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ORIGINAL PAPER

Liver Transplantation for Hepatopulmonary Syndrome in Brazil: Incidence and Survival

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ABSTRACT

Objective: To analyze liver transplants (LT) performed for hepatopulmonary syndrome (HPS) from 2012 to 2024 by characterizing recipient demographics and evaluating post-transplant survival using standardized survival-analysis methods. **Methods:** This retrospective observational study included 75 adult patients who underwent LT for severe HPS. Data were extracted from the Brazilian National Transplant System database (Sistema Nacional de Transplantes do Brasil), whose records were prospectively entered from 2012 to 2024. Descriptive analyses were performed, followed by Kaplan-Meier survival estimation and log-rank tests for group comparisons. A multivariable Cox proportional hazards model was used to evaluate independent predictors of mortality. Exploratory analyses using *t*-test and analysis of variance were conducted to support interpretation. **Results:** The cohort had a mean age of 48.75 years, with 60% male and 40% female recipients. Overall Kaplan-Meier estimated survival was 72.7% at 1 year and 63.6% at 3 years after transplantation. Kaplan-Meier analysis demonstrated a trend toward better survival in male recipients, although this difference did not reach statistical significance (log-rank p = 0.088; Cox p = 0.059). Racial distribution included 48% Brown, 45.33% White, and 6.67% Black patients; survival did not differ significantly among racial groups (global log-rank p = 0.63). When diagnostic etiologies were grouped into clinically meaningful categories, no significant survival differences were observed (global log-rank p = 0.63). The Cox model did not identify independent predictors of post-transplant mortality. **Conclusion:** Post-transplant survival among patients transplanted for HPS in Brazil did not differ significantly according to sex, race, or underlying liver disease etiology. Observed trends should be interpreted cautiously due to the limited sample size. These findings provide important national-level data and support the need for larger multicenter studies to better define prognostic factors in this population.

Descriptors: Hepatopulmonary Syndrome; Liver Transplantation; Survival Rate.

Transplante Hepático por Síndrome Hepatopulmonar no Brasil: Incidência e Sobrevida

RESUMO

Objetivo: Analisar os transplantes hepáticos (TH) realizados por síndrome hepatopulmonar (SHP) no período de 2012 a 2024, caracterizando o perfil demográfico dos receptores e avaliando a sobrevida pós-transplante por meio de métodos padronizados de análise de sobrevida. **Métodos:** Estudo observacional retrospectivo que incluiu 75 pacientes adultos submetidos ao TH por SHP grave. Os dados foram extraídos do banco de dados do Sistema Nacional de Transplantes do Brasil, cujos registros foram alimentados prospectivamente no período de 2012 a 2024. Realizaram-se análises descritivas seguidas de estimativas de sobrevida pelo método de Kaplan-Meier e testes de *log-rank* para comparação entre grupos. Um modelo multivariável de riscos proporcionais de Cox foi utilizado para avaliar preditores independentes de mortalidade. Análises exploratórias com teste *t* e análises de variância foram conduzidas para auxiliar a interpretação dos resultados. **Resultados:** A coorte apresentou idade média de 48,75 anos, com 60% de receptores do sexo masculino e 40% do sexo feminino. A sobrevida global estimada pelo método de Kaplan-Meier foi de 72,7% em 1 ano e 63,6% em 3 anos após o transplante. A análise de Kaplan-Meier demonstrou uma tendência a melhor sobrevida entre os receptores do sexo masculino, embora essa diferença não tenha atingido significância estatística (*log-rank* p = 0,088; Cox p = 0,059). A distribuição racial incluiu 48% de pacientes pardos, 45,33% brancos e 6,67% negros; não houve diferença

significativa de sobrevida entre os grupos raciais (*log-rank* global p = 0,63). Quando as etiologias diagnósticas foram agrupadas em categorias clinicamente relevantes, também não se observaram diferenças significativas de sobrevida (*log-rank* global p = 0,63). O modelo de Cox não identificou preditores independentes de mortalidade pós-transplante. **Conclusão:** A sobrevida pós-transplante em pacientes transplantados por SHP no Brasil não diferiu significativamente de acordo com sexo, raça ou etiologia da doença hepática de base. As tendências observadas devem ser interpretadas com cautela devido ao tamanho amostral limitado. Esses achados fornecem dados relevantes em nível nacional e reforçam a necessidade de estudos multicêntricos com amostras maiores para melhor definição de fatores prognósticos nessa população.

