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ORIGINAL PAPER

Factors Associated with Waitlist Time on Liver Transplantation

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ABSTRACT

Objectives: Liver transplantation (LT) is the main therapy for patients with cirrhosis or fulminant liver failure. However, there is a disproportion between the demand and availability of organs, such that the waitlist mortality ranged from 20 to 38% when the only allocation criterion was the time of inclusion on the waitlist. Brazil then adopted the Model for End-stage Liver Disease (MELD) score, aiming to prioritize patients with a higher risk of death for LT. Therefore, this study aimed to determine factors associated with waitlist time for LT. **Methods:** Retrospective cohort study of adult patients listed for LT from October 2012 to December 2019 in a single state in Brazil. **Results:** The study analyzes 1,262 patients (869 males, 68.91%; median age, 53.33 ± 11.48 years; median waitlist time, 103.88 ± 162.05 days; median MELD Sodium [MELD-Na] score of 22.41 ± 6.09). Alcoholic liver cirrhosis (n = 369; 29.24%) and chronic viral hepatitis (n = 295; 23.38%) were the most prevalent reasons for LT. Blood groups O (n = 534; 42.31%) and A (n = 474; 37.56%) prevailed among the recipients. The state capital and its metropolitan region accounted for 91.20% (n = 1,151) of all liver transplants performed. Most donors were deceased (n = 1,258; 99.68%). Patients with MELD-Na scores > 21 ($p < 0.001$), non-O blood group ($p = 0.002$), age < 53 years ($p = 0.003$), and those listed ≥ 2017 spent ≤ 30 days on the waitlist ($p < 0.001$). **Conclusion:** A waitlist period of ≤ 30 days was associated with higher MELD-Na scores, younger ages, non-O blood groups, and LT listings before 2017.

Descriptors: Liver Transplantation; MELD; Quality, Performance Improvement; Health; Waitlist.

Fatores Associados ao Tempo de Espera no Transplante Hepático

RESUMO

Objetivos: O transplante hepático (TH) é a principal terapia para pacientes com cirrose ou insuficiência hepática fulminante. No entanto, há uma desproporção entre a demanda e a disponibilidade de órgãos, de modo que a mortalidade na lista de espera variou de 20 a 38% quando o único critério de alocação era o tempo de inclusão na lista de espera. O Brasil adotou então o escore *Model for End-stage Liver Disease* (MELD), com objetivo de priorizar pacientes com maior risco de morte para TH. Portanto, este estudo teve como objetivo determinar fatores associados ao tempo de espera para TH. **Métodos:** Estudo de coorte retrospectivo de pacientes adultos listados para TH de outubro de 2012 a dezembro de 2019 em um único estado do Brasil. **Resultados:** Foram analisados 1.262 pacientes no estudo [869 homens, 68,91%; mediana de idade, 53,33 ± 11,48 anos; mediana de tempo em lista de espera, 103,88 ± 162,05 dias; mediana do escore MELD Sódio (MELD-Na) de 22,41 ± 6,09]. A cirrose hepática alcoólica (n = 369; 29,24%) e a hepatite viral crônica (n = 295; 23,38%) foram os motivos mais prevalentes para TH. Os grupos sanguíneos O (n = 534; 42,31%) e A (n = 474; 37,56%) prevaleceram entre os receptores. A capital do estado e sua região metropolitana foram responsáveis por 91,20% (n = 1.151) de todos os transplantes de fígado realizados. A maioria dos doadores era falecida (n = 1.258; 99,68%). Pacientes com escores MELD-Na > 21 ($p < 0,001$), grupo sanguíneo não O ($p = 0,002$), idade < 53 anos ($p = 0,003$) e listados ≥ 2017 permaneceram ≤ 30 dias em lista de espera ($p < 0,001$). **Conclusão:** Um período ≤ 30 dias na lista de espera de TH foi associado a pontuações MELD-Na mais altas, idades mais baixas, grupos sanguíneos não O e listagens de TH antes de 2017.

