Precision Dialysis: Leveraging Big Data and Artificial Intelligence

Ehsan Nobakht, Wubit Raru, Sherry Dadgar, and Osama El Shamy

The long-term mortality of patients with kidney failure remains unacceptably high. There are a multitude of reasons for the unfavorable status quo of dialysis care, such as the inadequate and suboptimal pattern of uremic toxin removal resulting in a metabolic and hemodynamic “roller coaster” induced by thrice-weekly in-center hemodialysis. Innovation in dialysis delivery systems is needed to build an adaptive and self-improving process to change the status quo of dialysis care with the aim of transforming it from being reactive to being proactive. The introduction of more physiologic and smart dialysis systems using artificial intelligence (AI) incorporating real-time data into the process of dialysis delivery is a realistic target. This would enable machine learning from both individual and collective patient treatment data. This has the potential to shift the paradigm from the practice of population-driven, evidence-based data to precision medicine. In this review, we describe the different components of an AI system, discuss the studied applications of AI in the field of dialysis, and outline parameters that can be used for future smart, adaptive dialysis delivery systems. The desired output is precision dialysis; a self-improving process that has the ability to prognosticate and develop instant and individualized predictive models.

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The number of patients with end stage kidney disease (ESKD) receiving dialysis has exceeded 2.5 million globally and expected to double to 5.4 million by 2030.[1,2] Since its introduction by Dr Willem Kolff in 1943, hemodialysis has saved patients with kidney failure from imminent death; however, premature death has remained unacceptably high.[1,2] A factor that could be responsible for this is that dialysis does not fully replace the kidneys' functions and that it mainly removes small nonprotein bounded uremic toxins.[3] Approximately one-quarter of patients die within the first year of dialysis initiation.[1] Suboptimal outcomes of patients labeled as receiving “adequate dialysis” according to widely accepted parameters, such as Kt/V, indicate the need for revisiting the definition of adequate dialysis.

Over the past decades, modifications in dialysis delivery systems have not resulted in a significant improvement in patient outcomes.[4] Poor quality of life of patients receiving dialysis with overwhelming symptoms, such as insomnia, pruritus, anxiety and depression, remains an important challenge.[3] The conventional 3 times weekly hemodialysis practice is largely administered because of logistic and cost concerns rather than clinical outcomes.[5] Patients on thrice-weekly dialysis experience a metabolic and hemodynamic “roller coaster” of fluid, toxin, and solute removal that may contribute to poor outcomes. Despite the lower dialytic clearance of peritoneal dialysis (PD),[6] outcomes of patients on PD, at least in the short term, are comparable with patients on hemodialysis,[1,7] which may in part be related to the shorter interdialytic period.

Conventional dialysis does not provide automatic dynamic responses to unexpected (yet common) hemodynamic changes during a patient's treatment. For example, the reaction to a drop in blood pressure during dialysis is frequently delayed until the patient experiences symptoms of hypotension or the dialysis nurse notices the reading and responds to the situation. The greater the frequency of such episodes is, the greater the likelihood of loss of residual kidney function and increased potential for cardiac, cerebral, and gut ischemia.[3] This is reactionary dialysis care and delivery. Although there is a limited number of small studies in the dialysis space, large-scale well-conducted studies are needed for the operationalization of artificial intelligence (AI) approaches in dialysis delivery.

Innovation in dialysis delivery systems is needed to build an adaptive and self-improving process minimizing the metabolic and hemodynamic “roller coaster” to change the status quo of dialysis care with the aim of transforming it from being reactive to being proactive. The nephrology community (patients and providers) and the dialysis industry is overdue a future in which the technological advancement in dialysis care and delivery can at least match and ideally outpace the innovations and improvements seen in other industries from electric vehicles, handheld communication devices, and entertainment products.

ARTIFICIAL INTELLIGENCE

AI is a field of study of computations enabled to perceive, reason, and act.[8] Machine learning (ML) is considered a branch of AI that is capable of self-improvement and learning from experience without the need for explicit programming for a specific task (Fig 1).[9] AI can help solve

