Changes in the indications for living donor liver transplantation: single-institution experience of 3,145 cases over 10 years

Sang-Hyun Kang, Shin Hwang, Chul-Soo Ahn, Ki-Hun Kim, Deok-Bog Moon, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Gil-Chun Park, Jung-Man Namgoong, Young-In Yoon, Hui-Dong Cho, Jae-Hyun Kwon, Yong-Kyu Chung, Jin-Uk Choi, Sung-Gyu Lee

Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: To understand the changing demands and recent trends in the indications for living donor liver transplantation (LDLT), the present study aimed to analyze the indications for LDLT performed in a high-volume transplantation center over 10 years.

Methods: The liver transplantation database at our institution was searched to identify patients who underwent LDLT during a 10-year period from January 2008 to December 2017. The study subjects (n=3,145) were divided into two groups: adult patients (n=3,019, 92.7%) and pediatric patients (n=126, 3.9%).

Results: In the adult recipients, the primary diagnoses were hepatitis B virus (HBV)-associated liver cirrhosis (n=1,898, 62.9%), alcoholic liver disease (n=482, 16.0%), hepatitis C virus-associated cirrhosis (n=203, 6.7%), acute liver failure (n=127, n=4.2%), and other diseases (n=157, 5.2%). The mean Model for End-Stage Liver Disease score was 15.6±8.8 (range, 6–40). The proportion of patients with HBV-associated liver disease gradually decreased, but the proportion of those with alcoholic liver disease increased. Hepatocellular carcinoma (HCC) was diagnosed in 1,467 patients (48.6%). The mean proportion of patients with HCC was 63.1% among those with HBV-associated liver disease. In pediatric recipients, the primary diagnoses were biliary atresia (n=51, 40.5%), liver failure of various causes (n=37, 29.4%), metabolic disease (n=22, 17.5%), hepatoblastoma (n=12, 9.5%), and infectious diseases (n=4, 3.2%).

Conclusions: Our results showed that there were some significant changes in the indications of LDLT. We believe that our results may reflect the real changes in the indications of LDLT and they will be useful for predicting further changes in the future.

Keywords: Living donor liver transplantation; Hepatitis B virus; Liver cirrhosis; Pediatric transplantation; Biliary atresia
INTRODUCTION

Liver transplantation (LT) is the established treatment for a variety of end-stage liver diseases. In countries with a shortage of deceased donors, living donor liver transplantation (LDLT) is performed as the main type of LT. In Korea, the most common indication for LT in adults is hepatitis B virus (HBV)-associated liver cirrhosis, whereas alcoholic liver cirrhosis and hepatitis C virus (HCV)-associated liver cirrhosis are the main indications of LT in Western countries. However, aggressive antiviral treatments for both HBV and HCV have recently been introduced, which has led to significant changes in the distribution of various LT indications in Korea. Furthermore, the Model for End-Stage Liver Disease (MELD) score was recently adopted to allocate deceased donor livers for transplantation, so noticeable changes have occurred in the indications for deceased donor LT (DDLT) as well. Specifically, the number of alcoholic liver disease (ALD) cases undergoing DDLT has markedly increased. In pediatric patients under 12 years of age, the Pediatric End-Stage Liver Disease (PELD) score is used [1-4].

However, few data are currently available regarding the recent changes in indications for LDLT in Korea, even though clinicians may benefit from a better understanding of the changing demands and recent trends in the indications for LDLT in adult and pediatric patients. Therefore, in the present study, we aimed to analyze the institutional data regarding indications for LDLT performed in a high-volume transplantation center over 10 years.

METHODS

The protocols of this retrospective cohort study were approved by the Institutional Review Board of the Asan Medical Center (IRB No. 2018-0739).

The LT database at our institution was searched to identify patients who underwent LT during a 10-year period from January 2008 to December 2017. Only LDLT cases were included in the present study, because DDLT rates were greatly influenced by the annual incidence of deceased donors and the recent adoption of MELD score-
based allocation. Retransplantation cases were excluded to avoid unnecessary bias.

