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Predictive Cardiometabolic Risk Profiling of Patients Using Vascular Age in Liver Transplantation*

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Abstract— **Liver transplantation is the last therapeutic option in patients with end-stage liver diseases. The adequate clinical management of transplant-patients impacts their vital prognosis and decisions on many occasions are made from the interaction of multiple variables involved in the process. This work is based on the National Liver Transplantation Program in Uruguay. We performed predictive analysis of cardiometabolic diseases on the transplanted cohort between 2014 and 2019, considering vascular age as a key factor. This aims at classification of the cohort based on the vascular age of the evaluated patients before transplantation for risk-profiling. Predicted high-risk group of the patients showed substantial deterioration of post-transplant health-conditions, including higher mortality rate. In our knowledge, this is the first study in Latin America incorporating vascular age toward predictive analysis of cardiometabolic risk factors in liver transplantations. Predictive risk-modeling using vascular age in a pre-transplantation scenario provides significant opportunity for early prediction of post-transplant risk factors, leading to efficient treatment with anticipation.**

Clinical Relevance— **This study under the National Liver Transplantation Program of Uruguay illustrates the importance of pre-transplant vascular age in predicting post-transplant cardiometabolic risks and diseases.**

I. Introduction

Liver transplantation is the last therapeutic option in patients with end-stage liver disease. It is a complex process and deals with numerous health-indicators of the patients. Cardiometabolic diseases are frequently responsible for high morbimortality in patients with liver transplants. Patients with underlying cardiovascular and metabolic pathologies are prone to complications after the transplant. Metabolic syndrome, defined by obesity, hypertension, dyslipidemia, and hyperglycemia, is diagnosed among liver transplant recipients and is aggravated post-transplantation, influencing long-term survival [1]. Four of the most prominent chronic diseases – cardiovascular diseases, cancer, chronic obstructive pulmonary disease and type 2 diabetes are linked by common and preventable biological risk factors, notably high blood pressure, high blood cholesterol and overweight, and by related major behavioral risk factors. These risk factors strongly influence the entire process of transplantation, including the patients' health after the transplant. Several studies have highlighted the importance of cardiovascular risk factors and Framingham Risk Score as predictors of negative post-transplant outcomes, including long-term mortality [2][3][4]. The assessment of cardiometabolic risks at an early stage of the transplantation process facilitates having better post-transplant results, also in the long-term. For that reason, it is important to communicate the cardiometabolic risks [5] to the patients at the entry-point of the transplantation program and a follow-up of the same throughout the entire timeline, to let them have better control of their health and act accordingly to improve their health during the transplantation and recovery process.

This study is focused to the patients registered under the National Liver Transplantation Program, Uruguay and is aimed at analyzing the cardiometabolic risks during the pre- and post-transplantation timeline of the cohort. In this perspective, all the health-indicators of the cohort have been considered at the entry-point of the program and vascular age has been introduced to analyze the pre-transplant cardiometabolic risks. Also, we validated the cardiometabolic risks and post-transplant deaths through a post-transplantation follow-up in the transplanted patients pertaining to vascular age.

II. Methods

A. Description of the cohort

The cohort considered in this study consists of 165 patients (85 males and 80 females). Among them, 92 patients were transplanted in a span of 5 years (2014 to 2019), whereas 2 patients were not considered in this analysis (for having other

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complications like hepatorenal conditions), making the cohort of transplanted patients considered as 90.

TABLE I. NATIONAL LIVER TRANSPLANTATION PROGRAM, URUGUAY (JANUARY 2014 TO DECEMBER 2019)

Total Number of patients evaluated	165
Patients had contraindications for liver transplants and thus not included in the waiting list	25
Patients waiting to get transplanted	28
Patients transplanted	92 (considered in this study: 90)
Patients dead while in waiting list	20
Patients dead	43 (Post-transplant deaths: 17)
Patients alive	122 (Post-transplant survivals: 75)

This cohort of transplanted patients consisted of 58 males and 32 females. In the primary evaluation at the entry-point to the transplantation program, 29% of the patients showed obesity, 30% with arterial hypertension, and 32% with diabetes. The transplanted patients have an average waiting time of 5 months from the entry-point of the transplantation program to receiving the transplant.

