A Prediction Model of Sufficient Filter Lifespan in Anticoagulation-free CRRT Patients

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Research

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Abstract

Background: Anticoagulation-free continuous renal replacement therapy (CRRT) was recommended by the current clinical guideline for patients with increased bleeding risk and contraindications of citrate and resulted in heterogeneous filter lifespan. There was no prediction model to identify the patients would have sufficient filter lifespan when they have to accept CRRT without the use of any anticoagulation. The purpose of our present study is to develop a clinical prediction model of sufficient filter lifespan in anticoagulation-free CRRT patients.

Method: Patients who underwent anticoagulation-free CRRT in our center between June 2013 and June 2019 were retrospectively included. The primary outcome was sufficient filter lifespan (≥ 24 hours). The final model was established by using multivariable logistic regression analysis. And, the prediction model was validated in an external cohort.

Results: A total of 170 patients were included in the development cohort. Sufficient filter lifespan were observed in 80 patients. The probability of sufficient filter lifespan could be calculated using the following regression formula: P (%) = exp (Z)/1 + exp (Z), where Z = 0.49896*(0.08552*BMI)+(0.44107*T)+(0.03373*MAP)-(0.03389*WBC)+(1.51579*[vasopressor=1])-(0.01132*PLT)+(0.00422*ALP)-(2.66910*pH)-(0.00214*UA)+(0.05992*BUN)+(0.00400*Db)–(0.00014*D-dimer)+(0.02818*APTT). The area under the curve (AUC) of the stepwise model and internal validation model was 0.82 (95%CI [0.76-0.88]) and 0.8 (95%CI [0.74-0.87]), respectively. At the optimal cut-off value of -0.1052, the positive predictive value and the negative predictive value of the stepwise model was 0.77 and 0.79, respectively. The AUC of the external model was 0.82 (95%CI [0.69-0.96]).

Conclusion: The use of a prediction model instead of an assessment based only on coagulation parameters could facilitate the identification of the patients with filter lifespan of ≥ 24 hours when they accepted anticoagulation-free CRRT.

Background

Renal replacement therapy (RRT) is applied in 12%-15% of intensive care unit (ICU) patients and 75% of the RRT modalities were continuous renal replacement therapy (CRRT) [1]. Anticoagulation is a key intervention to maintain the patency of the extracorporeal circuit [2].

Unfractionated heparin (UFH) is the most widely used anticoagulant for CRRT worldwide [3]. However, critically ill patients are commonly complicated with impaired coagulation or increased bleeding risk [4]. A platelet count of < 50 × 10⁹/L was seen in 12%-15% of the critically ill patients and a prolonged global coagulation time (i.e. prothrombin time [PT] or activated partial thromboplastin time [APTT]) in 14%-28% [5]. The reported bleeding incidence in patients underwent heparin anticoagulated CRRT ranged from 4%-25% [6, 7]. Therefore, the increased bleeding risk limits the applicability of heparin in critically ill patients [7]. Regional citrate anticoagulation (RCA) are gaining increasing popularity due to its advantage over heparin in terms of prolonged filter lifespan and reduced bleeding risk [8]. The KDIGO guideline recommended RCA as the preferred anticoagulation strategy in patients without citrate contraindications, including severe liver failure and shock with muscle hypoperfusion [4]. The reported incidences of liver dysfunction and shock with hypoperfusion in ICU patients were 2%-5% [9, 10] and 40% [11, 12], respectively. Therefore, a significant number of ICU patients had the contraindications of both heparin and citrate.

