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Review

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Beyond Human Limits: Harnessing Artificial Intelligence to Optimize Immunosuppression in Kidney Transplantation

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Abstract

The field of kidney transplantation is being revolutionized by the integration of artificial intelligence (AI) and machine learning (ML) techniques. AI equips machines with human-like cognitive abilities, while ML enables computers to learn from data. Challenges in transplantation, such as organ allocation and prediction of allograft function or rejection, can be addressed through AI-powered algorithms. These algorithms can optimize immunosuppression protocols and improve patient care. This comprehensive literature review provides an overview of all the recent studies on the utilization of AI and ML techniques in the optimization of immunosuppression in kidney transplantation. By developing personalized and data-driven immunosuppression protocols, clinicians can make informed decisions and enhance patient care. However, there are limitations, such as data quality, small sample sizes, validation, computational complexity, and interpretability of ML models. Future research should validate and refine AI models for different populations and treatment durations. AI and ML have the potential to revolutionize kidney transplantation by optimizing immunosuppression and improving outcomes. AI-powered algorithms enable personalized and data-driven immunosuppression protocols, enhancing patient care and decision-making. Limitations include data quality, small sample sizes, validation, computational complexity, and interpretability of ML models. Further research is needed to validate and enhance AI models for different populations and longer-term dosing decisions.

Keywords: Artificial intelligence; Machine learning; Kidney transplant; Immunosuppression

Introduction

In the dynamic field of medicine, artificial intelligence (AI) has become a prominent topic of discussion, extending its influence on various disciplines, including transplantation. By equipping machines with cognitive abilities, AI has brought about a revolution in healthcare practices. AI involves the development of computer systems that possess human-like cognitive abilities such as reasoning, problem-solving, and learning. By creating software and systems that mimic human intelligence, AI enables machines to exhibit intelligent behavior. Machine learning (ML), a subset of AI, focuses on developing algorithms and models that allow computers to learn from data without explicit programming [1]. ML algorithms are trained on extensive datasets, enabling them to recognize patterns, make predictions, and continuously enhance their performance. Three broad categories shape the landscape of ML algorithms: supervised learning, unsupervised learning, and reinforcement learning. These categories facilitate the decoding of relationships between input variables and known outputs, the discovery of hidden patterns in unlabeled data, and the iterative refinement of prediction models, respectively.

In the context of solid organ transplantation, numerous challenges persist throughout the transplant process. Allocating organs to suitable recipients, considering factors such as patient demographics, comorbidities, genetics, and graft quality, remains a significant challenge due to the limited supply of donor organs. Additionally, the growing complexity of transplant candidates, including advanced age and associated risk factors, necessitates personalized treatment strategies that optimize immunosuppressive therapy while mitigating the risks of infections, malignancies, and medication-induced side effects [2]. The role of AI on kidney transplant has been extensively reviewed recently, with most of the discussion being on various aspects of AI in kidney transplantation, such as waitlist prioritization, donor-recipient matching, rejection prediction, and post-transplant outcomes [1, 3]. This review article aimed to specifically delve into the optimization of immunosuppression - an essential component of successful kidney transplantation.

Achieving the delicate balance between underimmunosuppression and overimmunosuppression is crucial in kidney transplantation, considering the risks of rejection, infections, and medication-related complications. By integrating AI-powered algorithms, personalized and data-driven immunosuppression protocols can be developed, enabling clinicians to make informed decisions and improve patient care.

Immunosuppression Optimization by AI

Clinicians face challenges in accurately dosing immunosup-

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pressive medications due to multiple drug interactions and narrow therapeutic windows. Predicting the response to therapy can be complicated, impacting graft survival, adverse events, and length of hospital stay. To address these challenges, researchers have employed ML modeling to improve the accuracy of tacrolimus dosing and other immunosuppressive drug dosing after renal transplant compared to clinicians' decisions. ML models provide a more precise approach to dosing immunosuppressive medications, aiding in personalized treatment for transplant patients.

