Identifying Modifiable Predictors of Long-Term Survival in Liver Transplant Recipients With Diabetes Mellitus Using Machine Learning

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Diabetes mellitus (DM) significantly impacts long-term survival after liver transplantation (LT). We identified survival factors for LT recipients who had DM to inform preventive care using machine-learning analysis. We analyzed risk factors for mortality in patients from across the United States using the Scientific Registry of Transplant Recipients (SRTR). Patients had undergone LT from 1987 to 2019, with a follow-up of 6.47 years (standard deviation [SD] 5.95). Findings were validated on a cohort from the University Health Network (UHN) from 1989 to 2014 (follow-up 8.15 years [SD 5.67]). Analysis was conducted with Cox proportional hazards and gradient boosting survival. The training set included 84.67% SRTR data (n = 15,289 patients), and the test set included 15.33% SRTR patients (n = 2769) and data from UHN patients (n = 1290). We included 18,058 adults (12,108 [67.05%] men, average age 54.21 years [SD 9.98]) from the SRTR who had undergone LT and had complete data for investigated features. A total of 4634 patients had preexisting DM, and 3158 had post-LT DM. The UHN data consisted of 1290 LT recipients (910 [70.5%] men, average age 54.0 years [SD 10.4]). Increased serum creatinine and hypertension significantly impacted mortality with preexisting DM 1.36 (95% confidence interval [CI], 1.21-1.54) and 1.20 (95% CI, 1.06-1.35) times, respectively. Sirolimus use increased mortality 1.36 times (95% CI, 1.18-1.58) in nondiabetics and 1.33 times (95% CI, 1.09-1.63) in patients with preexisting DM. A similar effect was found in post-LT DM, although it was not statistically significant (1.38 times; 95% CI, 1.07-1.77; $P = 0.07$). Survival predictors generally achieved a 0.60 to 0.70 area under the receiver operating characteristic for 5-year mortality. LT recipients who have DM have a higher mortality risk than those without DM. Hypertension, decreased renal function, and sirolimus for maintenance immunosuppression compound this mortality risk. These predisposing factors must be intensively treated and modified to optimize long-term survival after transplant.

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Liver transplantation (LT) is a lifesaving intervention for patients with cirrhosis. Despite improvements in post-LT survival, long-term quality and quantity of life has been impacted by comorbidities such as diabetes mellitus (DM).[1] DM, whether preexisting or occurring after transplant, affects >50% of transplant recipients.[1] The use of immunosuppressive medications such as corticosteroids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors is a critical factor in exacerbating preexisting DM (pre-DM) and triggering posttransplant DM (PTDM).[2]

Pre-DM negatively impacts post-LT outcomes. Pre-DM, and to a lesser degree PTDM, is associated

Abbreviations: AUPR, area under the precision–recall curve; AUROC, area under the receiver operating characteristic; BMI, body mass index; c-index, concordance index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CoxPH, Cox proportional hazards; DM, diabetes mellitus; ESRD, end-stage renal disease; GBS, gradient boosting survival; LT, liver transplantation; ML, machine learning; NAFLD, nonalcoholic

with the risk of developing end-stage renal disease (ESRD) and major cardiovascular events post-LT.[3] Pre-DM also increases the risk of death post-LT by 40% compared with LT recipients who do not have DM.[4] The harmful effects of DM are particularly exacerbated in LT recipients, with patients having a 2 to 3 times higher risk of cardiovascular mortality.[5]

PTDM is a metabolic complication that affects long-term survival post-LT. PTDM occurs in up to 50% of solid organ transplant recipients and 25% of LT recipients.[2] It is defined by one of the following criteria: (1) 2 fasting plasma glucose levels ≥126 mg/dL (≥7.0 mmol/L) ≥30 days apart, (2) use of an oral hypoglycemic agent for ≥30 consecutive days, (3) use of insulin therapy for ≥30 consecutive days, (4) hemoglobin A1c level of ≥6.5%.[6] It is increasingly recognized as a negative predictor of posttransplant survival and is associated with a 2-fold higher risk in cardiovascular events, graft loss, and infections.[7] Developing PTDM has also been shown to lower 10-year post-LT survival rates compared with post-LT recipients without DM (63% versus 74.9%, respectively).[8] Despite adverse impacts on long-term survival, there are no definitive guidelines regarding the management of LT recipients with this comorbidity.

The complexity of interactions between different variables in transplantation makes machine learning (ML) particularly suitable for identifying significant predictors of adverse outcome in diabetic transplant recipients. ML algorithms can be used to predict risk factors related to desired outcomes using training and validation. This allows for a better understanding of the relationships between factors and outcomes that may be missed with traditional biostatistical methods.

We used ML algorithms to investigate pre-LT and post-LT factors that impact survival in LT patients with DM. We also evaluated how pre-DM and PTDM affect post-LT survival. By identifying factors that affect post-LT survival, clinical measures aimed at addressing these factors can be employed to improve post-LT survival.

fatty liver disease; OPTN, Organ Procurement and Transplantation Network; Pre-DM, preexisting diabetes mellitus; PSC, primary sclerosis cholangitis; PTDM, posttransplant diabetes mellitus; SHAP, Shapley additive explanation; SRTR, Scientific Registry of Transplant Recipients; SD, standard deviation; UHN, University Health Network.

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Study Design

DATA SOURCES

We used the following 2 data sources in our study: (1) the Scientific Registry of Transplant Recipients (SRTR) data set for training and testing and the (2) University Health Network (UHN) liver clinic data set for external testing on a separate geographical cohort. For this study, ethics approval was obtained from the Research Ethics Boards at the University Health Network.

