Predicting Kidney Allograft Survival with Explainable Machine Learning

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Abstract

Introduction. Despite the progress made in the survival of allografts, some risk factors contribute to worsening kidney function or loss of transplants. The aim of this study is to evaluate a new machine learning method to identify variables predicting early graft loss in kidney transplant patients and to assess the usefulness of this information for clinical decision making. **Material and Methods.** A retrospective cohort study carried out with 627 kidney transplant patients followed at least three months. The data was treated, pre-processed and features automatically selected to choose a machine learning algorithm, training and parameterization of the model, and finally, the analysis of the features that most impacted the prediction of the model based on explainability and interpretation of predictions. The models were evaluated using the Area Under the Curve (AUC), and the SHAP (SHapley Additive exPlanations) algorithm was used to interpret the model's predictions. **Results**. The final model achieved a precision of 0.81, a sensitivity of 0.61, a specificity of 0.89 and AUC of 0.84. The patient's serum creatinine levels at discharge proved to be the most important decision-making factor in the model for allograft loss. Patients with a weight equivalent to a BMI closer to normal before a kidney transplant are less likely to lose a graft than patients with BMI lower than normal. The patient's age at transplantation and Polyomavirus (BKPyV) infection also have a great impact on the model's decisions. **Conclusions.** The main characteristics that impacted early allograft loss were the patient's serum creatinine levels at discharge, pre-transplant weight, age, and BKPyV infection. We showed machine learning tools that can be effectively used for medical decision-making in the transplantation field.

Keywords: Machine Learning; Artificial Intelligence; Outcome Assessment; Kidney Transplantation; Explanatory modeling.

1. Introduction

Kidney transplantation is the best choice of therapy for patients with end-stage chronic kidney disease (CKD) providing lower rates of cardiovascular events, mortality, and improving the patient's quality of life when compared to dialysis modalities [1]. These better outcomes justify policies aimed at increasing the number of patients who benefit from the transplantation [1-5].

Important progress in allograft survival can be attributed to improvement of the surgery procedure, immunogenetic compatibility analysis between recipient and donor, organ preservation, new immunosuppressive treatment protocols to prevent or treat allograft rejection that remains a major problem for long-term allograft survival [6-8]. Despite these advances, addition important post-transplant risk factor for kidney function remains the cellular rejection mediated by T lymphocyte CD8+ in 10% of cases or by B lymphocyte *de novo* donor specific antibodies mediated rejection (ABMR) in 90% of kidney transplant patient with strong negative impact in long-term allograft survival. [9-11]. Complications or the need for a surgical re-approach may occur and account for the immediate or very early loss of the graft. Delayed graft function requiring dialysis in the first week after transplantation may cause worsening kidney function [7]. In addition, transplant patients with recurrent urinary tract bacterial infections, and viral or fungal infections episodes, occurrence of patient malignancies as the resulted of the prolonged use of immunosuppressant drug treatments and recurrence of underlying disease are subject to a reduction in the rate of graft survival or even graft loss causing a return to dialysis therapy or waiting list for a second transplant [12-18].

In nephrology, artificial intelligence methods, have been used to improve clinical care, dialysis conditions, and follow-up kidney transplant patients [19-23]. The use of this new approach in transplantation field has helped to find unknown functional relationships and predictive risk factors for allograft loss [24]. Additionally, it facilitates the identification of associations between large amounts of data and the generation of solutions with a high degree of accuracy [25].

Given an increasing demand and the scarcity of organs available for donation, the optimization of kidney transplant outcomes is still necessary to increase the graft survival rates. Advanced techniques, especially based on machine learning, can allow better prediction of transplant outcomes, and suggest early interventions to prevent graft loss and, consequently, the patient's return to the waiting list for another transplant. The aim of this study was to evaluate a new machine learning method to identify demographic and clinical variables predicting an early

graft loss in kidney transplant patients and to assess the usefulness of this information for clinical decision making.

2. Material and methods

2.1 Patients

This retrospective cohort study was carried out in the Hospital of Medical Sciences of the Faculty of Medical Sciences, Belo Horizonte, Minas Gerais, Brazil. Six hundred and twenty-seven kidney transplant patients were evaluated as a convenience sample composed between 2008 and 2018 and were followed in the hospital ambulatory at least three months after transplant. The criteria for inclusion were 18-65 years of age, both genders, and were followed as described in the patient follow-up. Exclusion criteria were having had an early graft loss due to surgical problems or participating in other clinical studies. The participants received a kidney transplant from living (LD) or deceased donors (DD). The database was composed of pre-transplant, clinical and laboratory test information of the recipient and the donor, transplant procedure information and outcomes data that were obtained anonymously by hospital clinical staff during the study. The labeling variable used in machine learning analyzes was allograft loss *yes* or *no* within three months after transplantation. The immunogenetic evaluation consisted of HLA-A, -B, -DRB1 typing for the genetic pairing of the recipients and donors, detection of anti-HLA antibodies performed by solid-phase immunoassay-single antigen beads (SPI-SAB) and crossmatches performed by complement-dependent cytotoxicity for T and B lymphocytes method. This study has been approved by the Human Research Ethics Committee of the Minas Gerais Faculty of Medical Sciences, MG State, Brazil, under license #2.122.409.

