

Optimizing Mycophenolate Therapy in Renal Transplant Patients Using Machine Learning and Population Pharmacokinetic Modeling



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Introduction

Mycophenolic acid (MPA) is a key immunosuppressant for renal transplant patients, typically used with calcineurin inhibitors and prednisone. It's administered as mycophenolate mofetil (MMF), an ester prodrug of MPA that fully hydrolyzes to MPA, or as enteric-coated mycophenolate sodium (EC-MPS). Its use requires careful individualization due to pharmacokinetic variability. Low MPA levels increase graft rejection risk, while high levels increase toxicity, such as gastrointestinal and hematological issues[1][2]. Population pharmacokinetics (PopPK) optimizes MPA therapy by identifying patient-specific factors for exposure-based dosing adjustments. However, traditional PopPK faces challenges like relying on simplistic models and struggling with individual variability, leading to difficulties in real-time predictions. Machine learning (ML) can improve predictive accuracy and reveal complex relationships between drug concentrations and clinical factors [3]. Integrating PopPK insights with ML will support a personalized MPA dosing strategy, reducing rejection and toxicity risks and enhancing transplant outcomes.

Objective

This study aimed to:

- Develop and validate two popPK models for MPA (EC-MPS and MMF) in renal transplant patients.
- Apply ML techniques to identify and quantify predictive factors for MPA levels while uncovering potential correlations between MPA levels and clinical and biochemical parameters.
 - Examine the relationship between plasma and saliva MPA concentrations.

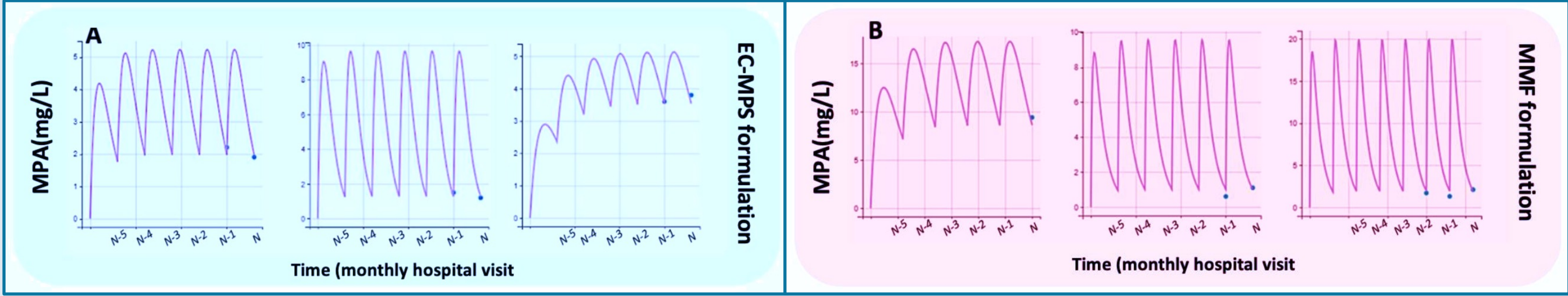
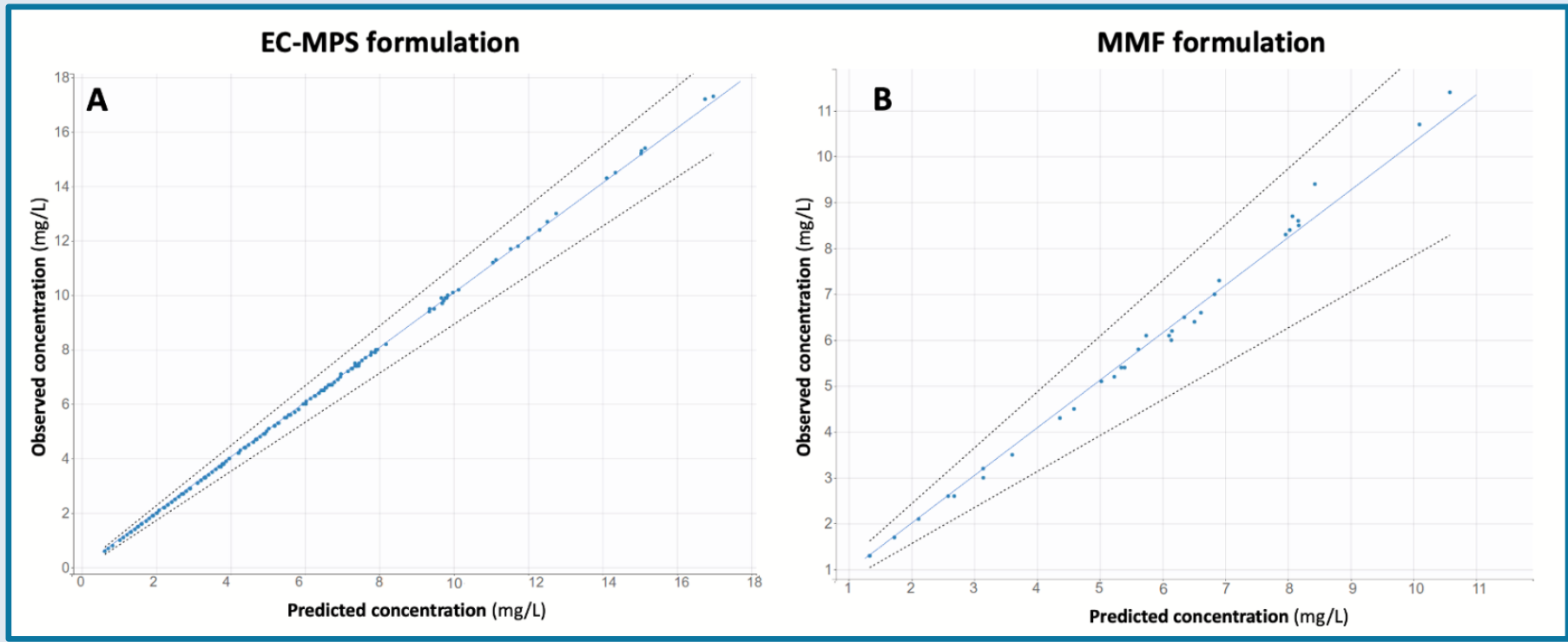


