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Development of a predictive model for nafamostat mesylate dosing in hemodialysis

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Abstract

Background Nafamostat mesylate, an anticoagulant with a short half-life, is useful during hemodialysis for patients at high risk of bleeding. Research on the appropriate dosage of nafamostat has been insufficient. This study aimed to investigate the optimal dosage of nafamostat using a dosage prediction model.

Methods We retrospectively analyzed medical records from 12 centers affiliated with Yeolin Medical Foundation over an 8-month period. Candidate predictor variables were evaluated using bootstrapping and stepwise regression to determine feature importance. Predictive models were compared based on performance metrics.

Results In total, 308 sessions from 88 patients without dialyzer clotting were selected. The average nafamostat dose was 21.90 ± 6.82 mg/h. The top four important features were oral anticoagulant use, dry body weight, age, and hemoglobin level. The best-performing model using 12 variables showed a root mean squared error of 4.11 mg/h and an adjusted R^2 value of 0.49. Multivariable linear regression showed that oral anticoagulant use (coefficient − 14.20, 95% confidence interval [CI] -18.28 to -10.12, $P < 0.001$) and age (-0.13, 95% CI -0.19 to -0.08, $P < 0.001$) were associated with a lower nafamostat dose, whereas dry body weight (coefficient 0.15, 95% CI 0.09 to 0.22, $P < 0.001$) and hemoglobin level (1.13, 95% CI 0.51 to 1.76, $P < 0.001$) were associated with a higher dose.

Conclusion The nafamostat dosage prediction model can be used to calculate the dose required for individual patients. However, further studies for model improvement and external validation are required.

Clinical trial number Not applicable.

Keywords Anticoagulant, Dosage prediction, Hemodialysis, Nafamostat

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Introduction

Nafamostat mesylate is a synthetic serine protease inhibitor known for its potent anticoagulant activity by inhibiting enzymes, such as factors XIIa, Xa, and thrombin, in the coagulation cascade [1]. It is used in hemodialysis (HD), continuous kidney replacement therapy (CKRT), and extracorporeal membrane oxygenation (ECMO). It has also been utilized for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and has recently been studied as a potential candidate for coronavirus disease (COVID-19) treatment [2].

Nafamostat has a short half-life of approximately 5–8 min [3] and is beneficial in HD when anticoagulation cannot be discontinued despite the elevated risk of bleeding. This is particularly relevant when the risk of clotting in the extracorporeal circulation is also high. Anticoagulation therapy for HD patients at high risk of bleeding is not standardized and varies widely across countries, with nafamostat being primarily used in South Korea and Japan [4].

Excessive use of nafamostat can exacerbate bleeding lesions, increase the risk of allergic reactions, and lead to higher economic costs. Conversely, insufficient use may result in inadequate anticoagulation, making it difficult to maintain effective dialysis. The optimal dose of nafamostat as an anticoagulant has not been thoroughly investigated. Several studies have reported favorable results when comparing low-dose heparin therapy with nafamostat, administered at a dosage of 35 mg/h in Korea and Japan [5, 6] and 20–50 mg/h in China [7].

This study aimed to assess the clinical prediction models for nafamostat dosing in hemodialysis patients with bleeding risk by retrospectively collecting the data of patients who were effectively anticoagulated with nafamostat.

Methods

Data source and study population

We retrospectively analyzed the medical records from July 2023 to March 2024 across 12 centers affiliated with the Yeolin Medical Foundation, a primary care provider for HD.

Inclusion criteria were as follows: (1) patients undergoing HD with a bleeding tendency or bleeding-related condition, (2) those in a perioperative state, and (3) patients with thrombocytopenia (platelet count < 50,000/mm^3) who received nafamostat during dialysis. Cases were excluded if records on post-dialysis coagulation status were missing.

A total of 955 HD sessions from 119 patients who received nafamostat were initially screened. After excluding 536 sessions with missing coagulation data, 419 HD sessions from 104 patients were finally included in the study. Among these, 308 sessions belonged to the non-clotted group, which was used for model development (Fig. 1). The study was approved by the Public Institutional Review Board (P01-202408-01-011).