Methods

We performed a comprehensive systematic review of articles focusing on the use of AI or ML on immunosuppression management in kidney transplantation within the last decade, limiting our search to English language publications. We conducted our search across two major electronic databases, PubMed MEDLINE and EMBASE, up to July 1, 2023. Employing a combination of relevant key terms and synonyms, including "kidney transplant", "artificial intelligence", "machine learning", and "immunosuppression", and aliases, we meticulously screened retrieved articles. This process began with the removal of duplicates, followed by independent abstract assessments by two authors. Discrepancies in article selection were resolved through consensus. Subsequently, selected articles underwent full-text examination to make the final inclusion decisions. Reference lists of included studies were also reviewed for relevant articles. In total, our systematic search identified nine studies meeting our criteria, where ML protocols were employed to adjust conventional immunosuppressive agents in kidney transplant patients. These studies are detailed further, categorized by the specific immunosuppressant under investigation.

Tacrolimus

In a prospective study with 80 kidney transplant patients at the Oslo University Hospital, Storset et al [4] investigated the use of computerized dosing of tacrolimus in *de novo* renal transplant recipients. They compared the effectiveness of computerized dosing with conventional dosing by experienced transplant physicians. The results demonstrated that computerized dose individualization significantly increased the proportion of tacrolimus concentrations within the target range as compared to conventional dosing. The time to achieve target levels was also shorter in high-risk patients. Additionally, computerized dosing showed benefits in terms of glucose metabolism and renal function.

One of the earliest studies in this context was probably by McMichael et al [5], who published a paper that presents an evaluation of an innovative dosing system aimed at optimizing FK 506 and prednisone, called the "intelligent" dosing system (IDS), which was developed to standardize patient management and improve patient care. The algorithm utilized stochastic open loop control theory to optimize drug dosing and has been shown to accurately predict plasma levels of FK 506. The IDS was designed to be simple and accurate, with an easy-to-use interface that required no previous computer experience. The system used a knowledge base containing facts and rules to determine the best course of action for dosing. The paper presented dosing examples and observed versus predicted plasma levels to demonstrate the effectiveness of the IDS. A prospective validation study demonstrated that the model achieved a 95% accuracy rate in describing the correlation between FK 506 dosage and FK 506 plasma level. Furthermore, the study found no biases in the dosing predictions. Importantly, the study also confirmed that the dosing predictions made by the model were unbiased, indicating that the model was reliable in providing accurate estimations. The authors conclude that the IDS is a simple and accurate automated drug dosing program that can improve patient outcomes.

Using a dataset from the Vienna General Hospital, Seeling et al [6] developed a knowledge-based system for guiding tacrolimus therapy in kidney transplant patients. The goal of the study was to identify adaptation rules for tacrolimus therapy based on a clinical dataset and integrate them into a clinical decision support system. The authors utilized patient data from 1995 to 2008 collected from the Department of Nephrology and Dialysis of the Vienna General Hospital. The dataset included patient demographics, laboratory parameters, time since kidney transplantation, and other immunosuppressive drugs administered. The researchers used a regression tree to create homogeneous groups of data and developed semi-automated models for these groups to predict the drug concentration for the next ward round. The models were used to create a knowledge base that was integrated into a clinical decision support system for tacrolimus therapy planning to guide nephrologists. The paper also highlights the importance of creating separate knowledge bases for each hospital due to differences in medication methods and views.

In a study with a large Chinese cohort of renal transplant recipients, Tang et al [7] compared the performance of multiple linear regression (MLR) and various ML techniques in predicting the stable dose of tacrolimus. A total of 1,045 renal transplant patients were included in the study, with 80% randomly selected as the derivation cohort and the remaining 20% as the validation cohort. ML models including artificial neural network (ANN), regression tree (RT), multivariate adaptive regression splines (MARS), boosted regression tree (BRT), support vector regression (SVR), random forest regression (RFR), lasso regression (LAR), and Bayesian additive regression trees (BART) were compared with MLR. Among the ML models, the RT model performed the best in both the derivation and validation cohorts, showing higher prediction accuracy compared to MLR. The RT model demonstrated a prediction accuracy of 0.71 in the derivation cohort and 0.73 in the validation cohort. The study highlights the potential of ML models, particularly the regression tree model, in predicting the stable dose of tacrolimus in renal transplant recipients.

