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ORIGINAL ARTICLE

Diabetes mellitus and blood glucose variability increases the 30-day readmission rate after kidney transplantation

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Abstract

Introduction: Inpatient hyperglycemia is an established independent risk factor among several patient cohorts for hospital readmission. This has not been studied after kidney transplantation. Nearly one-third of patients who have undergone a kidney transplant reportedly experience 30-day readmission.

Methods: Data on first-time solitary kidney transplantations were retrieved between September 2015 and December 2018. Information was linked to the electronic health records to determine diagnosis of diabetes mellitus and extract glucometric and insulin therapy data. Univariate logistic regression analysis and the XGBoost algorithm were used to predict 30-day readmission. We report the average performance of the models on the testing set on bootstrapped partitions of the data to ensure statistical significance.

Results: The cohort included 1036 patients who received kidney transplantation; 224 (22%) experienced 30-day readmission. The machine learning algorithm was able to predict 30-day readmission with an average area under the receiver operator curve (AUC) of 78% with (76.1%, 79.9%) 95% confidence interval (CI). We observed statistically significant differences in the presence of pretransplant diabetes, inpatient-hyperglycemia, inpatient-hypoglycemia, minimum and maximum glucose values among those with higher 30-day readmission rates. The XGBoost model identified the index admission length of stay, presence of hyper- and hypoglycemia, the recipient and donor body mass index (BMI) values, presence of delayed graft function, and African American race as the most predictive risk factors of 30-day readmission. Additionally, significant variations in the therapeutic management of blood glucose by providers were observed.

Conclusions: Suboptimal glucose metrics during hospitalization after kidney transplantation are associated with an increased risk for 30-day hospital readmission. Optimizing hospital blood glucose management, a modifiable factor, after kidney transplantation may reduce the risk of 30-day readmission.

KEYWORDS
blood glucose, insulin therapy, readmission risk, solid-organ transplantation

1 | INTRODUCTION

Early hospital readmissions are associated with increased healthcare costs and higher morbidity. Consequently, the reduction of early hospital readmissions (defined as occurring within 30 days after discharge) has become a national priority and an important quality metric.[1] Inpatient hyperglycemia has been associated with poorer hospital outcomes, increased readmissions, increased mortality and health care costs, in a variety of populations studied, independent of a diagnosis of diabetes mellitus (DM).[2–5]

In 2012, the Affordable Care Act instituted the Hospital Readmissions Reduction Program (HRRP), overseen by the Centers for Medicare and Medicaid Services (CMS).[6] The HRRP prioritizes the reduction of readmissions within 30 days for six conditions.[6] CMS is authorized to cut Medicare reimbursements to hospitals with higher than predicted risk-adjusted readmission rates for each hospital based on its performance during a rolling performance period.[6] Furthermore, with various efforts in measuring and publicly reporting of hospital outcomes,[7,8] improving measures such as risk-adjusted readmission rates have become important in various clinical conditions.

Successful kidney transplantation reduces morbidity and mortality among patients with end-stage renal disease, and is a cost-effective option in comparison to continued dialysis.[9–11] In 2021, there were nearly 25 000 kidney transplants performed in the U.S.[12] Studies have reported nearly one-third of patients who have undergone a kidney transplant experience readmission within 30 days.[13,14] Early readmissions in these patients are associated with poorer outcomes, including higher mortality, and allograft failure.[15–17]

Several studies have analyzed the variables contributing to 30-day readmission after kidney transplantation.[16,18–20] Identifying which are modifiable could lead to changes in practice that produce better outcomes. However, although inpatient hyperglycemia has been shown to be a risk factor for hospital readmissions in various populations, the relationship between inpatient glucose control and hospital readmissions among patients receiving a kidney transplant has not been studied. We performed a retrospective analysis to examine the association between different inpatient glucometrics and risk of 30-day readmissions occurring in a cohort of patients undergoing a kidney transplant. The analysis leverages a well-established machine learning (ML) algorithm that is able to capture non-linear relationships between the risk factors and occurrence of readmissions.[21] More broadly, our study contributes to our prior work in better understanding, measuring, screening, and managing glucometrics for patients who undergo transplantation.[22–27]

