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Optimizing Tacrolimus Dosing During Hospitalization After Kidney Transplantation: A Comparative Model Analysis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The optimization of tacrolimus dosing during the early postoperative hospitalization period is essential to prevent rejection, minimize nephrotoxicity, and minimize the risk of opportunistic infections. Patient pharmacokinetic variability poses challenges in dose adjustment. This study aimed to evaluate tacrolimus dosing optimization using machine learning and statistical methods.

Material/Methods: We conducted a retrospective study of 749 kidney transplant recipients at Seoul St. Mary's Hospital between January 2015 and December 2019. Data on tacrolimus doses, trough levels, and other clinical variables were collected and analyzed during the first 12 postoperative days of hospitalization. Three approaches were evaluated: Extreme Gradient Boosting (XGBoost), Elastic Net regression (EN), and Linear regression (LR). The models were trained and validated using 5-fold cross-validation, with performance assessed using R^2 errors and alignment with clinically acceptable error margins.

Results: Elastic Net showed the best performance with R^2 (Coefficient of Determination) of 0.861±0.044 and RMSE (Root Mean Square Error) of 0.930±0.220. Linear Regression and XGBoost provided clinically relevant predictions but with slightly lower accuracy. External validation was not performed, limiting the generalizability of the results.

Conclusions: The Elastic Net is a practical and reliable model for predicting the optimal tacrolimus dose. Machine learning and statistical methods are useful tools for optimizing tacrolimus dosing during hospitalization after kidney transplantation. Future studies should incorporate multi-center validation to improve clinical applicability.

Keywords: Transplantation • Tacrolimus

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Introduction

Tacrolimus is one of the most important immunosuppressive agents used in renal transplantation, essential for maintaining appropriate trough levels to optimize transplant outcomes [1,2]. Unlike other immunosuppressive agents such as steroids and mycophenolic acid, tacrolimus requires careful management to balance trough levels; very high levels can lead to graft injury due to calcineurin inhibitor (CNI) toxicity and can increase the risk of opportunistic infections, including those from the BK virus and cytomegalovirus (CMV). High trough levels are associated with increased risks of hypertension, diabetes, hyperlipidemia, and cardiovascular complications [3]. Conversely, trough levels that are too low can lead to graft rejection, highlighting the challenge of maintaining a therapeutic range that is both narrow and variable among individuals [4]. Managing tacrolimus levels after transplantation is critical yet challenging owing to its narrow therapeutic window and significant interpatient variability. This variability is influenced by factors such as CYP3A4 and CYP3A5 enzyme activities, patient demographics, and clinical characteristics [5-9]. The initial tacrolimus dose is typically based on the patient's body weight, followed by adjustments guided by the ongoing monitoring of trough levels. Research indicates that maintaining an optimal tacrolimus trough level early after transplantation is vital for a favorable prognosis [10]. Maintaining optimal tacrolimus levels during the initial hospitalization period is critical for minimizing rejection risk and improving transplant outcomes. Machine learning, a branch of artificial intelligence developed in the fields of pattern recognition and computational learning theory, is increasingly being applied in various medical fields. These algorithms are designed to develop models that learn from and make predictions based on empirical data, thereby enhancing decision making processes beyond the capabilities of static program instructions [11]. Artificial intelligence is being studied in various medical fields [12-15], but its clinical application is still limited. Machine learning has been widely explored in kidney transplantation, particularly for predicting graft survival, delayed graft function, and the use of immunosuppressive agents [16-18]. However, its application in real-time tacrolimus dose optimization during hospitalization remains underexplored. Our study employed machine learning and advanced statistical methods to retrospectively analyze tacrolimus dosing, drug concentrations, and clinical characteristics of patients who underwent kidney transplant during their hospital stay. This study aimed to develop and validate predictive models, including XGBoost, elastic net regression (EN), and linear regression (LR), to provide daily tacrolimus dose recommendations. These models were designed to enhance decision making and maintain consistent dosing during the critical early postoperative period. This study aimed to develop a predictive model using machine learning and statistical methods to determine the most appropriate tacrolimus dose to maintain optimal trough levels at the time of patient discharge.

