A machine learning approach for predicting treatment response of hyponatremia

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Running head: Predicting treatment response of hypoNa

Abstract

Hyponatremia leads to severe central nervous system disorders and requires immediate treatment in some cases. However, a rapid increase in serum sodium (s-Na) concentration could cause osmotic demyelination syndrome. To achieve a safety hyponatremia treatment, we develop a prediction model of s-Na concentration using a machine learning. Among the 341 and 47 patients admitted to two tertiary hospitals for hyponatremia treatment (s-Na <130 mEq/L), those who were admitted to the general unit with urine sodium <20 mEq/L or treated with desmopressin were excluded. Ultimately, 74 and 15 patients (342 and 146 6-hourly datasets) were included in the learning and validation data, respectively. We trained the prediction model using three regression algorithms for shallow machine learning to predict s-Na every 6 h during treatment with the data of patients with hyponatremia (median s-Na: 112.5 mEq/L; range: 110.0–116.8 mEq/L) from one hospital. The model was validated externally using the data of patients with hyponatremia (median s-Na: 117.0 mEq/L; range: 112.9–120.0 mEq/L) from another hospital. Using 5–7 predictors (water intake, sodium intake, potassium intake, urine volume, s-Na concentration, serum potassium concentration, serum chloride concentration), the support vector regression model showed the best performance overall (root mean square error=0.05396; R^2=0.92), followed by the linear regression and regression tree models. The predicted s-Na levels, using explainable machine learning algorithms and clinically accessible parameters, correlated well with the actual levels. Thus, our model could be applied to the treatment of hyponatremia in clinical practice.

Key words: Hyponatremia, Predictive machine learning tool, Revised Adrogué–Madias formula, Prevention of osmotic demyelination syndrome, Monitoring for electrolyte abnormalities

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1. Introduction

Hyponatremia, defined as a serum sodium (s-Na) concentration of <135 mEq/L, is the most common electrolyte disorder in clinical practice [1]. Hyponatremia occurs in 15%–30% of hospitalized patients [2-4], with higher frequencies observed in elderly individuals [3] and cancer patients [5]. Based on its extracellular fluid volumes, hyponatremia is classified into three subtypes: hypovolemic, euvolemic, and hypervolemic [6]. Hypovolemic hyponatremia is caused by vomiting, diarrhea, primary renal failure, and diuretic use, resulting in the depletion of extracellular fluid volumes. Euvolemic hyponatremia can be due to inappropriate antidiuretic hormone secretion and adrenal insufficiency secondary to hypopituitarism. Hypervolemic hyponatremia occurs with edematous diseases, including congestive heart failure, liver cirrhosis, and nephrotic syndrome. Although hyponatremia is classified into these three subtypes, the identification of the causes of hyponatremia, as well as differentiation between hypovolemic hyponatremia and euvolemic hyponatremia, remains challenging because of its complex pathology [7]. Therefore, the definitive diagnosis of etiology often remains elusive before treatment initiation, particularly during the early treatment phase [8].

Rapid s-Na correction with intravenous infusion of hypertonic saline is warranted when symptoms of hyponatremia due to cerebral edema are evident, because it could lead to cerebral herniation and even death [1]. However, rapid s-Na correction could cause osmotic demyelination syndrome (ODS), which manifests as impaired consciousness and tetraplegia. Prevention of ODS is crucial in the treatment of hyponatremia because ODS has no effective treatment and can be life-threatening [9]. To minimize the risk of ODS, a correction rate of s-Na of <8–10 mEq/L per 24-h period is recommended [10]. However, ODS may occur in patients with severe hyponatremia (frequency rate: 0.3%–1.1%) due to occasional rapid s-Na changes even when treated by a

specialist [11].

In recent years, artificial intelligence technology has been increasingly applied in medical research to support diagnosis and predict treatment efficacy and prognosis in various fields. However, while studies have been conducted on hyponatremia to predict its onset in hospitalized patients and after pituitary surgery [12, 13], there has not been any research that reports the prediction of treatment-dependent s-Na concentration in patients with hyponatremia.

In the current study, to address the clinical need for the safe treatment of patients with severe hyponatremia, we trained a highly explainable shallow machine learning model that can predict the s-Na concentrations of patients undergoing fluid infusion treatment.

2. Materials and methods

Patients

Patients admitted to two tertiary care hospitals, Nagoya University Hospital and the Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, for hyponatremia treatment between April 2015 and March 2020 were included in this study. Clinical data of patients treated in acute care units, where time series data can be obtained every few hours, were extracted from the electronic medical records of both hospitals for analysis. Patients with a urinary Na (u-Na) concentration of <20 mEq/L were excluded because their cause of hyponatremia was mainly dehydration and completely different from that of patients with a u-Na concentration of >20 mEq/L. Moreover, patients who were administered desmopressin (DDAVP) to prevent a rapid increase in s-Na during hyponatremia treatment [14] were excluded because their urine volumes could be affected. The machine learning model was trained and validated internally using data from Nagoya Daini Hospital as training data; it was validated externally using data from Nagoya University Hospital

as test data.

Predictors used in the model

The following major laboratory values related to fluid volume and osmolality were extracted as candidates for predictors: s-Na, serum potassium (s-K), serum chloride (s-Cl), serum glucose, blood urea nitrogen, creatinine, estimated glomerular filtration rate, uric acid, total protein, albumin, hematocrit, plasma osmolality, u-Na concentration, urine osmolality, plasma renin activity, plasma arginine vasopressin, plasma aldosterone, serum cortisol, plasma adrenocorticotropic hormone, human atrial Na diuretic peptide, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), urine volume, total water administered by infusion and drinking (water intake), Na administered by infusion (Na-IN), and potassium (K) administered by infusion (K-IN). Among these candidates, s-Na, s-K, s-Cl, water intake, Na-IN, K-IN, and urine volume were selected as predictors because they are frequently measured and recorded in practice when treating hyponatremia (Fig. 1A).