2.2 Follow-up of patients

The patients were monitored after the KT as follows: weekly during the first month, every 15 days in the second month, every 30 days from the third month for the first year. At any time, additional visits were made according to the patient needs. Serum creatinine levels were measured for graft function evaluation. To assess the impact of age on graft loss, donors and recipients were stratified using the point at 40 years considering the recipient/donor pair based on these variables were allocated into four different groups of studies (patient <40y/donor <40a, patient <40y/donor ≥40a, patient ≥40y/donor <40a, patient ≥40y/donor ≥40a). Transplant loss early was defined as a

loss within the first 90 days after transplant, except for an early transplant loss due to surgical problems.

2.3 Immunosuppressive therapy

The immunosuppression protocol was performed according to Lasmar et al, 2019 [26]. Briefly, patients with anti-HLA antibody detected by SPI-SAB with calculated PRA (PRAc) ≥50% or re-transplanted received induction immunotherapy with rabbit anti-thymocyte globulin (rATG) (Thymo, Genzyme, Mississauga, Canada). For maintenance triple immunosuppressive therapy was used tacrolimus (TAC) or cyclosporine A (CYA) associated with prednisolone (PRED), and sodium mycophenolate (MPA). Patients with cell rejection were treated with methylprednisolone and those with corticosteroid-resistant rejection were treated with rATG immunotherapy. Patients with ABMR were treated using a combination of plasmapheresis, MPA, and immunotherapy with rATG. Inversion of rejection was defined as a return blood level of serum creatinine within 20 days of antirejection therapy.

2.4 Data pre-processing and model's construction

The data was treated and pre-processed. The features were automatically selected to choose the machine learning algorithm, training and parameterization of the model, and finally, the analysis of the features that most impacted the prediction of the model based on explainability and interpretation of predictions. Through the existing features, new ones were created from the combination of two or more, as well as the application of relationships, such as the mean, which allowed additional analysis of the behavior of the data. The One-Hot Encoding technique was applied to categorical features and to encode them in a One-Hot numerical matrix. It was also necessary to use techniques such as data imputation, data augmentation, as well as normalization to optimize the model performance in the processing and interpretability of data for generation of predictive information. LightGBM and Extreme Gradient Boosting XGBOOST algorithms were evaluated to verify the performance of each of them. LightGBM presents perfomance only slightly better than that of XGBOOST. This way, all experiments in this study were performed using LightGBM which is effective in dealing with a large number of data instances and a large number of features. LightGBM also speeds up the training process of conventional gradient tree boosting methods by up to over 20 folds while achieving almost the same accuracy by containing two

techniques Gradient-based One-Side Sampling (GOOS) and Exclusive Feature Bundling (EFB) [27].

2.5 Models evaluation

The Area Under the Curve (AUC), which defines the area under the Receiver Operating Characteristic (ROC) curve, was the metric used to assess the performance of the model, due to its completeness in the analysis of sensitivity and specificity that may reflect reliability of the model with high precision [28]. To improve the robustness of the estimations, K-Fold Cross-Validation was used. Briefly, the dataset was randomly shuffled and splitter into 50 folds. At each iteration, a group of folds was used as a test set, and the other groups were considered as a training data set. Through a customized greedy algorithm, only the features that collaborated to obtain the best model were selected of which only the first fifteen features that most contribute to the increment of the AUC Score metric were kept.

2.6 Interpretation

Model predictions were interpreted using the SHapley Additive exPlanations (SHAP) algorithm that assigns each feature and significance value to a particular prediction [29]. The SHAP framework identifies the class of methods of importance of additive features and shows that there is a unique solution in this class that adheres to desirable properties.

3. Results

Demographic, clinical, laboratory data from samples and main outcomes can be observed in Table 1. Baseline experiments were performed with two gradient boosting algorithms, XGBoost and LightGBM, which were selected based on their performance consistent with the nature of the data set. The algorithm that was chosen was LightGBM, as it presents a higher metric, as well as a shorter training time (0.84 *versus* 0.82 for XGBoost). The database was separated into training of 70% and testing of 30% in the proportion using the Stratified Train-Test Split technique. A fine-tuning of the model was carried out to further optimize its performance. However, there was no significant variation, so that the model metrics remained the same as those presented in the baseline experiments. The training of the model was performed by Repeated Stratified K-Fold Cross-Validation, with a value of 'k' equal to 50 and with 5 repetitions for each fold. The value of 'k' was

high due to the low amount of data, which ensured the high reliability of the results obtained and an improvement in the metrics obtained by this model.

The final model had a precision of 0.81, a sensitivity of 0.61, a specificity of 0.89 and AUC of 0.84. The ROC-AUC Score is shown in Figure 1. Through the analysis of sensitivity, it was possible to observe that the existence of a smaller number of instances with the occurrence of early renal graft loss negatively affects the accuracy of the model for detecting cases in which the patient might suffer a renal graft loss. The features that have the greatest impact on the model´s decision were listed, as well as their degree compared to the others, being ordered according to importance in Figure 2.

