Development of an Artificial Intelligence Model to Guide the Management of Blood Pressure, Fluid Volume, and Dialysis Dose in End-Stage Kidney Disease Patients: Proof of Concept and First Clinical Assessment

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Keywords

Hemodialysis · Artificial intelligence · Intradialytic hypotension · Dialysis adequacy · Fluid overload · Hemodynamics · Heart rate · Personalized medicine · Medical decision-making

Abstract

Background: Fluid volume and blood pressure (BP) management are crucial endpoints for end-stage kidney disease patients. BP control in clinical practice mainly relies on reducing extracellular fluid volume overload by diminishing targeted postdialysis weight. This approach exposes dialysis patients to intradialytic hypotensive episodes. **Summary:** Both chronic hypertension and intradialytic hypotension lead to adverse long-term outcomes. Achieving the optimal trade-off between adequate fluid removal and the risk of intradialytic adverse events is a complex task in clinical practice given the multiple patient-related and dialysis-related factors affecting the hemodynamic response to treatment. State-of-the-art artificial intelligence has been adopted in other complex decision-making tasks for dialysis patients and may help personalize the multiple dialysis-related pre-

scriptions affecting patients' intradialytic hemodynamics. As a proof of concept, we developed a multiple-endpoint model predicting session-specific Kt/V, fluid volume removal, heart rate, and BP based on patient characteristics, historic hemodynamic responses, and dialysis-related prescriptions. **Key Messages:** The accuracy and precision of this preliminary model is extremely encouraging. Such analytic tools may be used to anticipate patients' reactions through simulation so that the best strategy can be chosen based on clinical judgment or formal utility functions.

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Introduction

Fluid volume and blood pressure (BP) management are crucial clinical performance indicators of dialysis adequacy in end-stage kidney disease (ESKD) patients. The

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prevalence of hypertension among ESKD patients ranges between 40 and 90% according to the BP definition used, the population selected, and the timing of measurement [1, 2]. A notable example is represented by a multicenter study including 2,535 North-American prevalent dialysis patients [1]. In this cohort, 86% of the patients had a weekly mean of predialysis systolic BP (SBP) >150 mm Hg or a diastolic BP >86 mm Hg. Hypertension is more prevalent among ESKD patients that are initiating renal replacement therapy, since most of them present with relatively severe extracellular fluid volume expansion [3].

Clinical BP control relies mainly on reducing extracellular fluid volume overload by decreasing targeted post-dialysis weight. This approach, consisting in probing “dry weight,” exposes dialysis patients to intradialytic hypotensive (IDH) episodes. IDH episode is reported in 10–20% of all hemodialysis sessions, depending on the criteria, dialysis modality, or population selected. Acute volumic changes due to the ultrafiltration (UF) rate that occur during hemodialysis sessions are associated with BP and heart rate changes that contribute to repetitive hemodynamic stress and potential systemic or local ischemic insult on target organs [3].

Supporting Dialysis Prescriptions with Artificial Intelligence: Rationale

Despite significant progresses in technical aspects, fluid volume and BP control are still a challenging situation for clinicians in hemodialysis patients. On the one hand, fluid volume removal, osmolality changes, and electrolyte imbalance are well-known interacting key players of hemodynamic instability and maltolerance of hemodialysis session [3, 4]. On the other hand, inadequate control of fluid overload and high BP may favor the occurrence of cardiovascular events and mortality. It is now established, that both chronic fluid overload and hypertension and intradialytic hemodynamic stress due to hypovolemia are associated with poor long-term patient outcomes including cardiovascular morbidity (hospitalization), altered quality of life, and mortality [5].

Fluid volume management and BP control may be addressed by diet guidance (e.g., salt restriction), pharmacological interventions (e.g., antihypertensive medications), and dialysis prescription (e.g., low dialysate sodium, longer treatment time, and hypothermic dialysis). Additionally, instrumental assessments may help tailor such prescriptions to patients’ needs (e.g., body composition evaluation by bioelectrical impedance, volemia mon-

itoring, etc.). Unfortunately, none of them has been proved individually sufficient to prevent dialysis-induced hemodynamic stress. Today, it is obvious that a combination of several of these approaches is required to achieve this primary goal and to improve the cardiovascular outcome of hemodialysis patients. Furthermore, the fine-tuning of such prescription is complicated by individual variations on a weekly basis and on patient’s health conditions.

