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# Impact of serum albumin levels on supratherapeutic PT-INR control and bleeding risk in atrial fibrillation patients on warfarin: A prospective cohort study

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ABSTRACT

*Background:* Since warfarin is primarily bound to serum albumin, hypoalbuminemia is likely to increase the free fraction of warfarin and to increase the risk of bleeding. We prospectively evaluated the impact of serum albumin levels (ALB) on international normalized ratio of prothrombin time (PT-INR) control and hemorrhagic events in atrial fibrillation (AF) patients treated with warfarin.

*Methods:* Seven hundred fifty-five non-valvular AF patients on warfarin were enrolled. PT-INR control and major bleeding events (MB, International Society on Thrombosis and Haemostasis) were prospectively followed and were related to ALB at enrollment.

*Results:* Twenty-seven patients developed MB during 1-year follow-up. In univariate/multivariate analyses, ALB (OR = 0.49, 95% CI 0.26–0.99, p = 0.04) and hemoglobin levels (OR = 0.78, 95% CI 0.65–0.92, p = < 0.01) were predictive for the annual risk of MB. In Spearman's rank correlation analysis, the baseline ALB was inversely correlated with the percentage of the time in PT-INR > 3.0 ($\rho = -0.15$, $p < 0.0001$), but neither 2.0 ≤ PT-INR ≤ 3.0 ($\rho = 0.056$, $p = 0.13$) nor PT-INR < 2.0 ($\rho = -0.008$, $p = 0.82$) during 1-year follow-up, suggesting that patients with low ALB had a directional tendency to be supratherapeutic control of PT-INR. The ROC curve showed that a cutoff of ALB was 3.6 g/dl to identify MB (AUC = 0.65). In Kaplan-Meier analysis, patients with ALB <3.6 g/dl (23/80, 29%) had more MB than those with ALB ≥3.6 g/dl (87/675, 13%, log-rank = 16.80, p < 0.0001) during long-term follow-up (3.8 ± 2.0 years).

*Conclusions:* Hypoalbuminemia increases the likelihood of supratherapeutic PT-INR control and the risk of MB. ALB can be a practical surrogate marker to prevent excessive warfarin control and warfarin-related MB.

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## 1. Introduction

Oral anticoagulation (OAC) is central to prevention of thromboembolism in atrial fibrillation (AF). Although direct oral anticoagulants (DOACs) have become popular because of their efficacy and safety, warfarin is still the treatment of choice in clinical practice. Warfarin reduces stroke risk but increases life-threatening bleeding events.

The efficacy and safety of warfarin are evaluated by the international normalized ratio of prothrombin time (PT-INR) and are ensured by strict control of PT-INR levels within the therapeutic range (2.0 < PT-INR < 3.0) [1]. However, achieving optimal PT-INR control still remains a challenge. PT-INR levels fluctuate depending on patient conditions; bleeding risk increases when PT-INR exceeds the therapeutic range.

Hypoalbuminemia is associated with bleeding risk in patients on warfarin. Warfarin is bound to plasma proteins, primarily to albumin, and thus hypoalbuminemia likely increases the free fraction of warfarin, which may enhance its anticoagulation effects. Bleeding prediction scores are used to evaluate warfarin-related hemorrhagic risk in clinical practice but show only permissive predictability [2–5]. Serum albumin levels would influence PT-INR control and can be an additional predictive biomarker for warfarin-related bleeding. Information on this, however, is limited.

The present study prospectively investigated the impact of serum albumin levels on PT-INR control and bleeding events in AF patients on warfarin.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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## 2. Methods

### 2.1. Study population

This is a single-center prospective study. Between April 2009 and March 2011, we enrolled 1086 consecutive patients with non-valvular AF patients in Fujita Health University Hospital (Fig. 1). All patients had maintained warfarin therapy for more than one year before enrollment. Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was reviewed and approved by the review board of Fujita Health University.

