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ORIGINAL RESEARCH

Classification of Laboratory Test Outcomes for Maintenance Hemodialysis Patients Using Cellular Bioelectrical Measurements

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Background: End-stage kidney disease (ESKD) patients often face complications like anemia, malnutrition, and cardiovascular issues. Serological tests, which are uncomfortable and not frequently conducted, assist in medical assessments. A non-invasive, convenient method for determining these test results would be beneficial for monitoring patient health.

Objective: This study develops machine learning models to estimate key serological test results using non-invasive cellular bioelectrical impedance measurements, a routine procedure for ESKD patients.

Methods: The study employs two machine learning models, Support Vector Machine (SVM) and Random Forest (RF), to determine key serological tests by classifying cell bioelectrical indicators. Data from 688 patients, comprising 3,872 biochemical–bioelectrical records, were used for model validation.

Results: Both SVM and RF models effectively categorized key serological results (albumin, phosphorus, parathyroid hormone) into low, normal, and high. RF generally outperformed SVM, except in classifying calcium levels in women.

Conclusion: The machine learning models effectively classified serological test results for maintenance hemodialysis patients using cellular bioelectrical indicators, therefore can help in making judgments about physicochemical indicators using electrical signals, thereby reducing the frequency of serological tests.

Keywords: serological test results, cellular bioelectrical indicators, machine learning, End-stage kidney disease

Introduction

Chronic kidney disease (CKD) is a common renal dysfunction syndrome with complex pathogenesis.[1–5] The disease is characterized by progressive and irreversible loss of renal function.[6] Treatments for CKD include medical therapies, dialysis, and renal transplant. End-stage kidney disease (ESKD) indicates kidney failure. Dialysis and renal transplant are widely used to prolong ESKD patients' lives and to improve their general quality of life. Maintenance hemodialysis (MHD) entails a short treatment time with high-quality removal of small molecular substances; as such, most ESKD patients rely on MHD to live.[7–9] Patients receiving MHD need precise fluid management and appropriate drug treatment. Their serum biochemical indices must therefore be closely monitored. ESKD patients also often suffer from cardiovascular diseases. This comorbidity renders it important to measure serum biochemical indices frequently. However, many patients find serum biochemical tests to be uncomfortable and undesirable. These tests have other drawbacks as well: different serum biochemical indices require distinct detection methods, and the results for some indices can take several

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days to process. A convenient serological composition estimation method would enrich the understanding of patients' serological composition status.

The bioelectrical impedance obtained via Body Composition Monitor (BCM) tests reflects a person's electrical characteristics, which are influenced by chemical and physical components of the body. Large impedance differences exist between biological tissues.[10] Impedance also varies with one's physiological state. Compared with normal impedance, the pathological change in biological tissues is significant.[10] Bioelectrical impedance analysis (BIA) is widely employed to assess the human body. In bioelectrical impedance measurement, electrodes are placed on the hands and feet, where the currents can travel through the body from one limb to another. BIA uses a wide range of frequencies. Signals of 1 kHz to 1 MHz lower frequencies tend to travel around cells (extracellular), while higher frequencies can pass through cell membranes and thus move both intra- and extracellularly. Since different body tissues (like muscle, fat, and bone) have distinct electrical properties, the impedance to electrical currents varies accordingly. Currently, BIA is mostly limited to measuring patients' body fat and water. Hemodialysis patients' dry weight should be evaluated before dialysis. BCM testing is a common means of doing so. Nescolarde et al[11] adopted a bioelectrical impedance vector analysis (BIVA) method to establish the relationship between hydration and mortality in MHD patients. Specifically, the authors classified patients based on hydration status and predicted their survival rates. Several scholars have also used BIVA to measure hydration in the human body.[12–14]

Studies have shown that BIVA can indicate one's nutritional status[15,16] and body composition.[17–19] BCM testing is closely related to certain biochemical indicators. Classification of serum biochemical indices with readily available, routinely measured BCM data would represent important practical advances. Research and applications related to using BCM data to assess serum biochemical components in humans remain relatively rare. Zhang et al[20] performed an analysis showing that BIA is related to the main serum biochemical indicators in the human body. Bioelectrical impedance is frequency-dependent. However, Zhang et al[20] only used BIA information with a single frequency of 50 kHz; all other data were ignored. Neglecting these data could compromise estimation accuracy and robustness.