B. Vascular Age

An indicator of cardiovascular risk factors is the Vascular Age, also known as Heart Age. It is based on the measurement scale for general cardiovascular disease risk functions under Framingham Heart Study, translated to sex-specific risk scores [6]. The vascular age of a patient with cardiovascular risk factors is defined as the age that an individual of the same sex as a patient would have if she or he were to have the same absolute risk but controlled risk factors. In this respect, vascular age is an ideal tool for communicating the cardiometabolic risks to the patients through the representation of the risks using a simple and perfectly understandable score [7]. This study has several objectives pertaining to cardiometabolic risks of the patients. Primarily the Framingham Cardiovascular Risk was used based on the Framingham Heart Study Cardiovascular Disease [6] considering predictors like age, diabetes, smoking, treated and untreated systolic blood pressure, total cholesterol, and HDL. The focal goal was the identification of early signs of cardiometabolic risks using vascular age as a key parameter. More specifically, in this case, the difference between vascular age and chronological age was considered as the key differentiating feature (Δage = vascular age - chronological age).

Patients with vascular age higher than their respective chronological age (Δage>0) were speculated to have higher possibilities of cardiometabolic risks, even in the post-transplantation period. On the contrary, patients with vascular age lesser or equal to their chronological age (Δage<=0) were considered to have lower cardiometabolic risks.

C. Predictive model for the transplant-event

Considering all the features of the study (Table II), a logistic regression model has been designed to predict the transplant-event on the entire cohort, primarily to identify the relevance of the cardiometabolic parameters in the transplantation. Also, the key objective includes assessing the importance of vascular age for analyzing the cardiometabolic risks through a detailed follow-up after the transplant.

D. Pre- and Post-transplant Cardiometabolic Risks

Firstly, the cardiovascular risks of the entire cohort at their entry-point to the liver transplant program were calculated. Following that, the entire cohort was separated with respect to their vascular age with the intention of creating risk-profiles of patients based on their cardiometabolic risks. Based on Δage, two groups were formed, and their respective health indicators (evaluated at the entry-point of the transplantation program) were compared. Once the patients are transplanted, a follow-up is performed as a part of the post-transplantation treatment. In this part, the groups of transplanted patients separated by Δage were retained and their health-status was analyzed after transplantation, through a maximum time period of 5 years, with the intervals of 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months. Especially, the post-transplant development of risks associated to cardiometabolic diseases was taken into consideration, the cohort was separated into two groups based on their Δage. Finally, in addition to the classifications based on vascular age, a separate classification has been done for the patients who died after transplantation, to find relationships with the Δage. One of the allied objectives of this study was the analysis of post-transplant deaths and their relationships with cardiometabolic risk factors.

III. RESULTS

At the entry-point of the transplantation program, the entire cohort of 90 patients showed an average age of 50±12 years, Framingham Cardiovascular Risk of 13.71±11.72, vascular age 59±18 years and Δage 9±14 years. After separating the cohort based on their vascular age into Δage>0 and Δage<=0, though the cohorts didn't show significant differences for several features before transplant, liver conditions among the two groups showed sharp differences. For example, cohort with Δage>0 showed more than thrice the number of patients with cirrhosis compared to the other group with Δage<=0. Also, the two groups separated based on their Δage showed distinctive properties in the post-transplant phase.

TABLE II. TRANSPLANTED PATIENTS SEPARATED BY ΔAGE

Features	**Δage > 0**	**Δage <= 0**
Number of patients (total=90)	65	25
General Characteristics of the cohort	Male: 44 | Female: 21	Male: 14 | Female: 11
Age [years]	49 ± 13	51 ± 11
MELD-Na score	18 ± 8	18 ± 10
Weight [kg]	83 ± 17	78 ± 14
BMI [kgm^{-2}]	28.48 ± 5.31	27.33 ± 3.96
Systolic Pressure [mmHg]*	119 ± 14	106 ± 15
Diastolic Pressure [mmHg]*	69 ± 9	64 ± 8
Smoking*	23 %	2 %
Diabetes	37 %	10 %
Arterial Hypertension*	29 %	3 %
Obesity	27 %	7 %
Chronic Liver Disease	4 %	3 %
Post-transplant Deaths	16%	3%
Hematology		

