Artificial Intelligence in Nephrology: How Can Artificial Intelligence Augment Nephrologists' Intelligence?

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Keywords

Kidney disease · Artificial intelligence · Big data ·
Diagnostics and prognostics · Treatment

Abstract

Background: Artificial intelligence (AI) now plays a critical role in almost every area of our daily lives and academic disciplines due to the growth of computing power, advances in methods and techniques, and the explosion of the amount of data; medicine is not an exception. Rather than replacing clinicians, AI is augmenting the intelligence of clinicians in diagnosis, prognosis, and treatment decisions. **Summary:** Kidney disease is a substantial medical and public health burden globally, with both acute kidney injury and chronic kidney disease bringing about high morbidity and mortality as well as a huge economic burden. Even though the existing research and applied works have made certain contributions to more accurate prediction and better understanding of histologic pathology, there is a lot more work to be done and problems to solve. **Key Messages:** AI applications of diagnostics and prognostics for high-prevalence and high-morbidity types of nephropathy in medical-resource-inadequate

areas need special attention; high-volume and high-quality data need to be collected and prepared; a consensus on ethics and safety in the use of AI technologies needs to be built.

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Artificial intelligence and Its Present Applications in Medicine

Introduction of Artificial intelligence

Artificial intelligence (AI) now plays a critical role in almost every area of our daily lives and academic disciplines; medicine is not an exception.

What is AI? According to the father of the field, McCarthy [1], AI is defined as the science and engineering of creating intelligent machines that behave in a way that could be considered intelligent if it was a human being. In the past decades, the growth of computing power, advances in methods and techniques, and the explosion of the amount of data hugely expanded the capacity of AI in resolving a broader spectrum of tasks.

One of the major branches of AI is machine learning, which is defined as the study of algorithms and statistical

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models that computer systems use to learn from sample data and past experience without being explicitly programmed to perform specific tasks. With the capacity of identifying hidden patterns in the data, machine learning can be used to solve various problems, such as finding associations of two variables, classifying subjects by certain criteria, making predictions based on baseline characteristics, and recognizing objects with similar patterns. Popular machine-learning algorithms include support vector machine, random forest, gradient boosting trees, and artificial neural network (ANN).

Deep learning is a subfield of machine learning based on ANN, which is inspired by the idea of mimicking the biological structure of human brains. Deep-learning models can learn multiple levels of representation of data with a multiple-processing-layers model structure, achieving higher model performance than ever before. This cutting-edge technology has dramatically transformed the paradigm of speech recognition, visual object recognition, and many other domains such as drug discovery and genomics. Popular techniques include fully connected neural network, convolutional neural network (CNN), recurrent neural network (RNN), generative adversarial network (GAN), and deep reinforcement learning, among others.

Rather than replacing human intelligence with AI, an alternative understanding of AI can be represented as “augmented intelligence”. This is especially true in the field of medicine, where AI is now, and will be, enhancing and augmenting the intelligence of clinicians, aiding clinicians to move towards more personalized diagnosis, risk prediction, and treatment.

Where Can AI Augment Clinicians’ Work?

Diagnostics

The capacity of AI to diagnose disease risk is developing rapidly. One common application is in the field of radiology, due to the large volumes of medical image data. Traditionally, trained physicians visually assess medical images and report their findings based on prior knowledge. Until now, a series of AI tools have been developed to aid the clinicians in identifying features in images quickly and precisely [2, 3]. In the study by Esteva et al. [3], a deep CNN model was developed based on a dataset of 129,450 clinical images to diagnose skin cancer, which is able to classify skin cancer at a comparable level to dermatologists. They said that by embedding the CNN model into smartphones, the reach of dermatologists could be extended in a low-cost way.

AI could also reduce missed diagnoses as well as misdiagnoses by ingesting medical images and informing

physicians with a second opinion. A CNN framework was constructed by Liu et al. [4] from Google, Inc., to aid the pathological diagnosis of breast cancer metastasis in lymph nodes. The results reported significant improvements from the aspects of speed, accuracy, and consistency of diagnosis. It could reduce the false negative rate to a quarter of the rate experienced by human pathologists. AI-aided diagnostics is promising to help improve the availability of healthcare access and healthcare quality.