2 | MATERIALS AND METHODS

2.1 | Study cohort

The study has been approved by Mayo Clinic Office for Human Research Protection. Patients undergoing a kidney transplant between September 25, 2015 and December 25, 2018 were retrieved from the electronic health records (EHR). Only patients undergoing first time solitary kidney transplants were selected. Individuals who required readmission within the first 30 days following the index admission were then selected. Data on age, sex, race, kidney function, and length of index hospital stay were extracted. To account for differences in the complexity of care in the hospital, Medicare Severity Diagnosis Related Group (MS-DRG) values were retrieved.[28] International Classification of Diseases, Tenth Revision codes were utilized to determine which cases had a diagnosis of DM.

2.2 | Post-transplant immunosuppression protocol

After a brief admission (typically hours), patients undergo kidney transplantation. As per described in our previous methodology,[22] the standard immunosuppression protocol is induction therapy with either Campath (alemtuzumab), rabbit antithymocyte immunoglobulin, or basiliximab. All patients receive a 5-day tapering course of glucocorticoids (methylprednisolone intravenous 500 mg on day 1, 250 mg on day 2, and 125 mg on day 3, followed by oral prednisone 60 mg on day 4 and 30 mg on day 5), after which a majority of patients receive steroid-free maintenance immunosuppression using mycophenolate mofetil and tacrolimus. The few patients who receive ongoing steroid therapy (those who are immunologically higher risk or have a diagnosis of glomerulonephritis as a cause of their kidney failure) receive the same initial 5-day tapering course in an identical fashion to that given those who are on steroid avoidance and subsequently gradually lowered to a maintenance of prednisone 5 mg.

2.3 | Assessment of inpatient glycemic control

Point-of-care blood glucose (POC-BG) measurements were used to assess glycemic control. POC-BG measurements were obtained using a NovoStat glucometer (Nova Biomedical, Waltham, MA).[29] POC-BG data were used to calculate the patient-stay average blood glucose level ($BedGluc_{avg}$) and during the last 24 h before discharge (average patient blood glucose level during the last 24 h before discharge [$L24BedGluc_{avg}$]) as has been calculated previously.[22,23,30,31] Additional glucometrics included the average maximum (patient-stay average daily maximum blood glucose level [$BedGlucMax_{avg}$]) and minimum (patient-stay average daily minimum blood glucose level [$BedGlucMin_{avg}$]) POC-BG values. In accordance with current guidelines, hyperglycemia was defined as glucose > 180 mg/dL.[32–34] The percentage of patients who had a $BedGluc_{avg}$ greater than 180 mg/dL was calculated, and the proportion of patients experiencing a hypoglycemic event (POC-BG < 70 mg/dL) was determined. Hemoglobin A1c (Hgb A1c) was included in the data when available.

2.4 | Definitions of inpatient insulin regimen

A basal-bolus regimen (e.g., long-acting insulin combined with rapid-acting insulin with meals and correction doses as needed for

hyperglycemia) is the recommended method of insulin management of hyperglycemia in hospitalized patients.[32–34] Data on administered insulin therapy was extracted from the pharmacy information system. Insulin type was classified as basal or bolus, and patterns of insulin administration were then defined as *none*, *bolus only*, or *basal-bolus* as previously described.[30,31,35,36] Due to the small number of cases ($N = 7$), basal-only insulin was not included. The overall regimen used during the hospital stay was determined. To examine changes in insulin regimen throughout the hospital stay, patterns of administration were determined during the first, middle, and last 24 h (first 24 h of patient admission [F24h], middle 24 h of patient admission [M24h], and last 24 h of patient admission [L24h]) of the hospital stay as previously described.[23] Our previous reports have shown that different insulin regimens may be applied to patients with and without DM. Thus, data on insulin was stratified by DM status.[22,36]

2.5 | Statistical analysis

We conducted a baseline descriptive analysis of the study cohort. Means and standard deviations (SDs) were calculated for continuous variables, as well as the relative prevalence ratio in the form of percentages for categorical variables. The number of days between discharge and readmission was calculated and displayed in day increments. The distribution of insulin therapy was determined according to DM status. Missing data were imputed using the MedImpute algorithm, which accounts for time-dependencies in observational data.[37]

Univariate and multivariate logistic regression models were trained to examine the association between risk conferred by various glucometrics of interest measured anytime during hospital stay as well as patient characteristics and the risk of 30-day readmission. The relative risk ratio is reported for each independent variable as well as the corresponding 95% confidence intervals (CIs) and *p*-values.