Figure 2. Individual fittings to the experimental concentration-time data of the MPA plasma model from EC-MPS formulation (A) and MMF formulation (B)

Individual models of PK parameters in the EC-MPS model

$$\text{Log}(Cl_i) = \log(9.3) + 0.33 * \log\left(\frac{\text{Diff}_{in\text{months}}}{21}\right) + 1.27 * \log\left(\frac{TDD}{1500}\right) + n_{IDCl_i} + n_{IOVCl_{ij}}$$



$$\text{Log}(k_{ai}) = \log(0.23) + n_{IDk_{ai}} + n_{IOV_{k_{ai}j}}$$

$$\text{Log}(V_i) = \log(196.43) + n_{IDV_i} + n_{IOV_{V_{ij}}}$$

Figure 1. Individual predicted versus observed concentration data for the final population pharmacokinetic models of the two MPA formulations: (A) EC-MPS formulation and (B) MMF formulation.

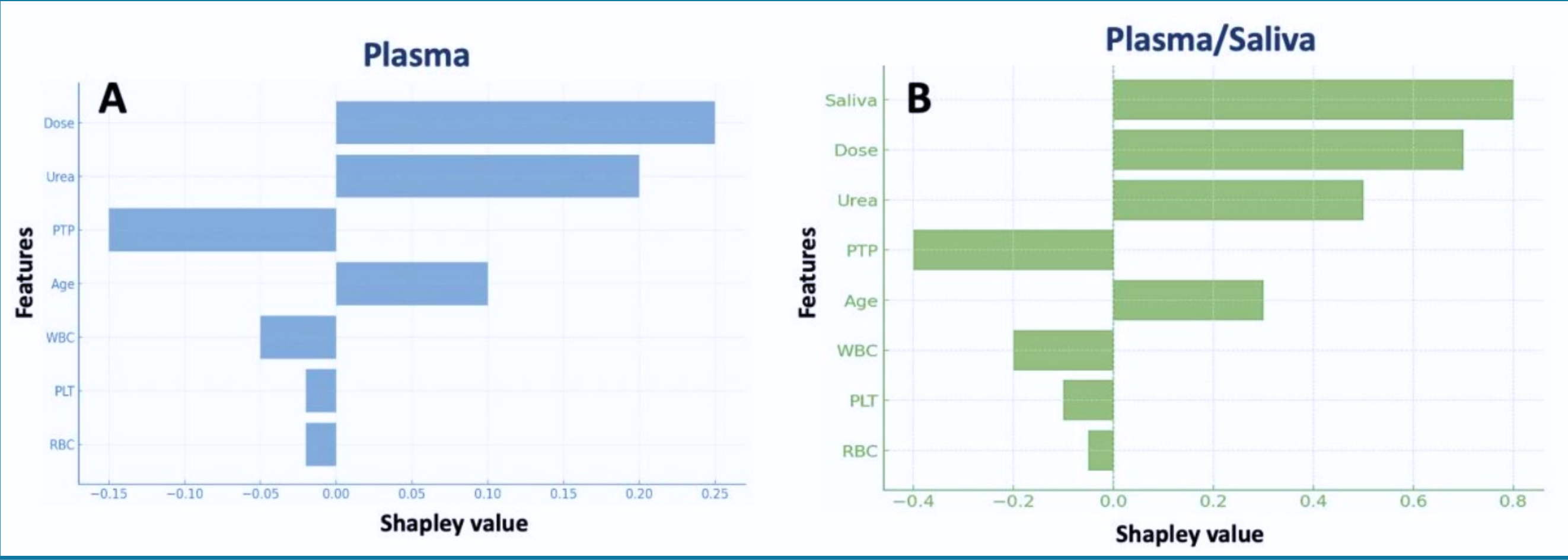


Figure 3. Shapley summary plots for the boosted trees regression analysis showing the contribution of each feature to the plasma MPA levels, without (panel A) and with (panel B) saliva MPA data.

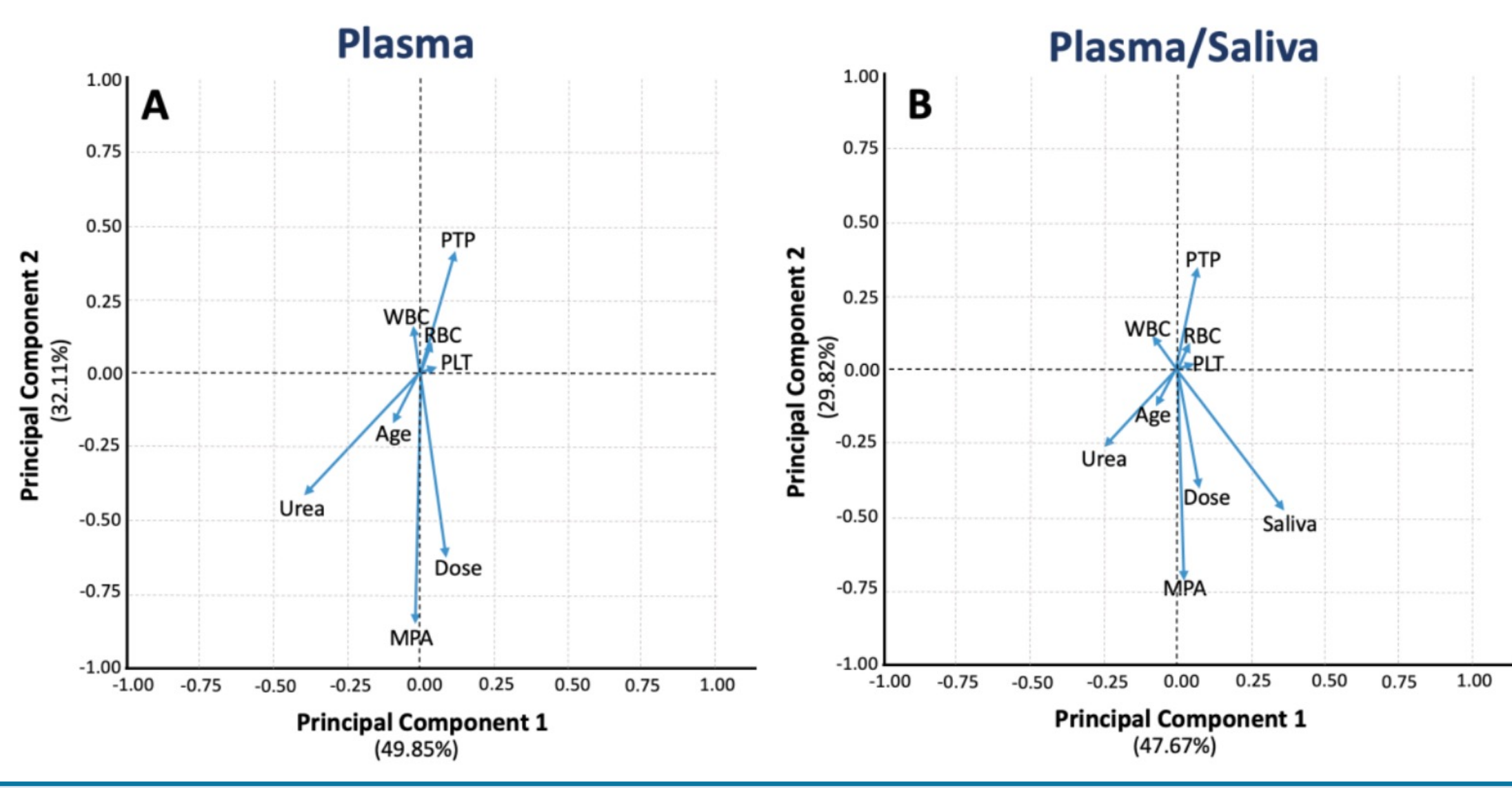


Figure 4. Principal component analysis showing the loading plots without (panel A) and with (panel B) saliva data. The features shown refer to MPA levels, Age, Dose, Urea, PTP, RBC, PLT, and WBC vectors.

