Hepatocellular carcinoma patients are advantaged in the current Brazilian liver transplant allocation system. A competing risk analysis

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ABSTRACT – Background – In Brazil, the Model for End-Stage Liver Disease (MELD) score is used to prioritize patients for deceased donor liver transplantation (DDLT). Patients with hepatocellular carcinoma (HCC) receive standardized MELD exception points to account for their cancer risk of mortality, which is not reflected by their MELD score. Objective – To compare DDLT rates between patients with and without HCC in Rio Grande do Sul, the Southernmost state of Brazil. Methods – We retrospectively studied 825 patients on the liver-transplant waiting list from January 1, 2007, to December 31, 2016, in a transplant center located in Porto Alegre, the capital of Rio Grande do Sul, to compare DDLT rates between those with and without HCC. The time-varying hazard of waiting list/DDLT was estimated, reporting the subhazard ratio (SHR) of waiting list/DDLT/dropout with 95% confidence intervals (CI). The final competing risk model was adjusted for age, MELD score, exception points, and ABO group. Results – Patients with HCC underwent a transplant almost three times faster than patients with a calculated MELD score (SHR 2.64; 95% CI 2.10-3.31; P<0.001). The DDLT rate per 100 person-months was 11.86 for HCC patients vs 3.38 for non-HCC patients. The median time on the waiting list was 5.6 months for patients with HCC and 25 months for patients without HCC. Conclusion – Our results demonstrated that, in our center, patients on the waiting list with HCC have a clear advantage over candidates listed with a calculated MELD score.

INTRODUCTION

With the primary objective of reducing mortality among patients on the waiting list for deceased donor liver transplantation (DDLT), in July 2006, the Brazilian National Transplant System (Sistema Nacional de Transplantes, SNT), coordinated by the Brazilian Ministry of Health(1,2), changed the criteria for allocation of deceased donor allografts, which were based exclusively on time on the waiting list, to severity-based criteria. The SNT adopted the Model for End-Stage Liver Disease (MELD) scoring system to rank patients according to their clinical urgency. The MELD score, which is calculated using serum bilirubin, international normalized ratio (INR) of prothrombin time, and serum creatinine, provides an objective score to accurately determine the risk of short-term mortality for patients with chronic liver disease(2,3).

However, the MELD score may not reflect prognosis in all cases, as it is based on liver function, and some conditions require prioritization because they do not share similar mortality rates and may have disease progression as a driving factor. In patients with hepatocellular carcinoma (HCC), the cancer rather than parenchymal disease, reflected by the MELD score, may determine the prognosis. In the MELD-based allocation system, wait-listed HCC patients, many of whom with preserved synthetic liver function, would be competing for scarce donor grafts with noncompetitive determinants of priority, i.e., lower MELD scores. Based on studies on tumor growth that estimated a waiting list dropout rate of 15% for one tumor <2 cm and of 30% for one tumor 2–5 cm or ≥3 cm, in the United States, it was determined that the MELD scores for these patients should be 24 and 29, respectively(4,5). Additional “exception points” were granted every three months if the patient with HCC remained within the Milan criteria(6,7). Therefore, in that country, in parallel to the introduction of the MELD score and priority exception points for patients with HCC, the percentage of DDLT performed for HCC increased from 7% to 22%, and most patients underwent a transplant within three months of waiting list registration(8,9). Furthermore, compared with non-HCC patients, candidates with HCC have been consistently shown to have greater access to DDLT and lower dropout rates(8-12).

In the United States, in order to avoid the prioritization of HCC patients over other patients on the DDLT waiting list, adjustments and changes have been made to these “exception points”. Thus, since 2015, patients with a new initial HCC exception application must be registered with their calculated MELD (cMELD) score. At six months, candidates will receive a score of 28. Extensions are applied every three months and, if granted, the MELD score is increased to 30, 32, and then 34(13).

In Brazil, since the introduction of the MELD score for allocation of deceased donor grafts, standardized MELD exception
points that are assigned by the SNT to patients with HCC have not been changed, and their impact on allocation has not been evaluated. The objective of this study was to compare DDLT rates between patients with and without HCC in Rio Grande do Sul, the Southernmost state of Brazil.

