Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v26i1.541_ENG

ORIGINAL PAPER

Liver Transplantation in Brazil between 2010 and 2021: 30-day Survival

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Section editor: Ilka de Fátima Santana Ferreira Boin

Received: Oct. 20, 2023 | Accepted: Nov. 26, 2023

How to cite: Nascimento SML, Fabris MEM, Barros JM, Ribeiro LM, Frizanco AB, Santiago, ALP, Hoffmann-Santos HD, Nogueira PLB. Liver Transplantation in Brazil between 2010 and 2021: 30-day Survival. BJT. 2023.26 (01): e3823. https://doi.org/10.53855/bjt.v26i1.541_ENG

ABSTRACT

Introduction: In Brazil, the Unified Health System is responsible for more than 95% of liver transplants, providing a more equal service essential to health. However, there is a shortage of organs due to the growing demand and challenges to achieve the success of the procedure, due to the severity of the underlying diseases that impact on post-surgery survival. **Objective:** To investigate the rate of liver transplantation in all federative units of Brazil between 2010 and 2021, as well as to evaluate its relationship with survival of patients undergoing the procedure. **Methodology:** This is an epidemiological, observational, analytical study of the non-concurrent cohort type, with data obtained from the Hospital Information System regarding hospitalizations that underwent liver transplantation, in all units of the federation (UF) of Brazil between January 2010 and December 2021. **Results:** A total of 17,254 liver transplants were performed in the country, at a total cost of R$ 1,657,439,379.00 financed by SUS in patients with a mean age of 53.78 years. Females had a lower probability of survival than male patients. Regarding the 15-day hospital stay, patients without a diagnosis of liver failure had a survival probability of 86.4% (95%CI = 85.7 - 87.2) and patients with a diagnosis of liver failure had a survival probability of 81.7% (95%CI = 80.0 - 83.4). The lethality described was 12.29% AND there was no difference in survival regarding age (p=0.13), length of hospital stay (p=0.31), alcoholic liver disease (p=0.14) and fibrosis and cirrhosis of the liver (p=0.22). The probability of survival was statistically similar among transplant recipients who received liver from a deceased or living donor. **Conclusion:** The number of donors remains insufficient in the face of the extensive waiting list. The impact of baseline conditions on survival after surgery shows a higher negative outcome in patients with liver failure and in the female sex.

Descriptors: Organ Donor; Liver Transplantation; Epidemiology.

Transplante de Fígado no Brasil entre 2010 e 2021: Sobrevida de 30 dias

RESUMO

Introdução: No Brasil, o Sistema Único de Saúde, é responsável por mais de 95% transplantes hepáticos, disponibilizando de modo mais igualitário um serviço essencial à saúde. Todavia, há carência de órgãos frente à crescente demanda e desafios para alcançar o sucesso do procedimento, devido a gravidade das doenças de base que impactam na sobrevida pós cirurgia. **Objetivo:** Investigar a taxa de transplante de fígado em todas as unidades federativas do Brasil entre os anos de 2010 e 2021, bem como avaliar sua relação com sobrevida dos pacientes submetidos ao procedimento. **Metodologia:** Trata-se de um estudo epidemiológico, observacional, analítico do tipo coorte não concorrente, com dados obtidos do Sistema de Informações Hospitalares referentes a hospitalizações que realizaram transplante de fígado, em todas as unidades da federação (UF) do Brasil entre janeiro de 2010 e dezembro de 2021. **Resultados:** Foram realizados no país 17.254 transplantes de fígado, à um custo total de R$ 1.657.439.379,00 financiado pelo SUS em pacientes com idade média de 53,78 anos. O sexo feminino apresentou probabilidade de sobrevida menor que pacientes do sexo masculino. Quanto ao período 15 dias de internação hospitalar, os pacientes sem diagnóstico de insuficiência hepática apresentaram probabilidade de sobrevida de 86,4% (IC95% = 85,7 - 87,2) e os pacientes com diagnóstico de insuficiência hepática com probabilidade de sobrevida de 81,7% (IC95% = 80,0 - 83,4). A letalidade descrita foi de 12,29% e não houve diferença de sobrevida quanto a faixa etária (p=0,13), período de internação (p=0,31), doença alcoólica do fígado (p=0,14) e fibrose e cirrose hepática (p=0,22). A probabilidade de sobrevida foi estatisticamente semelhante entre transplantados que receberam fígado de doador falecido ou vivo. **Conclusão:** A quantidade de doadores permanece insuficientes frente a extensa lista de espera. O impacto das condições de base na sobrevida após cirurgia, observa-se desfecho negativo maior nos pacientes com insuficiência hepática e no sexo feminino.