Regarding warfarin control, the target PT-INR range was set to 2.0–3.0 but the therapeutic intensity was lowered (PT-INR 1.6–2.6) in elderly patients (≥70) based on the Japanese guideline recommendation [6]. The quality of anticoagulation control was evaluated by the time in therapeutic range (TTR) according to the Rosendaal method, which uses linear interpolation to assign a PT-INR value to each day between two successive measured PT-INR values [7]. TTR was calculated as the percentage of time during which the interpolated PT-INR values lie between 2.0 and 3.0 or 1.6 and 2.6 based on patient age, ranging from 0% to 100%; TTR ≥60% was considered as the optimal anticoagulation control [8].

A complete medical history was obtained from all patients, and baseline blood count and biochemical tests were performed at the time of enrollment. The $CHADS_2$ score (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke [doubled]) [9], the $CHA_2DS_2$-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, previous stroke [doubled], coronary artery disease/peripheral arterial disease, age ≥65 years, sex female) [10], and the HAS-BLED score (hypertension, age >65 years, previous stroke, previous bleeding, labile INR, hepatic or renal disease, drug/drink) [2] were calculated to evaluate thromboembolic and bleeding risk.

### 2.2. Exclusion criteria

Patients with valvular atrial fibrillation (prosthetic or not) were excluded. Non-Japanese patients and patients younger than 20 years old were excluded. We excluded patients who required temporary interruption of warfarin for surgical treatment or any other invasive procedure or who discontinued oral anticoagulation on a doctor's recommendation (advanced age) or because of patient preference (Fig. 1).

### 2.3. Clinical follow-up and major bleeding events

All patients were prospectively followed up after enrollment ($3.8 \pm 2.0$ years). PT-INR measurements were taken more than eight times per year and warfarin dosage was adjusted to achieve the target therapeutic range of PT-INR. Blood count and biochemical tests were performed with each PT-INR measurement. The percentage of time in PT-INR < 2.0, the percentage of time in 2.0 ≤ PT-INR ≤ 3.0, and the percentage of time in 3.0 < PT-INR, for one year after the enrollment were calculated with the Rosendaal method (total time in each PT-INR range/year, Fig. 2A); each value was related to the serum albumin levels at enrollment. Major bleeding events (MB) were reported according to the definition of the International Society of Thrombosis and Haemostasis if they occurred while a patient was receiving warfarin during the follow-up period and met at least 1 of the following 4 conditions: (1) associated with death within 30 days, (2) associated with blood transfusion, (3) associated with bleeding into a critical anatomic site, or (4) cited as the main reason for a hospitalization [11].

### 2.4. Statistical analysis

Categorical data were expressed as frequencies and percentages, and they were compared by $\chi^2$ test. Continuous data were expressed as a mean or median with inter quartile range (IQR). Comparisons between