For these patients, CRRT was suggested to be proceed without the use of any anticoagulant [4]. In clinical practice, approximately 33%-50% patients did not receive any anticoagulants during CRRT [13–15]. The averaged or median filter lifespan of anticoagulation-free CRRT ranged from 10 [16] to 40 [17] hours, which were associated with
significant heterogeneity. For anticoagulation-free CRRT, 60% of the filters were replaced because of filter failure before the accomplishment of a treatment regiment (commonly 24 hours) [18]. Several parameters, including platelet (PLT), international normalized ratio (INR), and APTT were reported to be related to the filter lifespan in anticoagulation-free CRRT patients. However, the specific cut-off points have not been determined for these parameters to indicate the possibility of sufficient filter lifespan for anticoagulation-free CRRT [4]. To the best of our knowledge, there was no effective model to predict sufficient filter lifespan in anticoagulation-free CRRT patients as well [19]. The development of an effective prediction model for sufficient filter lifespan would be helpful for the individual choice of anticoagulation strategy for CRRT patients.

Therefore, the aim of our present study is to develop a clinical prediction model to predict sufficient filter lifespan for a treatment regiment (commonly 24 hours) in anticoagulation-free CRRT patients.

Methods

Study design

Our present study is a retrospective cohort study and was performed in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement [20]. This study was performed in accordance with the Declaration of Helsinki and was approved by the ethic committee of our hospital. The informed consent was waived regarding the retrospective nature of our present study.

Development cohort

Critically ill patients who underwent CRRT between June 2013 and June 2019 in our center (a tertiary teaching hospital with more than 2000 CRRT patients per year) were retrospectively screened. The inclusion criteria included: 1) adult patients (≥ 18 years); and 2) received anticoagulation-free CRRT. Patients were excluded if they fulfilled any of the following criteria: 1) received systemic anticoagulation within 24 hours prior to or during CRRT for indications other than CRRT; 2) received other extracorporeal therapies (i.e. Plasmapheresis, plasma exchange, hemoperfusion, or extracorporeal membrane oxygenation [ECMO]) during CRRT; 3) switched to systemic heparin or regional citrate anticoagulation after the start of a anticoagulation-free CRRT regiment; 4) patients underwent CRRT via arteriovenous fistula; 5) patients with missing data of important parameters (i.e. liver function, coagulation parameters, or filter lifespan); 6) the first circuit was replaced within 24 hours due to selective reasons (i.e. imaging procedures, transport, low blood pressure, resuscitation discharge, surgery, or death); or 7) the center venous catheter function was insufficient for the targeted blood flow.

Validation cohort

A separate external validation cohort was retrospectively recruited to assess the generalizability of the prediction model. The patients who underwent CRRT between January 2018 and December 2019 in West China Hospital of Sichuan University were screened according to the inclusion and exclusion criteria employed in the development cohort.

CRRT protocol in the development cohort

Continuous veno-venous hemofiltration (CVVH) was the modality routinely adopted during the study period. The machines used for CRRT were the Prismaflex System (Gambro) and DIAPACT (Braun), which were equipped with Multiflow-100 (0.9 m², AN69 membrane) and AV600 (polysulfone, 1.4 m²; Fresenius) hollow-fiber filters, respectively. The vascular access was built by inserting a 13.5F double lumen catheter into the femoral vein or jugular vein. Blood flow was maintained at 200 ml/min. Commercially available replacement fluid was infused at a rate of 2 L/h with a
ratio of pre to post-dilution of 1:1. In cases of large body size (weight > 100 kg), the prescribed dose was set at 20–25 ml/kg/hour according to the recommendations of the 2012 KDIGO guideline [4]. A bicarbonate buffered fluid was infused pre-filter separately at an appropriate rate depending on the acid-base status of the patients. The ultrafiltration rate (UFR) was adjusted according to the hemodynamic parameters and the goal of treatment.

**CRRT protocol in the validation cohort**

Continuous venovenous hemodiafiltration (CVVHDF) was the sole CRRT modality used in the validation cohort. CVVHDF was performed using the Prismaflex System (Gambro) machine equipped with several types of filters including ST150, M150, and M100. The parameters of CVVHDF were following: blood flow rate 200 ml/min; dialysate flow rate 1 L/hour; and, replacement fluid flow rate 1 L/hour with pre-, post- or hybrid dilution models.