Response

We used the s-Na concentration at 6 h (s-Na6h) as the response. When treating hyponatremia, physicians typically perform blood examinations every 2–3 h during the acute phase to determine the s-Na concentration. We selected 6 h as the time interval for simulation based on the assumption that even if there was a large discrepancy between the s-Na predicted by the model and the actual value, it would be clinically manageable in 6 h.

Data preparation and preprocessing

Datasets extracted from the electronic medical records were converted to timetable data; one time was associated with each row for each patient, and timestamps were resampled as hourly units after removing the time window from admission to discharge. Regarding laboratory values among the predictors, linear interpolation was performed to compensate for the missing values to process the data for machine learning because the measurement intervals varied depending on the case and elapsed time.

The semi-structured data, such as intravenous infusion, are heterogeneous and require standardization. For example, infusion formulations have various compositions that may have multiple different names, depending on the pharmaceutical company, and some formulations may be mixed before administration. Therefore, we created master data for each infusion formulation and combination of formulations so that the dosage (mL) could be converted to the actual dosages of water (mL), Na (mEq), and K (mEq). Regarding water intake, Na-IN, and K-IN, we referred to the infusion master data to determine the amount of water, Na, and K administered each hour. Regarding urine volume, if it was not recorded hourly, then the urine volume was divided equally by the time elapsed from the previous recording time to distribute the urine volume.

Regarding s-Na6h after the reference time, only the measured values of s-Na were used; the complementary values were not used. The s-Na, s-K, and s-Cl values comprised the reference time values (T = t). Urine volume was the amount of urine output during the 6 h before the reference time (t − 6 to t). Water intake, Na-IN, and K-IN were determined using the treatment information pertaining to the number of hours from the reference time (t to t + 6) (Fig. 1B). During preprocessing of the data, normalization was performed by transforming the data so that all measurements had values between 0 and 1.

Machine learning model

We trained and tested the following three regression algorithms for shallow machine learning: linear regression, decision tree, and support vector regression (SVR). All these models were implemented using MATLAB version R2022a, which is a commercially available mathematics software and programming language tool commonly used for machine learning (MathWorks, Inc., Natick, MA, USA). To predict s-Na6h, we trained the model using only the data derived from Nagoya Daini Hospital and performed 10-fold cross-validation. Then, we examined the differences in accuracy between the training models based on combinations of 5–7 predictors. Subsequently, the accuracy of the learning models was externally validated using the Nagoya University Hospital dataset. During this study, shallow machine learning was selected for modeling because the number of datasets was too small for deep learning, owing to its relatively high explanatory potential compared to deep learning, and because it could be used as a benchmark for comparisons of the accuracy of other models in the future.

Ethical approval

This research has been complied with all the relevant national regulations and institutional policies and according to the tenets of the Helsinki Declaration and has been approved by Nagoya University Hospital Institutional Review Board (approval number 2020-0384).

After extracting data from the electronic medical records, pseudonymization and storage were performed in accordance with the guideline associated with the Japanese law regarding the protection of personal information and the protocol approved by the ethics committee.

3. Results

Learning data

During the 5-year period, from April 2015 to March 2020, a total of 341 patients were admitted to the Department of Endocrinology and Diabetes of Nagoya Daini Hospital for hyponatremia treatment (Fig. 2A). Of these, 234 patients treated in the general unit were excluded. For patients treated in intensive care units (ICUs) and other acute care units using critical care progress charts, it was possible to retrospectively collect information regarding infusion therapy and fluid delivery. Ten patients with u-Na <20 mEq/L, suggesting dehydration, were excluded. The u-Na concentration of one patient was not measured. Moreover, 22 patients who received DDAVP to prevent a rapid increase in s-Na during hyponatremia treatment were excluded. Finally, 342 6-hourly datasets of 74 patients were used as learning data to train the model.

Validation data

To obtain validation data, target patients were selected using the same criteria as those used for patients at Nagoya Daini Hospital (Fig. 2B). During the 5-year period, from April 2015 to March 2020, 47 patients were admitted to the Department of Endocrinology and Diabetes of Nagoya University Hospital for hyponatremia treatment. Of these, 31 patients treated in the general unit were excluded. For patients treated in the emergency departments and ICUs using critical care progress charts (Fortec ACSYS; Koninklijke Philips N.V., Eindhoven, the Netherlands), it was possible to retrospectively collect information regarding infusion therapy and fluid delivery. Only one patient with u-Na <20 mEq/L, suggesting dehydration, was excluded. No patients were administered DDAVP during treatment. Finally, 146 6-hourly datasets of 15 patients were used as

validation data to externally validate the model.

Patient characteristics

Table 1 summarizes the characteristics of patients included in the learning and validation datasets. Data are expressed as median (interquartile range [IQR]) or number (percentage). For patients included in the learning datasets, the median age was 78.0 years (IQR: 69.3–86.0 years), and 64.9% were women. On admission, the median s-Na concentration was 112.5 mEq/L (IQR: 110.0–116.8 mEq/L), median plasma osmolality was 238.5 mOsm/L (IQR: 228.3–245.0 mOsm/L), median u-Na concentration was 62.0 mEq/L (IQR: 43.3–94.8 mEq/L), and median urine osmolality was 362.0 mOsm/kg (IQR: 259.5–510.8 mOsm/kg).