Prediction

The field of prognosis has seen rapid growth in the use of AI techniques. Traditionally, prediction of prognostics relied on statistical models and clinician’s practice experience. Statistical models always require a number of strong assumptions (e.g., independence of observations and no multicollinearity among variables) [5, 6]. Under the scenario of big data, the assumptions rarely hold. Machine-learning algorithms are typically used without making as many assumptions of the underlying data. More than that, a machine-learning model can learn complicated patterns of health trajectories of vast numbers of features and patients, which have demonstrated high predictive accuracy, verified and replicated with numerous validation studies [7]. For example, Motwani et al. [8] developed a machine-learning model to predict all-cause mortality in patients with suspected coronary artery disease by combining clinical and computed tomographic angiography data, achieving a higher discrimination performance than traditional risk prediction methods.

Despite its promise, the growing field of machine learning in prognosis is experiencing a variety of growing pains. The biggest challenge is the un-transparency issue, as most machine-learning algorithms are so-called “black boxes” and cannot be explained and reported in a similarly transparent way as traditional methods.

Treatment

In a large healthcare system with tens of thousands of physicians treating numerous patients, there is variation in how patients with similar clinical conditions are treated. To characterize subgroups of patients with heterogeneous treatment responses is essential for personalized medicine and improved care. Traditionally, the randomized controlled trial has been serving as the gold standard of evidence-based treatment efficacy evaluation. The statistical methods used to analyze randomized controlled trial data have also provided important insights from observational data. However, it has been shown to be challenging to generate curated data sets by experts, tailor the

treatment models to regional practices, identify potential confounders from high-dimensional data, and automatically extract relevant variables from observational data using traditional methods [9]. In comparison, machine-learning methods can hopefully sort through these problems and help physicians identify a personalized treatment pathway for a unique patient. For example, Komorowski et al. [10] applied reinforcement learning to learn a treatment recommendation model for intensive care, which can identify optimal treatment strategies for sepsis with high accuracy. In a large independent validation cohort, the AI model was validated and shown to have on average reliably higher value than human clinicians [10].

AI could also promisingly allow referral decisions or treatment to be personalized at an earlier stage than is currently possible [11]. For example, REVOLVER (Repeated Evolution of Cancer) developed by Cancer Research London is able to identify patterns in DNA mutation within cancers and forecasts future genetic changes, allowing clinicians to stay one step ahead of cancer and leading to personalized cancer treatment [12].

AI in Nephrology

Kidney disease is an important medical and public health burden globally, with both acute kidney injury and chronic kidney disease bringing about high morbidity and mortality as well as a huge economic burden [13–15]. Patients with kidney disease have a high heterogeneity in disease manifestation, progression, and treatment response. AI can help shed light on the precision medicine in kidney disease for more precise phenotype and outcome prediction.

Recently, Chen et al. [16] made a step towards precision nephrology by developing a machine-learning-aided risk prediction model for immunoglobulin A nephropathy (IgAN). Compared with the previous prediction models for IgAN which used standard modeling with a small number of predefined variables, Chen et al. [16] employ supervised machine-learning methods to well capture the useful information under the big data. They used the eXtreme Gradient Boosting (XGBoost) approach to learn the regularity directly from the 36 candidate features without pre-steps of feature selection. XGBoost is an ensemble learning method which generates a series of iteratively constructed decision trees on the previous ones. The method has both precise prediction performance and generalization ability in various amounts of risk prediction tasks, such as achieving a C statistic of

0.84 for the prediction of end-stage kidney disease or a 50% reduction in estimated glomerular filtration rate within 5 years after the biopsy diagnosis. Another advantage of the XGBoost model is that it can handle the missing values automatically. Thus, the model is applicable in practice even when some of the variables are missing for a given patient. Using the most important variables identified from this model, Chen et al. [16] then constructed a validated simplified scoring scale model that is easy to use in clinical practice.