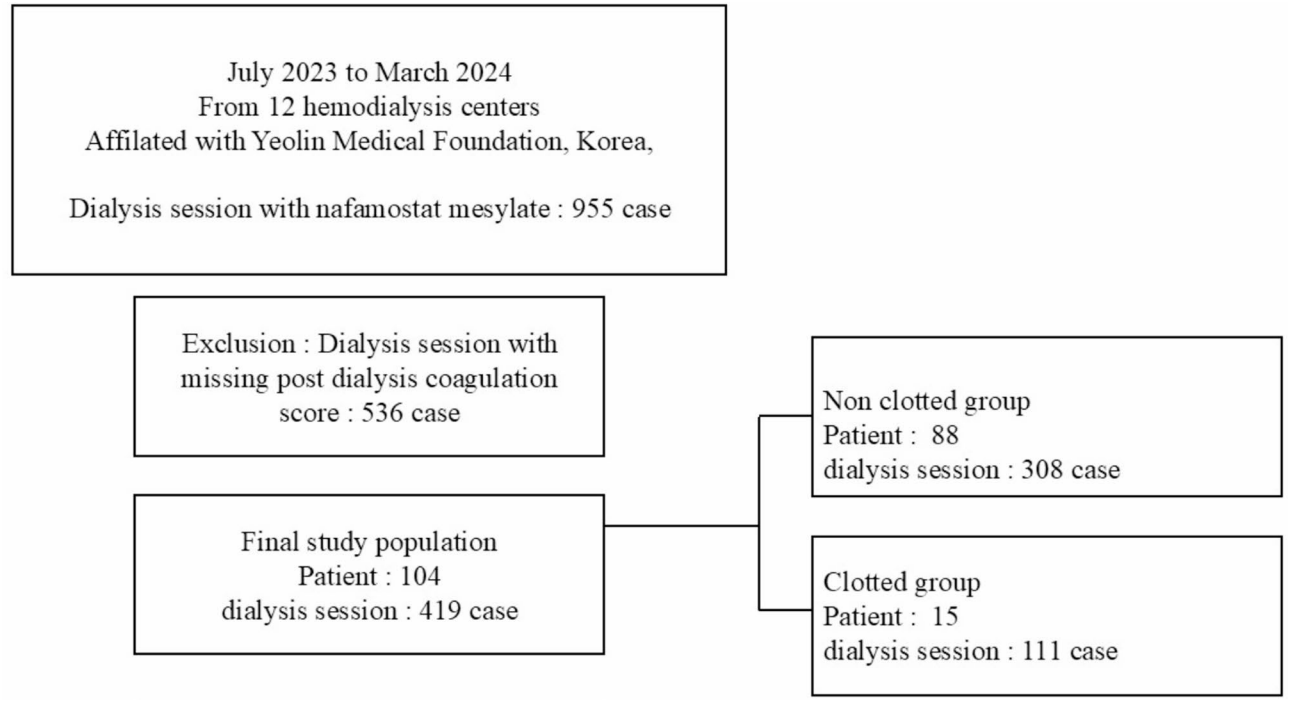

Fig. 1 Flowchart of the study population

Data collection and variables

Data on demographics, underlying medical history, medications, vascular access, laboratory tests, dialysis prescriptions, coagulation status, and hemostatic status were collected. In this study, the index date was defined as the day that the patient was prescribed nafamostat. End stage renal disease (ESRD) vintage was defined as the period from the onset of ESRD (first day of HD, peritoneal dialysis, or kidney transplantation) to the index date. Body surface area (BSA) was calculated using the Mosteller formula: square root [(height (cm) × weight (kg))/3600]. Malignancy history was categorized as no history, cured for more than 5 years, currently under treatment, cured for less than 5 years, and a hematological malignancy. Autoimmune diseases were defined as lupus nephritis or other related conditions. Laboratory test results were collected within 30 days of the index date. Heparin dose was determined as the total dose administered during dialysis in the previous session. Treatment modalities were categorized into conventional HD, pre-dilution on-line hemodiafiltration (HDF), and post-dilution on-line HDF. The collected dialysis membrane material was either polysulfone (PS) or cellulose triacetate. A delay in hemostasis was defined as a delay in hemostasis for >15 min after the end of dialysis. An oral anticoagulant agent was defined as warfarin or a non-vitamin K antagonist oral anticoagulant. Data on treatment modality and medication history of oral anticoagulant and antiplatelet agents were collected both at the index date and during a usual HD session without bleeding.

Definition of the clotted and non-clotted groups

The HD nurse visually assessed the coagulation status of the dialysis membrane and vein drip chamber at the end of each dialysis session. The clotting score was recorded as follows [8].

Clotting Score of the Membrane.

- Score 0: A clean filter.
- Score 1: Traces of coagulation present in the filter.
- Score 2: An intermediate state between previous and next scores.
- Score 3: A fully clotted extracorporeal circuit, resulting in the interruption of the HD session.

Clotting Score of the Vein Chamber.

- Score 0: No visible clots in the drip chambers.
- Score 1: Traces of coagulation in the drip chambers.
- Score 2: Visible clots present in the vein chamber.
- Score 3: Obstruction of the venous chamber.

Patients who obtained a clotting score of 2 or higher for the membrane or vein chamber were defined as the clotted group, whereas the others were defined as the non-clotted group.

Dose adjustment of Nafamostat

The nafamostat dose was determined by the attending nephrologists at each center based on their clinical experience and a comprehensive evaluation of thrombotic risk, bleeding risk, and prior response to anticoagulants.

Initial nafamostat dosing protocols across the 12 participating institutions were classified into three types: 12.5 mg/h in four centers, 25 mg/h in three centers, and a variable dose of 12.5, 25, or 37.5 mg/h depending on the patient's prior heparin use in five centers.

After the initial administration, the dose was adjusted at the clinician's discretion according to the degree of circuit clotting and bleeding observed at the end of each dialysis session.

Specifically, the dose was increased by 12.5 mg/h in the presence of excessive clotting and decreased by 12.5 mg/h when bleeding was observed.

Development of a model to predict Nafamostat dose

The dataset was randomly divided at the session level into a training set (70%) and a testing set (30%) using the hold-out method (see Supplementary Tables 1 and 2 for details). The train-test split procedure was used to assess model performance when making predictions on data that had not been used to train the model.

Multicollinearity among the candidate predictor variables was evaluated using variance inflation factors (VIFs), resulting in the selection of 16 final variables for model construction.

Feature selection was performed on the training dataset using a multivariable linear regression model. Bootstrapping was applied to ensure the model's robustness. Using resampling with replacement, we generated 10,000 bootstrap samples, each consisting of 216 cases from the training dataset, which represents 70% of the full 308-session dataset. Based on these results, multiple sets of predictor variables were selected to develop various prediction models.

Model 1: (Stepwise 99%) Oral anticoagulant + Dry body weight + Age.

Model 2: (Stepwise 97%) Model 1 + Hemoglobin + Cancer + Sex.

Model 3: (Stepwise 90%) Model 2 + Treatment modality + Membrane material.

Model 4: (Stepwise 80%) Model 3 + Ultrafiltration volume + Autoimmune disease.

Model 5: (Stepwise 70%) Model 4 + Blood flow rate + Antiplatelet agent.

Model 6: (Total) Model 5 + Membrane surface area + ESRD vintage + Heparin dose + Diabetes.

Bootstrap sampling and linear regression modeling were conducted for each model. Model performance was evaluated on training and testing datasets using lowest root mean square error (RMSE), mean absolute error (MAE), mean absolute percentage error (MAPE), and adjusted R^2. The model that showed the lowest RMSE was constructed using 12 variables that were consistently selected in at least 70% of the datasets. Further details and statistical analyses are presented in Fig. 2. Finally, the predicted nafamostat doses were calculated based on these 12 variables.

Statistical analysis

The relationships between demographic variables and clotting status were analyzed using the t-test for continuous variables after assessing normality, and the chi-square test for categorical variables. Continuous variables were expressed as the mean ± standard deviation. Categorical variables were expressed as absolute numbers and percentages. Feature selection was performed by applying bootstrapping to the training dataset, followed by stepwise multivariable linear regression on each bootstrap sample to identify consistently selected predictor variables. We calculated the predicted nafamostat dose using multivariable linear regression. To assess multicollinearity, we calculated VIFs for all predictors; as all values were below 10, we concluded that multicollinearity was not a significant issue. The statistical program R (version 4.4.1) was used for performing statistical and visualization analyses. A P value of < 0.05 was considered significant. To further explore the clinical relevance of the model, Model 5 was applied to all 419 dialysis sessions to calculate the predicted nafamostat dose. The difference between the predicted and actual doses (A – B, mg/h) was defined as underdosing. Logistic regression analysis was performed with circuit clotting as the dependent variable and A – B as the independent variable. Additionally, sessions were reclassified based on cutoff values of A – B ranging from 0 mg/h to + 5 mg/h in 1 mg/h increments. At each cutoff, logistic regression analysis was repeated under the condition of A – B > cutoff.

