

Haifang Dong¹, Pingping Zhang²

¹ Department of Family Medicine, The Affiliated Yangming Hospital of Ningbo University (Yuyao People's Hospital), Zhejiang Province, China

² Department of Infectious Diseases, The Affiliated Yangming Hospital of Ningbo University (Yuyao People's Hospital), Zhejiang Province, China

DEVELOPMENT AND VALIDATION OF PREDICTIVE MODELS INTEGRATING SERUM CHLORIDE AND NEUROHORMONAL INDICATORS FOR DIURETIC RESISTANCE IN HEART FAILURE

<i>Objective</i>	To explore the predictive values of serum chloride ion (Cl ⁻) concentration and neurohormonal indicators for diuretic resistance (DR) in patients with heart failure (HF).
<i>Material and methods</i>	A total of 150 patients with chronic HF treated between January 2022 and January 2024 were enrolled. Patients were allocated into a DR group (n=45) and a non-DR group (n=105) based on their responses to diuretics during hospitalization. Serum Cl ⁻ , N-terminal pro-B-type natriuretic peptide (NT-proBNP), plasma renin activity (PRA), norepinephrine (NE), furosemide dosage, and the use of tolvaptan (yes/no) was recorded. Least Absolute Shrinkage and Selection Operator regression analyses was used to screen variables. Logistic regression, Random Forest, and eXtreme Gradient Boosting (XGBoost) models were constructed and evaluated.
<i>Results</i>	DR incidence was 30.0%. Cl ⁻ concentrations were significantly lower, whereas NT-proBNP, PRA, and NE were higher in the DR group (p<0.05). Six variables were identified by LASSO regression, including serum Cl ⁻ , NT-proBNP, NE, PRA, daily dose of furosemide, and tolvaptan use. All three models demonstrated good predictive performance (AUC values of 0.83, 0.86, and 0.89 for Logistic regression, Random Forest, and XGBoost analyses, respectively). The XGBoost model achieved the highest AUC (0.89), indicating superior discriminative ability, the Random Forest model was slightly better in accuracy and in the machine learning F1 score, whereas the Logistic regression model offered better interpretability. Variable importance analysis revealed that NT-proBNP was the most stable predictor of DR. Low Cl ⁻ concentration also exhibited a high predictive value in the Random Forest and XGBoost models.
<i>Conclusion</i>	Indicators of serum Cl ⁻ and neurohormonal activation are valuable for predicting DR in HF patients. The XGBoost model outperforms other machine learning models in terms of discriminatory power and potential clinical applications.
<i>Keywords</i>	Chloride ion; diuretic resistance; heart failure; neurohormonal indicator
<i>For citations</i>	Haifang Dong, Pingping Zhang. Development and Validation of Predictive Models Integrating Serum Chloride and Neurohormonal Indicators for Diuretic Resistance in Heart Failure. <i>Kardiologiia</i> . 2026;66(5):77–85. [Russian: Хайфан Дун, Пинпин Чжан. Разработка и валидация прогностических моделей, объединяющих концентрацию хлоридов в сыворотке крови и нейрогормональные показатели, для оценки резистентности к диуретикам при сердечной недостаточности. <i>Кардиология</i> . 2026;66(5):77–85].
<i>Corresponding author</i>	Pingping Zhang. Email: zhangppnuayh@hosp-edu.cn

Introduction

Heart failure (HF) is a critical global public health problem leading to persistent increases of incidence, hospital re-admission, and death, so the optimization of congestion management and the improvement of prognosis have become an important clinical focus [1]. As a core approach for mitigating capacity load and alleviating symptoms, diuretics are widely applied in the treatment of chronic HF. However, some patients continue to experience fluid retention and have insignificant weight loss after treatment with conventional and even higher doses of diuretics, a condition known as diuretic resistance (DR) [2]. DR not only indicates poor fluid capacity control but it also closely correlates

with prolonged hospitalization time, increased readmission rate, and raised mortality risk. Consequently, the early identification of and intervention in DR are of significant clinical importance [3].

The development of DR is associated with decreased renal function, neurohormonal system over activation, and electrolyte disturbance [4]. In this regard, the role of serum chloride ion (Cl⁻) has gained increasing attention in recent years. Cl⁻ plays a vital role in maintaining acid-base balance and electrolyte homeostasis, which is likely to influence the diuretic response by regulating the renin-angiotensin-aldosterone system (RAAS) [5]. It has been proven that hypochloremia is highly associated with reduced efficacy of

Prediction of Diuretic Resistance in Heart Failure

Study Cohort

- 150 patients with chronic heart failure
- DR group: n=45 (30%)
- Non-DR group: n=105

Key Predictors (LASSO-selected)

- Serum chloride (Cl^-) ↓
- NT-proBNP ↑
- PRA, NE ↑
- Furosemide dose, Tolvaptan use

Modeling Strategy

- Logistic Regression
- Random Forest
- XGBoost
- Train/Test split: 7:3

Main Findings

- ↓ Cl^- + ↑ Neurohormonal activation → Diuretic resistance
- XGBoost achieved best discrimination (AUC = 0.89)
- NT-proBNP most stable predictor

diuretics and poor HF outcomes, but its specific role in predicting DR has not yet been systematically researched [6]. Also, neurohormonal-related indicators, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), plasma renin activity (PRA), and norepinephrine (NE), can reflect the degree of congestion and neurohormonal activation in HF, so these factors are potentially valuable in assessing DR risk [7].

