Toward Advancing Long-Term Outcomes of Kidney Transplantation with Artificial Intelligence

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Abstract: After decades of pioneering advances and improvements, kidney transplantation is now the renal replacement therapy of choice for most patients with end-stage kidney disease (ESKD). Despite this success, the high risk of premature death and frequent occurrence of graft failure remain important clinical and research challenges. The current burst of studies and other innovative initiatives using artificial intelligence (AI) for a wide range of analytical and practical applications in biomedical areas seems to correlate with the same trend observed in publications in the kidney transplantation field, and points toward the potential of such novel approaches to address the aforementioned aim of improving long-term outcomes of kidney transplant recipients (KTR). However, at the same time, this trend underscores now more than ever the old methodological challenges and potential threats that the research and clinical community needs to be aware of and actively look after with regard to AI-driven evidence. The purpose of this narrative mini-review is to explore challenges for obtaining applicable and adequate kidney transplant data for analyses using AI techniques to develop prediction models, and to propose next steps in the field. We make a call to act toward establishing the strong collaborations needed to bring innovative synergies further augmented by AI, which have the potential to impact the long-term care of KTR. We encourage researchers and clinicians to submit their invaluable research, including original clinical and imaging studies, database studies from registries, meta-analyses, and AI research in the kidney transplantation field.

Keywords: kidney transplantation; graft failure; death; prediction models; artificial intelligence

1. Introduction

After decades of pioneering advances and improvements, kidney transplantation is now the renal replacement therapy of choice for most patients with end-stage kidney disease (ESKD) because it offers higher survival rates and arguably better quality of life after transplantation. Despite this success, the high risk of premature death and frequent occurrence of graft failure requiring return to dialysis or re-transplantation remain important challenges for the research community and a constantly perceived threat for kidney transplant recipients (KTR) [1,2]. Moreover, the occurrence of graft failure imposes a huge socio-economic impact due to the higher costs for dialysis [3], decreased quality of life, and increased mortality risk [4]. Furthermore, taking into account the scarcity of organ donors, the prevention of re-transplantation through improvements in graft survival stands as an issue of paramount importance as it may translate into relief from the existing organ shortage [5]. This underscores a great need for early identification—allowing, in turn, timely management—of KTR at high risk of graft failure and other adverse long-term outcomes post-kidney transplantation, such as post-transplant diabetes, cardiovascular events, malignancy, and death.

Artificial intelligence (AI) in medicine is a developing field that promises meaningful improvements in patient care. Currently, the clinical and research community is observing a burst of studies and other innovative initiatives using AI for a wide range of analytical and practical applications in biomedical areas. This trend also holds true in the kidney
Transplantology, which is evident from the number of studies using AI techniques for the prediction of kidney transplant outcomes that have been published over the last decades, but mostly over the last 5 years, and particularly in 2020 (Figure 1).

![Publications using AI for kidney transplant outcomes prediction until 2020](image)

Figure 1. Publications using artificial intelligence to develop prediction models for kidney transplant outcomes.

2. AI and Kidney Transplantation, and Modeling

In this context, the broad term AI is not a specific technology, but refers to the set of non-traditional methods and techniques that allow analyzing different types of clinical data either to find patterns or correlations within the data, or to generate predictive models with diverse applications, such as diagnosis and management of a disease or intervention [6]. Among these, machine learning (ML) refers to the set of algorithms that improve its results automatically through experience. It also includes the statistical techniques to produce models from training data without being explicitly programmed to do so, and without human intervention or command in every process [7]. This is opposed to traditional methods of statistical analysis and modeling where every step of data analysis is performed by a human. The different machine learning algorithms used for this purpose can be classified as supervised (e.g., decision trees, K-nearest neighbors), unsupervised (e.g., K-means clustering, hierarchical clustering), reinforcement learning (e.g., Q-learning, TD-Lambda), and deep learning (DL). DL is sub-field of ML that in recent years has increasingly been used in the biomedical field. It is based on multiple networks of nodes, often loosely simulating a set of neurons in a biological brain, modeling its connections, inputs, and outputs and weighing different variables of these connections to produce a prediction model [8].