Reaching the optimal trade-off minimizing the risk associated with hemodynamic management while reaching dialysis treatment adequacy (i.e., Kt/V, fluid removal, etc.) is still a challenging situation for the nephrologist, given the complex interaction of all these factors. Even though the majority of ESKD patients today are in target for dialysis adequacy key indicators, such achievements may still be paid by a high rate of preventable procedure-related hemodynamic side effects.

Artificial intelligence can be used to predict the individualized, session-specific patient reaction to dialysis-related prescriptions on multiple relevant hemodynamic parameters (e.g., intradialytic heart rate and BP changes and trends) and dialysis adequacy parameters (e.g., Kt/V and fluid removal) so that the best strategy can be chosen based on clinical judgment or formal utility functions.

Artificial intelligence has already been successfully applied at the point of care to support physicians in the decision-making process [6–9]. The availability of accurate, longitudinal, real-life data is a key factor for the development of reproducible predictive models. The clinical system EuCliD[®] is an international electronic health record repository allowing point-of-care data collection of routine clinical practice information. Such detailed information includes anthropometric and sociodemographic information, results of biochemistry essays, diagnoses, medications, functional status, and dialysis access status collected by the clinical staff or automatically recorded via electronic upload of laboratory registries. Additionally, body composition and treatment data including fluid volume status, and serial monitoring of hemodynamic parameters such as BP, fluid volume and refilling rate capacity, body and dialysate temperature, fluid flow and blood flow, dialysate and plasma electrolyte concentrations as well as body weight changes are recorded for each dialysis session.

By exploiting such wealth of information, we developed a patient- and session-specific artificial neural network (ANN) to predict SBP and heart rate profiles, post-dialysis body weight, and the Kt/V for each hemodialysis session.

Table 1. Observed average dialysis-related endpoints and model prediction error

	Mean	SD	Model ME	Model MAE
Minimum SBP of the session, mm Hg	113.0	23.5	−0.16	9.3
Postdialysis heart rate, bpm	71.1	13.8	0.04	7.3
Postdialysis weight, kg	70.1	15.5	0.00	0.23
Kt/V	1.89	0.43	0.00	0.13

SD, standard deviation; ME, mean error; MAE, mean absolute error.

Model Development and Validation

An ANN [10] is a computational model based on a set of interconnected processing units organized in successive layers, loosely inspired by the neurons in the human brain, that learn to compute a specific input-output mapping by tuning a set of parameters (the weights of the connections between the units) in response to being exposed to a sufficiently large set of input and output data pairs (Fig. 1). A distinctive advantage of multilayer ANN models over traditional regression techniques is the ability to approximate any continuous function while being free of prespecified distributional assumptions. This property is particularly useful to simultaneously model multiple, heterogeneous outcomes especially when complex interactions and nonlinear effects exist between predictor variables and the outcomes of interest. Such an advantage can be achieved even with relatively simple feed-forward ANNs (that is, where connections exist only from a layer of neurons to the subsequent one) of moderate complexity and size. As no assumptions on variable distribution and form of the input-output relationship need to be imposed, the ANN approach is more flexible and more easily adapts to complex prediction problems compared to standard regression models, and even more so when compared to rule-based decision systems, which need to explicitly list a (long, and often incomplete) set of conditions and corresponding results, with no generalization capability. On the other hand, an ANN, if properly trained, can automatically infer input-output relationships from the data itself and generalize this knowledge to unseen, new data.

Our current model includes roughly 60 variables representing patient characteristics, their historical record of physiological reactions, and outcomes of previous dialysis sessions, predialysis data, and the prescribed dialysis dose for the index session. The data set used for modeling consists of 766,000 records, each representing a dialysis

Fig. 1. Schematic depiction of a multilayer feed-forward ANN. An ANN can have an arbitrary number of inputs, hidden layers, and units in each layer. Each connection between the units has a weight value that gets tuned in response to training on input-output examples. After training, the output of the ANN can be employed to predict outcomes of interest, based on the historical data used to feed the training process.

session recorded in the Spanish NephroCare centers from January 2015 to January 2018; 80% of the records have been used to train and validate the model (70% for training and 10% for validation), while the remaining 20% have been used to test it after the model was finalized. The mean and standard deviation of the considered endpoints and the corresponding prediction error, expressed as the mean absolute error and mean error in the test set, are reported in Table 1.

