

Impact of the MELD score on the survival of hepatocellular carcinoma transplantation patients in Brazil: a systematic review.

Impacto do escore MELD na sobrevida de pacientes portadores de carcinoma hepatocelular, transplantados no Brasil: revisão sistemática.

MARCEL VASCONCELLOS¹ ; LUÍZA MAGALHÃES ZAMITH¹

ABSTRACT

This study aimed to analyse the predictive value of Model For End-Stage Liver Disease (MELD) score on medium- and long-term survival in transplanted hepatocellular carcinoma (HCC) patients in Brazil. The study was registered with International Prospective Register of Systematic Reviews (PROSPERO) under N# 152,363. Inclusion criteria were based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations. The search was performed on the indexed databases of Lilacs, SciELO, PubMed, and Cochrane Library, and used as search strategy the following Medical Subject Headings (MeSH) terms: (((“MELD Score”) OR “Model For End-Stage Liver Disease”) AND “Hepatocellular Carcinoma”) AND (“Brazil”). We included full-text articles published from January 2006 to October 2019. The initial search found 162 articles. After reading the available abstracts and full texts, 156 articles were excluded, totaling six articles for qualitative analysis. Although the small number of eligible articles was a limiting factor of the study, our results partially corroborated those found in the United States, United Kingdom, and Ireland. In these countries, unlike Brazil, MELD prognostic model has shown a strong association with post-liver transplant (LT) survival. However, the low predictive capacity of the model in medium- and long-term has been similar to the one of our study. The urgency of the development and validation of a post-transplant survival model for patients with HCC is set, improving the organ allocation system in Brazil.

Keywords: Liver Transplant. Hepatocellular Carcinoma. Survival Analysis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is responsible for over 90% of primary hepatic malignancies and considered the sixth most commonly diagnosed malignant disease in the world¹. Due to its late diagnosis, the average patient survival ranges approximately from six to 20 months, with a five-year survival inferior than 12%².

In Brazil, 70% to 80% of HCC cases are associated with cirrhosis secondary to chronic infection with either hepatitis B or C viruses³. In 2006, a new policy for equitable allocation of liver grafts called Model For End-Stage Liver Disease (MELD) began to be implemented in the country with a scoring system which comprises a range of values from 6 to 40. This model of end-stage liver disease is considered a well-established method (area under ROC curve [AUC] 0.78-0.87) as a three-month mortality predictor of patients still on the waiting list for an organ⁴.

As an indicator of the severity of end-stage biochemical dysfunction of the receptor, MELD score uses a logarithmic calculation involving serum creatinine, bilirubin, and International Normalized Ratio (INR), which assesses the tendency for blood coagulation according to the following formula: $[0.957 \times \text{Log e} (\text{creatinine mg/dl}) + 0.378 \times \text{Log e} (\text{bilirubin mg/dl}) + 1.120 \times \text{Log e} (\text{INR}) + 0.643] \times 10^4$.

Although patients with HCC have lower physiological MELD score, such patients are at increased risk of death related to tumor progression, as well as waiting list removal due to metastasis or clinical decompensation. Thus, Brazilian legislation has determined that patients with HCC, meeting Milan eligibility criteria, obtain an initial MELD score of 20 points, which may progress to 24 and 29 points every three months if the liver transplant (LT) is not performed after six months⁵.

1 - Serra dos Órgãos University Center (UNIFESO), Medicine School, Teresopolis, RJ, Brazil.

Milan criteria are defined by the presence of a nodule larger than 5cm in diameter or a maximum of three nodules, each one smaller than 3cm in diameter⁶. Such criteria shorten waiting list time during the course of end-stage liver disease^{7,8}. The adoption of an additional corrected MELD (MELDc) score for these patients has reduced waiting list time and increased the number of transplants. However, the impact of MELD score on these patients' survival remains controversial^{9,10}.

It should also be added that the ideal system should not only define the probability of death on the waiting list, but also predict the risk of death after transplantation, increasing its usefulness⁹.

The objective of this review was to analyse the predictive value of MELD score on medium- and long-term survival in transplanted HCC patients in Brazil.

METHODS

Search strategy

Analysis and inclusion criteria followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)¹¹ recommendations and the study was registered with International Prospective Register of Systematic Reviews (PROSPERO)¹² under N# 152,363.

Lilacs, SciELO, PubMed, and Cochrane Library databases were retrospectively consulted from January 2006 to October 2019, using as search strategy the following Medical Subject Headings (MeSH) terms: (((“MELD Score”) OR “Model For End-Stage Liver Disease”) AND “Hepatocellular Carcinoma”) AND (“Brazil”). The search did not include language restrictions.

