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ORIGINAL RESEARCH

# Correlation between anticoagulant therapy strategy and bleeding risk in patients with atrial fibrillation based on MIMIC-ED database

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## Abstract

**Background**: Current bleeding risk scores lack precision in elderly and comorbid populations. This study addresses this gap by developing a model tailored to atrial fibrillation (AF) patients undergoing diverse anticoagulation therapies. **Methods**: Clinical data of 6968 AF patients who underwent prophylactic early anticoagulation therapy were screened and gathered from the Medical Information Mart for Intensive Care-Emergency Department (MIMIC-ED) database. Patients were divided into a bleeding group (n = 280) and a non-bleeding group (n = 6688) based on the occurrence of bleeding. The bleeding risks related to diverse anticoagulant therapy approaches among AF patients were contrasted, and the clinical data of the two groups were compared. Significant differences in clinical data between the two groups were selected to establish a predictive model for post-anticoagulation bleeding in AF patients. **Results**: Bleeding occurred in 4.02% of patients. Apixaban had the lowest bleeding rate (2.94%), while Warfarin (4.42%) and Enoxaparin (5.22%) showed higher risks. Independent predictors included gender, age, dementia, malignancy, liver disease, metastatic tumors, Warfarin use and platelet count. The predictive model achieved an Area Under the Curve (AUC) of 0.726 (95% Confidence Interval (CI): 0.693–0.760) with 53.9% sensitivity and 82.4% specificity. **Conclusions**: The risk of bleeding after anticoagulation therapy in AF patients is influenced by multiple factors, including basic demographic characteristics (gender, age), comorbid chronic conditions (dementia, malignant cancer, severe liver disease, and metastatic solid tumors), medication use (Warfarin) and laboratory indicators (Platelet Count). The bleeding risk predictive model established in this study shows excellent diagnostic performance and capable of offering significant decision support for individualized management of anticoagulation therapy.

## Keywords

MIMIC-ED database; Atrial fibrillation; Anticoagulation therapy; Bleeding risk

## 1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice, with its incidence increasing annually and becoming a major risk factor for stroke and thromboembolic events worldwide [1]. A critical issue in the management of AF patients lies in the choice of anticoagulation therapy. While anticoagulation therapy proves to be efficacious in averting thromboembolic events for AF patients, it simultaneously elevates the risk of bleeding [2, 3], particularly for those receiving combined anticoagulation and antiplatelet therapy [4]. In recent years, as the variety of anticoagulants keeps increasing, clinicians are confronted with more treatment options, but balancing the anticoagulant effect and the risk of bleeding still poses a challenge in clinical decision-making [5, 6]. The Medical Information Mart for Intensive Care Emergency Department (MIMIC-ED) database, as a large-scale clinical data resource, provides abundant information on the treatment and prognosis of AF patients [7]. This study compares bleeding rates across anticoagulants (Warfarin, Apixaban, Enoxaparin) and identifies predictors to guide individualized therapy. This study aims to investigate the correlation between anticoagulation strategies and bleeding risk in AF patients, with a focus on high-risk subgroups (*e.g.*, elderly patients and those with comorbidities such as malignancy or liver disease). We hypothesize that novel oral anticoagulants (NOACs) like Apixaban confer a lower bleeding risk compared to traditional agents (*e.g.*, Warfarin), and that a predictive model incorporating demographic, clinical and laboratory factors can enhance patient treatment efficacy and safety.

## 2. Methods


  

## 2.1 Study subjects

The data for this study originated from the MIMIC database, and the process for obtaining access to MIMIC-ED is briefly described as follows: ① Completion of registration on the Physionet website (https://physionet.org/). ② Registration on the Collaborative Institutional Training Initiative (CITI) Program website (https://about.citiprogram.org/) and completion of the health information privacy and protection course, followed by obtaining a certificate (ID: 66822508) upon passing the exam. ③ Uploading the certificate onto the Physionet website for applying to access the MIMIC database. The utilization of the MIMIC database does not entail ethical concerns, and patient clinical data can be downloaded by means of Structured Query Language (SQL) language.

Upon successfully gaining access to the MIMIC database, in accordance with the inclusion and exclusion criteria, clinical data of a total of 6968 AF patients who underwent prophylactic early anticoagulation therapy between 2008 and 2019 were screened out and collected from the MIMIC-ED database. These patients were divided into a bleeding group (n = 280) and a non-bleeding group (n = 6688) based on whether they experienced bleeding.

Inclusion criteria: ① Patients with atrial fibrillation; ② Hospital stay >1 day; ③ Age >18 years; ④ Received prophylactic early anticoagulation therapy.

Exclusion criteria: ① Incomplete information; ② Information from patients with multiple Intensive Care Unit (ICU) admissions.

The specific inclusion process of patients is shown in Fig. 1.

## 2.2 Data extraction

Postgre SQL was used to import the MIMIC database into Navicat Premium 15.0 software (PremiumSoft CyberTech Ltd., Hong Kong, China). Data for AF patients (International Classification of Diseases (ICD)-9 code 42731) were retrieved from the MIMIC database, with the outcome indicator being bleeding (complication—bleeding (Major Bleeding After Laparoscopy (MBAL)), ID 228426). The following information was extracted for AF patients:

① Outcome indicator: Complication—bleeding (MBAL), ID 228426.