Bioelectrical impedance values at different frequencies capture the external performance of extracellular resistance, intracellular resistance, and cell membrane capacitance.[21] The metric of cell membrane capacitance is associated with bioelectrical impedance as well. The phospholipid bilayer is akin to a capacitor in electrical properties. Transmembrane resistance reflects the cell barrier's permeability. The permeability of the cell barrier and transmembrane resistance are negatively correlated. It is thus particularly important to study the capacitance and resistance of biological cells. Extracellular resistance, intracellular resistance, and cell membrane capacitance can each be derived from routine BCM measurements. They are also complementary to single-frequency BIA data. The present work is the first to use these derived measurements to estimate MHD patients' biochemical composition to facilitate the determination of serum biochemical indices. As bioimpedance measurement is convenient, patient's physical condition can be estimated in a fast manner, allowing for early biochemical testing when necessary, and enables earlier detection of issues during dialysis treatment.

Methods

Subjects

This investigation involved a cross-sectional and prospective examination of 688 patients with uremia and regularly undergoes dialysis (280 women, 408 men: age range: 22–75; average age: 55.9 [women], 52.6 [men]). The data were collected from July1st, 2020, to July 1st, 2022. The authors had access to information that could identify individual participants during and after data collection. Patients who had experienced a severe cardiovascular or cerebrovascular event, severe infection, liver dysfunction, pneumonic insufficiency, essential thyroid infection, threatening tumor, or psychological illness within the month were excluded. All patients were informed of the potential risks and treatment as required by the National Hospital Management Regulations and signed informed consent for standard dialysis medications.

Measurements

The dataset in this study comprised two sections, namely a bioelectrical dataset and a biochemical dataset. The bioelectrical dataset consisted of 1,565 impedance records. The biochemical dataset contained 274,872 records of 11 serological test results: blood urea nitrogen (BUN), calcium (Ca), creatinine (Cr), albumin (Alb), total cholesterol (CHOL), low-density lipoprotein cholesterol (LDLC), phosphorus (P), hemoglobin (Hb), 25-hydroxyvitamin D3 (25-OH-D3), N-terminal B-type natriuretic peptide (NT-proBNP), and parathyroid hormone (PTH).

Patient attributes (eg, date of birth and other point-by-point individual data) were gathered before impedance estimations. Anthropometric factors (ie, height [H] in meters and weight [W] in kg) were measured. Each patient's body weight was estimated with a non-programmed gauging instrument (Seca, Hamburg, Germany) with minimal clothes; stature was estimated with a stadiometer (Seca, Hamburg, Germany).

Body mass index (BMI) was calculated as W/H^2. Amounts of BUN, Ca, Cr, Alb, CHOL, LDLC, and P were determined using a computerized science analyzer (Beckman Coulter AU5800). NT-proBNP and 25-OH-D3 were discerned with an immunology analyzer (COBAS E-602). PTH was estimated via a mechanized immunoassay analyzer (Beckman Coulter DxI 800). Hb focus was estimated with a robotized hematology analyzer (Sysmex XN-9000).

The four-electrode impedance technique enables bioelectrical impedance measurement with four electrodes placed on the same side of the patient's body, specifically the dorsum of hand (rd1), the midline that spans across the wrist bones (bl1), the dorsum of foot (rd2) and the midline passing through the ankle joint (bl2). Besides, the measurement side should be opposite to the arteriovenous fistulas side of patients. The Body Composition Monitor (BCM, Fresenius Medical Care, Germany, OP-ZHS 9/11.13) injects currents with frequencies from 1kHz to 1MHz as input signals from the dorsum of hand and foot electrodes (rd1, rd2). The response voltages are detected by the other two electrodes, thus the impedance value of the human body circuit can be calculated. Multi-frequency characteristics were estimated using a multi-frequency impedance analyzer. As stated in Section 1, instead of using traditional BIA and BIVA indices[20] the original extracellular resistance, intracellular resistance, and cell membrane capacitance (respectively Re, Ri, and Cm, introduced below) were measured with this multi-frequency impedance analyzer before being exported and used to deduce body topology–independent indices (ρe, ρi, ε). Cell bioelectrical indicators (extracellular resistance [Re, Ohm], intracellular resistance [Ri, Ohm], and cell membrane capacitance [Cm, nF]) were automatically derived from multi-frequency characteristics using the multi-frequency impedance analyzer and bioelectrical impedance spectroscopy.[22] Extracellular resistivity (ρe, Ohm·m) and intracellular resistivity (ρi, Ohm·m) were estimated as Re·BMI and Ri·BMI, respectively. Cell membrane permittivity (ε) was estimated as Cm/W.