To enhance the power of the study, we applied the XGBoost algorithm to predict the outcome of interest (30-day readmission).[21] XGBoost is a well-established ML method that is commonly used in the binary classification setting for tabular data. Contrary to traditional statistical models, XGBoost can capture non-linear relationships in the data by leveraging a large number of tree-based models that are built in an iterative fashion, creating a strong ensemble learning method. Each tree aims to improve upon the previous model. Thus, the algorithm constructs consecutive trees that correct upon the errors of earlier ones. As a result, XGBoost achieves superior performance compared to other ML algorithms. In addition, this method allows us to use as input a wider set of variables that may even be highly correlated due to its ability to model non-linear interactions among the risk factors. We used as independent variables the risk factors presented in Table 1 and the metabolic treatment information for the first, middle, and last 24 h of the admission per patient, as summarized by Figures 3, 4. The training of the algorithm was conducted on 75% of the total samples (in-sample partition), and 25% was used for performance evaluation (out-of-sample partition). Hyper-parameter tuning was conducted using 10-fold cross-validation. The discrimination performance of the downstream model was evaluated on five independent partitions of the data to ensure statistical significance, using the area under the receiver operator curve (AUC) metric. Each random partition maintained the same outcome prevalence ratio between the in-sample and out-of-sample datasets. To identify the risk factors that drive the algorithm's risk prediction, we computed the importance score for every feature measured by Gain in F-score, which captures the relative contribution of each variable in the derived models.[38] In the Results section, we report the features that ranked highest in terms of the feature importance score and directly derive clinical insights from our ML method. All statistical analyses were conducted using version 3.7 of the Python programming language and the Scikit-learn library.[38]

3 | RESULTS

3.1 | Patient characteristics according to readmission status

A total of 1036 patients underwent kidney transplant procedure. The cohort consisted of 437 patients (42%) with DM prior to transplant procedure. Patients with DM had a longer median length of hospital stay after the procedure compared to the non-diabetics (4.0 vs. 3.0, $p < .001$).

The highest percentage of readmissions occurred within the first 7 days following discharge for both patients with and without DM. There were 224/1036 patients (22%) who required readmission within 30 days following discharge from their index hospital stay (Table 1). Patients requiring readmission were comparable in age, sex, and race to those not requiring readmission (Table 1), except for African American patients who had a higher risk of readmission (odds ratio [OR] 2.17; 95% CI 1.36, 3.6, $p = .001$). In univariate logistic regression analyses, the length of hospital stay had a small but significant association with 30-day readmission risk, rising 6% for every additional day spent in the hospital following transplant (OR 1.06; 95% CI 1.02, 1.108, $p < .01$). Similarly, the risk of readmission was 78% higher for every additional value of the MS-DRG index (OR 1.78; 95% CI 1.38, 2.29; $p < .01$) (Table 1). The risk of rehospitalization increased 97% (OR 1.97; 95% CI 1.46, 2.66; $p < .01$) among those with known DM and for patients with presence of delayed graft function (OR 1.67; 95% CI 1.24, 2.25; $p < .001$).

3.2 | Relationship between inpatient glycemic control and readmissions

Analysis of glycemic variables showed that patients with hyper- and hypoglycemia correlated with greater odds of readmission (Table 1). Although no significant differences were detected in $BedGluc_{avg}$ between readmission cohorts, patients who experienced at least one episode of hyperglycemia had an 86% increase in risk of 30 day readmission (OR 1.86; 95% CI 1.31, 2.65; $p < .01$), while those who

TABLE 1 Comparison of patients undergoing first time kidney transplant (September 2015 to December 2018), according to 30-day readmission status[a].