METHODS

Study population
This was a retrospective cohort study. Eligible participants were all patients aged >18 years, of both sexes, who were listed for DDLT from January 2007 to December 2016 in a transplant center located in Porto Alegre, the capital of Rio Grande do Sul.

Patients on the waiting list due to severe acute liver failure, need for liver retransplantation, and approved non-HCC exception points were excluded.

The primary exposure was HCC. To this end, candidates approved for HCC exception points (HCC candidates) were identified and their waiting list outcomes were compared to those of candidates without HCC (non-HCC candidates). Patients were followed until December 31, 2017, to potentially have at least 1-year follow-up.

This study followed the guidelines for reporting observational studies and was approved by the institutional research ethics committee. Informed consent was waived due to the non-interventional design of the study and retrospective nature of data collection. All investigators signed a data use agreement to ensure the ethical and secure use of the data.

Priority for patients with HCC
Patients with HCC are included in the waiting list with exception points when imaging tests based on the Barcelona Consensus Statements and the Guidelines of the American Association for the Study of Liver Diseases identify one lesion ≥2 cm and ≤5 cm, or two or three ≥2 cm and ≤3 cm, with no indication for resection. In other words, lesions <2 cm are not considered a small modification of the Milan criteria. Tumor progression on chest tomography and bone scintigraphy should be excluded. In our center, when the expected waiting time for liver transplantation is greater than six months, patients receive locoregional therapy: percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), or transcatheter arterial chemoembolization (TACE), according to the number, size and location of nodules. HCC patients are included in the waiting list with the following extra points granted: 20 points at listing, 24 after three months, and 29 after six months. Patients receive increasing points as long as they continue to meet the Brazilian modified Milan criteria. In Rio Grande do Sul, since its implementation, the number of points assigned to patients with HCC has not been changed.

Waiting list mortality/dropout
For the purposes of this analysis, a waiting list mortality/dropout for an HCC registration occurred for any of the following withdrawals: death on the waiting list; patient is too sick to undergo a transplant; or contraindication related to HCC (defined as tumor progression beyond the modified Milan criteria, metastatic disease, and/or presence of macrovascular invasion on imaging examination). A waiting list mortality/dropout for non-HCC registration was defined similarly, except for the withdrawals related to HCC.

Statistical analysis
Patient characteristics were expressed as mean and standard deviation for continuous variables and as counts and percentages for categorical variables. Groups were compared using Student’s t test or the Mann-Whitney test for continuous variables. Categorical variables were compared using Pearson’s chi-square test or Fisher’s exact test as appropriate.

In addition to the Cox regression model, the time-varying hazard of waiting list/DDLT was also estimated, reporting the subhazard ratio (SHR) of waiting list/DDLT/dropout with 95% confidence intervals (CI) in a competing risk (CR) model. To this end, the Fine and Gray method was used, where the association between DDLT and HCC was estimated while accounting for the CR of mortality. This method does not censor the occurrence of death while on the waiting list, thus allowing direct modeling of the subdistribution of the cumulative incidence function of waiting list/DDLT/dropout. Fifty-three candidates were excluded from the CR analysis: 29 for clinical improvement (none of them with HCC); 10 for leaving the waiting list (five with HCC); and 14 for being transferred to another transplant center (five with HCC). The final CR model was adjusted for age, MELD score, exception points, and ABO group. Patients who were still on the waiting list were censored on December 31, 2017. Data on demographic characteristics, MELD score on the day of inclusion, date of inclusion, death, exclusion, transplantation, and liver function parameters were recorded for each patient in the cohort.

Data were analyzed using IBM-SPSS version 22.0 (IBM, Armonk, NY, USA) and R version 3.6.0 using the cmprsk package. P<0.05 was considered statistically significant.

Ethical approval
This study was approved by the institutional Research Ethics Committee (approval number: 1.417.586). Informed consent was waived due to the non-interventional design of the study and retrospective nature of data collection. All investigators signed a data use agreement to ensure the ethical and secure use of the data.