② Baseline information: Age, gender, race, length of hospital stay, length of ICU stay.

③ Baseline comorbidities: Smoker, acute kidney injury, sepsis, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatism, peptic ulcer, mild liver disease, diabetes, paraplegia, renal disease, malignancy, severe liver disease, metastatic solid tumor, Acquired Immune Deficiency Syndrome (AIDS).

④ Laboratory tests within 24 hours of ICU admission: White Blood Cell Count (WBC), Red Cell Distribution Width (RDW), Platelet Count (PLT), Red Blood Cell Count (RBC), Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized Ratio (INR), Hemoglobin (Hb).

⑤ Anticoagulation drug use: Dabigatran, Rivaroxaban, Enoxaparin, Apixaban, Warfarin. Anticoagulant dosing followed standardized protocols: Apixaban (5 mg twice daily), Warfarin (target INR 2–3) and Enoxaparin (1 mg/kg twice daily). Treatment duration spanned from initiation during

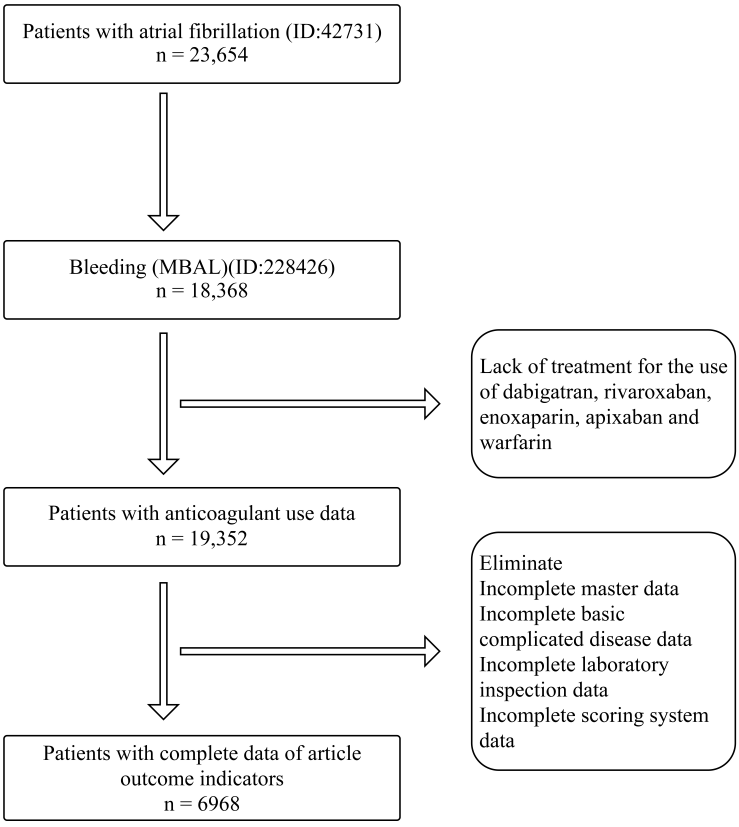


**FIGURE 1. Patient inclusion process.**

hospitalization to 30 days post-discharge.

⑥ Scoring systems: Acute Physiology and Chronic Health Evaluation (APS) III score, Sequential Organ Failure Assessment (SOFA) score, Logistic Organ Dysfunction System (LODS) score.

### 2.3 Statistical analysis

This study utilized PostgreSQL 9.6 and SPSS 25.0 (IBM Corp., Armonk, NY, USA) for data extraction and statistical analysis, respectively. Continuous variables were expressed as mean ± standard deviation, normality was assessed using Shapiro-Wilk tests. Non-normally distributed variables (*e.g.*, platelet count) were analyzed with Mann-Whitney U tests. And comparisons between groups with normally distributed data were performed using independent sample *t*-tests. Univariate analysis was conducted between the bleeding group and the non-bleeding group to screen for risk factors associated with bleeding risk in AF patients. Variables with $p < 0.05$ in the univariate analysis were included in a multivariate Logistic regression model to analyze independent factors related to anticoagulation therapy strategies and bleeding risk. The formula was: $\text{logit}(P) = \beta 0 + \beta 1X1 + \ldots + \beta nXn$, where P is the probability of bleeding. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Based on the Logistic regression analysis, a prediction model was established, and the discriminant performance of the model was assessed using the receiver operating characteristic curve (ROC), with the area under the curve (AUC) calculated. Internal validation was performed using 10-fold cross-validation to assess model stability. The mean AUC remained consistent ($0.712 \pm 0.021$), indicating minimal overfitting. All statistical tests were two-sided, and a *p*-value $< 0.05$ was considered statistically significant.

## 3. Results

### 3.1 Comparison of bleeding rates after different anticoagulation therapies

The bleeding rate among atrial fibrillation patients after anticoagulation therapy was 4.02% (280/6968). The primary anticoagulation strategy employed was warfarin (77.28%, 5385/6968), followed by the novel oral anticoagulant Apixaban (20.48%, 1427/6968), then Enoxaparin (12.66%, 882/6968), and lastly Dabigatran and Rivaroxaban, which together accounted for only 0.52% (36/6968). Among atrial fibrillation patients, different anticoagulation therapies exerted a remarkable influence on bleeding rates, where the novel oral anticoagulant Apixaban presented the lowest bleeding rate, while warfarin and Enoxaparin had relatively higher bleeding rates. Specific details are provided in Table 1.