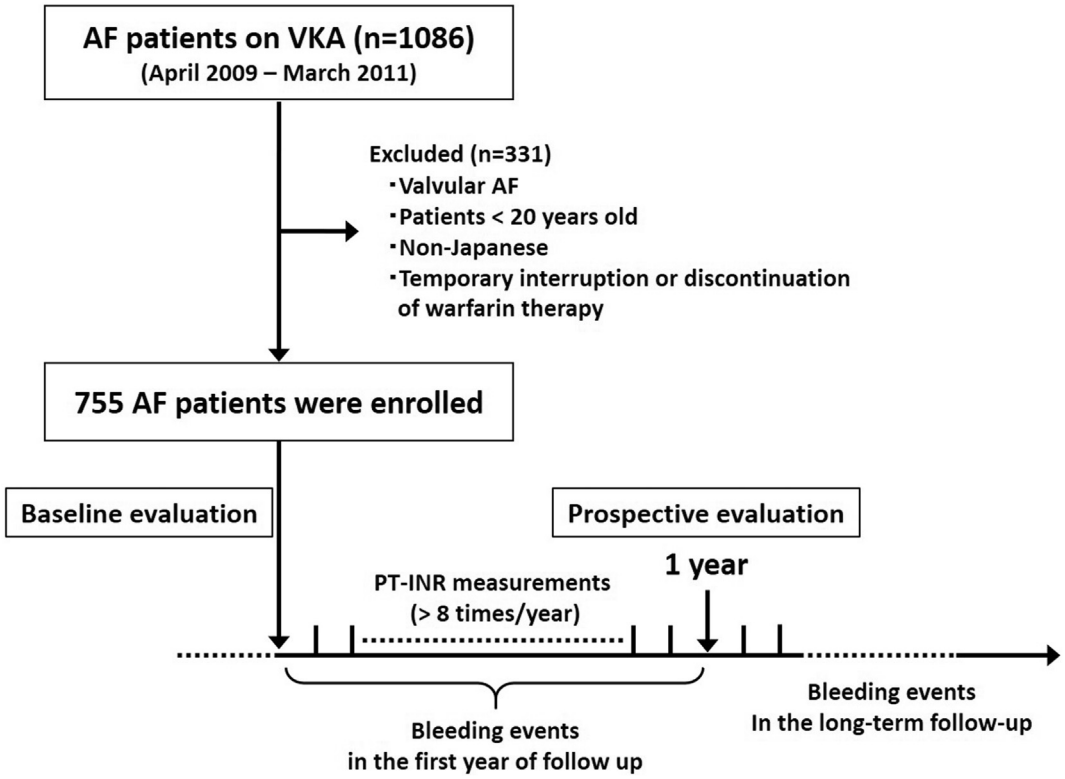


**Fig. 1.** Study design and patient enrollment.

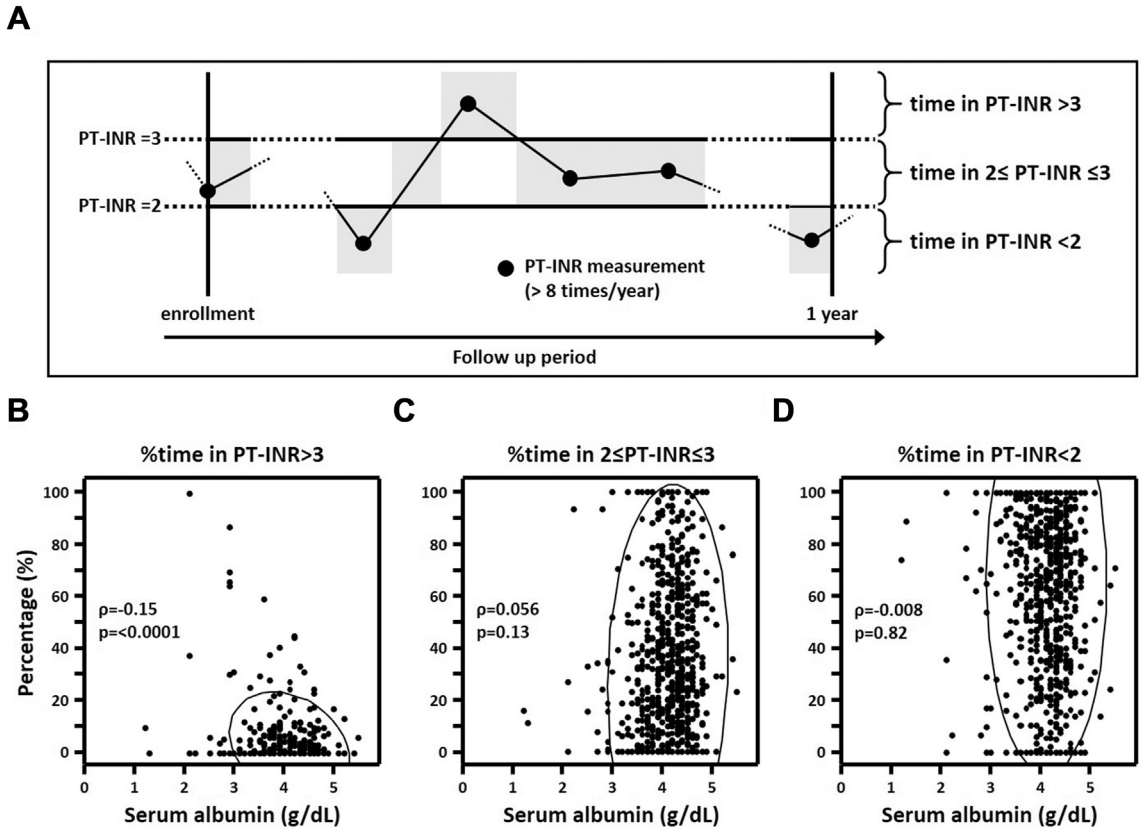


**Fig. 2.** Relationship between the basal serum albumin levels and PT-INR control during 1-year follow-up. A. Measurement of the percentage of time (%time) in 3.0 < PT-INR, 2.0 ≤ PT-INR ≤ 3.0, and PT-INR < 2.0, using the Rosendaal method (total time in each PT-INR range/year). B. Spearman's rank correlation analysis for relationship between the basal serum albumin levels and %time in PT-INR > 3.0 during 1-year follow-up. B. Relationship between the basal serum albumin levels and %time in 2.0 < PT-INR < 3.0. C. Relationship between the basal serum albumin levels and %time in PT-INR < 2.0.

two groups were performed using unpaired *t*-test or Wilcoxon analysis for continuous variables. All categorical variables that were significant on univariate Logistic analysis were included in multivariate analysis to identify significant risk factors and to calculate odds ratios and 95% confidence intervals (95% CI). The follow-up period was calculated from the date of registration to that of the event or censoring. Event-free survival rate was calculated using Kaplan-Meier survival analysis, and log-rank statistics were used for group comparisons. $p < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Baseline patient characteristics

Seven-hundred fifty-five patients were enrolled (37% female, median age 70 years, IQR 64–76). Baseline patient characteristics are summarized in Table 1. Median TTR for one year before enrollment was 51.1% (IQR 18.5–77.0). The median $CHADS_2$ score, $CHA_2DS_2$-VASc score, and HAS-BLEAD score were 2 (IQR 2–3), 4 (IQR 3–5), and 4 (IQR 3–5), respectively. The serum albumin levels at enrollment were 4.2 (3.9–4.4).