RESULTS

Study population
From January 1, 2007, to December 31, 2016, 950 patients were listed for DDLT, of whom 125 were excluded from the analysis for the following reasons: need of transplantation for acute liver failure (n=27); retransplantation (n=42); and non-HCC priority exception points (n=46). Therefore, the cohort consisted of 825 patients, divided into two groups: 396 patients listed with a cMELD score and 429 with approved HCC priority exception points for those meeting the Brazilian modified Milan criteria: nodule of at least 2 cm (one lesion ≥2 cm and ≤5 cm, or two or three ≥2 cm and ≤3 cm) (FIGURE 1).

Demographic data for the groups with and without HCC are shown in TABLE 1. At study entry, patients with HCC were older than patients listed with a cMELD score (median age, 58.3±7.2 vs 55.0±10.0 years; P<0.001). Most patients were white men with cirrhosis associated with hepatitis C virus. HCC candidates had significantly lower cMELD scores at study entry than non-HCC candidates (mean ± SD: 18.19±4.7 vs 11.8±4.7; P<0.001).

HCC and DDLT
A Cox regression model of time to DDLT and a CR model for HCC were fitted to the data to compare waiting list outcomes.
Hepatocellular carcinoma patients are advantaged in the current Brazilian liver transplant allocation system. A competing risk analysis

Factors included in the model were age, MELD score, exception points, and ABO group. Candidates with HCC on the waiting list for DDLT had better outcomes than candidates included with a cMELD score. Patients listed with HCC underwent a transplant almost three times faster than patients listed with a cMELD score (SHR 2.64; 95% CI 2.10–3.31; P<0.001) (FIGURE 2). In addition, the DDLT rate per 100 person-months was 11.86 for patients with HCC vs 3.38 for candidates with a cMELD score. The median time on the waiting list was 5.6 months and 25 months for patients with HCC and a cMELD score, respectively.

### DISCUSSION

After the implementation of the MELD-based allocation system, coupled with HCC exception points, studies in large North American databases have shown that patients with HCC consistently had greater access to DDLT and lower dropout rates than candidates included in the waiting list without HCC (9,10,12,19). Consequently, the liver allocation policy adopted by the United Network for Organ Sharing (UNOS) for HCC patients was altered to reduce this distortion (19). Currently, in the United States, HCC patients are listed with a cMELD score in the first six months on the list. Patients who are still within the transplant criteria after six months receive a MELD score of 28, which increases every three months, up to a maximum of 34 (19).

In Brazil, the MELD score has been used in the allocation of grafts for DDLT since 2006 (11). To allow access to liver transplantation for patients with HCC within the Brazilian modified Milan criteria...
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(Partially funded by the National Council for Scientific and Technological Development (CNPq), Brazil. The authors thank the Liver Transplantation Group at Santa Casa de Misericórdia de Porto Alegre, RS, Brazil. The authors would also like to thank Professor Dr. Mário Wagner for his assistance with statistical analysis.

**Acknowledgements**

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Authors’ contribution

Rodríguez S: conceptualized and designed the data, collected the data, analyzed and interpreted the data, drafted the article, and critically revised the article. Fleck Jr AM, Mucenic M, Marroni C: critically revised the article. Brandão A: conceptualized and designed the data, collected the data, analyzed and interpreted the data, drafted the article, and critically revised the article.