Thishya et al [8] explored the use of ANN and logistic regression (LR) models to predict the bioavailability of tacrolimus and the risk for post-transplant diabetes in patients with renal transplantation. The study investigated the role of genetic polymorphisms in *ABCB1* and *CYP3A5* in predicting the bioavailability of tacrolimus. The ANN model, with five-fold cross-validation, demonstrated a good correlation with the ex-

perimental data of tacrolimus bioavailability. Factors such as younger age, male gender, and optimal body mass index were associated with lower bioavailability of tacrolimus. Genetic polymorphisms, specifically *ABCB1* 1236 C>T, 2677G>T/A, and *CYP3A53*, were found to be inversely or positively associated with the bioavailability of tacrolimus. Gender bias was observed in association with the *ABCB1* 3435 C>T polymorphism. Additionally, synergistic interactions between CYP3A53 and ABCB1 2677 G>T/A were identified as determinants of the risk for post-transplant diabetes. The LR model revealed an independent association of ABCB1 2677 G>T/A with post-transplant diabetes. The study employed multifactor dimensionality reduction analysis (MDR) to identify synergistic interactions between CYP3A5*3 and ABCB1 2677 G>T/A as important factors contributing to the risk of post-transplant diabetes. Overall, the ANN and MDR models utilized in this study provide insights into the individual and synergistic effects of variables in modulating the bioavailability of tacrolimus and the risk for post-transplant diabetes in patients with renal transplantation.

Cyclosporine

In their study, Camps-Valls et al [9] investigated the use of neural networks to personalize the dosage of cyclosporine A (CyA) in kidney transplant patients. They employed different types of neural networks, including multilayer perceptron (MLP), finite impulse response (FIR), and Elman recurrent networks. The researchers created a two-model scheme where the blood concentration predicted by the first model served as input for the dosage prediction model. They trained the models using data from 22 patients for training and tested them on data from 10 patients. The ensemble of FIR and Elman networks demonstrated the best performance, achieving an r value of 0.977 in the validation set. The authors highlighted that neural models are suitable for this task due to their accuracy, precision, and robustness.

In another study, Goren et al [10] discusses the use of the adaptive-network-based fuzzy inference system (ANFIS) to predict CyA blood levels in renal transplantation patients. The model was implemented using therapeutic drug monitoring (TDM) data collected from 138 patients, with 20 input parameters including concurrent use of drugs, blood levels, sampling time, age, gender, and dosing intervals The results of the study showed that the ANFIS model produced eight rules and exhibited a root mean square error (RMSE) of 0.045 with respect to the training data and an error of 0.057 with respect to the checking data in the MATLAB environment. This indicates that the ANFIS model was able to effectively predict CyA concentration in blood samples. The authors concluded that their model could effectively assist physicians in choosing the best therapeutic drug dose in the clinical setting.

Mycophenolic Acid (MPA)

Although initially marketed as a fixed-dose drug, mycophenolate mofetil (MMF) faces challenges due to its pharmacokinetic variability, which results in different processing and elimination rates among individuals. Another challenge is the weak relationship between the dose of MMF and the exposure of the body to its active form, MPA. A recent consensus of the international association of therapeutic drug monitoring and clinical toxicology [11], recommended MPA therapeutic drug monitoring by estimating the MPA area under the curve (AUC) to optimize treatment and improve patient outcomes. Woillard et al [12] developed a machine-learning model to accurately estimate the concentration of MMF in transplant patients. The models for estimating the concentration of MMF in patients who have received kidney or heart transplants were developed using extreme gradient boosting (Xgboost R package) ML models. The models were trained on a total of 12,877 MPA AUC from 0 to 12 h (AUC0 - 12 h) requests from 6,884 patients sent to the Immunosuppressant Bayesian Dose Adjustment expert system for AUC estimation and dose recommendation based on MPA concentrations measured at least at three sampling times (about 20 min, 1 and 3 h after dosing). The data were split into a training set (75%) and a test set (25%), and the Xgboost models in the training set with the lowest root mean squared error (RMSE) in a 10-fold cross-validation experiment was evaluated in the test set and in four independent full-pharmacokinetic (PK) datasets from renal or heart transplant recipients. The models were based on two or three concentrations, differences between these concentrations, relative deviations from theoretical times of sampling, presence of a delayed absorption peak, and five covariates (dose, type of transplantation, associated immunosuppressant, age, and time between transplantation and sampling). The authors showed that the model allowed for accurate estimation of the AUC of MPA over a 12-h period. These models can be utilized for routine exposure estimation and dose adjustment of MPA. Furthermore, the researchers plan to implement these ML models in a dedicated web interface for convenient use.