Descritores: Transplante de Fígado; MELD; Qualidade, Melhoria de Desempenho; Saúde; Lista de Espera.

INTRODUCTION

Liver transplantation (LT) is the main treatment for patients with liver cirrhosis or fulminant liver failure. Nonetheless, the disproportion between demand and availability of organs leads to several months of waitlist time.[1] Initially, the criteria for organ allocation only considered compatibility of ABO blood group and waitlist time. At that time, the mortality rates while waiting for a transplant was approximately 38%.[2] Thus, in the early 2000s, big countries such as United States and Brazil have adopted the Model for End-Stage Liver Disease (MELD) score as the decision-making guide for liver allocation.[2,3] This score dictates the risk of death within 3 months for cirrhotic patients, prioritizing organ allocation to those with higher mortality risks.[4] MELD use changed not only the dynamics of the LT waitlist but also the characteristic of the patients who underwent LT.[3]

There is wide research on this subject. Even though, most of them evaluated small populations through only few months. Therefore, this study analyzed LT patients on the waitlist over a 7-year period after MELD score setting in the state of Paraná (PR), Brazil, to assess epidemiological characteristics and factors associated with waitlist time.

MATERIALS AND METHODS

A retrospective cohort study was carried out with data from the medical records of the Central de Transplantes do Paraná, Brazil, the state agency responsible for the registry and organization of LT waitlist and allocation of organ-donors. The study was duly submitted and approved by the Research Ethics Committee of Pontifícia Universidade Católica do Paraná (PUCPR) (protocol number 3.355.576) and is in conformation to the 1975 Helsinki Declaration.

Data were collected regarding a time-range from October 2012 to December 2019, related to receptors age, gender, blood type (ABO system), main causes of LT/cirrhosis, time spent on waitlist, year of LT performing, MELD Sodium (MELD-Na) score before LT, type of donor (deceased or living, unrelated), and the hospital where the procedure was performed. The areas in the state from which recipients and donors originated were also recorded. Patients with hereditary hemochromatosis, secondary biliary cholangitis, Budd-Chiari syndrome, familial amyloidotic polyneuropathy, hepatopulmonary syndrome, alpha1-antitrypsin deficiency, and hepatic metastasis were classified under "other causes of liver transplantation/cirrhosis". Patients younger than 18 years, medical records with incomplete or absent data, cases of retransplantation, or double transplantation were excluded. For comparison purposes, participants were divided into two groups: < 31 days and ≥ 31 days in LT waitlist.

Data were tabulated in spreadsheets. The results of continuous quantitative variables were determined by the number of observations (n), mean, minimum, and maximum values. Qualitative variables were determined by the classification number (n) and its percentage. To analyze the association between dichotomous variables, 2 × 2 tables were constructed and chi-square test was used. Values of $p < 0.05$ indicated statistical significance. Statistical analysis was performed using the STATA version 16 software.

RESULTS

A total of 1,360 medical records were initially selected for analysis. Of them, 98 were excluded following exclusion criteria, leaving 1,262 for final analysis. The epidemiological analysis of participants is shown in Table 1.

Table 1. Demographic and clinical characteristics of participants.

Variables	n (%)
Recipient sex	
Female	393 (31.09)
Male	869 (68.91)
Mean age (years)	53.33 ± 11.48
MELD-Na (points)	22.41 ± 6.09
Time on LT waitlist (days)	103.88 ± 162.05
Causes of LT/cirrhosis	
Alcoholic	369 (29.24)
Chronic hepatitis B and/or C	295 (23.38)
Cryptogenic	150 (11.89)
AIH, PBC, and PSC	109 (8.64)
NASH	94 (7.45)
HCC	123 (10.45)
Fulminant hepatitis	25 (1.98)
Other causes	97 (7.69)