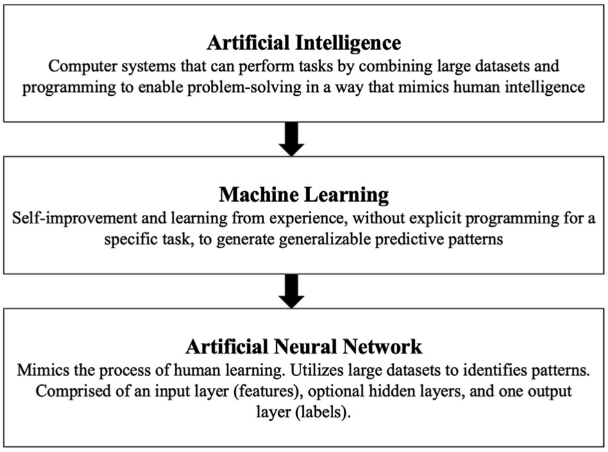

Figure 1. A summary of artificial intelligence.

multidimensional nonlinear problems. Although there is no clear line to distinguish statistical models from ML, the focus of traditional statistical models is to draw inference from a sample, whereas ML is mainly designed to produce generalizable predictive patterns.[10]

A subset of ML called "deep learning" is made of artificial neural network (ANNs) (Fig 1). Inspired by the function of biologic neurons, the neural networks have been developed to mimic the process of human learning. In contrast to conventional ML, which is required to be carefully designed by human engineers, the process of deep learning by ANNs is based on a general-purpose learning procedure that learns from data and identifies patterns in a large data set.[11] An ANN has one input layer (features), optional hidden layers and one output layer (labels).[9,12] For example, an image is an array of pixels. Each pixel has a value in the corresponding neuron in the first layer of the neural network. Let us assume that the learned feature in the first layer is the presence or absence of edges at particular orientations of an image. The second layer may detect motifs of particular arrangements of the edges, and the third layer may assemble those motifs into larger combinations corresponding to parts of familiar objects, and subsequent layers may detect the object using a combination of these learned features.[11]

To validate its performance, the ANN needs to be trained by data sets that are diverse and representative of problem domain proportionate to the size of the network and the complexity of the desired output and the number of features selected and eventually tested on a separate data set before it can be used for a practical purpose.[9] Complex relationships between features and labels beyond the abilities of human can be learned by ANNs when performing tasks. A clinical application of this would be using heterogeneous data obtained from electronic medical records, images, continuous monitoring data, vital signs, laboratory parameters and geonomics, pharmacogenomics for learning process and providing predictions to support clinical decisions.[12]

There is a growing role for AI in health care, creating new standards of care, risk, care debt gap identification, and care variation reduction.[13] It is expected that AI-driven approaches will result in incremental changes in health care.[13] The US Food and Drug Administration (FDA) has cleared 700 AI algorithms for medical use, mostly in the field of radiology.[14] AI in medicine has been used to identify high risk patients for inhospital mortality, length of stay, and 30-day readmission rates.[15] It has also been used to identify known drug–drug interactions as well as predicting unknown drug interactions.[16] In nephrology, AI systems have been used to predict acute kidney injury[17] and chronic kidney disease progression[18] and applied in transplant[19,20] and nephropathology.[21,22] The prediction of glomerular filtration rate decline in autosomal dominant polycystic kidney disease, evaluation of risk of progressive IgA nephropathy[23], and the estimation of tacrolimus area under the curve in transplant recipients are among the examples.

AI IN THE DIALYSIS SPACE

Establishing dry weight for dialysis patients is challenging. Both intradialytic hypertension and hypotension are common complications and are associated with poor outcomes.[24-26] A deep learning model was applied to predict the risk of intradialytic hypotension using a time stamp-bearing data set of 261,647 hemodialysis sessions with 1,600,531 independent timestamps, such as time-varying vital signs.[27] The recurrent neural network model for predicting intradialytic hypotension achieved an area under the receiver operating characteristic curve of 0.94, which was higher than that obtained using multilayer perceptron, light gradient boosting machine, and logistic regression models ($P < 0.001$). AI algorithms such as the deep learning model can be used to predict the real-time risk of intradialytic hypotension.[27] A neural network using bioimpedance in 14 pediatric patients used blood pressure and blood volume monitoring to determine dry weight and compared the results with the dry weight determined by nephrologists.[28] The AI dry weight was found to be higher than the dry weight determined by nephrologists in 28.6% of the cases and lower in 50% of the cases. The mean difference between AI- and nephrologist-determined dry weights was 0.497 kg (−1.33 to +1.29 kg). In those patients with AI dry weight lower than nephrologist dry weight, systolic blood pressure decreased after dry weight was adjusted to AI dry weight (77th to 60th percentile, $P = 0.022$). Antihypertensive medications were reduced or discontinued in 28.7% of the cases. In those with AI dry weight higher than nephrologist dry weight, no hypertension was detected after dry weight was increased to AI dry weight. Symptoms associated with dry weight underestimation also subsided. In this study, AI predictions clearly outperformed experienced