In the Summary Plot, that combines the importance of features with their effects, each point on the graph was a Shapley Value for a feature and an instance. The position on the y-axis was determined by the feature and on the x-axis by the value of Shapley. The color represents the feature's importance value, from low to high. The overlapping points can be distorted in the y-axis direction, so that one can get a sense of the distribution of values by feature, which are ordered according to their importance for the model's decision making (Figure 3).

The patient's serum creatinine levels at discharge proved to be the most important decision-making factor in the model regarding the occurrence or not of allograft loss, indicating that low creatinine values at discharge was associated with a reduction in the chances of graft loss while high levels associated with an increase this chance. Patients with weight equivalent to a BMI closer to the normal value (18-24 kg/m^2 for women and 18-25 kg/m^2 for men) before kidney transplantation have lower probability of graft loss when compared to patients with less weight, most likely a malnourished patient (Figure 3).

Patient aging prior to transplant also has a large impact on model decisions. Recipients, even if older, who receive a kidney from young donors, have a lower probability of early graft loss in comparison with patients that received kidney from older donors (Figure 3). Polyomavirus (BKPyV) infection also has impacts on the model's decisions. Recipients infected by BKPyV had higher SHAP value than patients that do not present this virus. Through analysis of the explainability, it is possible to see that the presence of post-transplant BKPyV infection may contribute to allograft loss.

Considering all the causes of early graft loss, the main features that explain this event were the serum creatinine level at hospital discharge after transplantation, recipient's weight before transplantation, patient's age, BKPyV infection after transplantation, old recipient transplanted with

young donor, and the presence of comorbidity in the recipient before transplantation (Figure 4A). In most patients who lost the graft due to rejection, the important features to explain the graft loss were the same as those reported for all causes, except the recipient/donor pairing by age and comorbidity that were not important to explain graft loss event by rejection (Figure 4B). When infection is the cause of graft loss, it is observed that the age of the recipient and comorbidity as bone mineral disease play an important role in explaining the graft loss event (Figure 4C).

4. Discussion

In this retrospective cohort analysis of patients receiving a kidney transplant, the main features that impacted the output of the prediction model of early graft loss were, in this order of importance, patient serum creatinine levels at discharge, pre transplant weight, patient age, BKPyV infection. Serum creatinine levels are directly related to the good or bad kidney allograft function. Patients with allograft dysfunction have higher levels of serum creatinine, and smaller estimates of glomerular filtration rates. Nutritional status before transplantation is a determining factor for post-transplant good clinical outcomes such as surgical wound healing time and episodes of infections. Thus, the detection of nutritional status becomes essential, not only for the nutritional recovery of the recipient, but also to prevent complications after surgery and to increase long-term allograft survival [30-32]. The nutritional status of patients with CKD should not be neglected, as it is an important determinant of clinical outcomes and one of the main predictors of morbidity and mortality in dialysis and kidney transplant patients. Thus, the results of this study corroborate data from the literature that malnourished patients or those with low weight have a higher risk of graft failure [31].

Age is another important predictor factor for good kidney transplantation clinical outcome [33,34]. The patient's age before transplantation also has a high impact on the model's decisions. Young patients (<40y) have a lower probability of early graft loss than compared with elderly patients (≥40y) that had a significantly lower graft and patient survival rates [34]. In this study, older patients that received a kidney from a young donor had a lower probability of early graft loss. Renal transplantation does not offer significant medium-term survival benefit, relative time in waiting lists mainly for elderly recipients transplanted with grafts from older donors. This way, the combined effect of recipient and donor age on transplant outcome is important to optimize utilization of organs available for transplantation that should be offered to those patients who can really benefit from it.

In immunocompetent humans, the incidence of primary infection by BKPyV is in childhood, after which it lies latent in the genitourinary tract. Reactivation of the BKPyV may occur with immunosuppression. Approximately 2-5 % of kidney transplant recipients develop BK nephropathy. Over-immunosuppression has been implicated in the process. In kidney transplanted patients, active replication of BKPyV induces fibrosis leading to graft dysfunction and premature loss [35-37]. In this study, BKPyV infection was an important risk factor for graft loss. Therefore, periodic surveillance of BKPyV in transplant recipients is recommended, to allow for early clinical intervention and to improve long-term outcomes to avoid nephropathy [38]. Rejection was not a risk factor for graft loss in the analyzed period, possibly due to the use of rATG induction in groups at risk for ABMR, the use of an efficient immunosuppression protocol and successful treatments for rejection episodes.

Problems involving the use of machine learning applied to health areas have as specificity the importance of validating the results obtained through the model with physicians specialized in the specific area referred to by the study [39]. Assessing the variables that can predict allograft loss is a difficult issue due to the complexity of the data, including pre-transplant characteristics of the recipient and donor, transplant procedure, and variables related to clinical outcomes. This occurs due to the complexity infringed on the interpretability of the features, as well as its consequences for the patient, when placed under observation for a long-term [39]. In this study an intensive explanatory analysis was carried out, validated by three specialists in Immunogenetics or Nephrology to define and interpret the factors that most contribute to the renal graft loss and its explainability. These analyses were carried out through Shapley, which promotes the definition of importance values for each of the features used and allows a quick graphical display of results.