Data Combination

The two datasets were combined because the bioelectrical impedance and serological lists are not consistently estimated during diagnosis. Each patient's serological records were combined with their impedance records within 72 h of examination, resulting in 3,872 effective biochemical–bioelectrical records. Patient records included the following information: a serological record in serological test results; six bioelectrical records (ie, Re, Ri, Cm, ρe, ρi, ε); anthropometric characteristics (ie, age, height, weight); and a derived BMI. The data represented 3,872 10-dimensional independent variable records and 1-dimensional dependent variable records (ie, serological records).

Statistical Analysis

To determine common intra-individual associations in records, correlations between patients' bioelectrical indices and serological test results were evaluated using repeated measures correlation (rmcorr),[23] with $p < 0.01$ representing significance. Statistical analysis was performed in MySQL Community version 8.0.14 (Oracle Corporation), Python version 3.7.2 (Python Software Foundation), and R version 4.0.2.

Normalization

The z-score was used to normalize different indicators in the data. To eliminate the effects of data-based dimensions, all records x_i per indicator were replaced with a z-score z_i in subsequent analysis:

$$z_i^{'} = \frac{x_i - \bar{x}}{\sigma}$$

where $\bar{x}$ represents the indicator's average value, and δ denotes the indicator's variance.

Dimensionality Reduction

Principal component analysis (PCA) was performed to reduce the dimensionality of bioelectrical impedance records. Dimensionality reduction seeks to retain the most important features of high-dimensional data while removing noise and irrelevant information to expedite data processing. PCA continuously finds the coordinate axis with the largest variance in the orthogonal plane to achieve dimensionality reduction. In this study, with the use of PCA, the dimensionality of the independent variable records was reduced from 10 to 2.

Support Vector Machine and Random Forest

Support vector machine (SVM) and random forest (RF) are popular supervised machine learning models and have achieved great success in many scenarios. In this work, SVM and RF were applied to classify serological test results from the 10-dimensional PCA value of independent variable records. Each method's accuracy was then evaluated.

To explore the feasibility of classifying biochemical indices via bioelectrical impedance, a series of RF classification models and SVM classification models with the linear kernel were constructed. The measured biochemical indices were divided into either two or three levels: normal and high (for P and PTH); or low, normal, and high (for Hb, Ca, and Alb). The models were trained to classify biochemical indices based on bioelectrical impedance values. A large proportion (80%) of biochemical–bioelectrical records were randomly selected as the training set, and the remaining records constituted the test set (ie, to evaluate the trained models' classification accuracy). If the models' classifications were identical to the measured biochemical indices, then these results were treated as true classifications; they were labeled false classifications otherwise. The F1-score, precision rate, and recall rate in both the macro and weighted methods were computed on the test set to evaluate model performance.[24]

Confusion Matrix

A confusion matrix was constructed to convey the models' classification performance. This matrix is a table that is often used to display a classification model's performance on a set of test data for which true values are known. Matrix rows generally represent the instances in an actual class while columns represent the instances in an estimated class. In this work, there are three classes that represent the levels of serological indicators: Normal, Low, and High. The determined class is the results of SVM or RF calculated from bioimpedance values, and the actual class is the results of biochemical tests.

Results

Table 1 presents the intra-individual correlation matrix between bioelectrical and biochemical variables. Intra-individual correlation analysis of bioelectrical indices revealed that cell membrane capacitance (Cm) and cell membrane permittivity (ε) were more strongly associated with biochemical indices than other bioelectrical indices (Table 1). Intra-individual correlation analysis and RF model fitting showed similar results with respect to biochemical indices: Alb, P, and PTH displayed stronger correlations with bioelectrical indices than other biochemical indices (Table 1). Figures S1-S6 show the relationship between Alb, P, parathyroid hormone, and bioelectricity indicators in both genders. The bioelectrical values of cell membrane permittivity (ε) had a strong relationship with the biochemical indices of Alb (Figures S1 and S4), CHOL, P (Figures S2 and S5), and Hb and PTH (Figures S3 and S6) in both genders.

