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Development and validation of a prediction model for the risk of citrate accumulation in critically ill patients with citrate anticoagulation for continuous renal replacement therapy: a retrospective cohort study based on MIMIC-IV database

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Abstract

Background Acute kidney injury (AKI) is a common clinical syndrome, especially in the intensive care unit (ICU), with an incidence of more than 50% and in-hospital mortality of 30%. Continuous renal replacement therapy (CRRT) is an important supportive treatment for patients with AKI (Patel in Trauma Surg Acute Care Open e001381, 2024). Citrate is the preferred anticoagulant for critically ill patients requiring CRRT. Unfortunately, such patients may be confronted with citrate accumulation during citrate anticoagulation.

Methods The MIMIC-IV2.2 database was used to extract data of patients undergoing CRRT who opted for citrate anticoagulation during ICU admission, including 883 critically ill patients. These 883 patients were randomized into training ($n=618$) and Internal validation ($n=265$) groups at a ratio of 7:3. Least Absolute Shrinkage and Selection Operator(LASSO)-logistic regression was utilized to screen the variables and construct the prediction model, followed by the plotting of the nomogram. Then, Utilizing the retrospective data from the ICU at Jiangbei Hospital in Nanjing, China, from 2014 to 2024 ($n=200$) for external model validation, the model was evaluated with discriminant analysis, calibration curves, decision curve analysis, and rationality analysis.

Results A total of 883 critically ill patients undergoing CRRT were included, consisting of 542 males and 341 females, with a mean age of 65 ± 14 years. Additionally, there were 618 patients in the training set and 265 in the validation set. A total of 47 independent variables were obtained, among which 15 independent variables were screened with LASSO regression and included in the multivariate logistic analysis. The five risk factors ultimately included in the prediction model were height, hepatic insufficiency, mechanical ventilation, prefilter replacement rate, and albumin. The area under the receiver operating characteristic curve (ROC) of the model was 0.758 (0.701–0.816), 0.747 (0.678–

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0.817), and 0.714 (0.632–0.810) for the training set, internal validation set, and external validation set, respectively. The calibration curves in the training set and internal/external validation sets showed a high degree of consistency between predicted values and observed values (according to the Hosmer-Lemeshow test, the P-values were 0.7673, 0.2401, and 0.4512 for the training set, internal validation set, and external validation set, respectively). In addition, the Decision-Curve(DCA) revealed that the model had good clinical applicability. Nomo-score comparisons exhibited the rationality of the model.

Conclusion The model developed based on LASSO-logistic regression can reliably predict the risk of citrate accumulation in critically ill patients with citrate anticoagulation for CRRT, providing valuable guidance for the application of early measures to prevent the occurrence of citrate accumulation and to improve the prognosis of patients.

Keywords Continuous renal replacement therapy, Citrate accumulation, Nomogram, MIMIC-IV, Intensive care unit

Background

CRRT is widely used for the treatment of critically ill patients with aAKI. As reported, approximately 5–10% of AKI patients require CRRT during ICU admission [2], with a mortality rate of 30–70% [3]. In clinical practice, heparin and citrate are the two main anticoagulants for CRRT. Compared to heparin anticoagulation, citrate anticoagulation is associated with a lower risk of circuit loss, filter failure, bleeding, and heparin-induced thrombocytopenia [4, 5]. Therefore, the 2012 Kidney Disease Improving Global Outcomes guidelines recommend citrate anticoagulation as the first choice for CRRT in critically ill patients without contraindications to citrate [6].

Citrate, which is weakly acidic, is mainly metabolized in the citric acid (Krebs or tricarboxylic acid) cycle in the liver, kidneys, and muscle, thus yielding bicarbonate. The metabolism of citric acid, however, becomes saturated. If the infusion of citric acid exceeds the body's metabolic capacity, it will result in accumulation of citrate [7]. At present, routine monitoring of citrate concentration is lacking. Accordingly, citrate accumulation is generally diagnosed by a total calcium/ionized calcium ratio of $\geqq 2.5$. Citrate accumulation can manifest as high anion gap (AG) acidosis, hypocalcemia, and elevated lactate concentration [8]. Several retrospective studies have reported that the incidence of citrate accumulation in patients with citrate anticoagulation for CRRT was in the range of 2.9–23.2% [7, 8], with a very high mortality rate of 40–100% [7, 9].

However, there is a lack of effective tools to predict the occurrence of citrate accumulation in patients with citrate anticoagulation for CRRT during the ICU admission. The aim of this study was to identify independent risk factors associated with citric acid accumulation in ICU patients and to develop a predictive model represented by a nomogram. This holds considerable significance for guiding the formulation of appropriate initial CRRT prescriptions in clinical practice.

Methods

Data source and ethics statement

The Medical Information Mart for Intensive Care (MIMIC)-IV v2.2 database (https://physionet.org/content/mimiciv/2.2/) is a publicly available critical care database collaboratively developed by the Massachusetts Institute of Technology(MIT) Laboratory of Computational Physiology, Beth Israel Deaconess Medical Center (BIDMC), and Philips. The MIMIC-IV database has several improvements based on MIMIC-III, including data update and partial table reconstruction, which collects the clinical data of over 190,000 patients and 450,000 hospital records in BIDMC from 2008 to 2019 and records detailed information on the demographics, laboratory tests, medications, vital signs, surgery, disease diagnosis, medication management, and follow-up survival status of patients. Our study was a retrospective study, he training set and internal validation set data are sourced from MIMIC-IV v2.2, while the external validation set is sourced from retrospective data of the ICU single-center records from 2014 to 2024 at Jiangbei Hospital, Nanjing, China. We had completed the necessary courses and individual training exams for accessing and using the database, obtained the corresponding certificate (Certificate No. 62661460), and gained permission to access the database. The MIMIC-IV database is a publicly available dataset that has undergone de-identification processing, The collection of the original data was conducted under IRB protocol 2001-P-001699/14, which granted exemption from informed consent for retrospective analysis of de-identified data. This study strictly adhered to the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor provisions. As a secondary analysis of existing anonymized data, this study was exempt from additional ethical review by our Institutional Review Board. Additionally, the external validation data uses de-identified medical records of ICU inpatients at Jiangbei Hospital in Nanjing, China, from the period of 2014–2024. The data extraction process did not include any information that could directly or indirectly identify patient identities.

According to the "Ethical Review Measures for Biomedical Research Involving Human Subjects" and the regulations of the hospital's ethics committee(Registration Number: BA-2025-01) (figure S1).

Participants

CRRT records of 1,406 admissions to ICUs for citrate anticoagulation of 1,308 patients were extracted from the mimiciv_derived module of MIMIC-IV v2.2. As well as the retrospective data of 230 CRRT citrate anticoagulation patients from the ICU of Nanjing Jiangbei Hospital in China from 2014 to 2024, The inclusion criteria were as follows: (1) a prescription for Regional Citrate Anticoagulation - Continuous Renal Replacement Therapy(RCA-CRRT) for renal replacement therapy; (2)The CRRT procedure is conducted throughout the patient's ICU admission.Exclusion criteria for participants were as follows: (1) patients younger than 18 years old; (2) CRRT patients with multiple ICU admissions for citrate anticoagulation, with only the record of the first ICU admission retained; (3) participants with incomplete data; and (4) patients with ICU stay < 24 h. as well as the retrospective data of 230 CRRT citrate anticoagulation patients from the ICU of Nanjing Jiangbei Hospital in China from 2014 to 2024. The process of patient selection is displayed in Fig. 1.