Results

The mean nafamostat dose in 419 dialysis sessions was 22.05 ± 6.68 mg/h, with no significant difference between the non-clotted (21.90 ± 6.82 mg/h) and clotted (22.46 ± 6.29 mg/h, $P = 0.700$) groups. The baseline characteristics of the clotted and non-clotted groups are summarized in Table 1. Compared with the patients in the non-clotted group, those in the clotted group tended to have a younger age, a higher dry body weight, higher hemoglobin levels, and higher nafamostat and heparin doses, although these differences were not significant.

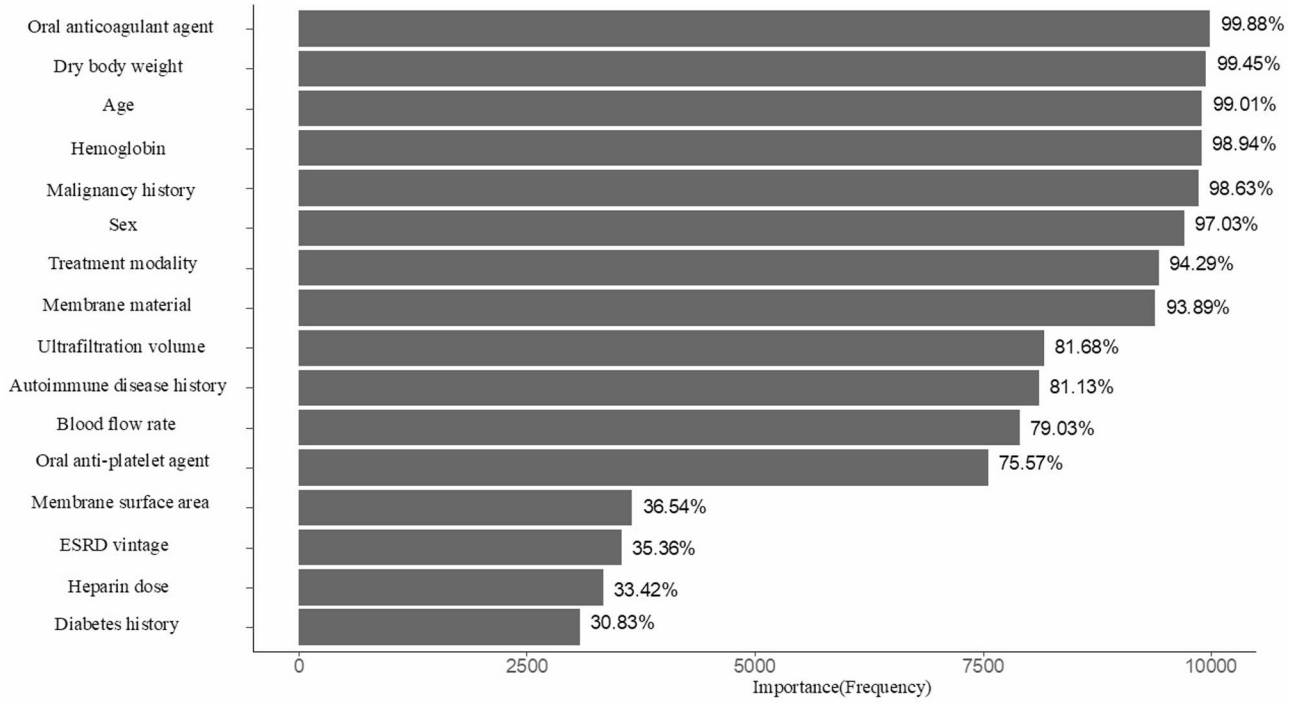

Fig. 2 Feature importance plot (stepwise bootstrap). Using resampling with replacement, we generated 10,000 bootstrap samples, each consisting of 216 cases from the training dataset. For each sample, we trained a stepwise multivariable regression model and recorded how frequently each variable was selected across all 10,000 models. The labels on the y-axis indicate the variable names. The x-axis shows the selection frequency (%). Estimates for predictors such as autoimmune disease history and membrane material are based on small sample sizes and should therefore be interpreted with caution

Table 1 Baseline characteristics of the patients in the non-clotted and clotted groups