For patients included in the validation data, the median age was 76.0 years (IQR: 73.0–78.0 years), and 66.7% were women. On admission, the median s-Na concentration was 117.0 mEq/L (IQR: 112.0–120.0 mEq/L), median plasma osmolality was 245.8 mOsm/L (IQR: 236.0–249.0 mOsm/L), median u-Na concentration was 73.0 mEq/L (IQR: 46.5–95.0 mEq/L), and median urine osmolality was 476.0 (IQR: 360.0–505.5). Significant differences ($p<0.05$; two-sample t-test) were observed between learning data and validation data for the following items: blood urea nitrogen, uric acid, cortisol, FT4, and arginine vasopressin (AVP). None of the patients included in both datasets had hyperglycemia (blood glucose concentrations >250 mg/dL). No patients presented with symptoms suggestive of ODS during or after treatment. None of the patients died. All patients were discharged home or to a rehabilitation facility.

Predictors

Figure 3A shows the candidate predictors and training datasets during the period from ICU

admission to discharge. The data window duration was set to 1 h. The frequency of each feature was calculated by dividing the total number of records by the total number of data windows for all patients, resulting in the following seven predictors with the highest frequency: s-Na, s-K, s-Cl, water intake, Na-IN, K-IN, and urine volume.

Data normalization

The seven selected predictors and one response were normalized as follows: water intake' = water intake/1000; Na-IN' = Na-IN/100; K-IN' = K-IN/10; urine volume' = urine volume e/1000; s-Na' = (136 – s-Na)/30; s-K' = (5.0 – s-K)/3; s-Cl' = (98- s-Cl)/30; and s-Na6h' = (136 - s-Na6h)/30. A distribution plot of the normalized data is shown in Figure 3B. The normalized results were as follows: water intake, 98.54%; Na-IN, 97.95%; K-IN, 97.08%; urine volume, 98.83%; s-Na, 97.37%; s-K, 97.66%; s-Cl, 77.19%; and s-Na6h, 97.08%.

Internal verification

The results of performing 10-fold cross-validation with various combinations of 5–7 predictors are presented in Table 2. The learning model using linear regression resulted in a root mean square error (RMSE) of 0.036768 and coefficient of determination (R^2) of 0.97 (Fig. 4A). The training model using SVR resulted in an RMSE of 0.037026 and R^2 of 0.97 (Fig. 4B). The training model using regression trees showed an RMSE of 0.056895 and R^2 of 0.93 (Fig. 4C). Among these three models, the linear regression model showed the highest accuracy, which corresponded to the root mean square deviation (RMSD) between the predicted and measured s-Na values was 1.11 mEq/L. The SVR model trained with five predictors (excluding s-K and s-Cl) showed the best accuracy among all combinations of predictors (RMSE of 0.036466 and R^2 of 0.97) (Table 2).

External validation

All training models were validated using the validation data from Nagoya University Hospital. Table 3 shows the external validation results with various combinations of 5–7 predictors. The linear regression model resulted in an RMSE of 0.0544170 and R^2 of 0.92 (Fig. 5A). The SVR model resulted in an RMSE of 0.0539600 and R^2 of 0.92 (Fig. 5B). The regression tree model resulted in an RMSE of 0.0593740 and R^2 of 0.91 (Fig. 5C). Among these three models, the SVR model showed the highest accuracy, which corresponded to the RMSD between the predicted and measured s-Na values was 1.62 mEq/L. The SVR model with all seven predictors had the best accuracy among all combinations of predictors.

4. Discussion

In this study, we developed a machine learning model to predict s-Na at 6 h using clinically accessible parameters, such as s-Na, s-K, s-Cl, Na-IN, K-IN, water intake, and urine volume. According to the internal validation of accuracy with 10-fold cross-validation, the linear and SVR models showed high accuracy with RMSE of 0.037, and the RMSD between the predicted and measured s-Na values was 1.11 mEq/L. The external validation on these models further showed high accuracy with RMSE of 0.054 for the linear and SVR models, and the RMSD between the predicted and measured s-Na values was 1.62 mEq/L. Furthermore, the prediction accuracy did not significantly decrease even if one or two fewer predictors were missing, suggesting it would be applicable to cases in which some information are not available.

We selected several parameters as predictors in this study (Fig. 1A). Although other candidates as predictors, such as body weight and u-Na, may exist, these were not employed because they are

not usually measured in the acute phases of treatment in clinical settings. Instead, we included not only s-Na, Na-IN, water intake, and urine volume but also s-K, s-Cl, and K-IN as predictors in this study, leading to the establishment of a predicting model for s-Na with high accuracy. K-IN is involved in the Adrogué–Madias formula [15], and a previous study showed that s-Cl is a good predictor for delayed hyponatremia after transsphenoidal surgery [16]. However, these results and ours do not necessarily imply that s-K, s-Cl, and K-IN have direct effects on s-Na, and explaining the results derived from artificial intelligence and machine learning models is sometimes difficult.

Hyponatremia is the most common electrolyte abnormality in general hospitalized patients. Even mild hyponatremia without apparent symptoms is associated with cognitive deficits [17], gait disturbance [18], and increased rates of falls and fractures [19-21]. Furthermore, hyponatremia is correlated with the increased mortality of patients with various diseases, such as lung cancer [22] and sepsis [23]; elderly patients [24]; and patients undergoing surgical intensive care [25]. Recent meta-analysis studies have confirmed that hyponatremia is a frequent presentation in up to 20% of hospitalized patients and is associated with longer hospital stays and readmissions [26]. However, selecting an appropriate treatment for hyponatremia and predicting s-Na response to that treatment is challenging, and patient-specific s-Na prediction algorithms are required. Our current s-Na prediction models could address this need and will help physicians, including those not specializing in endocrinology or nephrology, select an appropriate treatment.