SRTR is a collection of clinical data submitted by members of the Organ Procurement and Transplantation Network (OPTN).[9] SRTR records clinical information of transplant recipients in the United States. Each transplant center is required to routinely submit data. At data curation, SRTR consisted of 165,867 distinct LT patients having transplants from October 1, 1987, to March 1, 2019. This study included 18,058 patients who were ≥18 years old, had undergone a successful LT, and whose records contained complete data for all of the investigated features (details in Supporting Fig. 1). The SRTR data set contains high missingness in diabetic information, resulting in less patients included. We split the data set as a training and test set prospectively; all patients who had transplants in 2013 or later are considered held out from the training set (test, 15.33% [n = 2769] of SRTR data with 12.50% mortality [n = 346]). The training set contains 26.91% (n = 4260) mortality of 15,289

people (train, 84.67% of SRTR data). The reported results are presented on the held-out (test) data.

We used UHN liver clinic data to test our models on an independent cohort. At curation, it consisted of 2209 distinct LT recipients who had undergone LT from January 1989 to September 2014. Of the patients, 1290 (27.3% [n = 352] mortality) were within the inclusion criteria and contained no missingness for most of the features.

In this study, we only investigated the effects of nontransient DM on mortality. We excluded patients with transient DM from the UHN data set. The SRTR data set only starts reporting DM 6 months after transplant, for which we assume DM is no longer transient.

SELECTED FEATURES

We chose 26 features listed in Table 1 either because they were available in both data sets or their information was important to mortality prediction. Race, ethnicity, functional, life support, and work status were incorporated although they were highly missing (eg, race has 83.2% [n = 1073] missingness) in the UHN data because of their potential relevance to mortality. All included features had been measured at the time of transplant except for creatinine, BMI, and immunosuppressant data, which we retrieved at 1 year posttransplant given the stability of the immunosuppression maintenance regimen at that point and limited missingness. Details on data processing can be found in Supporting Information S1.

EXPERIMENTAL SETUP

Our experiment was set up as follows:

1. We numerically assessed the DM impact on patient survival. We investigated by (1) training survival models to predict general and cardiovascular mortality on all LT recipient data and (2) assessing the effect/importance of pre-DM and PTDM for mortality. For cardiovascular mortality, we only included patients who are presumed to be alive at the time of follow-up or had died from cardiovascular causes (See Supporting Information S2 for population numbers).
2. We showed how the survival of patients with no DM, pre-DM, and PTDM rely on different factors. We investigated this by (1) training survival models on each group (nondiabetic, pre-DM, and PTDM) separately and (2) comparing the feature importance from each model. We sought to identify which features were especially important for recipients who had pre-DM.

Methods

SURVIVAL ANALYSIS

We used 2 survival methods to predict time to mortality. We employed the Cox proportional hazards model (CoxPH).[10] We report the 95% confidence intervals (CIs) of each feature's hazard ratio from the CoxPH. For every 1 unit increase of a feature, the hazard score of an individual is multiplied by the amount of that feature's hazard ratio. CIs that overlap the value of 1 indicate an insignificant feature. CIs with a lower bound greater than 1 indicate that the feature increases mortality risk. CIs with an upper bound lower than 1 indicate that the feature helps aid for survival. Reported *P* values are corrected for multiple testing by false discovery rate (Benjamini/Hochberg) implemented by the statsmodels package in Python (USA).[11]

We also employed gradient boosting survival (GBS)[12] as there are possibilities of impacts of nonlinear features on mortality and interactions between features. These cannot be captured well with CoxPH without further feature processing. Gradient boosting is an ensemble of shallow decision trees that were trained in iterations. Each training iteration would introduce a new decision tree, and it will upweight samples that were misclassified in the previous samples. GBS is a gradient boosting that is trained to optimize survival prediction. There is not any hazard ratio for each feature; we used the Shapley additive explanation (SHAP) value to represent each feature's contribution to the model's predicted risk score.[13] Positive value indicates that the feature increases mortality risk and vice versa. To calculate the overall feature importance, we calculate the mean of each patient's absolute SHAP value for that feature. Therefore, the importance represents the nonnegative contribution of this feature to the risk score.

Supporting Information S2 provides details on both survival models. To assess the performance stability and importance of the models, we conducted each experiment across 5-fold cross-validation and report these metrics with the average and standard deviation (SD) across the 5 experiments.

PERFORMANCE METRICS

The concordance index (c-index) is a standard way to compare survival methods. It is an indicator of an accurate ordering of patients with respect to time to event.

TABLE 1. Description of Features Used and Their Summary Statistics Among SRTR (n = 18,058) and UHN Clinic Data (n = 1290)