Table 1 Intra-Individual Correlation Between Electrical and Biochemical Values

Men	Ri	Re	Cm	ρi	ρe	ε
BUN	1.66×10^{-4}	-1.49×10^{-3}	-3.17×10^{-3}	1.27×10^{-5}	-1.34×10^{-4}	−0.25
Ca	1.47×10^{-5}	3.15×10^{-4}	1.05×10^{-4}*	6.97×10^{-8}	1.94×10^{-5}	7.17×10^{-3}*
Cr	−0.02	−0.3	−0.07	-3.51×10^{-4}	−0.02	−5.11
Alb	-2.03×10^{-3}	0.02**	5.17×10^{-3}**	-5.08×10^{-5}	1.20×10^{-3}**	0.32**
CHOL	-4.50×10^{-4}	1.92×10^{-3}	5.50×10^{-4}*	-1.13×10^{-5}	6.90×10^{-5}	0.05**
LDLC	1.36×10^{-5}	2.03×10^{-3}*	6.18×10^{-5}	-6.26×10^{-7}	3.45×10^{-5}	0.02
P	-3.04×10^{-4}*	5.39×10^{-4}	4.84×10^{-4}**	-1.42×10^{-5}**	1.89×10^{-5}	0.03**
Hb	-2.69×10^{-3}	0.08**	3.50×10^{-4}	-1.84×10^{-4}	3.45×10^{-3}**	0.03
NT-proBNP	5.91*	−9.74	−1.86	0.25*	−0.35	-0.13×10^{3}
PTH	−0.16**	0.2	0.18**	-4.39×10^{-3}	0.01	11.49**
Women	**Ri**	**Re**	**Cm**	**ρi**	**ρe**	**ε**
BUN	-1.55×10^{-3}	4.58×10^{-3}	0.01	-3.38×10^{-5}	4.43×10^{-4}	0.67
Ca	-1.39×10^{-5}	4.82×10^{-5}	-1.29×10^{-4}	9.59×10^{-8}	2.76×10^{-6}	-5.77×10^{-3}
Cr	−0.1	9.29×10^{-3}	0.6	-4.32×10^{-3}	8.28×10^{-3}	32.06
Alb	-1.82×10^{-3}	2.71×10^{-3}	6.11×10^{-3}**	-1.00×10^{-4}	1.80×10^{-4}	0.45**
CHOL	-2.80×10^{-4}*	-5.15×10^{-4}	2.92×10^{-4}	-2.06×10^{-5}**	-1.12×10^{-5}	0.05**
LDLC	-1.93×10^{-5}	-4.72×10^{-4}	-1.17×10^{-4}	-1.75×10^{-6}	-2.09×10^{-5}	−0.02
P	-5.12×10^{-4}**	4.69×10^{-4}	2.02×10^{-3}**	-2.34×10^{-5}**	8.80×10^{-5}*	0.10**
Hb	-9.75×10^{-3}**	0.03	0.03**	-4.94×10^{-4}**	1.68×10^{-3}*	1.78**
NT-proBNP	−0.14	−6.17**	0.01	0.11	−0.05	−34.46
PTH	−0.15	0.43	0.32**	-6.93×10^{-3}	0.04**	29.49**

Notes: *p < 0.05; **p < 0.01.

Abbreviations: BUN, blood urea nitrogen; Ca, calcium; Cr, Creatinine;Alb, Albumin; CHOL, total cholesterol; LDLC, low-density lipoprotein cholesterol; P, PhosphoRus; Hb, hemoglobin; NT-proBNP, N-terminal B-type natriuretic peptide; PTH, parathyroid hormone; Ri, intracellular resistance; Re, extracellular resistance; Cm, cell membrane capacitance; ρi, intracellular resistivity; ρe, extracellular resistivity; ε, cell membrane permittivity.

Table 2 lists the contribution rates of PCA variances to the biochemical indices. The first two PCA variances contributed more than 99.8% in total to all biochemical indices. Tables 3 and 4 show the F1-score, precision rate, and recall rate of the SVM model and the RF model, respectively. The RF model outperformed the SVM model in classifying biochemical indices in most cases. The precision rates, recall rates, and F-scores for the RF model were greater than 0.6 among men, with most scores exceeding 0.7. Among women, the precision rates, recall rates, and F-scores were above 0.6 for all indices. The RF model also showed good performance in classifying Hb in women along with Alb in both genders, with all scores higher than 0.8. The results show higher F-scores in SVM model fitting and RF model fitting (Tables 2 and 3). In terms of model fitting, the RF model performed well when estimating most serological indicators of interest, especially Alb (Tables 2 and 3).

Figures 1–5 display the confusion matrices for classification models based on SVM and RF. The values in the matrix represent the probability that SVM or RF correctly classifies each variable. Figure 1 depicts the confusion matrix of RF when classifying Alb in both genders. As pictured, RF tended to label samples as "low", causing some samples to be classified incorrectly. Similar results emerged when estimating men's Ca. Figure 2 shows that RF tended to label samples

Table 2 Contributing Rate of the Variance in the Result of Principal Component Analysis

Men	1st PCA Dimension	2nd PCA Dimension	Total
Hb	0.9591	0.0396	0.9987
Ca	0.9668	0.0317	0.9986
P	0.9602	0.0378	0.9981
PTH	0.9710	0.0272	0.9983
Alb	0.9595	0.0388	0.9984
Women	**1st PCA Dimension**	**2nd PCA Dimension**	**Total**
Hb	0.9392	0.0591	0.9984
Ca	0.9438	0.0547	0.9985
P	0.9465	0.0522	0.9988
PTH	0.9524	0.0465	0.9990
Alb	0.9344	0.0637	0.9982

Abbreviations: Hb, hemoglobin; Ca, calcium; P, PhosphoRus; PTH, parathyroid hormone; Alb, Albumin.

