

Predictive Analysis of Cardiometabolic Risks in Liver Transplantation — A Case Study in Uruguay

Parag Chatterjee, Andreina Tesis, Mario Gonzalez, Ofelia Noceti, Josemaria Menendez, Solange Gerona

Abstract— Cardiovascular diseases are the leading cause of mortality worldwide. In 2021, an estimated 48 million individuals in Latin America were living with heart and circulatory diseases. In the context of liver transplantation, cardiometabolic risk factors play a crucial role not only during the procedure but also in the long-term post-transplantation period, significantly impacting patient survival and recovery. This study analyzes a cohort from the National Liver Transplantation Program of Uruguay, employing machine learning to predict the occurrence of post-transplant cardiometabolic diseases based on pre-transplant health indicators. Over a five-year period, multiple machine learning models were evaluated, with the Extra Trees algorithm achieving the highest predictive accuracy of 88% (AUC: 0.94). The findings highlight the potential of predictive analytics in improving early risk assessment and preventive strategies, ultimately enhancing the prediction of patient outcomes in liver transplantation.

Clinical Relevance— This is the first national-level study validating machine learning algorithms for cardiometabolic risk prediction in liver transplantation patients within the National Liver Transplantation Program in Uruguay. By leveraging pre-transplant clinical data, the proposed model provides a data-driven approach for early risk stratification, supporting clinicians in making informed decisions to mitigate post-transplant cardiometabolic complications.

I. INTRODUCTION

Cardiovascular diseases (CVD) have contributed as the number 1 cause of death globally, counting to an estimated 17.9 million lives each year. Cardiovascular diseases are a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions. Four out of five deaths from cardiovascular diseases are caused due to heart attacks and strokes, and one third of these deaths occur prematurely in people under 70 years of age [1]. Early detection of risks related to cardiovascular indicators and identification of people at a higher risk of cardiovascular diseases enable the possibility of providing appropriate and timely treatment, to prevent premature deaths. Addressing behavioral risk factors

is a crucial component of cardiovascular disease prevention. Nonetheless, complementing preventive approaches, the timely identification of risk factors and the subsequent communication of risk profiles and preventive strategies to patients are of paramount importance. This remains a challenge in low- and middle-income countries, where integrated primary care systems are often underdeveloped compared to those in high-income countries. Considering at least three quarters of the world's deaths caused by cardiovascular diseases occur in low- and middle-income countries [1], it is highly important for the existing healthcare systems to focus on early detection and prevention. Aligning with the perspective of precision medicine in offering predictive and personalized healthcare, artificial intelligence has a significant role in this domain.

Cardiometabolic risks and diseases often intertwine and interact with other diseases and therapeutic procedures. In liver transplantation, cardiovascular disease is the leading cause of non-graft-related deaths and has increased prevalence in liver allograft recipients. Augmented cardiometabolic risk factors in transplant-patients often lead to post-transplantation metabolic syndrome including obesity, hypertension, dyslipidemia, and diabetes mellitus, impacting on morbidity and mortality of the transplanted patients [2]. It has been illustrated by several studies that recipients of liver transplant have a significantly increased risk of cardiovascular events and deaths compared to an age- and sex- matched general population [3]. We have previously reported a strong relationship between pre-transplantation vascular age and post-transplantation cardiometabolic diseases. Also, vascular age indicated significant impact in classifying the cohort in terms of post-transplantation survival [4], [5].

This study aims at analyzing the cardiometabolic risks among the patients enrolled at the National Liver Transplantation Program of Uruguay. Specifically, it pursues two main objectives: to evaluate the evolution of cardiometabolic risk factors throughout the transplantation process and during the post-transplantation period; and to develop and assess machine learning models to predict post-transplantation cardiometabolic complications. This eventually would help enhancing pre-transplant risk stratification and support more effective preventive and therapeutic strategies in the post-transplant setting.

Parag Chatterjee, Andreina Tesis, and Mario Gonzalez are with the University of the Republic (*Universidad de la República*), Uruguay.

Ofelia Noceti, Josemaria Menendez, and Solange Gerona are with the National Program of Liver Transplantation, Army Forces Hospital,

(*Dirección Nacional de Sanidad de la Fuerzas Armadas*), Montevideo, Uruguay. (**Corresponding Author email: paragc@ieee.org**).

