

Changing trends in the etiology of liver transplantation in Türkiye: A multicenter study

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Abstract

Background and Aim: This study aimed to identify the indications for liver transplantation (LT) based on underlying etiology and to characterize the patients who underwent LT.

Materials and Methods: We conducted a multicenter cross-sectional observational study across 11 tertiary centers in Türkiye from 2010 to 2020. The study included 5,080 adult patients.

Results: The mean age of patients was 50.3±15.2 years, with a predominance of female patients (70%). Chronic viral hepatitis (46%) was the leading etiological factor, with Hepatitis B virus infection at 35%, followed by cryptogenic cirrhosis (24%), Hepatitis C virus infection (8%), and alcohol-related liver disease (ALD) (6%). Post-2015, there was a significant increase in both the number of liver transplants and the proportion of living donor liver transplants ($p<0.001$). A comparative analysis of patient characteristics before and after 2015 showed a significant decline in viral hepatitis-related LT ($p<0.001$), whereas fatty liver disease-related LT significantly increased ($p<0.001$).

Conclusion: Chronic viral hepatitis continues to be the primary indication for LT in Türkiye. However, the proportions of non-alcoholic fatty liver disease (NAFLD) and ALD-related LT have seen an upward trend over the years.

Keywords: Etiology; HBV; NAFLD; liver transplantation.

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Introduction

Cirrhosis and its complications are the predominant indications for liver transplantation (LT) globally.^[1] Cirrhosis, both with and without hepatocellular carcinoma (HCC), is a leading cause of death worldwide. Cirrhosis ranks as the 11th most common cause of mortality, while HCC stands as the 16th most common; combined, they contribute to 3.5% of all global deaths.^[2] In Western countries, the most prevalent causes of cirrhosis are hepatitis C virus (HCV) infection, alcohol consumption, and non-alcoholic fatty liver disease (NAFLD), whereas hepatitis B virus (HBV) infection is the principal cause in developing countries.^[3] In Türkiye, HBV infection continues to be a significant contributor to liver-related morbidity and mortality.^[4,5] HBV-related cirrhosis, with or without HCC, accounts for about 40–50% of LT cases.^[6]

NAFLD has become an increasingly critical public health issue worldwide. From 1988 to 2008, while the prevalence of chronic liver disease (CLD) and cirrhosis remained stable, the incidence of NAFLD and NAFLD-related cirrhosis steadily rose.^[7–11] By 2014, NAFLD-related cirrhosis had emerged as the second most common reason for LT in the United States, representing 17.4% of all LTs.^[10] In Türkiye, NAFLD prevalence exceeds 30%,^[12] with higher rates observed in patients with obesity, type 2 diabetes mellitus (T2DM), hyperlipidemia, and metabolic syndrome (MeS).^[13,14] This study aims to identify the indications for LT by underlying etiology and to examine the characteristics of patients who underwent LT in the past decade.

Materials and Methods

We conducted a multicenter, cross-sectional retrospective observational study at 11 tertiary centers in Türkiye from 2010 to 2020. The study included 5,080 adult patients who underwent LT. To analyze the changing etiology patterns over time, we divided the timeframe into two periods: January 1, 2010, to December 31, 2014 (first period), and January 1, 2015, to December 31, 2020 (second period). Cirrhosis was defined using clinical, biochemical, and histological findings when available. International Classification of Diseases, Tenth Revision (ICD-10) codes, were employed to identify cirrhosis and its complications. Indications

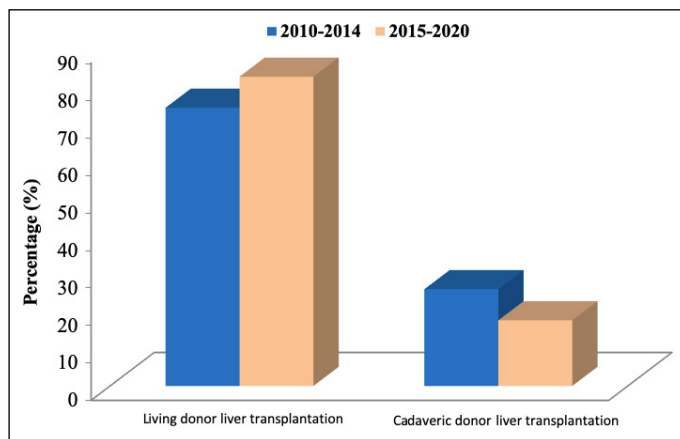


Figure 1. Live and cadaveric liver transplant before January 2015 and after January 2015.