More than building a machine-learning predictive model, Chen et al. [16] also wrapped their model into an online calculator [17], enabling clinicians to apply it in real-world settings. As illustrated in Figure 1, with baseline characteristics of a patient typed in, the risk calculator automatically predicts the 5-year prognosis of this patient and classifies him/her as high-, moderate-, or low-risk category. Based upon the personalized risk stratification, nephrologists are able to identify patients who suffer from a higher risk of deterioration, and thereby improve care for them by scheduling more frequent visits and monitoring their risk factors closely.

Along with the work by Chen et al. [16], other endeavors have been made in developing AI for the prediction, diagnosis, and treatment of kidney diseases [18–23]. Tomasev et al. [20] recently used deep-learning methods to make a continuous prediction of AKI by developing a RNN model on sequential health record data of 703,782 veterans, enabling clinicians to act with sufficient context and enough time [20]. Kolachalama et al. [21] utilized another class of ANN, CNN, to gain an insight into the association of pathological fibrosis identified from histologic images with clinical phenotypes for chronic kidney disease patients, facilitating the diagnostics and prognostics of these phenotypes [21]. Barbieri et al. [23] established a decision support system, the Anemia Control Model (ACM), to recommend suitable erythropoietic-stimulating agent doses based on a machine-learning model trained on about 170,000 clinical records, supporting nephrologists in making decisions related to anemia treatment in hemodialysis patients. This system was clinically validated by a retrospective study that consisted of a 12-month control phase and a 12-month ACM-guided care phase encompassing 752 hemodialysis patients, where primary outcomes of hemoglobin values and fluctuation improved significantly in the ACM phase [23].

Scenarios where AI can augment clinicians' work, selected examples in nephropathy and other type of diseases, and AI methods they used in each scenario are summarized in Table 1.

Fig. 1. Online calculator of the Nanjing IgAN Risk Stratification System.

Future Possibilities and Challenges of AI in Nephrology

Nephrology AI in Diagnostics, Prognostics, and Treatment for High-Prevalence and High-Morbidity Types Needs to Be First Developed

Kidney diseases are known to be highly multifactorial, have complex and overlapping clinical phenotypes and morphologies, and have late diagnosis and chronic progression [24]. Even though the existing research and applied works have made certain contributions to more accurate and timely prediction and better understanding of histologic pathology, there is a lot more to be done to unleash the full potential of AI and bring real benefits to patients and clinicians in nephrology.

AI-aided diagnostics tools need special attention from researchers. As the kidney plays an important role in internal environment homeostasis maintaining, kidney diseases usually involve other organs, and some systemic diseases also affect the kidney, which leads to the possibility of misdiagnosis and missed diagnosis of kidney disease. AI can help clinicians reduce misdiagnosis and missed diagnosis by guiding them in further examination in certain biomarkers or providing second opinions. In addition, AI tools will play an essential role in quantitative analysis of pathological images, improving the efficiency and accuracy of pathologists' work. Prognostics is also key to nephropathy given its chronic progression.

Individualized prediction models powered by AI are highly necessary for precise risk stratification of patients. Personalized medicine is another key approach to improved prognosis and survival for kidney disease patients. As AI techniques such as reinforcement learning, recursive partitioning, and clustering are capable of identifying subgroups of patients with heterogeneous responses to various treatment regimens, AI has the potential to recommend appropriate treatment to certain patients.

The very first steps can start with developing AI in diagnostics, prognostics, and treatment for high-prevalence and high-morbidity/mortality types of kidney disease, such as IgA nephropathy, diabetic nephropathy, lupus nephritis, and end-stage kidney disease.

Real-World AI Applications Will Most Likely Augment Healthcare in Medical-Resource-Inadequate Areas

In areas with inadequate medical resources, some developing countries and rural areas, for example, the life expectancies and health conditions of residents are generally poor due to limited access to qualified healthcare providers [25]. AI by its nature is suited to be applied in such areas, given that a single AI clinical decision support system has the capacity to serve a large population encompassed within its scope.