### 3.2 Comparison of clinical data between the two patient groups

Compared with the non-bleeding group, the bleeding group had a lower proportion of males (52.50% *vs.* 60.39%, $p = 0.008$), a higher average age ($78.38 \pm 12.67$ *vs.* $74.60 \pm 10.85$, $p < 0.001$), and a higher proportion of patients with dementia, malignant cancer, severe liver disease and metastatic solid tumors. Additionally, the bleeding group had a lower proportion of patients treated with Apixaban and a higher proportion treated with warfarin. The levels of PLT, red blood cells (RBC), and hemoglobin (He) were lower in the bleeding group, while the red blood cell distribution width (RDW) was higher. See Table 2 for specific details.

### 3.3 Multivariable analysis of risk factors for bleeding after anticoagulation therapy in atrial fibrillation patients

The results of the Logistic regression analysis indicated that gender, age, dementia, malignant cancer, severe liver disease, metastatic solid tumor, use of warfarin, and PLT were independent predictors of bleeding after anticoagulation therapy in atrial fibrillation patients. Specific details are provided in Table 3.

### 3.4 Construction of a predictive model for bleeding after anticoagulation therapy in atrial fibrillation patients

The independent predictors of bleeding after anticoagulation therapy in atrial fibrillation patients were included in a Logistic regression model. Specific details are provided in Table 4.

### 3.5 ROC curve analysis

The predictive model for bleeding after anticoagulation therapy in atrial fibrillation patients demonstrated good diagnostic performance, with an Area Under the Curve (AUC) of 0.726 (95% Confidence Interval: 0.693–0.760). The diagnostic sensitivity and specificity of the model were 53.9% and 82.4%, respectively. Specific details are provided in Table 5 and Fig. 2.

## 4. Discussion

Patients suffering from AF have a high likelihood of experiencing thromboembolic events and typically require

**TABLE 1. Comparison of bleeding rates after different anticoagulation therapies.**

| | Warfarin (n = 5385) | Apixaban (n = 1427) | Enoxaparin (n = 882) | Dabigatran (n = 32) | Rivaroxaban (n = 4) |
|---|---|---|---|---|---|
| Bleeding | 238 (4.42) | 42 (2.94) | 46 (5.22) | 2 (6.25) | 0 (0.00) |
| Non-bleeding | 5147 (95.58) | 1385 (97.06) | 836 (94.78) | 30 (93.75) | 4 (100.00) |
| $\chi^2$ | | | | | 3392.643 |
| *p* | | | | | <0.001 |

**TABLE 2. Comparison of clinical data.**

| Type | Non-bleeding group (n = 6688) | Bleeding group (n = 280) | $t/\chi^2$ | $p$ |
|---|---|---|---|---|
| Gender | | | | |
| F | 2649 (39.61) | 133 (47.50) | 6.978 | 0.008 |
| M | 4039 (60.39) | 147 (52.50) | | |
| Age | 74.60 ± 10.85 | 78.38 ± 12.67 | 4.909 | <0.001 |
| Race | | | | |
| White | 4988 (74.58) | 211 (75.36) | | |
| Black | 365 (5.46) | 15 (5.35) | 0.519 | 0.915 |
| Asian | 164 (2.45) | 5 (1.79) | | |
| Other | 1171 (17.51) | 49 (17.50) | | |
| Los hospital | 14.53 ± 14.87 | 15.47 ± 18.06 | 1.027 | 0.304 |
| Los ICU | 4.38 ± 6.08 | 4.49 ± 6.97 | 0.294 | 0.769 |
| AKI | | | | |
| N | 1401 (20.95) | 54 (19.29) | 0.449 | 0.503 |
| Y | 5287 (79.05) | 226 (80.71) | | |
| Sepsis | | | | |
| N | 3219 (48.13) | 121 (43.21) | 2.603 | 0.107 |
| Y | 3469 (51.87) | 159 (56.79) | | |
| Myocardial infarct | | | | |
| N | 5098 (76.23) | 216 (77.14) | 0.125 | 0.724 |
| Y | 1590 (23.77) | 64 (22.86) | | |
| Congestive heart failure | | | | |
| N | 2905 (43.44) | 121 (43.21) | 0.005 | 0.942 |
| Y | 3783 (56.56) | 159 (56.79) | | |
| Peripheral vascular disease | | | | |
| N | 5490 (82.09) | 237 (84.64) | 1.199 | 0.274 |
| Y | 1198 (17.91) | 43 (15.36) | | |
| Cerebrovascular disease | | | | |
| N | 5589 (83.57) | 226 (80.71) | 1.584 | 0.208 |
| Y | 1099 (16.43) | 54 (19.29) | | |
| Dementia | | | | |
| N | 6497 (97.14) | 238 (85.00) | 122.632 | <0.001 |
| Y | 191 (2.86) | 42 (15.00) | | |
| Chronic pulmonary disease | | | | |
| N | 4550 (68.03) | 183 (65.36) | 0.883 | 0.347 |
| Y | 2138 (32.97) | 97 (34.64) | | |
| Rheumatic disease | | | | |
| N | 6444 (96.35) | 269 (96.07) | 0.060 | 0.807 |
| Y | 244 (3.65) | 11 (3.93) | | |
| Peptic ulcer disease | | | | |
| N | 6526 (97.58) | 278 (99.29) | 3.411 | 0.065 |
| Y | 162 (2.42) | 2 (0.71) | | |
| Mild liver disease | | | | |
| N | 6250 (93.45) | 254 (90.71) | 3.238 | 0.072 |
| Y | 438 (6.55) | 26 (9.29) | | |