In current clinical practice, DR is identified mainly based on empirical judgment in the absence of quantitative predictive tools. Although some studies have explored individual predictors of diuretic resistance, systematic comparisons of predictive models integrating serum electrolytes and neurohormonal indicators remain limited, particularly with respect to model performance and non-linear interactions. Thus, the present study aimed to combine serum Cl^- and neurohormonal concentrations with medication data to establish DR prediction models through Least Absolute Shrinkage and Selection Operator (LASSO) regression-based variable screening. The performance of three modeling strategies [Logistic regression, Random Forest, and eXtreme Gradient Boosting (XGBoost)] was evaluated to assess their predictive ability and potential clinical utility in identifying diuretic resistance.

Material and methods

Study design and subjects

To ensure the basic stability in model construction, the following formula was employed to estimate the sample

size: $N = k \times c/P$ [8], where k represents the number of model variables (6), c denotes the minimum number of outcome events per variable (set at 5 in this study), and P is the estimated incidence rate of DR (30%). The required minimum sample size was calculated as $N = 6 \times 5/0.30 = 100$. A total of 150 patients and 45 DR events were finally included in this study, thus, meeting the minimum requirement for model stability based on the events-per-variable [8]. The study was approved by the hospital Ethics Committee.

In this single-center, retrospective, observational study, 150 patients with chronic HF who sought treatment in our hospital from January 2022 to January 2024 were identified. Subsequently, 45 patients who developed DR were assigned to a non-DR group, and 105 patients who did not have DR were assigned a non-DR group.

DR was determined according to one of the following criteria [9]:

- 1) Fractional excretion of filtrated sodium (FeNa) $<0.2\%$ at 2 h after intravenous administration of diuretics;
- 2) Urinary sodium excretion <50 mmol in random sampling at 1–2 h after diuretic administration;
- 3) Intravenous administration of furosemide at a dose up to 80 mg/d (or other equivalent doses) that failed to adequately relieve the symptoms and signs of hypervolemia. For standardization, an intravenous furosemide dose of 80 mg/day (or equivalent loop diuretic dosage) was used as a reference dose for assessing diuretic response,

Table 1. Baseline data

Variable	DR group (n=45)	Non-DR group (n=105)	t/ χ^2	p
Age (yr.)	70.3±10.9	67.3±11.7	1.43	0.154
Male	29 (64.4)	64 (61.0)	0.16	0.686
BMI (kg/m ²)	25.7±3.8	24.9±4.2	1.10	0.272
Cl ⁻ (mmol/l)	96.2±3.5	100.3±4.3	5.74	<0.001
Na ⁺ (mmol/l)	135.6±3.2	137.2±2.9	2.86	<0.001
NT-proBNP (pg/ml)	234±85	172±73	4.51	<0.001
PRA (ng/ml/hr)	4.4±1.9	3.3±1.8	3.44	<0.001
PAC (pg/ml)	214±48	188±44	3.24	<0.001
NE (pg/ml)	865±170	740±160	4.28	<0.001
LVEF (%)	37.6±7.9	42.2±9.2	2.87	<0.001
NYHA HF class [II/III/IV]	5/27/13	32/62/11	11.47	0.003
eGFR (ml/min/1.73 m ²)	68±18	75±19	2.13	0.035
Daily dose of furosemide (mg)	48.6±12.3	42.9±11.5	2.76	0.007
Tolvaptan combination therapy	16 (35.6)	20 (19.0)	4.71	0.030

Data are mean±SD, number, or number (percentage). BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRA, plasma renin activity; PAC, plasma aldosterone concentration; NE, norepinephrine; LVEF, left ventricular ejection fraction; NYHA HF, New York Heart Association heart failure; eGFR, estimated glomerular filtration rate.

regardless of previous home doses. Urinary Na⁺ concentration was determined by an ion-selective electrode assay using random urine samples collected 1–2 h after diuretic administration.

All patients were hospitalized due to chronic HF with volume overload requiring adjustment of diuretic therapy, but without symptoms of acute decompensated HF at admission [10]. Cardiac function parameters included left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) HF class. Renal function was assessed by the estimated glomerular filtration rate (eGFR), which was calculated from the serum creatinine concentration by the CKD-EPI creatinine equation [11]. Serum creatinine concentration was detected using an ADVIA 2400 biochemical analyzer (Siemens, Germany).

Information on diuretic therapy during hospitalization was documented for all patients, including daily dosage of furosemide (mg/day) and tolvaptan (Sanofi, 15 mg/tablet, p.o.) combination therapy. The data on all laboratory tests and medication were sourced from the electronic medical record system and central testing database. To ensure the objectivity and consistency of data collection, two independent researchers extracted the data using a standardized, pre-defined case report form. Any discrepancies between the two researchers were resolved through discussion or by consulting a third senior researcher.

Clinical outcomes, such as in-hospital mortality, ICU admission, and length of stay, were not predefined endpoints in this study, as the primary objective was to establish and validate predictive models for diuretic resistance.