30-Day readmission status	Yes $N = 224$	No $N = 812$	OR (CI)	*p*-values
Age (year)	53 (14)	53 (14)	1.0 (.99, 1.01)	.933
Male sex (%)	60	59	1.04 (.77, 1.40)	.808
Race/ethnicity (%)				
White race	66	67	.93 (.68, 1.28)	.666
African American	7	11	2.17 (1.36, 3.6)	.001
Asian race	6	23	1.61 (.94, 2.75)	.080
Hispanic ethnicity	18	20	.87 (.60, 1.28)	.484
Length of index hospital stay (day)	5.1 (3.8)	4.1 (3.6)	1.06 (1.02, 1.11)	<.01
MS-DRG	3.52 (.71)	3.35 (.41)	1.78 (1.38, 2.29)	<.001
Presence of delayed graft function (%)	57	44	1.67 (1.24, 2.25)	<.001
Donor deceased (%)	87	78	1.58 (1.01, 2.46)	.045
Diabetes (%)	55	39	1.97 (1.46, 2.66)	<.001
Glucometrics				
$BedGluc_{avg}$	152 (32)	140 (30)	1.0 (.99, 1.01)	.430
Patients with hyperglycemia (at least one value of BedGluc > 180 mg/dL [%])	79	66	1.86 (1.31, 2.65)	<.001
Patients with hyperglycemia ($BedGluc_{avg}$ > 180 mg/dL [%])	17	15	1.19 (.80, 1.78)	.390
Patients with hypoglycemia (%)	25	13	2.2 (1.54, 3.17)	<.001
$BedGlucMax_{avg}$	245 (79)	224 (71)	1.0 (1.00, 1.01)	<.001
$BedGlucMin_{avg}$	87 (25)	94 (24)	.99 (.98, 1.00)	<.001

$BedGluc_{avg}$, patient-stay average blood glucose level; $BedGlucMin_{avg}$, patient-stay average daily minimum blood glucose level; $BedGlucMax_{avg}$, patient-stay average daily maximum blood glucose level; LOS, length of stay; MS-DRG, Medicare Severity-Diagnosis Related Group; KDPI, Kidney Donor Profile Index; $L24BedGluc_{avg}$, average glucose 24 h prior to discharge.

[a]Data are medians (±SD) for continuous variables.

experienced hypoglycemia had a greater than two-fold higher risk (OR 2.2; 95% CI 1.54–3.17; $p < .01$) (Table 1).

Multivariate analysis was first performed using Logistic Regression. The downstream AUC of the resulting model was 66% with (64.9%, 67.1%) 95% CI. We hypothesized that a more advanced ML algorithm, such as XGBoost, could lead to superior discrimination performance.[21] The average AUC performance of the XGBoost models on the out-of-sample set for five independent splits of the data was 78% with (76.1%, 79.9%) 95% CI. Figure 1 illustrates the average receiver operator curves for both the in-sample and out-of-sample partitions. The index admission length of stay, presence of hyper- and hypoglycemia, the recipient and donor body mass index (BMI) values, presence of delayed graft function, and African American race were the seven most predictive risk factors for the outcome of interest (see Figure 2). Note that the XGBoost model is not a linear model, and thus, the impact of each independent variable on the outcome of interest is not fixed. Furthermore, XGBootst allows for various interactions between variables. Thus, the effect of each predictor on each individual patient changes based on the presence or absence of other risk factors. For example, the impact of hyperglycemia on a patient's risk of readmission may vary depending on the recorded BMI or the patient's age. Contrary to a logistic regression model, where the relative risk ratio does not vary for each risk factor, ML models such as XGBoost are able to capture complex relationships between the variables and generate insights more suitable for personalized medicine. For this reason, we only report the most predictive features rather than a value for each coefficient.