Feature	Description	Summary Statistic in SRTR	Summary Statistic in UHN
Pre-DM	Whether a patient was diagnosed as diabetic before transplant (0, no; 1, yes)	4634 (25.66)	220 (17.05)
Development of PTDM	Whether patient was diagnosed as diabetic at any time after transplant (0, not diagnosed; 1, diagnosed)	3158 (17.49)	224 (17.36)
Latino ethnicity*	Ethnicity (0, non-Latino or unknown; 1, Latino)	2553 (14.14)	0 (0.00)
Race*	Race: White		
White	White	15,426 (85.42)	159 (12.33)
Black	Black	1678 (9.29)	5 (0.39)
Native American	Native American	87 (0.48)	1 (0.08)
Asian	Asian	730 (4.04)	45 (3.49)
Pacific Islander	Pacific Islander	20 (0.11)	0 (0.00)
Life support	Whether patient was on life support (recorded at time of transplant)	1043 (5.78)	NaN
Work status*	Working for income (recorded at time of transplant)	2961 (16.40)	NaN
Functional status*:	Functional status (recorded at time of transplant)/able to perform activities of daily living with:		
No assistance	No assistance	4764 (26.38)	NaN
Some assistance	Some assistance	7757 (42.96)	NaN
Total assistance	Total assistance	5537 (30.66)	NaN
Presence of pretransplant malignancy*	Pretransplant malignancy	938 (5.19)	NaN
BMI	BMI 1 year after transplant	27.57 (SD 5.41)	26.38 (SD 4.98)
Sex	Sex (0, female; 1, male)	12,108 (67.05)	910 (70.54)
Age at time of transplant	Age at the time of transplant	54.21 (SD 9.98)	54.01 (SD 10.40)
COPD	Whether treated with drug for COPD (recorded at time of transplant)	369 (2.04)	112 (8.68)
Hypertension	Whether treated with drug for systemic hypertension (recorded at time of transplant)	4743 (26.27)	577 (44.73)
Peripheral vascular disease	Symptomatic peripheral vascular disease (recorded at time of transplant)	190 (1.05)	8 (0.62)
Pulmonary embolism	Pulmonary embolism (recorded at time of transplant)	70 (0.39)	8 (0.62)
Angina/coronary artery disease	Angina/coronary artery disease	467 (2.59)	31 (2.40)
Albumin	Albumin (g/dL) at time of transplant	3.01 (SD 0.73)	2.91 (SD 0.56)
Bilirubin	Bilirubin (mg/dL) at time of transplant	8.31 (SD 10.86)	6.57 (SD 8.54)
High creatinine	Whether serum creatinine ≥1.5 mg/dL at 1 year after transplant	4523 (25.05)	221 (17.13)
Indication for transplant			
Autoimmune hepatitis	Primary diagnosis: autoimmune hepatitis	495 (2.74)	48 (3.72)
Hepatitis C	Hepatitis C	1184 (6.56)	462 (35.81)
NAFLD	Nonalcoholic fatty liver disease (NAFLD)	26 (0.14)	92 (7.13)
Alcohol liver disease	Alcohol-related disease	3536 (19.58)	200 (15.50)
PBC	Primary biliary cholangitis	629 (3.48)	59 (4.57)
PSC	Primary sclerosing cholangitis	966 (5.35)	104 (8.06)
Immunosuppression prescribed 1 year after transplant (a patient can be prescribed multiple):			
Corticosteroids	Prednisone (Deltasone (Pharmacia Corp, USA), Orasone (Pharmacia Corp, USA)), Methylprednisolone (Solu-medrol (Pfizer, USA), Medrol (Pfizer, USA), A-Methapred (HOSPIRA, USA))	8129 (45.02)	228 (17.67)
Cyclosporine	Sandimmune ((Novartis, Swiss); cyclosporine A), Neoral ((Novartis, Swiss); CyA-NOF: Cyclosporine-A new oral formulation), Cyclosporin, Sang Cy A, Gengraf (Abbott cyclosporine), EON (generic cyclosporine), and other generic cyclosporine	1903 (10.54)	181 (14.03)

TABLE 1. *Continued*

Feature	Description	Summary Statistic in SRTR	Summary Statistic in UHN
Tacrolimus	Prograf ((Astellas, USA); FK506), Astagraf XL ((Astellas, USA); extended release tacrolimus), Generic tacrolimus (generic Prograf)	15,347 (84.99)	390 (30.23)
Sirolimus	Rapamune ((Pfizer, USA) sirolimus, Rapamycin)	1758 (9.74)	59 (4.57)
Antimetabolite–imuran or methotrexate	Imuran (Prometheus, USA; azathioprine (AZA)) , Methotrexate (Folex PFS, Mexate-AQ (BRISTOL MYERS, USA), Rheumatrex (DAVA Pharmaceuticals, Inc, USA))	268 (1.48)	35 (2.71)
Antimetabolite–mycophenolate	CellCept (Genentech, USA; MMF: Mycophenolate Mofetil), Myfortic (Novartis, Swiss; mycophenolate acid), generic MMF (generic CellCept)	11,305 (62.60)	304 (23.57)
Antithymocyte globulin	Atgam (Pfizer, USA), Thymoglobulin	56 (0.31)	8 (0.62)
Everolimus	Zortress (Novartis, Swiss (everolimus))	233 (1.29)	7 (0.54)
Graft cold ischemic time	Total cold ischemic time (hours)	6.55 (SD 3.20)	6.06 (SD 3.45)
Acute rejection	Whether patient had any acute rejection episodes within 1 year after transplant	1085 (6.01)	344 (26.67)
Ascites	Ascites	14,118 (78.18)	534 (41.40)
Spontaneous bacterial peritonitis	Spontaneous bacterial Peritonitis	1711 (9.48)	48 (3.72)
Previous abdominal surgery	Previous abdominal surgery	7837 (43.40)	167 (12.95)

NOTE: SI (International System of Units) conversion factors: to convert albumin to g/L, multiply values by 10. To convert bilirubin to μmol/L, multiply by 17.1. To convert serum creatinine to μmol/L, multiply by 88.4. For discrete features, number of samples and percentages are reported. For continuous features, mean (SD) are reported. All features are recorded at the time of transplant except for prescribed immunosuppressants, creatinine, and BMI.
*Features that are imputed for UHN data set.