### 3.2. Factors associated with bleeding events

Twenty-seven (3.6%) patients developed MB during the 1-year follow-up. We compared the baseline characteristics of patients with and without MB. Age and HAS-BLED score were significantly higher in patients with MB than those without MB; body weight, and the basal albumin and hemoglobin levels were decreased (Table 2). The average serum albumin levels during the 1-year follow-up period were also significantly lower in patients with MB than those without MB (3.5 ± 0.7 mg/dl vs. 4.1 ± 0.5 mg/dl, $p < 0.0001$). In multivariate analysis, the serum albumin levels (OR = 0.49, 95% CI 0.26–0.99, $p = 0.04$) and hemoglobin levels (OR = 0.78, 95% CI 0.65–0.92, $p = < 0.01$) were predictive for the annual risk of MB (Table 3).

### 3.3. Association between baseline serum albumin levels and PT-INR control

Fig. 2 demonstrates a dot-plot of percentage of time in PT-INR < 2.0, 2.0 ≤ PT-INR ≤ 3.0, and PT-INR > 3.0, during 1-year follow-up as a function of the baseline serum albumin levels. In Spearman's rank correlation analysis, the basal serum albumin levels had an inverse correlation with the percentage of time in PT-INR > 3.0 during 1-year follow-up ($\rho = -0.15$, $p < 0.0001$, Fig. 2B) whereas it had no correlation with the time in 2.0 ≤ PT-INR ≤ 3.0 ($\rho = 0.056$, $p = 0.13$, Fig. 2C) or in PT-INR < 2.0 ($r = -0.008$, $p = 0.82$, Fig. 2D). This suggests that patients with low serum albumin levels had a directional tendency to be supratherapeutic PT-INR control.

### 3.4. Hypoalbuminemia is predictive for major bleeding

We examined the predictability of basal serum albumin levels to identify bleeding events during long-term follow-up (3.8 ± 2.0 years). The ROC curve showed an optimal cutoff of serum albumin levels was 3.6 g/dl to identify bleeding events; the area under the curve was 0.65 (Fig. 3A). The Kaplan-Meier analysis demonstrated that patients with the basal serum albumin levels <3.6 g/dl (23/80, 29%) had more bleeding events than those with the values ≥3.6 g/dl (87/675, 13%, log-rank 16.80 $p < 0.0001$) during follow-up period (Fig. 3B).