3.3 | Patterns of insulin therapy

Examination of insulin regimens employed during the last 24 h of the index hospital stay, stratified according to DM and readmission status, showed different patterns on how therapy was applied. In those DM patients not requiring readmission, overall 86% were on insulin compared to 74% of individuals who were readmitted (Figure 3). Use of basal-bolus insulin was similar between readmission cohorts ($p = .87$). Bolus-only insulin therapy was greater ($p < .001$) among individuals not requiring readmission, while a greater percentage ($p < .001$) of those

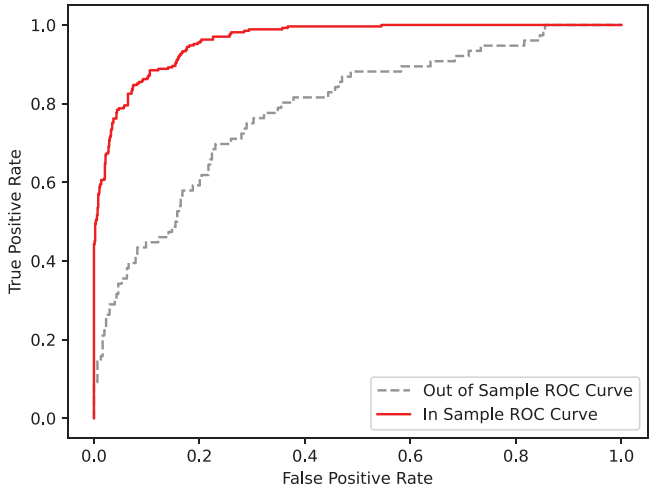

FIGURE 1 Area under the receiver operator curves for the in sample (training) and out of sample (testing) data.

readmitted were on no therapy (Figure 3). In patients without a history of DM, use of basal-bolus insulin therapy was almost never ($N = 3$) applied, and the majority were on bolus-only insulin therapy during the last 24 h of the hospital stay. The proportion of patients on bolus-only or no insulin therapy was similar between readmission categories (Figure 3).

There was a lack of consistent pattern of how insulin therapy was utilized throughout the course of the hospital stay. It appeared very varied and based on the discretion of the provider. For instance, among patients with DM (Figure 4, top panel), some patients would remain on basal-bolus or bolus only therapy throughout the hospital, while in other instances, the type of insulin therapy would vary from time segment to time segment. Similar observations were noted for those without DM (Figure 4, bottom panel).

4 | DISCUSSION

It is well established that hospital readmission is associated with increased morbidity, mortality, and cost of care. It is also a key metric employed by CMS and other organizations to rate the performance of hospitals and healthcare systems. With the increasing efforts in improving the transparency of the outcomes in the healthcare sector through public reporting and other activities,[7,8] reducing readmissions has become more important than ever. Suboptimal glucose metrics during hospitalization are among the factors known to be associated with an increase in readmissions in various disease states.[2–5] This analysis is among the few studies to evaluate the relationship between such suboptimal glucose metrics and hospital readmissions among patients receiving a kidney transplant.[39–41] We report that the presence of hypoglycemia and hyperglycemia during the hospitalization after kidney transplantation, as well as the recipient and donor BMI values, presence of delayed graft function, and African American race are important risk factors for 30-day hospital readmission. Our results are derived via an ML model that achieves good discrimination performance (AUC) on five bootstrapped samples of unseen data. Consistent with prior reports from the authors' institution, most patients with DM were on basal-bolus insulin the 24 h prior to discharge. Insulin therapy was also deemed necessary among a large percentage of patients without DM, although a bolus-only regimen was felt to be adequate to achieve glucose control. A more detailed assessment of how insulin regimens were used showed a lack of consistency in how therapies were applied throughout the hospital stay. This "therapeutic chaos"