Data extraction

Participant clinical data was extracted using Navicat Premium software (version 16.0; https: navicat.com.cn) from the MIMIC-IV database and the electronic medical record system of the ICU at the Jiangbei Hospital in Nanjing, China.Data on the first ICU admission were collected, such as Age, Gender, Height, Weight, Complications (Sepsis, Shock, Diabetes, Mechanical ventilation, Hepatic insufficiency, AKI, Chronic kidney disease [CKD]), CRRT mode, Blood flow rate, Citrate rate, Dialysate rate, Prefilter replacement rate, Postfilter replacement rate, Total replacement rate, TMP(Transmembrane pressure), Temperature, Heart rate, Mean arterial pressure (MAP), Respiratory rate, Oxygen saturation (SpO2), White blood cells (WBC), Hemoglobin (Hgb), Platelets (PLT), Hematocrit (HCT), Serum albumin, Total bilirubin (TBIL), Aspartate aminotransferase(AST), PH, Oxygen partial pressure (PaO2), Carbon dioxide partial pressure (PaCO2), Lactate (Lac), Prothrombin time (PT), Activated partial thromboplastin time (APTT), Erythromycin use, Metformin use, Voriconazole use, Norepinephrine dose, Epinephrine dose, Phenylephrine dose, Dopamine dose, Vasoactive-inotropic score (VIS), and Acute Physiology Score III (APSIII), which were used as independent variables (a total of 47 variables).

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation, and variables without normal distribution were presented as the median and the interquartile range. Categorical variables were summarized as the number of cases and percentage (%). Continuous variables were compared with the *t*-test or nonparametric test, while categorical variables were compared with the Pearsons chi-square test or Fisher's exact test. When the data contained less than 20% missing values, multiple interpolation was applied to the missing data, and data with more than 20% missing values were excluded. Forty-seven variables were finally identified. Baseline description and analysis of variance were performed with the compareGroups package and automatic identification. Tables with statistics were generated with the CBCgrps package. LASSO regression analysis was conducted with the glmnet package. Multivariate logistic regression analysis was carried out with the glm package. Forest plot 1 was generated with the forestplot package. Discriminant analysis was performed with the pROC package. The confusion Matrix uses the caret package. Calibration curves were produced with the val.prob function in the rms package and the calibrate function. The ResourceSelection package was used for the Hosmer-Lemeshow test, and the dcurves package was utilized for decision curve analysis (DCA). The nomogram was obtained with the rms package.

Nomogram construction and validation

The development and validation of a multivariable prediction model were reported per the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis [10] statement. Based on inclusion criteria and exclusion criteria, 883 patients were ultimately included in our study from the MIMIC-IV database.These patients were randomized into training ($n = 618$) and validation ($n = 265$) sets at a ratio of 7:3. Predictive variables were selected in two steps.Furthermore, the ICU single-center data from the Jiangbei Hospital in Nanjing, China, served as an external validation ($n = 200$). First, LASSO regression analysis [11] was utilized to determine potential confounders associated with the probability of citrate accumulation in critically ill patients with citrate anticoagulation for CRRT. The model was improved by constructing a penalty function with LASSO regression to obtain a simpler model that compressed some coefficients and set some coefficients to zero, thus retaining the advantage of subset shrinkage. Second, multivariate logistic regression analysis was conducted with variables selected by LASSO regression, and variables with $P < 0.05$ were selected with the backward method to construct the model [12]. The prediction model was validated with discriminant evaluation,

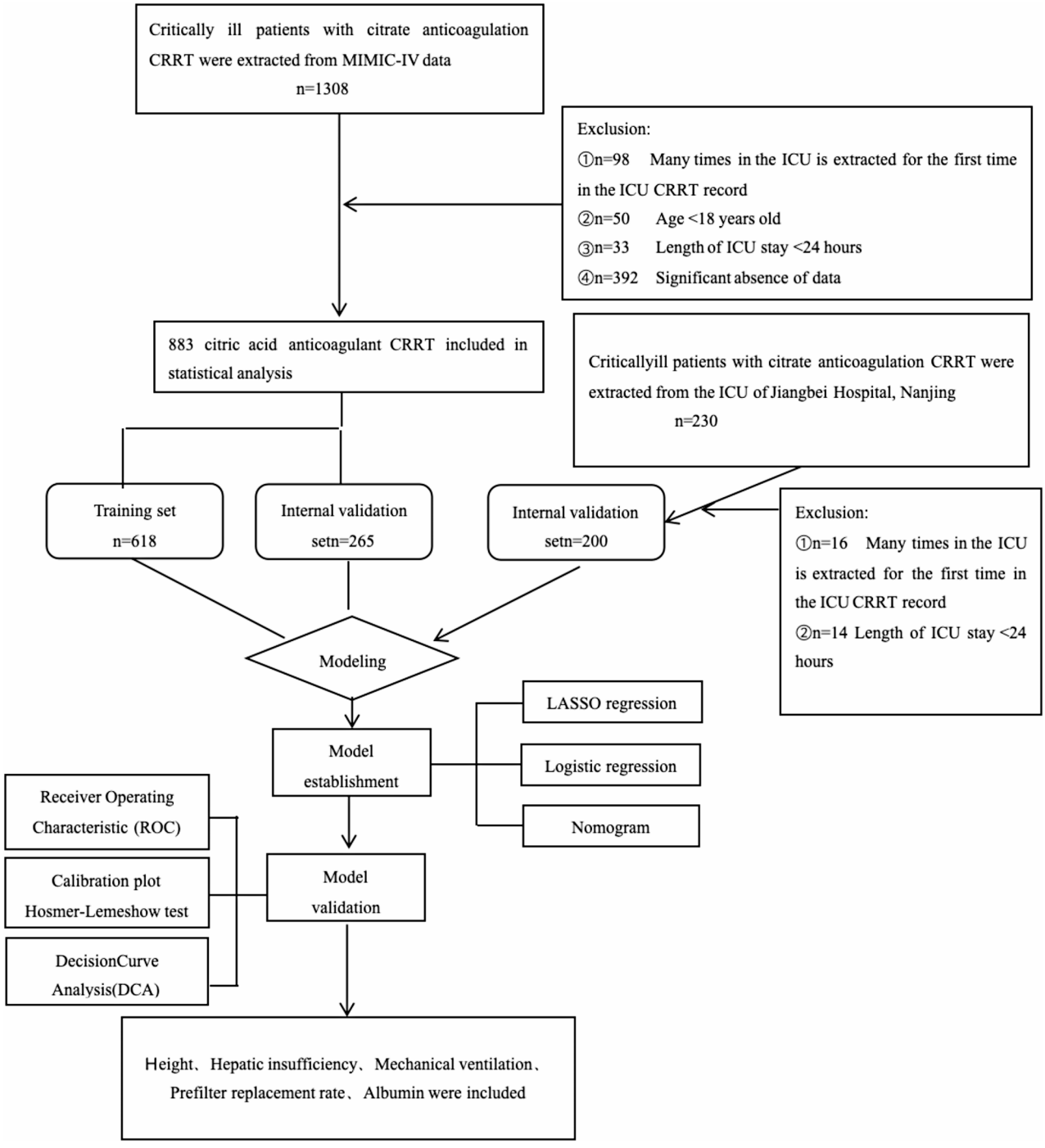

Fig. 1 Detailed process of patient selection

calibration evaluation, clinical applicability evaluation, and rationality evaluation. In our study, the area under the receiver-operating characteristic (ROC) curve was used to evaluate the ability of the model to distinguish citrate accumulation from no citrate accumulation, and calibration curves were utilized to evaluate the consistency between the risk predicted by the model and the actual incidence of citrate accumulation. DCA was conducted to assess the clinical applicability of the model, and Nomo-score plots were employed to evaluate the rationality of the model.