Several predictors of long-term graft survival have been identified, such as renal function at 1 year after transplantation, acute rejection, infections, inadequate immunosuppressive therapy [40,41]. The underlying disease that causes end-stage renal disease in the patient can also plays a role in the transplantation outcome, such as diabetes and arterial hypertension [42, 43], because they can increase a thrombotic risk, due to diabetic angiopathy, as also atherosclerosis [44,45]. However, many of the known factors are late predictors of post-transplantation, with few early predictors studied. Risk factors identified early, ideally before transplantation, may be important for identifying recipients vulnerable to early transplant loss [46]. Given the scarcity of organs for transplantation and the increase in the number of recipients on the waiting list for a kidney, it became important to know the main risk factors for graft loss to guide intervention measures for

transplant follow up to improve graft and patient survival. Thus, this study has the clinical impact by describing predictor variables of graft loss. Indirectly, this has an economic impact, because the patient's return to dialysis is more costly to the healthcare system than maintaining a functional transplant.

5. Conclusions

In conclusion, the main feature that impacted early transplant loss were the patient's serum creatine levels at discharge, pre-transplant weight, age, and BKPyV infection. The machine learning tools used in this study proved to be efficient in corroborating with scientific evidence that was validated by experts in nephrology, immunogenetics and contributed to the inclusion of useful features in the predictive model and improved information for medical decision-making.

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Conflict of interest statement

The authors declare that they have no known competing personal relationships or financial interests that could have appeared to influence this manuscript.

Authorship

RAFO and AAV contributed with the conception and design of the study, RAFO and MROS made acquisition of data, LHMS and AAV analysis and interpretation of data, RAFO, EN, LHMS and MROS drafting the article. RAFO and AAV reviewed the manuscript critically for important intellectual content. All authors approve the final version of the manuscript to be submitted.

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Legends

Figure 1: Receiver Operating Characteristic (ROC) curve. The green line shows the best miniaturized model predictions and the blue dotted one shows random predictions.

Figure 2: Degree of impact of features on the model´s decision.

Figure 3: Detailing the impact of features on model output. Red points are associated with spectra for which the corresponding statistical feature shows a relatively high value. Blue points are associated with spectra for which the corresponding statistical feature shows a relatively low value. Further, there is a vertical line separating spectra associated with either negative (points on the left) or positive decisions (points on the right). For instance, points located in the left side are those for which the model provided a negative decision, that is, no allograft loss.

Figure 4: Features that explain graft loss due to different causes: A) all causes, B) rejection, C) infection regardless of the etiologic agent.

Table 1: Demographic characteristics, laboratorial parameters and clinical data of patients and outcomes after kidney transplantation.

Features	Absolute value (%)
RECIPIENT	
Gender	
Male	397 (63)
Female	230 (37)
Recipient age (year, mean ± SD)	44.92 ± 12.47
Etiology of CKD ($n = 624$)	
Hypertensive nephropathy	59 (9.46)
Diabetes mellitus	84 (13.46)
Glomerulopathy	127 (20.35)
Autosomal polycystic kidney disease	54 (8.65)
Undetermined/Other	300 (48.08)
Time in dialysis (month/ median/ min-max/ interquartile range)	40.61 / 28.00 / 0-258 / 44.25
Second transplantation	30 (4.78)
% PRAc HLA Class I (mean ±SD)	8.86 ± 20.52
PRAc I = 0%	423 (67.46)
PRAc I > 1%	204 (32.54)
% PRAc HLA Class II (mean ±SD)	6.00 ± 17.86
PRAc II = 0%	512 (81.66)
PRAc II > 1%	115 (18.34)
Laboratorial parameters	
BMI (mean ±SD)	24.09 ± 4.35
Albumin (mg/dL) (mean ±SD)	4.27 ± 0.60
Cholesterol (mg/dL) (mean ±SD)	178.20 ± 53.05
Total lymphocytes (mean ±SD)	1783.46 ± 640.81
DONOR	
Donor age (year, mean / median / min-max)	42.31 / 43.00 / 7-73
sCr (mg/dL) before KT (mean ±SD)	1.06 ± 0.81
TRANSPLANT PROCEDURE	
HLA-A, -B, -DRB1 mismatching ($n = 624$)	
0	58 (9.29)
1 to 3	337 (54.01)
4 to 6	229 (36.70)
OUTCOMES	
Infection	
Cytomegalovirus	170 (27.11)
Polyomavirus	22 (3.53)
Urinary tract infection	280 (44.66)
Delay graft function	245 (39.07)
At least one rejection event	203 (32.38)
Graft rejection event (<3 months)	157 (25.04)
Graft loss	174 (27.75)
Early graft loss (<3 months)	64 (10.21)

CKD: chronic kidney disease. DSA: donor-specific antibody; SD: standard deviation. BMI: body mass index. PRA: Panel reactive antibody. HLA: Human Leucocyte Antigen. sCr: serum creatinine before transplantation.

