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One-Year Risk of Bleeding in Patients on a Stable Warfarin Dose After Prosthetic Heart Valve Surgery

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ABSTRACT

Purpose: Anticoagulation therapy is required to prevent thromboembolic complications in patients with heart valve surgery (HVS). However, caution must be taken due to the risk of bleeding. This study aimed to identify bleeding risk factors in patients with stable warfarin therapy and develop a predictive tool for high-risk patients.

Methods: This study is a nested case-control design using the Korean National Health Insurance Service-National Sample Cohort Data. We identified patients who underwent HVS and were prescribed warfarin within 1 week after the procedure. Of these, patients with the last two identical warfarin prescriptions within 6 months before the bleeding events were defined as the case group, while patients with no bleeding events within 6 months after HVS and two consecutive identical warfarin prescriptions were defined as the control group. Three machine learning models—logistic regression, support vector machine, and random forest—were trained and scored by fivefold validation to validate our feature selection processes. We developed a risk scoring system using adjusted odds ratios from multivariate logistic regression.

Results: Of 1 137 861 subjects, 1093 patients were eligible for the study cohort; 173 and 298 were selected as the case and control groups, respectively. After a series of machine learning processes, eight features were identified as significant risk factors for bleeding events.

Conclusion: Our finding suggests that furosemide, spironolactone, lacrimal system disorders, ursodeoxycholic acid, captopril, chronic kidney disease, zolpidem, and valsartan are the most important features for predicting bleeding events in patients taking a stable warfarin dose after HVS.

1 | Introduction

Valvular heart disease (VHD) is a significant and prevalent medical condition that affects more than 100 million people worldwide and is related to substantial morbidity and mortality [1]. VHD is a pathologic condition of heart valves that leads to either stenosis or regurgitation, eventually developing into heart failure [2]. VHD is often treated with heart valve surgery (HVS),

including valvuloplasty and valve replacement, to maintain adequate hemodynamics and prevent further cardiac disease [2]. According to the ACC/AHA guidelines, warfarin therapy is recommended for patients who have undergone valve replacement surgery with mechanical prosthetic valves [3]. To prevent disabling or fatal stroke caused by thrombosis, short- or long-term anticoagulation therapy is needed after prosthetic valve replacement [4]. However, the use of warfarin does come with potential

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Summary

- Warfarin therapy is required in patients undergoing heart valve surgery. However, bleeding complications cannot be prevented with traditional INR monitoring.
- Through a machine learning approach including 1341 variables, risk factors for bleeding in patients with stable warfarin therapy were disorders of the lacrimal system and chronic kidney disease.
- Comedications including furosemide, spironolactone, ursodeoxycholic acid, captopril, zolpidem, and valsartan were associated with a decreased risk of bleeding events.
- The scoring system we developed incorporates important features that can help identify patients at high risk of bleeding events and provide them with individualized care.

risks, including an increased risk of bleeding. Therefore, the ACC/AHA guidelines recommend carefully monitoring patients receiving warfarin therapy, with regular measurement of their International Normalized Ratio (INR) levels, to ensure they are within the target range [3, 5].

Anticoagulant therapy is commonly associated with bleeding events, leading to significant morbidity and mortality if not carefully monitored [6]. The risk of bleeding events is often highest during the beginning of therapy due to unstable INR, but factors contributing to bleeding events after INR stabilization remain unclear. The HAS-BLED bleeding risk prediction tool was developed based on data from the Euro Heart Survey to predict bleeding risk before initiating anticoagulant therapy in patients with atrial fibrillation [7]. However, studies have rarely been reported on patients taking stable doses of warfarin, and there are currently no guidelines for managing patients with stable INR [8, 9]. Several studies suggest that bleeding complications, including gastrointestinal bleeding and intracranial hemorrhage, are higher in Asian than in Caucasian patients [10–13]. Also, Asian patients show a much lower proportion of time in therapeutic range when taking warfarin than suggested by Western data [14]. Thus, we aimed to develop a bleeding risk prediction tool to guide warfarin treatment by taking a stable dose of warfarin after HVS; for this purpose, we used the nationwide claims data available in South Korea and machine learning strategies.

2 | Methods

2.1 | Data

We conducted a nested case-control study using the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort established by the NHIS in South Korea. The NHIS database includes all medical records of covered inpatient and outpatient visits, as well as the results of national health examinations, due to South Korea's single-payer national health system. The database contains diagnostic codes in the form of ICD-10 codes and prescriptions in the form of main ingredient codes, which include information on the main

ingredient, dose, administration route, and dosage. The Health Insurance Review and Assessment Service (HIRA) of South Korea is responsible for managing these codes [15, 16].