Material and Methods

Dosing and Timing Standardization

Tacrolimus trough levels were consistently measured at 8 AM daily to ensure comparability during hospitalization after kidney transplantation. Tacrolimus doses were decided daily, and the subsequent dose was adjusted accordingly to maintain optimal trough levels, considering discharge timelines and consistency during hospitalization. A 12-day period was selected to ensure data consistency while accounting for typical discharge schedules in the hospital setting.

Data and Preprocessing

This retrospective study evaluated 749 kidney transplant recipients from Seoul St. Mary's Hospital in South Korea between January 1, 2015, and December 12, 2019. After initial data cleaning, which involved excluding missing values, the effective sample size was reduced to 747 patients. We then focused on analyzing the daily tacrolimus dose and trough levels for 12 days after surgery, along with other clinical variables.

Feature Selection

The dataset included demographic data (age and sex), clinical variables (blood type, ABO incompatibility, height, weight, and BMI), medical histories (hypertension, diabetes, and coronary artery disease), and treatment specifics (induction agent, number of mismatches, use of rituximab before surgery, graft weight, and transplant type). Outliers, such as daily administered drug doses and tacrolimus trough levels, were included in the analysis owing to their clinical relevance despite their statistical deviation [19] (**Figures 1, 2**). A comprehensive feature selection process that included both univariate statistics and model-based techniques was used. Feature selection utilized univariate statistics and model-based feature selection techniques to filter meaningful predictors. Pearson's correlation coefficient and mutual information techniques were employed to capture both linear and non-linear relationships between the variables to ensure a robust selection process [20]. Features with a *P value* <0.05 were prioritized and those identified as significant through mutual information analysis were included (**Tables 1, 2**). Additionally, when choosing variables, it is important to consider whether they are linearly correlated. Multi-collinearity was considered for this purpose, indicating that 1 or more variables were linearly correlated with 1 variable. Multi-collinearity among the explanatory variables in a linear regression model can adversely affect a model's performance.

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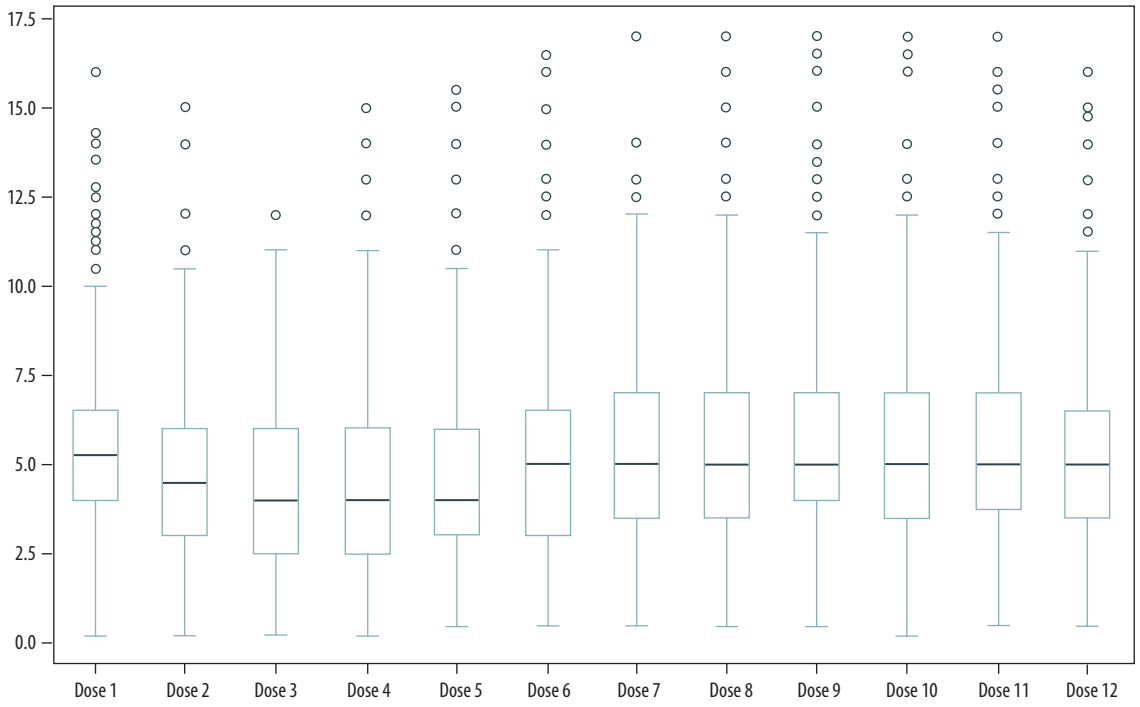