The study patients (n=3,145) were divided into two groups: adult patients (age ≥18 years; n=3,019, 92.7%) and pediatric patients (age <18 years; n=126, 3.9%). Only those diagnosed with hepatocellular carcinoma (HCC) before their LT were defined as patients with HCC, while patients with incidental HCC in the explanted livers were excluded from the analysis. Since HCC on a background of chronic liver disease cannot be categorized as either HCC or chronic liver disease, these two diseases were analyzed separately. Descriptive statistical analyses were performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The overall profiles of the 3,019 adult patients are summarized in Table 1. The number of cases of each disease was as follows: HBV-associated liver disease, 1,898 (62.9%); ALD, 482 (16.0%); HCV-associated liver disease, 203 (6.7%); acute liver failure, 127 (4.2%); and other diseases, 157 (5.2%). The mean MELD score was 15.6±8.8 (range, 6–40).

The annual numbers of adult LDLT cases over the 10-year study period, according to the primary indications, are depicted in Fig. 1. The overall number of adult LDLT cases gradually increased over the 10 years. The proportion of cases involving HBV-associated liver disease gradually decreased, while the proportion involving ALD noticeably increased (Figs. 2 and 3).

HCC was diagnosed in 1,467 patients (48.6%) before the LDLT operation. The annual proportion of HCC cases among all adult LT procedures fluctuated between 44.4% and 54.0% (Fig. 4). The proportion of annual cases for each disease category among patients undergoing LDLT with HCC is depicted in Fig. 5. After isolating the patients with HBV-associated disease, the annual proportion of
patients with HCC also fluctuated from 52.6% to 71.2%, with a mean value of 63.1% (1,198/1,898) (Fig. 6).

In 126 pediatric patients, the primary indications for LDLT are summarized in Table 2, in which the number of cases of each disease was as follows: biliary atresia, 51 (40.5%); liver failure of various causes, 37 (29.4%); metabolic disease, 22 (17.5%); hepatoblastoma, 12 (9.5%); and infectious diseases, 4 (3.2%). HCC was identified in two patients (1.6%). The annual case number of pediatric LDLT according to the primary indications over the 10 years are depicted in Fig. 7. The mean PELD score was 22.1±9.4 (range, 6–40).
DISCUSSION

Over the study period of 10 years, the annual number of LDLT cases gradually increased. The common indications for LDLT remained unchanged, but their proportions changed according to the changing demand. The increasing incidence of deceased donors and adoption of MELD score-based liver allocation also affected the real-world demand for LDLT in the present study [1-5].

In Korea, the most common indication for adult DLLT for a long time has been HBV-associated liver disease. HCC often develops in patients with this disease, so a diagnosis of HCC often prompts the decision to perform LDLT. In the present study, 63.1% of patients with HBV-associated liver disease had been diagnosed with HCC at the time of LDLT. Most of them had relatively low MELD score, usually less than 20, because they wanted to receive LDLT early, before progression to liver cirrhosis or more advanced HCC [6-8].

In our analysis, the most noticeable change was the progressive increase in the proportion of patients with ALD. In 2008, only 6.6% of patients (16/243) undergoing LDLT had ALD, but this gradually increased to 19.8% (69/348) in 2017. These results indicate that ALD is now regarded as a legitimate indication for LDLT in Korean society. After the adoption of MELD score-based allocation in Korea in June 2016, the proportion of patients receiving DDLT who had ALD significantly increased, because most of them had very high MELD scores of category 2 (MELD score ≥38) or upper category 3 (MELD score ≥35) [2-4]. We presume that such ALD patients have very high MELD score mainly because they often continue drinking until the terminal stage, and because they are neglected by family members and fail to maintain basic activities of daily living. In contrast, patients with ALD undergoing LDLT have a relatively favorable general condition, as well as a relatively long abstinence period [9-11].