Descritores: Síndrome Hepatopulmonar; Transplante de Fígado; Taxa de Sobrevida.

INTRODUCTION

Hepatopulmonary syndrome (HPS) is a serious complication of advanced liver disease, defined by the triad of hepatic dysfunction or portal hypertension, intrapulmonary vascular dilatations, and impaired arterial oxygenation. The condition is associated with significant morbidity and mortality, especially in its severe forms[1]. Liver transplantation (LT) remains the only definitive treatment capable of reversing the underlying pathophysiology and improving long-term outcomes[2,3].

Despite its clinical relevance, HPS remains underdiagnosed, and population-based data on outcomes after LT are limited, particularly in low- and middle-income countries[4]. In Brazil, the scarcity of nationwide analyses hinders the assessment of equity in access to transplantation, regional distribution, and post-transplant outcomes among patients with HPS.

Survival analysis is particularly relevant in this context, as it enables the appropriate handling of censored observations and provides a robust framework for evaluating time-to-event outcomes[5-7]. The present study aimed to describe the demographic profile of Brazilian patients undergoing HPS transplantation and to evaluate post-transplant survival using standardized survival analysis methods.

METHODS

Study design and population

This is a retrospective observational study of adult patients (≥ 18 years) who underwent LT for HPS between January 2012 and December 2024. All patients met clinical criteria for severe HPS and were registered in the Brazilian National Transplant System (*Sistema Nacional de Transplantes-SNT*).

Data sources

The data were extracted from the SNT, a prospectively updated database maintained by the Ministry of Health. The variables extracted included recipient age, sex, race, year of transplant, etiology of underlying liver disease, geographic origin, post-transplant survival time, and vital status at the last follow-up.

Variables and definitions

Survival time was defined as the number of months between transplantation and death or the last follow-up. Patients alive at the end of the follow-up period were considered right-censored. The etiologies of the underlying liver disease were grouped into clinically relevant categories to allow for more stable survival comparisons.

Statistical analysis

Descriptive statistics were used to define the demographic profile. Survival analysis was performed using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. Paired log-rank tests were applied to comparisons by sex and race, while a global log-rank test was used for diagnostic categories.

A multivariate Cox proportional hazards model was fitted to assess independent predictors of post-transplant mortality, including age, sex, and year of transplant, and diagnostic category. Hazard ratios (HR) with 95% confidence intervals (CI) were reported.

Exploratory analyses using Welch's t-test and one-way analysis of variance (ANOVA) were performed to aid interpretation of results; however, these were not considered primary survival analyses. Statistical significance was defined as a two-tailed p-value < 0.05. Analyses were conducted using R and Python software.

Ethical considerations

This research was approved by the Research Ethics Committee of the State University of Campinas under opinion number 7.002.293 (CAAE: 81204024.6.0000.5404).

RESULTS

Demographic profile

A total of 75 adult patients underwent LT for HPS during the study period. The mean age at transplantation was 48.75 years. Male recipients comprised 60% of the cohort. The racial distribution included 48% mixed-race patients, 45.33% white patients, and 6.67% black patients. Most transplants occurred in the South, Northeast, and Southeast regions of Brazil, as observed in Table 1.

Table 1. Demographic profile of adult patients transplanted for HPS in Brazil (2012-2024).

Characteristics	n	%
Total number of patients	75	100.0
Average age at transplant (in years)	48	-
Sex		
Male	45	60.0
Female	30	40.0
Race		
Mixed (brown)	36	48.0
White	34	45.3
Black	5	6.7
Underlying liver disease (grouped)		
HPS (isolated)	27	36.0
Alcoholic cirrhosis	13	17.3
Cryptogenic cirrhosis	12	16.0
Viral hepatitis (B or C)	10	13.3
Autoimmune/cholestatic disease	5	6.7
Other etiologies	8	10.7
Geographic region		
South	25	33.3
Northeast	24	32.0
Southeast	22	29.3
Central-West	4	5.3
North	0	0.0

Source: Elaborated by the authors. Percentages may not add up to 100% due to rounding. Diagnostic categories have been grouped to allow for stable survival comparisons.