Nonetheless, all AI-based approaches need data, often large sets of accurate data for training, validation, and testing. International efforts to create large datasets are expected to accelerate future advancements in the kidney transplantation field, and to pave the way toward alleviating the longstanding burden of adverse long-term outcomes post-kidney transplantation [9,10]. Such efforts require sufficient funding for setting up the architectures and communication systems that allow timely extraction and storage of the data, as well as for maintaining and potentially updating the resulting databases. An important premise to take into account is that the quality of the resulting prediction models will depend on how these data are collected, their amount, and their heterogeneity [6].
Indeed, because the great importance of collecting a large quantity of health-related data among human cohorts has increasingly been recognized, there have been many database initiatives specific to kidney diseases and kidney transplantation implementing a model of big data collection and storage [11–14], where different types of information are stored. It is relevant to point out that traditional statistics and modeling also use and analyze data gathered by these databases, generating relevant findings and the development of prediction tools and creating the need for quality data transversal for research [15]. In most countries, however, only rudimentary databases, derived from electronic health records (EHRs) or associated with the waiting-list system for organ transplantation, have been implemented. As recently shown by Thongprayoon et al. [16], the list of countries that have robust kidney transplant databases is short, and is mostly limited to the United States, Canada, China, Ireland, and a few European countries.

Table 1 provides an overview of the number, year and country of origin, aims, origin of database, sample size, and findings of the studies on kidney transplant outcomes performed with artificial intelligence. For the development of this table, a restricted literature search was performed on 4 January 2021, and included all articles up to December 2020 using the keywords “artificial intelligence”, “machine learning”, and “deep learning” paired with “kidney transplantation” through the PubMed and Google Scholar search engines, thus obtaining a total of 451 articles. A selection of 25 original articles studying kidney transplantation outcomes with AI methodologies were included. The reference lists in these articles were also searched for relevant studies on kidney transplant outcomes performed with artificial intelligence. We found 13 articles, for a total of 38 studies, which are described herein. The main finding that arises from this table is that most of the articles used data from established databases, often financed by the government, and the actual list of countries of origin of these databases is rather narrow, in agreement with recent observations by Thongprayoon et al. [16]. Moreover, studies that used established databases of this kind often included a larger number of patients than databases created for the purpose of the studies themselves. Important clinical findings and prediction models have arisen from these large and well-defined databases, yet a small number of studies have also produced and reported prediction models with acceptable performance using databases derived from small, single-center sources [17–19]. In relation to this, it should be noted that one of the main problems that may arise with such approaches is bias, ultimately limiting the potential and rate of success applying a model obtained from one hospital’s data or region to another hospital or region. This is of concern because it may lead to the exacerbation of health disparities as pointed out by many researchers [20,21], not only unfavorable disparities for specific groups within a country due to underrepresentation in the corresponding database, but also for whole populations belonging to countries that have not started or are lagging behind on the path to performing large data collection projects for Big Data and AI-based research. This, coupled with the increasingly higher impact of genomics in kidney transplantation [22], such as genome-wide association studies, could exclude entire populations from the benefits of advances in long-term post-kidney transplant follow-up and management. Moreover, seemingly powerful models derived from biased databases may have the counterintuitive effect of leading to a false sense of general and robust capacity for prediction and identification of high-risk patients.

Data bias is an inherent problem of AI that is exacerbated by the black-box nature of AI models, and by lack of contextual specificity. Some approaches to solve this problem include weighing data for underrepresented populations, or establishing a “human in the loop” process to monitor possible biases. This phenomenon is still present when trying to develop a “general population” AI model, as it only becomes feasible when the data reflect the vast and rich diversity of populations [23].
Table 1. Studies in the field of kidney transplantation that have used AI for data analysis.