Variable	Total	Non-clotted group	Clotted group	*P*-value
	Mean ± SD/ *N*(%)	Mean ± SD/ *N*(%)	Mean ± SD/ *N*(%)	
Sample size, N	419	308	111	
Age, years	59.24 ± 13.91	59.79 ± 14.37	57.71 ± 12.46	0.257
Sex				0.238
Male	165 (39.38%)	127 (41.23%)	38 (34.23%)	
Female	254 (60.62%)	181 (58.77%)	73 (65.77%)	
Body surface area, m^2	1.71 ± 0.21	1.69 ± 0.20	1.74 ± 0.23	0.070
ESRD vintage, years	6.31 ± 7.64	6.43 ± 7.73	5.98 ± 7.39	0.844
Nafamostat dose, mg/h	22.05 ± 6.68	21.90 ± 6.82	22.46 ± 6.29	0.700
Heparin dose, $IU/10^3$	2.78 ± 1.00	2.77 ± 1.00	2.81 ± 1.01	0.817
Ultrafiltration volume, L	2.19 ± 1.13	2.18 ± 1.07	2.22 ± 1.30	0.978
Dry body weight. kg	64.57 ± 14.16	63.61 ± 13.20	67.24 ± 16.30	0.068
Blood flow rate, mL/min	261.00 ± 47.53	261.49 ± 46.70	259.64 ± 49.94	0.826
Dialysate flow rate, mL/min	482.10 ± 68.40	483.44 ± 64.21	478.38 ± 79.09	0.663
Membrane surface area, m^2	1.68 ± 0.34	1.67 ± 0.33	1.70 ± 0.37	0.291
Hemoglobin, g/dL	10.03 ± 1.18	9.99 ± 1.21	10.15 ± 1.08	0.108
Platelet count, $10^3/\mu L$	217.44 ± 85.97	215.92 ± 87.01	221.70 ± 83.24	0.392
C-reactive protein, mg/dL	1.34 ± 2.06	1.23 ± 1.96	1.63 ± 2.30	0.169
No delayed hemostasis	382 (91.17%)	283 (91.88%)	99 (89.19%)	0.274
Hemostasis delayed	21 (5.01%)	16 (5.19%)	5 (4.50%)	
Missing data	16 (3.82%)	9 (2.92%)	7 (6.31%)	
Membrane clot score				< 0.001
0	186 (44.39%)	178 (57.79%)	8 (7.21%)	
1	170 (40.57%)	130 (42.21%)	40 (36.04%)	
2	57 (13.60%)	0 (0.0%)	57 (51.35%)	
3	6 (1.43%)	0 (0.0%)	6 (5.41%)	
Vein chamber clot score				< 0.001
0	222 (52.98%)	199 (64.61%)	23 (20.72%)	
1	129 (30.79%)	109 (35.39%)	20 (18.02%)	
2	60 (14.32%)	0 (0.0%)	60 (54.05%)	
3	8 (1.91%)	0 (0.0%)	8 (7.21%)	
Vascular access type				0.752
Arteriovenous fistula	302 (72.08%)	222 (72.08%)	80 (72.07%)	
Arteriovenous graft	110 (26.25%)	80 (25.97%)	30 (27.03%)	
Permanent cuffed tunneled catheter	7 (1.67%)	6 (1.95%)	1 (0.90%)	
Treatment modality				0.847
Conventional HD	290 (69.21%)	214 (69.48%)	76 (68.47%)	
Pre-dilution on-line HDF	29 (6.92%)	20 (6.49%)	9 (8.11%)	
Post-dilution on-line HDF	100 (23.87%)	74 (24.03%)	26 (23.42%)	
Membrane material				0.405
Polysulfone	409 (97.61%)	299 (97.08%)	110 (99.10%)	
Cellulose triacetate	10 (2.39%)	9 (2.92%)	1 (0.90%)	
Diabetes history	150 (35.80%)	116 (37.66%)	34 (30.63%)	0.226
Malignancy history				0.179
No medical history	373 (89.02%)	272 (88.31%)	101 (90.99%)	
Cured for more than 5 years	9 (2.15%)	9 (2.92%)	0 (0.0%)	
Under 5 years or in treatment	21 (5.01%)	17 (5.52%)	4 (3.60%)	
Hematological malignancy	16 (3.82%)	10 (3.25%)	6 (5.41%)	
Autoimmune disease				0.046
None	400 (95.47%)	294 (95.45%)	106 (95.50%)	
Lupus nephritis	15 (3.58%)	13 (4.22%)	2 (1.80%)	
Thrombotic Microangiopathy	4 (0.95%)	1 (0.32%)	3 (2.70%)	

Table 1 (continued)

Variable	Total	Non-clotted group	Clotted group	*P*-value
	Mean ± SD/ *N*(%)	Mean ± SD/ *N*(%)	Mean ± SD/ *N*(%)	
Antiplatelet agent	151 (36.04%)	109 (35.39%)	42 (37.84%)	0.730
Oral anticoagulant agent	9 (2.15%)	8 (2.60%)	1 (0.90%)	0.500

SD, standard deviation; ESRD, end stage renal disease; HD, hemodialysis; HDF, hemodiafiltration

Data are expressed as mean ± SD for continuous variables or N (%) for categorical variables. P-values were calculated using t-tests or chi-square tests, as appropriate. The P-value for hemostasis status (0.274) reflects a comparison across three categories. Clot score P-values (< 0.001) are based on group-defining variables. The autoimmune disease P-value (0.046) should be interpreted with caution due to small sample sizes

Table 2 Metrics for each model

Model	Train RMSE	Train MAE	Train MAPE	Adjusted R^2	Test RMSE	Test MAE	Test MAPE
Model 5	4.70 (4.66, 4.74)	3.33 (3.30, 3.36)	0.18 (0.17, 0.18)	0.49 (0.49, 0.50)	4.11 (4.06, 4.15)	3.07 (3.02, 3.12)	0.18 (0.17, 0.18)
Model 6	4.63 (4.59, 4.67)	3.27 (3.24, 3.31)	0.17 (0.17, 0.17)	0.50 (0.49, 0.51)	4.19 (4.13, 4.24)	3.11 (3.06, 3.17)	0.18 (0.18, 0.18)
Model 4	4.89 (4.85, 4.93)	3.47 (3.44, 3.50)	0.19 (0.18, 0.19)	0.46 (0.45, 0.46)	4.36 (4.33, 4.40)	3.39 (3.36, 3.42)	0.20 (0.20, 0.20)
Model 3	5.21 (5.17, 5.24)	3.97 (3.94, 4.00)	0.21 (0.21, 0.21)	0.39 (0.38, 0.40)	4.77 (4.73, 4.81)	3.61 (3.57, 3.65)	0.22 (0.22, 0.23)
Model 2	5.35 (5.32, 5.39)	4.13 (4.10, 4.16)	0.22 (0.22, 0.23)	0.37 (0.36, 0.37)	4.82 (4.78, 4.85)	3.72 (3.69, 3.75)	0.23 (0.23, 0.23)
Model 1	5.82 (5.78, 5.85)	4.55 (4.52, 4.58)	0.25 (0.25, 0.25)	0.27 (0.26, 0.27)	5.40 (5.38, 5.42)	4.10 (4.08, 4.12)	0.26 (0.26, 0.26)

Bootstrapping was used to calculate the metrics, presented as mean (95% CI)

Model 1: (Stepwise 99%) Oral anticoagulant + Dry body weight + Age

Model 2: (Stepwise 97%) Model 1 + Hemoglobin + Cancer + Sex

Model 3: (Stepwise 90%) Model 2 + Treatment modality + Membrane material

Model 4: (Stepwise 80%) Model 3 + Ultrafiltration volume + Autoimmune disease

Model 5: (Stepwise 70%) Model 4 + Blood Flow rate + Antiplatelet agent

Model 6: (Total) Model 5 + Membrane surface area + ESRD vintage + Heparin dose + Diabetes

RMSE, root mean squared error; MAE, mean absolute error; MAPE, mean absolute percentage error; CI, confidence interval; ESRD, end stage renal disease

Only the history of autoimmune disease showed a significant difference between the two groups.