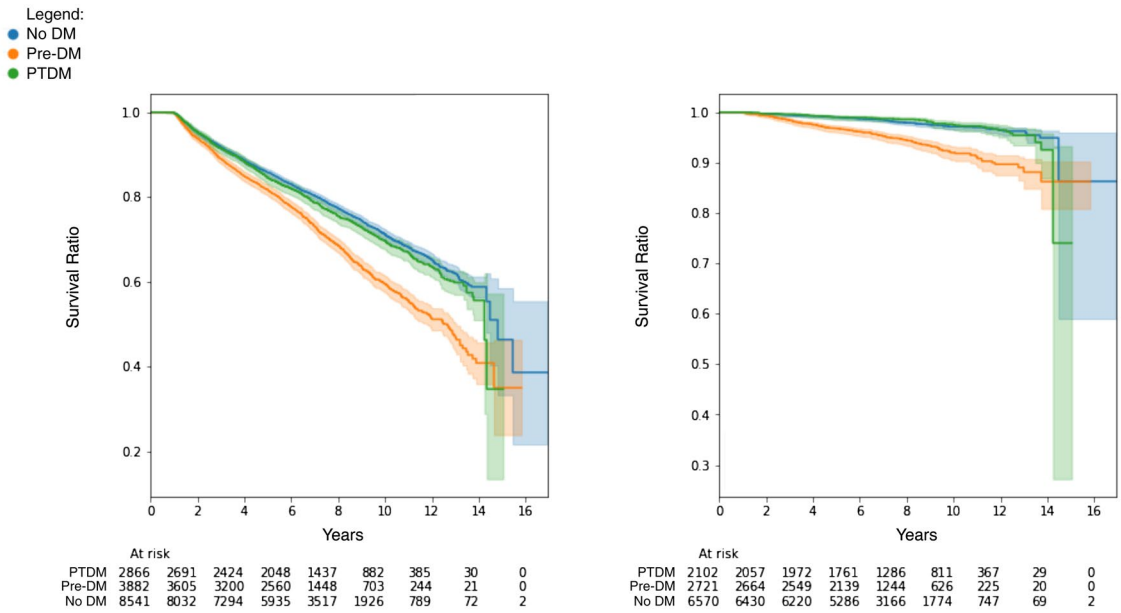

FIG. 1. Kaplan-Meier survival curves of training set in general (left) and cardiovascular (right) mortality. Pretransplant DM statistically lowers survival in both cases.

We also used area under the receiver operating characteristic (AUROC) and area under the precision-recall curve (AUPR) to compare performances of predictors for 5-year and 10-year mortality. Supporting S3 provides explanations on these metrics.

Results

DM IS ASSOCIATED WITH WORSE SURVIVAL

Our analysis clearly shows that DM lowers survival (Fig. 1). Using CoxPH, pre-DM increases general mortality by 1.37 (95% CI, 1.27-1.48; $P < 0.001$) times and cardiovascular mortality by 2.52 (95% CI, 1.97-3.23; $P < 0.001$) times. GBS analysis showed that pre-DM is a predictive factor for general mortality (rank mode, third; importance, 0.095 [SD 0.006]) and cardiovascular mortality (rank mode, first; importance, 0.322 [SD 0.027]). Overall, pre-DM significantly reduces patient survival.

PTDM's hazard ratios on general and cardiovascular mortality were not statistically significant (1.03 [95% CI, 0.95-1.12; $P = 0.64$] and 0.84 [95% CI, 0.60-1.18; $P = 0.47$], respectively). GBS analysis concluded that PTDM did not account for a significant amount of importance for predicting general and cardiovascular mortality. This may be attributed to the incomplete data collection for cardiovascular mortality and PTDM status, resulting in a lower number of samples.

Because pre-DM largely affects mortality compared with PTDM, a separate analysis on patients with pre-DM and PTDM was conducted. Combining patients with pre-DM and PTDM in 1 analysis or 1 training set may result in averaging out the effects of each feature for patients with pre-DM and PTDM.

PERFORMANCES OF CoxPH AND GBS

CoxPH's performance on the general mortality prediction is provided in Table 2. CoxPH achieves a c-index of 0.60 (SD 0.00) for predicting mortality in patients with no DM, 0.59 (SD 0.00) for patients with pre-DM, and 0.70 (SD 0.01) for patients with PTDM in the SRTR test set. Similarly, CoxPH performs comparatively well in the UHN data set with a c-index of 0.63 (SD 0.01) for patients with no DM, 0.61 (SD 0.01) for patients with pre-DM, and a slightly lower 0.58 (SD 0.01) for patients with PTDM. Looking at 10-year mortality in the SRTR test set, CoxPH obtains 0.60 (SD 0.00) AUROC and 0.26 (SD 0.01) AUPR for patients with pre-DM and 0.72 (SD 0.01) AUROC and 0.24 (SD 0.02) AUPR for patients with PTDM. The model also translates to the UHN data set, showing 0.62 (SD 0.02) AUROC and 0.37 (SD 0.02) AUPR for patients with pre-DM and 0.72 (SD 0.01) and 0.27 (SD 0.01) AUPR for patients with PTDM at the 10-year

TABLE 2. Performance of CoxPH on Predicting General Mortality

Group	All	No DM	Pre-DM	PTDM
SRTR test, total n; mortality n (mortality %)	2769; 346 (12.50)	1725; 186 (10.78)	752; 128 (17.02)	292; 32 (10.96)
UHN, total n; mortality n (mortality %)	1290; 352 (27.29)	846; 221 (26.12)	220; 63 (28.63)	224; 68 (30.36)
c-index SRTR, mean (SD)	0.63 (0.00)	0.60 (0.00)	0.59 (0.00)	0.70 (0.01)
c-index UHN, mean (SD)	0.61 (0.01)	0.63 (0.01)	0.61 (0.01)	0.58 (0.01)
AUROC 5-year SRTR, mean (SD)	0.64 (0.00)	0.60 (0.00)	0.61 (0.00)	0.72 (0.01)
AUROC 5-year UHN, mean (SD)	0.64 (0.01)	0.65 (0.01)	0.62 (0.02)	0.64 (0.02)
AUROC 10-year SRTR, mean (SD)	0.63 (0.00)	0.60 (0.00)	0.60 (0.00)	0.72 (0.01)
AUROC 10-year UHN, mean (SD)	0.63 (0.00)	0.64 (0.01)	0.62 (0.02)	0.61 (0.01)
AUPR 5-year SRTR, mean (SD)	0.19 (0.00)	0.15 (0.00)	0.25 (0.01)	0.23 (0.02)
AUPR 5-year UHN, mean (SD)	0.20 (0.01)	0.20 (0.01)	0.21 (0.02)	0.19 (0.01)
AUPR 10-year SRTR, mean (SD)	0.20 (0.00)	0.16 (0.00)	0.26 (0.01)	0.24 (0.02)
AUPR 10-year UHN, mean (SD)	0.31 (0.01)	0.29 (0.00)	0.37 (0.02)	0.27 (0.01)

NOTE: Numbers in test set along with mortality are displayed. Values reported across 5 cross-validations (mean [SD]). For a complete list of all the performances, see Supporting Table 2.

mortality. These numbers indicate that these analyses generalized to patients with a different geographical location, which implies that our analysis of how features are associated with mortality are meaningful.