Figure 1. Distribution of tacrolimus doses over hospitalization days. *Figures were created using Pandas, version 1.5.3 (Python Software Foundation).*

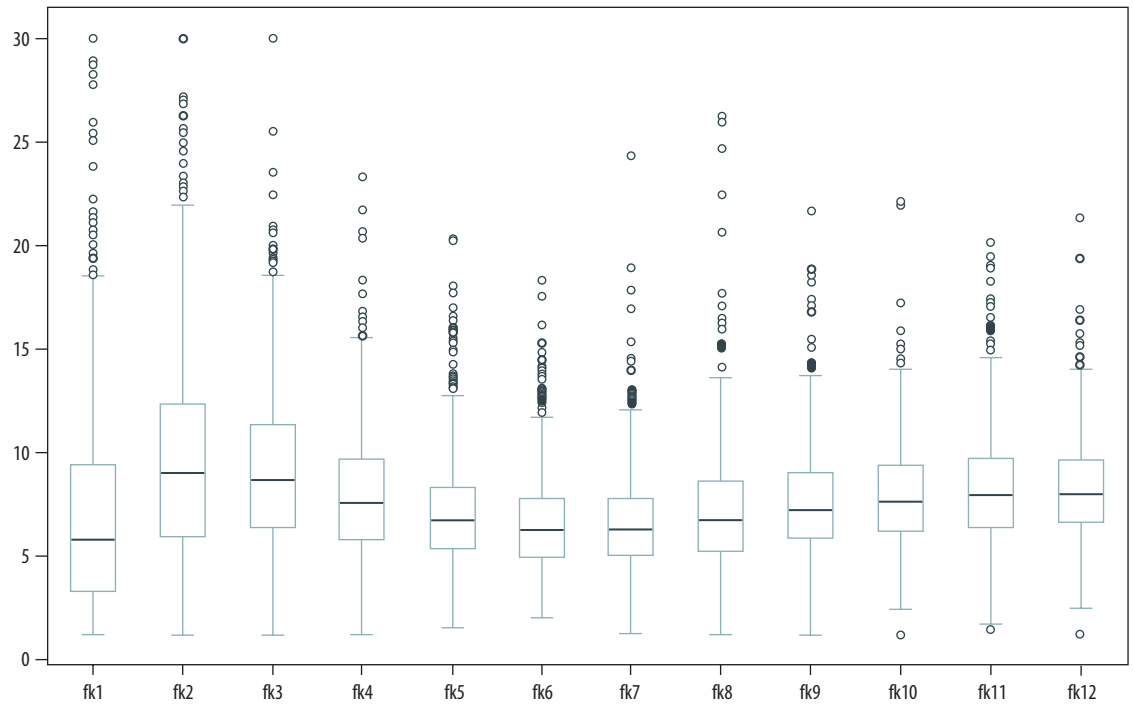

Figure 2. Distribution of tacrolimus trough level over hospitalization days. *Figures were created using Pandas, version 1.5.3 (Python Software Foundation).*

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Table 1. Mutual information Top 15 (tacrolimus dose).