Candidate predictor variables and feature importance selection

Among the collected variables, vascular access, dialysate flow rate, and BSA were excluded due to multicollinearity. C-reactive protein levels and platelet counts were excluded due to missing data. When variables were available for both the index date and the usual date without bleeding, the index date was selected for analysis based on relevance to the treatment session.

Feature selection was performed to evaluate the importance of the 16 candidate predictor variables (Fig. 2). Oral anticoagulant use was the most important predictor variable, appearing in 99.88% of the models. Oral anticoagulant agents, dry body weight, and age were included in more than 99% of the models, whereas hemoglobin, malignancy history, and sex were included in more than 95% of the models. The proportion of models that included the 12 variables appearing in at least 70% of the models is shown.

The performance of six models was evaluated using standard regression metrics: RMSE, MAE, MAPE, and adjusted R^2, as presented in Table 2. Model 5, which included 12 variables (Stepwise ≥ 70%), was identified as the top-performing model. It demonstrated the best predictive performance, with an adjusted R^2 of 0.49 (95% CI: 0.49–0.50) in the training dataset. In the test dataset, the RMSE was 4.11 mg/h (95% CI: 4.06–4.15), indicating that the average prediction error between the model estimates and the actual nafamostat dosage was 4.11 mg/h. This corresponds to approximately 12% of the standard empirical dose of 35 mg/h. The MAE was 3.07 mg/h (95% CI: 3.02–3.12), and the MAPE was 18% (95% CI: 17–18%).

Table 3 summarizes the results of the multivariable linear regression analysis for nafamostat dose prediction using Model 5. A total of 12 variables were significantly associated with nafamostat dose, with six showing negative and six showing positive associations. Table 4 provides the corresponding calculation formula for nafamostat dose prediction.

Variables associated with a lower predicted dose included:

- Oral anticoagulant use (– 14.20, 95% CI – 18.28 to – 10.12, $P < 0.001$),
- Malignancy history (under 5 years or in treatment) (– 3.92, 95% CI – 6.91 to – 0.94, $P = 0.010$),
- Age (– 0.13 per year, 95% CI – 0.19 to – 0.08, $P < 0.001$),
- Cellulose triacetate membrane (vs. polysulfone: –6.23, 95% CI – 10.20 to – 2.27, $P = 0.002$),
- Female sex (– 3.17, 95% CI – 4.89 to – 1.45, $P < 0.001$),

Table 3 Linear regression analysis of the relationship between predictor variables and Nafamostat dose with training dataset

	Univariable		Multivariable, Model 5	
Variable	**Coefficient (95% CI)**	***P*-value**	**Coefficient (95% CI)**	***P*-value**
Oral anticoagulant agent	-12.02 (-17.00, -7.03)	< 0.001	-14.20 (-18.28, -10.12)	< 0.001
Dry body weight, kg	0.11 (0.05, 0.18)	< 0.001	0.15 (0.09, 0.22)	< 0.001
Age, years	-0.20 (-0.25, -0.14)	< 0.001	-0.13 (-0.19, -0.08)	< 0.001
Hemoglobin, g/dL	0.99 (0.27, 1.71)	0.008	1.13 (0.51, 1.76)	< 0.001
Malignancy history				
No medical history	reference		reference	
Cured for more than 5 years	-3.46 (-8.92, 2.00)	0.214	-3.20 (-7.44, 1.05)	0.139
Under 5 years or in treatment	-5.25 (-8.89, -1.60)	0.005	-3.92 (-6.91, -0.94)	0.010
Hematological malignancy	5.57 (1.08, 10.06)	0.015	7.72 (3.45, 12.00)	< 0.001
Sex				
Male	reference		reference	
Female	-2.38 (-4.14, -0.63)	0.008	-3.17 (-4.89, -1.45)	< 0.001
Treatment modality				
HD	reference		reference	
Pre-dilution on-line HDF	2.47 (-1.03, 5.97)	0.165	4.47 (1.65, 7.28)	0.002
Post-dilution on-line HDF	2.83 (0.87, 4.79)	0.005	2.56 (0.71, 4.41)	0.007
Membrane material				
Polysulfone	reference		reference	
Cellulose triacetate	-0.63 (-5.51, 4.26)	0.801	-6.23 (-10.20, -2.27)	0.002
Ultrafiltration volume, L	-0.78 (-1.60, 0.04)	0.061	-1.11 (-1.95, -0.27)	0.010
Autoimmune disease				
No medical history	reference		reference	
Lupus nephritis	3.48 (-0.89, 7.85)	0.118	4.22 (0.91, 7.52)	0.013
TMA	3.12 (-10.44, 16.69)	0.650	3.74 (-6.37, 13.85)	0.467
Blood flow rate, mL/min	0.01 (-0.01, 0.03)	0.241	-0.03 (-0.05, -0.01)	0.018
Antiplatelet agent	3.41 (1.67, 5.16)	< 0.001	1.69 (0.13, 3.26)	0.034
Membrane surface area, m^2	1.97 (-0.66, 4.60)	0.142		
ESRD vintage, years	-0.18 (-0.29, -0.07)	< 0.001		
Heparin dose, IU/10^3	1.95 (1.12, 2.78)	< 0.001		
Diabetes history	0.42 (-1.35, 2.19)	0.641		

Results of other models' multivariable regression analyses are provided (see Supplementary Table 3 for details). Estimates for lupus nephritis and cellulose triacetate membrane subgroups are based on small sample sizes and should be interpreted with caution

CI, confidence interval; HD, hemodialysis; HDF, hemodiafiltration; TMA, thrombotic microangiopathy; ESRD, end stage renal disease; DM, diabetes mellitus

- Ultrafiltration volume (– 1.11 per L, 95% CI – 1.95 to – 0.27, $P = 0.010$).