Tolerance

Operative tolerance, a state of long-term allograft acceptance without continuous immunosuppression, is an important tenet for the success of solid organ transplantation that can help minimize exposure of immunosuppressive treatments. In a recent study, Fu et al [13], investigated the identification of potential biomarkers for allograft tolerance in kidney transplantation using ML techniques. The study utilized three publicly available gene expression datasets from peripheral blood lymphocytes of 63 tolerant patients. The researchers compared 14 different ML models to predict spontaneous kidney graft tolerance, and the best subset selection (BSS) regression approach emerged as the most powerful model. It exhibited a sensitivity of 91.7% and a specificity of 93.8% in the test group, as well as a specificity of 86.1% and a sensitivity of 80% in the validation group. Using the BSS model, a feature set comprising five genes (*HLA-DOA*, *TCL1A*, *EBF1*, *CD79B*, and *PNOC*) was identified as predictive of allograft tolerance. Furthermore, the downregulation of *EBF1* was identified as an independ-

ent predictor of graft rejection and graft loss. By employing a two-gene signature (*EBF1* and *HLA-DOA*) as input to their classifier, the researchers achieved an AUC value of 84.4%.

Overall, this study highlights the potential of ML in uncovering gene sets that could influence tolerance to renal allografts. The identified genes, particularly *EBF1*, hold promise as novel biological targets and may guide patient selection for immunosuppressant withdrawal in clinical practice.

Advantages of AI-Powered Algorithms

AI and ML algorithms are promising new tools for improving immunosuppressive drug adjustments in kidney transplantation. AI-powered algorithms can consider individual patient characteristics, such as age, gender, weight, genetic polymorphisms, and concomitant medications, to develop personalized dosing regimens. This can help to optimize drug efficacy and minimize side effects. AI algorithms can also analyze large datasets of patient data to identify patterns and relationships that may be difficult to detect by human experts. This can lead to more accurate and efficient drug dosing. Additionally, AI algorithms can help to reduce the risk of human error in drug dosing, which is especially important for complex dosing regimens or for patients taking multiple medications. The integration of AL/ML techniques in the realm of kidney transplantation holds the promise of not only predicting immunosuppressive drug levels but also synergizing with existing quality improvement initiatives [14]. Finally, AI algorithms can be used to monitor patient drug levels and adjust dosing regimens in real-time.

Limitations

Limitations of most of the studies include data quality, small sample sizes, and inconsistency in the number of cases used for model training, which can affect generalization. Inconsistent data collection and classification may lead to the use of incorrect features and introduce bias. Prospective and external validation of AI models is lacking, and their improvement over traditional methods may be marginal in certain transplantation aspects. ML algorithms can be computationally complex and time-intensive. Interpretability of ML models is a challenge. Ensuring rigorous validation, considering computational resources, and assessing the nature of the data and clinical questions are important. Fairness evaluation and integration of non-clinical variables are necessary for equitable systems. None of the studies conducted so far have been validated on geographically distant cohorts, and they have primarily focused on acute tacrolimus dosing. It remains unclear whether these approaches would be beneficial for longer-term dosing decisions. Further research is needed to determine the effectiveness of these methods in different populations and for extended treatment durations.