Several studies have used machine learning methods to predict the onset of hyponatremia and for cluster classification of hyponatremia patients. Theerthagiri *et al.* used a multilayer perception and multivariate linear regression algorithm and have shown that the s-Na of patients with normonatremia could be predicted based on their history of health issues [13]. Voglis *et al.* have revealed that the machine learning model could predict the occurrence of hyponatremia after

298 pituitary surgery, thus potentially reducing morbidity and improving patient safety [12].
299 Thongprayoon *et al.* have identified three clinically distinct phenotypes with differing mortality
300 risks among a heterogeneous cohort of hospitalized patients with hyponatremia using an
301 unsupervised machine learning approach [27]. However, no studies have provided predictions of
302 the s-Na concentration of patients with hyponatremia based on the treatment choice. By using our
303 s-Na predicting model developed in the current study, we can select an appropriate treatment for
304 the safely correction of s-Na to prevent from a rapid increase in s-Na, which is the risk for ODS.
305 The Adrogué–Madias formula is a widely recognized clinical tool for calculating ΔNa after
306 infusing 1 L based on three parameters: the amount of Na and K in a 1 L infusion and total body
307 water [15]. However, its accuracy in predicting s-Na is limited to only when 1 L of fluid is
308 administered, and the relationship between infusion volume and s-Na variability is not always
309 linear [28]. In addition, measuring accurate total body water volume, which is included in input
310 variables, is challenging in patients with severe hyponatremia in the acute phase when plasma AVP
311 secretion and urine output are constantly changing, which could prevent physicians from using the
312 Adrogué–Madias formula. In contrast, our current prediction model requires only clinically
313 accessible and available parameters and thus could be more widely used to predict s-Na in clinical
314 practice.
315 There are several limitations to this study. First, only severe cases were employed in this study
316 so that accurate hourly data in intensive care electronic medical record systems were analyzed.
317 Thus, the study data were obtained from a limited number of hospitals and did not include a large
318 number of patients. Second, we excluded cases with u-Na <20 mEq/L and those with therapeutic
319 interventions with DDAVP from the analysis because they have different pathology and may
320 respond differently to the treatment. In cases of hyponatremia with dehydration, sufficient fluid

supplementation with appropriate Na concentrations is needed. Strict s-Na monitoring is required for water intoxication since s-Na is likely to rise quite quickly. We could further address these cases by accumulating more data in future. Third, the predictors did not include information about the elapsed time since the onset of hyponatremia. While our model showed high accuracy in the prediction of s-Na, it is possible that responses of s-Na to treatment are different between the early and late stages of treatment. Fourth, this study focuses on the acute phase (6 h) of severe hyponatremia treatment and the prevention of rapid increase in s-Na. Therefore, predicting s-Na at 12 and 24 h from the initiation of the treatment would be possible if we use this model every 6 h with measured parameters. However, in a situation where measuring parameters every 6 h is difficult, as in this case, predictive models for s-Na at 12 or 24 h need to be established.

In conclusion, the predicted s-Na levels, using explainable machine learning algorithms and clinically accessible parameters, correlated well with the actual levels in the current study. Thus, our model could be applied to the treatment of hyponatremia in clinical practice.

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6. Disclosure

None of the authors have any potential conflicts of interest associated with this research.

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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7. Roles/Contributions

Conceptualization: TK, SO, DH, YA, HA. Data curation: TK, SO. Formal analysis: TK, SO. Funding acquisition: DH, HA. Investigation: TK, SO, DH, YA. Methodology: TK, SO. Project administration: SO, DH, HA. Resources: SO, DH, YA, HA. Software: TK, SO. Supervision: SO, DH, HA. Validation: TK. Visualization: TK. Writing: TK. Review and editing: TK, SO, DH, YA, HA.

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Figure legends

Figure 1. Seven predictors and data processing methods.

(A) Seven predictors of the serum sodium (s-Na) concentration at 6 h (s-Na6h).

The s-Na6h was used as the response (T = t + 6). The predictors were s-Na, serum potassium (s-K), serum chloride (s-Cl), urine volume (water-OUT), water intake (water-IN), sodium infusion (Na-IN), and potassium infusion (K-IN). For the s-Na6h, only the measured values of s-Na were used; the complementary values were not used. The s-Na, s-K, and s-Cl values were those at the reference time (T = t). Water-OUT was the amount of urine output during the 6 h before the reference time (t − 6 to t). Water-IN, Na-IN, and K-IN were determined using the treatment information pertaining to the number of hours from the reference time (t to t + 6).

(B) Data processing methods.

All recorded times (in minutes and seconds) were recombined as 1-h units. To obtain laboratory values of the predictors, linear completion was performed to compensate for missing values. For water-IN, Na-IN, and K-IN, we referred to the infusion master data to determine the amounts of water, Na, and K administered each hour. For water-OUT, if the urine volume was not recorded hourly, then the urine volume was divided by the elapsed time from the previous recording time to distribute the urine volume. For the response (s-Na6h), only the measured values of s-Na were used; the complementary values were not used.

Figure 2. Study flow diagram.

(A) Learning data. A total of 341 patients were admitted to the Department of Endocrinology and

Diabetes of Nagoya Daini Hospital for hyponatremia treatment. We excluded 234 patients treated in the general unit. Ten patients with u-Na <20 mEq/L and one patient without u-Na measurement data were excluded. Additionally, 22 patients who received desmopressin (DDAVP) to prevent overcorrection of s-Na were excluded. Finally, 342 6-hourly datasets of 74 patients were used as learning data to train the model.

(B) Validation data. A total of 47 patients were admitted to the Department of Endocrinology and Diabetes of Nagoya University Hospital for hyponatremia treatment. Thirty-one patients treated in the general unit were excluded. One patient with u-Na <20 mEq/L was excluded. No patients were administered DDAVP during treatment. Finally, 146 6-hourly datasets of 15 patients were used as validation data for external validation of the model.

Figure 3. Selection of predictors and distribution of normalized data.

(A) Number of records. The total number of training data windows (bar graph, right vertical axis) and the ratio of the number of training data records to the number of data windows of predictor candidates (line chart, left vertical axis) during the period from intensive care unit (ICU) admission to discharge are shown. The data window duration was set to 1 h.