Table 3 F1-Score, Precision and Recall of Support Vector Machine

Target	Precision	Recall	F1_score
Men			
Hb	0.319	0.318	0.321
Ca	0.333	0.342	0.347
P	0.365	0.353	0.362
PTH	0.417	0.419	0.439
Alb	0.350	0.351	0.352
Women			
Hb	0.409	0.419	0.447
Ca	0.347	0.333	0.352
P	0.320	0.310	0.321
PTH	0.269	0.257	0.273
Alb	0.314	0.314	0.315

Abbreviations: Hb, hemoglobin; Ca, calcium; P, PhosphoRus; PTH, parathyroid hormone; Alb, Albumin;

Table 4 F1-Score, Precision Rate and Recall Rate of Random Forest

Target	Precision	Recall	F1_score
Men			
Hb	0.733	0.779	0.849
Ca	0.844	0.860	0.880
P	0.842	0.848	0.855
PTH	0.662	0.703	0.857
Alb	0.711	0.753	0.829

(*Continued*)

Table 4 (Continued).

Target	Precision	Recall	F1_score
Women			
Hb	0.617	0.677	0.871
Ca	0.779	0.802	0.820
P	0.753	0.766	0.786
PTH	0.515	0.543	0.627
Alb	0.650	0.662	0.682

Abbreviations: Hb, hemoglobin; Ca, calcium; P, PhosphoRus; PTH, parathyroid hormone; Alb, Albumin.

as "normal"; some "low" samples were hence misclassified as "normal." This phenomenon may have been due to an imbalanced sample, a conjecture requiring more in-depth study. Results regarding PTH in men and P in women were relatively more accurate: Figures 3 and 4 indicate that the classifications were not imbalanced. Additionally, the number of false negative classifications and false positive classifications was approximately equal.

Discussion

This study presents a pioneering attempt to test the correlations between cell bioelectrical indicators and important serological test results in a group of ESKD patients receiving MHD. To the best of the authors' knowledge, this effort marks the first time that RF has been used to classified serological test results via bioelectrical indices.

Research suggests that SVM enjoys good performance when estimating serological test results through BIVA.[20] Despite sharing the same dataset, the SVM model in Zhang et al[20] did not adequately estimate Ca and PTH in men or P in women. By adopting PCA, the current study shows that cell bioelectrical indicators (ie, Ri, Re, and Cm, derived automatically from multi-frequency characteristics using a multi-frequency impedance analyzer with the BIS method) are closely related to these serological test results. Integrating the RF model and cell bioelectrical indicators significantly improves these indices' classification accuracy (Table 3 and Table 4). This approach nearly fully mitigates the tendency documented by Zhang et al[20] to misclassify normal PTH levels as high in men and to misclassify high P levels as normal in both men and women (Figures 3 and 4).

This study further shows that cell bioelectrical indicators are strongly associated with patients' body water, anemia, nutritional status, and CKD–MBD status. Results underline the potential clinical applicability of cell bioelectrical