Conclusions

In this comprehensive review, we have examined the studies that specifically investigate the use of AI-based algorithms to predict immunosuppressive drug levels (Table 1) [4, 5, 7-10, 12]. However, it is important to acknowledge that tailoring immunosuppression involves considering various factors beyond drug levels. Numerous studies have explored the application of ML techniques in optimizing donor-recipient matching, facilitating the identification and availability of potential donors, predicting allograft function and rejection, and assessing post-transplant survival outcomes. Incorporating all this valuable information will contribute to the personalized approach to immunosuppression in kidney transplant patients. By leveraging AI, we can enhance outcomes, provide more accurate personalized care, and shape the future of kidney transplantation. Further advancements and integration of AI technology are necessary to realize its full potential in optimizing immunosuppression strategies for kidney transplant patients.

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Conflict of Interest

The author has no conflict of interest to declare.

Author Contributions

Both authors actively contributed to the selection, reviewing, interpreting the studies, and preparing the manuscript, engaging in writing, and revising the article before its submission.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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Table 1. Description of the AI Models Used in the Reviewed Studies

Model (referenced to the studies where used)	Description	Advantages	Disadvantages
Artificial neural network (ANN) [7, 8]	A computer model that mimics the structure and function of the human brain. ANNs are made up of interconnected nodes, called neurons, that process information in a similar way to biological neurons. ANNs can be used to solve a wide variety of problems, including classification, regression, and forecasting.	Can learn complex relationships between variables	Computationally expensive to train
		Handles large amounts of data	Difficult to interpret
		Can be used to make predictions without a priori knowledge of the problem domain	Prone to overfitting
Computerized dosing (BestDose Sofware) [4]	A software program that uses AI to calculate and recommend the optimal dose of medication for a patient. BestDose Software takes into account the patient's individual characteristics, such as age, weight, kidney function, and other medications they are taking, to calculate a safe and effective dose.	Personalized dosing recommendations	Dependence on accurate input data
		Reduces medication errors	May not account for rare or unusual cases
		Considers multiple patient factors	Initial setup and integration can be time-consuming
Intelligent dosing system (IDS) [5]	Broader term for a system that uses AI to calculate and recommend medication doses. IDS can include computerized dosing software, as well as other systems that use AI to make decisions about patient care.	Offers a holistic approach to dosing decisions	Can be expensive to implement and maintain
		Can incorporate various AI models and data sources	May require specialized training to use
			May not be suitable for all patients
Regression tree (RT) [7]	A type of decision tree that is used to predict a continuous value, such as the price of a house or the number of customers who will visit a store on a given day. RTs work by splitting the data into subsets based on the values of the input variables, and then predicting the output value for each subset.	Simple and interpretable	Prone to overfitting with deep trees
		Handles non-linear relationships	Less accurate than some complex models for certain tasks
		Can be used for both regression and classification	Limited modeling power for highly complex data
Multivariate adaptive regression splines (MARS) [7]	A type of non-linear regression model that can be used to model complex relationships between variables. MARS works by combining a set of linear splines to create a more flexible model.	Flexibility in capturing complex relationships	May require larger datasets for accurate modeling
		Automatic feature selection	Complexity in model interpretation
		Effective for data with interactions	Sensitive to noisy data
Boosted regression tree (BRT) [7]	A type of ensemble learning model that combines the predictions of multiple regression trees to produce a more accurate prediction. BRTs are often used for regression tasks, such as predicting the price of a house or the number of customers who will visit a store on a given day.	Improved prediction accuracy	Computationally intensive and may require more time

Table 1. Description of the AI Models Used in the Reviewed Studies - *(continued)*