Variable screening, model formation and evaluation

After detection and grouping of baseline variables, 11 candidate variables that were statistically different between the DR and non-DR groups were used for the ini-

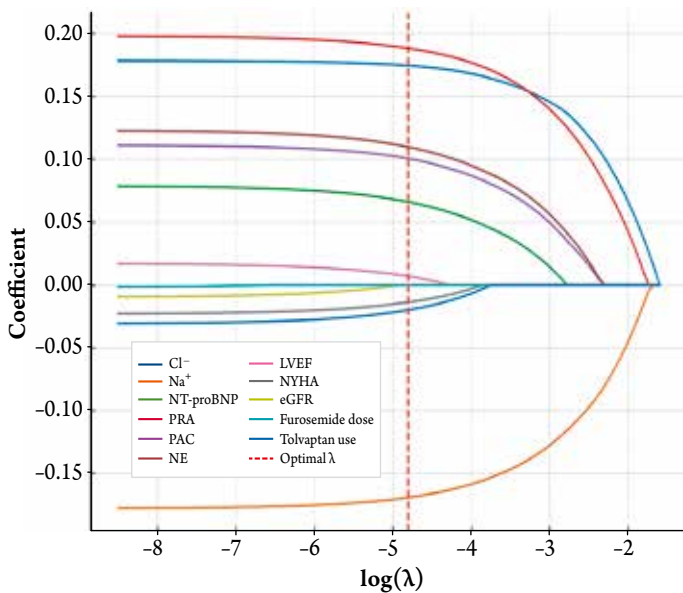
tial variable evaluation. Then, the variables were screened by LASSO regression prior to modeling. The optimal regularization parameter λ was determined via 10-fold cross-validation, and six variables with non-zero coefficients were ultimately identified for subsequent machine learning modeling.

The six identified variables, namely serum Cl⁻, NT-proBNP, NE, PRA, daily furosemide dose, and tolvaptan combination therapy, were utilized for the further establishment of three prediction models, namely, a traditional Logistic regression model, a Random Forest model in ensemble learning mode, and an XGBoost model with a gradient boosting framework. The presence or absence of DR was set as the dependent variable, while the six selected variables screened out by LASSO regression were determined as the independent variables for all three models. During modeling, the total samples were randomly assigned into a training set and a test set at a 7:3 ratio. The former was used for model training, and the latter was employed for predictive performance evaluation.

To comprehensively assess the predictive ability of the three models, such indicators as area under the receiver operating characteristic (ROC) curve (AUC), accuracy, precision, recall, and the machine learning F1 score were separately calculated, and comparisons were made based on their overall performance. Additionally, to further enhance the interpretability and clinical utility of the models, variable contribution and importance analyses were conducted for all three models.

In the Logistic regression model, the strength of association between each variable and DR occurrence was assessed with the help of the regression coefficient (β), p-value, odds ratio (OR), and 95% confidence interval (CI) [12]. In the Random Forest model, variable importance was calculated using the Mean Decrease Gini impurity, thus distinguishing the key

Figure 1. LASSO regression path [$\log(\lambda)$ vs. regression coefficient]*



* Where λ denotes the regularization parameter. The change trends of regression coefficients for variables under varying λ values are illustrated, which are used for variable selection. As λ increases, the regression coefficients of partial variables gradually approach zero, achieving the purpose of variable screening and dimension reduction. The red dashed line indicates the optimal λ value determined through cross-validation

variables that influence the model decisions holistically [13]. In the XGBoost model, the SHapley Additive exPlanations (SHAP) method was introduced to systematically analyze the positive and negative contributions of different variables to the prediction results at both global and individual concentrations [14]. Moreover, visual graphs were generated to illustrate the promoting or suppressing effects of the variables on the models' prediction results. This enhances the clinical understanding of the prediction mechanisms of the models and should increase trust in the models' analyses.

Statistical analysis

Statistical analyses were performed using R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria) and Python (version 3.10; Python Software Foundation, Wilmington, Delaware, USA). A two-tailed $p < 0.05$ signified a statistically significant difference. All measurement data are presented as (mean $\pm$ standard deviation (SD)) and compared between groups with independent-samples t-test or Mann-Whitney U-test based on whether or not the data were distributed normally. Enumeration data are expressed by (number (percentage)) and analyzed using chi-square tests (χ^2 test). The R Language “glmnet” package was employed to complete LASSO regression modeling, and the optimal λ value was screened out through 10-fold cross-validation [15]. Logistic regression was utilized to further probe the independent associations between variables