**Definitions**

Illness severity was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) score. Increased bleeding risk [21] was defined according to the following criteria: 1) coagulopathy (APTT > 60 s, INR > 2, or PLT count < 60 × 10^9/L); 2) active bleeding; 3) post-surgery within 24 hours; or 4) experienced major bleeding within 48 hours. Contraindications to citrate included severe liver failure (total bilirubin > 34.2 µmol/L) [22], shock with muscle hypoperfusion (serum lactate > 2 mmol/L) [23], and hypoxemia (PaO₂ < 60 mmHg).

**Outcomes**

Sufficient filter lifespan was defined as filter lifespan ≥ 24 hours. Filter lifespan was defined as the time interval (hours) between initiation and cessation of an individual circuit. Filter failure was confirmed by 1) transmembrane pressure (TMP) > 300 mmHg, 2) visible clots, or 3) inability to operate the blood pump [24, 25].

**Factors included in the analysis**

Thirty-seven factors (Additional file 1: Table S1) were included in the analysis based on their clinical significance and previous reports [26]. Data including demographic characteristics, admission diagnosis, pre-existing disease, illness severity, indications of CRRT, risk of bleeding, contraindications for citrate, laboratory tests, mechanical ventilation (MV), vasoactive agents use, transfusion requirement, and CRRT protocol characteristics were collected from the patient medical records. In order to control confounding bias, only the first circuit in the first session was analyzed for patients who received several sessions of CRRT during one admission.

**Missing data**

The missing data were addressed by mean imputation using SPSS (IBM Corporation) software version 24. All the imputations were performed before the univariable and multivariable analyses.

**Statistical analysis**

Normal distribution and non-normal distribution continuous variables were presented as mean ± standard deviation (SD) and median (interquartile range [IQR]) and compared using Student's t test and the Wilcoxon test, respectively. For categorical variables, data were presented as counts (percentage), and were compared using Chi-square test or Fisher's exact test. The filter survival probability at different time points were graphically analyzed using Kaplan–Meier survival curves with Log-rank test.

All the candidate factors were included in a multivariable logistic regression model with the continuous variables retained on the original scale. The collinearity test was performed at first and variables with variance inflation factor
(VIF) greater than 10 were eliminated. Thereafter, a stepwise approach was employed for the final model selection based upon Akaike Information Criterion (AIC) [27] measures of model quality and performance. We also developed a full model and a multivariable fractional polynomial (mfp) model. Nomograms [28] were constructed based on the results of the models. Discrimination and calibration of the models were assessed by the area under the receiver operating characteristic (ROC) curve (AUC) with a 95% confidence interval (CI) and the calibration curve, respectively [29]. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated at the optimal cut-off values of the models which were identified according to the maximum Youden Index. In addition to external validation, the performance of the models were internally validated by using bootstrapping (BS) (1000 times). Statistical differences in the AUCs were compared using the Delong test [30]. A 2-sided P-value < 0.05 was considered statistically significant. All statistical analyses were performed by using the R software (The R Foundation; http://www.r-project.org; version 3.4.3).

Results

Model development

Patients characteristics

During the study period, a total of 496 adult patients who underwent anticoagulation-free CRRT were identified, and 326 patients were excluded. The remaining 170 patients were included in the development cohort. The most common reason for patient exclusion was systemic anticoagulation within 24 hours before CRRT (34%) followed by important data missing (10%, Fig. 1).

