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Intermittent hypoxemia during hemodialysis: AI-based identification of arterial oxygen saturation saw-tooth pattern

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Abstract

Background Maintenance hemodialysis patients experience high morbidity and mortality, primarily from cardiovascular and infectious diseases. It was discovered recently that low arterial oxygen saturation (SaO_2) is associated with a pro-inflammatory phenotype and poor patient outcomes. Sleep apnea is highly prevalent in maintenance hemodialysis patients and may contribute to intradialytic hypoxemia. In sleep apnea, normal respiration patterns are disrupted by episodes of apnea because of either disturbed respiratory control (i.e., central sleep apnea) or upper airway obstruction (i.e., obstructive sleep apnea). Intermittent SaO_2 saw-tooth patterns are a hallmark of sleep apnea. Continuous intradialytic measurements of SaO_2 provide an opportunity to follow the temporal evolution of SaO_2 during hemodialysis. Using artificial intelligence, we aimed to automatically identify patients with repetitive episodes of intermittent SaO_2 saw-tooth patterns.

Methods The analysis utilized intradialytic SaO_2 measurements by the Crit-Line device (Fresenius Medical Care, Waltham, MA). In patients with an arterio-venous fistula as vascular access, this FDA approved device records 150 SaO_2 measurements per second in the extracorporeal blood circuit of the hemodialysis system. The average SaO_2 of a 10-second segment is computed and streamed to the cloud. Periods comprising thirty 10-second segments (i.e., 300 s or five minutes) were independently adjudicated by two researchers for the presence or absence of SaO_2 saw-tooth pattern. We built one-dimensional convolutional neural networks (1D-CNN), a state-of-the-art deep learning method, for SaO_2 pattern classification and randomly assigned SaO_2 time series segments to either a training (80%) or a test (20%) set.

Results We analyzed 4,075 consecutive 5-minute segments from 89 hemodialysis treatments in 22 hemodialysis patients. While 891 (21.9%) segments showed saw-tooth pattern, 3,184 (78.1%) did not. In the test data set, the rate of correct SaO_2 pattern classification was 96% with an area under the receiver operating curve of 0.995 (95% CI: 0.993 to 0.998).

Conclusion Our 1D-CNN algorithm accurately classifies SaO_2 saw-tooth pattern. The SaO_2 pattern classification can be performed in real time during an ongoing hemodialysis treatment, provide timely alert in the event of respiratory instability or sleep apnea, and trigger further diagnostic and therapeutic interventions.

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Keywords Hemodialysis, Arterial oxygen saturation, Sleep apnea, One-dimensional convolutional neural networks

Background

Maintenance hemodialysis (HD) patients suffer from unacceptable high morbidity and mortality, with cardiovascular disease (CVD) being the main cause of hospitalization and death. The association between low arterial oxygen saturation (SaO_2) during dialysis and poor patient outcomes is well established [1, 2]. Physiologically, the transport of oxygen to peripheral tissues and organs depends on cardiac output, hemoglobin concentration, and saturation of hemoglobin molecules with oxygen. In HD patients, heart failure is a well-recognized cause of tissue hypoxia. Less appreciated is peripheral hypoxia due to structural and functional pathologies of the respiratory system, resulting in reduced SaO_2. Next to cardiac output and hemoglobin concentration, SaO_2 is a crucial determinant of the amount of oxygen delivered to tissues and organs. Clinically, SaO_2 can be assessed using both invasive and non-invasive methods. Recent advancements have introduced technologies that enable continuous monitoring of SaO_2 in the HD extracorporeal blood circuit during a treatment session. These innovations have proven valuable for identifying intradialytic hypoxemia [2], monitoring COVID-19 patients [3], and tracking other important clinical outcomes [1] such as respiratory instability [4]. Nocturnal hypoxemia is associated with cardiovascular complications in incident hemodialysis patients [5]. Prolonged intradialytic hypoxemia (PIH), defined as SaO_2 below 90% for more than one third of the HD treatment time, is associated with increased hospitalization and mortality rates. In addition, maintenance HD patients with PIH show a pro-inflammatory phenotype, as indicated by higher inflammatory markers, lower serum albumin levels, and resistance to erythropoietin. Furthermore, PIH is more prevalent in HD patients with comorbidities such as congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) [1]. Intradialytic hypoxemia is also associated with peridialytic hypertension, possibly related to sympathetic activation and endothelin-1 secretion [6].