were categorized into several groups: viral hepatitis, alcohol-related liver disease (ALD), NAFLD, autoimmune liver diseases (autoimmune hepatitis [AIH], primary biliary cholangitis [PBC], primary sclerosing cholangitis [PSC]), and miscellaneous factors, based on ICD-10 diagnostic codes. Etiological diagnoses adhered to international criteria. Patients with acute liver failure, those who underwent retransplantation or multi-organ transplantation were excluded. A specialized electronic case report form (CRF) was designed for data collection and recording, with each center entering relevant data into the CRF. This study received approval from the local ethical committee of Dokuz Eylul University School of Medicine (Date: May 05, 2022, No: 2022/19-14).

Definitions

The primary endpoints of this study were to identify the indications for LT by underlying cause before and after January 2015. The secondary endpoints focused on defining the clinical characteristics of patients who underwent LT. Patients were monitored at regular intervals in an outpatient clinic during the follow-up period.

Statistical Analysis

The Shapiro–Wilk test verified the normality assumption. Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were presented as frequencies (n) and percentages (%). The Pearson chi-square and Fisher’s Exact test were utilized to examine relationships between categorical variables. The independent t-test was applied for parametric comparisons between two independent groups. Post-hoc analysis included Bonferroni correction. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). A two-sided $p < 0.05$ was considered statistically significant.

Results

Our study enrolled a total of 5,080 liver transplant recipients. The majority of these patients were female (69.6%), with a mean age of 50.3 ± 15.2 years (range: 18–86 years). Chronic viral hepatitis was the most prevalent indication for LT in the cohort, accounting for 46.4% of cases. The leading etiology was HBV infection (35.2%), followed by cryptogenic cirrhosis (CC) (23.5%), HCV infection (8.2%), and alcohol-related liver disease (ALD) (6.2%). Among the participants, 939

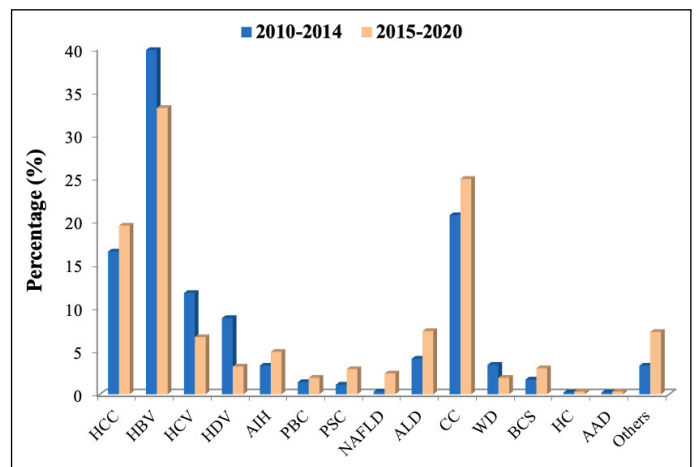


Figure 2. Indications for liver transplantation before January 2015 and after January 2015.

patients (18.5%) had been diagnosed with hepatocellular carcinoma (HCC) prior to LT. A significant majority (79.7%) underwent living donor liver transplantation (LDLT), while the rest (20.3%) received cadaveric donor LT (Fig. 1). The baseline characteristics of the patients are presented in Table 1.

Post-2015, there was a notable increase in the number of liver transplants (from 1,244 to 2,807 transplants) and the proportion of LDLTs (from 74.2% to 82.5%) ($p < 0.001$). Comparing patient characteristics before and after January 2015, there was a significant reduction in viral hepatitis-related LTs (from 60.3% to 42.8%) ($p < 0.001$), while the proportion of fatty liver disease-related LTs, including NAFLD and ALD, significantly increased (from 4.4% to 9.8%) ($p < 0.001$) (Table 1). HBV infection remained the primary reason for LT, though its proportion decreased from 39.8% to 33.1% ($p < 0.001$). Notably, NAFLD-related cirrhosis became the most rapidly increasing indication for LT (Fig. 2). After 2015, the incidence of HCC-related LTs significantly increased from 16.5% to 19.5% ($p = 0.011$). Interestingly, the proportion of LTs related to cryptogenic cirrhosis rose from 20.7% to 24.9% over the years ($p = 0.001$).