Study selection

During the study selection, the evaluation of titles and abstracts identified in the initial search was independent and blindly performed by two researchers, obeying the following inclusion and exclusion criteria: inclusion criteria- patients of both genders, aged over 12 years, with or without cirrhosis, with hepatocellular carcinoma (HCC) classified according Milan criteria; exclusion criteria- transplanted patients for acute liver failure/ fulminant hepatitis and those undergoing multiple organ transplants, such as “split-liver” or “domino liver transplantation”.

RESULTS

Eligible studies

The initial search in the indexed databases resulted in a total of 162 articles: 38 in Lilacs, 36 in SciELO, 20 in PubMed, and 68 in Cochrane Library. The reading of the available abstracts and full texts led to the exclusion of 156 articles (96.2%). Of these, 155 articles (95.6%) did not meet the inclusion criteria or had no pertinence to the study. One study (0.6%) was excluded because it was a duplicate. At the end, six articles (3.7%) were eligible for the qualitative analysis (Table 1)¹³⁻¹⁸.

DISCUSSION

The development and validation of a model which can safely predict post-transplant outcome based on pre-transplant variables are an extremely complex task, since independent events which occur in the perioperative period, such as graft rejection, biliary complications, vascular complications, and the surgical team's own ability, can interfere with the primary outcome of the study.

Table 1. Selected studies.

Title	Objectives	Journal/Year	Characteristics
MELD and other predictors of survival after liver transplantation. Brandão <i>et al.</i> ¹³	To examine how reliable MELD scoring system is in predicting post-transplant survival.	Clin Transplant 2009	(n=436); AUC or C-statistic (0.60) Low discriminatory power between MELD and post-LT survival.
The impact of the model for end-stage liver disease (MELD) on liver transplantation in one center in Brazil. Freitas <i>et al.</i> ¹⁴	To compare liver transplant results in the pre-MELD era with the MELD era.	Arq Gastroenterol 2010	Survival in one-year time period was statistically the same in the MELD era and in the pre-MELD era: 74.6% in the pre-MELD era and 70.9% in the MELD era.
Employment of meld score for the prediction of survival after liver transplantation. Batista <i>et al.</i> ¹⁵	To analyse the overall accuracy of the preoperative MELD score for predicting post-liver transplant survival (post-LT) and explore predictors of medium-term survival (24 months).	Rev Col Bras Cir 2012	Cumulative survival at 12 and 24 months of the 208 studied patients was 74.5% and 71.1%, respectively. Preoperative MELD score showed low discriminatory power for predicting post-LT survival. For HCC stratum, the corresponding value of AUC for 24-month survival prediction was 0.59.
Impact of model for end-stage liver disease score on long-term survival following liver transplantation for hepatocellular carcinoma. Roma <i>et al.</i> ¹⁶	To report post-liver transplant survival of patients with HCC in Brazil for a period of ten years.	Transplant Proc 2012	Overall survival in ten-year time period was 67% (n=71). Implantation of MELD score had little impact on long-term survival after transplantation for HCC.
Impact of MELD score implementation on liver allocation: experience at a Brazilian center. da Silva Machado <i>et al.</i> ¹⁷	To evaluate the impact of MELD scoring system on liver allocation and mortality after liver transplant in Southern Brazil.	Ann Hepatol 2013	There was no significant correlation between MELD scores in LT and post-LT survival. During the 18-month follow-up, the post-LT mortality rate was 25.4% before and 20% after MELD implantation (not significant).
Model for End-Stage Liver Disease, Model for Liver Transplantation Survival and Donor Risk Index as predictive models of survival after liver transplantation in 1,006 patients. Aranzana <i>et al.</i> ¹⁸	To compare the performance of MELD score, among others, in the prognosis of post-liver transplant survival.	Clinics 2015	(n=164) patients with HCC (16.3%). Findings were similar to those by Nagler <i>et al.</i> (2005), who obtained a 0.61 C-statistic for MELD and showed a relationship between MELD score and post-transplant survival.