Recently, we observed distinct intermittent oscillatory saw-tooth pattern (STP) of SaO_2 in patients on HD [4]. In some instances, through detailed clinical observation, we were able to link STP to sleep-related breathing disturbances. This finding is significant, as sleep-disordered breathing is common in dialysis patients [7]. A study found that 37% of males and 34% of females with end-stage kidney disease (ESKD) treated with dialysis had sleep apnea syndrome (SAS). SAS was significantly associated with age, obesity, diabetes, hypertension, and other sleep disorders [8, 9]. These findings highlight the importance of monitoring SaO_2 during HD, as early identification of and intervention for intradialytic hypoxemia could mitigate its impact on long-term morbidity and mortality in this vulnerable population.

A recent study using recurrence analysis quantifies an optimal recurrence threshold (ε_{opt}) to identify STP [4]. Constructing ε_{opt} time series with a rolling window allows real-time detection of intermittent high-frequency high-amplitude STP. ε_{opt} correlates highly with SaO_2 desaturation density, and, using oxygen desaturation index as a surrogate for the apnea–hypopnea index, ε_{opt} accurately distinguishes SAS events.

One-dimensional convolutional neural networks (1D-CNN) have gained significant attention in the medical field, particularly for analyzing time series of biomedical signals such as electrocardiograms (ECG) and electroencephalograms (EEG). These networks can efficiently process time-series data and other one-dimensional formats without extensive pre-processing. Applications include patient-specific ECG classification and early diagnosis of diseases [10].

Quasi-continuous measurement of SaO_2 in the extracorporeal circuit by the Crit-Line monitor (CLM) affords the opportunity to follow the temporal evolution of SaO_2 during HD. Against this backdrop, we aimed to automatically identify repetitive episodes of intermittent STP using 1D-CNNs.

Methods

In HD patients with an arterio-venous fistula as vascular access, the oxygen saturation in the extracorporeal HD circuit resembles SaO_2. SaO_2 during HD was measured using the CLM (Fresenius Medic Care North America, Waltham, MA), a device certified by the US Food and Drug Administration (FDA) for the measurement of hematocrit and oxygen saturation in the extracorporeal blood circuit of the HD system. CLM measures oxygen saturation and hematocrit 150 times per second. These measurements are then averaged over a 10-second period and the respective means transmitted to Amazon Web Services (AWS) via Apache KAFKA, a real time streaming software [11].

Patient selection

To build our AI model, we collected intradialytic SaO_2 recordings from HD patients. The inclusion criteria were (a) being an in-center maintenance hemodialysis patient, and (b) availability of CLM SaO_2 recordings. The patients were dialyzed in clinics of the Fresenius Kidney Care network that comprises about 2,500 clinics in the US. In about 600 of these clinics, CLM is used as a standard of care. There were no exclusion criteria. These rather

wide inclusion criteria and the absence of exclusion criteria ensure that the base population is typical for a US HD population and that the results are generalizable. In these about 600 clinics, we have collected data from about 500,000 HD treatments. Out of these treatments we selected 89 treatments from 22 patients.

Visual inspection

We segmented the treatment time series into 5-minute consecutive sections, each segment had 30 SaO_2 measurements. The 5-minute segments were visually inspected and independently adjudicated by two researchers who categorized them as either no saw-tooth pattern (NSTP, stable and consistent SaO_2 with minimal fluctuations; Fig. 1A) or STP. NSTP indicates respiratory stability. In contrast, STP shows much greater variability and fluctuations with noticeable peaks and troughs over time; it indicates respiratory instability (Fig. 1B). The visual classification of SaO_2 patterns by the two independent observers was based on two characteristics: amplitude and duration. NSTP were considered SaO_2 variations with an amplitude of less than 2%, with only occasional isolated spikes exceeding 5% in amplitude and lasting less than 30 s. In contrast, STP were considered by oscillations in SaO_2 with an amplitude greater than 5% and a duration exceeding 30 s. Severe STP had an SaO_2 < 90%. The reason for the < 90% SaO_2 criterion was that earlier work showed that intradialytic SaO_2 < 90% is associated with increased morbidity and mortality [1]. Discrepancies between the two observers were resolved through a joint review.