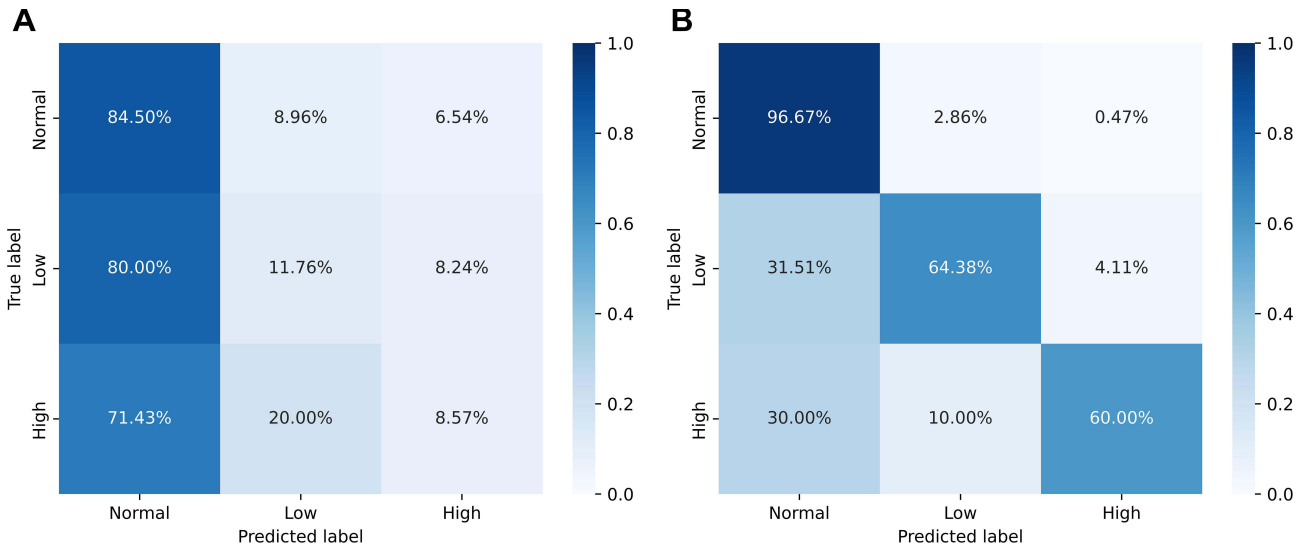

Figure 1 Confusion matrix between the Albumin classified by the model in both genders. (**A**) support vector machine, (**B**) the random forest.

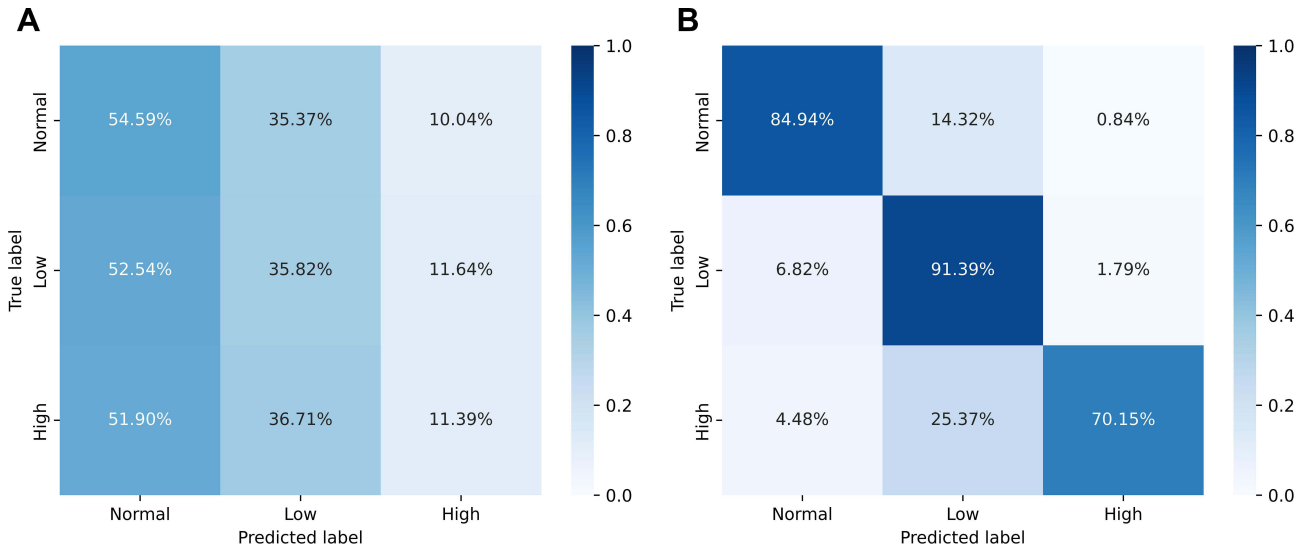

Figure 2 Confusion matrix between the Calcium classified by the model in both genders. (**A**) support vector machine, (**B**) the random forest.