Figure 2. ROC curves of three machine learning models for predicting DR

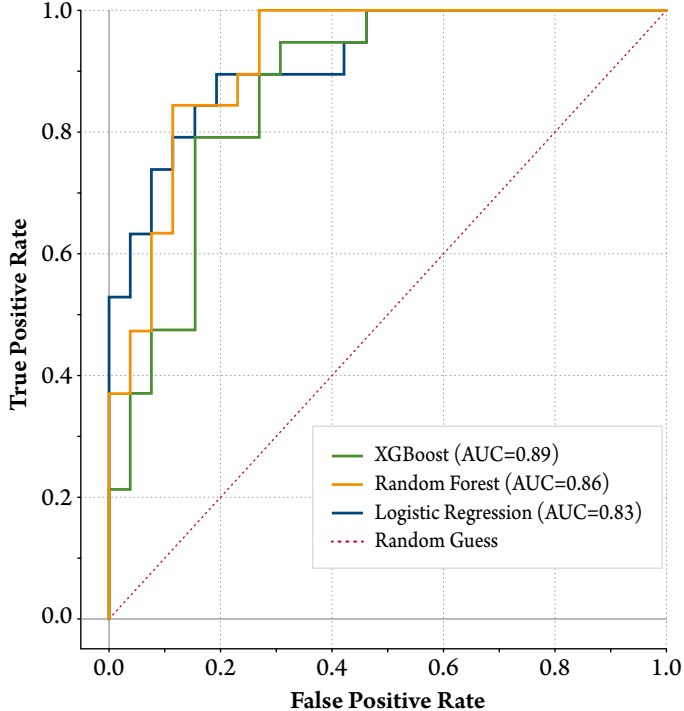


Table 2. Indicators for assessing DR predictive ability of the three machine learning models

Indicator	Logistic regression model	Random Forest model	XGBoost model
AUC	0.83	0.86	0.89
Accuracy	0.80	0.84	0.82
Precision	0.77	0.84	0.79
Recall	0.74	0.80	0.79
F1 score	0.75	0.82	0.79

and DR. The establishment and visual analysis of all machine learning models were accomplished by use of Python Language, primarily leveraging “scikit-learn”, “xgboost”, and “shap” libraries [12–14].

Results

Baseline data

Among the 150 patients with chronic HF, the DR incidence rate was 30.0% (Table 1). There were no significant differences in age, gender, and body mass index (BMI) between the two groups ($p > 0.05$), indicating demographic comparability. Among the 45 patients with DR, 25 (55.6%) had insufficient response to intravenous furosemide (80 mg/day), 12 (26.7%) had urinary sodium < 50 mmol, and eight (17.8%) had FeNa $< 0.2\%$. In addition, nine patients (20.0%) simultaneously fulfilled two or more of these criteria. Compared with those in the non-DR group, the serum Cl⁻ concentration in the DR group was significantly lower, while NT-proBNP, PRA, PAC, and NE concentrations were significantly higher, suggesting greater congestion and

Table 3. Impacts of different variables on DR in HF patients uncovered by Logistic regression analysis

Variable	Regression coefficient	Standard error	Z	p	OR	95% CI
Serum Cl ⁻	0.043	0.081	0.527	0.598	1.044	0.890–1.223
NT-proBNP	0.004	0.001	4.034	<0.001	1.004	1.002–1.006
NE	2.176	0.883	2.464	0.014	8.807	1.560–49.679
PRA	0.805	0.636	1.266	0.206	2.237	0.643–7.775
Daily dose of furosemide	0.060	0.029	2.112	0.035	1.062	1.004–1.123
Tolvaptan combination therapy	3.530	1.199	2.945	0.003	34.106	3.257–357.180

OR, odds ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NE, norepinephrine; PRA, plasma renin activity.

stronger neurohormonal activation in the DR group. In addition, the DR group exhibited significantly lower LVEF and eGFR and significantly higher NYHA HF class, furosemide dose and rate of tolvaptan combination therapy than the non-DR group.

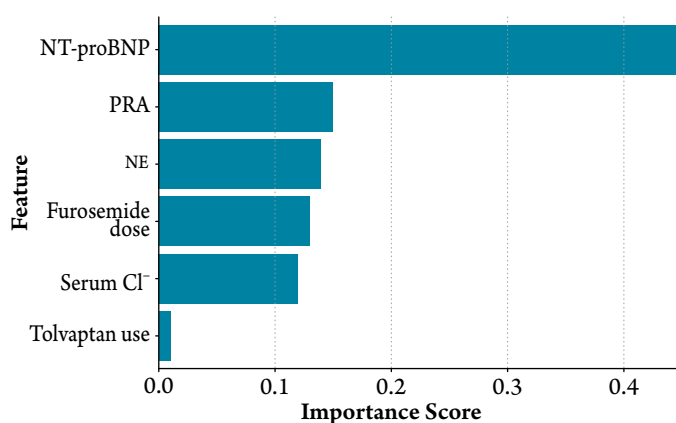
Although clinical outcomes were not predefined endpoints and were not statistically analyzed, review of the hospital records showed that all enrolled patients completed hospitalization without severe complications and were discharged in stable condition.

Variables screened by LASSO regression

LASSO regression was performed for variable selection, with the presence or absence of DR as the dependent variable and 11 clinical variables that showed significant between-group differences in the baseline analysis as independent variables. The optimal regularization parameter λ was determined through 10-fold cross-validation, under which the variables with non-zero coefficients included serum Cl⁻, NT-proBNP, NE, PRA, daily furosemide dose, and tolvaptan combination therapy [15]. The obtained variables were incorporated into subsequent model construction (Figure 1).