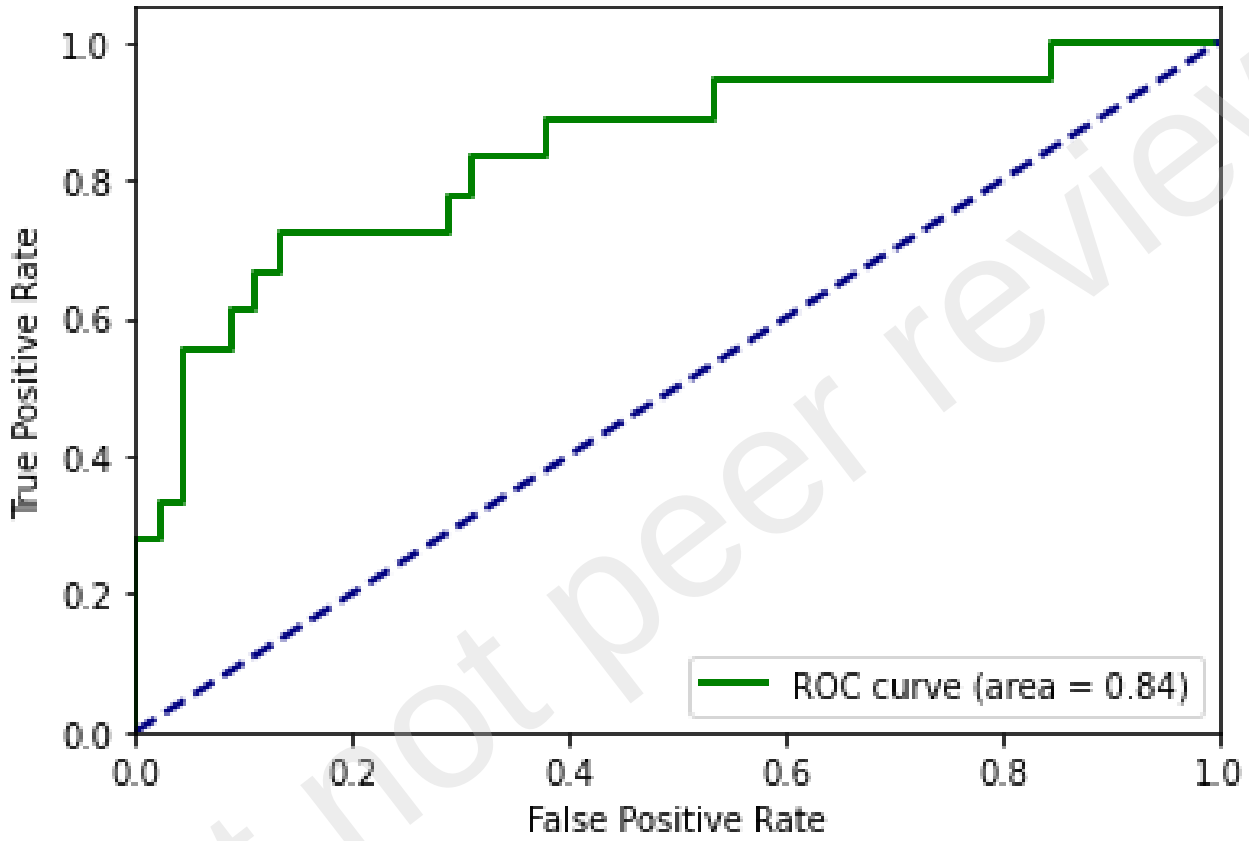


Figure 1

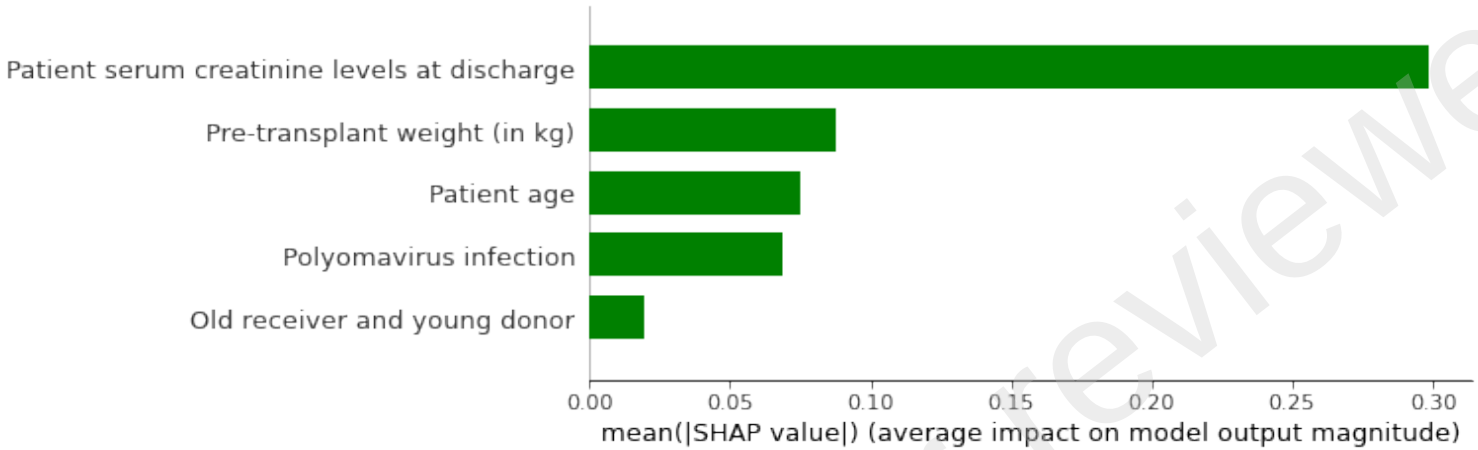