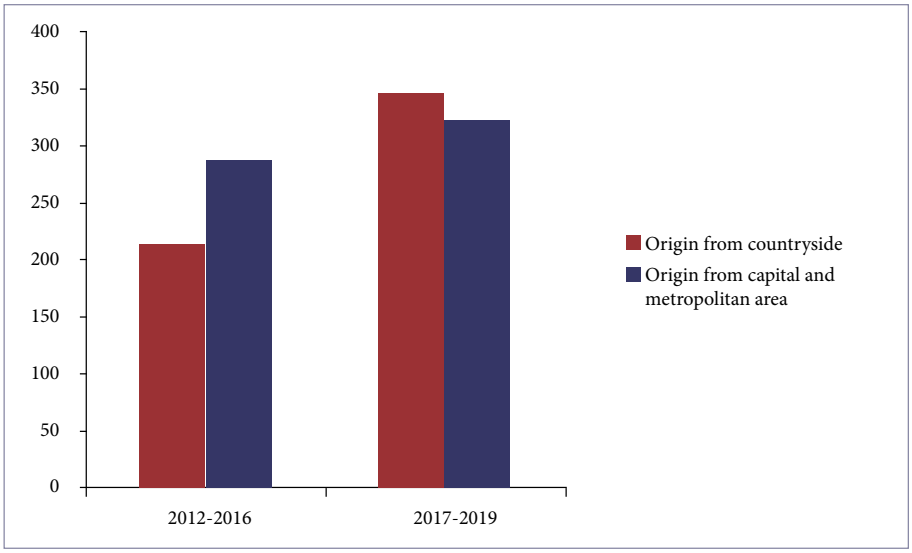
continue...

Table 1. Continuation...

Variables	n (%)
Blood group	
A	474 (37.56)
AB	84 (6.66)
B	170 (13.47)
O	534 (42.31)
Donor type	
Deceased	1,258 (99.68)
Alive	4 (0.32)
City where LT was carried out	
Curitiba (capital)	1,151 (91.20)
Cascavel	88 (6.98)
Londrina	11 (0.87)
Maringá	12 (0.95)
Year of LT	
2012	16 (1.27)
2013	90 (7.13)
2014	79 (6.15)
2015	121 (9.59)
2016	201 (15.93)
2017	246 (19.49)
2018	288 (22.82)
2019	221 (17.51)

Source: Elaborated by the authors.
AIH: autoimmune hepatitis; HCC: hepatocellular carcinoma; NASH: nonalcoholic steatohepatitis; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis.

The state area from which most of the LT recipients originated changed over the years (Fig. 1). In time-range from 2012 to 2016, the patient origin predominance were capital and metropolitan area (n = 289 vs. n = 217 from the countryside). However, from 2017 to 2019, this relationship inverted with more recipients from the countryside (n = 347 vs. n = 321) than from the capital and metropolitan area, $p = 0.002$).



Source: Elaborated by the authors.

Figure 1. Origin of LT recipient from 2012 to 2019 in PR, Brazil.

Comparing the time-range of ≤ 30 days on the LT waitlist, participants with MELD-Na scores ≤ 20 received fewer organs than those with MELD-Na scores of ≥ 21 (n = 146 vs. n = 335, $p = 0.000$, respectively). Correlations between time spent on the LT waitlist and other variables are shown in Table 2.

Table 2. Factors associated with a time spent in LT waitlist of up to 30 days

	Time on LT waitlist		*p*-value
	< 31 days	≥ 31 days	
Sex			
Male	324	485	$p = 0.339$
Female	157	208	
Age (years)			
< 53	219	256	$p = 0.003$
≥ 53	262	437	
Blood group			
Non-O	305	375	$p = 0.002$
O	176	318	
LT recipient origin			
Countryside	227	337	$p = 0.628$
Capital and metropolitan region	254	356	
Year of transplant			
2012-2016	174	333	$p = < 0.001$
2017-2019	344	411	

Source: Elaborated by the authors.