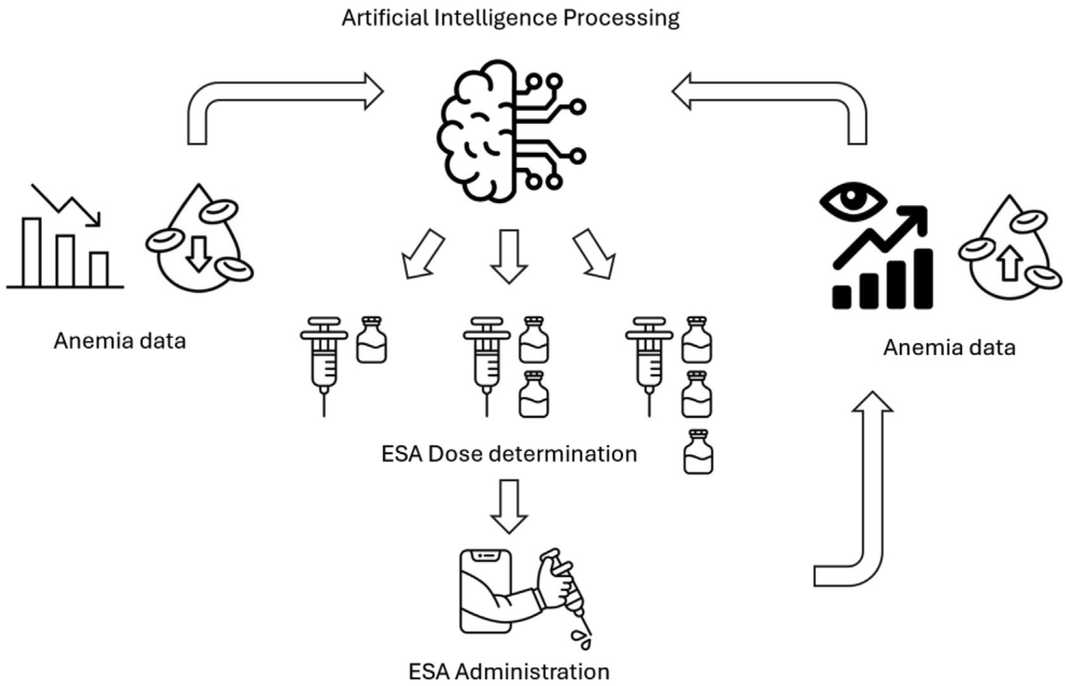

Figure 2. Artificial intelligence empowered clinical decision support system provides individualized recommended dose of an erythrocyte-stimulating agent based on the predicted response to the erythrocyte-stimulating agent.

nephrologists, indicating a potential role for AI-assisted dry weight adjustments in hemodialysis patients.

An AI algorithm has been used to improve anemia management in patients on hemodialysis aiming for optimized use of erythropoietic-stimulating agents (ESAs) (Fig 2). The Anemia Control Model (ACM) was used in 3 pilot clinics as part of routine practice for an observation period of 12 months.[29] The ACM calculates the ESA dose based on an ANN model in which patients' clinical parameters are considered as the input. The model will predict the future hemoglobin (Hb) concentration. The algorithm simulates the effect of varying doses of ESA and suggests an optimal prescription to achieve the Hb target. A control group of 653 hemodialysis patients were treated by physicians according to standard of care without the ACM (group 1). A matched group of 640 patients were treated by physicians who had access to the ACM recommendations (group 2). Darbepoetin consumption declined by 25% in group 2, and despite instances of physicians rejecting ACM guidance, the percentage of Hb values at target range increased by 6%. In the subset of patients in group 2 whose physicians accepted the suggestions of the ACM, a more decisive improvement in Hb was noted (83.2% Hb values on target; median darbepoetin 20 [interquartile range, 80] mcg/month).[29]

DIALYSIS ADEQUACY

Urea clearance has been the mainstay of measuring dialysis adequacy. The volume of distribution of urea reflects total body fluid given that urea is neither highly protein bound nor lipophilic. Kt/V is a dimensionless construct that relates the clearance of urea to its volume of distribution. K is the urea clearance of the dialyzer, t is the dialysis duration in minutes, and V is the urea volume of distribution in milliliters corrected for volume lost during ultrafiltration.[5,30] Kt/V is a predictor of mortality for patients receiving dialysis[31,32]; however, using Kt/V as the sole marker of dialysis adequacy can be misleading. Kt/V does not account for clinical symptoms, volume control, nutritional status, and other biochemical factors influencing clinical outcomes. Moreover, the kinetic behavior of urea molecules is not similar to other small solutes such as guanidine compounds that, in contrast to urea, are known to be toxic.[33] In addition, the assumption is that the Kt/V of one dialysis session is representative of all other sessions, which is most likely not the case. Therefore, it can be challenging to determine the true "adequacy" of dialysis using Kt/V.