Figure 2

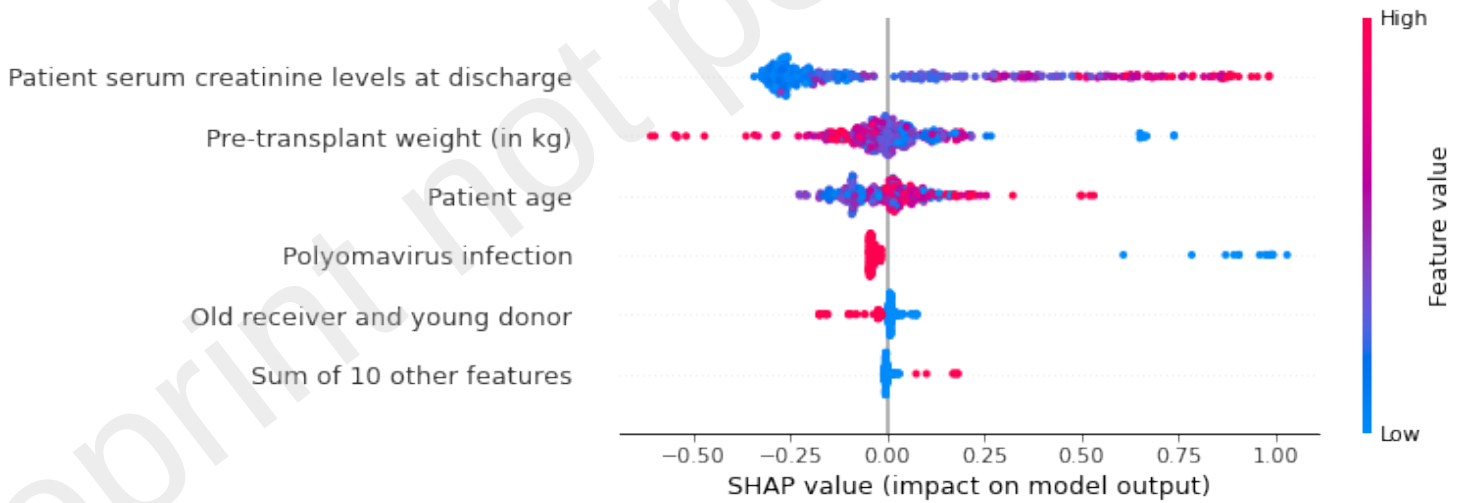
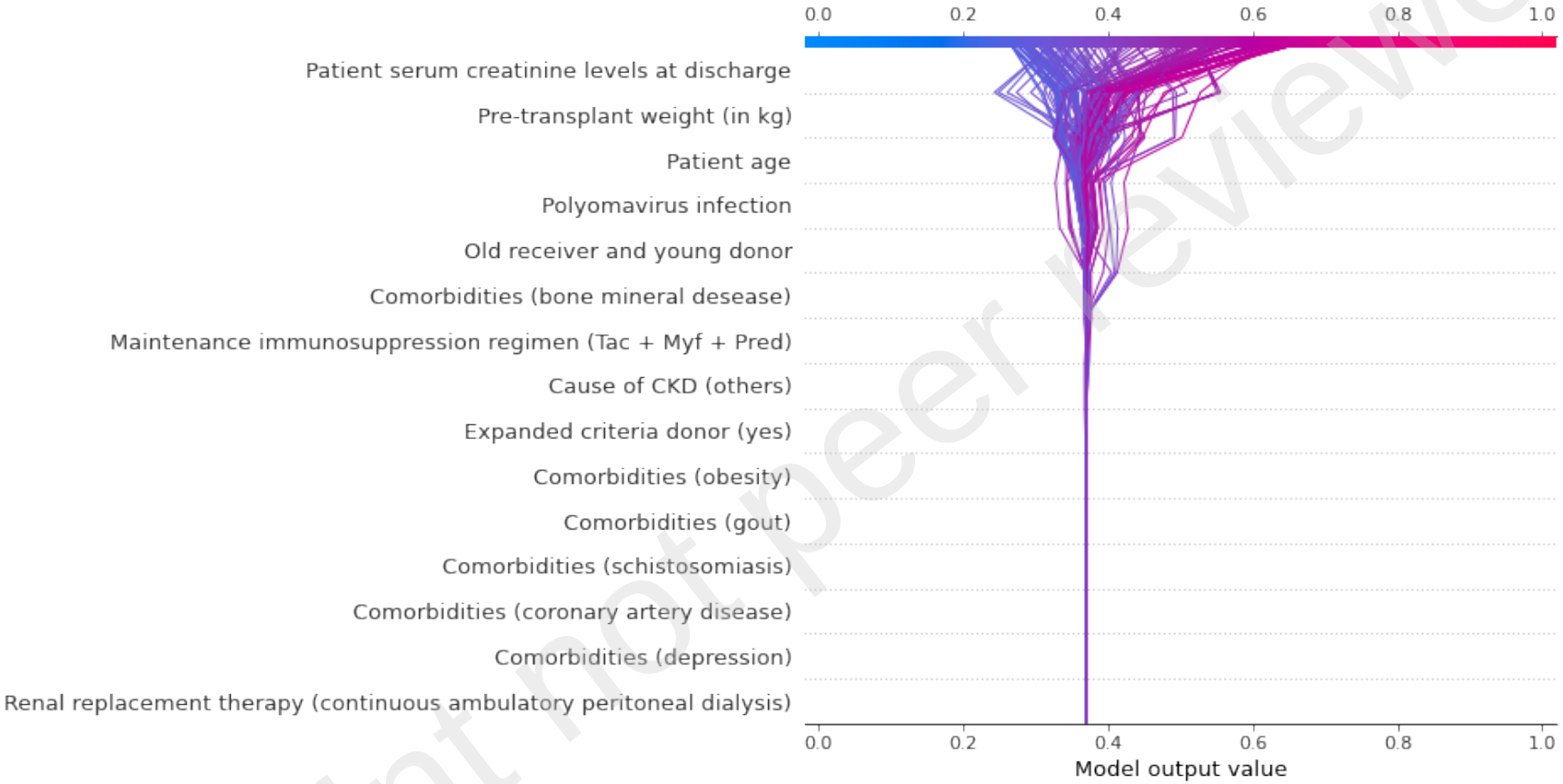