**Table 1**
Baseline patient characteristics (n = 755).

| | |
|---|---|
| Age, years | 70 (64–76) |
| Gender, female | 277 (37) |
| Body weight, kg | 55 (47–65) |
| Persistent AF | 486 (64) |
| $CHADS_2$ score, points | 2 (2–3) |
| $CHA_2DS_2$-VASc score, points | 4 (3–5) |
| HAS-BLED score, points | 4 (3–5) |
| Comorbidities | |
| CHF | 479 (63) |
| Hypertension | 521 (69) |
| Diabetes | 233 (31) |
| Age >75 years | 210 (28) |
| Age >65 years | 522 (69) |
| Previous stroke | 195 (26) |
| CAD | 195 (26) |
| Hepatic disease[a] | 100 (13) |
| Renal disease[b] | 109 (14) |
| Previous bleeding | 79 (10) |
| Medication | |
| Amiodarone | 39 (5) |
| Beta-blocker | 344 (46) |
| Antiarrhythmic drug | 131 (17) |
| Anti-platelets/NSAIDs | 319 (42) |
| Laboratory data | |
| GOT, IU/L | 24 (20−30) |
| GPT, IU/L | 19 (14–27) |
| Serum albumin, g/dL | 4.2 (3.9–4.4) |
| Serum creatinine, mg/dL | 0.87 (0.71–1.08) |
| Hemoglobin, g/dL | 13.3 (11.9–14.6) |
| Platelet, $\times 10^4$/ml | 17.5 (14.3–21.3) |
| Echocardiography | |
| LVEF, % | 55 (45–60) |
| Left-atrial diameter, mm | 43 (38–49) |
| TTR, % | 51.1 (18.5–77.0) |

Data given as n (%) or median with inter quartile range (IQR). CAD, coronary artery disease; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NSAID, non-steroidal anti-inflammatory drug; TTR, time in therapeutic range; GOT, Glutamic Oxaloacetic Transaminase; GPT, Glutamic Pyruvic Transaminase.
[a] Defined by cirrhosis or elevated liver transaminases enzymes >3 times than the upper limit of normal and elevated total bilirubin >2 times higher than the upper limit of normal.
[b] Defined by estimated glomerular filtration rate < 30 mL/min/1.73m$^2$.

**Table 2**
Comparison of patient characteristics between bleeding and no bleeding groups in 1-year follow-up.

| | Bleeding (n = 27) | No bleeding (n = 728) | p value |
|---|---|---|---|
| Age, years | 72 (67–80) | 70 (64–76) | 0.03 |
| Gender, female | 13 (48) | 264 (36) | 0.21 |
| Body weight, kg | 48 (40–55) | 56 (47–65) | 0.002 |
| Paroxysmal AF | 7 (26) | 262 (36) | 0.28 |
| $CHADS_2$ score, points | 3 (2–4) | 2 (2–3) | 0.05 |
| $CHA_2DS_2$-VASc score, points | 5 (4–6) | 4 (3–5) | 0.01 |
| HAS-BLED score, points | 4 (3–5) | 3 (3–4) | 0.007 |
| Comorbidities | | | |
| CHF | 19 (70) | 460 (63) | 0.45 |
| Hypertension | 18 (67) | 503 (69) | 0.79 |
| Age >75 years | 13 (48) | 197 (27) | 0.02 |
| Age >65 years | 23 (85) | 499 (69) | 0.07 |
| Diabetes | 10 (37) | 223 (31) | 0.48 |
| Previous stroke | 10 (37) | 185 (25) | 0.18 |
| CAD | 9 (33) | 186 (26) | 0.36 |
| Hepatic disease | 7 (26) | 93 (13) | 0.05 |
| Renal disease | 10 (37) | 99 (14) | 0.0007 |
| Previous bleeding | 6 (22) | 73 (10) | 0.04 |
| Medication | | | |
| Amiodarone | 1 (4) | 38 (5) | 0.73 |
| Beta-blocker | 15 (56) | 329 (45) | 0.29 |
| Antiarrhythmic drug | 2 (7) | 129 (18) | 0.17 |
| Anti-platelets/NSAIDs | 16 (59) | 303 (42) | 0.07 |
| Laboratory data | | | |
| GOT, IU/L | 25 (20−31) | 24 (20–30) | 0.81 |
| GPT, IU/L | 19 (9–24) | 19 (14–27) | 0.20 |
| Serum albumin, g/dL | 3.9 (3.5–4.3) | 4.2 (3.9–4.4) | 0.007 |
| Serum creatinine, mg/dL | 1.00 (0.75–1.22) | 0.87 (0.71–1.07) | 0.09 |
| Hemoglobin, g/dL | 11.2 (9.6–13.2) | 13.3 (12.0–14.7) | <0.0001 |
| Platelet, $\times 10^4$/ml | 16.9 (13.4–25.9) | 17.6 (14.4–21.2) | 0.96 |
| Echocardiography | | | |
| LVEF, % | 55 (45–60) | 55 (45–60) | 0.54 |
| Left-atrial diameter, mm | 43 (37–48) | 43 (38–49) | 0.99 |
| TTR, % | 29.5 (13.6–72.1) | 51.5 (18.7–78.0) | 0.13 |

