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

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**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

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## HIGHLIGHTS

- This study aimed to analyze the indications for living donor liver transplantation performed in a high-volume transplantation center over 10 years.
- There were some significant changes in the indications, such as decrease in hepatitis B virus-associated liver disease and increase in alcoholic liver disease.

## 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-

**Table 1.** Indications for living donor liver transplantation in 3,019 adult patients

| Disease | No. of cases |
|---|---|
| Hepatitis B virus infection | 1,898 |
| Hepatitis C virus infection | 203 |
| Alcoholic liver disease | 236 |
| Cryptogenic liver cirrhosis | 152 |
| Acute liver failure | 123 |
| Others | |
| Cholestatic | |
| Primary sclerosing cholangitis | 29 |
| Primary biliary cirrhosis | 27 |
| Secondary biliary cirrhosis | 18 |
| Biliary atresia | 3 |
| Vanishing bile duct syndrome | 1 |
| Vascular | |
| Budd-Chiari syndrome | 11 |
| Portal biliopathy | 1 |
| Metabolic | |
| Wilson disease | 15 |
| Citrullinemia type III | 2 |
| Amyloidosis | 1 |
| Glycogen storage disease | 1 |
| Hemosiderosis | 1 |
| Hepatocellular | |
| Autoimmune hepatitis | 27 |
| Non-alcoholic steatohepatitis | 1 |
| Cytomegalovirus hepatitis | 1 |
| Neoplastic | |
| Epithelioid hemangioendothelioma | 4 |
| Perihilar cholangiocarcinoma | 1 |
| Intraductal papillomatosis | 1 |
| Neuroendocrine tumor | 1 |
| Intraductal papillary biliary neoplasm | 1 |
| Unclassified | |
| Polycystic liver disease | 6 |
| Congestive heart failure-induced liver failure | 2 |
| Caroli disease | 1 |
| Cavernous hemangioma | 1 |



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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

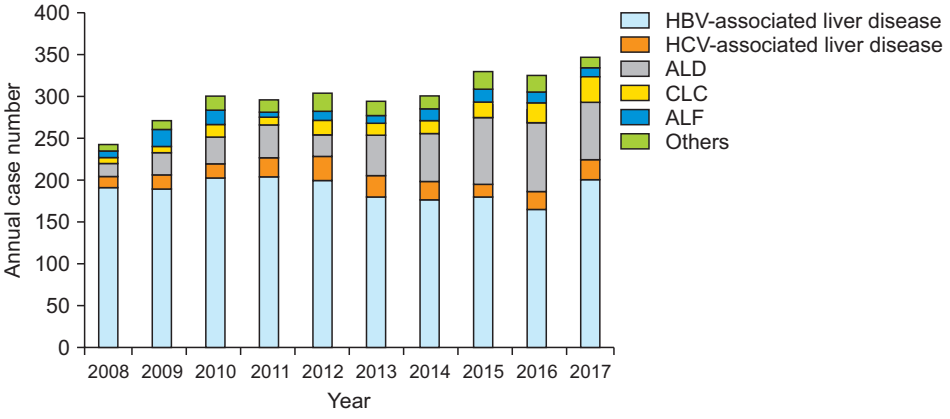


**Fig. 1.** Cumulative incidences of annual case numbers in adult patients according to the six categories. HBV, hepatitis B virus-associated liver disease; HCV, hepatitis C virus-associated liver disease; ALD, alcoholic liver disease; CLC, cryptogenic liver cirrhosis; ALF, acute liver failure.

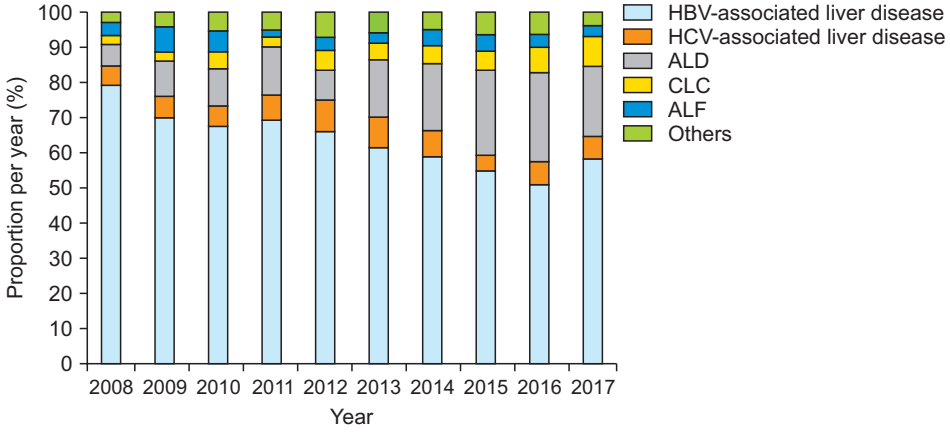


**Fig. 2.** Changes in the proportions of annual cases per disease category in adult patients. HBV, hepatitis B virus-associated liver disease; HCV, hepatitis C virus-associated liver disease; ALD, alcoholic liver disease; CLC, cryptogenic liver cirrhosis; ALF, acute liver failure.