DISCUSSION

The predominant LT recipient in PR was a 50-year-old male, with an O blood type and alcoholic or chronic hepatitis cirrhosis. Similar characteristics were found in the United Network for Organ Sharing (UNOS) database from the United States.[5]

Patients spent nearly 105 days on the LT waitlist with a MELD-Na score of 22. A study conducted in the United Kingdom found similar results, with an average MELD score of 18 and a corresponding LT waiting time of 152 days.[6]

During the past years, more LT centers were opened in the countryside of PR. The higher the number of medical centers specialized in LT, the higher the number the patients diagnosed with cirrhosis, listed, and transplanted. In our opinion, this is the main reason for the change observed after 2016 regarding the origin of recipients and the heightened of transplant surgeries.

Transplanting patients near their residence is another important factor to consider when analyzing the sustainability of LT centers, especially considering the costs associated with a recipient with a MELD-Na score of ≥ 20. In 2017, the United States Department of Health and Human Services established an LT allocation policy that also considered as criteria the distance between the hospitals where the recipient and organ donor were admitted.[7,8] As the costs of LT are rising year by year, a regionalized program that favors the neighborhood area of the receipt could reduce parts of these expenses.

Patients with MELD-Na scores ≤ 20 received fewer transplants than those with MELD-Na > 20 scores when a 30-day time on the waiting list was considered (n = 146 vs. n = 335, $p = 0.000$, respectively). We believe this is because higher MELD-Na scores correspond to a higher mortality risk, even though the score originally estimates the risk of death in a 3-month period. Thus, patients with higher scores are prioritized and tend to receive transplants earlier than those with lower scores.

In our sample, more non-type O blood recipient received their LT than those with O type within the 30-day waitlist period (n = 305 vs. n = 176, $p = 0.002$, respectively). We do not have a specific explanation for this, but possible reasons could be the following: more offer of organs from these blood types vs. a sample bias of our study. A Dutch study conducted with 517 patients found that, although individuals with type O blood tend to clinical deterioration when compared to other blood groups, there are no statistically significant correlations between blood type and tendency to transplantation.[9] Despite this, an Italian study with 21,000 patients found results similar to ours.[10]

The retrospective design and data analysis from a single state in Brazil may be considered limitations of this study, as the results may not reflect nationwide or worldwide reality.

However, this is one of the largest studies conducted with liver transplant recipients in Brazil, with all data collected from an official governmental agency and with all state transplantation units included. These characteristics make this study a significant epidemiological survey of southern Brazil, being the largest conducted in the past 10 years.

Curitiba is highlighted as the city with the highest number of liver transplants performed in PR. Moreover, donors from Curitiba and the metropolitan region predominated in the present analysis.

Since 2017, LT quantitatively increased while waiting time impaired. Considering the ≤ 30-day on the waitlist period, LT was predominantly performed in individuals with MELD-Na scores of ≥ 21 compared to those with MELD-Na scores of ≤ 20, and after this period, the relationship inverted itself. Furthermore, the preeminence was reversed, and there is a greater number of

recipients from the countryside compared to those from Curitiba and the metropolitan region. It was also observed that non-O recipients wait less on the waitlist because a higher number of non-O transplants are performed.

CONCLUSION

In summary, it was demonstrated that the epidemiological profile of liver recipients in PR is mostly men, around 50 years of age, with blood type O, with alcoholic liver cirrhosis or chronic viral hepatitis, and from Curitiba or the metropolitan region. Although being a developing country, Brazil is similar to developed countries concerning the LT epidemiological profile, and even then presents a reduced waiting time for LT within the same comparison.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Karvat JGV, Monteiro GR, Marchiori JGO, Miglioli MC, Ribeiro NB and Tafarel JR; **Conception and design:** Karvat JGV, Monteiro GR, Marchiori JGO, Miglioli MC, Ribeiro NB and Tafarel JR; **Data analysis and interpretation:** Karvat JGV, Monteiro GR, Marchiori JGO, Miglioli MC, Ribeiro NB and Tafarel JR; **Article writing:** Karvat JGV, Monteiro GR, Marchiori JGO, Miglioli MC, Ribeiro NB and Tafarel JR; **Critical revision:** Karvat JGV, Monteiro GR, Marchiori JGO, Miglioli MC, Ribeiro NB and Tafarel JR; **Final approval:** Marchiori JGO.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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