Variables associated with a higher predicted dose included:

- Dry body weight (0.15 per kg, 95% CI 0.09 to 0.22, $P < 0.001$),
- Hemoglobin (1.13 per g/dL, 95% CI 0.51 to 1.76, $P < 0.001$),
- Hematological malignancy (7.72, 95% CI 3.45 to 12.00, $P < 0.001$),
- Treatment modality (pre-dilution on-line HDF: 4.47, 95% CI 1.65 to 7.28, $P = 0.002$; post-dilution on-line HDF: 2.56, 95% CI 0.71 to 4.41, $P = 0.007$),
- Lupus nephritis (4.22, 95% CI 0.91 to 7.52, $P = 0.013$),
- Antiplatelet agent use (1.69, 95% CI 0.13 to 3.26, $P = 0.034$).

In univariate analysis, both ESRD vintage and heparin dose were significantly associated with nafamostat dosage. ESRD vintage was negatively associated (– 0.18 per year, 95% CI – 0.29 to – 0.07, $P < 0.001$), and higher heparin dose was positively associated (1.95 per 1,000 IU, 95% CI 1.12 to 2.78, $P < 0.001$). However, in the full multivariable model including all candidate variables (Model 6; see Supplementary Table 3 for details), neither variable remained significant (ESRD vintage: –0.00, 95% CI – 0.13 to 0.13, $P = 0.995$; heparin dose: –0.08, 95% CI – 1.04 to 0.88, $P = 0.864$).

To evaluate the association between underdosing (A – B, mg/h; A = predicted dose, B = actual dose) and circuit clotting, logistic regression analysis was performed using all 419 dialysis sessions. The results showed a trend toward increased clotting risk with greater underdosing, although the association was not statistically significant (odds ratio = 1.036, $\beta = +0.0362$, $P = 0.075$).

Table 4 Nafamostat dose prediction model using model 5

Data for calculations			Example
Coefficients and mean values			Obtain the linear predictor: Σ(X · Coefficient)
Values	Coefficients	Test data	
(Intercept)	20.047	1	20.047
Oral anticoagulant agent			
No	0	1	0
Yes	-14.202	0	0
Dry body weight, kg	0.151	60	9.06
Age, years	-0.134	50	-6.7
Hemoglobin, g/dL	1.134	10	11.34
Malignancy history			
No medical history	0	1	0
Cured for more than 5 years	-3.196	0	0
Under 5 years or in treatment	-3.924	0	0
Hematological malignancy	7.723	0	0
Sex			
Male	0	0	0
Female	-3.174	1	-3.174
Treatment modality			
HD	0	1	0
Pre-dilution on-line HDF	4.466	0	0
Post-dilution on-line HDF	2.562	0	0
Membrane material			
Polysulfone	0	1	0
Cellulose triacetate	-6.234	0	0
Ultrafiltration volume, L	-1.108	2.5	-2.77
Autoimmune disease			
No medical history	0	1	0
Lupus nephritis	4.216	0	0
Thrombotic microangiopathy	3.74	0	0
Blood flow rate, mL/min	-0.03	250	-7.5
Antiplatelet agent			
No	0	1	0
Yes	1.694	0	0
Nafamostat mg/h			20.303

By entering the patient's characteristics in the test data field, the expected nafamostat dosage can be calculated

A 50-year-old female patient's virtual data was used as an example

HD, hemodialysis; HDF, hemodiafiltration

In an additional analysis using cutoff values, the risk of circuit clotting was significantly increased in the higher underdosing ranges (A – B > + 2 mg/h; see Supplementary Tables 4 and Supplementary Fig. 1 for details).

Discussion

Anticoagulation is essential during HD to prevent clotting in the extracorporeal circuit. Intravenous unfractionated heparin is commonly administered during HD in patients who are not at heightened risk of bleeding or heparin allergies. In patients with a high risk of bleeding, systemic anticoagulation is often contraindicated, necessitating alternative strategies, such as maintaining a high blood flow rate, intermittent saline flushing, reducing dialysis duration, or using heparin-coated dialyzers.

Nevertheless, in patients who are at a high risk of both bleeding and extracorporeal circuit clotting, these measures alone may not ensure adequate dialysis. Although no standardized approach exists for such cases, several alternative anticoagulation methods have been proposed, including low-dose heparin, sodium citrate-containing dialysate, epoprostenol, and regional citrate anticoagulation. Among them, nafamostat is a widely used alternative anticoagulant in South Korea and Japan.

In the 2021 Korean Society of Nephrology hemodialysis guidelines, nafamostat is conditionally recommended (Grade B) as an alternative to heparin for anticoagulation in patients undergoing HD at high risk of bleeding [4]. However, the guidelines also state that the level of

evidence supporting this recommendation is low owing to the lack of large-scale randomized trials.

Nafamostat has been investigated as an anticoagulant during HD in patients at a high risk of bleeding since the 1980s. However, in the absence of randomized controlled trials, no established guidelines exist for optimal dosing. According to the approved drug labeling, nafamostat is administered at 20–50 mg/h, with dose adjustments made based on clinical symptoms. Clinical data suggest an average dose of 35 mg/h.

The findings of a few previous studies examining nafamostat dosing during HD are summarized as follows.

Akizawa et al. [5] evaluated nafamostat dose adjustments in 107 patients at high risk of bleeding based on residual blood clotting in the dialyzer and clot formation in the drip chamber of the extracorporeal circuit. They reported an optimal dose of 34.2 ± 1.2 mg/h and recommended a dose range of 20–50 mg/h. Yang et al. [6] conducted a study in patients with intracerebral hemorrhage, comparing nafamostat at 35 mg/h with a low-dose heparin regimen (1,000/200). This study reported better hematoma outcomes in the nafamostat group. Kim et al. [9] compared nafamostat at a dose of 35 mg/h with low-dose heparin therapy (1,000/500) as a control. Their findings indicated less bleeding and reduced extracorporeal circuit clotting in the nafamostat group versus the control group, whereas no significant difference was found in hemostasis between the two groups. Kim et al. [10] investigated a low-dose nafamostat regimen (12.5 mg/h) and compared it with an intermittent saline flushing protocol. Their results showed no significant intergroup difference in bleeding incidence but a significant reduction in extracorporeal circuit clotting in the nafamostat group.

In the present study, the mean nafamostat dose across 419 dialysis sessions was 22.05 ± 6.68 mg/h, which was generally lower than the doses reported in previous studies. However, clotting severe enough to interrupt dialysis occurred in only 10 sessions (2%).