Study outcomes

The primary outcome was the probability of citrate accumulation in critically ill CRRT patients with topical citrate anticoagulation during CRRT after the ICU

admission. The blood gas and biochemical indicators were recorded in detail, and total calcium, AG, PH, and ionized calcium were detected, followed by the calculation of the total calcium/ionized calcium ratio. Of note, ionized calcium and total calcium examinations were conducted during CRRT and within half an hour of each other to calculate the total calcium/free calcium ratio. The diagnostic criteria for citrate accumulation were the total calcium/ionized calcium of ≧2.5 and high AG acidosis (PH < 7.35, AG > 12) [13, 14].

Results

Characteristics of the included patients

From the MIMIC-IV 2.2 database, we retrospectively identified 1308 ICU patients undergoing CRRT and ultimately included 883 eligible patients in the current study. From the single-center study of 230 patients in the ICU of Jiangbei Hospital, Nanjing, China, 200 were ultimately included in the external validation. Table 1 lists the baseline characteristics of all included patients. There were no significant differences in 47 independent variables between the training and validation sets ($P > 0.05$), indicating that the training and validation sets were well comparable.Citrate accumulation can increase hospital stay, ICU stay, length of stay, in-hospital mortality, and ICU mortality (Table S1).

Screening of independent variables for the prediction model

The data with over 20% missing values were removed. A total of 15 potential predictive variables with non-zero coefficients in the LASSO regression were selected from the 47 characteristic variables in the complete dataset. The lasso filter feature variables are shown in Fig. 2. The lambda.min was considered when features were selected to construct the prediction model. The identified potential predictive variables included hepatic insufficiency, albumin, PT, SpO2, MAP, APTT, PLT, dialysate rate, weight, prefilter replacement rate, WBC, PaCO2, height, Hgb, and mechanical ventilation, as shown in (Figure S2).

Construction of the prediction model

The logistic multivariate analysis included 15 characteristic variables selected by LASSO regression. Ultimately, the independent risk factors identified were height [OR 0.965, 95% CI (0.941–0.989)], hepatic insufficiency [OR 2.885, 95% CI (1.685–5.023)], mechanical ventilation [OR 0.511, 95% CI (0.296–0.894)], prefilter replacement rate [OR 0.999, 95% CI (0.999-1)], albumin [OR 1.625, 95% CI (1.127-2),355)] (Fig. 3) and a prediction model was constructed. To visually represent the model, an Nomodiagram was developed (Fig. 4). Each variable is assigned a score on the upper score axis corresponding to its contribution to the risk probability of citric acid accumulation in CRRT patients treated with citric acid anticoagulation in the ICU as shown on the lower axis.For example, if AKI patients in ICU were treated with citric acid anticoagulation, their height was 150 cm, respiratory failure was treated with mechanical ventilation, hepatic insufficiency was monitored at Child-pughB grade, albumin was 30 mg/dl, and prefilter replacement rate was 2000 ml/h, then the total score was 195, and the corresponding rate of citric acid accumulation was 30%.

Validation of the prediction model

After bias correction, the analysis of the ROC curve indicates that the model's AUC (95% confidence interval [95%CI]) on the training set, internal validation set, and external validation set are 0.759 (0.701 – 0.816), 0.747 (0.678 – 0.817), and 0.714 (0.632–0.810), respectively, demonstrating the model's good discriminative ability (Fig. 5). The calibration curves in the training set, internal validation set, and external validation set are close to the diagonal, indicating a high degree of consistency between the model's predicted results and the actual outcomes, with P-values obtained from the Hosmer-Lemeshow test being 0.7673, 0.2401, and 0.2514 for the training set and validation sets, respectively (Fig. 6). The confusion matrix heatmap has been improved to provide a more comprehensive assessment of the predictive model's performance. Upon analyzing the confusion matrix of the validation set, it was observed that there were 18 true positive samples, 61 true negative samples, and 13 false positive samples (Fig. 7). Additionally, there were 177 false negative samples. Further calculations yielded an accuracy of 0.72, a sensitivity of 0.58, a specificity of 0.74, a recall rate of 0.58, and an F1 score of 0.33 (Table S2). Sensitivity reflects the model's ability to correctly identify patients at risk of citrate accumulation (true positives), while specificity indicates its capacity to exclude patients without the condition (true negatives). The F1-score, as a harmonic mean of precision and recall, highlights the trade-off between false positives and false negatives.In the decision curve, the red line was drawn, indicating the use of nomograms to predict citrate accumulation. For comparison, the red (diagonal) and green (horizontal) lines represent two extreme scenarios (red line: full intervention, green line: no intervention at all). The decision curve revealed that the net benefit of the model reached its maximum at threshold probabilities of 0.03 – 0.60, 0.03 – 0.50, and 0.11–0.46 in the training set, internal validation set, and external validation set (Fig. 8). To evaluate the rationality of the model, the Nomo score chart was used to compare the Nomo score differences with and without citric acid accumulation. The results showed significant differences in the Nomo scores in both the validation and training sets, highlighting the good rationality of the nomogram (Figure S3).