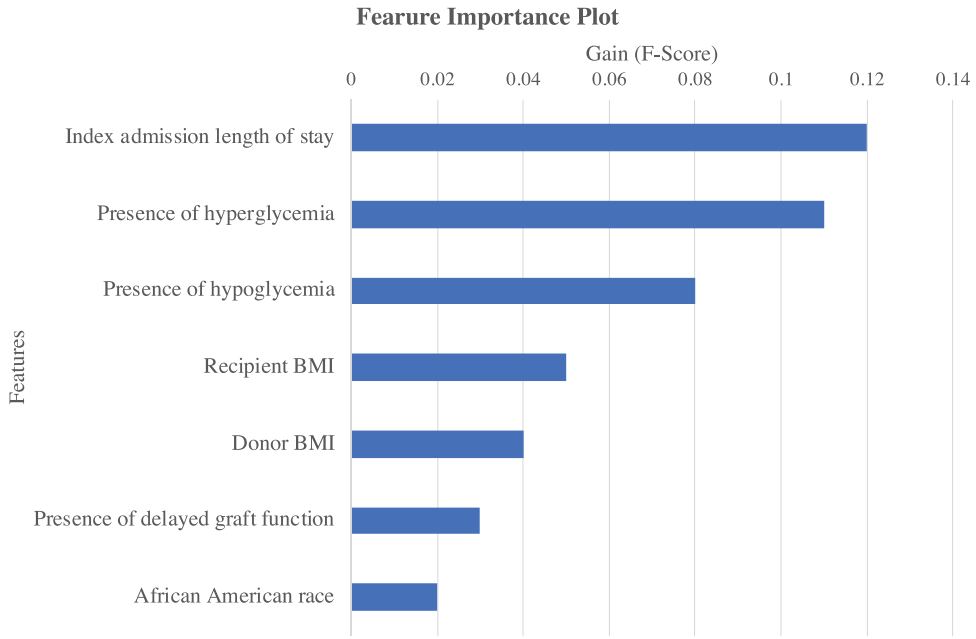

FIGURE 2 XGBoost model feature importance plot measured by Gain in F-score.

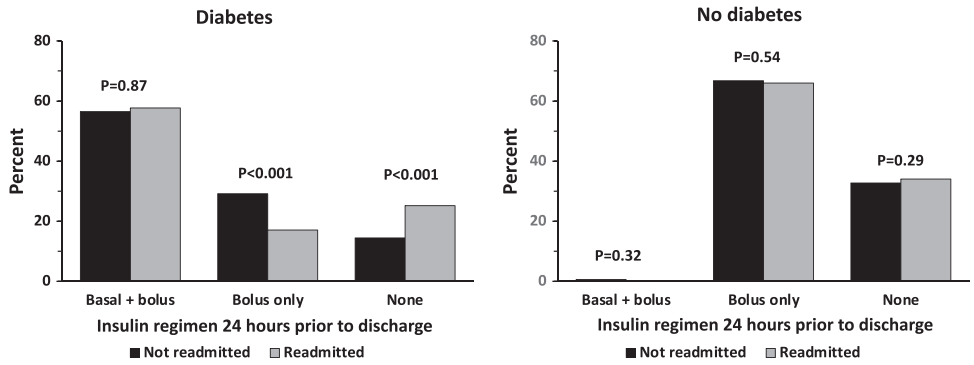

FIGURE 3 Insulin regimen 24 h prior to discharge.