II. METHODS

A. Description of the cohort

The cohort considered for this study consists of 143 patients (58 males and 32 females) registered under the National Liver Transplantation Program of Uruguay, who were transplanted between 2014 and 2021. At the entry-point of the transplantation program, around 40 health-indicators are assessed. Patients are categorized into a priority list based on their MELD-Na score (Table I), and upon satisfying the criteria, enter to the waiting list. After transplantation, the health indicators of the patients are monitored for a period of five years on an average.

B. Evolution of Cardiometabolic Diseases in the cohort

The health indicators for cardiometabolic diseases have been analyzed from the patients in the waiting list for liver transplantation, continuing through the follow up till 5 years after receiving the transplant. Features like smoking, arterial hypertension, obesity, new onset diabetes after transplantation (NODAT), and chronic kidney disease were analyzed for the follow up period, starting from 6 months after the transplantation, and periodically at 12 months, 24 months, 36 months, 48 months, and till 60 months.

C. Machine Learning for the prediction of post-transplantation cardiometabolic risk factors

Given the importance of early prediction of cardiometabolic diseases with the aim of efficient prevention, machine learning models were used to predict the occurrence of cardiometabolic diseases in the patients after receiving the transplant, based on the pre-transplantation clinical data. Supervised models were implemented to estimate the cardiometabolic risk of patients in the post-transplantation period. Rather than focusing solely on the impact of individual predictors, the primary aim was to capture the overall pattern of the post-transplant cardiometabolic outcomes, and to evaluate the potential of machine learning techniques in forecasting such events in a holistic manner.

III. RESULTS

In the prima-facie analysis of the transplanted cohort, 29% of the cohort showed obesity, whereas 30% and 32% showed arterial hypertension and diabetes respectively. From the entry-point of the transplantation program till receiving the transplant, the patients continue in the waitlist for a mean period of 5 months.

TABLE I. FEATURES AT THE ENRTY-POINT OF THE LIVER TRANSPLANTATION PROGRAM

Number of patients (total=143)	Male: 91 Female: 52
<i>General Characteristics of the cohort</i>	
Age [years]	50 ± 12
MELD-Na score	18 ± 8
Weight [kg]	82 ± 16 ± 17
BMI [kgm ⁻²]	28.16 ± 4.95

Systolic Pressure [mmHg]	115 ± 15
Diastolic Pressure [mmHg]	67 ± 9
Smoking	26%
Diabetes	47%
Arterial Hypertension	32%
Obesity	33%
Chronic Kidney Disease	8%
Post-transplantation Deaths	19%
<i>Hematology</i>	
Total Cholesterol [mgdl ⁻¹]	158 ± 95
HDL [mgdl ⁻¹]	35 ± 23
LDL [mgdl ⁻¹]	97 ± 59
Platelets [x1000 ml ⁻¹]	120 ± 72
Total Cholesterol/ HDL	10.21 ± 23.14
Glycemia [mgdl ⁻¹]	109 ± 48
Total Bilirubin [mgdl ⁻¹]	5.65 ± 7.83
International Normalized Ratio (INR)	1.74 ± 0.97
<i>Liver conditions</i>	
Hepatocellular Carcinoma	26%
Cirrhosis	68%
Acute Liver Failure	2%
Tumoral	7%

The cardiometabolic risk factors showed distinct characteristics and evolution during post-transplantation period.

TABLE II. EVOLUTION OF CARDIOMETABOLIC RISKS IN THE POST-TRANSPLANTATION PERIOD TILL 5 YEARS

(% of patients)	Pre-transplant	6 M	12 M	24 M	36 M	48 M	60 M
Smoking	25.56	1.11	3.33	4.44	4.44	4.44	4.44
Arterial Hypertension	32.22	48.8 9	58.8 9	58.8 9	60.0 0	60.0 0	72.2 2
New Onset Diabetes After Transplant	46.67	51.1 1	52.2 2	52.2 2	53.3 3	56.6 7	56.6 7
Chronic Kidney Disease	6.67	18.8 9	24.4 4	27.7 8	28.8 9	28.8 9	28.8 9
Obesity	33.33	18.8 9	27.7 8	27.7 8	34.4 4	35.5 6	35.5 6

Plotting the cardiometabolic risk factors (Table II) graphically (Figure 1), each risk showed a different progression. Arterial hypertension showed a 33% increase just in 6 months from the transplant and ended to a 124% increase in 5 years. Risks like smoking, directly induced by behavioral factors, showed a descent in the first 6 months post-transplantation, mostly maintaining stable throughout the entire follow-up period, with a total decrease of 82.63% from the pre-transplant evaluation. Diabetes showed a gradual increment of 21.43% compared to pre-transplantation levels, and chronic kidney disease showed sharp increase during the first year of transplantation, followed by steady increase during the remaining course of the follow-up. The differences of the aforementioned features were significant ($p < 0.001$), compared to the pre-transplantation values, except obesity ($p = 0.3$). However, though obesity showed a strong decline in the transplanted cohort during the first 6 months from transplantation, during the remaining follow-up period till 5 years, was pronounced substantially.