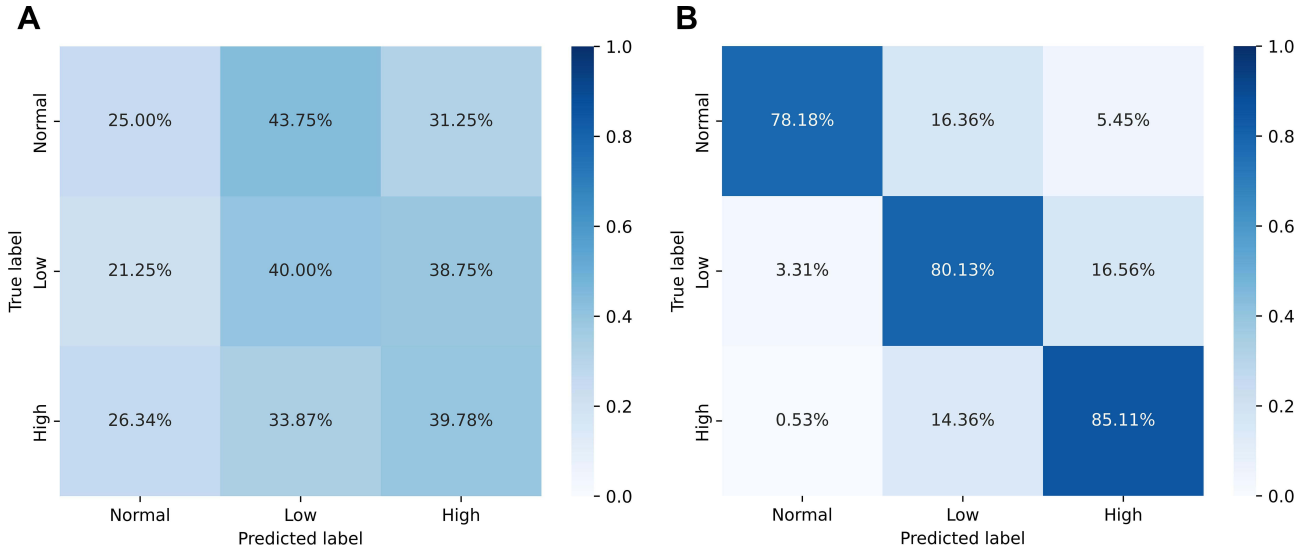

Figure 3 Confusion matrix between the parathyroid hormone classified by the model in both genders. (**A**) support vector machine, (**B**) the random forest.

indicator analysis based on an RF classification model. This type of analysis can supplement biochemical testing as a routine evaluation strategy: healthcare professionals can use an impedance analyzer and the RF classification model to estimate patients' biochemical indices through routine bioelectricity measurements as a complement to biochemical tests. A patient's condition can therefore be assessed frequently to enable timely and comprehensive intervention. Proactive care may reduce complications from cardiovascular diseases among ESKD patients. This implication holds great importance for uremia treatment. With our methods, patient's physical condition can be estimated in a convenient and fast manner, allowing for early biochemical marker testing when necessary, therefore enables earlier detection of issues during dialysis treatment and reducing the frequency of serological tests.

Promising results notwithstanding, this research shares shortcomings with that of Zhang et al.[20] For example, a low level of Alb continued to be misclassified as normal in this study (Figure 1), although this tendency was not as strong as in Zhang et al.[20] Compared with Zhang et al,[20] the propensity to misclassify "low" and "high" Ca as "normal" in men has been overcome; however, "normal" tended to be misclassified as "low" more often in the present work (Figure 2). Other

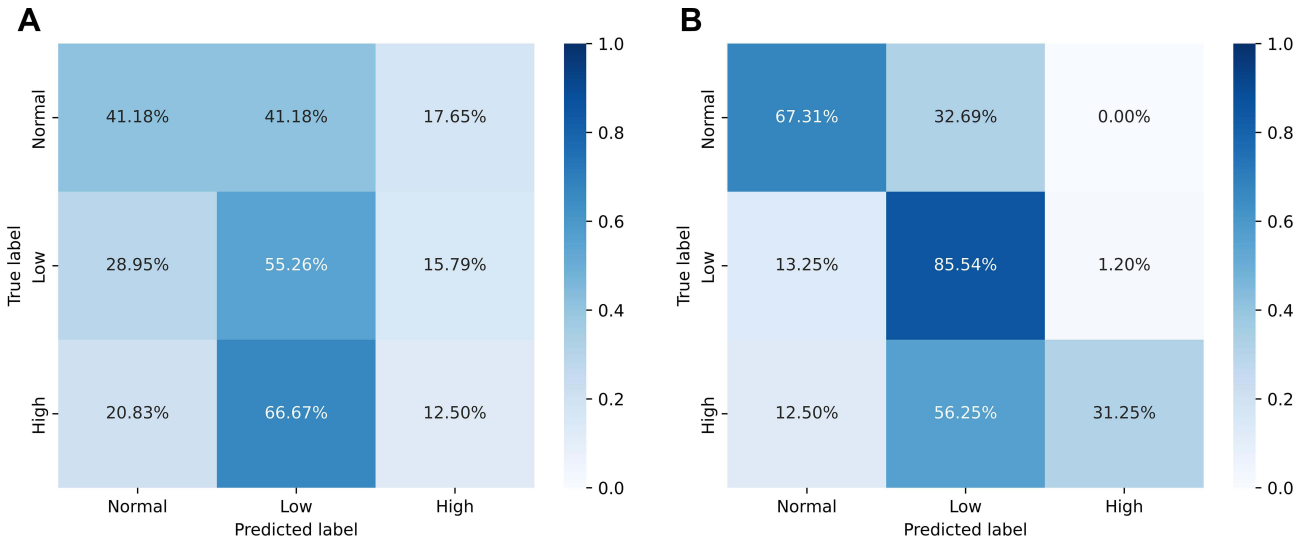

Figure 4 Confusion matrix between the Phosphorus classified by the model in both genders. (**A**) support vector machine, (**B**) the random forest.