(B) Normalized data distribution. This is a box-and-whisker diagram of the normalized data. The x indicates the mean, the middle horizontal line indicates the median, and the boxes indicate the first through third quartile ranges. The upper and lower ends of the vertical bars indicate the maximum and minimum values, respectively, excluding the outliers.

Figure 4. Ten-fold cross-validation of the training data.

(A) Linear regression model. (B) Support vector regression model. (C) Regression tree model.

The results of 10-fold cross-validation of the training data are shown. The linear regression model showed the highest accuracy, which corresponded to the root mean square deviation (RMSD) between the predicted and measured s-Na values of 1.11 mEq/L.

Figure 5. External validation of each model.

(A) Linear regression model. (B) Support vector regression (SVR) model. (C) Regression tree model.

The external validation results of the validation data are shown. The SVR model showed the highest accuracy, corresponding to the RMSD between the predicted and measured s-Na values of 1.62 mEq/L.

Table 1: Clinical characteristics of the study population

	Learning data	*n* = 74	Validation data	*n* = 15	*p* value
Sex, female	48 (64.9%)	74/74	10 (66.7%)	15/15	0.894
Age (years)	78.0 (69.3–86.0)	74/74	76.0 (73.0–78.0)	15/15	0.985
Hospitalization (days)	11.5 (9.0–16.8)	74/74	13.0 (9.0–15.0)	15/15	0.793
Na (mEq/L)	112.5 (110.0–116.8)	74/74	117.0 (112.0–120.0)	15/15	0.179
K (mEq/L)	3.90 (3.50–4.60)	74/74	4.10 (3.90–4.75)	15/15	0.490
Cl (mEq/L)	81.5 (77.0–85.0)	74/74	83.0 (79.0–86.5)	15/15	0.667
BUN (mg/dL)	12.35 (9.50–18.85)	74/74	11.10 (7.95–14.30)	15/15	**0.008**
CRN (mg/dL)	0.610 (0.470–0.908)	74/74	0.590 (0.480–0.700)	15/15	0.248
eGFR (mL/min/1.73 m^2)	71.70 (49.13–99.80)	74/74	84.50 (66.60–108.95)	15/15	0.435
UA (mg/dL)	3.145 (2.190–5.393)	68/74	2.50 (1.70–3.60)	15/15	**0.016**
TP (g/dL)	7.13 (6.60–7.62)	74/74	7.00 (6.50–7.25)	15/15	0.447
ALB (g/dL)	3.99 (3.49–4.42)	72/74	3.90 (3.50–4.20)	15/15	0.829
HCT (%)	33.55 (30.33–35.65)	74/74	32.40 (30.75–35.65)	15/15	0.943
GLU (mg/dL)	125.0 (103.3–146.0)	74/74	105.0 (98.0–181.5)	15/15	0.757
p-Osm (mOsm/L)	238.5 (228.3–245.0)	74/74	245.8 (236.0–249.0)	15/15	0.197
F (μg/dL)	23.90 (17.00–35.00)	73/74	12.00 (8.00–20.85)	15/15	**<0.001**

ACTH (pg/mL)	26.70 (13.45–45.50)	71/74	22.30 (13.10–33.30)	15/15	**0.007**
PAC (pg/mL)	126.50 (77.70–199.45)	71/74	116.50(75.40–136.75)	12/15	0.351
PRA (ng/mL/h)	1.20 (0.40–2.05)	71/74	1.50 (0.80–2.78)	12/15	0.337
TSH (μIU/mL)	1.560 (0.840–2.690)	73/74	1.361 (0.782–2.342)	15/15	0.780
FT3 (pg/mL)	2.160 (1.730–2.640)	73/74	2.000 (1.800–2.270)	14/15	0.253
FT4 (ng/dL)	1.570 (1.400–1.700)	73/74	1.220 (0.965–1.325)	15/15	**<0.001**
AVP (pg/mL)	1.60 (0.90–4.20)	69/74	0.70 (0.60–2.03)	14/15	**0.001**
u-Na (mEq/L)	62.0 (43.3–94.8)	74/74	73.0 (46.5–95.0)	15/15	0.956
u-Osm (mOsm/kg)	362 .0 (259.5–510.8)	72/74	476.0 (360.0–505.5)	11/15	0.557

Data are expressed as median (interquartile range) or *n* (%). All statistical tests were two-sided, and significance was defined as a *p*-value of <0.05.

ACTH, adrenocorticotropic hormone; ALB, albumin; AVP, arginine vasopressin; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cl, chloride; CRN, creatinine; eGFR, estimated glomerular rate; F, cortisol; FT3, free triiodothyronine; FT4, free thyroxine; GLU, glucose; hANP, human atrial sodium diuretic peptide; HCT, hematocrit; K, potassium; Na, sodium; PAC, aldosterone; PRA, renin activity; p-Osm, plasma osmolality; TP, total protein; TSH, thyroid-stimulating hormone; UA, uric acid; u-Na, urinary sodium; u-Osm, urine osmolality.