Training

We randomly allocated the 5-minute SaO_2 time series segments to either training (80%) or test (20%) data sets. Initially, most segments in the training data were NSTP. To address this class imbalance in the training data, we up-sampled the STP group to match the number of NSTP samples. This was done by randomly selecting STP segments with replacement from the original pool and replacing the original STP samples in the training dataset with the newly selected ones. The test data set was not changed. The updated training dataset was then shuffled and randomly partitioned into two subsets. To improve model generalization, random Gaussian noise (mean = 0, standard deviation = 0.1) was added to every

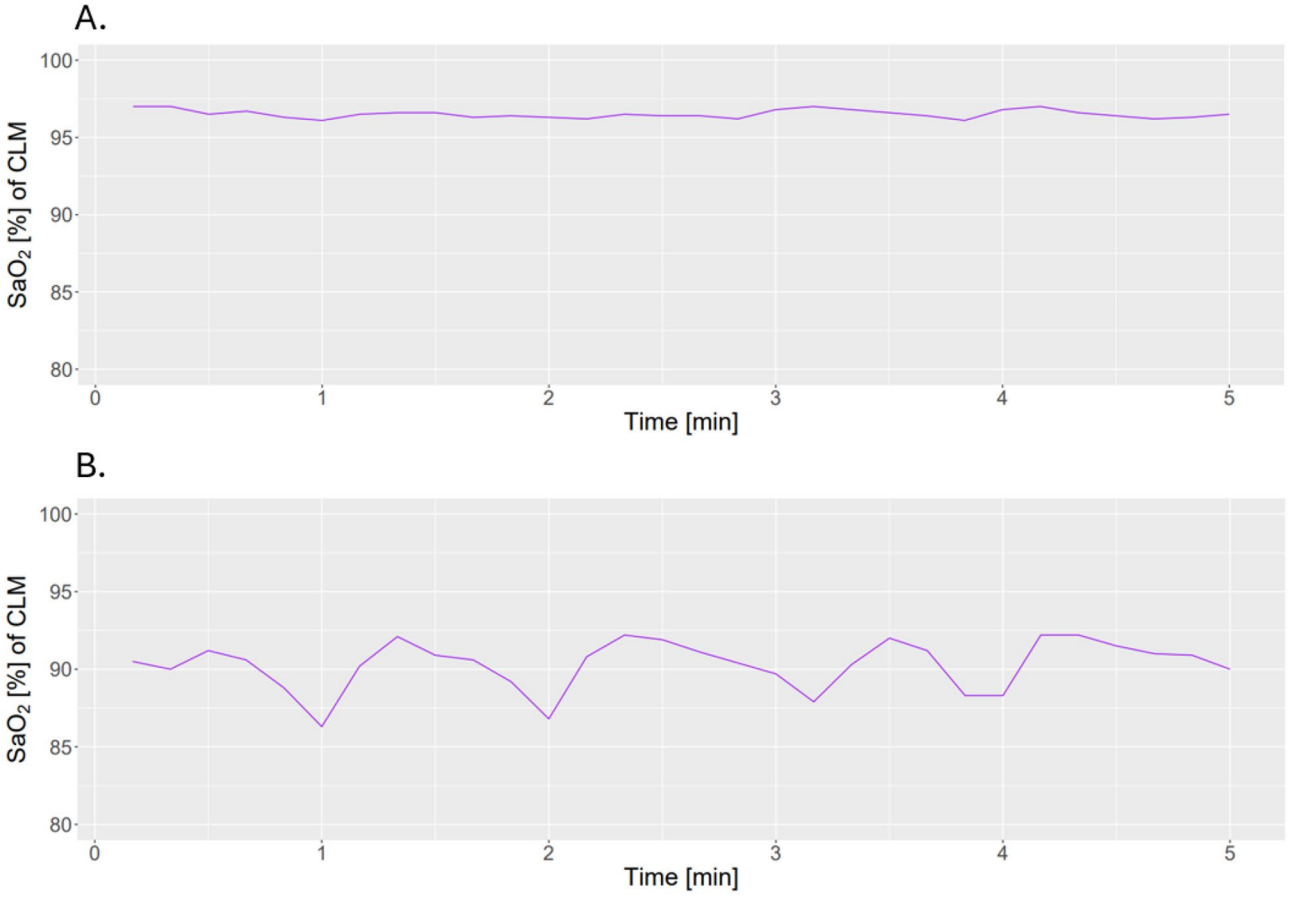

Fig. 1 Two examples of SaO_2 time series. Panel (**A**) shows an SaO_2 time series without saw-tooth pattern. Panel (**B**) shows a SaO_2 saw-tooth pattern with about one cycle per minute

SaO_2 measurement in one subset, which was then used to train the 1D-CNN. The other subset served as the validation set for computing the validation error throughout the optimization process.