In more recent years, we encountered patients with HCV-associated liver disease more frequently than be-

**Table 2.** Indications for living donor liver transplantation in 126 pediatric patients

| Disease                                      | No. of case |
|----------------------------------------------|-------------|
| Biliary atresia                             | 51          |
| Metabolic                                    |             |
| Progressive familial intrahepatic cholestasis| 6           |
| Wilson disease                               | 6           |
| Methylmalonic acidemia                       | 3           |
| Ornithine transcarbamylase deficiency        | 2           |
| Alagille syndrome                            | 1           |
| Alpha-1 antitrypsin deficiency               | 1           |
| Benign recurrent intrahepatic cholestasis    | 1           |
| Primary hyperoxaluria type I                 | 1           |
| Glycogen storage disease                     | 1           |
| Liver failure                                |             |
| Acute liver failure of unknown causes        | 20          |
| Toxic hepatitis                              | 9           |
| Total parenteral nutrition-induced liver failure| 2         |
| Congestive heart failure-induced liver failure| 2         |
| Cryptogenic liver cirrhosis                  | 2           |
| Neonatal hepatitis                           | 1           |
| Primary sclerosing cholangitis               | 1           |
| Hepatoblastoma                               | 12          |
| Infection                                    |             |
| Epstein-Barr virus hepatitis                 | 2           |
| Hepatitis A virus-associated acute liver failure| 1         |
| Hepatitis B virus-associated liver failure    | 1           |

Fig. 6. Changes in the annual proportions of adult patients with hepatocellular carcinoma (HCC) among those with hepatitis B virus-associated liver disease.
fore [12,13]. Contrary to our expectation, the proportion of patients with HCV-associated liver disease had not increased noticeably. We suggest two potential reasons for this: (1) that the increase in LDL T recipients with HCV-associated liver disease was more marked in recent years than during the study period and (2) that many patients with HCV receiving direct-acting antiviral agent became seronegative, which might lead to a decrease in advanced liver cirrhosis.

With the increase in the incidence of deceased donors, the need for urgent LDL T in patients with acute liver failure has decreased [14]. Furthermore, adoption of MELD score-based allocation gives organ allocation priority to patients with high MELD score [2-5]. However, in the present study, highly urgent LDL T had to be performed in some patients with rapidly deteriorating fulminant hepatic failure, because the timing of DDL T allocation is usually unpredictable. Until the incidence of deceased donors increases markedly in Korea, LDL T will still be necessary in highly urgent cases.

Pediatric LT is more influenced by the incidence of deceased donors than in adult LT, because the pool of pediatric recipient candidates is small and the chance of split LT is high. Adoption of PELD score might not lead to significant changes in pediatric LT, probably because there is no shortage of deceased donors permitting liver splitting relative to the pool size of pediatric candidate recipients [2,15-17].

Many patients with metabolic diseases other than Wilson’s disease have not benefited from the adoption of MELD/PELD score, because no exceptions to MELD score are permitted in the current Korean deceased donor liver allocation system. Many pediatric patients with metabolic diseases show low PELD scores, even when their condition is deteriorating, so the parents of such pediatric patients must elect to perform LDL T [2,15].

LDLT to treat neoplastic diseases other than HCC has sporadically been performed in our institution. Epithelioid hemangoendothelioma and hepatoblastoma are established eligible indications for adult and pediatric LT, respectively [18-21]. Some studies have used LDL T to treat perihilar cholangiocarcinoma [22-24], which we do not regard as an eligible indication for LDL T because it entails a high risk of tumor recurrence.

Our high-volume experience of LDL T constituted approximately one-third of Korean LDL T cases nationwide. Thus, our results likely reliably reflect the real-world situation regarding LDL T in Korea. Indeed, we performed this study mainly because data are still lacking regarding recent changes in indications for LDL T. A collection of similar high-volume studies from the other major Korean LT centers will be helpful to visualize the landscape of LDL T in Korea.

There were some limitations in the present study. It was a retrospective, single-center study, although the sample number was large enough to perform analysis. Furthermore, DDL T and retransplantation cases were excluded to avoid unnecessary bias. To generalize our results, nationwide multi-center studies are necessary.