Supporting Table 2 provides a comprehensive list of the performance of each model where the performances of CoxPH and GBS can be compared side by side. In general, the performances of CoxPH and GBS were quite comparable. CoxPH tended to have a higher c-index than GBS except for the predictions of patients with PTDM in the SRTR test set. GBS outperforms CoxPH for the c-index calculated in the UHN data set, except for patients with pre-DM, where the CoxPH c-index performance is higher than GBS. The performance of both models on the SRTR and UHN data sets are comparable for most of the predictions. Other than the prediction on general mortality for patients with PTDM, the c-indexes of the SRTR test set and UHN set are quite similar with less than 0.100 difference. This implies that the overall findings discovered from the SRTR data are not specific to SRTR.

DIFFERENT FEATURES IMPORTANT FOR PRE-DM AND PTDM

General Mortality

We found different mortality features among patients with no DM, pre-DM, and PTDM. The different effects of each feature for each group are plotted in Figs. 2 and 3 as well as listed in Supporting Tables 3 and 4. Figure 4 displays how each top 10 feature contributes to GBS-predicted risk scores. In Fig. 4, we can assess whether having a lower or higher value for that feature increases the mortality risk.

Looking at the presented CoxPH hazard ratios, having high creatinine and hypertension were associated with an increase in general mortality risk of patients with pre-DM by 1.36 times (95% CI, 1.21-1.54; $P < 0.001$) and 1.20 times (95% CI, 1.06-1.35; $P = 0.03$), respectively. The hazard ratios for creatinine and hypertension in patients with pre-DM were slightly higher than those in patients with no DM and PTDM.

A slightly higher body mass index (BMI) reduced general mortality 0.96 times (95% CI, 0.95-0.97; $P < 0.001$) in nondiabetics and 0.96 times (95% CI, 0.94-0.97; $P < 0.001$) in patients with pre-DM and PTDM. Some factors were significant across both patients with no DM and pre-DM, for example, the use of sirolimus and age at time of transplant. The use of sirolimus was associated with an increase in general mortality by 1.36 times (95% CI, 1.18-1.58; $P < 0.001$) in nondiabetics, 1.33 times (95% CI, 1.09-1.63; $P = 0.03$) in patients with pre-DM, and 1.38 times (95% CI, 1.07-1.77; $P = 0.07$) in patients with PTDM. Using GBS, we found that the sirolimus effect on mortality in patients with DM is not associated with any particular cause of death (see Supporting Fig. 3).

	General Mortality			Cardiovascular Mortality		
	Important for No DM	Important for Pre-DM	Important for PTDM	Important for No DM	Important for Pre-DM	Important for PTDM
BMI	✓✓	✓✓	✓✓	✓		✓
Bilirubin	✓	✓	✓	✓	✓	✓
High creatinine		✓✓		✓✓	✓✓	✓
Age at time of transplant	✓✓	✓	✓	✓		✓
• Prescriptions: antimetabolite - mycophenolate • Previous abdominal surgery • Gender • Acute rejection	✓					
• Prescriptions: sirolimus • Prescriptions: corticosteroids	✓	✓				
Hypertension		✓				
COPD						✓
Graft cold ischemic time				✓		✓
• Albumin • Ascites • Functional status: no assistance • Prescriptions: cyclosporine						✓

FIG. 2. A table indicating key risk factors for each group. Features found to be important by CoxPH, that is, having a *P* value less than 0.05 after multiple testing correction, are marked by orange checkmarks. Features found to be important by GBS, that is, having more than 0.1 importance, are marked by blue checkmarks.