For the learning process we used the Keras open-source deep learning library [12] to build a 1D-CNN. The input layer of our 1D-CNN receives the 5-minute time-series segments of SaO_2. The first convolutional layer applies 32 filters, each with a kernel size of 6, to extract low-level temporal patterns from the input sequences. A Batch Normalization layer follows the convolution to normalize activations and accelerate training. A Max Pooling layer with a pool size of 3 and a stride of 2 is applied to reduce spatial dimensions while retaining the most important features. A second convolutional layer is applied to the pooled output to refine feature extraction. This layer has 32 filters with a kernel size of 3. Batch Normalization is again used to improve stability during training. Another Max Pooling layer with a pool size of 2 and a stride of 2 is applied. Following the convolutional and pooling layers, the output is flattened to a 1D vector to be fed into the fully connected layers. The fully connected layer with 32 neurons is applied to capture deeper representations of the extracted features. Finally, the model outputs a probability distribution over two classes using a softmax activation function, providing classification probabilities for NSTP and STP, respectively (Fig. 2).

The model was trained using the Adam optimizer from the Keras 3.5 library with a categorical cross-entropy loss function [13]. Training was conducted for 1,500 epochs with a batch size of 32 and a learning rate of 0.000003.

Test/validation

The model with the smallest validation error was chosen as the final model. This final model was then evaluated on the test set using the following metrics: accuracy, sensitivity, specificity, F_1-score and area under the receiver operating curve (AUC).

Results

We sampled 89 HD treatments with SaO_2 measurements from 22 in-center patients across four different clinics (Table 1). Continuous variables are reported as mean (± standard deviation) or median [Q1, Q3] and categorical variables are presented as proportions. In total, 4,075 consecutive 5-minute segments were adjudicated, 21.9% with STP and 78.1% with NSTP. The training dataset comprised 3,260 segments, while the test set contained 815 segments. Within the training set, NSTP and STP segments were distributed as 2,542 (78.0%) and 718 (22.0%), respectively. In the test set, these distributions were 642 (78.8%) for NSTP and 173 (21.2%) for STP (Table 2).

Our 1D-CNN model reached a 96.4% accuracy and an AUC of 0.995 (95% CI: 0.993 to 0.998) in the test set (Fig. 3). The respective confusion matrix is shown in Table 3. In the test data, the model reached 96.5% sensitivity, 96.4% specificity and 0.92 F_1-score, indicating that it can work as a reliable method to detect STP.

For external validation, we randomly selected 20 recent HD treatments from 18 clinics. For this sampling, we did not perform the up-sampling of STPs to ensure a more accurate representation of their actual prevalence. Within this external validation dataset, the model achieved a sensitivity of 95.1%, a specificity of 96.7%, and an F1-score of 0.79 (Table 4).