Table 1 Baseline characteristics of participants

Variables	Total ($n=1083$)	Training set ($n=618$)	Internal validation set($n=265$)	External validation set($n=200$)	*P*-value
Gender, n(%)					0.700
Female	412 (38.0%)	240 (38.8%)	240 (38.8%)	71 (35.5%)	
Male	671 (62.0%)	378 (61.2%)	378 (61.2%)	129 (64.5%)	
Age, years, median[IQR]	65.0 [54.5;74.0]	65.0 [54.0;75.0]	65.0 [54.0;75.0]	66.0 [56.0;75.0]	0.716
Weight, kg, median[IQR]	88.4 [73.2;104]	88.8 [73.6;104]	88.8 [73.6;104]	90.0 [74.8;108]	0.219
Height, cm, median[IQR]	170 [161;178]	170 [162;178]	170 [162;178]	170 [162;178]	0.767
Sepsis, n(%)					0.456
No	84 (7.76%)	53 (8.58%)	53 (8.58%)	12 (6.00%)	
Yes	999 (92.2%)	565 (91.4%)	565 (91.4%)	188 (94.0%)	
Shock, n(%)					0.636
No	101 (9.33%)	57 (9.22%)	57 (9.22%)	16 (8.00%)	
Yes	982 (90.7%)	561 (90.8%)	561 (90.8%)	184 (92.0%)	
Hepatic Insufficiency, n(%)					0.989
No	658 (60.8%)	375 (60.7%)	375 (60.7%)	121 (60.5%)	
Yes	425 (39.2%)	243 (39.3%)	243 (39.3%)	79 (39.5%)	
Mechanical Ventilation, n(%)					0.66
No	304 (28.1%)	168 (27.2%)	168 (27.2%)	56 (28.0%)	
Yes	779 (71.9%)	450 (72.8%)	450 (72.8%)	144 (72.0%)	
CVVH, n(%)					0.788
No	1031 (95.2%)	586 (94.8%)	586 (94.8%)	191 (95.5%)	
Yes	52 (4.80%)	32 (5.18%)	32 (5.18%)	9 (4.50%)	
CVVHD, n(%)					0.843
No	1060 (97.9%)	606 (98.1%)	606 (98.1%)	195 (97.5%)	
Yes	23 (2.12%)	12 (1.94%)	12 (1.94%)	5 (2.50%)	
CVVHDF, n(%)					0.93
No	75 (6.93%)	44 (7.12%)	44 (7.12%)	14 (7.00%)	
Yes	1008 (93.1%)	574 (92.9%)	574 (92.9%)	186 (93.0%)	
Diabetes, n(%)					0.591
No	649 (59.9%)	368 (59.5%)	368 (59.5%)	126 (63.0%)	
Yes	434 (40.1%)	250 (40.5%)	250 (40.5%)	74 (37.0%)	
Aki, n(%)					0.516
No	157 (14.5%)	83 (13.4%)	83 (13.4%)	32 (16.0%)	
Yes	926 (85.5%)	535 (86.6%)	535 (86.6%)	168 (84.0%)	
Crrt_parameter, ml/h, median[IQR]					
Blood_flow	120.00 [120.00;150.00]	120.00 [120.00;150.00]	120.00 [120.00;150.00]	120.00 [120.00;150.00]	0.561
Citrate	180.00 [180.00;200.00]	180.00 [180.00;200.00]	180.00 [180.00;200.00]	180.00 [180.00;200.00]	0.787
Dialysate Rate	700 [500;1000]	700 [500;1000]	700 [500;1000]	800 [500;1000]	0.627
Postfilter Replacement Rate	200 [200;200]	200 [200;200]	200 [200;200]	200 [200;200]	0.382
Prefilter Replacement Rate	1500 [1200;1800]	1600 [1200;1800]	1600 [1200;1800]	1500 [1200;1800]	0.228
Replacement Rate	1600 [1400;2000]	1700 [1400;2000]	1700 [1400;2000]	1650 [1400;2000]	0.349
Vital_signs, median[IQR]					
Map, mmHg	70.0 [58.0;84.0]	70.0 [58.0;83.0]	70.0 [58.0;83.0]	69.0 [56.0;82.2]	0.305
HR, bmp	95.0 [80.5;110]	95.5 [82.0;112]	95.5 [82.0;112]	94.0 [81.8;110]	0.147
Spo2,%	97.0 [93.0;100]	97.0 [93.0;100]	97.0 [93.0;100]	96.0 [93.0;99.0]	0.13
Laboratory test, median[IQR]					
Wbc, k/ul	12.7 [8.20;18.7]	12.6 [8.22;18.5]	12.6 [8.22;18.5]	12.8 [8.43;19.8]	0.921
RR, insp/min	21.0 [16.0;25.0]	21.0 [16.0;25.0]	21.0 [16.0;25.0]	21.0 [16.0;25.2]	0.634
Plt, k/lu	154 [90.0;235]	156 [90.2;235]	156 [90.2;235]	158 [95.0;250]	0.244
Hgb, mg/dl	9.50 [8.00;11.3]	9.50 [8.00;11.3]	9.50 [8.00;11.3]	9.50 [8.20;11.1]	0.979
Hct,%	29.5 [25.0;35.2]	29.4 [25.1;35.3]	29.4 [25.1;35.3]	29.0 [24.8;34.7]	0.962
Albumin, mg/dl	2.80 [2.30;3.26]	2.80 [2.30;3.30]	2.80 [2.30;3.30]	2.80 [2.40;3.20]	0.953
Calciumtotal, mmol/L	8.10 [7.60;8.80]	8.10 [7.60;8.80]	8.10 [7.60;8.80]	8.10 [7.70;8.80]	0.831

Table 1 (continued)

Variables	Total (*n* = 1083)	Training set (*n* = 618)	Internal validation set(*n* = 265)	External validation set(*n* = 200)	*P*-value
PH	7.32 [7.22;7.39]	7.32 [7.23;7.39]	7.32 [7.23;7.39]	7.31 [7.22;7.38]	0.59
Po2,mmHg	82.0 [50.0;152]	81.0 [50.0;154]	81.0 [50.0;154]	81.5 [49.0;142]	0.928
Co2,mmHg	40.0 [34.0;48.0]	40.0 [34.0;48.0]	40.0 [34.0;48.0]	41.0 [35.8;49.0]	0.698
Lac, mmol/L	2.40 [1.50;4.30]	2.40 [1.50;4.38]	2.40 [1.50;4.38]	2.25 [1.50;3.73]	0.662
PT, sec	17.1 [13.8;23.2]	17.0 [13.8;23.5]	17.0 [13.8;23.5]	16.5 [14.1;21.7]	0.908
APTT, sec	36.5 [30.2;48.3]	36.5 [29.6;48.0]	36.5 [29.6;48.0]	35.6 [30.3;49.2]	0.799
Anion_Gap, mmol/L	18.0 [15.0;23.0]	18.0 [15.0;23.0]	18.0 [15.0;23.0]	18.0 [15.0;22.2]	0.87
Tbil, umol/L	1.00 [0.50;3.45]	1.10 [0.50;3.38]	1.10 [0.50;3.38]	1.00 [0.50;3.10]	0.971
Alt, u/L	34.0 [17.0;125]	35.0 [17.0;120]	35.0 [17.0;120]	29.5 [17.0;103]	0.686
Ast, u/L	75.0 [33.0;246]	74.5 [33.0;241]	74.5 [33.0;241]	69.0 [33.8;232]	0.56
Metformin, n(%)					0.219
No	1077 (99.4%)	616 (99.7%)	616 (99.7%)	199 (99.5%)	
Yes	6 (0.55%)	2 (0.32%)	2 (0.32%)	1 (0.50%)	
Erythromycin, n(%)					0.744
No	1063 (98.2%)	607 (98.2%)	607 (98.2%)	195 (97.5%)	
Yes	20 (1.85%)	11 (1.78%)	11 (1.78%)	5 (2.50%)	
Vis Score	14.0 [5.00;27.0]	13.0 [5.00;27.8]	13.0 [5.00;27.8]	14.0 [5.00;26.0]	0.998
Apssiii	77.0 [63.0;94.0]	78.0 [64.0;94.0]	78.0 [64.0;94.0]	78.0 [63.0;92.2]	0.137
Hosp Day, d,median[IQR]	19.5 [9.92;33.7]	19.5 [9.66;33.5]	19.5 [9.66;33.5]	21.2 [10.9;34.8]	0.535
Icu Day, d,median[IQR]	9.59 [5.05;17.3]	9.51 [4.96;17.0]	9.51 [4.96;17.0]	9.94 [5.65;18.0]	0.685
Is Icu Dead, n(%)					0.832
No	601 (55.5%)	338 (54.8%)	338 (54.8%)	114 (57.0%)	
Yes	481 (44.5%)	279 (45.2%)	279 (45.2%)	86 (43.0%)	
Is Hosp Dead, n(%)					0.969
No	536 (49.5%)	304 (49.3%)	304 (49.3%)	99 (49.5%)	
Yes	546 (50.5%)	313 (50.7%)	313 (50.7%)	101 (50.5%)	
Death Within Hosp 28days, n(%)					0.926
No	602 (55.6%)	344 (55.8%)	344 (55.8%)	113 (56.5%)	
Yes	480 (44.4%)	273 (44.2%)	273 (44.2%)	87 (43.5%)	
Death Within Icu 28days, n(%)					0.705
No	558 (51.6%)	321 (52.0%)	321 (52.0%)	106 (53.0%)	
Yes	524 (48.4%)	296 (48.0%)	296 (48.0%)	94 (47.0%)	
Citrate_accumulation, n(%)					0.95
No	961 (88.7%)	550 (89.0%)	550 (89.0%)	177 (88.5%)	
Yes	122 (11.3%)	68 (11.0%)	68 (11.0%)	23 (11.5%)	