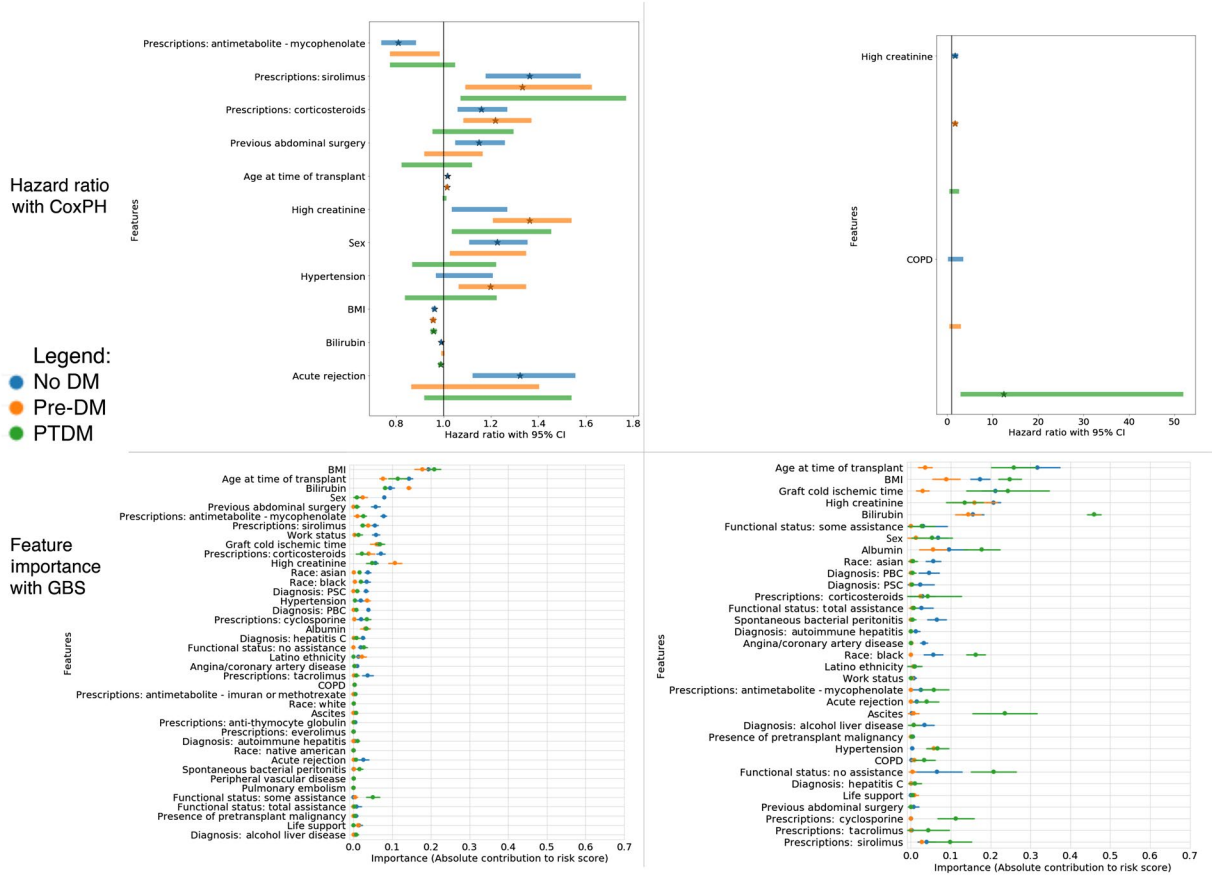

FIG. 3. (Top) Hazard ratio of select features in CoxPH and (bottom) feature importance of GBS in patients with no DM (blue), pre-DM (orange), and PTDM (green). CoxPH's hazard ratio is plotted with its 95% CIs. Features that are statistically significant ($P < 0.05$ after false discovery rate correction) are marked with a black star. GBS feature importances are plotted as mean and SD across 5 cross-validations for all features used. Features with 0 importance across runs are excluded. Exact values can be found in Supporting Tables 3 and 4.

In addition, a higher bilirubin reduced general mortality by 0.99 times (95% CI, 0.98-0.99; $P = 0.001$) in nondiabetics and 0.99 times (95% CI, 0.98-1.00; $P = 0.04$) in patients with PTDM.

From GBS analysis, bilirubin, creatinine, and hypertension had a slightly higher importance for predicting the general survival of patients with pre-DM. Bilirubin was an important predictor across all groups, although it had a higher importance for patients with pre-DM. Bilirubin had an importance of 0.14 (SD 0.01) for mortality prediction in patients with pre-DM compared with 0.10 (SD 0.01) in nondiabetics and 0.08 (SD 0.01) in patients with PTDM patients. Creatinine had a higher importance in patients diagnosed with pre-DM: 0.11 (SD 0.02) for patients with pre-DM and 0.06 (SD 0.01) in nondiabetics compared with 0.05 (SD 0.02) in patients with PTDM. Looking at Fig. 4, it is clear that in all groups having a high creatinine increased mortality risk. This is consistent with the findings of the CoxPH analysis. Hypertension accounted for 0.04 (SD 0.01) importance in patients with pre-DM and 0.02 (SD 0.01) in nondiabetics and 0.00 (SD 0.00) in patients with PDTM.

Generally, age and BMI were found to be important across all groups. BMI accounted for 0.19 (SD 0.01) importance in nondiabetics, 0.18 (SD 0.02) in patients with pre-DM, and 0.21 (SD 0.02) in patients with PTDM. In all groups, a low BMI increased mortality risk (eg, Supporting Fig. 2 for patients with pre-DM). Age accounted for 0.14 (SD 0.01), 0.08 (SD 0.01), and 0.11 (SD 0.02) in nondiabetics and patients with pre-DM and PTDM, respectively.