Feature (variable)	Mutual information
Tacrolimus dose 10th day	1.191
Tacrolimus dose 9th day	0.713
Tacrolimus dose 8th day	0.498
Tacrolimus dose 7th day	0.363
Tacrolimus dose 5th day	0.253
Tacrolimus dose 6th day	0.252
Tacrolimus dose 4th day	0.163
Tacrolimus trough level 8th day	0.1
Tacrolimus dose 3rd day	0.094
Tacrolimus dose 1st day	0.079
Tacrolimus trough level 3rd day	0.079
Tacrolimus trough level 1st day	0.075
Tacrolimus dose 2nd day	0.066
Age	0.065
Tacrolimus trough level 5th day	0.061

Table 2. Mutual information Top 15 (tacrolimus trough level).

Feature (variable)	Mutual information
Tacrolimus trough level 10th day	0.234
Body mass index	0.086
Tacrolimus dose 7th day	0.079
Tacrolimus trough level 8th day	0.05
Tacrolimus trough level 9th day	0.049
Weight	0.043
Tacrolimus dose 10th day	0.042
Tacrolimus dose 9th day	0.039
Tacrolimus dose 8th day	0.038
Tacrolimus trough level 6th day	0.031
Tacrolimus trough level 5th day	0.03
Tacrolimus trough level 4th day	0.022
Hospitalization period	0.021
Tacrolimus trough level 1st day	0.02
Coronary artery disease	0.016

Therefore, it is important to select explanatory variables with multi-collinearity. This can be checked using a measure called the variance inflation factor (VIF), which generally indicates that explanatory variables are multicollinear when the VIF value is ≥5. In this study, variables with a VIF value >5 were removed from the explanatory variable group [21]. The results

Table 3. VIF for drug dose regression model.

Feature (variable)	VIF
Graft weight	1.032
Age	1.1
Tacrolimus trough level 8th day	1.106
Tacrolimus trough level 1st day	1.337
Tacrolimus dose 10th day	1.341
Tacrolimus dose 1st day	1.429
Height	1.695
Weight	1.794

VIF – variance inflation factor.

Table 4. VIF for tacrolimus trough level regression model.

Feature (variable)	VIF
Graft weight	1.011
Hospital day	1.024
Tacrolimus trough level 10th day	1.059
Body mass index	1.079
Age	1.108
Height	1.152
Tacrolimus trough level 8th day	1.179
Tacrolimus dose 2nd day	1.325
Tacrolimus dose 10th day	1.359

VIF – variance inflation factor.

of multi-collinearity tests for the explanatory variables selected for the regression model are presented in **Tables 3 and 4**. CYP3A5 genotyping data were not included because of unavailability. However, its known effects on tacrolimus metabolism suggest that future studies should include genetic profiling.

Model Implementation and Validation

The dataset was split into 75% training and 25% test sets prior to model training. Finally, the model was tested on the holdout 25% test set to assess generalization performance. Overfitting was mitigated using L1/L2 regularization (for the Elastic Net), tree pruning (for XGBoost), and hyperparameter searching using random and grid searches. The models used in the analysis were multivariate linear regression, elastic net, and extreme gradient boosting (XGBoost). Owing to the limitations inherent in medical data collection, a 5-fold cross-validation method was implemented to ensure the robustness and generalizability of the models [22,23]. The performance

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Table 5. Baseline characteristics of the study population.