| n  | Year | Study Aim                                                                 | Database         | Patients (n) | Country of Origin | Findings and Conclusion                                                                 | Authors                     |
|----|------|---------------------------------------------------------------------------|------------------|--------------|-------------------|-----------------------------------------------------------------------------------------|-----------------------------|
| 1  | 1997 | DL to differentiate between rejection, acute tubular necrosis, and normally functioning kidneys | Miscellaneous   | 35           | Japan             | The DL network gave better diagnostic accuracy than the radiologist, by showing an association between the quantitative data and the corresponding pathological results | Abdolmaleki et al. [24]    |
| 2  | 1998 | DL to predict the occurrence of delayed graft function                    | Miscellaneous   | 100          | USA               | The model could accurately predict the occurrence and quality of early graft function    | Shoskes et al. [25]        |
| 3  | 2000 | DL to predict 1-year graft survival                                       | UNOS            | 35,366       | USA               | By more accurately predicting graft survival, the model may be used to refine existing rule-based transplant-allocation systems | Ahn et al. [26]            |
| 4  | 2002 | DL to model kidney graft rejection                                         | Miscellaneous   | 1542         | Unavailable       | The DL-based approach was useful for prediction of the occurrence and the type of rejection | Petrovsky et al. [27]      |
| 5  | 2003 | DL to predict delayed graft function and compare it with traditional logistic regression models | Miscellaneous   | 304          | USA               | DL is more sensitive but less specific than logistic regression methods.                 | Brier et al. [28]          |
| 6  | 2004 | DL for prediction of kidney graft failure at 2-year follow-up              | ANZDATA         | 1344         | Australia and New Zealand | Positive predictive power was low, indicating a need for improvement if this approach was to be useful clinically | Shadabi et al. [29]       |
| 7  | 2005 | Supervised ML algorithms for prediction of kidney graft failure at 4-year post transplantation | Miscellaneous | 497          | Germany            | The models allowed early identification of patients at risk of graft failure              | Fritsche et al. [30]      |
| 8  | 2007 | DL model to predict a delayed decrease of serum creatinine                | Miscellaneous   | 148          | Italy              | DL showed better overall accuracy than the logistic regression                            | Santori et al. [31]       |
| 9  | 2007 | Supervised ML models to predict the probability of kidney allograft survival at 1, 3, 5, 7, and 10 years | USRDS + UNOS    | 92,844       | USA               | The models demonstrated performance suggesting implementation in clinical decision support system | Krikov et al. [32]       |
| 10 | 2008 | Comparison of methods (traditional statistics vs. DL) to predict graft failure | USRDS + UNOS    | 57,389       | USA               | Logistic regression is able to achieve performance comparable to DL if there are no strong interactions or non-linear relationships among the predictors and the outcomes | Lin et al. [33]           |
| 11 | 2008 | DL model to predict 5-year graft survival of living-donor kidney transplants | Miscellaneous  | 1809         | Egypt             | DL networks were more accurate and sensitive than traditional statistical models in predicting 5-year graft survival | Akl et al. [34]           |
Table 1. Cont.

| n  | Year | Study Aim                                                                 | Database              | Patients (n) | Country of Origin | Findings and Conclusion                                                                                                                                                                                                 | Authors                  |
|----|------|----------------------------------------------------------------------------|-----------------------|--------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| 12 | 2009 | DL for prediction of kidney graft failure at 5-year follow-up             | Miscellaneous         | 316          | Iran              | A DL model had good accuracy and area under the ROC curve (AUC)                                                                                                                                                    | Ashfari et al. [35]      |
| 13 | 2010 | Supervised ML classifier for prediction of graft and patient survival     | UNOS                  | 1228         | USA               | The classifier for graft survival prediction performed with high prediction accuracy for the living and failed classes, respectively                                                                 | Li et al. [36]           |
| 14 | 2010 | Supervised ML for prediction of graft loss at 5-year follow-up            | Miscellaneous         | 194          | Italy             | ML may be a suitable alternative to traditional statistical methods, as it may allow analysis of the interactions between various risk factors beyond previous knowledge                                                                 | Greco et al. [37]        |
| 15 | 2010 | Supervised ML to predict chronic allograft nephropathy at 5-year follow-up| Miscellaneous         | 80           | Italy             | ML models predicted the onset of chronic allograft nephropathy, representing a valid alternative to traditional statistical models                                                                                     | Lofaro et al. [38]       |
| 16 | 2010 | DL to obtain a pattern classifier that predicts events of nephrotoxicity versus acute cellular rejection episodes | Miscellaneous         | 145          | Brazil            | The classification results were considered significant; however, higher rates of sensitivity would have been required to apply the classifier in clinical practice                                                                 | Hummel et al. [39]       |
| 17 | 2011 | Comparison of data mining methods for prediction of 3-year graft survival in patients with systemic lupus erythematosus | USRDS                 | 4754         | USA               | The performance of logistic regression and classification tree was not inferior to DL approaches, underscoring the need for larger amounts of training data to improve the performance of DL networks | Tang et al. [40]         |
| 18 | 2012 | Supervised ML to determine whether pretransplant donor and recipient variables, when considered together as a network, add incremental value to the classification of graft survival | USRDS                 | 7348         | USA               | ML enabled examination of variables to develop a robust predictive model                                                                                                                                             | Brown et al. [41]        |
| 19 | 2012 | Comparison of ML methods to predict the estimated glomerular filtration rate 1 year after transplantation | Eurotransplants database | 707          | Eight European countries * | The best ML model was a Gaussian support vector machine with recursive feature elimination                                                                                                                       | Lasserre et al. [42]     |
| 20 | 2015 | Comparison between logistic regression and Supervised ML methods for prediction of delayed graft function | Miscellaneous         | 497          | Belgium           | ML has the highest discriminative capacity, outperforming logistic regression, suggesting it is the most appropriate approach to predict delayed graft function                                                               | Decruyenaere et al. [43] |
Table 1. Cont.