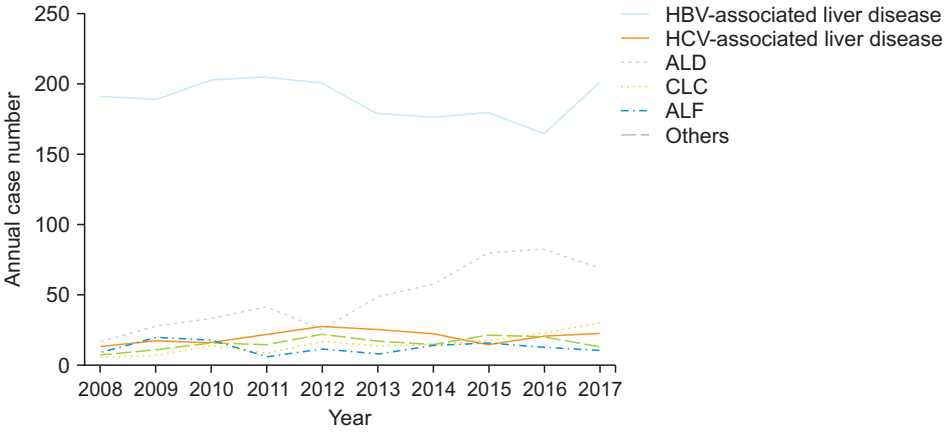


**Fig. 3.** Changes in the number of individual annual cases per disease category in adult patients. HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; CLC, cryptogenic liver cirrhosis; ALF, acute liver failure.

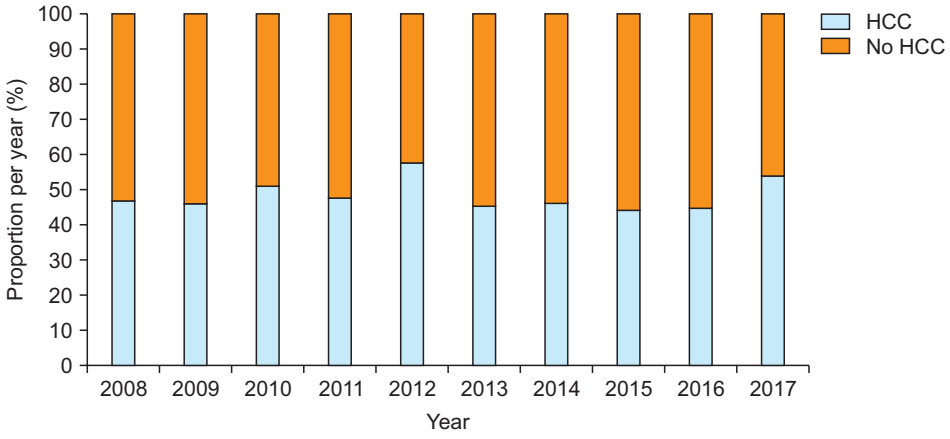


**Fig. 4.** Changes in the annual proportions of adult patients with hepatocellular carcinoma (HCC).

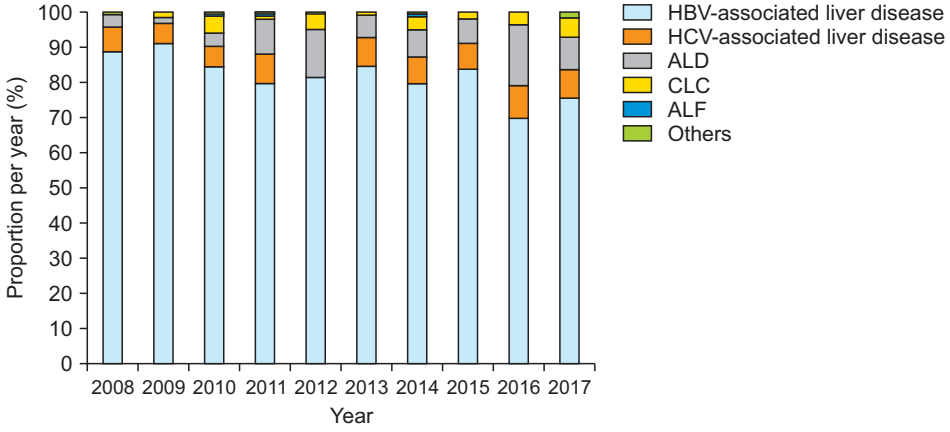


**Fig. 5.** Changes in the annual proportions of adult patients with hepatocellular carcinoma per disease category. HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; CLC, cryptogenic liver cirrhosis; ALF, acute liver failure.