Figure 3

Figure 4



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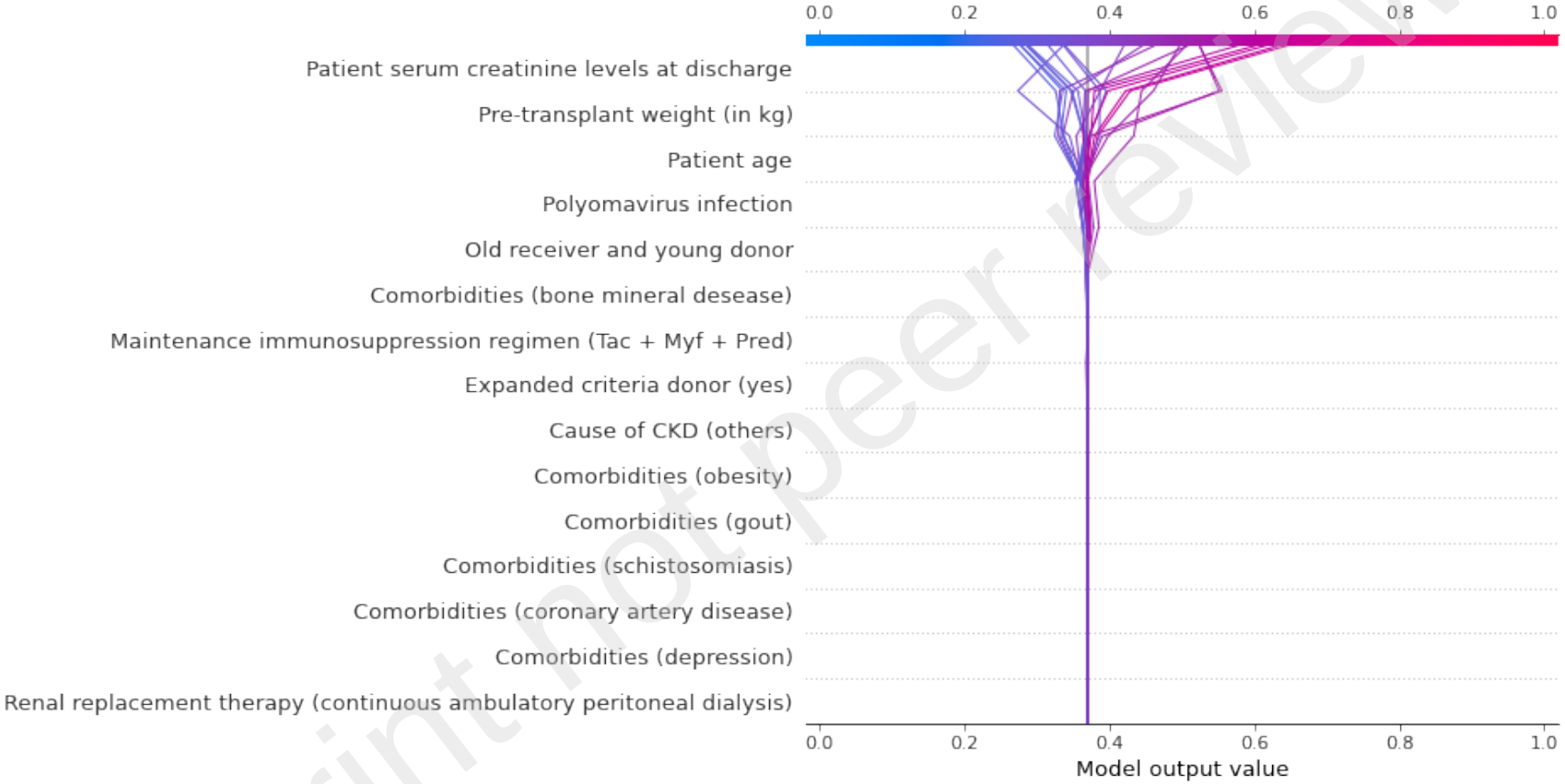