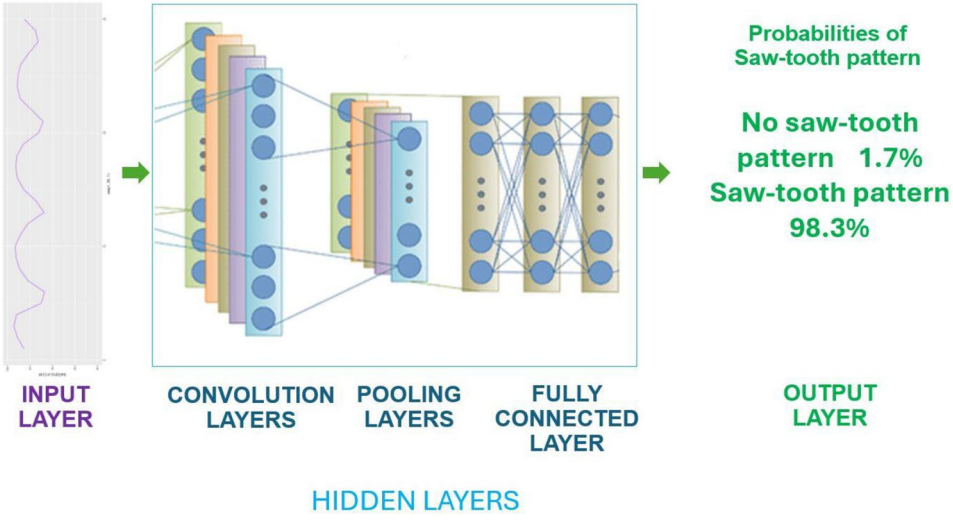

Fig. 2 Architecture of a 1-dimensional convolutional neural network (1D-CNN). In this example, a STP is presented to the input layer. The trained 1D-CNN computes the probabilities for NSTP and STP, respectively

Table 1 Patient and treatment characteristics

	Patients (*n* = 22)
Number of SaO_2measurements per patient	5,557 ± 2,933
Age (years)	64.7 ± 14.3
Gender	
Female, n (%)	5 (23)
Male, n (%)	17 (77)
Race	
White, n (%)	11 (50)
Non-white, n (%)	11 (50)
Vintage (median [Q1, Q3], years)	7.9 [6.4, 12.9]
Comorbidities	
Diabetes, n (%)	14 (64)
Congestive heart failure, n (%)	8 (36)
Chronic obstructive pulmonary disease, n (%)	3 (14)
Treatment parameters	
Pre-dialysis SBP (mmHg)	147.6 ± 24.7
Post-dialysis SBP (mmHg)	129.5 ± 22.4
Pre-dialysis DBP (mmHg)	73.1 ± 12.3
Post-dialysis DBP (mmHg)	66.1 ± 11.0
Pre-dialysis weight (kg)	85.0 ± 26.6
Post-dialysis weight (kg)	82.5 ± 25.7
Dialysis duration (min)	228.2 ± 29.5
Blood flow rate (mL/min)	416.0 ± 25.5
Dialysate flow rate (mL/min)	648.4 ± 63.1
Ultrafiltration volume (L)	2.5 ± 1.4

Table 2 Rate of saw-tooth pattern and no saw-tooth pattern among 5-minute segments in the training and test data, respectively

	Saw-tooth pattern	**No saw-tooth pattern**	**Total**
Training data	22.0% 718 / 3,260	78.0% 2,542 /3,260	100% 3,260
Test data	21.2% 173 / 815	78.8% 642 / 815	100% 815
Total	21.9% 891 / 4,075	78.1% 3,184 / 4,075	100% 4,075

Table 3 Confusion matrix of the classification performance in the test data set

		Prediction		
		Saw-tooth pattern	**No saw-tooth pattern**	**Total**
Actual	Saw-tooth pattern	96.5% 167 / 173	3.5% 6 / 173	100% 173
	No saw-tooth pattern	3.6% 23 / 642	96.4% 619 / 642	100% 642
	Total	190	625	815

Figure 4 shows the SaO_2 measurements of two different HD treatments. Both sessions were about four hours long. In Fig. 4A, NSTP was classified, while for the session shown in Fig. 4B the model classified STP for many of the 5-minute segments (shown in orange).

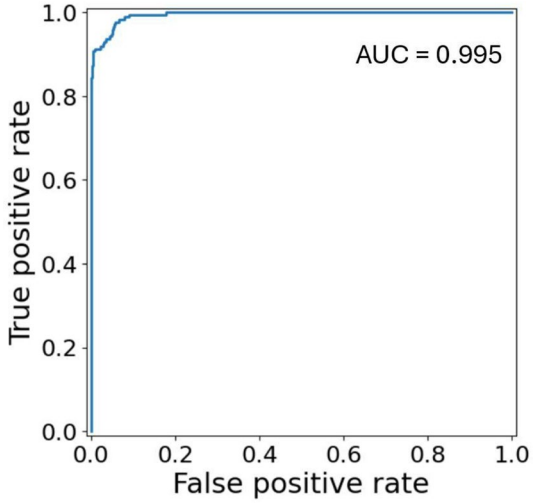

Fig. 3 Receiver operating curve and AUC on the test data set

Table 4 Confusion matrix of the classification performance in the external validation data set

		Prediction		
		Saw-tooth pattern	**No saw-tooth pattern**	**Total**
Actual	Saw-tooth pattern	95.1% 58 / 61	4.9% 3 / 61	100% 61
	No saw-tooth pattern	3.3% 27	96.7% 791 / 818	100% 818
	Total	85	794	879

To distinguish presumably benign from more concerning STP, we decided to further categorize STP in mild and severe STP. If a 5-minute segment was classified as STP and the minimum SaO_2 in that segment was below 90% then we classified it as severe STP. If a 5-minute segment was classified as STP and all SaO_2 measurements were equal or above 90% then we classified it as mild STP. Figure 5 shows the same HD treatment as Fig. 4B after separating mild and severe STP.