| n  | Year | Study Aim                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Database   | Patients (n) | Country of Origin | Findings and Conclusion                                                                                                                                                                                                 | Authors       |
|----|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| 21 | 2016 | Comparison of different DL methods to predict rejection and loss of the kidney and death of the patient within the next six or twelve months after each visit to the clinic using static and dynamic data                                                                                                                                                                                                                                                              | Miscellaneous | 2061         | Germany           | DL provides the best performance, and long-term dependencies are not as relevant in this task                                                                                                                                                                                      | Esteban et al. [44] |
| 22 | 2016 | Comparison of the effectiveness of ML and DL methods to predict kidney transplant survival                                                                                                                                                                                                                                                                                                                                                                                 | Miscellaneous | 513          | Iran              | A type of supervised ML, the C5.0 algorithm, was the top model with high validity that confirms its strength in predicting survival                                                                                                                                              | Shahmoradi et al. [45] |
| 23 | 2017 | Introduction of a comprehensive feature selection framework that accounts for medical literature, data analytics methods, and supervised ML methods for graft survival prediction model                                                                                                                                                                                                                                                               | UNOS       | 31,207       | USA               | The predictor set obtained through fused data mining model and literature review outperformed all other alternative predictors sets                                                                                                                                              | Topuz et al. [46] |
| 24 | 2017 | Evaluation of the predictive power of supervised ML algorithms and comparison of outcomes with traditional models                                                                                                                                                                                                                                                                                                                                  | Miscellaneous | 3117         | South Korea       | An ML-generated decision tree improved the accuracy of predicting graft failure over traditional statistical models, supporting the application of advanced ML techniques                                                                                               | DonYoo et al. [17] |
| 25 | 2017 | DL to model the survival function instead of estimating the hazard function to predict survival times for graft patients                                                                                                                                                                                                                                                                                                                                      | SRTR       | 131,709      | USA               | The DL model outperforms methods for survival analysis in terms of survival time prediction quality and concordance index                                                                                                                                                                | Luck et al. [47] |
| 26 | 2017 | Supervised ML classification models, in the context of a small dataset, for outcome prediction in a high-risk population                                                                                                                                                                                                                                                                                                                              | Miscellaneous | 80           | United Kingdom    | ML classifiers achieved high accuracy prediction                                                                                                                                                                                                                             | Shaikhina et al. [48] |
| 27 | 2017 | DL to predict kidney graft rejection and comparison of results with those obtained by logistic regression                                                                                                                                                                                                                                                                                                                                         | Miscellaneous | 378          | Iran              | DL methods showed higher total accuracy than logistic regression                                                                                                                                                                                                          | Tapak et al. [49] |
### Table 1. Cont.

| n  | Year | Study Aim                                                                 | Database       | Patients (n) | Country of Origin | Findings and Conclusion                                                                 | Authors |
|----|------|----------------------------------------------------------------------------|----------------|--------------|-------------------|----------------------------------------------------------------------------------------|---------|
| 28 | 2017 | Comparison of the performance of multiple linear regression and supervised ML approaches in pharmacogenetic algorithm-based prediction of tacrolimus stable dose | Miscellaneous  | 1045         | China             | Regression performed best among ML approaches and the ideal rate was higher than that of multiple linear regression | Tang et al. [50] |
| 29 | 2019 | Supervised ML for Kidney Transplantation Survival Prediction Model by donor-recipient combination | SRTR           | 120,818      | USA               | Online prediction tool (www.transplantmodels.com/kdpi-epts, accessed on 3 January 2021) that can support individualized decision-making on kidney offers in clinical practice | Bae et al. [18] |
| 30 | 2019 | ML (multiple methods) for Kidney Transplantation Outcomes Prediction Model | UNOS/OPTN      | 100,000      | USA               | Predictions from ML methods paired with traditional statistics (Cox regression) outperforms the state-of-the-art model currently in use in the kidney allocation system in the U.S. | Mark et al. [19] |
| 31 | 2020 | ML (multiple methods) to predict post-transplant severe pneumonia         | COTRS          | 531          | China             | An ML algorithm displayed high predictive performance, underscoring potential use for predicting severe pneumonia post-transplant | Luo et al., 2020 [51] |
| 32 | 2020 | Supervised ML to model risk at 3 and 12 months post-transplantation       | Miscellaneous  | 1241         | Germany           | An ML analysis produced robust models over a wide range of parameter settings          | Scheffner et al. [52] |
| 33 | 2020 | Comparison of multiple ML methods to predict severe pneumonia             | Miscellaneous  | 146          | China             | A type of supervised ML model (vector machine) had the best performance among the methods used | Peng et al. [53] |
| 34 | 2020 | Quantification of the benefit/harm of kidney transplantation during the COVID-19 pandemic using supervised ML approaches | SRTR/OPTN      | 300,441      | USA               | In most scenarios of COVID-19 dynamics and patient characteristics, immediate kidney transplantation provided survival benefit | Massie et al. [54] |
| 35 | 2020 | Comparison of supervised ML approaches to conventional regression to predict outcomes of kidney transplantation | SRTR/OPTN      | 133,431      | USA               | Performance was nearly identical yet higher using ML methods for prediction of delayed graft function, death-censored and all-cause graft failure, and death, except for rejection | Bae et al. [55] |
### Table 1. Cont.