**TABLE 2. Continued.**

| Type | Non-bleeding group (n = 6688) | Bleeding group (n = 280) | $t/\chi^2$ | $p$ |
|---|---|---|---|---|
| Diabetes | | | | |
| N | 4382 (65.52) | 197 (70.36) | 2.791 | 0.095 |
| Y | 2306 (34.48) | 83 (29.64) | | |
| Paraplegia | | | | |
| N | 6349 (94.93) | 265 (94.64) | 0.046 | 0.830 |
| Y | 339 (5.07) | 15 (5.36) | | |
| Renal disease | | | | |
| N | 4660 (69.68) | 189 (67.50) | 0.602 | 0.438 |
| Y | 2028 (30.32) | 91 (32.50) | | |
| Malignant cancer | | | | |
| N | 6067 (90.71) | 218 (77.86) | 50.252 | <0.001 |
| Y | 621 (9.29) | 62 (22.14) | | |
| Severe liver disease | | | | |
| N | 6614 (98.89) | 262 (93.57) | 58.426 | <0.001 |
| Y | 74 (1.11) | 18 (6.43) | | |
| Metastatic solid tumor | | | | |
| N | 6464 (96.65) | 256 (91.43) | 21.352 | <0.001 |
| Y | 224 (3.35) | 24 (8.57) | | |
| AIDS | | | | |
| N | 6681 (99.90) | 280 (100.00) | 0.293 | 0.588 |
| Y | 7 (0.10) | 0 (0.00) | | |
| APS III | 45.81 ± 18.68 | 46.20 ± 17.45 | 0.340 | 0.734 |
| SOFA | 5.61 ± 3.39 | 5.86 ± 3.46 | 1.247 | 0.212 |
| LODS | 5.13 ± 2.71 | 5.05 ± 2.47 | 0.522 | 0.602 |
| Dabigatran | | | | |
| Not used | 6658 (99.55) | 278 (99.29) | 0.415 | 0.519 |
| Used | 30 (0.45) | 2 (0.71) | | |
| Rivaroxaban | | | | |
| Not used | 6684 (99.94) | 280 (100.00) | 0.168 | 0.682 |
| Used | 4 (0.06) | 0 (0.00) | | |
| Enoxaparin | | | | |
| Not used | 5852 (87.50) | 234 (83.57) | 3.752 | 0.053 |
| Used | 836 (12.50) | 46 (16.43) | | |
| Apixaban | | | | |
| Not used | 5303 (79.29) | 238 (85.00) | 5.378 | 0.020 |
| Used | 1385 (20.71) | 42 (15.00) | | |
| Warfarin | | | | |
| Not used | 1541 (23.04) | 42 (15.00) | 9.898 | 0.002 |
| Used | 5147 (76.96) | 238 (85.00) | | |
| WBC | 12.13 ± 8.62 | 11.72 ± 6.83 | 0.787 | 0.431 |
| RDW | 15.07 ± 2.16 | 15.40 ± 2.24 | 2.496 | 0.013 |
| PLT | 200.18 ± 97.78 | 179.21 ± 95.00 | 3.519 | <0.001 |
| RBC | 3.54 ± 0.77 | 3.42 ± 0.74 | 2.393 | 0.017 |

**TABLE 2. Continued.**

| Type | Non-bleeding group (n = 6688) | Bleeding group (n = 280) | $t/\chi^2$ | $p$ |
|---|---|---|---|---|
| PT | 19.89 ± 12.58 | 20.34 ± 12.21 | 0.591 | 0.555 |
| PTT | 42.55 ± 26.22 | 43.47 ± 28.52 | 0.577 | 0.564 |
| INR | 1.85 ± 1.26 | 1.89 ± 1.16 | 0.530 | 0.596 |
| He | 11.32 ± 2.16 | 10.92 ± 2.21 | 3.056 | 0.002 |

*Note: Continuous variables: independent t-test or Mann-Whitney U; categorical variables: chi-square test. WBC: White Blood Cell Count; RDW: Red Cell Distribution Width; PLT: Platelet Count; RBC: Red Blood Cell Count; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; INR: International Normalized Ratio; He: hemoglobin; F: female; M: male; ICU: Intensive Care Unit; AKI: Acute kidney injury; N: no; Y: yes; AIDS: Acquired Immune Deficiency Syndrome; APS: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; LODS: Logistic Organ Dysfunction System.*