AKI, Chronic kidney disease (CKD), TMP(Transmembrane pressure), Mean arterial pressure (MAP), Oxygen saturation (SpO2), White blood cells (WBC), Hemoglobin (Hgb), Platelets (PLT), Hematocrit (HCT), Serum albumin, Total bilirubin (TBIL), Aspartate aminotransferase(AST), PH, Oxygen partial pressure (PaO2), Carbon dioxide partial pressure (PaCO2), Lactate (Lac), Prothrombin time (PT), Activated partial thromboplastin time (APTT), Vasoactive-inotropic score (VIS), and Acute Physiology Score III (APSIII)

Discussion

In the internal validation cohort, the prediction model constructed with five independent variables (including height, hepatic insufficiency, mechanical ventilation, prefilter replacement rate, and serum albumin) had a high value for predicting the occurrence of citrate accumulation in patients with citrate anticoagulation for CRRT during the ICU admission. To our knowledge, this study is the first to construct a prediction model for the risk of citrate accumulation in patients with citrate anticoagulation for CRRT during the ICU admission. The model's AUC in the training set is 0.758 (0.701–0.816), in the internal validation set and external validation set, the AUC is 0.747 (0.678–0.817) and 0.714 (0.632–0.810). Further results unveiled that this prediction model showed excellent discriminant power (Fig. 6), calibration (Fig. 7), clinical impact (Fig. 8), and rationality (Fig. S3). The confusion matrix in the validation set demonstrated an accuracy of 0.72, sensitivity (recall) of 0.58, specificity of 0.74, and F1-score of 0.33. In clinical practice, a high sensitivity is particularly critical for life-threatening conditions like citrate accumulation, as missing true positives (FN = 177) may delay interventions and worsen outcomes. The elevated FN rate could stem from the following factors: ① Class Imbalance: The incidence of citrate accumulation in our cohort was 11.2%, leading to a skewed

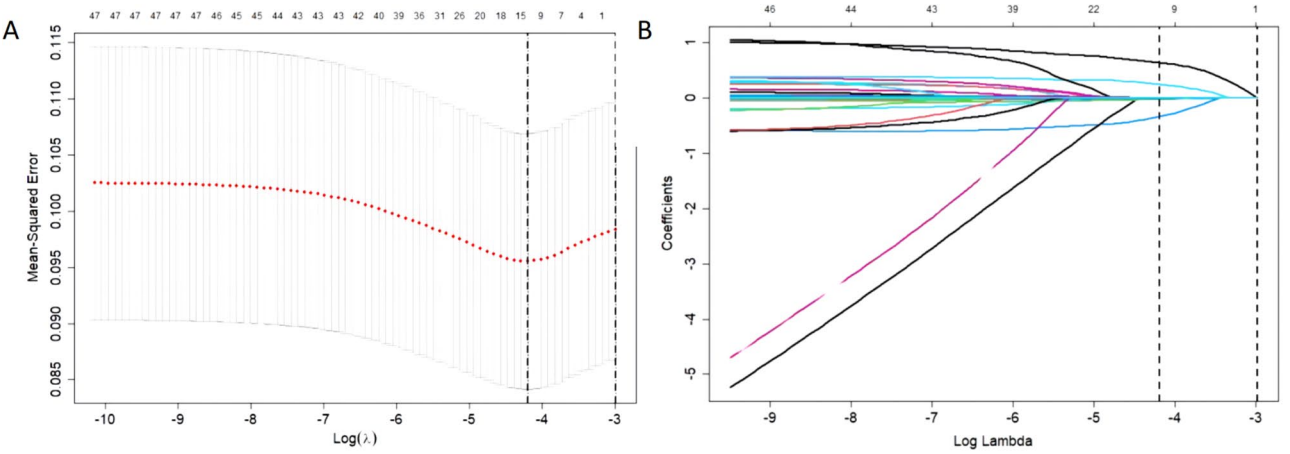

Fig. 2 Perioperative variable selection using a lasso logistic regression model. (**A**) Dotted vertical lines were depicted at the optimal values byusing the minimum criteria (lambda.min) and 1 SE of the minimum criteria (lambda.1se). (**B**) Lasso coeffcient profle of 47 vaniables. The coeficient profle is plotted according to the logarithmic sequence. Ten-fold cross-validation via minimum criteria was used to determinrpredictors of model resulted in four features with nonzero coeffcients

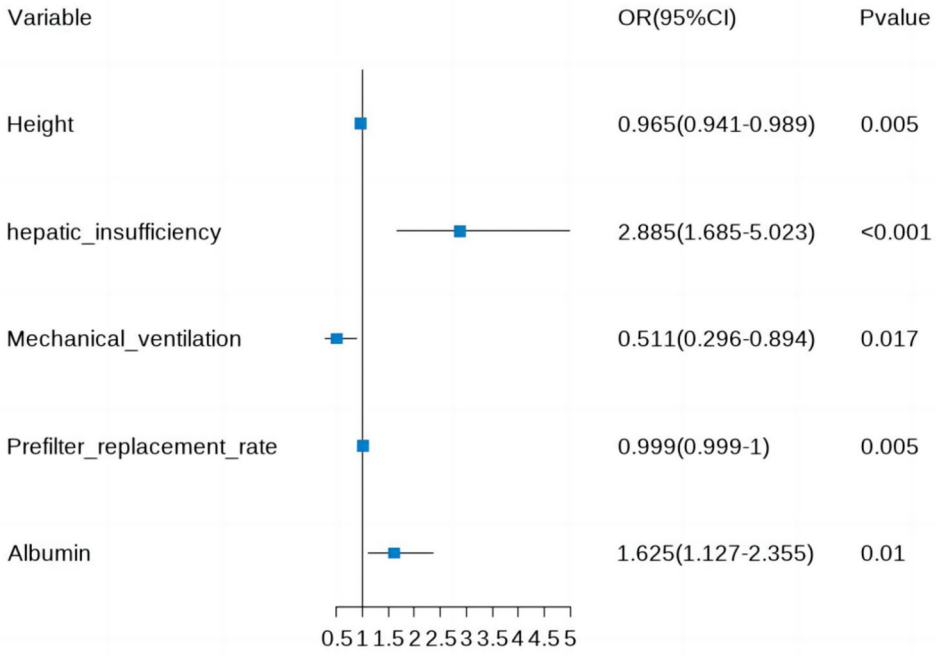

Fig. 3 Forest plot of the multivariate logistic analysis. Independent variables with $P < 0.05$ (height, hepatic insufficiency, mechanical ventilation, prefilter replacement rate, and serum albumin) were screened with the backward method to construct the model

distribution of outcomes. Models trained on imbalanced data often prioritize majority class prediction (negative outcomes). ② Threshold Selection: The default classification threshold (0.5) may not align with clinical priorities. Lowering the threshold (e.g., to 0.3) could improve sensitivity at the cost of increased false positives, which may be acceptable given the high stakes of missed cases. ③ Feature Limitations: Key dynamic variables (e.g., real-time citrate levels or lactate kinetics) were unavailable in the dataset, potentially limiting predictive accuracy. Despite these limitations, the model's AUC (0.747) and calibration performance suggest its utility in risk stratification. To mitigate FN risks, clinicians could implement proactive monitoring (e.g., frequent calcium ratio checks) for patients classified as low-risk by the model but with high-risk clinical features (e.g., liver dysfunction). Future studies should explore: Data Balancing Techniques: Oversampling (e.g., SMOTE) or cost-sensitive learning to address class imbalance.Threshold Optimization: Adjusting classification thresholds based on clinical risk-benefit trade-offsIntegration of Dynamic Biomarkers: Incorporating real-time citrate or lactate measurements