| n   | Year | Study Aim                                                                 | Database          | Patients (n) | Country of Origin | Findings and Conclusion                                                                                                                                                                                                 | Authors       |
|-----|------|---------------------------------------------------------------------------|-------------------|--------------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| 36  | 2020 | Supervised ML and logistic regression to predict delayed graft function from donor maintenance-related variables | Miscellaneous     | 443          | Brazil            | Some donor-maintenance related variables were associated with delayed graft function, suggesting a potential impact from poor clinical and hemodynamic status on the incidence of delayed graft function | Costa et al. [56] |
| 37  | 2020 | Building an ML application based on supervised regression ML to predict, in elderly populations, the likelihood of worse renal function one year after kidney transplant | Miscellaneous     | 118          | Brazil            | An ML application, Elderly KTbot, was capable of predicting worsened renal function one year after kidney transplantation                                                                                                                                               | Elihimas et al. [57] |
| 38  | 2020 | Supervised ML to build personalized prognostic models to predict delayed graft function | UNOS/OPTN         | 61,220       | USA               | Twenty-six predictors were identified via an ML model. DL outperformed the baseline logistic regression-based model                                                                                                                                                           | Kawakita et al. [58] |

Miscellaneous databases are either solely constructed for the purpose of the particular study and are property of the authors or parent institution, or are not disclaimed or unknown. ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; COTRS, China Organ Transplant Response System; OPTN, Organ procurement transplantation network; SRTR, Scientific registry of transplant recipients; UNOS, United Network for Organ Sharing; USRDS, United States Renal Data System. * Eurotransplants database: Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia.
3. Conclusion and Future Perspectives

The conversion of rudimentary databases that most countries already have to a standard set is a reasonable goal to work toward, as it would greatly benefit AI findings by increasing representation. As shown in Table 1, when countries develop and maintain a database, studies over those populations have access to a much larger number of patients, generating better and more reliable findings. It seems compelling to describe a standard database for the development of ethnic, gender, socioeconomic, and cross-border proof kidney transplant models, establishing a common minimum of epidemiological, clinical, laboratory, genomic, and imaging data, on both donors and recipients, with the collection of well-established and relevant long-term follow-up outcomes.

Kidney transplant databases should be one of the first widespread worldwide implementations of databases to take advantage of the growing field of AI in medicine, as the availability of more and more diverse datasets will enable better AI model generation, reducing biases derived from limited populations, without restricting findings that may be particular to one population. Still, many challenges plague this adoption as a standard, and future research will require broad inter-disciplinary initiatives to take full advantage of AI in the kidney transplantation field. Whether currently used and novel imaging modalities to study kidney transplant function prior to and post-kidney transplant may be enhanced by AI remains unexplored, yet huge potential is expected in upcoming years for the evaluation and follow-up of kidney transplant recipients [59]. It should be emphasized that the success envisioned by combining imaging and AI in kidney transplantation will largely depend on strong and long-lasting collaborations between fields. In this regard, Benjamens et al. recently made a call to encourage transplant organizations to aim for partnerships with diagnostic imaging societies [59]. We support this call, as it may lead to fruitful and innovative synergies further augmented by AI, with the potential to impact the long-term care of KTR.

Thus, we encourage researchers and clinicians to submit their invaluable research, including original clinical and imaging studies, database studies from registries, meta-analyses, and AI research in the kidney transplantation field.

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