**TABLE 3. Multivariable analysis of risk factors for bleeding after anticoagulation therapy in atrial fibrillation patients.**

| Variable | Coefficient ($\beta$) | Standard Error | Wald | $p$ | OR | 95% CI lower limit | 95% CI upper limit |
|---|---|---|---|---|---|---|---|
| Gender | 0.415 | 0.130 | 10.241 | 0.001 | 1.514 | 1.174 | 1.953 |
| Age | 0.030 | 0.007 | 20.396 | <0.001 | 1.031 | 1.017 | 1.044 |
| Dementia | 1.970 | 0.202 | 95.320 | <0.001 | 7.174 | 4.830 | 10.655 |
| Malignant cancer | 1.188 | 0.184 | 41.714 | <0.001 | 3.279 | 2.287 | 4.703 |
| Severe liver disease | 2.280 | 0.302 | 57.088 | <0.001 | 9.781 | 5.414 | 17.673 |
| Metastatic solid tumor | 0.753 | 0.274 | 7.581 | 0.006 | 2.124 | 1.242 | 3.631 |
| Apixaban | 0.048 | 0.253 | 0.036 | 0.850 | 1.049 | 0.639 | 1.723 |
| Warfarin | 0.965 | 0.254 | 14.440 | <0.001 | 2.625 | 1.596 | 4.318 |
| RDW | 0.006 | 0.032 | 0.039 | 0.844 | 1.006 | 0.945 | 1.072 |
| PLT | −0.003 | 0.001 | 12.829 | <0.001 | 0.997 | 0.996 | 0.999 |
| RBC | −0.070 | 0.126 | 0.311 | 0.577 | 0.932 | 0.729 | 1.193 |
| He | 0.019 | 0.048 | 0.154 | 0.695 | 1.019 | 0.928 | 1.119 |

*OR: odds ratios; CI: confidence intervals; RDW: Red Cell Distribution Width; PLT: Platelet Count; RBC: Red Blood Cell Count; He: hemoglobin.*

**TABLE 4. Logistic regression model for bleeding after anticoagulation therapy in atrial fibrillation patients.**

| Variable | Coefficient ($\beta$) | Standard Error | Wald | $p$ | OR | 95% CI lower limit | 95% CI upper limit |
|---|---|---|---|---|---|---|---|
| Gender | 0.413 | 0.129 | 10.266 | 0.001 | 1.511 | 1.174 | 1.944 |
| Age | 0.030 | 0.007 | 20.585 | <0.001 | 1.030 | 1.017 | 1.044 |
| Dementia | 1.963 | 0.199 | 97.247 | <0.001 | 7.117 | 4.819 | 10.513 |
| Malignant cancer | 1.187 | 0.180 | 43.271 | <0.001 | 3.276 | 2.300 | 4.666 |
| Severe liver disease | 2.273 | 0.290 | 61.402 | <0.001 | 9.713 | 5.500 | 17.152 |
| Metastatic solid tumor | 0.745 | 0.273 | 7.451 | 0.006 | 2.105 | 1.234 | 3.593 |
| Warfarin | 0.938 | 0.181 | 26.906 | <0.001 | 2.554 | 1.792 | 3.640 |
| PLT | −0.003 | 0.001 | 15.699 | <0.001 | 0.997 | 0.995 | 0.998 |
| Constant | −6.694 | 0.575 | 135.500 | <0.001 | 0.001 | | |

*OR: odds ratios; CI: confidence intervals; PLT: Platelet Count.*

**TABLE 5. Logistic regression model for bleeding after anticoagulation therapy in atrial fibrillation patients.**

| Variable | Cut-off | AUC (95% CI) | SE | *p* | Sensitivity | Specificity | Youden index |
|---|---|---|---|---|---|---|---|
| Gender | 1.500 | 0.539 (0.505–0.574) | 0.018 | 0.025 | 0.475 | 0.604 | 0.079 |
| Age | 83.756 | 0.612 (0.574–0.650) | 0.019 | <0.001 | 0.404 | 0.782 | 0.186 |
| Dementia | 0.500 | 0.561 (0.523–0.598) | 0.019 | 0.001 | 0.150 | 0.971 | 0.121 |
| Malignant cancer | 0.500 | 0.564 (0.527–0.601) | 0.019 | <0.001 | 0.221 | 0.907 | 0.128 |
| Severe liver disease | 0.500 | 0.527 (0.491–0.563) | 0.018 | 0.131 | 0.064 | 0.989 | 0.053 |
| Metastatic solid tumor | 0.500 | 0.526 (0.490–0.562) | 0.018 | 0.138 | 0.086 | 0.967 | 0.053 |
| Warfarin | 0.500 | 0.540 (0.507–0.573) | 0.017 | 0.022 | 0.850 | 0.230 | 0.080 |
| PLT | 133.500 | 0.567 (0.531–0.603) | 0.018 | <0.001 | 0.361 | 0.759 | 0.12 |
| Combined | 0.050 | 0.726 (0.693–0.760) | 0.017 | <0.001 | 0.539 | 0.824 | 0.363 |

*AUC: area under the curve; CI: confidence intervals; SE: Standard Error; PLT: Platelet Count.*