Discussion

Our primary finding demonstrates that a 1D-CNN can classify quasi-continuous intradialytic SaO_2 recordings with high accuracy into STP and NSTP, respectively. The method can be scaled easily, enabling efficient classification of a large volume of SaO_2 measurements. Given the prevalence and clinical significance of hypoxemia in HD patients, this result may hold important clinical implications.

While adequate SaO_2 is fundamentally important for health and quality of life, there is a notable knowledge gap about SaO_2 dynamics during HD. To address this issue, dialysis providers have implemented CLM devices in about 600 dialysis clinics across the US, many of which are connected to the cloud for seamless,

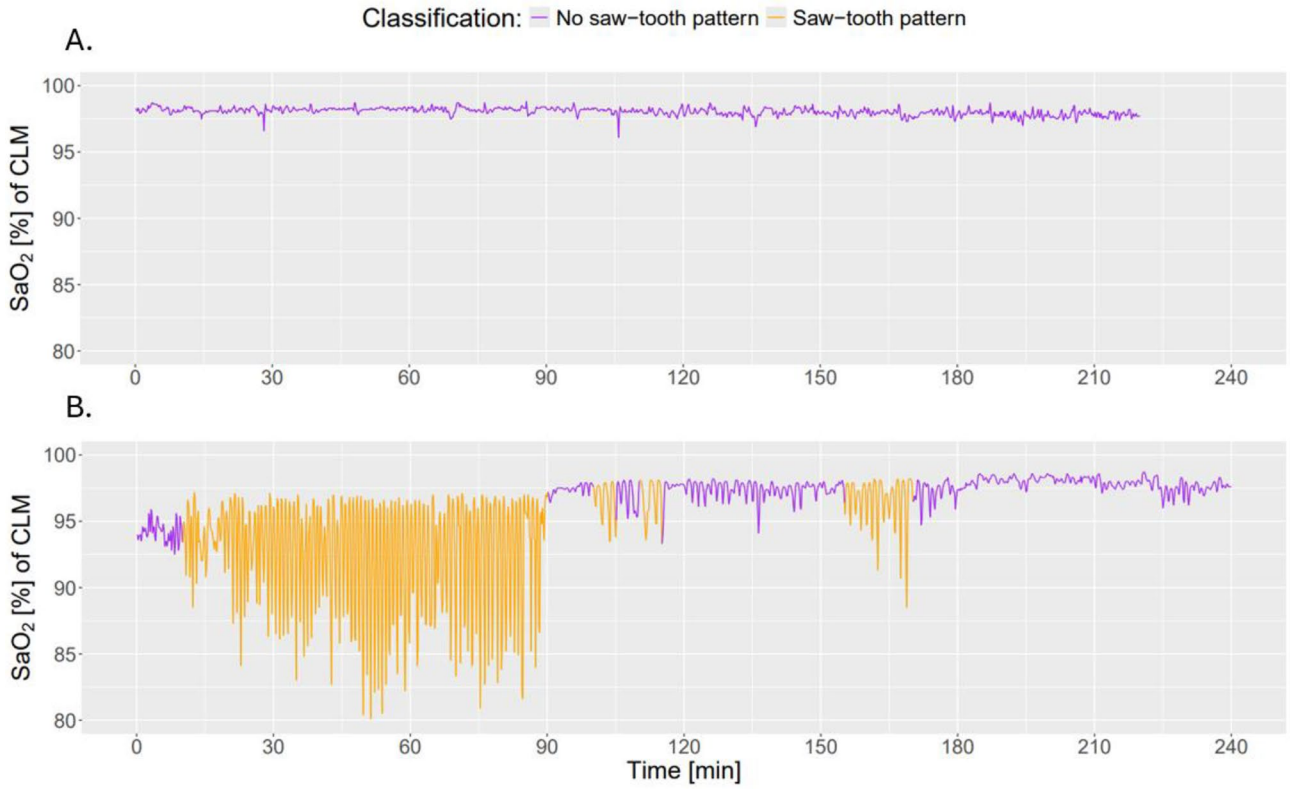

Fig. 4 Intradialytic SaO_2 measurements during two hemodialysis sessions. (**A**) Session without saw-tooth pattern classified. (**B**) Session with saw-tooth patterns (orange)