Features	Δage > 0	Δage <= 0
Total Cholesterol [$mgdl^{-1}$]	165 ± 108	138 ± 49
HDL [$mgdl^{-1}$]*	32 ± 20	45 ± 27
LDL [$mgdl^{-1}$]	106 ± 65	74 ± 32
Platelets [x1000 ml^{-1}]	121 ± 77	118 ± 61
Total Cholesterol/ HDL	12.84 ± 26.93	3.39 ± 2.44
Glycemia [$mgdl^{-1}$]*	119 ± 53	92 ± 18
Total Bilirubin [$mgdl^{-1}$]*	6 ± 6.96	4.74 ± 9.97
International Normalized Ratio (INR)	1.68 ± 0.65	1.89 ± 1.55
Liver conditions		
Hepatocellular Carcinoma	18 %	8 %
Cirrhosis	52 %	16 %
Acute Liver Failure	3 %	3 %
Cardiovascular risks		
Vascular Age [years]*	59 ± 18	46 ± 12
Vascular Age - Biological Age [years]*	9 ± 13	-5 ± 4
Framingham Cardiovascular Risk*	13.71 ± 11.78	6.04 ± 4.02

* p<0.05

With the objective of predicting the transplant event and assessing the impact of cardiometabolic features in the transplantation, through predictive model using logistic regression (Figure 1), a precision of 0.70 was reached, along with test accuracy 0.76, balanced accuracy 0.73, AUC 0.74 and AIC 81.25. The logistic regression being represented as $p = \frac{1}{1+e^{-y}}$ where y = (0.33 + 0.07*sex values + 0.07*pre-transplant diabetes + 0.05*glycemia + 0.04*hepatocellular carcinoma + 0.04*vascular age + 0.04*diastolic pressure + 0.03*Δage + 0.03*MELD score + 0.03*age + 0.02*statins + 0.02*lymphocytes + 0.02*basophils + 0.02*BMI + 0.01*total bilirubin – 0.01*creatinine – 0.01*INR – 0.02*neutrophils – 0.03*albumin), ignoring the features with coefficient rounded off to zero, points out to the significance of cardiometabolic features in the transplant event.

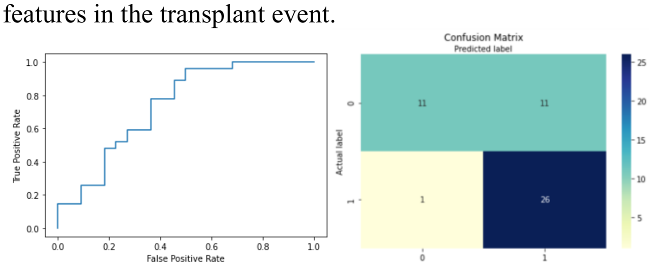

Figure 1. Logistic Regression to predict the transplant-event in the cohort

However, in the post-transplant follow-up of the transplanted patients separated in terms of their Δage (comparing Table III & IV), a better view to the health indicators and risk factors has been obtained. The accumulated risks (arterial hypertension, new-onset diabetes mellitus after transplantation, chronic kidney disease) and mortality over a period of 5 years showed significant difference (p<0.01, unpaired student's t-test) among the cohorts. Considering percentage of patients based on the entire cohort, patients with vascular age higher than chronological age showed a mortality of 22% in comparison to 12% in the patients with vascular age equal or lesser than their chronological age (Figure 2). Also, risk factors like arterial hypertension, new-onset diabetes mellitus after transplantation have been seen more pronounced in patients with Δage>=0.

TABLE III. FOLLOW-UP OF RISKS AND MORTALITY IN TRANSPLANTED PATIENTS (ΔAGE > 0)

Features	Pre-transplant	Post-transplant					
		6 months	12 months	24 months	36 months	48 months	60 months
Mortality	0%	11 %	12 %	15 %	18 %	20 %	22 %
Arterial Hypertension	38 %	57 %	66 %	66 %	68 %	68 %	78 %
New-onset diabetes mellitus after transplantation (NODAT)	51 %	55 %	57 %	57 %	58 %	62 %	62 %
Chronic kidney disease	6 %	20 %	25 %	28 %	29 %	29 %	29 %

TABLE IV. FOLLOW-UP OF RISKS AND MORTALITY IN TRANSPLANTED PATIENTS (ΔAGE <= 0)

Features	Pre-transplant	Post-transplant					
		6 months	12 months	24 months	36 months	48 months	60 months
Mortality	0 %	12 %	12 %	12 %	12 %	12 %	12 %
Arterial Hypertension	16 %	28 %	40 %	40 %	40 %	40 %	56 %
New-onset diabetes mellitus after transplantation (NODAT)	36 %	40 %	40 %	40 %	40 %	44 %	44 %
Chronic kidney disease	12 %	16 %	24 %	28 %	28 %	28 %	28 %

* all features significant (p<0.01) among the groups Δage<=0 & Δage>0, values expressed in % indicates the percentage of patients in each group (Δage>0, Δage<=0)