Descritores: Doador de Órgão; Transplante de Fígado; Epidemiologia.

INTRODUCTION

Liver transplantation is a surgical procedure to treat the final stage of chronic or acute liver disease. The history of the procedure dates back to 1963, when doctor Starlz, from the University of Colorado Health Sciences Center, performed the first successful liver transplant[1]. Since then, liver transplantation has become an established and widely used life-saving procedure around the world.

The first liver transplant in Brazil was performed in 1968 at the "*Hospital das Clinicas da Faculdade de Medicina de Universidade de São Paulo*" Clínicas Hospital of the Medical School of *USP* (*HCFMUSP*). Later, in 1990, this procedure was initiated by *Hospital Israelita Albert Einstein*[1]. As the holder of the world's foremost public transplantation program of organs, tissues and cells, the Unified Health System (*SUS*) is responsible for more than 95% of liver transplants in the country, making this essential service available to the public more equitably.[2,3].

Although a significant achievement, organ replacement treatment has not yet met the growing demand, resulting in a shortage of available livers. As a result, predictive strategies have been developed, such as MELD (Model for End-Stage Liver Disease), which is widely used worldwide to help manage the fair and efficient allocation of organs for patients needing liver transplantation [4,5].

In 2006, Brazil began using this urgent quantitative tool to select patients with higher MELD values, aiming to treat the most severe cases and reduce the number of deaths in the *"Sistema Nacional de Transplante"*: National Transplant System registry. Several risk factors can contribute to an increase in the MELD scale index. These include but are not limited to, the progression of underlying liver disease, complications such as hepatic encephalopathy and ascites, and coexisting conditions such as renal failure. Furthermore, alcohol consumption and the presence of viral hepatitis can also adversely influence the MELD index[6].

The MELD scale considers three laboratory parameters: serum bilirubin, serum creatinine and the INR (International Normalized Ratio) of prothrombin time. Based on the values of these parameters, the score, which varies from 6 to 40, is calculated. The higher the score, the greater the severity of the liver disease and the greater the urgency to perform the transplant.[7]. Corroborating a retrospective observational study carried out in patients with liver cirrhosis, the average MELD score of transplant patients who have died was 20.8m, with 12 of them having a MELD score ≥20, and another 9 having MELD scores between 13 and 19 [8].

The main causes associated with advanced stages of liver disease include viral infections, with the hepatitis C virus being the main culprit, abuse of alcohol, drugs, and other substances, hereditary conditions, cancer, and tumors [9-12] . Among the various conditions that promote advanced stages of acute or chronic liver disease, excessive alcohol consumption is a very common cause. Alcoholic liver disease, which includes alcoholic liver cirrhosis, affects men more than women. However, the risk of cirrhosis may increase in women who consume alcohol daily compared to prolonged abstinence from alcohol. Therefore, although the prevalence is higher in men, women may be at greater risk with lower levels of alcohol consumption. [9-12].