Construction of three machine learning models and evaluation of their ability to predict DR

The Logistic regression, Random Forest, and XGBoost models were constructed using the six screened variables, namely serum Cl⁻, NT-proBNP, NE, PRA, daily furosemide dose, and tolvaptan combination therapy, to assess their capability of forecasting the occurrence of DR in HF subjects. All three models were fitted on 70% of the training set and evaluated for performance on 30% of the independent test set. The indicators for evaluating predictive ability comprised AUC, accuracy, precision, recall, and F1 score (Figure 2 and Table 2). As shown in Figure 2, the ROC curves demonstrated good discriminatory ability for all three models, with AUC values of 0.83 for Logistic regression, 0.86 for Random Forest, and 0.89 for XGBoost. The XGBoost model achieved the highest AUC, whereas the Random Forest model showed slightly higher accuracy and F1 score. Overall, all three models demonstrated satisfactory predictive performance.

Figure 3. Variable importance ranking in the Random Forest model*

* Measured by the Mean Decrease Gini, higher scores indicate greater contributions of variables to the model

Results of Logistic regression analysis on variables

As revealed by Logistic regression analysis (Table 3), elevated NT-proBNP concentration had a significantly positive correlation with DR, implying that the capacity load indicators associated with aggravated HF may play a crucial role in poor diuretic response. The increased NE concentration also presented significant predictive value, suggesting a close relationship between over activation of neurohormonal system and DR. The increase in daily dose of furosemide significantly elevated the risk of DR, potentially indicating a vicious cycle of “dose elevation-resistance enhancement” in some patients. Similarly, tolvaptan application was found to be a significant predictor of DR, suggesting that tolvaptan is passively selected in some cases of refractory congestion and probably represents a state of water-sodium retention which is more difficult to control.

Results of importance analysis of variables in Random Forest model

In the Random Forest model, the importance of variables was evaluated using the Gini index [16]. Results showed that NT-proBNP was the most contributive predictor of DR, with an importance score significantly higher than other variables. This result implies that the Random Forest model, which is frequently adopted to split nodes in most decision tree mod-

els, probably reflects a close correlation between the severity of HF and a poor diuretic response. PRA ranked second in importance, demonstrating that the activation of the renin-angiotensin system is also an essential player in determining DR tendency. NE was close behind PRA, which further reinforced the function of the sympathetic nervous system activation in the development of this phenotype. In addition, the daily dose of furosemide and serum Cl^- displayed definite importance. Although these variables did not reach statistical significance in the Logistic regression model, they exhibited potential predictive value in the Random Forest model (Figure 3). These results may indicate that, in the context of non-linear relationships and variable interactions, these indicators retain identification ability in model decisions. Particularly, serum Cl^- is an electrolyte indicator mirroring the fluid capacity status and renal tubular function, so it is worthy of further attention in as a DR mechanism. Collectively, the Random Forest model revealed that multiple neurohormonal indicators, such as NT-proBNP, PRA, and NE, were highly associated with DR, and also that electrolytes and therapeutic interventions play potential roles in this pathway.

SHAP analysis results for the XGBoost model

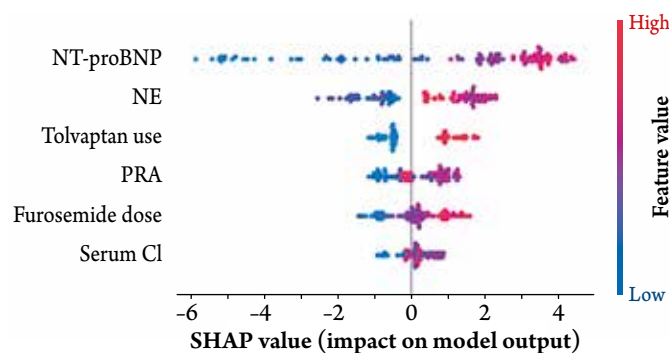
To improve the interpretability of the XGBoost model, the SHAP method was introduced to quantify the contributions of variables (Figure 4). The SHAP value represented the positive or negative effect of each variable on the prediction of individual patients, which was set as the horizontal axis, and its increases indicated the increased the model-predicted probability of the model in predicting “the presence of DR,” and vice versa. Colors denoted the numerical values of variables in a sample (red for high values and blue for low values). Each dot represents one patient.

According to this analysis, NT-proBNP was the variable most predictive of DR. As shown in the figure, individuals with a higher numerical value of NT-proBNP corresponded to a larger SHAP value, suggesting that such an elevation significantly facilitates the model’s prediction of DR presence. This finding coincides with clinical common sense that NT-proBNP is a crucial biomarker for HF severity, and its elevation hints greater congestion and cardiac stress, implying the possibility of reduced diuretic response.

The SHAP values of NE were primarily concentrated on the right side as well, which was particularly conspicuous in samples with higher values. This demonstrates that patients with higher sympathetic nervous system activation are more vulnerable to DR. This trend strengthens the association between neurohormonal activation and an adverse diuretic response.

Tolvaptan use exerted a significantly negative effect in the SHAP graph. In particular, the SHAP values for patients administered tolvaptan are concentrated on the left side of

Figure 4. SHAP summary plot for the XGBoost model*



* Each dot represents one patient. The horizontal axis shows the SHAP value, which indicates the contribution of each variable to the model-predicted probability of diuretic resistance (DR). Higher SHAP values indicate a greater contribution to predicting DR, whereas lower SHAP values indicate a lower contribution. Colors represent the value of each variable (red for high and blue for low)

the figure, indicating that the use of this drug is correlated with lower predicted risk. The results of model learning showed that tolvaptan might ameliorate patients’ diuretic response to some extent.