Due to the high prevalence and low awareness of kidney diseases, early diagnosis and intervention are rarely possible, especially in resource-inadequate areas. With the help

Table 1. Applications of AI in diagnosis, prediction, and treatment with selected examples in nephropathy and other diseases

Scenario	Examples	AI techniques	Methods	Type of disease
Diagnosis	Multiclass segmentation of digitized kidney tissue sections [18]	Deep learning	CNN	Kidney disease
	Segmentation and classification of diabetic glomerulosclerosis [19]	Deep learning and unsupervised learning	CNN, unsupervised methods	Kidney disease
	Classification of skin lesions and skin cancer with images [3]	Deep learning	CNN	Cancer
	Detecting cancer metastases on breast cancer pathological images [4]	Deep learning	CNN	Cancer
Prediction	ESRD prediction for IgAN patients [16]	Supervised learning	XGBoost algorithm	Kidney disease
	Continuous prediction of AKI [20]	Deep learning	RNN	Kidney disease
	Prediction of all-cause mortality in patients with coronary artery disease [8]	Supervised learning	LogitBoost algorithm	Cardiovascular disease
	Outcome prediction for lymphoma with gene-expression profiling [7]	Supervised learning	Weighted voting algorithm	Cancer
Treatment and patient care	Recommendation of anemia therapy in hemodialysis patients [22]	Deep learning	Reinforcement learning	Kidney disease
	Clinical decision support for anemia management in hemodialysis patients [23]	Deep learning	ANN	Kidney disease
	Making referral recommendation in retinal disease [11]	Deep learning	ANN	Retinal disease
	Treatment recommendation for sepsis in intensive care [10]	Deep learning	Reinforcement learning	Intensive care

of AI, health practitioners in such areas will be able to screen potential kidney disease patients and make referrals according to their risk levels. In other situations where qualified healthcare professionals are scarce for a large population, auxiliary patient management tools will serve to reduce unsatisfactory waiting time, manage intelligent follow-up of patients, and educate patients with kidney disease.

Availability of High-Volume and High-Quality Data Is a Major Challenge

Machine-learning models generally perform best when they have access to large amounts of diverse and comprehensive training data. Thus, a key issue for the application of machine learning will be leveraging large and diverse data sets to improve the performance of machine-learning models. The multi-modality data combining basic information, laboratory test and genetic data may help to build machine-learning models with higher accuracy since more comprehensive information is embedded. Another problem is the quality of the data. Although machine learning and AI techniques have a strong ability to deal with noisy data, it is ideal to train a model with cleaned and formatted data. Too noisy data will easily lead to unreliable conclusions. For example, Google tried to predict the seasonal prevalence of influenza using only

the search terms entered into its search engine in 2008 [26]. Because people's searching habits change dramatically with every passing year, the model was so poorly predictive of the future that it was quickly discontinued. Although it is a tough task, efforts should be made towards high-volume and high-quality clinical data.

Consensus on Ethics and Safety in the Use of AI Technologies Needs to Be Built

Aside from simply being put into use with superior efficacy and performance, AI entering the field of nephrology must adapt with ethical and safety concerns. Even though machine-learning and deep-learning models always achieve high performance in retrospective studies, these models do not guarantee wide applicability in different scenarios and may be subject to automation bias [27]. Indiscreet or overuse of AI in healthcare may lead to misleading diagnosis and treatment recommendation for patients as well as decreased vigilance and sense of responsibility of clinicians, which obviously violates the principle of "do no harm". Privacy of patients, data security, and data ownership are other major issues, given that current laws and regulations are insufficient to address the issues [28]. Hence, an international consensus on ethics and safety use of AI in nephrology needs to be built by the whole community.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

G.X., Z.L., and X.L. conceived and designed the study. Tiange C., Y.L., and Tingyu Y.C. wrote the manuscript. X.L., G.X., and Z.L. reviewed and edited the manuscript. Each author contributed important intellectual contents during manuscript drafting or revision and accepts accountability for the overall work.

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