Discussion

This multicenter study, involving the leading LT centers in Türkiye, identifies evolving trends in LT indications over the years. Chronic viral hepatitis (46%) emerged as the most frequent indication in our cohort, with HBV infection (35%) as the predominant etiology of cirrhosis. Notably, the proportion of HBV-related LTs decreased from 40% to 33%, aligning with previous studies that identified chronic viral hepatitis as a primary cause of cirrhosis and HCC in Türkiye.^[4,5,15]

There has been a dramatic shift in the main indications for LT over time. Prior to 1980, malignancies represented 50% of all LT indications, but this figure declined to 10% by the 1990s. Currently, cirrhosis is the leading indication.^[11] The etiological trend of cirrhosis is evolving, influenced by effective treatments for viral hepatitis and rising prevalence of obesity and metabolic disorders. In Western populations, fatty liver diseases, including ALD and NAFLD, have become leading LT indications, surpassing HCV infection and HCC.^[11,16] NAFLD, in particular, has emerged as the fastest-growing etiology of cirrhosis. Prior to 2000, the proportion of NAFLD-related cirrhosis was negligible. However, in the United States, the proportion of NAFLD-related LT increased by 162% between 2003 and 2014.^[10]

Table 1. Characteristics of patients who underwent liver transplantation

Parameters	Periods				p
	Between 2010–2014 (n=1677)		Between 2015–2020 (n=3403)		
	n	%	n	%	
Age (years), mean±SD	50.0±1.9		50.7±5.8		0.707
Gender					0.930
Male	509	30.4	1037	30.5	
Female	1168	69.6	2366	69.5	
Liver transplantation					<0.001
Live LT	1244	74.2	2807	82.5	
Cadaveric LT	433	25.8	596	17.5	
HCC	277	16.5	662	19.5	0.011
Etiology					
Viral hepatitis-related	1012	60.3	1458	42.8	<0.001
HBV	668	40	1125	33.1	<0.001
HCV	196	11.7	223	6.6	<0.001
HDV	148	8.8	110	3.2	<0.001
Autoimmune liver diseases					
AIH	56	3.3	167	4.9	0.010
PBC	24	1.4	64	1.9	0.248
PSC	18	1.1	97	2.9	<0.001
NAFLD	5	0.3	82	2.4	<0.001
ALD	69	4.1	250	7.3	<0.001
CC	347	20.7	849	24.9	0.001
WD	57	3.4	65	1.9	0.001
BCS	28	1.7	103	3	0.004
HC	3	0.2	9	0.3	0.761
AAD	3	0.2	10	0.3	0.564
Others	55	3.3	245	7.2	<0.001

Statistical analysis (Student's t-test, Pearson chi-square test, Fisher's Exact test). SD: Standard deviation; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; AIH: Autoimmune hepatitis; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; NAFLD: Non-alcoholic fatty liver disease; ALD: Alcoholic liver disease; CC: Cryptogenic cirrhosis; WD: Wilson's disease; BCS: Budd-Chiari syndrome; HC: Haemochromatosis; AAD: Alpha1-antitripsin deficiency; LT: Liver transplantation.

In Türkiye, Degertekin et al.^[17] reported a high NAFLD prevalence of 48%. Our study found that, during the second period, there was a decrease in HBV-related LTs and an increase in NAFLD-related and ALD-related LTs ($p<0.001$), likely due to rising obesity, diabetes, and NAFLD prevalence in Türkiye.^[18–20] These findings corroborate previous studies that show a decline in viral hepatitis-related LTs and an increase in NAFLD- and ALD-related LTs.^[11,16,21]

This is the first multicenter study to detail recent etiological trends in LT indications in Türkiye. Its main strength lies in the retrospective analysis. Despite meticulous examination of patient characteristics in the CRF, potential misclassifications of cirrhosis etiology, especially in CC- and NAFLD-related cases, particularly before January 2015, cannot be ruled out.

Conclusion

While HBV infection remains the principal etiology for LT in Türkiye, NAFLD-related cirrhosis and LT represent a growing burden.

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Ethics Committee Approval: The Dokuz Eylul University Clinical Research Ethics Committee granted approval for this study (date: 25.05.2022, number: 2022/19-14).

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Conflict of Interest: The authors have no conflict of interest to declare.

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