4
Total cost (US dollar)	66,706.1 ± 23,742.8	67,703.3 ± 24,348.2	69,937.0 ± 26,509.3	71,807.5 ± 26,989.1	73,378.4 ± 28,303.7
Self-cost (US dollar)	5,238.1 ± 3,131.0	5,665.7 ± 3,281.8	6,072.2 ± 3,492.4	6,366.5 ± 3,508.7	6,647.3 ± 3,842.7

Values are presented as mean ± standard deviation.
LOS, length of hospital stay; ICU, intensive care unit.

Table 3. Mortality and postoperative complication

Variable	Total LT	LDLT	DDLT	P-value
No. of patients	7,316	5,412	1,904	
Mortality				
30-day	302 (4.1)	94 (1.7)	208 (10.9)	<0.001
90-day	545 (7.4)	195 (3.6)	350 (18.4)	<0.001
1-year	939 (12.8)	446 (8.2)	493 (25.9)	<0.001
Postoperative complication	2,104 (28.8)	1,040 (19.2)	1,064 (55.9)	<0.001
Cerebral infarction or hemorrhage	151 (2.1)	77 (1.4)	74 (3.9)	<0.001
Acute coronary events	25 (0.3)	12 (0.2)	13 (0.7)	0.003
Heart failure	258 (3.5)	130 (2.4)	128 (6.7)	<0.001
Pulmonary embolism	54 (0.7)	20 (0.4)	34 (1.8)	<0.001
Biliary tract complication	367 (5.0)	263 (4.9)	104 (5.3)	<0.001
Acute kidney injury	1,011 (13.8)	329 (6.1)	682 (35.8)	<0.001
Sepsis	470 (6.4)	199 (3.7)	271 (14.2)	<0.001
Wound infection	49 (0.7)	25 (4.6)	24 (0.4)	<0.001
Pneumonia	616 (8.4)	290 (5.4)	326 (17.1)	<0.001
Urinary tract infection	103 (1.4)	49 (0.9)	54 (2.8)	<0.001

Values are presented as number only or number (%).
LT, liver transplantation; LDLT, living donor LT; DDLT, DDLT, deceased donor LT.

Table 4. Multivariable Cox regression model for 1-year all-cause mortality after LT

Variable	HR (95% CI)	P-value
Age	1.02 (1.01–1.02)	<0.001
Female sex	1.02 (0.88–1.17)	0.831
Having a job	2.20 (1.31–3.70)	0.003
Household income level		
Q1 (lowest)	1	
Q2	0.84 (0.64–1.11)	0.217
Q3	0.89 (0.69–1.15)	0.376
Q4 (highest)	1.13 (0.89–1.43)	0.327
Medical aid program group	1.25 (0.88–1.78)	0.221
Unknown	1.40 (0.83–2.39)	0.206
Residence		
Urban area	1	
Rural area	1.15 (0.97–1.35)	0.101
Underlying disability		
Mild-to-moderate	1.17 (1.05–1.38)	0.032
Severe	2.10 (1.8–2.48)	<0.001
Hospital level		
A	1	
B	0.94 (0.56–1.59)	0.815
C	0.79 (0.68–0.92)	0.002
CCI score	1.06 (1.02–1.09)	0.002
Type of LT		
First LDLT	1	
First DDLT	2.10 (1.79–5.20)	<0.001
Re-LDLT	4.82 (3.10–7.75)	<0.001
Re-DDLT	4.65 (3.55–7.12)	<0.001
ICU LOS		
Main diagnosis at LT		
Liver cancer	1	
Liver cirrhosis	0.94 (0.78–1.13)	0.532
Liver cancer with liver cirrhosis	0.87 (0.73–1.03)	0.102
Others	0.93 (0.73–1.17)	0.511
Year of ICU admission		
2017	1	
2018	0.98 (0.80–1.21)	0.868
2019	0.91 (0.74–1.11)	0.344
2020	0.86 (0.70–1.03)	0.160
2021	0.95 (0.77–1.16)	0.586
Postoperative complication	1.72 (1.39–2.12)	<0.001
Cerebral infarction or hemorrhage	1.45 (1.08–1.94)	0.013
Acute coronary events	0.81 (0.38–1.75)	0.592
Heart failure	1.03 (0.79–1.34)	0.831
Pulmonary embolism	1.80 (1.13–2.85)	0.013
Biliary tract complication	0.99 (0.73–1.33)	0.937
Acute kidney injury	1.43 (1.22–1.68)	<0.001
Sepsis	2.04 (1.71–2.46)	<0.001
Wound infection	1.53 (0.92–1.21)	0.280
Pneumonia	1.27 (1.06–1.52)	0.010
Urinary tract infection	0.79 (0.51–1.21)	0.280

HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; LT, liver transplantation; LDLT, living donor LT; DDLT, deceased donor LT; ICU, intensive care unit; LOS, length of hospital stay.

related activities, including organ distribution [1,2,5,10]. In 2016, DDLT accounted for 34.5% of all liver transplants (508 annually) [10].

However, in South Korea, deceased donations have decreased recently [8]. According to KONOS, DDLT rapidly decreased to 357, accounting for 23.6% of the total LT cases by 2021 [10,13]. Alternatively, the number of people waiting for liver transplants is on the rise every year, reaching 6,388 in 2021, with an increase of 4.3% compared with that of the year before [10]. The average wait time for a LT is 201 days, and many people die during this time due to the extremely limited and declining number of brain-dead LT donors [10]. Since 2016, South Korea has used the Model of End-Stage Liver Disease (MELD) system to ensure that the patients with the worst prognosis receive LTs as soon as possible [8]. Given that DDLT can be performed with an average MELD score of up to 36.5 points, the risk of surgery increases in situations in which the condition is too severe, leading to progressively worse outcomes [8]. Consequently, South Korea has more LTs from living donors. The Korean culture has a strong sense of "family" and are willing to donate their organs to family members; in some Asian countries, these traits may be shared religiously and culturally [4]. Overall, these factors may contribute to the relatively high mortality rate of DDLT in South Korea compared to Western countries.

HBV infection and liver cancer are major causes of LT in South Korea [3,14]. Patients with liver cancer tend to undergo LDLT, which can be performed as an elective operation (not an emergency) for patients with a relatively lower MELD score [2]. Therefore, patients with LDLT have a much higher survival rate than DDLT [15]. However, redo operations in both DDLT and LDLT showed similarly worse outcomes in this study. This may be a reason for providing patients and their guardians with a more detailed explanation of worse outcomes after reoperation for liver surgery.

Asian LT centers have become global innovators, trailblazers, and catalysts for technological advancement, particularly in the field of LDLT [12,16]. With some high-volume centers performing more than 200 LDLTs per year with good outcomes for the donor and recipient, techniques to expand the living donor pool have also been adopted, such as ABO-incompatible, paired exchange, and dual-lobe LDLTs [1,12,17]. In this study, we found that level C hospitals showed lower mortality than levels A and B hospitals in the multivariable Cox regression model for 1-year all-cause mortality after LT. Level C included only 4 tertiary general hospitals with the highest number of medical staff and beds in hospitals, ICUs, operating rooms, and emergency rooms. In South Korea, tertiary general hospitals with abundant human resources and hospital facilities often actively perform LT [16,18,19]. Therefore, this result could be explained by a previous study by Yoo et al. [20], which showed that in-hospital and long-term mortality rates following LDLT were superior in centers with higher case volumes than in those with lower case volumes.

This study has a few limitations. First, because the NHIS database does not include such data, crucial information such as imaging and laboratory data or behaviors such as smoking, exercising, drinking alcohol, or maintaining a healthy diet were not included for adjustment in this study. Second, there was insufficient information to accurately assess disease severity. Third, the results may have been affected by residual confounders because of its retrospective database design. Third, since registered ICD-10 codes were used to define various diseases including postoperative complications, there might be some missing cases in this study. Lastly, we did not consider the patients who underwent surgery due to postoperative complications after LT.

In conclusion, LDLT is performed more frequently than DDLT in South Korea and is associated with lower rates of postoperative complications and mortality. The mortality rate increases with LT reoperation, irrespective of whether the first LT was DDLT or LDLT.

SUPPLEMENTARY MATERIALS

Supplementary Table 1 and Supplementary Fig. 1 can be found via https://doi.org/10.4174/astr.2024.107.5.245.

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Conflict of Interest

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

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Formal Analysis: TKO
Investigation: IAS
Methodology: TKO
Writing – Original Draft: TKO
Writing – Review & Editing: IAS

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