Moreover, PRA, daily dose of furosemide, and serum Cl^- also had a significant impact on some individuals. PRA exhibited different SHAP values across subjects, both positive and negative, suggesting that its impact may be modulated by specific pathological states, such as fluid capacity status and RAAS activity. Patients who were prescribed higher daily doses of furosemide (red dots in Figure 4) had SHAP values distributed to the right side, hinting a risk of poor diuretic response despite higher diuretic doses.

The serum Cl^- concentrations were also representative in the SHAP graph, where patients with lower Cl^- concentrations (blue dots in Figure 4) had SHAP values generally distributed to the right side. This indicates that “hypochloremia-induced DR” was identified and confirmed by the model.

In summary, the SHAP graphs not only reveal the directional relationship between variables and prediction results, but they also demonstrate the impact of specific numerical values on different patients. This method provides patient-level interpretability and may support a deeper understanding of the factors associated with DR in HF patients.

Discussion

In this study, the incidence rate of DR was approximately 30% among the study population, demonstrating that this phenomenon is not uncommon in clinical management and that it requires attention. The Logistic regression, Random Forest, and XGBoost models demonstrated good predictive abilities. Among them, the XGBoost model performed optimally, the Random Forest model presented slight advantages in accuracy and F1 score, and the Logistic regression

model possessed relatively weak predictive ability, but it had excellent interpretability and clinical applicability. Regarding the predictors, NT-proBNP was the most stable across the three models, while Cl^- , PRA, and NE had variations in ranking and contribution in different models.

In terms of serum electrolytes, the serum Cl^- concentration plays various roles in the different models. Based on the results of the present study, the Cl^- concentration failed to reach statistical significance in the Logistic regression model, whereas it manifested high predictive value in the Random Forest and XGBoost models. To be specific, the SHAP analysis for the XGBoost model showed that low Cl^- concentration was significantly contributory to DR prediction. Compared to Na^+ as the focus of traditional studies, Cl^- may be more crucial to HF outcome and diuretic response, which is consistent with recent literature reports [17]. Hypochloremia frequently occurs in patients with acute and chronic HF, which has an intimate association with poor prognosis and prominently indicates reduced diuretic efficacy [18]. Its mechanism likely involves the signaling effect of Cl^- in the distal convoluted tubule. Hypochloremia can stimulate renin secretion through tubuloglomerular feedback, activate RAAS, and then increase sodium and water reabsorption [19]. At the same time, Cl^- loss creates a low-chloride environment in cells, while hypochloremia promotes sodium reabsorption in proximal and distal renal tubules, thereby offsetting the natriuretic effect of diuretics [20]. The decrease in serum Cl^- concentration is often accompanied by neurohormonal activation and DR, and it is independently associated with poorer clinical outcomes [21]. This evidence highlights the pivotal role of Cl^- in the occurrence and development of DR, suggesting that maintaining Cl^- homeostasis is crucial for guaranteeing diuretic efficacy and breaking the vicious cycle of DR.

Among the neurohormonal indicators, NE concentration was a significant predictor in both Logistic regression and XGBoost models, PRA had a high rank of importance in the Random Forest model, and NT-proBNP elevation was markedly related to DR risk and remained highly stable in all three prediction models. The over activation of the sympathetic nervous system and RAAS is considered a core mechanism of DR. It has been shown that RAAS activation degree is negatively correlated with diuretic efficacy, and renin concentration is generally raised in hypochloremia patients [22]. Essentially, PRA reflects the degree of RAAS activation, and PRA elevation suggests a vicious cycle of “capacity loss-RAAS over activation-enhanced sodium and water reabsorption” that is closely associated with DR [23]. The increase of NE concentration indicates enhanced sympathetic excitability, and sympathetic activation causes constriction of afferent glomerular arterioles, leading to reduced renal blood flow and eGFR. This impairs effective

perfusion of diuretics to the kidneys, enhancing renal tubular reabsorption, and thereby attenuating diuretic efficacy [24]. These findings are also consistent with the observations in this study. The increment of NT-proBNP, a crucial indicator for assessing HF severity, often indicates the activation of the endogenous natriuretic peptide system at an early stage, which can alleviate the congestion. In the later stage of chronic HF, however, NT-proBNP elevation mainly reflects the failure of endogenous protective mechanisms and places irremediable congestion on the heart due to reduced receptor sensitivity and weakened signal transduction [25]. Therefore, NT-proBNP elevation can be regarded as an indirect biomarker of “treatment tolerance” to some extent, providing clues for determining the decline of diuretic efficacy [26].

With respect to drug application, the present study showed that the daily dose of furosemide correlated significantly with DR risk in the Logistic regression and XGBoost models, hinting at a vicious cycle of “dose escalation-response diminution” in some patients. In other words, when the dose is passively increased because of a weakened diuretic response, this further activates neurohormones and enhances renal tubular reabsorption. This ultimately undermines any therapeutic effect [27].

The significance of tolvaptan varied across the models: It emerged as an independent predictor of increased DR risk in the Logistic regression model, whereas it was found to pose a negative impact on DR prediction in SHAP analysis of the XGBoost model, suggesting that tolvaptan may improve the diuretic response only in some patients. Such a discrepancy may indicate that tolvaptan is mostly prescribed for patients with intractable capacity load in clinical practice, and its application may mark severe DR and confer therapeutic benefit in such cases. These findings suggest that medication factors should be clinically interpreted in combination with the specific disease stage, the clinician's prescription rationale, and a comprehensive assessment of patient's response, rather than simply classifying drug application as a risk or protective factor.