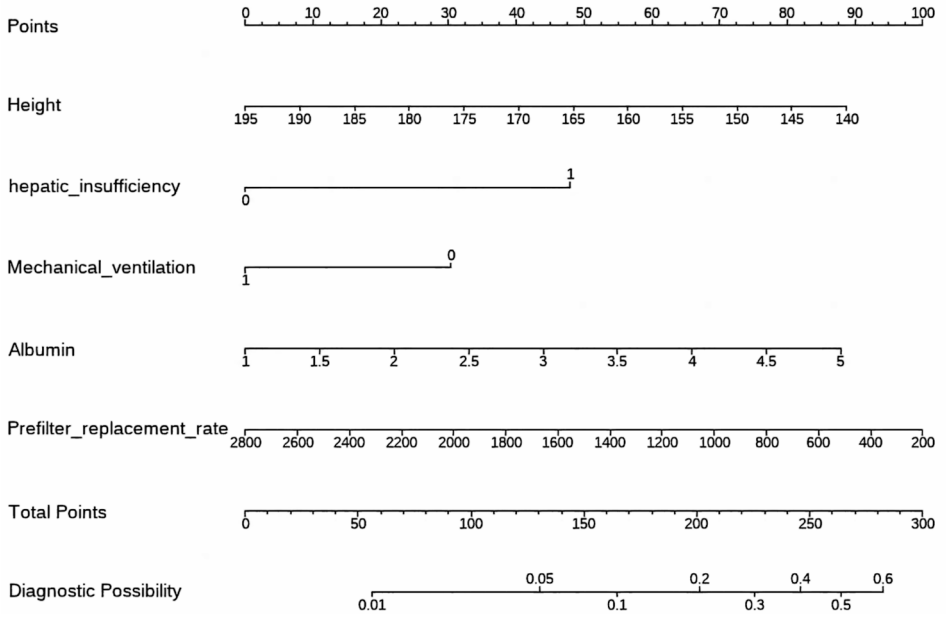

Fig. 4 The nomogram for predicting the risk of citrate accumulation in patients underwent RCA-CRRT. Each level of predictor indicates a certain score. A total score was generated by a summary of the score of each predictor. The total score corresponds to the probability of citrate accumulation in critically ill patients with citrate anticoagulation for CRRT

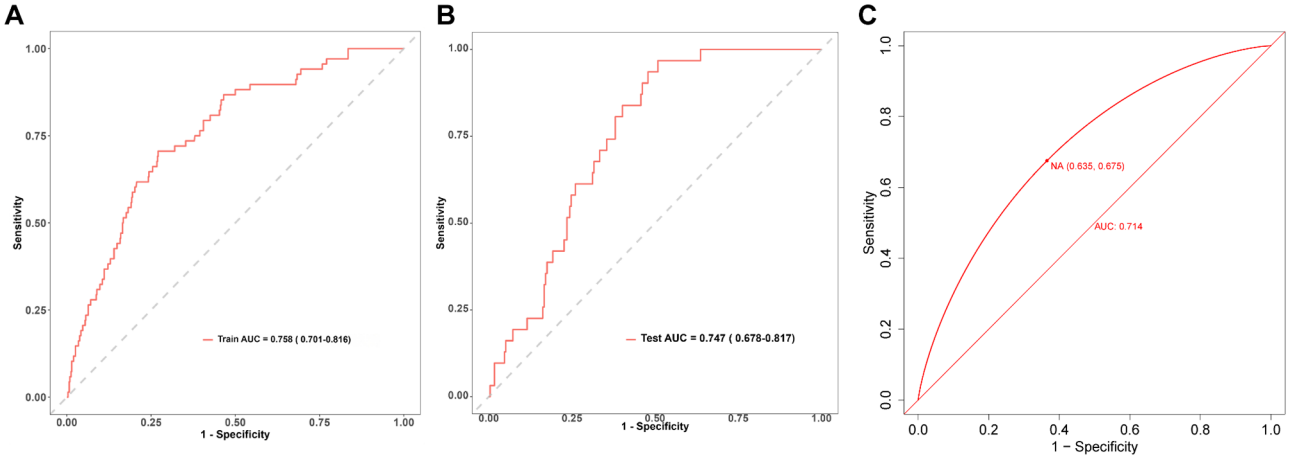

Fig. 5 ROC curve and AUC of the predictive model. (**A**) The ROC in the training group. (**B**) The ROC in the Internal validation group. (**C**) The ROC in the External validation groupROC: receiver operating characteristic; AUC: area under the curve

to enhance predictive power.The independent variables for our model were all extracted from MIMIC-IV v2.2 and ICU Electronic Medical Record System of Jiangbei Hospital, Nanjing, China, which included 1083 eligible patients. Since the independent predictive variables used can be easily collected or detected during hospitalization, they can be obtained during consultation and treatment. Among the variables included in the prediction model, some variables have been previously reported to be associated with the occurrence of citrate accumulation, and some variables were newly identified in this study. This study integrated these variables into a multivariable model for risk prediction, allowing for the individualized assessment of the risk of citrate accumulation in patients with citrate anticoagulation and therapeutic adjustment in clinical practice.

Since citrate is metabolized mainly by the liver and minimally by skeletal muscle in the human body, citrate clearance decreases from hepatocyte necrosis and mitochondrial damage in the presence of liver failure. A meta-analysis involving 10 observational studies and 1,241 patients with liver failure exhibited an incidence rate of citrate accumulation of 12% in patients with liver failure, higher than that in patients without liver failure [15]. Several studies have disclosed that lowering the initial citrate dose in patients with liver disease can prevent citrate

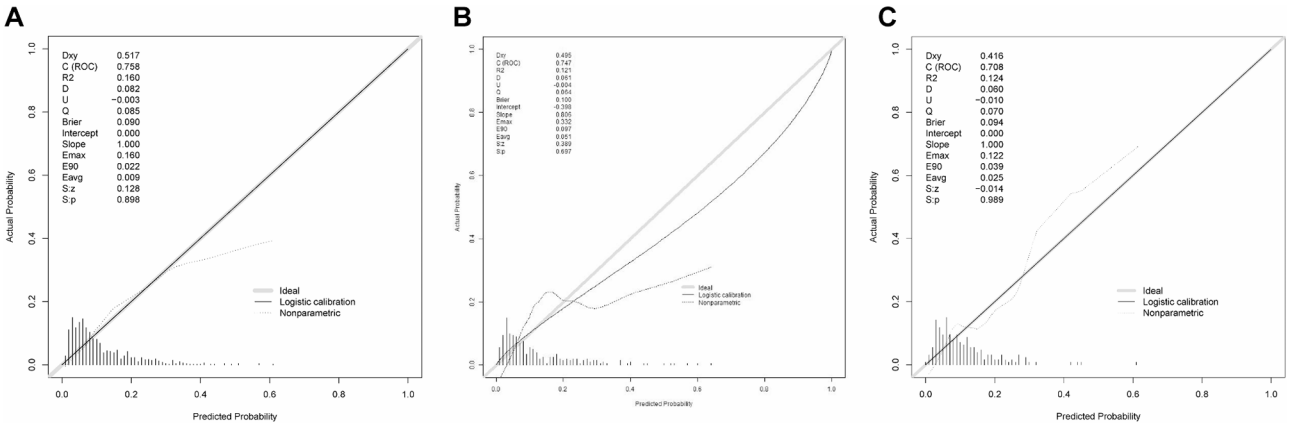

Fig. 6 Calibration plots of the predictive model. **A** Calibration curve of the model in the training set ($P=0.7673$ in the Hosmer-Lemeshow test); **B** Calibration curve of the model in the internal validation set ($P=0.2401$ in the Hosmer-Lemeshow test); **C** Calibration curve of the model in the External validation set ($P=0.2451$ in the Hosmer-Lemeshow test)According to the Hosmer-Lemeshow test, *P*-values were > 0.05 in the training and validation sets, suggesting no difference between the predicted probability of the model and the actual probability in the training and validation sets.The dashed line represents the original performance, and the solid dashed line represents the performance during internal validation by bootstrapping (B = 500 repetitions)