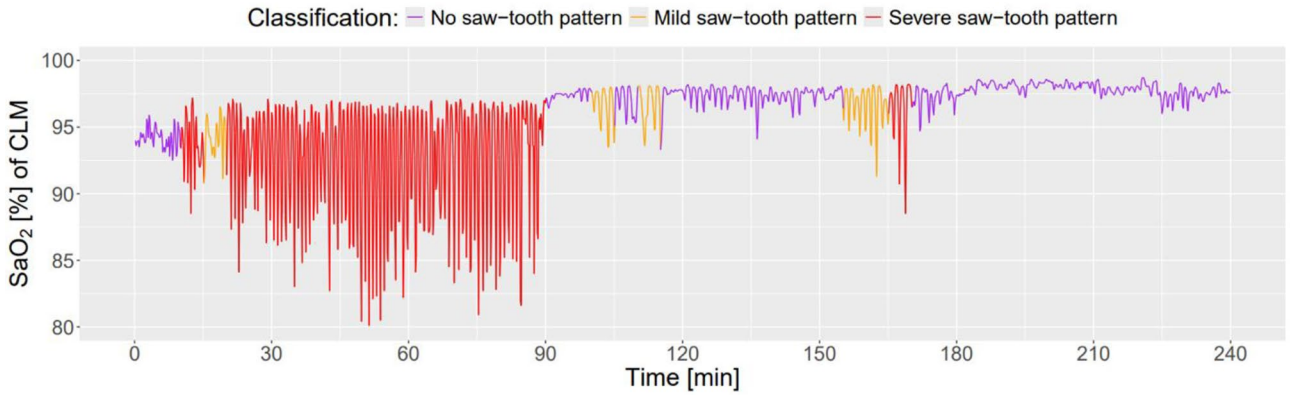

Fig. 5 Intradialytic SaO_2 measurements during a hemodialysis session with intermittent mild (orange) and severe (red) saw-tooth patterns

quasi-continuous data gathering. Recently, we collected over six billion intradialytic SaO_2 measurements from over 70,000 HD patients [14]. The analysis of such a vast data repository necessitates automated methods, which led us to develop an AI-based tool, a 1D-CNN. This model accurately classifies STP in SaO_2 time series recorded during HD. We plan to deploy the model in the cloud, focusing on quantifying the SaO_2 pattern at both the treatment and patient levels. This approach aims to enhance our understanding of intradialytic SaO_2 dynamics and their clinical correlates.

SaO_2 is a critical parameter in the management of patients undergoing HD, as it provides insights into the patient's respiratory and circulatory status. In HD patients, maintaining adequate SaO_2 is essential due to the unique physiological challenges posed by HD. Studies have shown that a significant proportion of hemodialysis patients experience episodes of hypoxia, with some reporting SaO_2 levels dropping below 90% during treatment [1]. SaO_2 serves as a prognostic indicator, with studies demonstrating that lower arterial oxygen saturation levels during HD are associated with poorer clinical

outcomes, including higher rates of hospitalization and mortality [1]. In addition, low SaO_2 during HD has been associated with intradialytic hypertension, possibly due to activation of the sympathetic nervous system activation, stimulation of the renin-angiotensin-aldosterone system (RAAS), and endothelin-1 release [6]. During the Covid pandemic, low SaO_2 before the diagnosis of Covid-19 identified patients at high risk for hospitalization and death [3].