The mean age of the included patients was 52.7 ± 15.6 years. The median APACHE II score was 24.5 (18–30). Half of the patients were on mechanical ventilation, and vasopressor were administrated in 56% of the included patients. The most common diagnosis before CRRT was multiple organ dysfunction syndrome (MODS) (34%), followed by liver failure (28%) and sepsis (26.5%). The most common indications for CRRT were acute kidney injury (AKI) (85%), severe metabolic acidosis (34%), and hyperkalemia (30%). The baseline characteristics of the development cohort were detailed in Table 1.
| Characteristics                  | All patients* (N = 170) |
|---------------------------------|------------------------|
| Age (year)                      | 52.7 ± 15.6            |
| T (°C)                          | 36.8 (36.5–37.4)       |
| Male sex                        | 120 (70.6)             |
| BMI (kg/m²)                     | 23 ± 3.75              |
| MAP (mmHg)                      | 79.6 (70.3–91.4)       |
| APACHE II score                 | 24.5 (18–30)           |
| SOFA score                      | 12.7 ± 4.2             |
| Mechanical ventilation          | 84 (49.4)              |
| Vasopressor use                 | 95 (55.9)              |
| Hb (g/L)                        | 95 (80.2–117)          |
| WBC (10⁹/L)                     | 12.7 (8.8–18.5)        |
| PLT (10⁹/L)                     | 59 (29–115)            |
| APTT (s)                        | 48.2 (37-63.8)         |
| INR                             | 1.55 (1.24–2.03)       |
| D-dimer (mg/L)                  | 11.7 (3.8–39.2)        |
| Total bilirubin (µmol/L)        | 57.6 (23.6-111.3)      |
| Direct bilirubin (µmol/L)       | 37.1 (11.2–76.6)       |
| ALP (IU/L)                      | 84 (55.2-140.2)        |
| Creatinine (µmol/L)             | 258.5 (180.5-443.5)    |
| BUN (µmol/L)                    | 18.6 (11.6–27.1)       |
| UA (µmol/L)                     | 472.8 (354.2-499.2)    |
| pH                              | 7.38 (7.3–7.44)        |
| Serum lactate (µmol/L)          | 4.1 (2.35–9.6)         |
| Diagnosis before CRRT           |                        |
| Sepsis                          | 45 (26.5)              |
| Post-cardiac surgery            | 19 (11)                |
| Severe pancreatitis             | 6 (3.5)                |
| MODS                            | 58 (34)                |
| Liver failure                   | 48 (28.2)              |
| Trauma                          | 9 (5.3)                |
Characteristics                      All patients* (N = 170)  
Exertional heat stroke             5 (3)                        
Others#                              27 (15.8)                
Indications for CRRT                 
AKI                                  144 (84.7)                
Fluid overload                       44 (25.8)                  
Severe metabolic acidosis           58 (34)                     
Hyperkalemia                         52 (30.5)                  
Hyponatremia                         20 (11.7)                  
Rhabdomyolysis                       12 (7)                      
Hypernatremia                        11 (6.4)                   
Hypokalemia                          7 (4)                       
Uremia                               6 (3.5)                    

Abbreviations: AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; ALP, alkaline phosphatase; BMI, Body Mass Index; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; Hb, hemoglobin; INR, International Normalized Ratio; MODS, multiple organ dysfunction syndrome; MAP, mean arterial blood pressure; PLT, platelet; SOFA, sequential organ failure assessment; T, body temperature; UA, uric acid; WBC, white blood cell. Data were expressed as mean ± SD, median (IQR) or n (%). *Variables with missing values were analyzed before imputations. #other diagnoses included acute kidney injury, cancer, hypovolemic shock, electrolyte disturbance, respiratory failure, anemia, uremia, pulmonary infection, coagulopathy, cerebral hemorrhage, cerebral infarction, gastrointestinal bleeding, chronic kidney diseases, peritoneal cavity infection, and acute fatty liver of pregnancy.

The most common causes of increased bleeding risk were thrombocytopenia (56%), APTT > 60 s (35%), and active bleeding (29%). The most frequent contraindication for citrate was shock with muscle hypoperfusion (69%, Additional file 2: Table S2).

CRRT profile

During CRRT, clotting occurred in 122 (72%) filters. The overall median filter lifespan was 21.5 (12.5–30.1) hours. Filter lifespan of ≥ 24 hours, defined as sufficient filter lifespan, were observed in 47% of the included circuits. Median filter lifespan of the clotted filters was 16 (10.5–25) hours. The accumulated filter survival probabilities at 12-, 24-, and 48-hour were 80%, 47%, and 7%, respectively (Fig. 2A).