In this study, the Logistic regression, Random Forest, and XGBoost models were simultaneously evaluated, and their predictive performance and clinical applicability were compared. All three models effectively predicted DR risk but with distinct characteristics. According to previous research, the Logistic regression model appears merely suitable for linear relationships, restricting its ability to identify complex interactions and nonlinear effects [28]. Consequently, Cl^- and PRA did not show statistically significant differences in the Logistic regression model employed in this study. This may result in underestimation of their predictive value. As an ensemble learning method, Random Forest emphasizes stability and resistance to overfitting. In this study,

the Random Forest model showed the highest recall and F1 score among the three models (Table 2), suggesting that it is more sensitive in identifying the minority of high-risk patients [29]. XGBoost under the Boosting framework aims to increase the precision of prediction through iterative error correction. Results showed that the XGBoost model had the highest AUC value (0.89), so it presented the optimal discriminatory power. It is worth noting that the XGBoost model combined with SHAP method can not only provide an overall ranking of variable contributions but also explain the positive or negative impacts of variables on prediction results at the individual level [30].

Limitations

The present study has some limitations. Firstly, this was a single-center, retrospective study with a limited sample size, so the results might have selection bias. Secondly, some indicators, such as PRA and NE, were susceptible to the influence of drug therapy and testing conditions, and the stability and reproducibility of their results should be confirmed by larger sample sizes. Thirdly, modeling was accomplished solely based on static data at admission without dynamic follow-up data. This was likely to result in an underestimation of the predictive value of some variables. In the future, multicenter large-sample prospective stud-

ies should be conducted to incorporate dynamic indicators, such as serum Cl^- and NT-proBNP, into continuous-time prediction models to develop real-time risk warning systems for DR in HF patients.

Conclusion

The importance of neurohormonal indicators, in particular serum Cl^- and NT-proBNP, in predicting DR in HF patients was demonstrated. By integrating these and other related variables into several machine learning models, the predictive precision and interpretability of DR data was enhanced. This approach should facilitate early identification of patients at high risk of DR. Future validation of these findings in larger-scale, multicenter populations is expected to improve individualized management of DR, and, thus, provide new insights for precision treatment of HF patients.

Data Availability

The experimental data used to support the findings of this study are available from the corresponding author upon request.

No conflicts of interest are reported.

The article was received on 22/09/2025

REFERENCES

- Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. *Nature Reviews Cardiology*. 2020;17(10):641–55. DOI: 10.1038/s41569-020-0379-7
- Shams E, Bonnice S, Mayrovitz HN. Diuretic Resistance Associated With Heart Failure. *Cureus*. 2022;14(1):e21369. DOI: 10.7759/cureus.21369
- Guo L, Fu B, Liu Y, Hao N, Ji Y, Yang H. Diuretic resistance in patients with kidney disease: Challenges and opportunities. *Biomedicine & Pharmacotherapy*. 2023;157:114058. DOI: 10.1016/j.biopha.2022.114058
- Acar S, Sanli S, Oztosun C, Afsar B, Sag AA, Kuwabara M et al. Pharmacologic and interventional paradigms of diuretic resistance in congestive heart failure: a narrative review. *International Urology and Nephrology*. 2021;53(9):1839–49. DOI: 10.1007/s11255-020-02704-7
- Arora N. Serum Chloride and Heart Failure. *Kidney Medicine*. 2023;5(4):100614. DOI: 10.1016/j.xkme.2023.100614
- Van Den Eynde J, Martens P, Dauw J, Nijst P, Meekers E, Ter Maaten JM et al. Serum Chloride and the Response to Acetazolamide in Patients With Acute Heart Failure and Volume Overload: A Post Hoc Analysis From the ADVOR Trial. *Circulation: Heart Failure*. 2023;17(10):e011749. DOI: 10.1161/CIRCHEARTFAILURE.123.011749
- Aimo A, Prontera C, Passino C, Emdin M, Vergaro G. Norepinephrine, plasma renin activity and cardiovascular mortality in systolic heart failure. *Heart*. 2021;107(12):989–95. DOI: 10.1136/heartjnl-2020-318791
- Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology*. 1996;49(12):1373–9. DOI: 10.1016/S0895-4356(96)00236-3
- Wei D, Dongjie RJ. Chinese expert consensus on the diagnosis and management of diuretic resistance in patients with heart failure. *Journal of Clinical Cardiology*. 2024;40(4):257–67
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *European Journal of Heart Failure*. 2022;24(1):4–131. DOI: 10.1002/ehf.2333
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI et al. A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*. 2009;150(9):604–12. DOI: 10.7326/0003-4819-150-9-200905050-00006
- Kim H-Y. Statistical notes for clinical researchers: logistic regression. *Restorative Dentistry & Endodontics*. 2017;42(4):342–8. DOI: 10.5395/rde.2017.42.4.342
- Breiman L. Random Forests. *Machine Learning*. 2001;45(1):5–32. DOI: 10.1023/A:1010933404324
- Nohara Y, Matsumoto K, Soejima H, Nakashima N. Explanation of machine learning models using shapley additive explanation and application for real data in hospital. *Computer Methods and Programs in Biomedicine*. 2022;214:106584. DOI: 10.1016/j.cmpb.2021.106584
- Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. *Journal of Statistical Software*. 2010;33(1):1–22. PMID: 20808728
- Liu Y, Zhang Y, Liu D, Tan X, Tang X, Zhang F et al. Prediction of ESRD in IgA Nephropathy Patients from an Asian Cohort: A Random Forest Model. *Kidney and Blood Pressure Research*. 2018;43(6):1852–64. DOI: 10.1159/000495818
- Koirala A, Pourafshar N, Daneshmand A, Wilcox CS, Mannemudhu SS, Arora N. Etiology and Management of Edema: A Review. *Advances in Kidney Disease and Health*. 2023;30(2):110–23. DOI: 10.1053/j.akdh.2022.12.002