The first study conducted in the USA has evaluated long-term post-LT survival in 1,472 patients. Results have shown that a pre-LT MELD of 26 has been associated with worse survival in short- and long-term (10 years) post-LT¹⁹. Studies conducted in Brazil, such as those by Brandão *et al.*¹³ and Batista *et al.*¹⁵, used the area under Receiver Operating Characteristic (ROC) curve (AUC) analysis as a summary measure of MELD score performance for post-LT survival prediction. The area under ROC curve, also called C-statistic, measures a model's prediction quality, with values from 0.7 considered clinically useful, while values equal to or inferior than 0.5 relate to scores with low discriminatory power^{13,20,21}. In both studies, the researchers found a low discriminatory power (AUC of 0.60 and 0.59, respectively) between MELD score and post-LT survival.

Freitas *et al.*¹⁴, in a comparative study between the results of liver transplantation in the pre-MELD era *versus* in the MELD era, observed that survival in one year did not show statistically significant differences between the studied periods: 74.6% *versus* 70.9%, respectively. da Silva Machado *et al.*¹⁷ reported that, after an 18-month follow-up, the post-LT mortality rate was 25.4% before and 20% after MELD implantation (statistically non-significant results), concluding that MELD score implantation had a minor impact on the long-term survival of patients with HCC.

Aranzana *et al.*¹⁸ compared, in a cohort of 164 patients with HCC (16.3%), the areas under ROC curve for post-transplant survival for MELD score at one year and two years after transplantation. The areas under the curve (AUC) for all these time intervals indicated that MELD-based predictions were more accurate than chance (i.e., >0.5).

It is noteworthy that the study conducted in Brazil was the only one to present a relationship between MELD value and post-LT survival.

Kamath *et al.*²² adduced that MELD model was not accurate in predicting survival in 15-20% of cases. However, the percentage did not refer exclusively to patients with HCC. Regarding medium- and long-term predictive capacity, Brazilian studies found a low discriminatory power of the score with post-LT survival^{13,15,16}.

In the United States, United Kingdom, and Ireland, MELD prognostic model is significantly associated with post-LT survival, but with low predictive capacity in medium- and long-terms, suggesting a combination of MELD score with a post-transplant survival model to be properly developed and validated⁴.

Despite the consensus among researchers on the urgency of the analysis of the predictive value of the post-LT MELD score^{6,10}, we observed a lack of articles in literature on the role of this model on post-LT medium- and long-term survival in patients with HCC.

CONCLUSIONS

Although the small number of eligible articles was a limiting factor of the study, our results partially corroborated those found in the United States, United Kingdom, and Ireland. In these countries, unlike Brazil, MELD prognostic model has shown a strong association with post-LT survival. However, the low predictive capacity of the model in medium- and long-terms has been similar to the one of our study.

The urgency of the development and validation of a post-transplant survival model for patients with HCC is set in order to improve the organ allocation system in Brazil.

R E S U M O

O objetivo do estudo foi o de analisar o valor preditivo do escore MELD (Model for End-Stage Liver Disease) na sobrevida de médio e longo prazo em pacientes portadores de carcinoma hepatocelular (CHC), transplantados no Brasil. O estudo foi registrado no PROSPERO (International Prospective Register of Systematic Reviews), sob o nº 152.363. Os critérios de inclusão basearam-se nas recomendações PRISMA. A pesquisa foi realizada nos bancos de dados indexados do Lilacs, SciELO, Pubmed e Cochrane Library, e utilizou como estratégia de busca os termos MeSH: (((("Meld Score") OR "Model for End-Stage Liver Disease") AND "Hepatocellular Carcinoma") AND ("Brazil")). Foram incluídos artigos com texto completo, publicados a partir de janeiro de 2006 até outubro de 2019. A busca inicial encontrou 162 artigos. Após a leitura dos resumos e textos completos disponíveis, foram excluídos 156 artigos, totalizando seis artigos para análise qualitativa. Embora o número reduzido de artigos elegíveis tenha sido um fator limitante do estudo, nossos resultados corroboraram parcialmente aos encontrados nos EUA, Reino Unido e Irlanda. Nestes países, ao contrário do Brasil, o modelo prognóstico MELD mostrou forte associação com a sobrevida pós-transplante hepático. No entanto, a baixa capacidade preditiva do modelo em médio e longo prazo, foi similar ao nosso estudo. Configura-se a premência do desenvolvimento e validação de um modelo de sobrevida pós-transplante aos portadores de CHC, aperfeiçoando o sistema de alocação de órgãos no Brasil.

Descritores: Transplante de Fígado. Carcinoma Hepatocelular. Análise de Sobrevida.

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Mailing address:

Marcel Vasconcellos

E-mail: marcelvasconcellos@unifeso.edu.br

marcelvet57@gmail.com