Risk factors for filter failure

In the univariate regression analysis, SOFA score, PLT, hemoglobin (Hb), hematocrit (Hct), APTT, total bilirubin (Tb), and direct bilirubin (Db) were significantly related to the sufficient filter lifespan. In the multivariate analysis, red blood cell (RBC), Hct, INR, Tb, and alanine aminotransferase (ALT) were removed from the model because of collinearity. Finally, the stepwise model demonstrated that temperature (T), mean arterial pressure (MAP), APTT, Db, alkaline phosphatase (ALP), blood urea nitrogen (BUN), and vasopressor use were positively related to sufficient filter lifespan, and BMI, white blood cell (WBC), PLT, D-dimer, uric acid (UA), and pH were negatively related to sufficient filter lifespan (Table 2).
### Table 2

Predictors in the univariate and multivariate analysis

| Predictors          | Univariate logistic regression |                  |                           | Multivariate logistic regression (stepwise model) |                  |                           |
|---------------------|-------------------------------|------------------|---------------------------|--------------------------------------------------|------------------|---------------------------|
|                     | Coefficient | OR   | 95%CI   | P value | Coefficient | OR   | 95%CI   | P value   |
| Intercept           |             | 0.49 |        |         | 0.09       | -0.08 | 0.91   | 0.82–1.01 | 0.10     |
| BMI (kg/m²) [13.5–36.5]a | -0.07     | 0.93 | 0.85–1.01 | 0.09 | -0.08     | 0.91 | 0.82–1.01 | 0.10     |
| T (°C) [3.5–40.2]   | 0.06        | 1.06 | 0.72–1.57 | 0.74 | 0.44       | 1.55 | 0.89–2.7 | 0.11     |
| SOFA [3–22]         | 0.11        | 1.12 | 1.02–1.22 | 0.01 |           |      |         |           |
| MAP (mmHg) [39–128] | -0.002      | 0.99 | 0.97–1.01 | 0.84 | 0.03       | 1.03 | 1.003–1.06 | 0.03     |
| WBC (× 10^{12}) [1.67–50.2] | -0.03     | 0.96 | 0.93–1.005 | 0.09 | -0.03      | 0.96 | 0.92–1.01 | 0.15     |
| PLT (× 10^9) [4-691] | -0.0081    | 0.99 | 0.98–0.99 | 0.001 | -0.01      | 0.98 | 0.98–0.99 | 0.001    |
| Hb (g/L) [14.6–177] | -0.01       | 0.98 | 0.97–0.99 | 0.02 |           |      |         |           |
| Hct [0.075–0.559]   | -3.79       | 0.02 | 0.0005–0.94 | 0.04 |           |      |         |           |
| APTT (s) [17.8–180] | 0.02        | 1.02 | 1.009–1.04 | 0.001 | 0.02       | 1.02 | 1.01–1.04 | 0.002    |
| D-dimer (mg/L) [0.31–16000] | 0.000      | 1    | 0.99–1.0001 | 0.97 | -0.0001 | 0.99 | 0.99–1 | 0.01     |
| Tb (µmol/L) [2.4–801] | 0.0027     | 1.002 | 1-1.005 | 0.04 |           |      |         |           |
| Db (µmol/L) [1-666] | 0.0032      | 1.003 | 1-1.006 | 0.04 | 0.004     | 1.004 | 0.99–1.008 | 0.10     |
| ALP (IU/L) [19–824] | 0.0016      | 1.001 | 0.99–1.004 | 0.21 | 0.0042     | 1.004 | 1.0005–1.007 | 0.02     |
| BUN (µmol/L) [3.8–69.9] | 0.02       | 1.02 | 0.99–1.04 | 0.06 | 0.059     | 1.061 | 1.02–1.1 | 0.001    |
| UA (µmol/L) [74-1691] | -0.0011    | 0.99 | 0.99–1.0004 | 0.15 | -0.002    | 0.99 | 0.99–0.99 | 0.02     |
| pH [6.95–7.61]      | -0.65       | 0.51 | 0.03–7.41 | 0.62 | -2.66     | 0.06 | 0.001–2.46 | 0.14     |
| Vasopressor (1)     | 0.51        | 1.66 | 0.90–3.07 | 0.10 | 1.51       | 4.55 | 1.7-12.14 | 0.002    |
The AUC of the stepwise model was significantly increased, compared with routinely tested coagulation parameters including APTT (P < 0.001), INR (P < 0.001), and PLT (P < 0.001). Furthermore, the AUC of the stepwise model was superior to that of the model including all of these 3 parameters as well (0.82 [0.76–0.88] vs. 0.7 [0.62–0.78], P = 0.0016). (Additional file 4: Figure S2).

