

Advances in the Application of Machine Learning for Tacrolimus Dosage Prediction

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Abstract

Objective Tacrolimus is an essential immunosuppressive agent widely applied for organ transplantation and autoimmune disease treatment. Nonetheless, its narrow therapeutic window and prominent interindividual variability in pharmacokinetics bring substantial difficulties to clinical individualized precision dosing. This review summarizes recent advances in machine learning (ML)-assisted tacrolimus individualized dose prediction, so as to provide evidence for clinical medication practice. **Methods** Systematic literature retrieval was conducted in four authoritative English databases including PubMed, Web of Science, Scopus and Embase, as well as three mainstream Chinese databases: China National Knowledge Infrastructure (CNKI), Wanfang Database and VIP Database. Original researches developing machine learning-based tacrolimus dose prediction models were enrolled. Relevant data were extracted, including endpoint parameters, follow-up duration, sample size, variable selection approaches, predictor variables and model evaluation metrics. **Results** Ten eligible articles were finally included after screening against predefined inclusion and exclusion criteria, covering liver transplantation, kidney transplantation, autoimmune diseases, heart and lung transplantation. Most included studies were single-center retrospective analyses. Popular machine learning algorithms adopted for initial or maintenance dose prediction consisted of Random Forest (RF), Extreme Gradient Boosting (XGBoost) and Long Short-Term Memory (LSTM). In pediatric liver transplant cohorts, Extremely Randomized Trees (ET) achieved the lowest median Absolute Percentage Error (APE) of 2.04 ng for initial dose prediction. For adult liver transplant recipients, LSTM yielded the minimal median Mean Percentage Error (MPE) of 8.8% in maintenance dose forecasting, which was statistically superior to Linear Regression (LR) and Population Pharmacokinetics (PPK) models. In kidney transplantation, RF obtained a coefficient of determination (R^2) of 0.95 for initial dose prediction, and Extra-Trees Regressor (ETR) attained an overall dose target achievement rate of 97.73% among perioperative renal transplant patients. Among autoimmune disease populations, XGBoost presented optimal performance: the R^2 for adult maintenance dose prediction was 0.54, with a predictive accuracy of 74.4% within the $\pm 30\%$ deviation range of actual doses. After integrating PPK-derived covariates, the hybrid XGBoost model improved the R^2 up to 0.74 for initial dose prediction in children with systemic lupus erythematosus. For combined liver, renal and cardiac transplant patients, XGBoost reached an R^2 of 0.941 in initial dose estimation, outperforming conventional Maximum. **Conclusion** Machine learning algorithms exert significantly better predictive performance than conventional approaches for tacrolimus dose optimization. However, current models are hampered by multiple drawbacks, such as inherent bias from retrospective design, insufficient evidence

for special populations, inadequate calibration assessment, limited model interpretability and poor reproducibility.

Keywords

Tacrolimus, Machine Learning, Individualized Medication