Methods

The study involved **80 renal transplant patients** on EC-MPS/MMF therapy, measuring MPA levels monthly in plasma and saliva, with one trough level per check-up after achieving a steady state. Collected data included demographics, time post-transplantation (PTP), renal function (urea, creatinine), and haematological parameters (WBC, RBC, PLT). A PopPK analysis using nonlinear mixed-effects modelling in Monolix™ 2023R1 developed two models based on plasma MPA concentrations:

- Model 1, using the EC-MPS formulation
- Model 2, using the MMF formulation.

Model validation included statistical and graphical methods, considering inter-, intra-individual, and inter-occasion variability for model selection.

The ML techniques used were **Principal Component Analysis (PCA)** and **ensemble methods (bagged and boosted Trees)**.

- PCA** was applied to visualize relationships among MPA dose, urea, PTP, MPA saliva levels, age, haematological parameters, and plasma MPA concentrations, identifying factors correlated with plasma MPA levels through loading vectors and clustering patterns.
- Ensemble learning** enhances prediction accuracy by employing multiple decision trees. Bagged trees train several decision trees on random subsamples of the dataset, thereby reducing variance and improving stability. They can also estimate feature importance based on tree splits. Boosted trees iteratively construct trees, rectifying errors to enhance accuracy and capturing nonlinear interactions[3].
- The **predictive performance** of these models was evaluated using **regression analysis**. For each method, two models were created: one with saliva levels and one without. The ML methods codes were written in Python v.3.10.8 using the libraries "sklearn", "XGBoost", "CatBoost", "MLxtend", "matplotlib", and "seaborn", etc.

Results

ML analysis validated the findings and provided insights into individualized treatment.

- Both PopPK models featured a **one-compartment structure with first-order absorption and elimination kinetics**.
- Total daily dose and PTP** were significant covariates affecting clearance.
- The models showed low relative standard error and minimal inter-individual variability, confirming their robustness; **goodness of fit plots highlighted their predictive ability** (Fig.1,2).

- Boosted and bagged trees analyses identified **MPA (or MMF) dose** as the main predictor, affirming its strong influence on MPA levels (Fig.3).
- Urea and PTP** were also important predictors, with **age** showing moderate effect.
- Incorporating **saliva** concentration data improved predictive performance, with **saliva** emerging as the most influential variable, followed by dose, urea, and PTP.
- Regression analysis yielded a coefficient of determination, R² value of more than 0.91, indicating strong predictive accuracy of the ensemble trees models.

PCA confirmed these results, indicating **dose** as the primary determinant of MPA levels (Fig.4).

- Urea** had a positive relationship with **MPA concentration** and an **inverse** relationship with **PTP**, WBC, RBC, and PLT, which clustered together, indicating a shared influence.
- Age** was positioned between **urea** and **PTP**, showing a moderate but distinct impact.
- With saliva concentrations included, correlation patterns shifted slightly: **MPA (plasma) remained closely tied to dose and urea**, while **saliva displayed a new but weaker correlation with MPA levels**.

Conclusion

This study integrated traditional popPK modeling with ML techniques to understand MPA pharmacokinetics better and enhance pharmacotherapy in transplant patients.

- It confirmed that **MPA dose** primarily influences MPA levels, as evidenced by bagged trees and PCA analyses, aligning with the pharmacokinetic principle of dose-dependent MPA exposure [3].
- Urea** and **post-transplant time** affected MPA variability, emphasizing the significance of patient-specific factors in immunosuppressive therapy [4].
- The relationship of **urea** with **MPA levels** suggests altered metabolism or clearance in renal impairment cases [2].
- The inverse relationship observed between **PTP** and **MPA** levels, along with urea, aligns with decreasing MPA levels over time after transplantation and stabilization of renal function.
- Age** moderately impacts drug levels, influenced by renal function and dosing [1].
- The moderate correlation between saliva and plasma concentrations indicates that **saliva** monitoring alone may be inadequate for MPA dosing adjustments, although saliva levels remain significant predictors of plasma levels, suggesting a complementary monitoring role.

The developed models offer a practical method to personalize MPA dosing, ensuring accurate immunosuppressive treatment for kidney transplant patients [3][4].

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