Data given as n (%) or median with inter quartile range (IQR). CAD, coronary artery disease; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NSAID, non-steroidal anti-inflammatory drug; TTR, time in therapeutic range; GOT, Glutamic Oxaloacetic Transaminase; GPT, Glutamic Pyruvic Transaminase.

## 4. Discussion

The present study demonstrated that the serum albumin levels were inversely correlated with the time in supratherapeutic PT-INR control (>3.0) among AF patients on warfarin, and that hypoalbuminemia increased the risk of MB in this population.

### 4.1. Serum albumin levels and PT-INR control

To our knowledge, this study is the first to demonstrate the impact of serum albumin levels on PT-INR controls among general AF patients on warfarin; those inversely correlated with the percentage of time in PT-INR > 3.0, but neither 2.0 ≤ PT-INR ≤ 3.0 nor PT-INR < 2.0. Major hemorrhage developed in AF patients on warfarin whose PT-INR levels were above the therapeutic range [12,13]. In Japanese studies, patients on warfarin gradually increased the hazard ratio of MB as PT-INR levels rose [14], and therefore the higher PT-INR levels were an independent predictor for MB in AF patients receiving warfarin [15]. Lip et al. also demonstrated that an unstable PT-INR control was one of the most significant risk factors for MB (HR 2.05) among the variables of HAS-BLED score in the SPORTIF III and V trials [16]. Identifying factors facilitating supratherapeutic PT-INR control is important to avoid serious hemorrhage.

Warfarin is highly bound to plasma proteins (about 97%), primarily to albumin, and thus hypoalbuminemia is likely to increase the free fraction of warfarin, which enhances the anticoagulation effects. Of note, rivaroxaban, a direct oral anticoagulant, also shows highly protein binding affinity. Hankey et al. demonstrated that among AF patients, low levels of serum albumin increased the risk of intracranial hemorrhage, associated with the enhanced anticoagulation efficacy of rivaroxaban, in the sub-analysis of ROCKET AF trial [17].

### 4.2. Serum albumin levels and bleeding events

The present study demonstrated that low levels of serum albumin are predictive for MB events. Many studies have evaluated the bleeding risk in AF patients with OAC; the various predictive factors, such as prior bleeding, anemia, renal impairment, hypertension, antiplatelet use, and advanced age, have been reported [2–5]. Similarly to the previous studies [3–5], low hemoglobin levels were a significant predictor for MB in this study; it may reflect a predisposition to bleeding or recent subclinical hemorrhage. However, there have been limited data on the relationship between serum albumin levels and bleeding risk in long-term follow-up. In a single UK cohort of AF patients on warfarin,

**Table 3**
Predictors for major bleeding.

| | Univariate OR (95% CI) | p value | Multivariate OR (95% CI) | p value |
|---|---|---|---|---|
| Age | 1.04 (0.99–1.09) | 0.06 | | |
| Body weight | 0.98 (0.96–1.00) | 0.06 | | |
| Serum albumin | 0.35 (0.20–0.64) | <0.01 | 0.49 (0.26–0.99) | 0.04 |
| Hemoglobin | 0.72 (0.61–0.85) | <0.01 | 0.78 (0.65–0.92) | <0.01 |
| HAS-BLED score | 1.52 (1.11–2.08) | <0.01 | 1.39 (0.99–1.93) | 0.05 |

Data given as odds ratio (OR) with 95% confidence interval (95% CI).