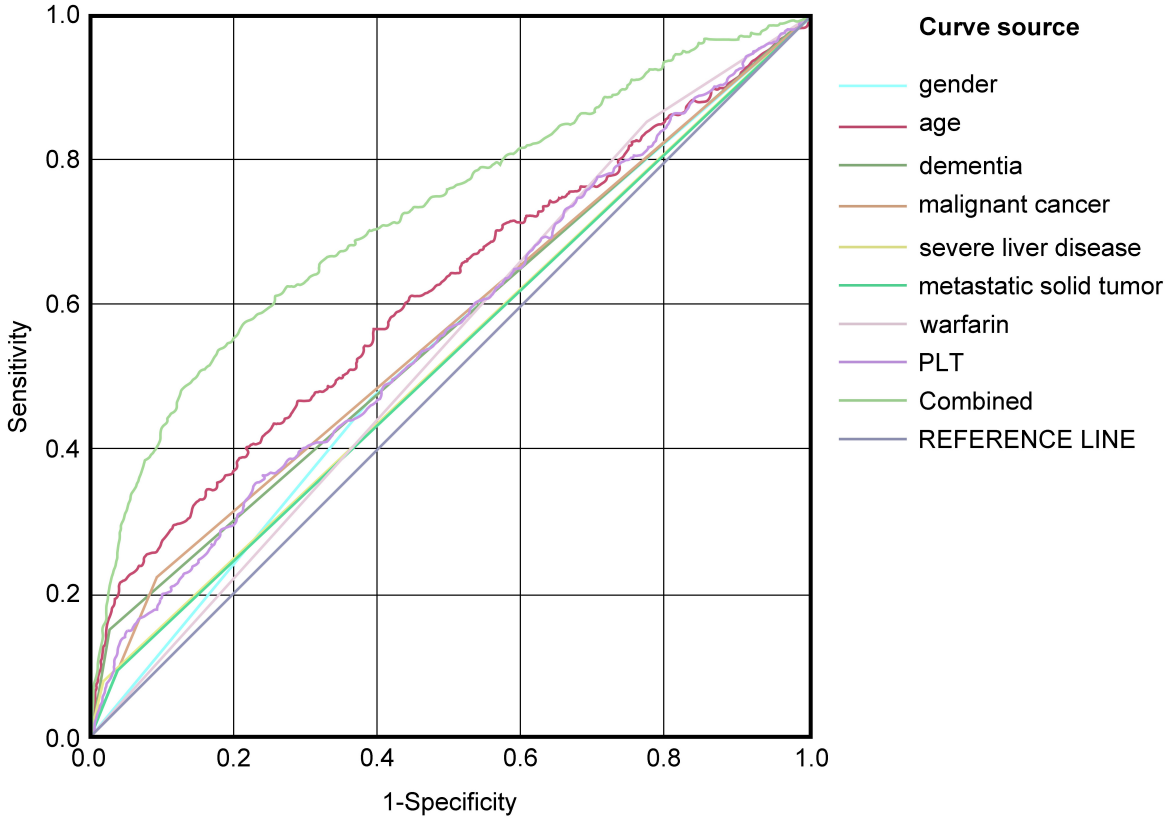


**FIGURE 2. ROC curve analysis.** PLT: Platelet Count.

preventive anticoagulation therapy [8, 9]. Kongebro's study [10] disclosed that individuals suffering from AF witnessed a twofold elevation in the risk of major bleeding after initiating oral anticoagulation therapy, whereas patients screened for subclinical bleeding did not exhibit a higher bleeding risk after the initiation of anticoagulation. Consequently, the predictive screening for bleeding subsequent to anticoagulation therapy in AF patients holds significant importance. However, existing bleeding risk assessment tools have certain limitations. The (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly (HAS-BLED)) score, which is a prevalently utilized bleeding risk assessment model, has difficulties in precisely identifying the truly high-risk individuals among elderly patients, limiting its application [11]. Furthermore, elderly AF patients encounter additional complexities in anticoagulation therapy because of clinical factors such as anemia, frailty, fall risk, cognitive impairment and polypharmacy. Other assessment tools, like the (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Re-bleeding, Hypertension, Anemia, Genetic factors, Excessive fall risk, Stroke (HEMORR2HAGES)) and Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) scores, build upon the HAS-BLED by incorporating additional factors such as malignancy, fall risk and anemia, making them more suitable for refined assessments in specific populations [12]. Studies have shown that incorporating aortic stenosis (AS) into

the scoring system can significantly improve the accuracy of predicting bleeding [13]. However, the 2024 European Society of Cardiology Guidelines for the Management of Atrial Fibrillation suggest giving priority to the management of modifiable bleeding risk factors (such as blood pressure control, limiting alcohol intake, and avoiding unnecessary antiplatelet or anti-inflammatory drugs) rather than merely relying on bleeding scores to direct anticoagulation therapy [14]. In clinical practice, there is a need to dynamically balance the risks of stroke and bleeding and conduct individualized assessments based on the patient's condition. Based on the MIMIC-ED database, this paper explores the correlation between anticoagulation therapy strategies and bleeding risk in AF patients, combines patient-specific factors, and proposes individualized anticoagulation therapy strategies for AF patients, providing new evidence for clinical decision-making.