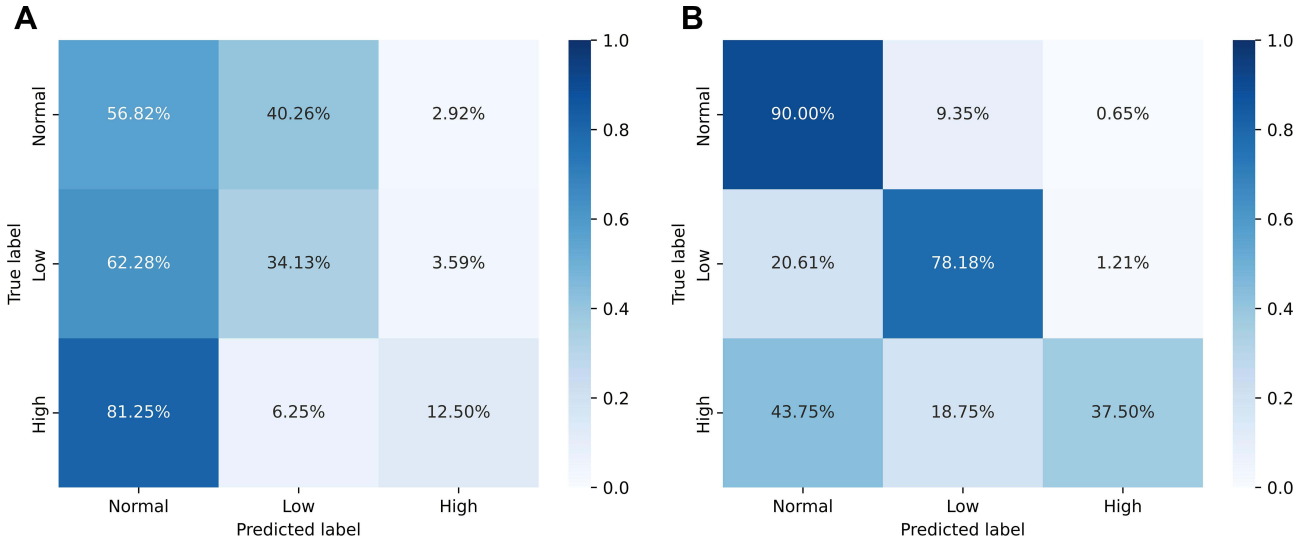

Figure 5 Confusion matrix between the hemoglobin classified by the model in both genders. (**A**) support vector machine, (**B**) the random forest.

limitations also exist. First, automatically generating derived values from multi-frequency characteristics using a multi-frequency impedance analyzer transformed a series of multi-frequency attributes into just a few variables. Important information may therefore have been lost in the derivation process. The effect of this information loss requires further investigation. Second, the relationships among cell bioelectrical indicators, multi-frequency characteristics, and body composition should be detailed in diverse patient groups (eg, of different ages or with different health conditions).

Conclusion

This study demonstrates that the cell bioelectrical indicators derived from multi-frequency characteristics are associated with the values of serological test results. Results showcase the accuracy of classifying serological test results in MHD through PCA and an RF classification model. Findings also delineate the relationship between bioelectrical impedance indices and serum biochemical indices. A novel method is hence proposed to estimate serum biochemical conditions

from routine bioimpedance measurement. This work represents an early effort to leverage an RF model to estimate serum biochemical status from common bioimpedance indices. The devised method may provide supplementary serological composition information to facilitate diagnosis while using available bioelectrical impedance measurements and reducing the frequency of serological tests.

Data Sharing Statement

Data are available at request through the corresponding author's email.

Ethics Approval and Consent to Participate

All patients were informed of the potential risks and treatment as required by the National Hospital Management Regulations and signed informed consent for standard dialysis medications. This research was performed in accordance with the Declaration of Helsinki.The treatment plan was affirmed by the Wuxi People's Hospital Medical Ethics Committee (approval number: ks202045).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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