In our analysis, the top four variables that significantly influenced nafamostat dosage were oral anticoagulant use, dry body weight, age, and hemoglobin level. Among these, oral anticoagulant use had the strongest impact as an independent factor, serving as a significant dose-reducing variable for nafamostat (coefficient: −14.20, 95% CI − 18.28 to − 10.12, $P < 0.001$). Dose adjustments for heparin or low-molecular-weight heparin (LMWH) have been explored in several small-scale studies involving patients undergoing HD receiving oral anticoagulants. Under certain conditions, some studies have suggested that HD can be performed without additional heparin when using standard oral anticoagulants with an international normalized ratio of 2–3 [11]. Other studies proposed that heparin or LMWH dosing should be reduced to less than 50% of the standard dose in patients receiving oral anticoagulants [12]. The European Best Practice Guidelines recommend individualized heparin dose reduction in patients taking oral anticoagulants to ensure that a minimal effective dose is required to prevent thrombosis [13].

This study aimed to develop a predictive model rather than to establish causal relationships; therefore, the regression coefficients should be interpreted as statistical associations rather than causal effects. Nevertheless, several variables may provide clinical insights, and further studies are needed to validate these associations.

The coefficient for dry body weight was 0.15 (95% CI: 0.09 to 0.22, $P < 0.001$), indicating that each 10-kg increase in dry body weight corresponded to a 1.51-mg/h increase in nafamostat dosage. Although nafamostat has traditionally been prescribed based on hourly dosing (mg/h), a weight-based approach (mg/kg/h) could potentially better reflect its pharmacologic effects. Weight-based dosing (mg/kg/h) has been increasingly adopted in recent studies involving extracorporeal therapies such as continuous kidney replacement therapy and extracorporeal membrane oxygenation, as well as in pharmacokinetic investigations and clinical trials for COVID-19 therapies. In contrast, there is a lack of evidence supporting the application of mg/kg/h dosing for nafamostat in hemodialysis patients. To date, all previous studies have employed dosing in mg/h units [5–7, 9, 10], and this approach is also reflected in the drug's approved labeling in South Korea. Nonetheless, body weight is widely regarded as a clinically relevant determinant of drug dosing. In the present study, dry body weight exhibited high importance in the feature importance plot and was significantly and positively associated with nafamostat dosage. It was therefore included in the final prediction model. These findings suggest the potential utility of developing weight-based dosing strategies in future clinical practice. A weight-based dosing model (mg/kg/h) was developed by modifying Model 5 to account for dry body weight. The model demonstrated an adjusted R^2 of 0.53, RMSE of 0.07 mg/kg/h, MAE of 0.05 mg/kg/h, and MAPE of 19%, and is presented (see Supplementary Tables 5 and 6 for details).

Age was a dose-reducing factor (coefficient: −0.13, 95% CI: −0.19 to −0.08, $P < 0.001$). According to Model 5, a 10-year increase in age was associated with a 1.34 mg/h reduction in the predicted nafamostat dosage. The study participants ranged in age from 25 to 93 years.

Although age was a key variable in the model, the underlying mechanisms remain unclear. One possible explanation is that clinicians may have prescribed lower doses for older patients due to concerns about bleeding risk. Another explanation is that age-related physiological changes may enhance the pharmacologic effect of nafamostat. Aging is associated with changes in body

composition, such as reduced muscle mass and total body water and increased body fat, which can lead to a decreased volume of distribution for hydrophilic drugs. Nafamostat, being hydrophilic, may show elevated plasma concentrations as a result [14]. Another potential mechanism is that age-related declines in paraoxonase-1 (PON1) activity may slow nafamostat metabolism and prolong its duration of action. PON1 is a representative plasma arylesterase and is commonly used as the reference enzyme in arylesterase activity assays [15]. Nafamostat is primarily metabolized by arylesterases in the blood and by carboxylesterase 2 in the liver [16]. These mechanisms suggest that older patients may achieve adequate anticoagulation with lower doses of nafamostat, supporting the consideration of age-adjusted individualized dosing in clinical practice.

Among the top predictors of nafamostat dosage, hemoglobin level ranked fourth in the importance plot. In Model 5, hemoglobin level had a coefficient of 1.13 (95% CI: 0.51 to 1.76, $P < 0.001$); that is, the model estimated a 1.13 mg/h increase in nafamostat dose for each 1-g/dL increase in hemoglobin level. This finding may be interpreted in light of previous reports indicating that erythropoietin use increases hemoglobin and hematocrit levels, potentially necessitating higher anticoagulant doses to prevent circuit clotting [13, 17].

In addition to these key predictors, there are variables with relatively lower importance in the model that require interpretation and discussion. The adsorption properties of nafamostat may also play an important role in dose determination depending on the type of dialysis membrane used. Nafamostat, which carries a positive charge owing to its amidine and guanidine groups, exhibits greater adsorption onto negatively charged membrane materials, such as polyacrylonitrile and polyester-polymer alloy dialyzers, than onto uncharged PS membranes [18]. The membrane materials used in this study were polysulfone (PS; FX series, Fresenius Medical Care, Germany) and symmetric cellulose triacetate (CTA; SUREFLUX, Nipro Corporation, Osaka, Japan), both of which exhibited minimal nafamostat adsorption. A previous study on nafamostat adsorption in AN69ST membranes found minimal nafamostat adsorption in PS membranes, whereas no adsorption was observed in CTA membranes [19]. In the current study, the nafamostat dosage tended to be lower with the use of CTA membranes than with the use of PS membranes. However, this finding was based on a small subgroup ($n = 10$), and the estimates may therefore be unstable and should be interpreted with caution.

In the predictive model, a history of lupus nephritis increased the nafamostat dose by 4.216 mg/h. Systemic lupus erythematosus is generally known to be a prothrombotic condition, and anticoagulant therapy may be necessary particularly in cases complicated by antiphospholipid syndrome [20]. There is currently no evidence to suggest that higher doses of anticoagulants are required during hemodialysis in patients with lupus nephritis. According to Table 1 of this study, among the 15 dialysis sessions involving patients with a history of lupus nephritis, 13 sessions were classified into the non-clotted group and only 2 sessions into the clotted group, suggesting a higher frequency of non-clotted outcomes. No abnormalities were observed in platelet counts in this group. The mean nafamostat dose in the lupus nephritis group ($n = 15$) was 23.81 ± 7.32 mg/h, which was higher than that in the non-lupus nephritis group ($n = 404$), 21.98 ± 6.66 mg/h; however, the difference was not statistically significant ($p = 0.242$, Mann–Whitney U test). This distribution is likely attributable to chance, given the small number of cases, and the effect estimate should therefore be interpreted with caution.