In conclusion, our results showed that there were some significant changes in the indications for LDL T. The proportion of patients with HBV-associated liver disease gradually decreased over the 10-year study period, while that of patients with ALD increased. Half of the adult LDL T recipients had HCC, indicating that LDL T is accepted as an established treatment for HCC. We believe that our results may reflect real changes in the indications for LDL T and that they will be useful for predicting further changes in
the near future.

ACKNOWLEDGMENTS

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

Funding/Support
This study was supported by the intramural research fund of Asan Medical Center Organ Transplantation Center and was supported by research grant from the Korean Society for Transplantation (2020-01-01003-008).

ORCID
Sang-Hyun Kang https://orcid.org/0000-0002-8518-1941
Shin Hwang https://orcid.org/0000-0002-9045-2531
Chul-Soo Ahn https://orcid.org/0000-0002-3844-3646
Ki-Hun Kim https://orcid.org/0000-0002-4016-0995
Deok-Bog Moon https://orcid.org/0000-0002-8209-3540
Tae-Yong Ha https://orcid.org/0000-0001-9932-0212
Gi-Won Song https://orcid.org/0000-0002-4235-0434
Dong-Hwan Jung https://orcid.org/0000-0001-5984-023X
Gil-Chun Park https://orcid.org/0000-0003-1631-3258
Jung-Man Namgoong https://orcid.org/0000-0002-9237-7440
Young-In Yoon https://orcid.org/0000-0002-9308-0366
Hui-Dong Cho https://orcid.org/0000-0001-8501-3385
Jae-Hyun Kwon https://orcid.org/0000-0001-8605-9350
Yong-Kyu Chung https://orcid.org/0000-0002-2132-2450
Jin-Uk Choi https://orcid.org/0000-0001-8078-0593
Sung-Gyu Lee https://orcid.org/0000-0001-9161-3491

Author Contributions
Conceptualization: SH. Data curation & Formal analysis: TYH, GWS, CSA, DBM, KHK, DHJ, GCP, YIY, JMN, HDC, JHK, YKC, JUC. Funding acquisition: SH. Methodology: SH. Project administration: SH, SGL. Visualization: SH. Writing—original draft: SH, SHK. Writing—review & editing: SH.

REFERENCES
1. Lee SG, Moon DB, Hwang S, Ahn CS, Kim KH, Song GW, et al. Liver transplantation in Korea: past, present, and future. Transplant Proc 2015;47:705-8.
2. Ha SM, Hwang S, Song GW, Ahn CS, Moon DB, Ha TY, et al. Successful introduction of Model for End-stage Liver Disease scoring in deceased donor liver transplantation in Korea: analysis of first 1 year experience at a high-volume transplantation center. Ann Hepatobiliary Pancreat Surg 2017;21:199-204.
3. Lee J, Lee JG, Jung I, Joo DJ, Kim SI, Kim MS, et al. Development of a Korean liver allocation system using model for end stage liver disease scores: a nationwide, multicenter study. Sci Rep 2019;9:7495.
4. Lee J, Kim DG, Lee JY, Lee JG, Joo DJ, Kim SI, et al. Impact of model for end-stage liver disease score-based allocation system in Korea: a nationwide study. Transplantation 2019;103:2515-22.
5. Min SI, Ahn C, Han DJ, Kim SI, Chung SY, Lee SK, et al. To achieve national self-sufficiency: recent progresses in deceased donation in Korea. Transplantation 2015; 99:765-70.
6. Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, Song GW, et al. Super-selection of a subgroup of hepatocellular carcinoma patients at minimal risk of recurrence for liver transplantation. J Gastrointest Surg 2011;15:971-81.
7. Hwang S, Lee SG, Belghiti J. Liver transplantation for HCC: its role. Eastern and Western perspectives. J Hepatobiliary Pancreat Sci 2010;17:443-8.
8. Yoon YI, Song GW, Lee SG, Hwang S, Kim KH, Kim SH, et al. Outcome of ABO-incompatible adult living-donor liver transplantation for patients with hepatocellular carcinoma. J Hepatol 2018;68:1153-62.
9. Hwang S, Lee SG, Kim KK, Kim KH, Ahn CS, Moon DB, et al. Efficacy of 6-month pretransplant abstinence for patients with alcoholic liver disease undergoing living donor liver transplantation. Transplant Proc 2006;38:2937-40.
10. Park YH, Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, et al. Living donor liver transplantation for patients with alcoholic liver disease. Korean J Hepatobiliary Pancreat Surg 2013;17:14-20.
11. Ahn CS, Hwang S, Kim KH, Moon DB, Ha TY, Song GW, et al. Long-term outcome of living donor liver transplantation for patients with alcoholic liver disease. Transplant Proc 2014;46:761-6.
12. Kim JM, Lee KW, Song GW, Jung BH, Lee HW, Yi NJ, et al. Outcomes for patients with HCV after liver transplantation in Korea: a multicenter study. Ann Surg Treat Res 2016;90:36-42.