Primary biliary cirrhosis and autoimmune hepatitis are more often in females. The worldwide prevalence of primary biliary cirrhosis is estimated at between 67 and 940 cases per one million inhabitants, affecting mainly females (1 man for every 10 women), with a greater preponderance in the age range between 40 and 60 years old [13,14]. Autoimmune hepatitis, although it can appear in any sex and age range, has a preference for young women (HAI type 1- most common form of the disease) or children (HAI type 2)[15,16] . From this perspective, it was observed that in Non-Alcoholic Fatty Liver Disease (NAFLD), older women have been associated with an unfavorable prognosis. NAFLD is a condition characterized by the high accumulation of lipids in hepatocytes, promoting their deterioration and consequent cellular damage in liver tissue. This process stimulates the formation of fibrosis, ultimately culminating in chronic liver cirrhosis. Furthermore, liver cirrhosis increases the risk of serious complications, such as hepatocellular carcinoma [17,18].

Therefore, understanding and analyzing epidemiological data related to liver transplants is fundamental for developing strategies and public health policies to prevent and treat liver diseases. In this context, this research aimed to investigate the rate of liver transplantation in all Brazilian States between 2010 and evaluate its relationship with the survival rates of patients undergoing the procedure.

METHODS

An epidemiological, observational, analytical, non-concurrent cohort study was carried out, with data obtained from the Hospital Information System (*SIH-DATASUS*) regarding hospitalizations of people aged 18 years or over who underwent procedures with codes 05.05.02.005-0 (liver transplantation with and organ from deceased donor) and 05.05.02.006-8 (liver transplantation with an organ from a living donor) in all Brazilian Federation Units (FUs), between January 2010 and December 2021.

The microdata on authorizations for approver hospital admissions (SIH-RD) are stored monthly for each Federation Unit and year, so to obtain the necessary to download 3888 monthly databases, something that was possible due to the automation made possible by the R language package *microdatasus* (version 2.0.1) [19] . The following variables were included in the study: gender, age range, FUs and region of residence, date of hospitalization, date of discharge, length of stay, diagnosis, progression, procedure performed and total cost of hospitalization.

The variable alcoholic liver disease was extracted from ICD-10 codes in category K70, the variable fibrosis and cirrhosis was obtained from diagnoses with ICD-10 codes in category k74, and the variable liver failure from ICD-10 codes in category K72. The survival analysis is considered as an outcome the time interval between the date of hospitalization and the date of the discharge occurring within 30 days. These were patients with the event of interest occurring after this period.

The Kaplan-Meier curve was used to compare survival functions between groups, and Cox regression was used to fit a multivariate model to identify prognostic factors for death. All analyses were conducted using the R software (version 4.1.3) through its integrated development environment RStudio (version 2021.09.2), considering a significance level of 0,05. As this is public data made available and previously anonymized by DATASUS, there was no need to proceed with the Ethics Committee.

RESULTS

17.254 liver transplants were performed in Brazil, totaling R$1.657.439.379,00 in hospitalization costs financed by the *SUS* in patients with an average age of 53.78 years (95% CI = 53,60 - 53,96) with a lethality of 12.29% (95% CI = 11,81-12,79).

Table 1 shows the profile of liver transplant recipients in the population during the study period, and it is observed that the majority of patients were male, aged between 46 and 59 years, living in the Southeast region, with liver fibrosis and cirrhosis and, as an outcome the upward trend. There were more transplants from deceased donors between 2016-2021, but more transplants form living donors between 2010-2015.

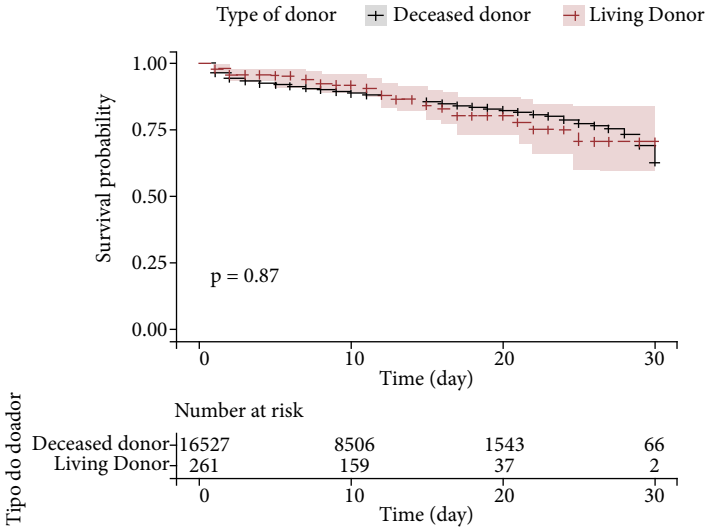
Table 1. Epidemiological profile of liver transplants in Brazil in the population aged 18 years and over. Performed between January 2010 and December 2021.