Table 2: Differences in the prediction accuracy of 10-fold cross-validation based on combinations of predictors

Modeling \ Predictors												
	Water-IN	•		•	•	•	•	•	•	•	•	•
	Na-IN	•	•		•	•	•	•	•	•		•
	K-IN	•	•	•		•	•	•	•			•
	Water-OUT	•	•	•	•		•	•	•	•	•	•
	s-Na	•	•	•	•	•		•	•	•	•	•
	s-K	•	•	•	•	•	•		•		•	
	s-Cl	•	•	•	•	•	•	•		•	•	
Linear regression	RMSE	0.036768	0.037210	0.037191	0.036674	0.037295	0.11897	0.036604	0.036708	0.036519	0.036977	0.036500
	R^2	0.97	0.97	0.97	0.97	0.97	0.69	0.97	0.97	0.97	0.97	0.97
Support vector regression linear kernel c=0.2337, γ=0.0234	RMSE	0.037026	0.037328	0.037171	0.036934	0.037388	0.11923	0.036789	0.036856	0.036624	0.037044	0.036466
	R^2	0.97	0.97	0.97	0.97	0.97	0.69	0.97	0.97	0.97	0.91	0.97
Regression tree model 3 nodes, 8 branches	RMSE	0.056895	0.066843	0.067919	0.067541	0.066918	0.132440	0.065747	0.083242	0.059638	0.060565	0.072663
	R^2	0.93	0.90	0.90	0.90	0.90	0.62	0.91	0.85	0.92	0.92	0.88

Cl, chloride; K, potassium; K-IN, potassium infusion; Na, sodium; Na-IN, sodium infusion; R^2, coefficient of determination; RMSE, root mean square error; water-IN, water intake; water-OUT, urine volume.

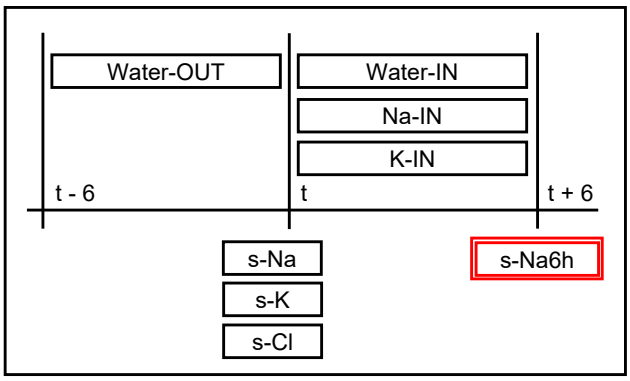
Table 3: Differences in the prediction accuracy of external validation based on combinations of predictors

Modeling \ Predictors		Water-IN	Na-IN	K-IN	Water-OUT	s-Na	s-K	s-Cl				
	Water-IN	•		•	•	•	•	•	•	•	•	•
	Na-IN	•	•		•	•	•	•	•	•		•
	K-IN	•	•	•		•	•	•	•			•
	Water-OUT	•	•	•	•		•	•	•	•	•	•
	s-Na	•	•	•	•	•		•	•	•	•	•
	s-K	•	•	•	•	•	•		•		•	
	s-Cl	•	•	•	•	•	•	•		•	•	
Linear regression	RMSE	0.054417	0.055691	0.056090	0.054547	0.053714	0.111310	0.054492	0.054821	0.054608	0.055971	0.054813
	R^2	0.92	0.92	0.92	0.92	0.93	0.68	0.92	0.92	0.92	0.92	0.92
Support vector regression linear kernel c=0.2337, γ=0.0234	RMSE	0.053960	0.055766	0.055585	0.053992	0.054335	0.128150	0.054364	0.054647	0.054215	0.055235	0.054584
	R^2	0.92	0.92	0.92	0.92	0.92	0.57	0.92	0.92	0.92	0.92	0.92
Regression tree model 3 nodes, 8 branches	RMSE	0.059374	0.068756	0.060310	0.060269	0.067869	0.095449	0.063258	0.080811	0.058820	0.057892	0.087652
	R^2	0.91	0.88	0.91	0.91	0.88	0.76	0.90	0.83	0.91	0.91	0.80

Cl, chloride; K, potassium; K-IN, potassium infusion; Na, sodium; Na-IN, sodium infusion; R^2, coefficient of determination; RMSE, root mean square error; water-IN, water intake; water-OUT, urine volume.

Figure 1. Seven predictors and data processing methods.

(A) Seven predictors of the serum sodium (s-Na) concentration at 6 h (s-Na6h).



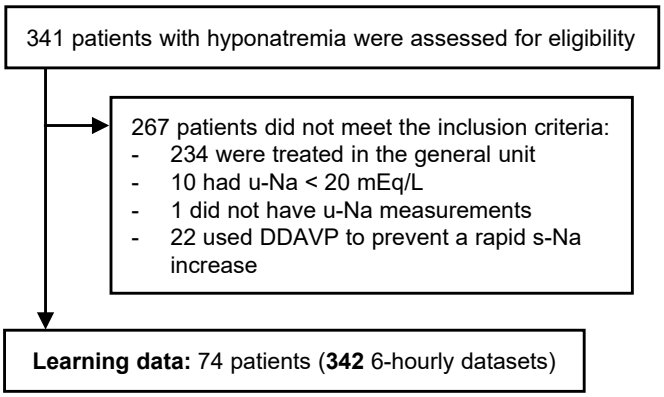
(B) Data processing methods.

Predictors / Date	Time	s-Na	s-Na'	s-K'	s-Cl'	Na-IN'	K-IN'	Water-IN'	Water-OUT'
yyyy/mm/dd	t – 6	…	…	…	…	…	…	…	20
yyyy/mm/dd	t - 5	…	…	…	…	…	…	…	20
yyyy/mm/dd	t - 4	…	…	…	…	…	…	…	20
yyyy/mm/dd	t - 3	…	…	…	…	…	…	…	60
yyyy/mm/dd	t - 2	…	…	…	…	…	…	…	60
yyyy/mm/dd	t - 1	NaN	119.92	4.742	94.67	NaN	NaN	NaN	40
yyyy/mm/dd	**t**	NaN	119.96	4.772	94.84	44.42	11.54	300	40
yyyy/mm/dd	t + 1	120	120.02	4.797	95.02	NaN	NaN	NaN	…
yyyy/mm/dd	t + 2	NaN	120.62	4.697	95.62	NaN	NaN	NaN	…
yyyy/mm/dd	t + 3	NaN	121.21	4.598	96.21	55.00	4.42	189	…
yyyy/mm/dd	t + 4	NaN	121.81	4.499	96.81	78.50	0	303.33	…
yyyy/mm/dd	t + 5	NaN	122.40	4.399	97.40	77.13	NaN	NaN	…
yyyy/mm/dd	t + 6	123	123	4.3	98.00	…	…	…	…

s-Na6h

Figure 2. Study flow diagram.