However, to date, the relationship between SaO_2 STP and outcomes in HD patients is unknown. The reasons for this knowledge gap are multifaceted. First, it was only a few years ago that cloud-connected CLM devices were deployed, enabling the necessary data storage. Second, these newer CLM devices report SaO_2 every 10 s, a significant improvement over the previous devices, which reported only once per minute. Nevertheless, it is conceivable that the ability to classify SaO_2 STP could inform clinical decision-making or diagnostic and therapeutic interventions. For example, SaO_2 STP are associated with SAS. This pattern typically reflects the intermittent nature of oxygen desaturation events that occur during apneic episodes. Galuzio et al. [4] highlight that oximetry data in HD patients can reveal intermittent oxygen desaturations that correlate with the apnea–hypopnea Index (AHI), a key metric used to assess the severity of sleep apnea. Furthermore, the relationship between SaO_2 and SAS is underscored by findings from Jhamb et al. [15], who reported that lower mean oxygen saturation is associated with increased mortality risk in patients with advanced kidney disease, many of whom may also suffer from undiagnosed SAS. In addition, SAS in HD patients is associated with inflammation and oxidative stress [16]. In HD patients with SaO_2 STP, specific clinical exploration and testing for SAS could be considered. If confirmed, e.g., through polysomnography, appropriate treatment could be initiated. This is relevant, as sleep-disordered breathing is frequent in dialysis patients [7]. The reported prevalence of sleep apnea is >50% among dialysis patients [17–19]. SAS is a condition that is associated with lower health-related quality of life [20] and increased cardiovascular and mortality risk in kidney patients [15, 21].

Other methods have been developed to identify SaO_2 STP. Galuzio et al. [4] devised a method that builds on dynamical systems theory and not on AI. The authors have developed a metric to quantify the occurrence of abnormal behaviors in the time series. This approach achieves an area under the ROC curve between 0.93 and 0.94 to identify SaO_2 pattern indicative of SAS. It will be interesting to see the relative performance of the two approaches in a well-defined patient cohort with a clinical diagnosis of SAS.

When implemented at scale, the 1D-CNN will allow us to identify SaO_2 STP and to investigate clinical correlates of the SaO_2 STP, including demographic factors, laboratory data as well as treatment-related parameters. Additionally, one can examine the relationship between quantifiable measures of the SaO_2 STP and key clinical outcomes, including hospitalization and mortality. This correlation seeks to provide deeper insights into the clinical significance of these patterns.

The quantification of STP at treatment level and patient level could also be used as feature inputs for other predictive models, e.g. hospitalization predictive model. With current cloud setting, this saw-tooth pattern recognition could be performed in real-time during the dialysis treatment and trigger a more specific diagnostic evaluation (e.g., polysomnography for definitive diagnosis of SAS) and therapeutic interventions.

Conclusions

In summary, we have developed an AI-based tool capable of detecting irregularities in SaO_2 time series collected during hemodialysis. This tool will deepen our understanding of intradialytic SaO_2 dynamics and support the implementation of advanced diagnostic and therapeutic interventions.

Abbreviations

SAS	Sleep apnea syndrome
SaO_2	Arterial oxygen saturation
HD	Hemodialysis
AI	Artificial intelligence
NSTP	No saw-tooth pattern
STP	Saw-tooth pattern
1D-CNN	One-dimensional convolutional neural networks
PIH	Prolonged intradialytic hypoxemia
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
ESKD	End-stage kidney disease
ε_{opt}	Optimal recurrence threshold
ECG	Electrocardiograms
EEG	Electroencephalograms
CLM	Crit-line monitor
FDA	US Food and Drug Administration
AWS	Amazon web services
AUC	Area under the receiver operating characteristic curve
CI	Confidence interval

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Author contributions

H.Z. and P. K. developed the method and H.Z. and A.N.B. worked on the analysis. H.Z., P. K. and A.N.B. wrote the manuscript, H.Z. and A.N.B. prepared the figures and all authors reviewed the manuscript.

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Data availability
As this was an internal quality improvement project, data will not be shared publicly.

Declarations

Ethics approval and consent to participate
The study was reviewed by the Western Institutional Review Board-Copernicus Group (WCG® IRB). The WCG® IRB determined that this research is exempt under 45 CFR § 46.104(d)(4) and that no patient consent was needed.

Competing interests
P. Kotanko and H. Zhang are employees and A. Nandorine Ban is a contractor of the Renal Research Institute, a wholly owned subsidiary of Fresenius Medical Care. P. Kotanko holds stock in Fresenius Medical Care. P. Kotanko and H. Zhang are inventors on patents in the field of dialysis. P. Kotanko is on the Editorial Board of Blood Purification, Kidney and Blood Pressure Research, and Frontiers in Nephrology.

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