www.ekjt.org
13. Kim JM, Lee KW, Song GW, Jung BH, Lee HW, Yi NJ, et al. Increased survival in hepatitis C patients who underwent living donor liver transplant: a case-control study with propensity score matching. Ann Surg Treat Res 2017;93:293-9.

14. Jung BH, Hwang S, Song GW, Jung DH, Ha TY, Park GC, et al. Updated status of deceased-donor liver graft allocation for high-urgency adult patients in a Korean high-volume liver transplantation center. Transplant Proc 2015;47:580-3.

15. Kim JS, Kim KM, Oh SH, Kim HJ, Cho JM, Yoo HW, et al. Liver transplantation for metabolic liver disease: experience at a living donor dominant liver transplantation center. Pediatr Gastroenterol Hepatol Nutria 2015;18:48-54.

16. Oh SH, Kim KM, Kim DY, Kim Y, Song SM, Lee YJ, et al. Improved outcomes in liver transplantation in children with acute liver failure. J Pediatr Gastroenterol Nutr 2014;58:68-73.

17. Oh SH, Kim KM, Kim DY, Song SM, Kim T, Hwang S, et al. Clinical experience of more than 200 cases of pediatric liver transplantation at a single center: improved patient survival. Transplant Proc 2012;44:484-6.

18. Jung DH, Hwang S, Hong SM, Kim KH, Lee YJ, Ahn CS, et al. Clinicopathological features and prognosis of hepatic epithelioid hemangioendothelioma after liver resection and transplantation. Ann Transplant 2016;21:784-90.

19. Sakamoto S, Kasahara M, Mizuta K, Kuroda T, Yagi T, Taguchi T, et al. Nationwide survey of the outcomes of living donor liver transplantation for hepatoblastoma in Japan. Liver Transpl 2014;20:333-46.

20. Tajiri T, Kimura O, Fumino S, Furukawa T, Iehara T, Souzaki R, et al. Surgical strategies for unresectable hepatoblastomas. J Pediatr Surg 2012;47:2194-8.

21. Namgoong JM, Choi JU, Hwang S, Oh SH, Park GC. Pediatric living donor liver transplantation with homograft replacement of retrohepatic inferior vena cava for advanced hepatoblastoma. Ann Hepatobiliary Pancreat Surg 2019;23:178-82.

22. Schüle S, Altendorf-Hofmann A, Uteß F, Rauchfuß F, Freesmeyer M, Knösel T, et al. Liver transplantation for hilar cholangiocarcinoma: a single-centre experience. Langenbecks Arch Surg 2013;398:71-7.

23. Ramanan P, Cummins NW, Wilhelm MP, Heimbach JK, Dierkhising R, Kremers WK, et al. Epidemiology, risk factors, and outcomes of infections in patients undergoing liver transplantation for hilar cholangiocarcinoma. Clin Transplant 2017;31:e13023.

24. Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012;143:88-98.