Variables	Deceased Donor, N = 16,983[1]	Living Donor, N = 271[1]
Gender		
Female	5329 (31,38%)	106 (39,11%)
Male	11654 (68,62%)	165 (60,89%)
Age range		
18-30 years	1049 (6,18%)	25 (9,23%)
31-45 years	2416 (14,23%)	42 (15,50%)
46-59 years	6801 (40,05%)	114 (42,07%)
60 and older	6717 (39,55%)	90 (33,21%)
Year of hospitalization		
2010-2015	7385 (43,48%)	160 (59,04%)
2016-2021	9598 (56,52%)	111 (40,96%)
Region of residence		
Midwest	768 (4,52%)	2 (0,74%)
Northeast	3533 (20,80%)	11 (4,06%)
North	476 (2,80%)	14 (5,17%)
Southeast	7817 (46,03%)	231 (85,24%)
South	4389 (25,84%)	13 (4,80%)
Progressed to		
Medical discharge	14899 (87,73%)	234 (86,35%)
Death	2084 (12,27%)	37 (13,65%)
Days of hospitalization	10,00 (7,00 - 14,00)	12,00 (7,00 - 17,00)
Alcoholic liver disease		
No	14454 (85,11%)	228 (84,13%)
Yes	2529 (14,89%)	43 (15,87%)
Fibrosis and cirrhosis of the liver		
No	6731 (39,63%)	108 (39,85%)
Yes	10252 (60,37%)	163 (60,15%)
Liver failure		
No	13558 (79,83%)	218 (80,44%)
Yes	3425 (20,17%)	53 (19,56%)

[1]n (%); Median (IQR)

Source: Elaborated by the authors.

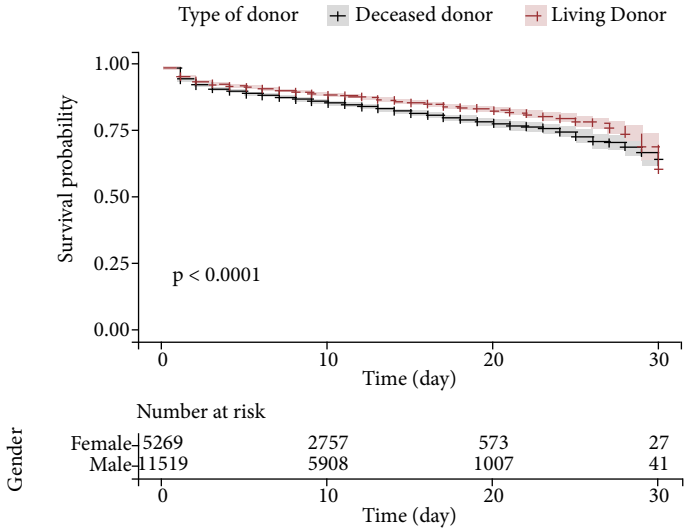
The probability of survival was statistically similar between transplant recipients who received liver from a deceased or living donor (Fig.).



Source: Elaborated by the authors.

Figure 1. Kaplan-Meier curve of 30-day survival functions among patients who underwent liver transplantation in Brazil (2010-2021), according to the type of organ donor.

Female patients had a statistically lower survival probability than male patients (Fig. 2). After 15 days of hospital admission, those who were male had a survival probability of 86,8% (95%CI= 86,0 -87,6); however, in female patients, this probability was 82.7% (95%CI= 81,4 -84,0).