(A) Learning data.



(B) Validation data.

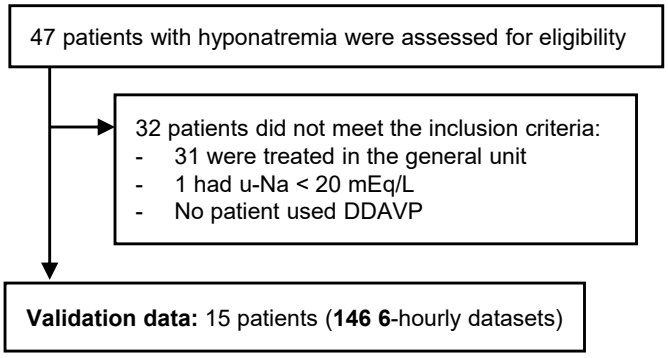
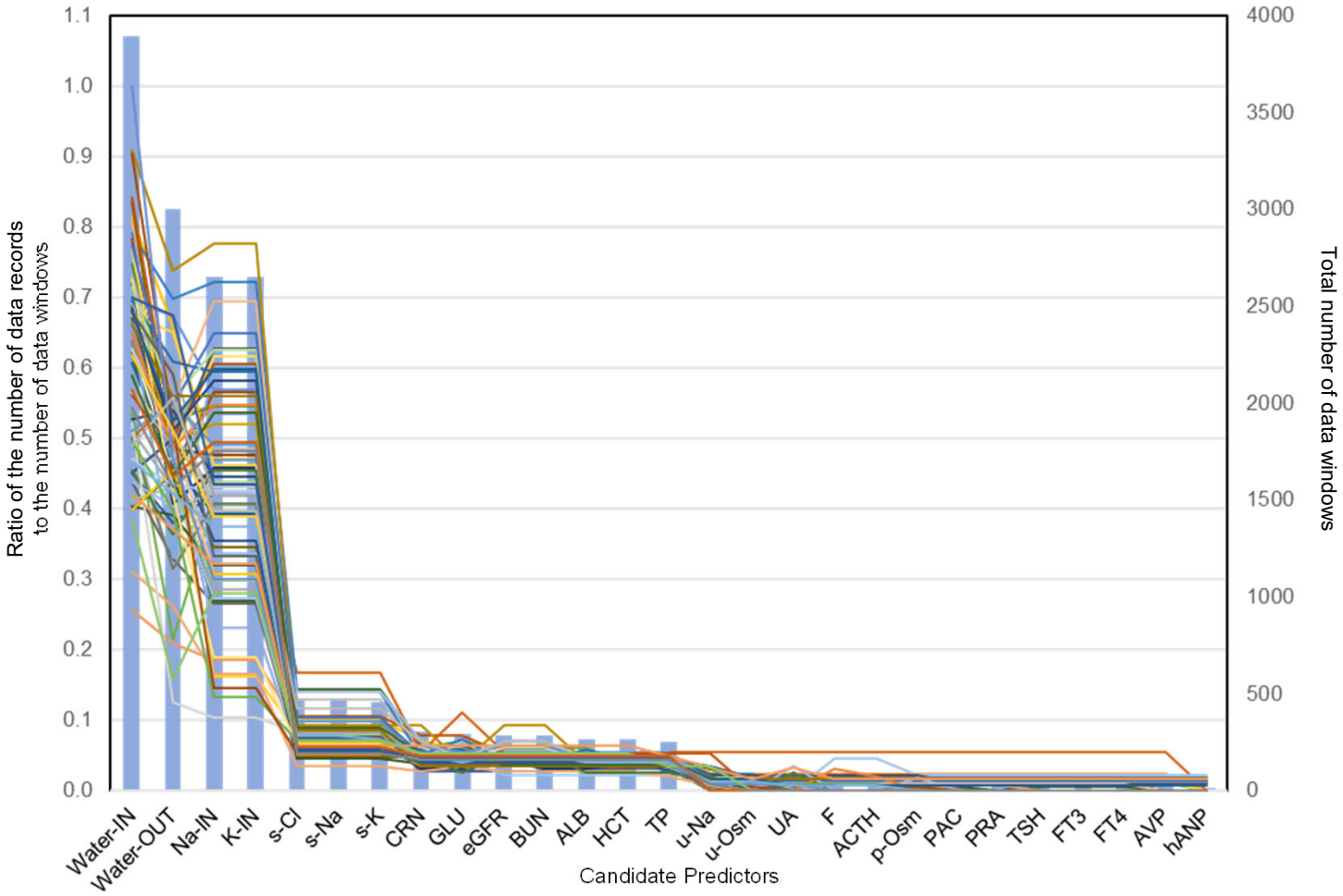


Figure 3. Selection of predictors and distribution of normalized data.

(A) Number of records.



(B) Normalized data distribution.