18. Zandijk AJL, Van Norel MR, Julius FEC, Sepehrvand N, Pannu N, McAlister FA et al. Chloride in Heart Failure: The Neglected Electrolyte. *JACC: Heart Failure*. 2021;9(12):904–15. DOI: 10.1016/j.jchf.2021.07.006
19. Rivera FB, Alfonso P, Golbin JM, Lo K, Lerma E, Volgman AS et al. The Role of Serum Chloride in Acute and Chronic Heart Failure: A Narrative Review. *Cardiorenal Medicine*. 2021;11(2):87–98. DOI: 10.1159/000515604
20. Kazory A, Ronco C. Emergence of Chloride as an Overlooked Cardiorenal Connector in Heart Failure. *Blood Purification*. 2020;49(1–2):219–21. DOI: 10.1159/000503774
21. Kurashima S, Kitai T, Matsue Y, Nogi K, Kagiya N, Oishi S et al. Trajectory of serum chloride levels during decongestive therapy in acute heart failure. *International Journal of Cardiology*. 2023;375:36–43. DOI: 10.1016/j.ijcard.2022.12.041
22. Amatruda JG, Scherzer R, Rao VS, Ivey-Miranda JB, Shlipak MG, Estrella MM et al. Renin-Angiotensin-Aldosterone System Activation and Diuretic Response in Ambulatory Patients With Heart Failure. *Kidney Medicine*. 2022;4(6):100465. DOI: 10.1016/j.xkme.2022.100465
23. McNally RJ, Faconti L, Cecelja M, Farukh B, Floyd CN, Chowienczyk PJ. Effect of diuretics on plasma renin activity in primary hypertension: A systematic review and meta-analysis. *British Journal of Clinical Pharmacology*. 2021;87(5):2189–98. DOI: 10.1111/bcp.14597
24. Puleo F, Kim K, Frame AA, Walsh KR, Ferdous MZ, Moreira JD et al. Sympathetic Regulation of the NCC (Sodium Chloride Co-transporter) in Dahl Salt-Sensitive Hypertension. *Hypertension*. 2020;76(5):1461–9. DOI: 10.1161/HYPERTENSIONAHA.120.15928
25. Mauch J, Puthenpura M, Martens P, Engelman T, Grodin JL, Segar MW et al. Adequacy of Loop Diuretic Dosing in Treatment of Acute Heart Failure: Insights from the BAN-ADHF Diuretic Resistance Risk Score. *The American Journal of Cardiology*. 2025;244:18–27. DOI: 10.1016/j.amjcard.2025.02.018
26. Baumberger J, Dinges S, Lupi E, Wolters T, Stüssi-Helbling M, Cippà PE et al. Prevalence and Characteristics of Upfront Diuretic Resistance in Acute Heart Failure: The P-Value-AHF Study. *ESC Heart Failure*. 2025;12(1):688–94. DOI: 10.1002/ehf2.15069
27. Biegus J, Zymliński R, Testani J, Fudim M, Cox ZL, Guzik M et al. The Blunted Loop Diuretic Response in Acute Heart Failure is Driven by Reduced Tubular Responsiveness Rather than Insufficient Tubular Delivery. The Role of Furosemide Urine Excretion on Diuretic and Natriuretic Response in Acute Heart Failure. *European Journal of Heart Failure*. 2023;25(8):1323–33. DOI: 10.1002/ejhf.2852
28. Kokori E, Patel R, Olatunji G, Ukoaka BM, Abraham IC, Ajekiigbe VO et al. Machine learning in predicting heart failure survival: a review of current models and future prospects. *Heart Failure Reviews*. 2024;30(2):431–42. DOI: 10.1007/s10741-024-10474-y
29. Xing F, Luo R, Liu M, Zhou Z, Xiang Z, Duan X. A New Random Forest Algorithm-Based Prediction Model of Post-operative Mortality in Geriatric Patients With Hip Fractures. *Frontiers in Medicine*. 2022;9:829977. DOI: 10.3389/fmed.2022.829977
30. Riveros Perez E, Avella-Molano B. Learning from the machine: is diabetes in adults predicted by lifestyle variables? A retrospective predictive modelling study of NHANES 2007–2018. *BMJ Open*. 2025;15(3):e096595. DOI: 10.1136/bmjopen-2024-096595