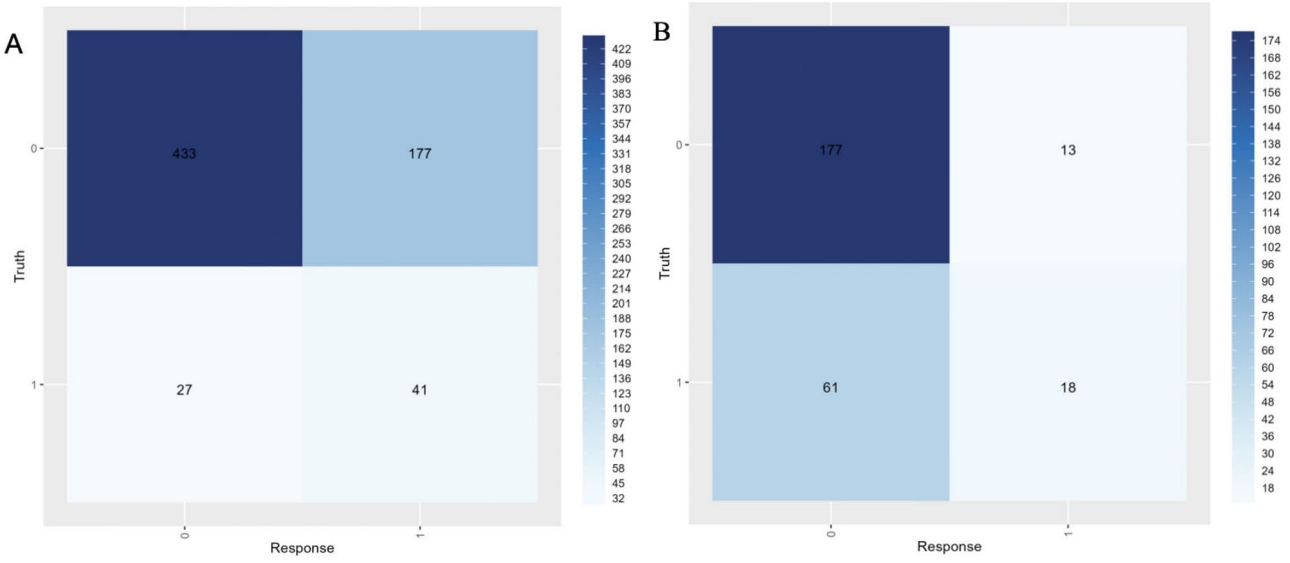

Fig. 7 Confusion matrix map heat map. (**A**) Training set confusion matrix. (**B**) Verification set confusion matrix.True Positive (TP), True Negative(TN), False Positive(FP), False Ngeative(FN)

accumulation and toxicity [16]. The KDIGO guidelines also include liver failure as a contraindication to citrate anticoagulation, which was confirmed by our results that hepatic insufficiency (Hepatic insufficiency which were defined as total bilirubin was greater than 2 mg/dL or ChildpughB、Child-pughC) was a risk factor for the development of citrate accumulation (odds ratio [OR], 2.885; 95%CI, 1.685 – 0235; $P<0.001$), with an incidence rate of citrate accumulation of 11.2%. Therefore, for patients with liver dysfunction, the total calcium/ionized calcium ratio should be closely monitored because citrate accumulation is likely to occur during citrate anticoagulation, and the dosage of citrate can be reduced or the mode of anticoagulation can be changed in the presence of citrate accumulation.

Citrate is predominantly converted to bicarbonate in the liver by the tricarboxylic acid cycle, which is one of the most important processes of aerobic respiration in cells and is dependent on the participation of oxygen. In the presence of intracellular hypoxia or tissue hypoperfusion, the tricarboxylic acid cycle cannot be carried out effectively, predisposing citrate accumulation [17]. A prior study revealed that PaO2 < 80 was a risk factor for citrate accumulation in patients with liver failure [18]. Another study demonstrated that the incidence of citric acid accumulation within 48 h was higher in hyperlacticemia (Lac > 4.0mmol/L) compared to normal lactate

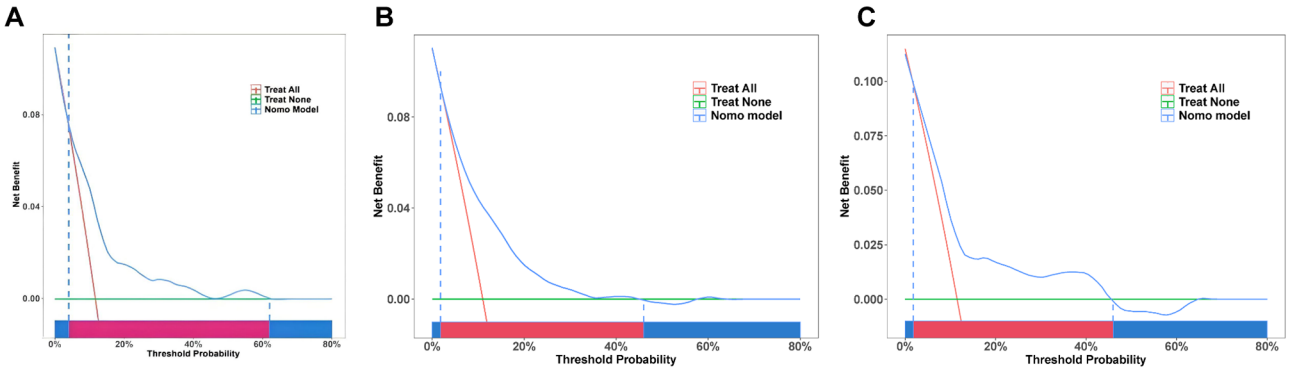

Fig. 8 DCA of the nomogram. (**A**) DCA in the training group. (**B**) DCA in the internal validation group. B)DCA in the External validation groupGreen-solid line: The patient does not apply the nomogram and the net benefit is zero; Red-solid line: All patients are treated by the nomogram. The area enclosed by the three lines presents the clinical utility of the nomogram. DCA: decision curve analysis

(Lac < 2.0mmol/L), with rates of 6.33% and 0.77%, respectively. The slope intercept of lactic acid kinetics within 48 h was positive and significantly higher (+ 0.2 vs. -0.006 mmol/L/h; $p < 0.001$), indicating that both initial elevated lactate concentration and lactate kinetics should be considered when assessing the risk of citrate accumulation [19]. Hyperlactatemia is dominated by type A hyperlactatemia and is associated with ischemia and hypoxia. Statistically, approximately 60% of critically ill patients in ICUs require invasive mechanical ventilation [20]. Mechanical ventilation can effectively ameliorate hypoxemia, thereby repressing tissue hypoxia-induced hyperlactatemia and favoring the tricarboxylic acid cycle. Our study also strongly demonstrated that mechanical ventilation was a protective factor against citrate accumulation (OR, 0.55; 95%CI 0.296 – 0.894; $P = 0.017$). Accordingly, prompt invasive mechanical ventilation in critically ill patients in ICUs may reduce the occurrence of citrate accumulation in the presence of hypoxemia.