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).


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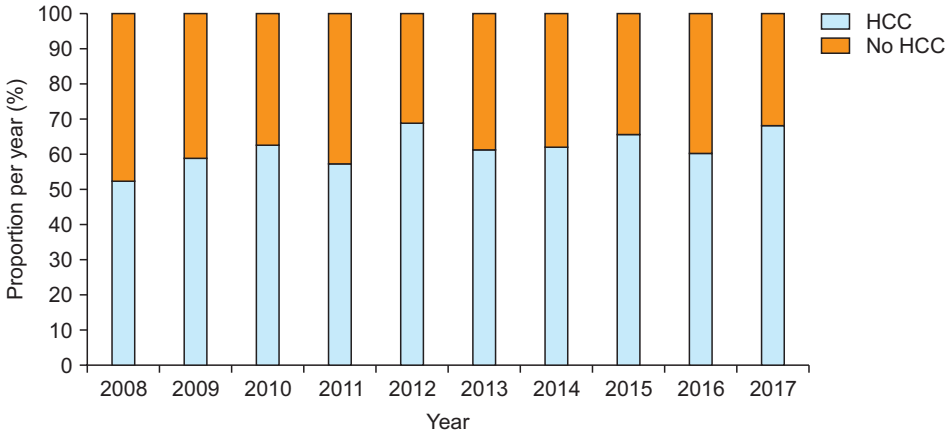


**Fig. 6.** Changes in the annual proportions of adult patients with hepatocellular carcinoma (HCC) among those with hepatitis B virus-associated liver disease.

**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 |

## 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 an 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-

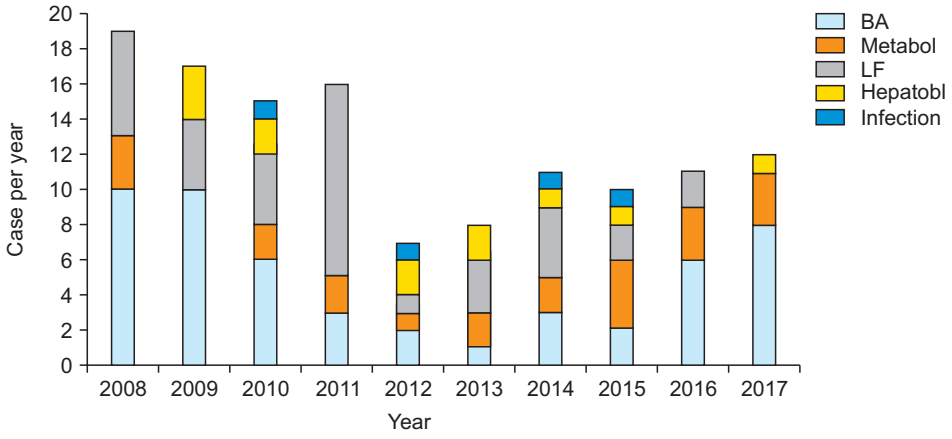


**Fig. 7.** Cumulative incidences of annual case numbers among pediatric patients according to the five categories. BA, biliary atresia; Metabol, metabolic disease; LF, liver failure; Hepatobl, hepatoblastoma; Infection, infectious disease.

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 LDLT 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 LDLT 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 LDLT had to be performed in some patients with rapidly deteriorating fulminant hepatic failure, because the timing of DDLT allocation is usually unpredictable. Until the incidence of deceased donors increases markedly in Korea, LDLT 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 LDLT [2,15].

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

Our high-volume experience of LDLT constituted approximately one-third of Korean LDLT cases nationwide. Thus, our results likely reliably reflect the real-world situation regarding LDLT in Korea. Indeed, we performed this study mainly because data are still lacking regarding recent changes in indications for LDLT. A collection of similar high-volume studies from the other major Korean LT centers will be helpful to visualize the landscape of LDLT 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, DDLT 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 LDLT. 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 LDLT recipients had HCC, indicating that LDLT is accepted as an established treatment for HCC. We believe that our results may reflect real changes in the indications for LDLT and that they will be useful for predicting further changes in


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the near future.

## ACKNOWLEDGMENTS

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

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