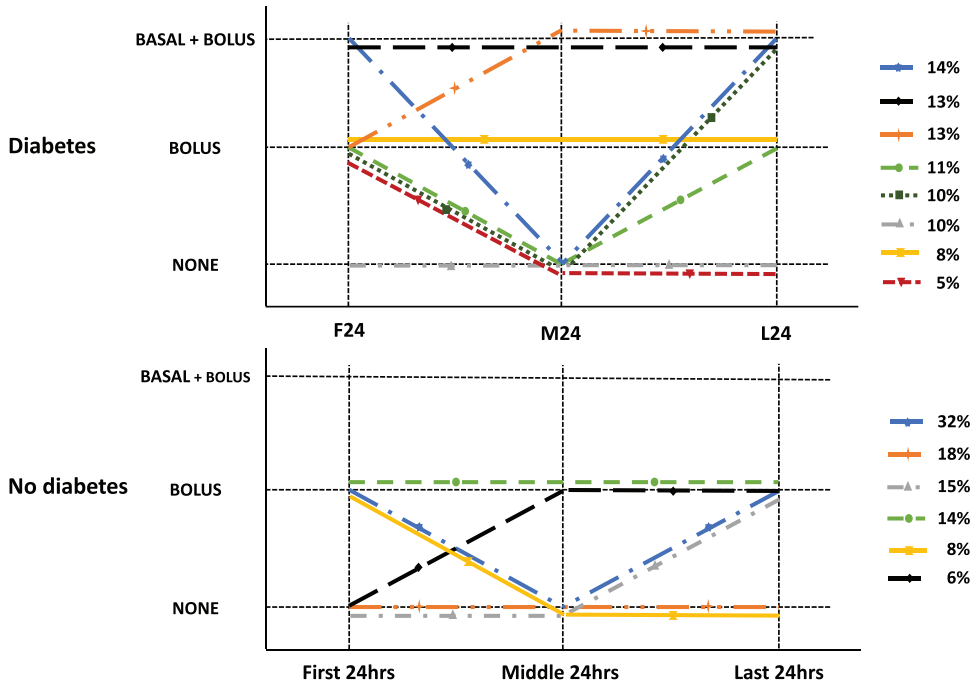

FIGURE 4 Distribution of insulin treatment regimens during the hospital admission. The percentages indicate the proportion of the population that followed each trajectory.

with regards to the use of inpatient insulin may be due to the changing clinical circumstances of the patient (e.g., tapering of steroids or change in nutritional intake), or from a lack of understanding on when to use specific regimens. Most likely it is a combination of factors. Practitioners tend to make decisions about insulin in a reactive rather than in a predictive manner, that is, they make changes based on the previous day's glucose patterns. In the absence of systematic clinical guidelines and due to the dynamic and complex trajectory of glucose metrics, there is an increased risk of uncontrolled hyper- and hypoglycemia. There are a few reported studies describing a personalized approach in DM management after kidney transplant. Our study highlights the need for robust studies to be done to study and prescribe the approach in DM management after a kidney transplant. Specifically, future studies could focus on the personalization of the optimal in-hospital insulin therapy after kidney transplantation based on a broader set of patient characteristics that dynamically change during the hospital stay. Future research can also extend our analysis to other major organ transplantations and contribute to the stream of the literature that aims at findings similarities and differences between kidney and other solid organ transplant patients.[24,25]

4.1 | Limitations

This was a single academic medical center and analysis used retrospective data from EHRs. As a result, other confounding factors may exist that could have affected the patients' trajectory of glucose control, which are not included in the data. These would include variables

such as postoperative infection, dietary intake and tacrolimus levels variations, steroid dosing information, and other factors resulting in transient insulin resistance. Future studies could focus on investigating the impact of these factors in combination with the independent variables included in our analysis. The difference in the performance of the ML model between the in-sample and out-of-sample data partitions is attributed to overfitting and could be remedied in future studies by expanding the sample size of the population. This retrospective analysis does not provide insight into the reasons underlying the decision-making behavior of clinicians regarding clinical assessment and prescriptions. This pertains to the inability to discover causal relations between the variables and the outcome of interest, which is not the output of our findings even though there is high degree of association connectivity between the two. In addition, blood glucose values were not captured in the form of continuous variables; instead, we defined three periods during which the blood glucose and insulin usage were recorded (first 24 h, middle 24 h, and the last 24 h). However, since the median length of hospital stay was 3 days, we expect that the proposed time periods capture all necessary information regarding metabolic factors.

5 | CONCLUSIONS

This study is among the first few demonstrating a higher risk of 30-day readmission among patients with suboptimal in-hospital blood glucose measurements after a kidney transplant. Our findings highlight the need for further investigation of metabolic factors and their association with the risk of hospital readmission across other transplanted organs, as well as novel strategies to manage blood glucose measurements. We believe that medical care institutions would benefit from standardization of protocols that optimize the in-hospital blood glucose management in this patient population which may minimize the likelihood of 30-day readmission, reduce expenditures, and improve allograft and patient survival.

AUTHOR CONTRIBUTIONS

Agni Orfanoudaki conducted the analysis, contributed to the discussion, wrote, reviewed, and edited the manuscript. Janna Castro and Heidi E. Kosiorek collected the data. Harini A. Chakkera and Curtiss B. Cook led the data collection, contributed to the discussion and results interpretation, wrote, reviewed, and edited the manuscript. Soroush Saghafian reviewed and edited the manuscript. All authors approved the final version of the manuscript. Agni Orfanoudaki is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Preliminary data was submitted and accepted as a poster for the 2022 American Transplant Congress meeting.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Mayo Clinic. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of Mayo Clinic.

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