**Final model selection**

The full model and the mfp model did not show better accuracy than the stepwise model. Furthermore, the complicated formula of the mfp model compromised the convenience for application. Therefore, the stepwise model was the most parsimonious model under the premise of guaranteeing discrimination performance and was selected for the final model.
Accordingly, the probability of sufficient filter lifespan could be calculated using the following regression formula: $P(\%) = \exp(Z)/1 + \exp(Z)$, where $Z = 0.49896\cdot(0.08552\cdot\text{BMI}) + (0.44107\cdot\text{T}) + (0.03373\cdot\text{MAP}) - (0.03389\cdot\text{WBC}) + (1.51579\cdot[\text{vasopressor} = 1]) - (0.01132\cdot\text{PLT}) - (0.00422\cdot\text{ALP}) - (2.66910\cdot\text{pH}) - (0.00214\cdot\text{UA}) + (0.05992\cdot\text{BUN}) + (0.00400\cdot\text{Db}) - (0.00014\cdot\text{D-dimer}) + (0.02818\cdot\text{APTT})$. In order to facilitate the application in clinical practice, we developed a Microsoft Excel spreadsheet (Additional file 5: the Excel calculator) and a nomogram (Additional file 6: Figure S3) based on this formula. An optimal cut-off value of $Z$ was identified as -0.1052. The final model could discriminate 61 out of the 80 patients with filter lifespan of \( \geq 24 \) hours and, the PPV and the NPV were 0.77 and 0.79, respectively. Furthermore, the median filter lifespan was significantly longer in patients with $Z > -0.1052$ (26 [24-38.25] hours vs. 15.5 [9.75–21.5] hours, $P < 0.001$, Fig. 2B).

**External validation**

After the screening, 44 cases were included in the external validation cohort (Additional file 7: Figure S4). The baseline characteristics of these patients are showed in Additional file 8: Table S3. There were no significant differences in age, body temperature, male proportion, BMI, MAP, and APACHE II score between development cohort and validation cohort. The AUC of the ROC of the external validation model was 0.82 (95%CI [0.69–0.96], Additional file 9: Figure S5A). According to the optimal cut-off value of the development model, 18 out of the 28 patients with sufficient filter lifespan were discriminated and the sensitivity, specificity, PPV, and NPV were 0.64, 0.81, 0.85, and 0.56, respectively. The median filter lifespan was significantly longer in patients above the cut-off value (32 [24–51] hours vs. 23 [16–29] hours, $P = 0.03$, Additional file 9: Figure S5B). The overall median filter lifespan in the validation cohort was 26.5 (21–46.2) hours.

**Discussion**

In our present study, we found out that, in patients with increased bleeding risk who underwent anticoagulation-free CRRT, lower PLT, UA, and D-dimer as well as higher MAP, APTT, ALP, and BUN, and the use of vasopressor were independently related to longer filter lifespan. Our prediction model could effectively discriminate patients with sufficient filter lifespan in both the development and validation cohort. A patient with $Z > -0.1052$ most likely could have sufficient filter lifespan for anticoagulation-free CRRT. In addition, the probability of sufficient filter lifespan could be calculated by using a nomogram or an Excel calculator.