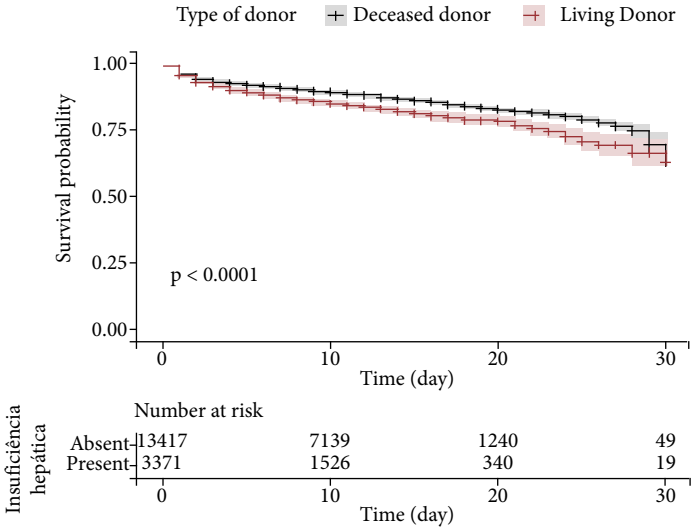


Source: Elaborated by the authors.

Figure 2. Kaplan-Meier curve of 30-day survival functions among patients who underwent liver transplantation in Brazil (2010-2021), according to gender.

Survival showed a statistically significant difference between patients with or without a diagnosis of liver failure (Fig. 3). After 15 days of hospital admission, patients without a diagnosis of liver failure had a survival probability of 86,4$ (95%CI = 85,7 - 87,2), and patients with a diagnosis of liver failure had a survival probability of 81,7% (95%CI = 80,0 - 83,4).

There was no difference in survival regarding age range (p=0,13), length of stay (p=31), alcoholic liver disease (p=0,14), and liver fibrosis and cirrhosis (p=0,22) when compared with residents of the Southeast region, the risk of death was 21% lower among patients residing in the Central-West region (HR = 0,79; 95%CI = 0,63-0,99; p=0,045) and 13% lower among patients from the South region (HR = 0,87; 95%CI = 0,78 - 0,97;p=0,011), however, statistically similar among residents of the Northeast and North regions, regardless of gender, age range, and the period of hospitalization.



Source: Elaborated by the authors.

Figure 3. Kaplan-Meier curve of 30-day survival functions among patients who underwent liver transplantation in Brazil (2010 - 2021), according to diagnosis of liver failure.

DISCUSSION

In cases of terminal liver disease, liver transplantation may be recommended, whether from a living donor or a cadaver [20]. Concerning the 11-year period analyzed in this research, 17.254 transplants were identified, with an average of 1.568 transplants/year. Between 2010 and 2015, there was a greater prevalence of organs from living donors, while between 2016 and 2021, there was a prevalence of deceased donors. When comparing the donor type, data analysis showed statistically similar parameters of survival probability among transplant recipients who received livers from living or deceased donors, showing no influence on the patient's recovery or the success of the liver transplant.

Liver replacement therapy often emerges as the only therapeutic option for various liver diseases. However, the demand for organs considerably exceeds the available supply [21]. The shortage of viable organs is a significant social and public health problem, as although the donor's liver can regenerate, it is necessary to maintain a minimum amount of liver tissue in the donor to avoid any damage to the donor's health [22].

Despite these challenges, the country carried out 17.254 liver transplants through the *SUS* from 2010 to 2021, totaling a cost of R$ 1.657.439.379,00 in government-run hospitalizations. Public service is crucial in this context since the average cost per transplant patient is R$ 17.462,60 ± 20.087,99 [23]. This contributes to greater equality of access to high-cost treatments.

This study observed a significant increase in liver transplants among males. This phenomenon may be directly related to the high consumption of alcoholic beverages in Brazil. A bibliographic review of the epidemiological profile of victims of alcoholism concluded that the prevalence is high among men, single people, and those with low socioeconomic power [24].

