Advances in Machine Learning-Based Prediction for Personalized Tacrolimus Therapy in Liver Transplant Recipients

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Abstract

Objective Tacrolimus is a cornerstone immunosuppressant following liver transplantation, characterized by a narrow therapeutic window and significant interindividual pharmacokinetic variability, which necessitates routine therapeutic drug monitoring. This study systematically reviews the application of machine learning algorithms in the personalized tacrolimus therapy for liver transplant patients, aiming to provide evidence-based guidance for the individualized clinical use of tacrolimus. *Methods* A systematic literature search was performed in 4 English databases (PubMed, Web of Science, Scopus, and Embase) and 3 Chinese databases (China National Knowledge Infrastructure, Wanfang Database, and *China Science and Technology Journal Database*) to identify studies on machine learning approaches in tacrolimus therapy for liver transplant patients. Original research focusing on machine learning models for the individualized application of tacrolimus in this population was included. Data including sample characteristics, variable selection methods, included predictors, and model predictive performance were extracted from the eligible literature, and the advantages and limitations of existing models were systematically summarized. *Results* A total of 10 studies were included, comprising 2 in pediatric and 8 in adult liver transplantation populations. The majority employed single-center retrospective study designs, with sample sizes ranging from 32 to 443 participants. Stepwise regression was the most frequently used method for variable selection, and commonly included predictors comprised demographic characteristics, postoperative time, genetic polymorphism, and concomitant medication. Among machine learning algorithms, extreme gradient boosting (XGBoost), gradient boosting decision tree (GBDT), and random forest (RF) were the most widely applied. The XGBoost model demonstrated the optimal predictive performance, with coefficient of determination (R^2) ranging from 0.82 to 0.91 and root mean square error (RMSE) of 0.90 to 2.0 ng/mL, substantially outperforming traditional pharmacokinetic models. Time-series models, particularly long short-term memory (LSTM) networks, exhibited notable advantages in handling high-dimensional data and dynamic changes in tacrolimus concentrations, achieving goodness-of-fit values exceeding 0.89. Regarding model validation, internal cross-validation predominated in early studies, whereas external multicenter validation has been increasingly adopted in recent years. Most models achieved prediction accuracy exceeding 80% within ±20% of the measured drug concentration, confirming their generalizability. However, currently established machine learning models generally lack calibration performance evaluation and external validation, and face limitations including low interpretability and limited reproducibility. *Conclusion* Machine learning-based prediction models demonstrate favorable accuracy and potential clinical utility in guiding personalized tacrolimus therapy for liver transplant recipients. Nevertheless, current models are constrained by

inherent biases of retrospective studies, insufficient investigation on special populations, inadequate calibration assessment, limited interpretability, and poor reproducibility, warranting further investigation.

Keywords

Tacrolimus, Machine Learning, Individualized Medication