**Risk factors of filter failure**

Fealy, N. et al [25] found in a randomized controlled trial (RCT) that longer APTT (hazards ratio [HR] 0.98, $P = 0.002$) and decreased platelet count (HR 1.19, $P = 0.03$) were independently associated with a reduced likelihood of circuit clotting. The similar association of APTT [31] and platelet count [32, 33] with CRRT filter lifespan were reported in observational studies as well. Zhang Z. et al [34] reported that lower pH was significantly associated with longer filter lifespan in a multivariable Cox regression model. These evidences demonstrated the reliability of the predictors in our present model. However, the mechanism of filter failure is highly sophisticated [35–39] and could not be solely interpreted or predicted by classical markers of coagulation including PT, APTT, and platelet count [40]. A recent meta-analysis [26] divided non-anticoagulant determinants of filter lifespan into vascular access factors, circuit factors, and patient factors. Therefore, a clinical prediction model, which was commonly based on more comprehensive indicators, could most likely provide more accurate prediction for filter failure and sufficient lifespan.

The appropriate lifespan of a single filter has not yet been well defined [41]. We choose 24 hours as the cut-off value based on the following reasons. First, 24 hours is a therapy span in our routine practice and the treatment target could be reached in majority of patients within 24 hours. Second, an effective treatment time of 20 hours per day was
recommended [41], and it could be achieved by using only 1 circuit with a lifespan of $\geq 24$ hours, leaving 1–3 hours downtime per day [42]. In addition, most of the centers and studies defined successful prevention of clotting as no need for circuit change in the first 24 hours [43].

Relations to the previous studies

To our knowledge, studies developing prediction models for filter lifespan of CRRT are scarce. A prognostic model reported by Fu, X et al [19] included 302 cases and suggested that insufficient blood flow, without anticoagulation, and values of Hct, lactate, and APTT could be used to predict the likelihood of extracorporeal circuit clotting within 24 hours in patients underwent CRRT with all kinds of anticoagulation models. The AUC of this model was 0.79 (95% CI [0.7–0.87]). Despite both of the AUCs of this model and ours were more than 0.75, a threshold that was deemed as useful discrimination [29], our model has several advantages. First, we included only CRRT patients without the use of any anticoagulation, which could offer important information for the choice of anticoagulation strategies, mainly use or no use of anticoagulation. The study by Fu et al. [19] included patients with and without anticoagulation in their model. The use of anticoagulation definitely played a major role on the prolonged filter lifespan. And, the filter lifespan in patients accepted anticoagulation mainly attributed to the effective anticoagulation, including the anticoagulant types and the sufficient dose of anticoagulant. Therefore, the model by Fu et al. [19] could not offer key clue for the use or no use of anticoagulation for clinicians, especially for patients with relative contraindications to anticoagulation. Second, all the included predictors in our model were readily available prior to CRRT initiation, which could be helpful and useful for clinical decision making. Third, in addition to the regression formula, the nomogram and Excel calculator could provide more convenient and accurate prediction. At last, our model has been validated in an external validation cohort, which suggested very good reliability. Several previous studies also suggested the use of coagulation parameters and bleeding markers to determine the use of anticoagulation-free protocol. However, in the study by Morabito, S. et al [44], 45% of the patients who initially received anticoagulation-free protocol switched to heparin anticoagulation because the filter lifespan was less than 24 hours. In another study by Morabito, S. et al [18], 33 patients switched to RCA-CRRT because of early circuit clotting (<24 hours) without anticoagulation, and only 40% of the circuits reached a lifespan of more than 24 hours before switch. In our development cohort and validation cohort, of the patients who were predicted to have filter lifespan >24 hours, 77% and 85% had sufficient lifespan during their CRRT treatment. The results of the aforementioned 2 studies [18, 44] and our study indicated that the use of a prediction model instead of an assessment based only on coagulation parameters could significantly improve the discrimination ability to identify eligible patients for anticoagulant-free CRRT.

Clinical implications

Our model can facilitate the assessment of filter failure risk and the selection of appropriate anticoagulation for CRRT in patients with relative contraindications to anticoagulation. The patient with expected sufficient filter lifespan could initially underwent anticoagulation-free CRRT. For those patients with expected insufficient filter lifespan, a less risky anticoagulation strategies could be considered. Future studies with prospective, randomized, and multicenter design are warranted to validate our findings.