Feature (variable)	Total (N=749)
Sex	
Male	433 (57.8)
Female	316 (42.2)
Age	48.65±11.48, Range 16-75
>55	489 (65.3)
55~64	217 (29.0)
≤65	43 (5.7)
BMI	22.79±3.41, Range 22.79-38.8
DM	
No	513 (68.5)
Yes	236 (31.5)
Hypertension	
No	68 (9.1)
Yes	681 (90.9)
Coronary artery disease	
No	709 (94.7)
Yes	40 (5.3)
ABOi	
No	593 (79.2)
Yes	156 (20.8)
Dialysis modality	
No	174 (23.2)
Hemodialysis	484 (64.6)
Peritoneal dialysis	91 (12.1)
Donation type	
Living related	359 (47.9)
Living unrelated	13 (1.7)
Spouse	192 (25.6)
Deceased	185 (24.7)
Transplantation	
1st	672 (89.7)
2nd	72 (9.6)
3rd	5 (0.7)
Induction agent	
Simulect	522 (69.7)
Antithymocyte globulin	227 (30.3)
Rituximab	
No	461 (61.5)
Yes	288 (38.5)
Plasmapheresis	
No	553 (73.8)
Yes	196 (26.2)
Kidney weight (g)	187.18±41.94, Range 104-430
BUN (mg/dl)	20.17±12.54, Range 4.3-104.2
Creatinine (mg/dl)	1.31±1.37, Range 0.37-15.40
Admission duration (day)	16.80±7.04, Range 11-119
Tacrolimus trough level 11th day (ng/ml)	8.26±2.64, Range 1.40-20.10
Tacrolimus dose 11th day (Tablet)	5.47±2.62, Range 0.5-17.0
Tacrolimus trough level 12th day (ng/ml)	8.23±2.51, Range 1.20-21.30

Values are presented as number (%). DM – diabetes mellitus; BMI – body mass index; ABOi – ABO-incompatible; BUN – blood urea nitrogen.

metrics were primarily assessed using the mean absolute error (MAE) with additional metrics such as R^2, adjusted R^2, and root mean square error (RMSE), which were used to evaluate the overall effectiveness of the models. We also measured the underestimation and overestimation rates to gauge the accuracy of our predictions relative to the clinically acceptable error range of ±2 around the target tacrolimus trough level of 8, which was expressed as 75-125%.

Statistical Analyses

SPSS for Windows (ver. 24.0; SPSS, Inc., Chicago, IL, USA) and Python (version 3.90) were used for the statistical analyses. *P* value <0.05 was regarded as statistically significant.

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Table 6. Feature importance score (tacrolimus trough level) for each machine learning model.

Feature (variable)	Feature importance score (XGBoost)	Feature importance Score (LR)	Feature importance Score (EN)
Tacrolimus trough level 10th day	0.269	1.344	1.317
Tacrolimus dose 10th day	0.120	0.476	0.425
Graft weight	0.089	0.201	0.156
Tacrolimus trough level 9th day	0.126	0.072	0.0
Period from surgery to discharge	0.091	0.011	0.0
Body mass index	0.092	-0.05	0.0
Tacrolimus trough level 8th day	0.108	-0.125	-0.06
Tacrolimus trough level 7th day	0.105	-0.148	-0.126

XGBoost – extreme gradient boosting; LR – linear regression; EN – elastic net.

Table 7. Feature importance score (tacrolimus dose) for each machine learning model.

Feature (variable)	Feature importance Score (XGBoost)	Feature importance Score (LR)	Feature importance Score (EN)
Tacrolimus dose10th day	0.687	2.208	2.167
Tacrolimus dose 4th day	0.079	0.165	0.173
Tacrolimus dose 1st day	0.039	0.061	0.042
Tacrolimus trough level 8th day	0.049	0.049	0.005
Tacrolimus trough level 1st day	0.019	0.006	0.0
Age at transplantation	0.023	0.004	0.0
Height	0.027	0.001	0.0
Graft weight	0.029	-0.055	-0.032
Tacrolimus trough level 10th day	0.049	-0.242	-0.212

XGBoost – extreme gradient boosting; LR – linear regression; EN – elastic net.

Ethical Compliance

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul St. Mary's Hospital. This ensured that all research was conducted under stringent ethical standards, safeguarding the participant data and welfare throughout the study.