In this study, nafamostat was predicted to be administered at a higher dose during pre-dilution on-line HDF than during post-dilution on-line HDF, and this was also reflected in the predictive model (coefficient 4.466 vs. 2.562). This finding contrasts with the conventional understanding that pre-dilution on-line HDF reduces the risk of clotting by lowering the solute concentration. Several potential explanations may account for this observation. First, due to the retrospective nature of the study, confounding by physicians' empiric prescription adjustments may have occurred. For instance, in patients with a prothrombotic tendency who experienced bleeding, physicians may have switched to pre-dilution on-line HDF from post-dilution on-line HDF, even while using high-dose nafamostat, due to persistent concerns about clotting. Second, since this was not a within-patient comparison, the difference may reflect baseline characteristics of the patient groups rather than the dialysis modality. Pre-dilution on-line HDF is often preferred in patients who cannot tolerate high blood flow rates or who have a prothrombotic tendency. Finally, the infusion of replacement fluid in pre-dilution on-line HDF may have diluted the plasma concentration of nafamostat, thereby reducing its anticoagulant effect. Due to its short half-life, nafamostat may be more sensitive to such reductions than heparin.

The selection of predictor variables for model development was based on previous studies and clinical knowledge. Candidate variables were selected using a combination of bootstrapping and stepwise regression. While stepwise regression allows for the development of a more efficient model with fewer predictors, it can introduce optimism, particularly when the sample size is small [21].

In medical research, rare conditions often lead to variables with limited data being included in the model. For

this reason, bootstrapping was employed to enhance the robustness of the selection process [22]. To assess the goodness-of-fit of the clinical prediction model, adjusted R^2, RMSE, MAE, and MAPE were used. Adjusted R^2 reflects the model's fit in regression analysis and increases only when a meaningful variable is added, thereby helping to avoid overfitting. RMSE was defined as the square root of the mean of the squared differences between the observed and predicted values, reflecting the average magnitude of prediction error.

Model 5 had an adjusted R^2 of 0.49, an RMSE of 4.11 mg/h, and a MAPE of 18%, indicating a moderate level of predictive performance. Because training and evaluation were performed at the session level, different sessions from the same patient may appear across splits, yielding slightly optimistic performance compared with a patient-independent split. In routine practice, nafamostat dosing is usually adjusted in increments of 12.5 mg/h. Therefore, an error margin of approximately 4 mg/h may be considered clinically acceptable, as it is smaller than this adjustment step used in empiric physician-based dosing. This model may provide quantitative and evidence-based support for clinicians' dosing decisions.

This study has several limitations related to its design and data characteristics.

First, sessions with missing coagulation assessments were excluded, which may have introduced a selection bias. In addition, several potentially influential variables—including smoking history, prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, and inflammatory markers—were not assessed or were excluded due to missing data, which may have affected the predictive accuracy of the model. Among them, for platelet count, a subgroup analysis excluding missing values showed no significant association in the univariable analysis ($P = 0.167$), and its feature importance was low (37.28%).

Second, due to the small sample size, the use of a bootstrapping method may have led to an overestimation of infrequently observed variables, such as cellulose triacetate membranes, autoimmune disease history, and oral anticoagulant use. Accordingly, the estimated effects of these variables should be interpreted with caution.

Third, the model did not account for the repeated-measures structure of the dataset, which limits causal interpretation of the associations between individual variables and nafamostat dosage. Future studies could address this limitation by employing mixed-effects models or similar approaches to account for within-patient correlation.

Fourth, there is a potential for residual confounding. For instance, clinicians may have prescribed lower nafamostat doses when antiplatelet agents were used concurrently, or higher doses during hemodiafiltration. In the final model, antiplatelet agent use was associated with an increased predicted nafamostat dose. While this finding was unexpected, interpretation is limited by the fact that only the presence or absence of antiplatelet agent use was recorded, without detailed information on drug type or dosage.

Finally, the current prediction model represents an initial version that requires further refinement and external validation to assess its generalizability and clinical applicability. This step is critical for evaluating whether the model performs consistently across different institutions and patient populations. The model was developed using data from 12 centers within a single country and was internally validated using various methods but has not yet been tested externally. Given the substantial variability in dialyzer membranes and dialysis modalities across countries and institutions, these findings should be interpreted with caution before broader application. Future studies should aim to validate the model using independent external cohorts, such as data from hemodialysis patients in other countries or from additional institutions within the same country, to evaluate the model's generalizability and clinical utility.

Despite these limitations, nafamostat dosing has largely relied on empirical judgment to date, with limited availability of quantitative criteria. This study presents a preliminary model that incorporates various clinical characteristics to predict nafamostat dosage, providing a tool that may help clinicians estimate appropriate doses based on individual patient profiles.

Although its predictive accuracy is modest, it holds clinical relevance as a practical tool to support physician decision-making, particularly in a setting where standardized dosing guidelines are lacking.

Importantly, this study utilized real-world data from multiple centers and provided novel insights into clinical factors—such as oral anticoagulant use, age, dry body weight, and hemoglobin level—that have been considered influential in anticoagulation management. However, their influence on nafamostat use has not been previously investigated.

In conclusion, we developed an early-stage model for predicting nafamostat dosage in hemodialysis patients at high risk of bleeding. While the model demonstrated relatively limited predictive performance, it showed the potential to support individualized dosing strategies based on real-world clinical data.

Future research should focus on improving the model's accuracy through external validation and prospective studies, as well as evaluating its applicability across broader patient populations. Ultimately, this approach may contribute to safer and more effective anticoagulation strategies in hemodialysis practice.

Supplementary Information

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Supplementary Material 1

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Data availability
The datasets generated during the current study are available from thecorresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Bioethics and Safety Act of the Republic of Korea. The study was approved by the Public Institutional Review Board of the Republic of Korea (Approval No. P01-202408-01-011). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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