This study is the first to integrate metastatic solid tumors and dementia into a bleeding risk model for AF patients, addressing gaps in existing scores. Our findings emphasize the underrecognized role of malignancy and cognitive impairment in anticoagulation safety. The results of this study indicate that the overall probability of bleeding in AF patients after anticoagulation therapy is 4.02%, which is within a relatively consistent range compared to previous studies [15, 16]. Notably, the primary anticoagulation strategy in this study was warfarin, accounting for 77.28% of cases, suggesting that despite the emergence and gradual acceptance of NOACs, warfarin remains the dominant traditional anticoagulant. Among diverse anticoagulation strategies, Apixaban presented the lowest likelihood of bleeding, whereas Warfarin and Enoxaparin exhibited higher probabilities. This implies that NOACs, especially Apixaban, possess remarkable superiority in diminishing the bleeding risk. Zhao *et al*. [17] also found that anticoagulation strategies play a crucial role in the occurrence of bleeding in patients with non-valvular atrial fibrillation. Previous investigations have comprehensively disclosed the preponderance of NOACs over the traditional anticoagulant Warfarin in diminishing the bleeding risk. Unverdorben stated [18] that oral anticoagulation therapy markedly reduces the risk of major bleeding and all-cause mortality while averting stroke associated with AF. Comparably, the ENGAGE-AF study likewise demonstrated that Edoxaban has a lower occurrence of major bleeding in contrast to Warfarin. However, some studies have shown no difference in thrombotic events and major bleeding between warfarin and NOACs in the treatment of atrial fibrillation in adults with transthyretin cardiac amyloidosis [19]. T The possible cause could be that the amyloid deposition within the myocardium of patients with cardiac amyloidosis results in myocardial stiffness and microvascular pathology, altering local hemodynamics and cardiac structure, which may mask or alter the differences in the effects of different anticoagulants. NOACs directly target a single coagulation factor (such as Xa or IIa), while Warfarin produces a broad anticoagulant effect by inhibiting vitamin K-dependent coagulation factors (II, VII, IX, X), increasing the risk of bleeding [20]. The pharmacokinetic traits of NOACs are rather stable, and there is not the necessity for frequent dose modifications, while Warfarin is prone to dietary, genetic and drug-drug interactions, enhancing the possibility of adverse incidents. Researches have indicated that NOACs are markedly superior to Warfarin in diminishing the risk of intracranial hemorrhage. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) studies confirmed that compared to Warfarin, Apixaban and Dabigatran reduced the incidence of intracranial bleeding by approximately 50%–70%. This may be related to the more precise anticoagulant mechanism and drug effect of NOACs.

The results of the Logistic regression analysis in this study indicate that gender, age, dementia, malignant cancer, severe liver disease, metastatic solid tumor, warfarin, and PLT count are independent predictors of bleeding in AF patients after anticoagulation therapy. Similar to the study by Ferroni [21], the risk of gastrointestinal bleeding is higher in female AF patients treated with direct oral anticoagulants (DOACs) than in males. The relatively higher bleeding risk in female patients could be ascribed to their relatively lower vascular wall elasticity, comparatively weaker repair abilities after bleeding, and the potential impact of hormonal fluctuations. On coagulation function. Females have a smaller body surface area and lower body weight compared to males, resulting in higher drug concentrations when receiving the same anticoagulant dose, which increases the bleeding risk. The risk of bleeding rises markedly with advancing age, and elderly patients are especially at a high-risk level [22]. Aging is associated with decreased coagulation factor synthesis and increased vascular fragility, making elderly patients more susceptible to bleeding. Elderly patients often have multiple chronic diseases (such as hypertension and diabetes), which may further exacerbate the side effects of anticoagulant medications. Furthermore, research has indicated that elderly patients possess a greater likelihood of falling, thereby resulting in an augmented risk of traumatic bleeding associated with anticoagulant therapy [23]. Similar to the study by Dominguez [24], gender, dementia, and liver disease are predictors of major bleeding in AF patients. Owing to cognitive impairments, patients suffering from dementia frequently miss, take an incorrect dose, or overdose on anticoagulants, resulting in uncontrolled anticoagulation therapy. Their decreased mobility and judgment increase the risk of falls and bleeding events. Patients with dementia often have multiple coexisting chronic diseases that may require combination therapy, further increasing the bleeding risk. Cancer patients frequently encounter cancer-associated thrombosis (like disseminated intravascular coagulation), thereby enhancing the probability of bleeding. can lead to thrombocytopenia or bone marrow suppression, which further elevates the risk of bleeding triggered by anticoagulant therapy (such as disseminated intravascular coagulation), Enhancing the possibility of bleeding. Cancer chemotherapy and radiotherapy might result in thrombocytopenia or bone marrow suppression, thereby further escalating the risk of bleeding triggered by anticoagulant therapy [25]. Certain tumors, such as gastrointestinal tumors, can directly disrupt the mucosal barrier, increasing the local risk of bleeding. However, studies by Wang Chunli *et al*. [26] indicate that the combination of anticoagulant and anticancer drugs does not increase the risk of bleeding, suggesting that the increased bleeding risk in cancer patients is unrelated to the use of anticancer drugs. Patients