Citrate-calcium complexes (CCC) are largely removed by the hemofilter [21]. CCC clearance is very high (up to 60%) because of their low molecular weight (298 Daltons) associated with their high hydrosolubility. When the dialysate rate in the diffusive mode and the replacement rate in the convective mode are higher, more citrate is cleared and less citrate is returned to the tricarboxylic acid cycle, thereby lowering the risk of citrate accumulation [13]. A former study exhibited that citrate clearance was markedly higher in high-flux dialysis filters than in low-flux dialysis filters and that citrate was more efficiently removed at higher replacement rates [22]. Our results also confirmed that the prefilter replacement rate did correlate with citrate accumulation (OR, 0.999; 95%CI, 0.999 – 1.000; $P = 0.005$). Specifically, higher prefilter replacement rates were associated with higher citrate clearance and lower risk of citrate accumulation. Nevertheless, positive results were not observed in terms of dialysate rate in this study, which might be related to the low dialysate rate.

In the body, calcium exists in an ionized form (50%) or is bound to albumin (40%) or other ions (10%). Routine biochemical analysis determines total serum calcium and mostly uses colorimetric methods, such as Arsenazo III method and Ortho-cresolphthalein Complexone method. These methods detect the level of total calcium by enabling the release of calcium ions from protein-bound calcium and complex calcium in the blood samples and the reaction of calcium ions binding to staining agents. Blood gas analysis is used for the measurement of ionized calcium and uses the ion-selective electrode method. The elevated or lowered concentration of human serum albumin can affect total calcium concentrations in the biochemical analysis. Seemingly, an increase in human serum albumin concentrations can elevate total calcium concentrations measured by the biochemical analysis, thus overestimating the total calcium/ionized calcium ratio [23]. Several studies have confirmed that with the measurement of citrate concentration in blood as the gold standard, the lactalbumin-corrected total calcium/ionized calcium ratio is superior to other surrogate markers (including the albumin-corrected total calcium/ionized calcium ratio) in predicting citrate accumulation, suggesting that there is no need to correct total calcium levels with albumin [8]. Our study innovatively revealed that human serum albumin increased the risk of citrate accumulation, (OR, 1.625; 95%CI, 1.127–2.355; $P = 0.01$). At present, there are no articles or studies related to the mechanism by which serum albumin elevates the risk of citrate accumulation. Generally, high human serum albumin in ICU patients is associated with transfusion with human blood albumin. Nonetheless, it is currently unclear whether the transfusion of albumin increases the risk of citrate accumulation. Our study underscores that there is a need to be vigilant for the development of citrate accumulation in ICU patients with high human

serum albumin in the presence of citrate anticoagulation for CRRT.

Given that the risk of citrate accumulation is related to citrate concentrations, it is now generally accepted that the desired local anticoagulation effect can be achieved at a citrate concentration of 3.0 mmol/L. Intriguingly, the study by Poh et al. showed that a citrate concentration of 2.5 mmol/L had the same anticoagulant effect while significantly diminishing the incidence of hypocalcemia in the short-statured Asian population [24], implicating that short stature predisposes to a higher risk of citrate accumulation at the same amount of initial citrate concentration. Similarly, our prediction model also validated that height was a risk factor for citrate accumulation (OR, 0.965; 95%CI, 0.041 – 0.989; $P = 0.005$).

Limitations

However, there are several limitations that need to be addressed in the current study. First, while the use of de-identified intensive care data from the MIMIC-IV database provides valuable insights, we acknowledge the inherent ethical challenges in retrospective studies involving critically ill patients. These patients are often unable to provide direct consent during data collection, and their vulnerability raises concerns about privacy and secondary use of data. Nevertheless, the MIMIC database addresses these issues through rigorous de-identification processes and restrictive access protocols. Researchers must complete CITI training and sign a data use agreement to access the data, ensuring compliance with ethical standards. Second, due to database limitations, our study did not involve monitoring serum citrate concentrations, nor could it extract information about the usage duration, lifetime, and frequency of specific continuous renal replacement therapy (CRRT) filters, which might present potential confounding factors affecting the development of citrate accumulation. Third, incomplete data or patients with multiple admissions to the intensive care unit (ICU) may limit the general applicability of the study results. Fourth, as a retrospective study, patients with an ICU stay of less than 24 h were excluded, which may have the limitation of survivorship bias. Fifth, the confusion matrix showed a high false-negative rate (FN = 177), with a sensitivity of 0.58 and an f1 score of 0.33 in the validation set. Although the model demonstrated moderate discriminative ability (AUC = 0.747), the high FN rate indicates limitations in identifying true positive cases. Clinically, this could delay intervention for patients at risk of citrate accumulation, emphasizing the necessity of further optimizing the model. In summary, our findings suggest that our nomogram is effective in predicting the probability of citrate accumulation in critically ill patients undergoing continuous renal replacement therapy with citrate anticoagulation. Nonetheless, further prospective multicenter studies are needed to validate our results.

Conclusion

This study constructed a nomogram with five easily accessible parameters to predict the occurrence of citrate accumulation during CRRT with citrate anticoagulation and internally validated this nomogram. This nomogram can predict the probability of citrate accumulation in critically ill patients during CRRT with citrate anticoagulation, which enables the early identification of the occurrence of citrate accumulation and provides powerful guidance for clinical decision-making to improve patient prognosis.

Abbreviations

CRRT	Continuous Renal Replacement Therapy
MIMIC-IV	Medical Information Mart for Intensive Care IV
LASSO	Least absolute shrinkage and selection operator
ROC	Receiver operating characteristic
DCA	Decision-curve analysis
AUC	Areas under the curve
ICU	Intensive Care Unit
SD	Standard deviation
IQR	Interquartile range
MSE	Mean square error
RCA-CRRT	Regional Citrate Anticoagulation-Continuous Renal Replacement Therapy
MIT	Massachusetts Institute of Technology
AKI	Acute kidney injury
CKD	Chronic kidney disease
TMP	Transmembrane pressure
MAP	Mean arterial pressure
SpO2	Oxygen saturation
WBC	White blood cells
Hgb	Hemoglobin
PLT	Platelets
HCT	Hematocrit
PaCO2	Carbon dioxide partial pressure
PT	Prothrombin time
APTT	Activated partial thromboplastin time
VIS	Vasoactive-inotropic score
APSIII	Acute Physiology Score III

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-025-04106-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Author contributions
Zhiqing Hu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Zhiqing HuAcquisition, analysis, or interpretation of data: Zhiqing Hu, Shangxiang LiuDrafting of the manuscript: Zhiqing HuCritical revision of the manuscript for important intellectual content: Zhenglong Ye, Hui ZouStatistical analysis: Zhiqing Hu, Shangxiang LiuAdministrative, technical, or material support: Zhiqing Hu, Chengqing MeiSupervision: Zhiqing Hu, Zhenglong Ye, Hui Zou.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study is based on mimic-IV database, I have obtained the corresponding certificate, certificate number 62661460. Permission to access the data was obtained. This was a retrospective study, and all protected health information of the patients in the study was anonymized and had no ethical implications.A database retrospective study without a clinical trial number.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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