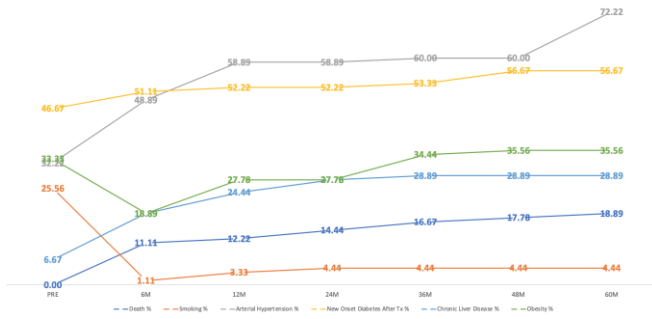


Figure 1. Progression of cardiometabolic risks in the transplanted cohort – follow up

Survival rates of the patients demonstrate a sharp descent within 6 months from the transplant, followed by a steady progression to a 18.89% post-transplantation mortality rate in 5 years. 82% of the patients who died post-transplantation showed a higher pre-transplantation vascular age compared to their respective chronological age. This emphasizes the need of predicting post-transplantation cardiometabolic diseases at the entry-point of the program.

To predict the occurrence of cardiometabolic disease in the transplanted patients, the cardiometabolic features were analyzed over the follow-up period, and at the endpoint of 5 years, each patient was labeled as positive or negative, in terms of cardiometabolic disease. At the first outset, a correlation analysis was performed, which illustrated a high correlation between the calculated vascular age at the entry-point of the program and the post-transplant cardiovascular risk.

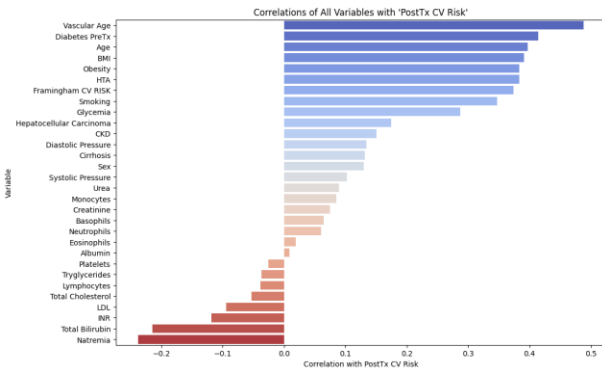


Figure 2. Correlation of Pre-transplant Features with Post-transplant Cardiovascular Risk

The patient cohort was split into 70-30 for train-test and appropriate 10-fold cross validation was used, considering a small cohort and diverse set of clinical features. Eleven supervised algorithms were used to predict the post-transplantation cardiovascular risk using baseline clinical features collected at the time of patient enrollment in liver transplantation program. As shown in Figure 3, the best performance was achieved by ExtraTrees classifier.

Model	Accuracy	AUC	Recall	Prec.	F1	Kappa	MCC
Extra Trees Classifier	0.8800	0.9405	0.9625	0.9014	0.9270	0.5839	0.5944
Ridge Classifier	0.8700	0.9045	0.9375	0.9103	0.9197	0.5807	0.5875
Ada Boost Classifier	0.8600	0.9061	0.9071	0.9121	0.9037	0.6232	0.6498
Random Forest Classifier	0.8100	0.8257	0.9625	0.8311	0.8856	0.3265	0.3622
Logistic Regression	0.8000	0.8664	0.8429	0.9014	0.8664	0.4289	0.4448
Decision Tree Classifier	0.8000	0.6417	0.9500	0.8256	0.8793	0.3143	0.3343
Gradient Boosting Classifier	0.7800	0.7292	0.9357	0.8131	0.8667	0.2412	0.2510
K Neighbors Classifier	0.7600	0.4863	0.9446	0.7836	0.8554	0.1200	0.1288
SVM - Linear Kernel	0.7600	0.6009	0.9625	0.7824	0.8591	0.0672	0.0718
Light Gradient Boosting Machine	0.7300	0.6637	0.8714	0.7984	0.8303	0.1538	0.1567
Extreme Gradient Boosting	0.7100	0.6830	0.8482	0.7914	0.8135	0.1467	0.1435

