Final progress report: Machine learning evaluation of liver transplant wait-list prioritization for patients with PSC

An impact report prepared for
PSC Partners Seeking a Cure Canada
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UHNITED UHN FOUNDATION

Thank you

To Mary Vyas, President of PSC Partners Canada,

On behalf of my research team, I would like to thank PSC Partners Canada and the PSC Partners Scientific/ Medical Advisory Committee (SMAC) for their tireless work and dedicated support to better care for people living with PSC. Your generous grant is supporting research that we believe will help PSC patients access more equitable, timely and appropriate care - improving outcomes for those living with end-stage disease.

As you are aware, our team has been developing an algorithm using machine learning to provide a more equitable alternative to the standard methods of distributing organs for transplantation. We are pleased to present our annual summary and scientific abstract detailing our updates and next steps. Last year, we reported that we had successfully developed an algorithm that predicts patient outcomes with a good degree of accuracy. Building upon this research, we are now examining the role of disease-specific variables to better optimize patient prioritization.

I trust that you will enjoy reading about the research progress that your support is making possible. Thank you for your ongoing partnership and generous support.

Sincerely,

Dr. Mamatha Bhat
Hepatologist and Clinician Scientist, Ajmera Transplant Centre,
University Health Network

Annual summary

Background

Due to the shortage of available donor organs, clinicians use the Model for End Stage Liver Disease (MELD-Na) score to assign a priority ranking to each patient awaiting a liver transplant, in order to prioritize the sickest patients and improve equity in organ allocation. However, the MELD-Na score is not sufficient in adequately reflecting the severity of certain rare diseases, including PSC, due to the exclusion of relevant disease-specific variables from patient data. The MELD-Na score is particularly inaccurate in subgroups such as women and patients with cholestatic disease. As a result, patients with PSC can stay on the transplant waitlist for longer, impacting their quality of life and putting them at an increased risk for adverse outcomes. Machine learning enables the use of disease-specific variables to build a more complex risk stratification model and allow for timely processing of large-scale datasets - finding patterns and signals that can aid clinicians in better predicting clinical outcomes.

Our main objective in this study is to develop a machine learning algorithm that optimizes outcome predictions in PSC patients on the waitlist for transplantation as an equitable alternative to the MELD-Na score. In year one (2022-2023), we successfully developed this algorithm, with a good degree of accuracy, by analyzing PSC-specific clinical features such as recurrent cholangitis, biliary stenting and concomitant IBD. We validated that the algorithm improves upon the MELD-Na score as a predictor of mortality in waitlisted PSC patients.

Progress update

Following a similar process of data collection in year one, we used patient information from the Scientific Registry of Transplant Recipients (SRTR) database and its Organ Procurement and Transplantation Network (OP-TN), and the University Health Network (UHN) database. The data was gathered, cleaned and prepared for analysis. Patients were excluded where their natural MELD-Na scores didn't reflect their waitlist outcomes. The analysis was completed and then reviewed by Dr. Mamatha Bhat.

Patients with PSC were categorized based on demographics and clinical and laboratory values, such as sex, race/ethnicity, weight and BMI, as well as WBC, platelets and bilirubin levels. Patient data from the UHN database also considered PSC-related complications such as frequency of cholangitis, superimposed cirrhosis, biliary dysplasia and removal surgeries.

Waitlist outcomes were categorized into three groups:

- Mortality on the waitlist, including patients delisted due to clinical deterioration and development of contraindications to liver transplant;
- Censored patients removed from the waitlist due to improvement in their condition or opting out of transplant, and;
- Patients who received a liver transplant.

We used the information from these two databases to refine the machine learning algorithm. Over 4,600 patients from the SRTR were used as a training dataset on three machine-based survival models to predict waitlist outcomes using the C-index, a statistical calculation that indicates the accuracy of predicting outcomes. We compared our models against current MELD score systems, MELD-Na and MELD 3.0, and further refined our top two performing models using regional data from the OP-TN and by training them on UHN patient data. The best performing model, Random Survival Forest (RSF), was further trained on shared features between the UHN and SRTR datasets and introduced to PSC-specific variables: cholangitis, number

of cholangitis episodes and the presence of cirrhosis. Additional PSC-specific complications were later added in the UHN dataset to further refine the algorithm.

After incorporating PSC-specific features, we listed them based on highest impact on the RSF model output. We found that MELD-Na scoring was the greatest predictor, and the addition of PSC-specific variables significantly contributed to the accuracy of the algorithm's predictive capabilities. This leads us to conclude that our machine learning algorithm makes more accurate outcome predictions for PSC patients on the waitlist for transplantation than other scoring tools. Our model further supports the conclusion that MELD scoring alone is not sufficient and that the incorporation of disease-specific variables contain valuable prognostic information.