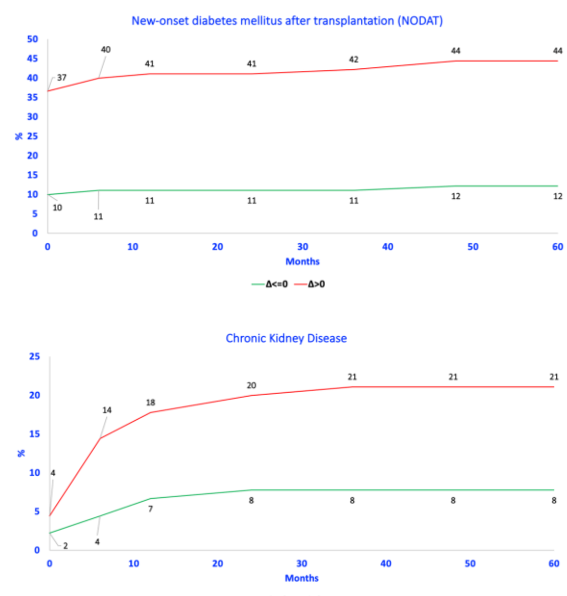

Figure 2. Post-Transplant cardiometabolic profiles and risks in patients (cohort separated by Δage<=0 and Δage>0).

Considering the mortality among the patients, 82% of patients suffering post-transplant deaths belonged to the group having vascular age greater than chronological age at their pre-transplant evaluation at the entry-point of the transplantation program. It provides a clear picture of the importance of vascular age in separating the cohort pertaining to their post-transplantation risks including mortality. Based on the analysis of the survival curves (Figure 3), most of the deaths happened in less than 6 months from the time of transplant; however, the group of patients having vascular age greater than chronological age showed almost five-fold higher mortality rate (16%) compared to the patients having vascular age lesser than their chronological age (3%).

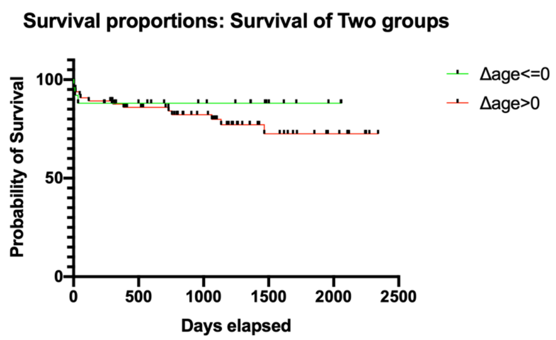

Figure 3. Kaplan-Meier post-transplant survival curves (Δage<=0 and Δage>0).

IV. DISCUSSIONS

In liver transplantation, the development of post-transplant cardiometabolic diseases can cause significant damage to the patient's health, including added complications in the post-transplant situation or recovery. In this respect, it is important to communicate to the patients the status of their cardiometabolic health before and throughout the entire process of transplantation [8],[9], [10], [11].

In this study, we performed a thorough longitudinal analysis of the transplanted patients, starting from the entry-point to the liver transplantation program till 5 years post-transplant, with the objective of separating the cohort in terms of vascular age as a predictive element for post-transplant risks and mortality. Vascular age is a simple parameter that stands impactful toward analyzing the cardiometabolic risks in a pre-transplant scenario. As the cohort was divided into two groups based on their vascular age, patients having vascular age higher than their chronological age demonstrated significantly higher rates of post-transplant cardiometabolic risks like obesity, hypertension, NODAT, and even acute kidney disease. Also, the group identified as high-risk based on their vascular age showed almost five-fold higher post-transplant mortality rate than the other group. Thus, vascular age serves as an important parameter in predictive risk modeling for liver transplantation patients. The importance of cardiometabolic risks in liver transplantation and pre-transplant profile of cardiovascular risk factors has shown evidence in impacting the long-term mortality after transplantation [2].

In our knowledge, this is the first study in Latin America incorporating vascular age toward predictive analysis of cardiometabolic risk factors in liver transplantations along with the analysis of the impact of cardiometabolic risks after transplant. The advantage of vascular age over all the existing indicators is its simplicity for calculation and ease of communicating to the patients in order to promote lifestyle and healthcare changes. In summary, this study highlights the use of vascular age as an assessment tool for cardiometabolic risks at the entry-point of liver transplantation program. Also, we summarily relate the importance of vascular age for determining post-transplant cardiometabolic diseases and impact on post-transplant mortality, emphasizing the need for using vascular age at the beginning of the pre-transplant analysis.

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