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**RESUMO – Contexto** – No Brasil, o escore MELD (Model for End-Stage Liver Disease) é utilizado para priorizar os pacientes para transplante hepático de doador falecido (THDF). Pacientes com carcinoma hepatocelular (CHC) recebem pontos de exceção padronizados pelo MELD para contrapenas a mortalidade do seu câncer, que não é refletido pelo seu escore MELD. **Objetivo** – Comparar as taxas de THDF entre pacientes com e sem CHC no Rio Grande do Sul, o Estado mais ao sul do Brasil. **Métodos** – Foram estudados retrospectivamente 825 pacientes em lista de espera de transplante de figado entre 1 de janeiro de 2007 e 31 de dezembro de 2016 em um centro de transplantes localizado em Porto Alegre, capital do Rio Grande do Sul, para comparação das taxas de THDF entre aqueles com e sem CHC. Foi estimado o risco variável no tempo de lista de espera/THDF, com relato da taxa de sub-risco (SHR) de lista de espera/THDF/desistência com intervalos de confiança (IC) de 95%. O modelo final de risco competitivo foi ajustado para idade, escore MELD, pontos de exceção e grupo ABO. **Resultados** – Os candidatos com CHC foram submetidos a um transplante quase três vezes mais rápido do que os pacientes com um escore MELD calculado (SHR 2,64; IC 95% 2,10-3,31; P<0,001). A taxa de THDF por 100 pessoas-mês foi de 11,86 para os pacientes com CHC vs 3,38 para os pacientes sem CHC. O tempo mediano de permanência em lista de espera foi de 5,6 meses para os pacientes com CHC e 25 meses para os pacientes sem CHC. **Conclusão** – Nossos resultados demonstraram que, em nosso centro, pacientes em lista de espera com CHC têm evidente vantagem sobre candidatos listados com um escore MELD calculado.

**DESCRIPTORES** – Transplante de figado. Carcinoma hepatocelular. Transplante de órgãos. Disparidades em assistência à saúde.
Hepatocellular carcinoma patients are advantaged in the current Brazilian liver transplant allocation system. A competing risk analysis -

18. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiological data. Am J Epidemiol. 2009;170:244-56.

16. Jarnagin W, Chapman WC, Curley S, D'Angelica M, Rosen C, Dixon E, et al. Surgical treatment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford). 2010;12:302-10.

14. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Bosi A, et al. A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waitlist. J Hepatol. 2014;60:290-7.

13. Mehta N, Dodge JL, Hirose R, Roberts JP, Yao FY. Predictors of low risk for dropout from the liver transplant waitlist for hepatocellular carcinoma through the lens of transplant benefit. Hepatology. 2017;65:1741-8.

12. Vitale A, Polacco M, Fasoli E. Liver transplantation for hepatocellular carcinoma through the lens of transplant benefit. Hepatology. 2017;65:1741-8.

11. Vitale A, Volk ML, de Feo TM, Burra P, Frigo AC, Morales RR, et al. Impact of two eras: room for improvement? Liver Transpl. 2007;13(11 Suppl 2):S36-43.

10. Goldberg D, French B, Abt P, Feng S, Cameron AM. Increasing disparity in waitlist mortality rates with increased model for end-stage liver disease scores for candidates with hepatocellular carcinoma versus candidates without hepatocellular carcinoma. Liver Transpl. 2012;18:434-43.

9. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Patients with hepatocellular carcinoma have highest rates of waitlisting for liver transplantation among patients with end-stage liver disease. Clin Gastroenterol Hepatol. 2016;14:1638-46.e2.

8. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Hepatology. 2011;53:1580-9.

7. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. Am J Transplant. 2006;6:1416-21.

6. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Improving liver allocation: MELD and PELD. Am J Transplant. 2004;4(Suppl 9):S261-7.

5. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Consequences of the implementation of the Model for End-stage Liver Disease system for liver allocation in Brazil. Transplant Proc. 2013;45:2111-4.

4. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Improving liver allocation: MELD and PELD. Am J Transplant. 2004;4(Suppl 9):S261-7.

3. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Consequences of the implementation of the Model for End-stage Liver Disease system for liver allocation in Brazil. Transplant Proc. 2013;45:2111-4.

2. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Consequences of the implementation of the Model for End-stage Liver Disease system for liver allocation in Brazil. Transplant Proc. 2013;45:2111-4.

1. Goldberg D, French B, Newcomb C, Liu Q, Sahota G, Wallace AE, et al. Consequences of the implementation of the Model for End-stage Liver Disease system for liver allocation in Brazil. Transplant Proc. 2013;45:2111-4.