Our preliminary results show that, while prediction of the postdialysis weight and Kt/V are virtually free of systematic error and a very small imprecision, modeling of the minimum SBP and heart rate has shown to be more difficult, possibly due to measurement errors by the ma-

Fig. 2. Simulated intradialytic SBP change due to variation in UF prescriptions. Each point of the simulation surface represents the resulting predicted intradialytic SBP drop (SBPD) given a specific combination of UF rate and treatment time for each patient. The simulation shows that Patient A (**a**) and Patient B (**b**) have a different hemodynamic reactivity.

Fig. 3. Optimization of UF prescription by simulated intradialytic SBP change. Each point of the simulation line represents the resulting predicted intradialytic SBP drop (SBPD) for a specific fluid removal target for Patient A. For Patients A and B, the relationship is not linear, and a steeper increase in SBPD is observed at higher UF volumes. Additionally, several equivolumetric combinations of treatment time and UF rate produce different SBPD estimates. FVL, fluid volume removal.

Table 2. Patient characteristics

	Patient A	Patient B
Weight, kg	80	98
Heart rate, bpm	76	68
DBP, mm Hg	82	60
Body fat mass, kg	40	57
Age, years	80	56
Diabetes vintage, years	10	30
HTN vintage, years	12	30
D-sodium, mEq/L	140	138
S-sodium, mEq/L	137	140
Ferritin	362	40
Hemoglobin	10	13
Glucose	225	97
Phosphate	5	8

DBP, diastolic BP; HTN, hypertension.

chine-integrated sensors and the naturally erratic variations in hemodynamic reaction physiology. Nevertheless, the mean absolute error shows acceptable average errors, which support the use of such a model in clinical practice. The error in SBP is less than the average white-coat effect and has presumably a small clinical significance in the context of hemodialysis patients who have SBP in the hypertensive range. Given that IDH episodes are defined by sustained and symptomatic decrease in SBPs >30 mm Hg or SBPs <90 mm Hg, our model appears to be sufficiently accurate and precise to allow physicians anticipating the risk of IDH before the beginning of each session. Fur-

thermore, the prediction error observed for the postdialysis heart rate model would most likely have marginal effect on our model's ability to discriminate serious tachy- or bradyarrhythmias considering that they are defined as >130 and <40 bpm for several seconds, respectively.

How Artificial Intelligence May Help Medical Decision-Making: A Use Case

The potential usage of the model can be illustrated by examining and comparing 2 real-life cases. For the sake of simplicity, we represent here a decision problem defined by concurrent management of two clinical endpoints (intradialytic fluid removal and SBP change) by manipulation of two prescription parameters (treatment duration and UF rate), during a specific dialysis session. Clinical data, prescriptions, and outcomes for the 2 patients have been extracted and anonymized from the Eu-CliD database and belong to patients who were active in the Spanish network at the time of manuscript preparation. Both Patients A and B were obese (BMI = 32), had multiple comorbidities including a long history of diabetes and hypertension, had similar predialysis SBP levels (110 vs. 115 mm Hg, respectively), estimated overhydration (>4 L for both), and received the same UF prescription (UF rate: 1 L/h; dialysis time: 240 min). However, only Patient A experienced a major hypotensive event during the index session. Despite similar in many respects, these 2 patients had several divergent characteristics (Table 2). Our model helps answer questions that lay

the basis for clinical management: were the hemodynamic reactions of both patients predictable? Would the adverse event experienced by Patient A have been preventable? By providing accurate simulations, our model facilitates session-specific prognostic reasoning and allows minimizing the risk of adverse events. Figure 2 reports the simulation of SBP variations following different UF prescriptions based on our model predictions for both patients. Model-driven simulation of the index session graphically shows that Patient A (Fig. 2a) is sensitive to hemodynamic shocks caused by variations in UF prescription, whereas Patient B (Fig. 2b) is strongly resilient to such variations. A closer look at Patient A's simulated reaction allows to detect a safer UF prescription while maximizing fluid removal (Fig. 3). The case could be further explored by assessing the impact of manipulating dialysate electrolyte compositions or the temperature on heart rate and BP changes so that multiple endpoints can be concurrently optimized.

In conclusion, our multiendpoint model may help formally integrate the optimization of several, interrelated treatment outcomes within a single multidimensional

decision-making process substituting limited single-endpoint treatment strategies mostly used in clinical practice [10].

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

C.B. contributed to manuscript conception and writing, the interpretation of results, and approved the final version of the manuscript. I.C. contributed to manuscript conception, data analysis, the interpretation of results, and approved the final version of the manuscript. L.N., D.B., B.C., F.M., and S.S. contributed to manuscript conception and writing, the interpretation of results, and approved the final version of the manuscript.

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