One of the challenges we faced with this study was the lack of PSC-specific data in the larger patient databases, resulting in the use of a smaller sample size when further refining the algorithm. We overcame this challenge by using cross-validation, concurrently training our model using the SRTR and UHN datasets.

We presented our research findings at the International Liver Transplant Society's 2023 annual meeting and the Canadian Society of Transplantation's 2023 annual meeting. We also recently submitted our manuscript, "Optimizing Prediction of Waitlist Outcomes in Patients with Primary Sclerosing Cholangitis through Inclusion of Disease-Specific Variables: the application of machine learning for patient benefit", to a peer reviewed journal. An abstract for this manuscript can be found in the appendix to this document. We are using this research to inform the development of our larger liver transplant waitlist prioritization work, which recently enabled us to attract CIHR funding to support this work.

Updated timeline

Building upon our progress from year one, we continued to refine our machine learning algorithm and improved its prediction accuracy, using the UHN database to further validate the algorithm. Through a literature search, we confirmed that the mortality rate of patients with PSC on the transplant waitlist is much higher than patients with other end-stage liver diseases, such as non-alcoholic steatohepatitis and alcoholic liver disease.

In addition, we demonstrated that since the MELD-Na score alone cannot consider individual patient characteristics, it therefore cannot be used to predict individual patient trajectories and outcomes. Using our model, we were able to accurately predict the individual trajectories of two PSC patients from the dataset, including the outcome of a 57 year-old-patient with PSC-related cirrhosis who had a decreased chance of survival.

As our next steps, we will test our machine learning algorithm on a larger patient dataset. We are in the process of acquiring multi-centre data for listed transplant patients across Canada. Once obtained, we will further refine our model to improve its prediction accuracy.

Summary of Expenses

	PROJECT EXPENSES (IN USD)
YEAR 1 (2022-2023)	
Post-doctoral Fellow with specialty in machine learning (0.3 full-time equivalent)	$22,000
Clinical Research Fellow (0.2 full-time equivalent)	$8,000
YEAR 2 (2023-2024)	
Machine Learning Analyst (0.5 full-time equivalent)	$30,000
TOTAL:	$60,000

Appendix

Optimizing Prediction of Waitlist Outcomes in Patients with Primary Sclerosing Cholangitis through Inclusion of Disease-Specific Variables: the application of machine learning for patient benefit

Dr. Mamatha Bhat
Hepatologist and Clinician Scientist, Ajmera Transplant Centre

ABSTRACT

Background and Aims: Liver transplantation (LT) remains essential in managing primary sclerosing cholangitis (PSC). However, the Model for End Stage Liver Disease (MELD) Na score currently used to prioritize patients does not adequately reflect the risk of waitlist mortality and dropout amongst patients with PSC. We sought to evaluate whether machine learning models could more accurately predict waitlist mortality and dropout for PSC patients on the LT waitlist, by considering PSC-specific disease modifiers such as history of cholangitis and concomitant IBD.

Methods: We retrospectively reviewed waitlist outcomes of 4,666 and 144 PSC patients from the Scientific Registry of Transplant Recipients (SRTR) and University Health Network (UHN) datasets respectively. We subsequently built three machine learning algorithms from the SRTR to predict waitlist outcomes using time dependent c-index. We then identified the best performing model, and introduced PSC-specific variables to assess their impact on the model. We compared our models with MELD-Na and MELD 3.0.

Results: Three machine learning algorithms were developed: Cox Proportional Hazard (CPH), Random Survival Forest (RSF) and DeepSurv. RSF was the best performing and subsequently fine-tuned using disease specific variables. The c-index for MELD 3.0 was below 0.7 at 1 month, 6 months and 1 year on waitlist when tested on UHN patients. The average c-index increase to above 0.9 with the introduction of PSC-specific variables trained and tested on UHN patients.

Conclusion and Relevance: Advanced machine learning models using PSC-specific clinical factors can outperform the MELD-Na score for prediction of waitlist mortality and dropout. Risk stratification tools that better account for disease specific factors have the potential to be adopted more broadly as application of advanced informatics in clinical practice grows.

Contact information

Thank you for your generous support, which is enabling Dr. Mamatha Bhat and her colleagues to continue to pursue new ways to improve transplant equity for patients living with PSC.

To learn more, please contact:

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