2.2 | Study Population

We aimed to identify risk factors and develop a bleeding risk scoring system for patients with HVS and on a stable warfarin dose. Our study cohort consisted of patients who underwent HVS and were prescribed warfarin within 1 week after surgery. We defined the case and control groups based on bleeding events that occurred after 6 months after surgery. Bleeding outcome was defined using ICD-10 codes (Supporting Table 1). Bleeding events in the first 6 months after the first warfarin prescription were excluded to remove the effect of initial INR instability. Patients with the last two identical warfarin prescriptions within 6 months before the first bleeding event were defined as stable warfarin dose patients and selected as the case group. We checked for a stable warfarin dose before the index date to ensure that patients were selected from all cases (the first bleeding event after 6, 9, or 12 months). We selected the earliest index date when patients met the definition of stable warfarin dose over time. The date of the first bleeding event was defined as the index date. We selected patients with two consecutive identical warfarin prescriptions and randomly assigned index dates within 6 months for the control group to consistently define stable patients. Additionally, we ensured a minimum 1-year duration before the index date for comprehensive feature assessment. Patients with any missing data were not included in the analysis. This study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki, and informed consent was waived due to the retrospective nature of the study.

2.3 | Features

To capture as many trends as possible in the data, we created features that could represent most comorbidities and comedications. We sub-stringed three-digit ICD-10 codes for comorbidities. For medications, the first four digits of the main ingredient codes represent the main ingredient. We again sub-stringed all the main ingredient codes from first to fourth to include every medication. Only oral medications were included to avoid the confounding effect of injections for supportive therapy (e.g., dextrose or saline solution). Features with no patients were excluded, resulting in 601 features for comorbidities and 740 for comedications. In addition, age and gender were included as basic patient characteristics. Patients were followed up for 1 year before the index date to assess the history of comorbidities and comorbid medications.

2.4 | Machine Learning Methods and Statistical Analysis

Random forest is an ensemble learning method for classification and regression operated by building numerous decision trees [17]. It provides feature importance by calculating the degree of contribution in classifying data. Based on computed feature importances, we identified the top 100 most important features in

distinguishing between the case and control groups. Sample size was calculated to be 174 in each group for having an 80% power of detecting an odds ratio of 3 at the 5% level of significance.

Multivariable logistic regression was used to assess the relationship between the bleeding outcome and multiple independent variables while controlling for the potential influence of confounding variables. We performed multivariable logistic regression with stepwise selection to determine the independent effects of each predictor variable on the bleeding outcome while accounting for the effects of other variables in the model. We removed features with minimal clinical correlation with the outcome, such as lactulose, pleural effusion, breathing abnormalities, etc. Using the selected features, we trained three different models: logistic regression, support vector machine, and random forest, to investigate the relationship between bleeding events and features. Nested cross-validation was carried out to optimize hyperparameters and evaluate the model. Randomized and grid searches were used to optimize hyperparameters for the three models. Fivefold cross-validation was used, and the data were shuffled before splitting into the training, test, and validation sets. To check the performance of the models with the entire dataset, we plotted the receiver operating characteristic (ROC) curve for each model (Figure 1).

Chi-square tests were conducted to detect the difference in the ratio of categorical features between the case and control groups. We conducted the Student's *t*-test for continuous features to evaluate the difference in mean values between the two groups. We then performed multivariable logistic regression with stepwise selection to calculate the adjusted odds ratios of final features. Features with a *p*-value < 0.05 were considered statistically significant. We used the ROC-area under the curve (ROC-AUC) score to evaluate the machine learning models. All statistical

analyses and machine learning were conducted using SAS version 9.4 software (SAS Inc., Cary, NC, USA) and the Scikit-learn package in Python version 3.5.2 (Python Software Foundation, Wilmington, DE, USA).

2.5 | Development of a Risk Scoring System

To score the features, we used the ranges of adjusted odds ratios as follows: odds ratios < 3.00 were assigned a score of 1, those ranging from 3.00 to 4.00 were given a score of 2, and those > 4.00 were given a score of 3. Odds ratios of < 1 were inverted. We calculated bleeding event scores based on these adjusted odds ratio ranges, resulting in a risk score range of 0–16. We validated the risk scoring system by plotting the ROC curve and calculating its AUC. TRIPOD-AI checklist was utilized to follow the reporting recommendations for this study of development and evaluation of the performance of a prediction model (Supporting Table 5).