Results

We conducted a comprehensive evaluation of regression models to predict the optimal tacrolimus dose after kidney transplantation, focusing on key performance metrics to determine the effectiveness of each model. **Figures 1 and 2** illustrate the variability in tacrolimus doses and trough levels during the 12-day hospitalization period, highlighting the challenges of individualized dosing and the maintenance of therapeutic levels in post-transplant care. In **Table 5**, baseline characteristics of the study population outline the demographic and clinical variables, including sex, age, BMI, and comorbidities, which are crucial for understanding the diversity within the study population and interpreting the variability in tacrolimus pharmacokinetics and response. The results of feature importance analyses are presented in **Tables 6 and 7**, showing that the tacrolimus trough level on the 10th day is the most influential attribute for predicting the tacrolimus level on the next day in the 3 machine learning models. **Tables 8 and 9** provide details of performance metrics such as R^2 (coefficient of determination), MAE, and RMSE, which are provided for the XGBoost, Linear regression, and Elastic Net models, presenting a granular analysis of each model's performance across multiple

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Table 8. Tacrolimus dose prediction performance metrics.

Model	Split	R^2	MAE	MAPE	MSE	RMSE
XGBoost	0	0.857	0.727	0.2	1.12	1.058
	1	0.856	0.657	0.186	0.88	0.938
	2	0.905	0.543	0.124	0.515	0.718
	3	0.842	0.634	0.14	0.729	0.854
	4	0.802	0.729	0.148	1.528	1.236
Average (Split=5) (mean±SD)		0.852±0.037	0.658±0.077	0.160±0.032	0.954±0.389	0.961±0.198
Linear regression	0	0.869	0.706	0.186	1.028	1.014
	1	0.862	0.606	0.143	0.842	0.917
	2	0.922	0.472	0.107	0.425	0.652
	3	0.848	0.597	0.131	0.704	0.839
	4	0.8	0.726	0.152	1.54	1.241
Average (Split=5) (mean±SD)		0.860±0.044	0.621±0.102	0.144±0.029	0.908±0.416	0.933±0.218
Elastic net regression	0	0.869	0.702	0.186	1.025	1.012
	1	0.863	0.607	0.138	0.837	0.915
	2	0.923	0.473	0.107	0.416	0.645
	3	0.849	0.595	0.131	0.698	0.835
	4	0.8	0.731	0.151	1.539	1.241
Average (Split=5) (mean±SD)		0.861±0.044	0.622±0.102	0.143±0.029	0.903±0.419	0.930±0.220

R^2 – coefficient of determination; MAE – mean absolute error; MAPE – mean absolute percentage error; MSE – mean squared error; RMSE – root mean square error.

cross-validation splits, showing the consistency and reliability of the models under various conditions. **Table 8** shows the tacrolimus dose prediction performance metrics. Elastic Net regression achieved the best results, with an R^2 (mean±SD) of 0.861±0.044, an MAE (mean±SD) of 0.622±0.102, and the lowest MSE (0.903±0.419). These findings demonstrate the robustness of the Elastic Net in handling pharmacokinetic variability and delivering accurate predictions. **Table 9** outlines the tacrolimus trough level predictions. Elastic Net regression again outperformed other models, with an average R^2 (mean±SD) of 0.278±0.122 and the lowest MSE (mean±SD=5.062±1.592). Although XGBoost performed well, particularly for non-linear relationships, its slightly higher error metrics show that Elastic Net has superior reliability and is the preferred model. Elastic Net regression consistently achieved the highest accuracy and reliability across multiple performance metrics for tacrolimus dose and trough level prediction.