Limitations

First, there were potential confounding factors and biases due to the retrospective nature of our present study. We had strictly predefined the inclusion and exclusion criteria and enrolled consecutive real-life patients over a 6-year period to reduce the selection bias and confounding factors. Second, the application of the model might be complex as the final model includes 13 variables. However, most of these predictors were clinically relevant and easily available in routine
practice. Furthermore, an Excel calculator was generated and would facilitate the clinical application of our model. Additionally, only Chinese patients were included in both the development and validation cohort. Further adjustment might be necessary when employ our model in other ethic population.

Conclusions

It is necessary to weigh the benefits against the adverse effects of the use of anticoagulation for CRRT patients with increased bleeding risk. For CRRT patients with contraindications of anticoagulation, the use of our model could identify the patients with sufficient lifespan if they accepted CRRT without the use of any anticoagulant. Our model most likely could facilitate the choice of an optimal anticoagulation strategy for an individual patient.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, alkaline phosphatase; AUC, area under the curve; AIC, Akaike Information Criterion; AKI, acute kidney injury; BMI, Body Mass Index; BUN, blood urea nitrogen; BS, bootstrapping; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; CI, confidential interval; Db, direct bilirubin; ECMO, extracorporeal membrane oxygenation; FDP, Fibrin degradation product; FFP, fresh frozen plasma; Hb, hemoglobin; HR, hazard ratio; Hb, hemoglobin; Hct, hematocrit; INR, International Normalized Ratio; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial blood pressure; MV, mechanical ventilation; MODS, multiple organ dysfunction syndrome; Neu, Neutrophil; NPV, negative predictive value; NLR, negative likelihood ratio; PLT, platelet; PT, Prothrombin time; PTA, prothrombin time activity; PPV, positive predictive value; PLR, positive likelihood ratio; RBC, red blood cell; RCT, randomized controlled trial; RCA, regional citrate anticoagulation; ROC, receiver operating characteristic curve; SOFA, sequential organ failure assessment; SD, standard deviation; T, temperature; Tb, total bilirubin; TMP, transmembrane pressure; UA, uric acid; UFH, unfractionated heparin; UFR, ultrafiltration rate; VIF, variance inflation factor; WBC, white blood cell.

Declarations

Ethics approval and consent to participate

Approval from the local scientific and ethics committee of the Xijing Hospital was obtained; they stated that no informed consent of the patient or next of kin was required regarding the retrospective nature of our present study.

Consent for publication

Not applicable

Availability of data and material

The datasets analyzed during the current study are available with the corresponding author on reasonable request.

Competing interests

The authors declare that there is no conflict of interest.

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Authors' contributions

Wei Zhang, Ming Bai and Ling Zhang contributed equally to this work. Wei Zhang, Ming Bai, and Shiren Sun conceived the study, participated in the design, collected the data, performed statistical analyses and drafted the manuscript. Yan Yu, Yangping Li, and Lijuan Zhao collected data of the development cohort and helped to draft the manuscript. Yuan Yue and Yajuan Li helped to collect the data of the development cohort. Ming Bai performed statistical analyses and revised the manuscript critically for important intellectual content. Min Zhang collected the data of the external validation cohort. Ling Zhang assisted in interpreting the findings, and provided critical revisions of the manuscript. Shiren Sun, Ping Fu and Xiangmei Chen helped to revise the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Figures
Figure 1

The participant flow diagram of the development cohort. CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; RCA, regional citrate anticoagulation
Figure 2

Kaplan–Meier curve for filter survival in the development cohort illustrating survival rate and numbers of survival filters at 12 hours, 24 hours, 36 hours, and 48 hours. A) Overall filters; B) Filters stratified by the optimal cut-off value of the stepwise model.
Figure 3

The predictive performance of the stepwise model and the internal validation model. A) ROC curve of the stepwise model; B) calibration curve of the stepwise model; C) ROC curve of the BS-stepwise model; D) calibration curve of the BS-stepwise model. AUC, area under the curve; BS, bootstrapping; ROC, receiver operating characteristic.

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