3 | Results

3.1 | Patient Selection

There were 1137861 patients in the NHIS-NSC data covering 2002–2019. Among them, 1093 patients had undergone HVS and were prescribed warfarin within 1 week after surgery. After excluding bleeding events occurring within the first 6 months after the first warfarin prescription to remove the effect of initial INR instability, 505 patients had bleeding events. Among them, 213 patients on a stable warfarin dose were selected as the case group. For the control group, 348 stable warfarin patients were randomly assigned index dates within 6 months from their last two identical

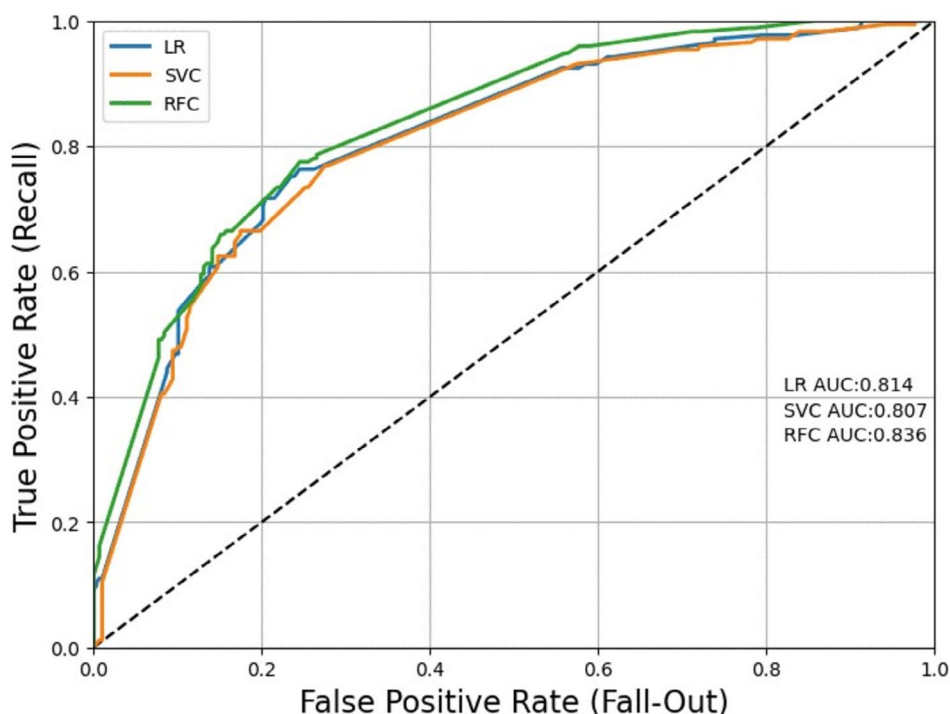


FIGURE 1 | ROC curves of the best models using the total dataset. LR, logistic regression; RFC, random forest classifier; SVC, support vector classifier.

warfarin prescriptions. These patients had no history of bleeding events after 6 months from the first warfarin prescription.

After excluding patients dismissed from the National Health Insurance system and those with an index date in 2002, 471 patients were included in the study, with 173 in the case group and 298 in the control group.

Age was significantly different between the two groups, with the mean age of the case group being 2.9years higher than that of the control group ($p=0.002$). However, there was no significant difference in gender distribution between the two groups ($p=0.720$).

3.2 | Important Features

We generated 1341 features from the data and employed a random forest classifier to select the top 100 features. The ROC-AUC score of the random forest model used to determine the top 100 features was 0.871. Among the top 100 features, 23 were found to have a statistically significant association with bleeding events after stepwise selection (Supporting Table 2). Features that had minimal clinical correlation with the outcome were excluded. After a subsequent stepwise selection, eight features were selected. Among the medication features, the use of furosemide, spironolactone, ursodeoxycholic acid, captopril, zolpidem, or valsartan was less frequent in the case group than in the control group, while the use of other medications was more frequent in the case group. A detailed summary of the features and their distribution in the case and control groups is provided in Table 1.

TABLE 1 | Cohort characteristics according to the significant features of bleeding complications.