Survival analysis

Comparisons of post-transplant survival by demographic and clinical variables are presented in Table 2.

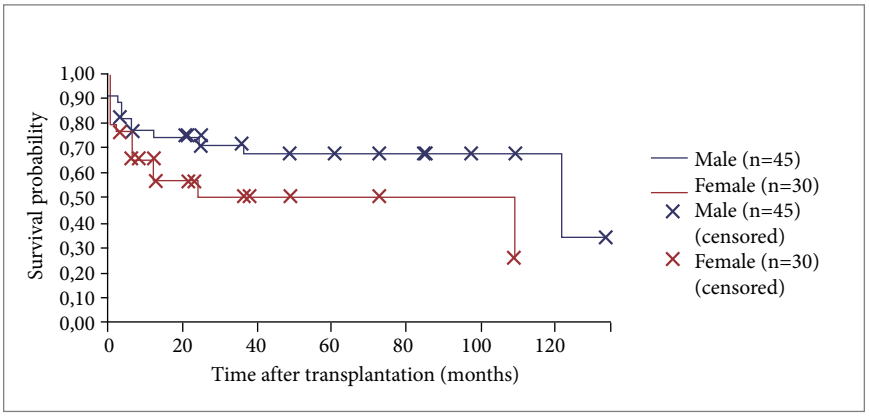
Table 2. Results of the log-rank p-value test for post-transplant survival according to demographic and clinical variables.

Variables	Comparison	*p*-value (log-rank *p*)
Sex	Male vs. Female	0.09
Race	White vs. Mixed-race (brown) vs. Black	0.63
Diagnostic category	All groups	0.63

Source: Elaborated by the authors.

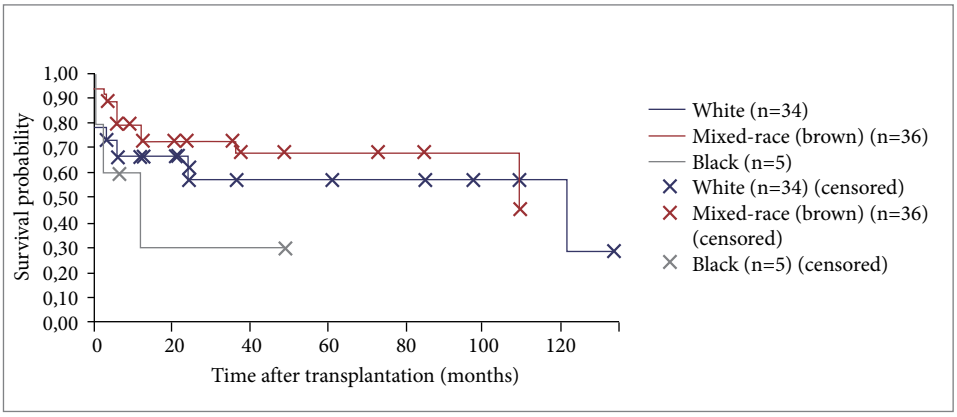
The Kaplan-Meier survival curves stratified by sex are shown in Fig. 1. Male recipients consistently had a higher probability of survival over time than females; however, this difference did not reach statistical significance (log-rank $p = 0.088$).

Survival curves stratified by race/ethnicity are presented in Fig. 2. No statistically significant differences in post-transplant survival were observed between white, brown, and black patients (overall log-rank $p = 0.63$). Although the curve for black patients appeared visually lower, this finding should be interpreted with caution, given the small number of individuals in this group.



Source: Elaborated by the authors.