Model (referenced to the studies where used)	Description	Advantages	Disadvantages
		Handles complex relationships and interactions	Sensitive to noisy data
		Robust against overfitting	Requires careful tuning of hyperparameters
Support vector regression (SVR) [7]	A type of regression algorithm that uses support vectors to find a hyperplane that best fits the data. SVRs are often used for regression tasks, such as predicting the price of a house or the number of customers who will visit a store on a given day.	Effective for high-dimensional data	Choice of kernel function affects performance
		Can handle non-linear relationships	May be sensitive to outliers
		Robust against overfitting	Can be computationally demanding for large datasets
Random forest regression (RFR) [7]	A type of ensemble learning model that combines the predictions of multiple regression trees to produce a more accurate prediction. RFRs are often used for regression tasks, such as predicting the price of a house or the number of customers who will visit a store on a given day.	High prediction accuracy	Lack of transparency and interpretability
		Handles complex relationships and interactions	Computationally intensive for large forests
		Robust against overfitting	Can become biased towards dominant features
Lasso regression (LAR) [7]	A type of regression algorithm that uses L1 regularization to shrink the coefficients of the model. This helps to prevent overfitting and improve the accuracy of the model. LAR is often used for regression tasks, such as predicting the price of a house or the number of customers who will visit a store on a given day.	Feature selection through coefficient shrinkage	May not perform well with highly correlated features
		Helps prevent overfitting	Sensitive to the choice of regularization strength
		Simplicity and interpretability	Limited for complex non-linear relationships
Bayesian additive regression trees (BART) [7]	A type of ensemble learning model that combines the predictions of multiple regression trees to produce a more accurate prediction. BARTs are similar to random forests, but they use a Bayesian approach to learning. This can lead to more accurate predictions, especially for small datasets.	Improved prediction accuracy	Computational complexity can be high
		Incorporates uncertainty through Bayesian framework	Requires careful hyperparameter tuning
		Suitable for small datasets	May be challenging to implement for large datasets
Multilayer perceptron (MLP) [9]	A type of artificial neural network that consists of multiple layers of interconnected neurons. MLPs are often used for classification and regression tasks.	Suitable for complex, non-linear relationships	Prone to overfitting without proper regularization
		Can handle large datasets	Requires a large amount of data for training

Table 1. Description of the AI Models Used in the Reviewed Studies - *(continued)*

Model (referenced to the studies where used)	Description	Advantages	Disadvantages
		Can learn intricate patterns	May be computationally demanding for deep networks
Finite impulse response (FIR) [9]	A type of filter that is used to process signals. FIR filters are linear and time-invariant, and they have a finite number of taps. FIR filters are often used in signal processing applications, such as audio processing and image processing.	Linear and time-invariant characteristics	Limited ability to handle dynamic systems
		Precise control over filter response	May require a large number of coefficients for complex filters
		Suitable for real-time processing	Not suitable for all signal processing tasks
Elman [9]	A type of recurrent neural network that is used to process sequential data. Elman networks have a context layer that stores the outputs of previous neurons. This allows the network to learn long-term dependencies in the data. Elman networks are often used in applications such as natural language processing and machine translation.	Effective for modeling sequential data Captures long-term dependencies	Complex architecture and training
		Suitable for tasks with temporal patterns	Sensitive to the choice of hyperparameters
			Limited performance on some complex tasks
Adaptive-network-based fuzzy inference system (ANFIS) [10]	A type of hybrid intelligent system that combines fuzzy logic and artificial neural networks. ANFIS systems can be used to model complex systems and make predictions. ANFIS systems are often used in applications such as control systems and forecasting.	Combines the strengths of fuzzy logic and neural networks	Requires expert knowledge for rule generation
		Effective for modeling complex and uncertain systems	Complexity in rule optimization
		Provides interpretability through fuzzy rules	Performance highly dependent on the quality of rules
XgBoost [12]	A type of ensemble learning model that combines the predictions of multiple decision trees to produce a more accurate prediction. XgBoost is a very powerful algorithm that can be used to solve a wide variety of machine learning problems. XgBoost is often used for classification and regression tasks.	High prediction accuracy	Lack of transparency and interpretability
		Handles complex relationships and interactions	Can be sensitive to noisy data
		Robust against overfitting	Requires careful tuning of hyperparameters
		Efficient training and prediction	

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