On the other hand, direct dialysate quantification (DDQ) is the most accurate and direct method of measuring dialytic urea nitrogen removal[34]; however, collecting the entire spent dialysate is not feasible or practical. A neural network model was applied to predict blood urea concentration during hemodialysis.[35] Using DDQ at 30-minute intervals during dialysis, total urea removal was measured in 15 hemodialysis patients. The neural network model was initially trained to learn the evolution of measured urea concentrations and was subsequently used in another group of 15 hemodialysis patients. The neural network was able to predict the dialysis duration needed to reach a target solute removal index with a prediction error of 10.9%. There was no significant difference between the predicted total urea nitrogen removal and urea nitrogen removal measured using DDQ. Although the prediction model was not exact at all intervals, predicted dialysis duration was comparable to the actual duration required to reach target urea removal, and the concept can be applied to intradialysis profiling of solutes based on individual clinical needs aiming to provide precision dialysis.

Given that malnutrition is common among dialysis population and associated with adverse outcomes[36], estimations of patients' protein catabolic rate (PCR) can be significantly consequential to the quality of dialysis delivered. PCR is indicative of interdialytic urea generation and is used as a parameter to reflect dietary protein intake. An ANN model was found to provide a more accurate correlation between estimated and calculated follow-up PCR ($P < 0.001$) compared with experienced nephrologists. The use of the ANN therefore enhances a nephrologist's ability to estimate and detect an unsatisfactory nutritional status.[37]

ADAPTIVE DIALYSIS PRESCRIPTION: SCIENCE FICTION OR REALITY?

Most patients on thrice-weekly dialysis receive the same dialysis prescription for weeks or months regardless of their dietary intake. This is despite variations in their dietary habits and changes over time. There is a push for the increased use of mobile food logging applications by patients, whereby they can log everything they eat and drink and photograph their meals. This will allow their dietitians to calculate the caloric and macronutrient content of their food and therefore help guide the clinical care team when implementing changes to the dialysis prescription.

Currently, a predialysis serum potassium level checked once a month is used as a representative of the entire month's dietary intake of potassium. This can be and often is misleading. Clinical validation of such approaches will be challenging; however, nephrologists should be prepared to respond and adjust the dialysis prescription as needed based on such data. Checking serum potassium levels every dialysis treatment may sound costly and cumbersome; however, using imperfect measurements such as potassium levels from i-STAT chemistry devices incorporated into dialysis machine functionality can serve as a tool to complement the data from food log applications. The implementation of this would require a clinical decision support system that can make recommendations to the dietitian and nephrologist about dietary adjustments and changes to the potassium bath based on a combination of food log application data and i-STAT potassium levels.

AI algorithms with input from blood volume monitoring and bioimpedance data in combination with biomarkers such as brain natriuretic peptide[38] and lung ultrasonography[39] present a possible step toward improving volume management in dialysis patients. Establishing a dry weight based on traditional methods appears to be unreliable and likely contributes to poor patient outcomes. Employing available biomarkers and imaging data may help develop algorithms to establish accurate dry weight and predict outcomes such as intradialytic hypotension. Such AI algorithms can recognize patterns and provide recommendations accordingly; however, this is not a replacement for clinical assessment.

DATA LAKE: FROM CLINICAL PARAMETERS TO DIALYZER MANUFACTURER

Data Lake is a centralized repository that stores large amounts of unprocessed data. Because the cost of data storage constantly decreases, this makes it more feasible to collect and store all dialysis patient and treatment data. This includes patients' demographics, comorbid conditions, laboratory results, and imaging data obtained using integrated electronic medical records, real-time vital sign measurements and/or wearable heart rhythm monitor data, blood volume monitoring, blood flow rate, dialysate flow rate, dialysate composition, dialysis consumables characteristics, dialyzer, and fiber manufacturer's model number, lot number, and so on.

Leveraging big data and AI algorithms, nephrologists and other members of the clinical care team may cautiously benefit from clinical decision support system. Dialysis patients can therefore benefit from their own treatment data as well as anonymous data from other patients to predict adverse events and provide dynamic responses. Direct feedback from the dialysis chair side to the dialysis equipment manufacturer would be also important to optimize the process and surgery, which may have clinical implications (Fig 3).