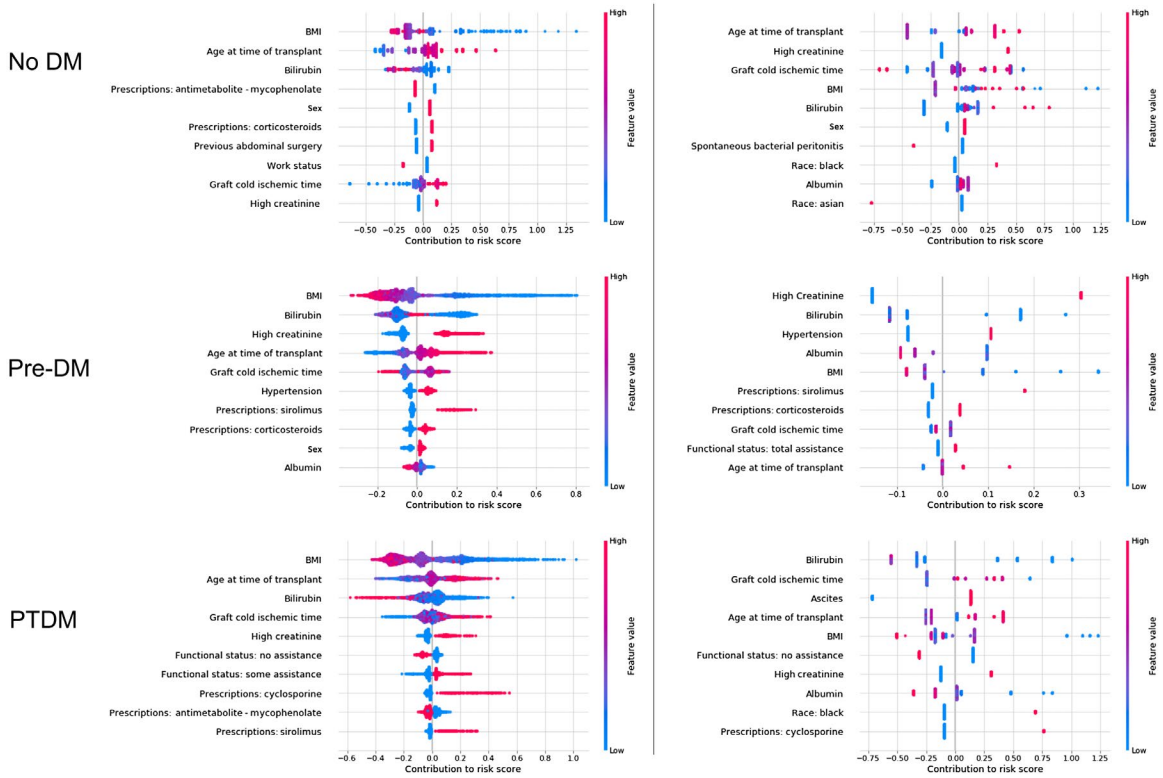

FIG. 4. How top 10 features in GBS contribute to predicted risk score. The first row of plots display how these features contribute to risk scores of general and cardiovascular mortality in patients with no DM, the second row is patients with pre-DM, and the third row is patients with PTDM. Each dot represents a sample in the training data colored by whether it has a high value (pink) or a low value (blue).

Cardiovascular Mortality

Comparing the CoxPH hazard ratios for cardiovascular mortality, creatinine was again shown to be important for patients with pre-DM in cardiovascular mortality. Its hazard ratios in nondiabetics and patients with pre-DM and PTDM were 1.70 times (95% CI, 1.17-2.46; $P = 0.04$), 1.69 times (95% CI, 1.19-2.41; $P = 0.03$), and 1.21 times (95% CI, 0.56-2.62; $P = 0.86$), respectively. GBS also revealed creatinine to be an important predictor. Creatinine's importance in nondiabetics and patients with pre-DM and PTDM were 0.21 (SD 0.02), 0.16 (SD 0.06), and 0.13 (SD 0.05), respectively.

Other important features in GBS included age, BMI, and albumin. Age accounted for 0.32 (SD 0.06), 0.04 (SD 0.02), and 0.26 (SD 0.06) in nondiabetics and patients with pre-DM and PTDM, respectively. BMI accounted for 0.17 (SD 0.02), 0.09 (SD 0.03), 0.25 (SD 0.03) in nondiabetics and patients with pre-DM and PTDM, respectively. Bilirubin accounted for 0.16 (SD 0.03), 0.14 (SD 0.03), 0.46 (SD 0.02) in nondiabetics and patients with pre-DM and PTDM, respectively. Hypertension had a 0.06 (SD 0.02) importance in patients with pre-DM. Having hypertension and the use of corticosteroids as well as sirolimus increased cardiovascular mortality for patients with pre-DM (Fig. 4).

OVERALL FINDINGS

Serum creatinine increased the risk of general mortality in patients with pre-DM by 1.36 times (95% CI, 1.21-1.54; $P < 0.001$) and had an importance of 9% (SD 2%) for general mortality prediction with GBS. Bilirubin reduced general mortality by 0.99 times (95% CI, 0.98-0.99; $P = 0.001$) in nondiabetics and 0.99 times (95% CI, 0.98-1.00; $P = 0.04$) in patients with PTDM. Similar trends were found for cardiovascular mortality. Creatinine increased cardiovascular mortality risk of nondiabetics by 1.70 times (95% CI, 1.17-2.46; $P = 0.04$) and patients

with pre-DM by 1.69 times (95% CI, 1.19-2.41; $P = 0.03$). Bilirubin was not found to reduce cardiovascular mortality significantly in CoxPH but was still found to be an important predictor in GBS for patients with DM. It accounted for a 0.14 to 0.46 change of risk score across all groups.

Discussion

DM affects a large proportion of LT recipients and has significant adverse impacts on long-term survival.[8] Consensus guidelines provide general recommendations for screening and treatment that are not targeted to this high-risk group of recipients.[14] Our study using the SRTR database provides a framework for developing such targeted guidelines in LT recipients. Pre-DM significantly increased both general and cardiovascular mortality in LT recipients. Hypertension and elevated serum creatinine were significant factors that compounded the risk of mortality among LT patients with DM. This suggests that LT recipients with DM should be carefully screened for hypertension and chronic kidney disease (both of which are complications of the most common immunosuppressants) and strictly managed to optimize long-term posttransplant survival.[2,7]

We also separated LT recipients into 3 categories (no DM, pre-DM, and PTDM) and examined factors that affected posttransplant survival in each group. For recipients without DM, the use of corticosteroids and sirolimus resulted in an increase in general posttransplant mortality, whereas the use of the antimetabolite mycophenolate was associated with a decrease in general posttransplant mortality.

For patients with pre-DM, elevated creatinine, hypertension, and use of steroids and sirolimus as immunosuppression affected posttransplant general survival. Use of sirolimus increases insulin resistance and has previously been associated with higher long-term mortality.[15] Elevated creatinine, age at time of transplant, and steroid use also affected posttransplant cardiovascular mortality. Regarding recipients with PTDM, the use of sirolimus for immunosuppression negatively impacted general survival.