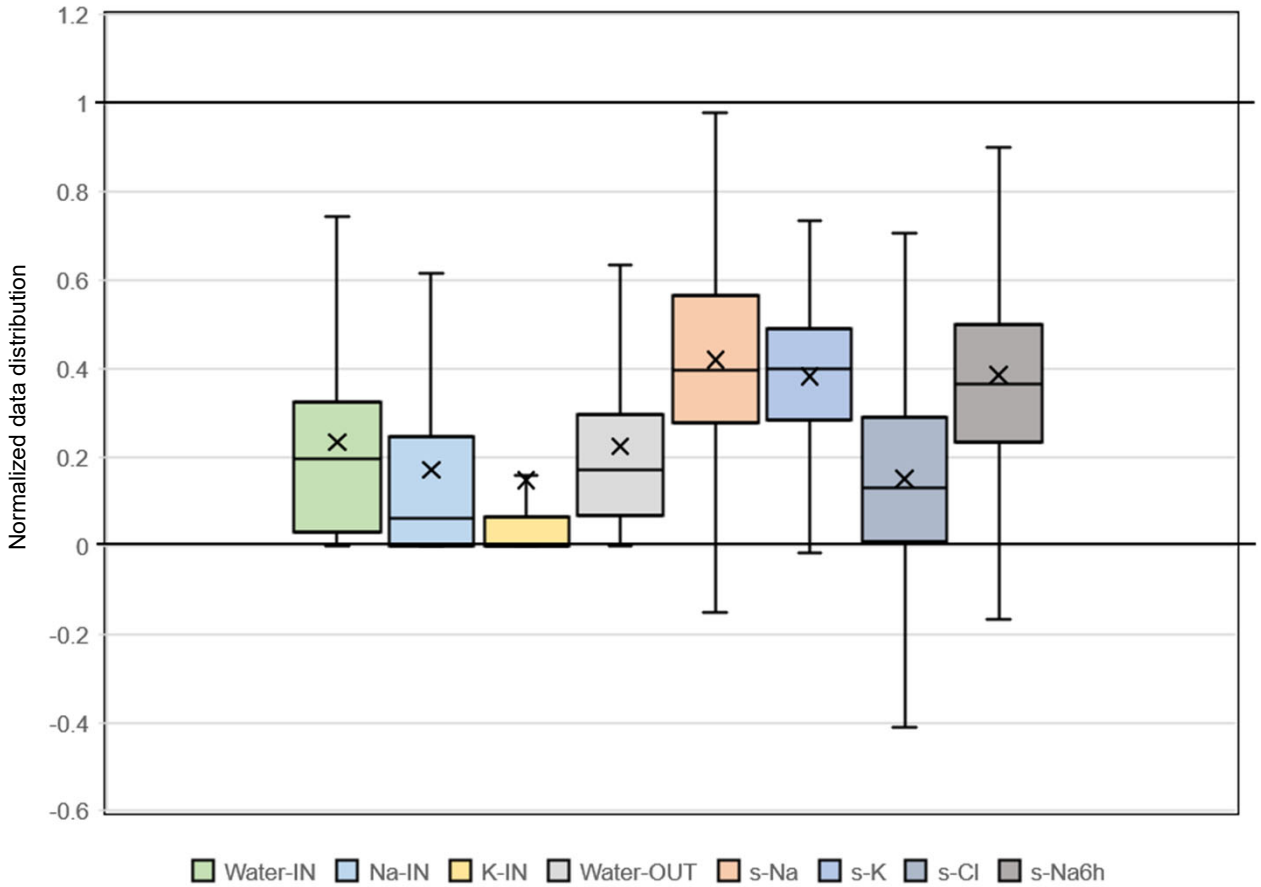


Figure 4. Ten-fold cross-validation of the training data.

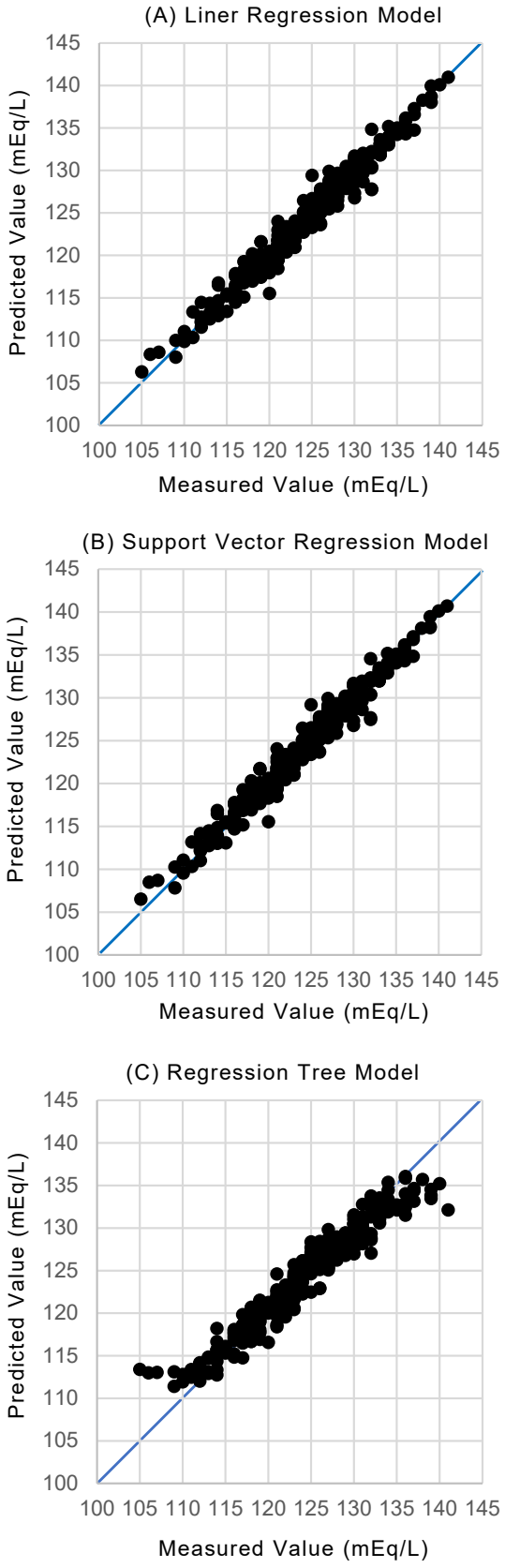


Figure 5. External validation of each model.