Feature	Bleeding group (n = 173)	Control group (n = 298)	p
Age, years	57.9 ± 12.4	55.0 ± 15.5	0.0257
Gender			
Male	88 (36.67%)	152 (63.33%)	0.9767
Female	85 (36.80%)	146 (63.20%)	
Furosemide	86 (24.71%)	262 (75.29%)	< 0.0001
Spironolactone	70 (22.44%)	242 (77.56%)	< 0.0001
Disorders of the lacrimal system	51 (53.68%)	44 (46.23%)	0.0001
Ursodeoxycholic acid	7 (10.29%)	61 (89.71%)	< 0.0001
Captopril	3 (9.68%)	28 (90.32%)	0.0012
Chronic kidney disease	12 (57.14%)	9 (42.86%)	0.0471
Zolpidem	24 (26.09%)	68 (73.91%)	0.0182
Valsartan	11 (19.30%)	46 (80.70%)	0.0036

3.3 | Models Trained With Selected Features

We trained the logistic regression classifier, support vector classifier, and random forest classifier using selected features. Hyperparameter optimization and model generalization were performed by fivefold cross-validation (Supporting Table 3). The resulting mean AUROC scores were 0.804 for logistic regression, 0.790 for support vector machine, and 0.810 for random forest (Table 2). We also evaluated the performance of the three models on the entire dataset by calculating their ROC-AUC scores, which were 0.814, 0.807, and 0.836 for logistic regression, support vector machine, and random forest, respectively. The ROC curves for each model are illustrated in Figure 1. These results suggest that the random forest model outperformed the other models in predicting bleeding events using the selected features.

3.4 | Risk of Bleeding Evaluated With Selected Features

Following adjustment for other variables, results indicate that comorbidities were associated with increased bleeding risks, while comedications decreased bleeding risks. Specifically, patients with a history of lacrimal system disorders or chronic kidney disease had a 3.66-fold (95% CI: 2.12–6.32) and 3.86-fold (95% CI: 1.37–10.85) increased risk of bleeding, respectively. On the other hand, the use of diuretics, including furosemide and spironolactone, as well as ursodeoxycholic acid, captopril, zolpidem, or valsartan, was associated with a decreased risk of bleeding with an adjusted odds ratio range of 0.211–0.521 (Table 3).

3.5 | Risk Scoring System

A risk scoring system was developed based on the adjusted odds ratios of the significant features, as shown in Table 3. To determine the relative importance of each risk factor by assigning weightings to them, we used adjusted odds ratios. Two features (disorders of the lacrimal system and chronic kidney disease) showed adjusted odds ratios between 3 and 4; thus, these were given two points for each feature. All other features showed adjusted odds ratios of <1, which were then inverted and given the scores between 1 and 3 accordingly. We observed that the proportion of patients in the case group tended to increase with a higher risk score (Supporting Table 4). In the risk scoring system, the maximum score was 16, and each scoring unit corresponded to a predicted increase in an odds ratio of 1.919. The

TABLE 2 | AUC scores of ROC curves in our models.

Model	Mean AUC	Min AUC	Max AUC
Logistic regression	0.804	0.753	0.859
Support vector machine	0.790	0.743	0.835
Random forest	0.810	0.763	0.867

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

scoring system was evaluated using a ROC curve with an AUC score of 0.813 (Figure 2).

4 | Discussion

This study used nationwide claims data to identify the one-year bleeding risk factors in patients taking stable warfarin doses. Using machine learning-based feature selection, we narrowed down 1341 features to the eight most essential features (furosemide, spironolactone, disorders of the lacrimal system, ursodeoxycholic acid, captopril, chronic kidney disease, zolpidem, and valsartan). The identification of medications as a significant risk factor is adjusted for the presence of related conditions; thus, it should be interpreted based on the presence or absence

of medication use. The logistic regression, support vector machine, and random-forest models trained with the selected features showed ROC–AUC scores of 0.804, 0.790, and 0.810, respectively, indicating that all models performed well predicting bleeding events. The high AUC scores of our models using claims data suggest that they could help distinguish patients who require more careful monitoring of bleeding events. Despite the limitations of administrative claims data, such as the inability to directly confirm comorbidities and comedications, this study highlights the potential utility of machine learning in predicting bleeding risks. Discussions of the selected features, which may be risk or protective factors for bleeding events while maintaining stable INR, are presented. Possible explanations are provided for these features. However, it is important to note that while machine learning model training and risk scoring system

TABLE 3 | Unadjusted and adjusted odds ratios of selected features and their scores.