ML has been used to identify patients most likely to benefit from LT along with factors affecting posttransplant complications and survival.[16] Using ML, Bhat and colleagues identified several predictors of development of PTDM, including increasing age at time of transplant, male sex, and obesity.[8] PTDM in turn has been found to be a risk factor for posttransplant cardiovascular events, graft loss, and development of infections.[17] In this study, we did not find PTDM to significantly impact mortality, which may be attributed to the lower number of samples caused by high missingness.

Despite the fact that patients with DM have worse posttransplant outcomes, few studies have looked at factors affecting survival in LT recipients with DM.[18] To our knowledge, our study is the largest to examine factors affecting survival in patients with DM post-LT. Factors that reduced survival include age at the time of transplant, presence of hypertension, elevated creatinine, and use of steroids or sirolimus as an immunosuppressant.

Cardiovascular compromise reduces long-term survival after LT.[5,19] Not only does hypertension increase the risk of heart disease but also it is a major risk factor for renal failure, similar to DM. Again, having multiple risk factors leads to significantly higher rates of developing chronic kidney disease. Similar to heart disease, the presence of pretransplant kidney dysfunction negatively impacts posttransplant survival.[20] This helps explain why the pretransplant creatinine level is an important factor affecting posttransplant outcomes in our study. Moreover, in LT recipients with pretransplant cardiovascular disease, elevated serum creatinine at 1 year posttransplant has been associated with higher cardiovascular events in the long term and consequently higher mortality.[21] Another study showed that pre-LT DM along with a ≥30% decrease in GFR within the first year after transplantation are predictors for advanced chronic kidney disease and long-term mortality.[22] Corticosteroids are a common immunosuppressant post-LT. However, one of the major side effects with these medications is hyperglycemia.[23] This often exacerbates and worsens PTDM glycemic control.[24] A steroid-free and mycophenolate mofetil–containing regimen has been shown to decrease risk of cardiovascular mortality, which is consistent with findings in our study.[25] Sirolimus received a black box warning from the US Food and Drug Administration in 2002 stating it was associated with higher mortality based on clinical trial findings.[15] Similarly, our study showed greater mortality in all LT recipients using sirolimus. Studies have demonstrated deleterious effects of hyperglycemia post-LT. Wallia and colleagues showed that posttransplant hyperglycemia was associated with increased risks of graft rejection

and infection.[26] Overall, these complications reduced posttransplant survival.

By identifying the presence of pre-DM as a risk factor for mortality post-LT, efforts can be made during the pretransplant period to identify patients with DM and optimize their diabetic management. Focus should be put on glycemic management with both nonpharmacological and pharmacological strategies. Patients with cirrhosis are often on a low-salt diet to minimize ascites and edema, and it is not feasible for most to engage in exercise. In addition, insulin is the drug of choice in patients with DM with cirrhosis because of the concerns regarding oral hypoglycemic agents such as metformin in the setting of impaired liver metabolism. The goal should be proper reduction of hemoglobin A1C levels to reduce the development of diabetic complications, which may certainly impact post-LT outcomes. By also identifying individual mortality risk factors among patients with pretransplant DM, screening for these risk factors should be undertaken and addressed when present.

We found that hypertension and chronic kidney disease synergize with DM to increase cardiovascular mortality in LT recipients. Given that cardiovascular mortality is 2 to 3 times higher in LT recipients compared with the general population, this suggests that we must be particularly watchful and monitor LT recipients closely for hypertension and chronic kidney disease especially in patients with DM. Interventions would include minimizing calcineurin inhibitors as much as possible, managing optimally hypertension and chronic kidney disease, and referring patients with all 3 risk factors to a cardiologist for screening and follow-up.

LIMITATIONS

The results of our study need to be interpreted in the context of our limitations. Our models were trained on patients from SRTR dataset with complete data on investigated features, which may cause bias in the analysis. Although sirolimus has previously been associated with higher mortality,[15] patients prescribed sirolimus may be a higher risk group as sirolimus tends to be prescribed to patients at higher risk of liver cancer recurrence and in those with chronic kidney disease. SRTR data regarding the diagnosis of hypertension at the time of transplant is limited by reports from individual transplant centers, which may be determined by varying systolic blood pressures thresholds. At our center, a diagnosis of hypertension was based on patients being started on antihypertensive medication before or at the time of transplant and was not based on blood pressure thresholds. We also assumed that hypertension pre-LT would persist posttransplant. In the UHN data, 725 of 820 patients (88.41%) with hypertension pre-LT had hypertension post-LT. Although we discovered increasing serum creatinine to be associated with increased mortality, we did not have glomerular filtration rate values and could not determine the degree of chronic kidney disease in an individual patient. In addition, data regarding creatinine levels posttransplant had a high degree of missingness, reducing data samples. We validated the performance of these models on UHN data, indirectly validating the significant features found important by the survival methods.

In our study, we only included recipients from the SRTR containing complete data. To examine for any potential bias in our results, we examined for differences in each feature used in the model for the SRTR and UHN data sets before and after excluding missing data. Overall, they are quite comparable, except for work status, functional status, hypertension, ascites, and whether patients were prescribed antimetabolite (Azathioprine or methotrexate). Another limitation is that pre-DM duration in the SRTR data set was not documented but could significantly impact the analysis.

Despite these limitations, our study is one of the largest to use ML in identifying post-LT mortality risk factors, specifically delineating factors in the highest risk diabetic recipients.

Conclusion

We identified risk factors for compromised posttransplant survival in LT recipients with DM using ML. Among patients with DM, hypertension, renal dysfunction, and use of sirolimus were the top ranked features that affected survival posttransplant. Therefore, patients with DM should not only have careful management of their DM but also accompanying hypertension and renal dysfunction management to optimize posttransplant survival. Calcineurin inhibitors may need to be favored as maintenance immunosuppression among recipients with DM given the higher risk of mortality among those taking sirolimus. These findings serve as a stepping stone to future efforts for recommendations to improve the long-term survival of LT recipients with DM.

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