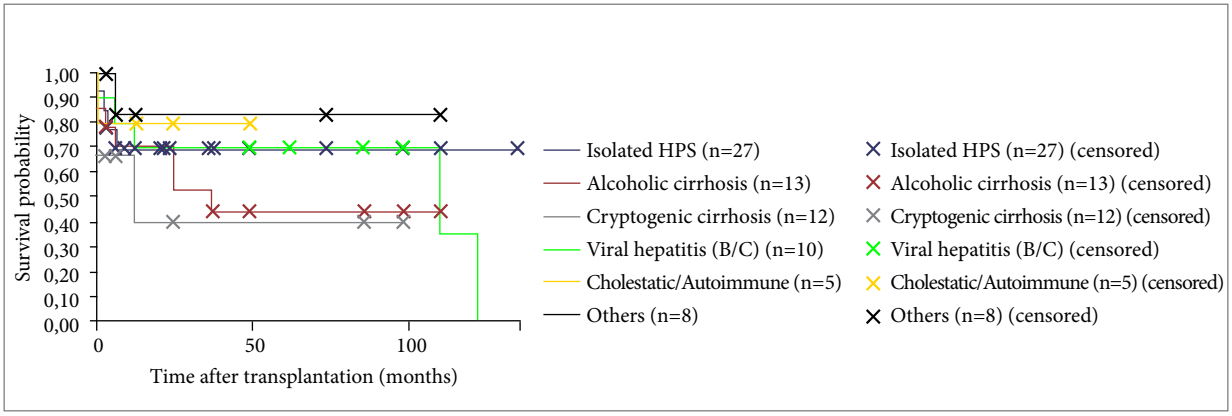
Figure 1. Kaplan–Meier survival curves for LT in HPS, stratified by sex. Symbols indicate right-censored observations. Curves were compared using the log-rank $p = 0.088$.



Source: Elaborated by the authors.

Figure 2. Kaplan–Meier survival curves for LT in HPS, stratified by race/ethnicity. Symbols indicate right-censored observations. Survival curves were compared using the log-rank $p = 0.63$.

Kaplan-Meier curves stratified by diagnostic groups are presented in Fig. 3. Survival probabilities were broadly similar across the diagnostic groups, with no statistically significant differences (overall log-rank $p = 0.63$).



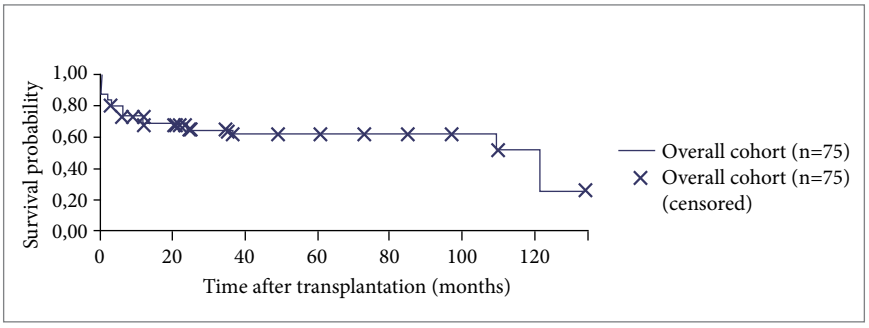
Source: Elaborated by the authors.

Figure 3. Kaplan–Meier survival curves for LT in HPS, stratified by diagnostic categories. Symbols indicate right-censored observations. Survival curves were compared using the log-rank $p = 0.63$.

The overall Kaplan–Meier survival curve for the entire cohort is shown in Fig. 4. A greater reduction in survival probability was observed in the first months after transplantation, followed by relative stabilization throughout the follow-up period. The

estimated post-transplant survival rate was 72.7% at 1 year and 63.6% at 3 years, demonstrating mid-term survival maintenance for the majority of the cohort.

Exploratory comparisons of survival time, conducted using Welch's t-test and ANOVA, revealed no additional statistically significant differences and, therefore, were not emphasized.



Source: Elaborated by the authors.

Figure 4. Kaplan-Meier overall survival curve after LT for HPS in the total cohort. Symbols indicate right-censored observations.

Cox regression model

In the multivariate analysis, no variable was an independent predictor of post-transplant mortality. Male sex showed a trend toward lower mortality risk (HR ≈ 0.46), although this did not reach statistical significance. Age, year of transplantation, and diagnostic category were not significantly associated with survival (Table 3).

Table 3. Cox proportional hazards multivariate model for post-transplant mortality.

Variable	Hazard Ratio (HR)	CI95%	*p*-value
Age (years)	1.00	0.97-1.03	0.99
Male sex	0.46	0.21-1.03	0.06
Alcoholic etiology	1.78	0.71-4.47	0.22
Year of the transplant	0.99	0.88-1.10	0.82

Source: Elaborated by the authors.