Figure 3. Performance comparison of the supervised models to predict occurrence of post-transplantation cardiometabolic diseases

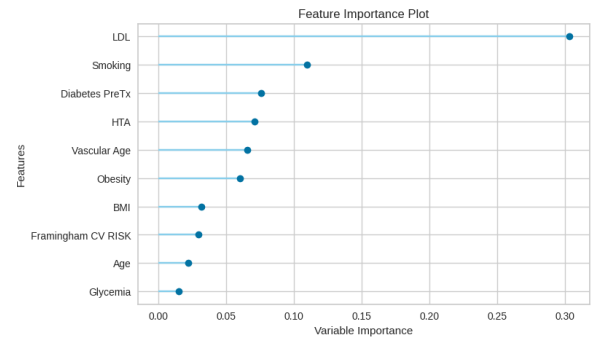


Figure 4. Feature importance of the best model to predict occurrence of post-transplantation cardiometabolic diseases

Figure 4 describes the features used by the models regarding their contribution in the prediction. Framingham risk score was excluded from the modeling to examine the independent contribution of each feature in the prediction without the confounding influence of a pre-calculated score. This approach underscores the potential of ML models to predict post-transplant cardiovascular risk using only standardized clinical data obtained at the time of patient enrollment to the transplantation program.

IV. CONCLUSION

In liver transplantation, the emergence of post-transplant cardiometabolic risk factors can seriously compromise patient health, including additional complications during recovery and throughout the post-transplant period [4]. Post-transplantation cardiometabolic diseases represent a major clinical challenge in liver transplant recipients, significantly affecting long-term morbidity and mortality. Notably, coronary heart disease has been identified as a key contributor to long-term mortality in liver transplant recipients [6]. Stratifying cardiometabolic risk and managing cardiovascular events based on pre-transplant health information is crucial to minimizing adverse outcomes [7].

The findings of this study highlight the importance of early risk prediction and stratification as means to enable timely and targeted preventive interventions. It also demonstrates the evolution of cardiometabolic risks in transplanted patients and

the effectiveness of machine learning models in predicting post-transplant cardiovascular complications. Integrating these predictive models into a clinical decision support system has the potential to enhance personalized treatment strategies, optimizing patient outcome throughout the transplantation process. Future efforts should prioritize the implementation of these models in real-world clinical workflows to further validate their efficacy and support more effective long-term management of transplant recipients. Future efforts should prioritize the implementation of such models in real-world clinical settings to validate their utility and support more effective long-term management of transplant recipients.

REFERENCES

- [1] World Health Organization, "Cardiovascular diseases (CVDs)," May 17, 2017. [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) (accessed May 15, 2021).
- [2] N. G. Kim, A. Sharma, and S. Saab, "Cardiovascular and metabolic disease in the liver transplant recipient," *Best Practice & Research Clinical Gastroenterology*, vol. 46–47, p. 101683, Jun. 2020, doi: 10.1016/j.bpg.2020.101683.
- [3] I. W. Graziadei and A. Cárdenas, "Cardiovascular diseases after liver transplantation-a still emerging and unsolved problem!: Editorial," *Liver Transpl.*, vol. 21, no. 7, pp. 870–872, Jul. 2015, doi: 10.1002/lt.24176.
- [4] P. Chatterjee *et al.*, "Predictive Cardiometabolic Risk Profiling of Patients Using Vascular Age in Liver Transplantation," in *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, Mexico, Nov. 2021, pp. 1715–1718. doi: 10.1109/EMBC46164.2021.9631071.
- [5] P. Chatterjee *et al.*, "Machine Learning in Healthcare Towards Early Risk Prediction — A Case Study of Liver Transplantation," in *Data analytics in biomedical engineering and healthcare*, 1st ed., Waltham: Elsevier, 2020. [Online]. Available: <https://www.elsevier.com/books/data-analytics-in-biomedical-engineering-and-healthcare/lec/978-0-12-819314-3>
- [6] J. Salyer, K. An, and S. Siddiqui, "Abstract P046: Cardiometabolic Risk Liver Transplant Survivors," *Circulation*, vol. 135, no. suppl_1, Mar. 2017, doi: 10.1161/circ.135.suppl_1.p046.
- [7] S. Desai, J. C. Hong, and S. Saab, "Cardiovascular risk factors following orthotopic liver transplantation: predisposing factors, incidence and management: Cardiovascular risk factors following orthotopic liver transplantation," *Liver International*, vol. 30, no. 7, pp. 948–957, Sep. 2009, doi: 10.1111/j.1478-3231.2010.02274.x.