Feature	Unadjusted odds ratio (95% CI)	p	Adjusted odds ratio ^a (95% CI)	p value	Score	
Furosemide	0.136 (0.086–0.215)	<0.0001	0.294 (0.146–0.590)	0.0006	Yes: 0	No: 2
Spironolactone	0.157 (0.103–0.239)	<0.0001	0.383 (0.200–0.733)	0.0038	Yes: 0	No: 1
Disorders of the lacrimal system	2.413 (1.527–3.813)	0.0002	3.657 (2.116–6.320)	<0.0001	Yes: 2	No: 0
Ursodeoxycholic acid	0.164 (0.073–0.367)	<0.0001	0.211 (0.087–0.511)	0.0006	Yes: 0	No: 3
Captopril	0.170 (0.051–0.568)	0.0040	0.226 (0.062–0.826)	0.0245	Yes: 0	No: 3
Chronic kidney disease	2.393 (0.987–5.801)	0.0534	3.856 (1.370–10.853)	0.0106	Yes: 2	No: 0
Zolpidem	0.545 (0.328–0.907)	0.0194	0.521 (0.284–0.954)	0.0346	Yes: 0	No: 1
Valsartan	0.372 (0.187–0.739)	0.0048	0.326 (0.144–0.741)	0.0006	Yes: 0	No: 2

Abbreviation: CI, confidence interval.

^aAdjusted for furosemide, spironolactone, age, pain in throat and chest, abnormalities of breathing, lactulose, disorders of lacrimal system, unspecified pleural effusion, ursodeoxycholic acid, ambroxol, *Lactobacillus acidophilus*, eperisone, erdosteine, captopril, sequelae of cerebrovascular disease, chronic kidney disease, unspecified shock, zolpidem, vasomotor and allergic rhinitis, valsartan, abnormal results of function studies, other headache syndromes, and foreign body on external eye.

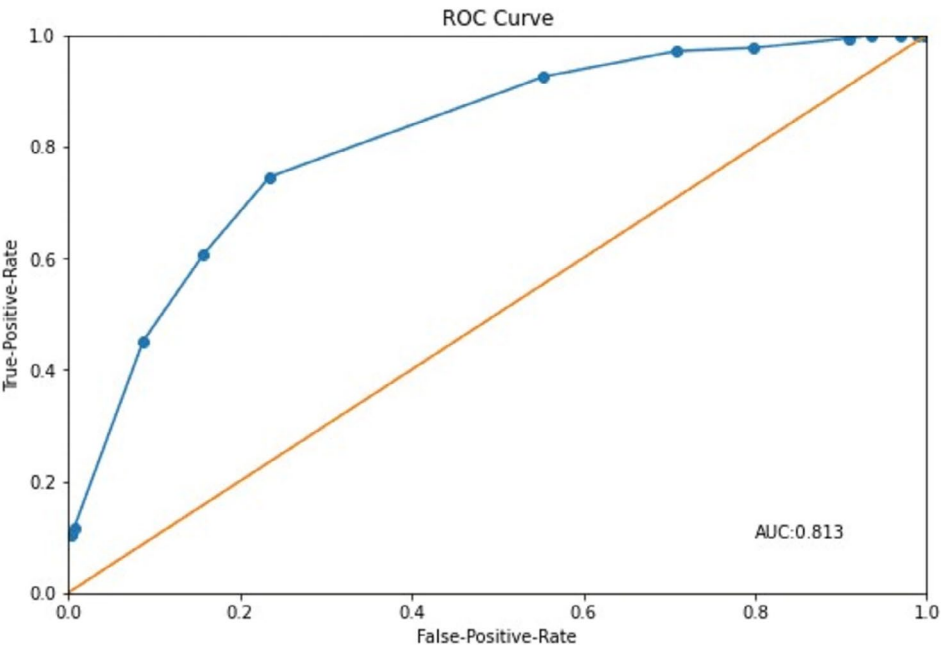


FIGURE 2 | Risk scoring system-based ROC curve.

development focus on inferring the odds of bleeding events, causality between features and the event is not guaranteed.

Prescribing certain antihypertensive drugs, including furosemide, spironolactone, captopril, or valsartan, decreased the risk of bleeding events in 1 year. Our results are related to the guidelines for HAS-BLED and ATRIA, which suggest that uncontrolled hypertension is a risk factor for bleeding events in patients with atrial fibrillation [7] [18]. The antihypertensive action of these medications may help reduce the incidence of bleeding incidents related to hypertension. Our finding of the significance of antihypertensive drugs after adjusting for comorbidities, including hypertension, can be supported by previous studies that suggest potential mechanisms for this effect. Pedersen et al. proposed that diuretics might increase the level of plasminogen activator inhibitor type-1 in blood, inhibiting tissue plasminogen activator and reducing fibrinolysis [19]. This mechanism may help to explain the decreased risk of bleeding events in patients prescribed diuretics. Helten et al. [20] demonstrated that using angiotensin-converting enzyme inhibitors increases platelet reactivity, possibly preventing bleeding.