DISCUSSION

This study provides a comprehensive assessment of post-transplant survival in adult patients undergoing LT for HPS in Brazil, from 2012 to 2024. The estimated overall survival was 72.7% at 1 year and 63.6% at 3 years, with outcomes relatively homogeneous across sex, race, and etiology of underlying liver disease, and no statistically significant differences.

In all Kaplan-Meier analyses, survival curves showed a steeper decline in the early post-transplant period, followed by relative stabilization over time. This pattern is consistent with the well-established natural history of LT, in which perioperative complications and early postoperative events account for a substantial portion of mortality. At the same time, patients who survive the initial period tend to have better long-term outcomes[3,8,9]. The similarity of this pattern in stratified analyses reinforces the overall homogeneity of post-transplant survival in this cohort.

When stratified by sex, male recipients consistently showed higher survival than female recipients; however, this difference did not reach statistical significance in either the log-rank test or the Cox proportional hazards model. Although this trend aligns with observations described in some transplanted populations, the lack of statistical significance and the limited sample size prevent definitive conclusions. These findings highlight the importance of cautious interpretation and suggest that sex, in isolation, may not represent a robust independent determinant of post-transplant survival in patients transplanted for HPS.

Survival analyses stratified by race revealed no significant differences between White, Mixed-race (brown), and Black patients. Although the Kaplan–Meier curve for Black patients visually shows lower survival, this observation should be interpreted with caution, given the small sample size in this subgroup. Database studies are particularly susceptible to imprecision in subgroup analyses with reduced sample sizes, and the findings of the present study should not be interpreted as evidence of racial disparities in post-transplant survival. Nevertheless, continuous monitoring of equity in access and outcomes remains a relevant priority in the Brazilian transplantation system.

Similarly, no significant differences in survival were observed between the grouped diagnostic categories. Patients transplanted for HPS in the context of alcoholic cirrhosis, cryptogenic cirrhosis, viral hepatitis, autoimmune or cholestatic diseases, as well as other etiologies, presented broadly comparable post-transplant survival. This finding suggests that, once transplantation is achieved in cases of severe HPS, the etiology of the underlying liver disease may exert only a limited influence on post-transplant survival, reinforcing the concept that HPS constitutes a unifying clinical condition in this setting[10,11].

The Cox multivariate proportional hazards model did not identify independent predictors of post-transplant mortality, including age, sex, and year of transplant, or diagnostic category. The observed trend of lower mortality risk among male recipients did not reach statistical significance, and no other covariate demonstrated a relevant association with survival. These results likely reflect a combination of limited statistical power and the intrinsic homogeneity of outcomes in this highly selected transplant population. In rare indications, such as HPS, the absence of statistically significant predictors should be interpreted as a meaningful finding rather than a limitation, underscoring the challenge of identifying prognostic factors in small national cohorts.

Some limitations must be noted. First, the retrospective nature of the registry data limits the availability of detailed clinical variables, including the severity of pre-transplant hypoxemia, perioperative complications, and post-transplant pulmonary recovery. Second, the relatively small sample size restricts the power to detect modest differences between subgroups, particularly in analyses stratified by race and diagnosis. Finally, the observational design prevents causal inferences. Despite these limitations, the use of a national transplant registry ensures comprehensive coverage and increases the generalizability of the findings in the Brazilian context.

CONCLUSION

Post-transplant survival in Brazilian patients undergoing LT for HPS did not differ significantly according to sex, race, or etiology of the underlying liver disease. Although some non-significant trends were observed, multicenter studies with larger sample sizes are needed to increase statistical power and better define prognostic factors. This study contributes to essential national data and supports the ongoing evaluation of equity and outcomes in LT for HPS.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Souza LP, Perales SR, Boin IFSF; **Conception and design:** Souza LP; **Data analysis and interpretation:** Souza LP; **Article writing: S**ouza LP, Perales SR, Boin IFSF; **Critical revision:** Souza LP, Boin IFSF; **Final approval:** Boin IFSF.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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Not applicable.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors declare that no artificial intelligence tools were used in the preparation, writing, data analysis, or review of this manuscript.

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