Discussion

Prediction of tacrolimus doses are critical in postoperative management during the post-kidney transplantation hospitalization period, when maintaining a therapeutic window is crucial. Elastic Net regression consistently outperformed the other models across both tacrolimus dose and trough level predictions. Linear Regression and XGBoost provided clinically relevant predictions but with slightly lower accuracy. Its ability to handle multi-collinearity and integrate feature selection ensures interpretable prediction. However, the slightly higher error metrics in XGBoost indicate limitations in clinical applicability compared to Elastic Net. The tendency of the XGBoost model to overestimate, while providing an opportunity for proactive dose adjustment, calls for careful calibration and monitoring to optimize its utility in clinical settings without compromising patient safety [24]. However, this does not imply that the Elastic Net regression model is applicable. Therefore, it is important to develop appropriate models for further research. Our study confirmed that a tacrolimus dose prediction model can be applied through statistical models and machine learning. This methodological innovation addresses a crucial gap in existing methodologies and broadens the scope of data analytics in clinical settings [25-27]. The use of both Pearson correlation coefficients and mutual information analysis proved pivotal, offering a robust approach for feature selection that captures the complexities often missed by

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Table 9. Tacrolimus trough level prediction performance metrics.

Model	Split	R^2	MAE	MAPE	MSE	RMSE
XGBoost	0	0.136	1.659	0.199	6.593	2.568
	1	0.371	1.622	0.222	4.326	2.08
	2	0.237	1.382	0.176	3.575	1.891
	3	0.267	1.789	0.251	4.93	2.22
	4	0.309	1.786	0.215	6.142	2.478
Average (Split=5) (mean±SD)		0.264±0.087	1.648±0.166	0.213±0.028	5.113±1.252	2.247±0.279
Linear regression	0	0.058	1.706	0.198	7.187	2.681
	1	0.379	1.621	0.224	4.269	2.066
	2	0.27	1.377	0.174	3.417	1.849
	3	0.367	1.601	0.227	4.257	2.063
	4	0.276	1.808	0.215	6.431	2.536
Average (Split=5) (mean±SD)		0.270±0.129	1.623±0.160	0.208±0.022	5.112±1.610	2.239±0.352
Elastic net regression	0	0.082	1.676	0.194	6.998	2.645
	1	0.387	1.61	0.223	4.213	2.053
	2	0.281	1.368	0.174	3.367	1.835
	3	0.372	1.604	0.228	4.222	2.055
	4	0.267	1.822	0.217	6.508	2.551
Average (Split=5) (mean±SD)		0.278±0.122	1.616±0.164	0.207±0.023	5.062±1.592	2.228±0.351

R^2 – coefficient of determination; MAE – mean absolute error; MAPE – mean absolute percentage error; MSE – mean squared error; RMSE – root mean square error.

conventional statistical methods [28,29]. Our study highlights the effectiveness of interpretable models such as Elastic Net and XGBoost for tacrolimus dosing. Compared to a previous study [18], which focused on stable dose prediction, our study focused on optimizing tacrolimus dosing during hospitalization after transplantation. Our approach balances accuracy with clinical practicality, making it easier to implement while maintaining a strong predictive performance in real-world settings. Our study has some limitations. It was conducted at a single institution and external validation was not performed. While internal validation using 5-fold cross-validation provided robust performance metrics, external validation with independent datasets was necessary to confirm the generalizability of the model. Future studies should focus on multi-center external validation to enhance clinical applicability and validate these models using large-scale datasets or multi-center studies to ensure reliability and applicability [30,31]. Additionally, CYP3A5 genotyping is known to significantly influence tacrolimus metabolism. Therefore, it was not included in this study because it is not routinely performed in clinical practice. This limitation may affect the accuracy of the model. Future studies should incorporate genetic profiling to improve personalized dose prediction.

Conclusions

Elastic Net regression demonstrated superior performance in tacrolimus dose prediction, offering a reliable and interpretable solution for managing pharmacokinetic variability in hospitalized patients post-kidney transplant. Future studies should aim to validate these findings across diverse populations and explore the application of Elastic Net in real-time clinical decision making. However, similar performance metrics across the models highlight the need to carefully consider model interpretability and clinical utility in practical applications. Future studies should perform external validation using multi-center datasets to confirm the generalizability of our model. Finally, further research is required to validate these findings and explore their integration into real-time clinical decision support systems.

Declaration of Figures' Authenticity

All submitted figures have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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