The relationship between ursodeoxycholic acid intake and bleeding events has not been widely studied. The reduced incidence of bleeding events in patients taking ursodeoxycholic acid may be related to improved liver function. The relationship between bleeding and liver function is still unclear, but some studies suggest a higher incidence of bleeding in patients with chronic liver disease [21–23]. Most hemostatic proteins and thrombopoietin are synthesized in the liver. Thus, reduced liver function may result in decreased blood clotting, increased prothrombin time, and an increased risk of bleeding events. Improved liver function due to ursodeoxycholic acid treatment may explain its ability to reduce bleeding risk [21].

Renal function is also linked to complex hemostatic disorders. Reduced renal function leads to uremia, which results in platelet dysfunction and impairs platelet-vessel wall interactions [24–26]. One mechanism that explains bleeding events caused by uremia is a defect in platelet adhesion mediated by GPIIb-IIIa-von Willebrand factor interaction [25]. Another mechanism is a defect in platelet secretion caused by an increase in prostaglandin I₂ and nitric oxide [26].

Underlying mechanisms of the relationship between other important features, including lacrimal system disorders or zolpidem and bleeding, need further researches to explain its association.

One limitation of our study is the lack of availability of laboratory test results that could have helped explain bleeding events. Since INR data were unavailable, we defined a stable warfarin dose based on more than two identical prescriptions. In addition, information on social factors such as smoking status, alcohol consumption, and economic status was not available for all the patients in our study. Another limitation is the use of diagnostic and prescription codes, which may have resulted in inaccuracies in diagnoses and medication adherence. We could have employed stricter criteria for patient selection to address this limitation, but we decided to use more flexible measures to avoid missing potential information in this exploratory study.

Despite these limitations, our study is the first to identify factors contributing to bleeding events in patients taking a stable warfarin dose after HVS. Our machine learning approach for feature selection was validated by training three models, which all showed high ROC–AUC scores indicating that our models predicted bleeding events well. We also developed a risk scoring system that demonstrated an excellent ROC–AUC score, which can guide clinical decision-making for these patients.

Our finding suggests that certain medications, such as furosemide, spironolactone, captopril, valsartan, and ursodeoxycholic acid, as well as comorbidities such as chronic kidney disease and disorders of the lacrimal system, are associated with the risk of bleeding events. We have developed a risk prediction scoring system that incorporates these features. The risk scoring system, developed from multivariate logistic regression, predicts the probability of bleeding events based on multiple risk factors. Coefficients derived from the regression quantify each risk factor's impact on the outcome. By assigning points to these coefficients and calculating a cumulative score for individuals, the system categorizes risk levels, aiding healthcare decisions and tailored interventions. Given that bleeding events among patients with stable INR can be difficult to predict, this risk scoring system offers a useful guide for identifying patients at high risk of bleeding, facilitating more targeted monitoring and intervention strategies.

4.1 | Plain Language Summary

Patients who undergo HVS need to take warfarin. This helps prevent issues related to blood clotting. However, it is important to know that the risk of bleeding complications cannot always be effectively monitored using the traditional International Normalized Ratio (INR) method. Therefore, our goal was to figure out what factors increase the risk of bleeding in patients who are on a stable warfarin treatment. We wanted to create a tool that could predict which patients are at a higher risk of bleeding. Through various machine learning processes, we found eight important factors that increase the chances of bleeding. Furosemide, spironolactone, lacrimal system disorders, ursodeoxycholic acid, captopril, chronic kidney disease, zolpidem, and valsartan were the most important features for predicting bleeding incidents in patients taking a stable warfarin dose after HVS. We then created a bleeding risk scoring system based on the adjusted odds ratios of these factors using a multivariate logistic regression.

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Ethics Statement

The study protocol was approved by the Institutional Review Board of Chungbuk National University (CBNU-202106-HR-0050).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data utilized in this study are derived from a public database that can be accessed by the National Health Insurance Service with authorization.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supporting Table 1:** ICD-10 codes for defining bleeding events **Supporting Table 2:** Selected features in association with bleeding events after stepwise selection **Supporting Table 3:** Hyperparameter grid and the best hyperparameters of each model **Supporting Table 4:** The number of patients by total risk score **Supporting Table 5:** TRIPOD Checklist: Prediction Model Development.