THE FUTURE AHEAD

It is too soon to draw conclusions about the applicability of AI algorithm-based practices on a population scale. The incorporation of large data sets is a prerequisite for the appropriate training of the AI algorithm and its implementation. On the other hand, access to large human data sets will raise other concerns including regulatory, access to protected health information, data leakage, ownership of data and informed consent issues.[12] Strict regulatory oversight for the development and monitoring of AI systems is needed to ensure safe and ethical AI-driven practices and models. That being said, there are barriers to the widespread integration of AI into clinical practice. Lack of physician awareness, concerns regarding its effect on the patient–doctor relationship, as well as uncertainty of stake holders about the return on investment are among the barriers. Developing guidelines to ensure the responsible use of AI is crucial. To help combat some of these concerns, the World Health Organization (WHO) has outlined considerations for regulation of AI for health,[40] and an executive order from the White House has been issued on

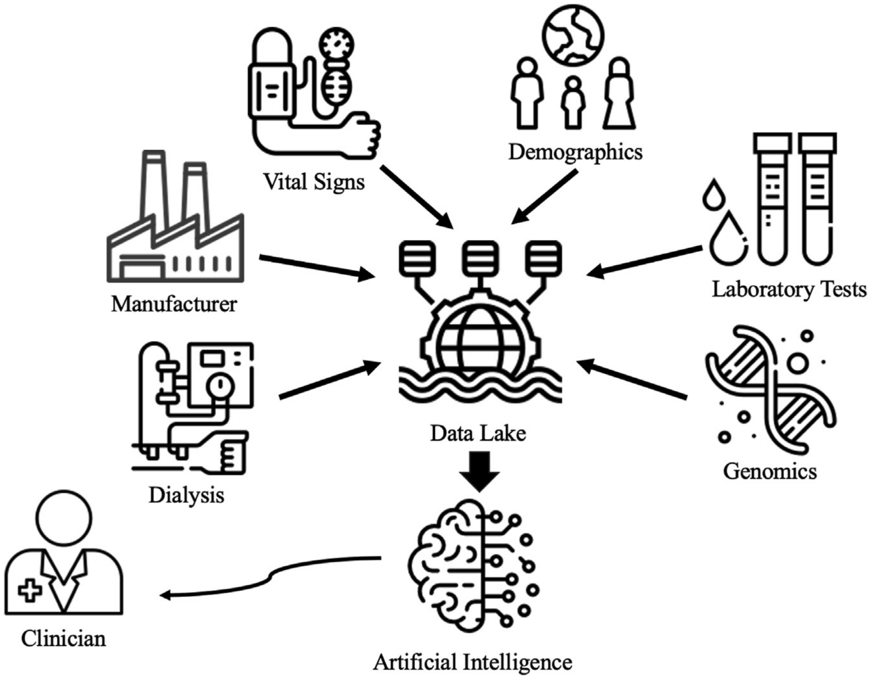

Figure 3. All data from continuous dialysis monitoring, vital signs, patient demographics, laboratory results, imaging results, and genetic testing results can be used as the input for the learning process to provide predictions and a clinical decision support system for clinicians.

the safe, secure and trustworthy use of AI while managing the risks, protecting privacy, civil rights and advancing equity.[41] The FDA has also outlined a regulatory approach tailored to AI and ML technologies used in medical devices.[42]

Caution is advised with the widespread incorporation of AI in dialysis. Prediction models are as accurate as the data used to generate them. For example, gaps in the data of dialysis patients that do not factor in crucial relevant clinical information such as hospitalization information, acute illnesses, and the effect of residual kidney function may adversely affect the AI-generated recommendations and management.

In conclusion, AI is a support system and not a replacement for clinical judgment and should not decrease the vigilance of practitioners. As technology advances and cost of data storage constantly decreases, it is feasible to collect patient information and dialysis treatment data. Using these large data sets, unbiased AI algorithms can be trained to identify patterns with clinical implications confirmed by clinicians. The introduction of more physiologic and smart dialysis systems equipped with AI approaches can enable learning from individual and collective treatment data and provide dynamic responses to unexpected changes during dialysis. The nephrology community should become familiar with the appropriate use and limitations of the AI-driven clinical decision support system. It is yet to be demonstrated how big data and AI tools could improve outcomes of dialysis patients.

ARTICLE INFORMATION

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