with severe liver disease have a higher risk of bleeding. The liver serves as the primary organ for the synthesis of coagulation factors, and any liver dysfunction will markedly reduce the production of coagulation factors, thereby causing impairment in coagulation. Patients suffering from liver disease frequently exhibit hypersplenism, which leads to thrombocytopenia and raises the bleeding risk. Moreover, liver dysfunction also postpones the metabolism of anticoagulant drugs, enhancing drug accumulation and toxicity. ROUBiN S R [27] Studies show that metastatic solid tumors are associated with a 20% increase in the risk of bleeding events, and patients with metastatic solid tumors and those undergoing radiotherapy have the highest risk of bleeding. Metastatic solid tumors will further heighten the bleeding risk on account of the inflammatory state and angiogenesis brought about by extensive metastatic tumors, thereby enhancing the risk of bleeding. Tumor invasion of blood vessels or organ surfaces can make local bleeding difficult to control, and the high bleeding risk is also associated with radiotherapy. Warfarin requires strict monitoring of the International Normalized Ratio (INR), and fluctuations in INR can easily lead to bleeding. The anticoagulant effect of Warfarin is susceptible to the influence of vitamin K intake and other medications, increasing the possibility of uncontrolled anticoagulation [28]. The polymorphism of *Cytochrome P450 Family 2 Subfamily C Member 9* (*CYP2C9*) and *Vitamin K Epoxide Reductase Complex Subunit 1* (*VKORC1*) genes has an impact on the metabolism of Warfarin, resulting in notable disparities in drug concentration and effectiveness concentration and efficacy among diverse patients. Furthermore, a study by Dakroub A [29] indicates that the use of Warfarin and chronic kidney disease are independent risk factors for death within one year in AF patients with gastrointestinal bleeding. Therefore, Warfarin should be used cautiously in patients with a high risk of bleeding. Low platelet levels serve as a direct manifestation of insufficient hemostatic capacity. Researches have demonstrated that the dynamic alterations of PLT during anticoagulant therapy could be utilized to prognosticate the bleeding risk, particularly for elderly patients or those with concomitant chronic disorders. This study shows that the bleeding prediction model for AF patients after anticoagulant therapy, constructed based on gender, age, dementia, malignant cancer, severe liver disease, metastatic solid tumor, Warfarin and PLT, has good diagnostic performance with an AUC of 0.726. The model's diagnostic sensitivity and specificity are 53.9% and 82.4%, respectively. Compared to HAS-BLED (AUC: 0.65–0.68) and ATRIA (AUC: 0.70), our model (AUC: 0.726) demonstrated superior discrimination, particularly in identifying low-risk patients (specificity: 82.4%). This highlights its potential for clinical prioritization. The prediction model established in this research possesses a moderate to high effectiveness in differentiating between bleeding and non-bleeding patients among AF patients who are undergoing anticoagulant therapy. The model's ability to identify true high-risk bleeding patients has room for improvement, but it has high accuracy in identifying low-risk patients, which helps avoid unnecessary risks due to over intervention. The model established within this study holds particularly significance for clinical practice, especially for elderly patients or those with complex pathologies, since it a is capable of aiding physicians in locating an appropriate balance between risk assessment and treatment decisions. Future studies could enhance predictive performance by integrating machine learning algorithms (*e.g.*, random forests) and novel biomarkers (*e.g.*, genetic polymorphisms or dynamic platelet function tests).

This study also has the following limitations: (1) owing to the constraint of database data extraction, the study failed to take antiplatelet therapy (such as aspirin or clopidogrel) into account that may confuse the risk of bleeding. (2) The MIMIC-ED database primarily includes U.S. patients, potentially limiting generalizability to non-Western populations. (3) The Racial diversity and regional treatment variations were not taken into analysis, which might bring about selection bias. (4) The study population was from the period of 2008 and 2019, which may be considered relatively old. Medical practices, diagnostic criteria, and patient characteristics may have evolved since then, potentially affecting the relevance and applicability of the findings to the current clinical context.

## 5. Conclusions

The diverse anticoagulant treatment approaches for patients with AF are closely related to the risk of bleeding. The bleeding prediction model for AF patients subsequent to anticoagulant therapy, which is established by taking into account factors such as gender, age, dementia, malignant cancer, severe liver disease, metastatic solid tumor, warfarin and PLT, demonstrates good diagnostic performance. Within his bleeding risk prediction model, gender and age serve as fundamental demographic factors that are associated with bleeding risk, while dementia, malignant cancer, severe liver disease, and metastatic solid tumor signify disease states and PLT constitutes. The model indicators are easily accessible and have certain clinical application value. However, despite the model's good diagnostic performance, there are still some limitations. The sensitivity of the model is required to be enhanced so as to identify patients with bleeding more precisely. Additionally, the model may not have covered all factors related to bleeding risk, such as genetic variations and drug interactions. In the future, there is a necessity for further optimization of model variables, accompanied by the validation of its external applicability and exploration of the practical application value of dynamic prediction tools in clinical settings. This will be conducive to better balance the dynamic relationship between stroke prevention and bleeding risk in AF patients, and offer them safe and effective anticoagulant treatment strategies.

### AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

### AUTHOR CONTRIBUTIONS

WQL, MXL—designed the study and carried them out; supervised the data collection; analyzed the data; prepare the manuscript for publication and reviewed the draft of the

manuscript. WQL—interpreted the data. Both authors have read and approved the manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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