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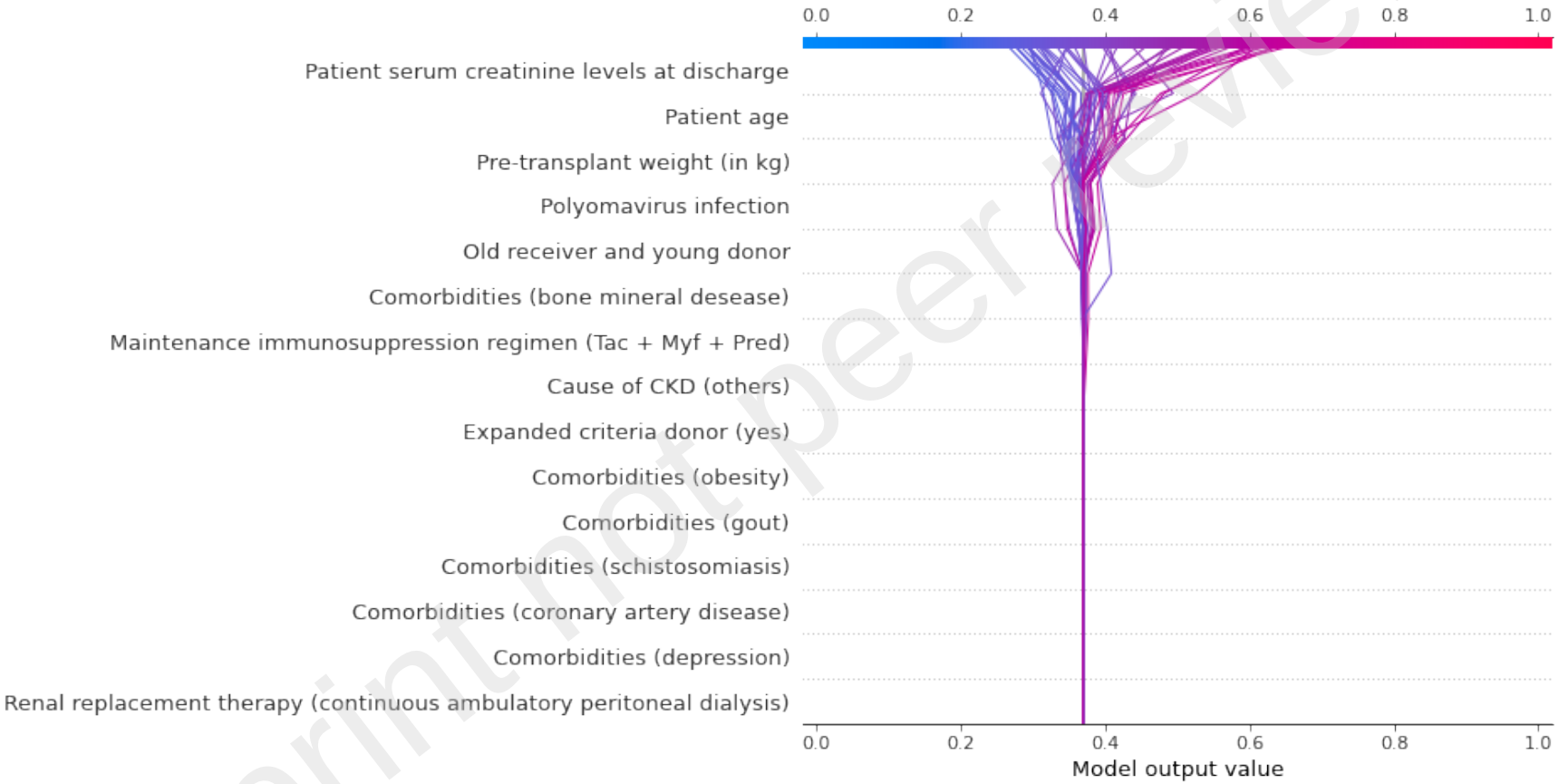

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