The age range with the highest prevalence in our study was 46 to 59 years old. This trend can be attributed to the chronic nature of the main causes of diseases that affect the liver, which often present imperceptible initial symptoms. Furthermore, men show a greater propensity to consume alcoholic beverages and less frequent health services, which results in late diagnoses. Consequently, liver transplantation emerges as the preferred treatment option in the advanced stages of these liver conditions [25,26].

From 2016 to 2021, there was a peak in the number of transplants. A reduction in procedures was expected due to the COVID-19 pandemic, which significantly impacted several health services, especially in 2020. However, the data from this research present similar results to the study that compared the number of solid organ transplants performed in 2019 to 2020, taking into account the pandemic in Brazil, revealing that liver transplantation was the least affected, showing a decrease of just 10,8% in the first three quarters of 2020 compared to 2019 [27].

Brazil's region with the highest number of transplants in this study was the Southeast. Corroborating, with a survey carried out by the Brazilian Transplant Registry that revealed, From 2013 to 2020, an increase in liver transplants in the Central-West (11,7%) and Southeast (1,5%), while there was a decrease in the South regions (15,6%), Northeast (33,7%) and North (60%) [28]. The Ministry of Health points to São Paulo as the main transplant location, and in the months of January to September 2023, 6.622 solid organ transplants were carried out in the country, of which 2.149 (32,45%) were carried out in São Paulo, reinforcing the region's protagonism southeast in this scenario [29].

Gender may play a significant role in the progression of some liver diseases and may affect the survival rate after transplantation [30]. Our results showed a greater number of men transplanted than women and higher survival rates in men. Therefore, gender is an important factor that must be considered when evaluating patients for liver transplantation and post-transplant follow-up [31].

The liver transplant waiting list follows a strict order that considers the patient's conditions to determine the need for prioritization, such as the MELD scale. One of the priority conditions is the presence of severe acute liver failure, regulated by specific legislation that establishes the flow of this prioritization. This regulation considers the patient's severity and their probability of survival after transplantation [32,33]. In the meantime, patients with aggravated liver failure have a high risk of complications, which contributes to lower postoperative survival [34,35]. In our study, after 15 days of hospital stay, it was found that patients without a diagnosis of liver failure had a survival probability of 86,4%, and patients with a diagnosis of liver failure had a survival probability of 81,7%. The literature shows that one of the factors related to the lower survival of pre -and post-transplant patients is related to hepatic encephalopathy, a severe complication of acute liver failure. Therefore, other causes of death arise from multiple organ failure and hemorrhage [36-38].

In Brazil, each location faces unique challenges that may vary and require specific actions. Although the transplant waiting list is nationwide, patients underlying conditions may vary depending on the region. Therefore, it is important to consider the particularities of each location when developing strategies and policies related to transplants. Another factor to be considered is that this work has limitations, the first of which is the quality of information collected from the Hospital Information System. This is secondary data, so errors may occur when filling out the system. Furthermore, scientific studies are needed to address the evolution of liver transplantation in Brazil, especially those that individually analyze donation indicators in different regions of the country. This information gap represents a challenge for a more complete and informed analysis, making it difficult to develop effective strategies in the field of liver transplants.

FINAL CONSIDERATIONS

Using epidemiological data from the Hospital Information System, survival rates were similar between transplant recipients from deceased or living donors. A lower survival rate was observed in females compared to males, as well as a significant difference between patients with and without a diagnosis of liver failure; the presence of liver failure is a basic condition that presents a high risk of progressing to more severe conditions, which justifies its prioritization on the transplant list.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Nascimento SML, Nogueira PLB, Fabris MEM; **Conception and design:** Nascimento SML; **Data analysis and interpretation:** Hoffmann-Santos HD; **Article writing:** Nascimento SML, Nogueira PLB, Fabris MEM, Barros JM, Ribeiro LM, Frizanco AB, Santiago ALP; **Critical revision:** Nogueira PLB; **Final approval:** Nogueira PLB.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

FUNDING

Not applicable.

ACKNOWLEDGEMENT

Not applicable.

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