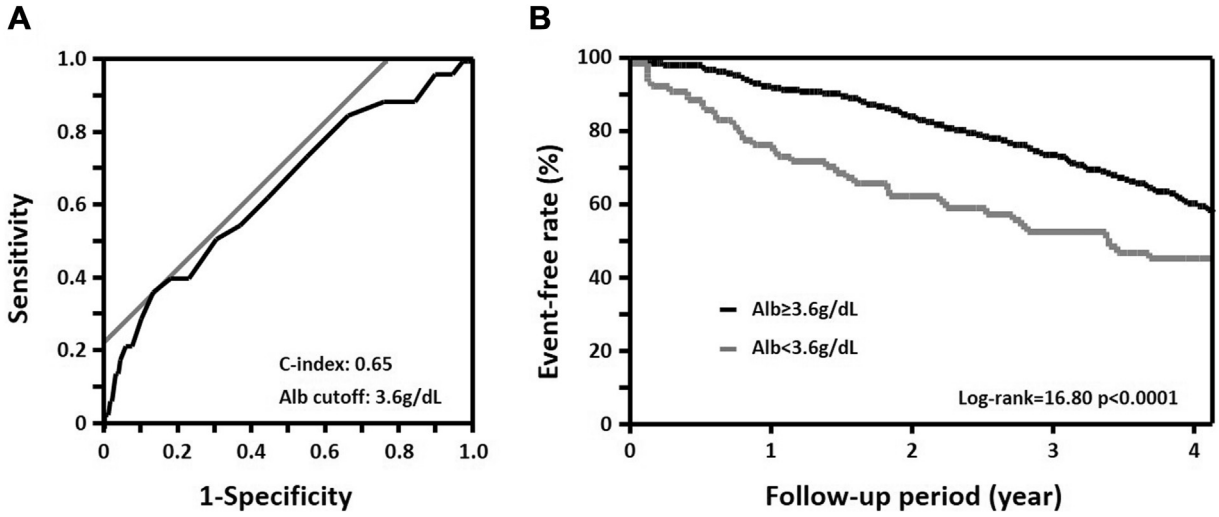


**Fig. 3.** Serum albumin levels as predictor for bleeding events. A. Receiver-operating characteristic curve (ROC) of serum albumin to identify bleeding events. Cutoff point (black arrow) and area under the curve (AUC) are shown. B. Kaplan-Meier event free survival curve for the occurrence of bleeding events in AF patients with serum albumin levels <3.6 (n = 80, 23 events) or >3.6 (n = 675, 87 events).

Abdelhafiz et al. retrospectively evaluated the influence of anemia, hypoalbuminemia, and renal impairments on bleeding events and reported that hypoalbuminemia was a significant predictor of all bleeding events (minor and major) in younger patients (aged <75 years) [18], being almost similar to the results in this study. Efird et al. demonstrated that serum albumin and creatinine levels were the strongest predictors of poor anticoagulation control and hemorrhages in patients with liver disease receiving warfarin [19]. However, only veterans were included and primary indication for warfarin was not only AF but also thromboembolism in the study, so the findings are not specific to the general AF population. Hankey et al. proposed a bleeding risk stratification schema based on eight significant predictors including serum albumin levels (PANWARDS nomogram) in AF patients treated with warfarin or rivaroxaban, but this schema is limited to stratify the risk of intracranial hemorrhage [17].

Hypoalbuminemia results from conditions such as malnutrition, inflammation, and cachexia, all of which increase the risk of bleeding. Liver dysfunction impairs the production of albumin and clotting factors, facilitating supratherapeutic PT-INR control, and increases bleeding events [19]. Hypoalbuminemia is also associated with age-related frailty; patients in this study with bleeding were older and thinner than those without. Low serum albumin levels may reflect underlying condition and diseases that facilitate serious hemorrhage. Levels of serum albumin and PT-INR fluctuate over time; a transient decrease in serum albumin increases the likelihood of supratherapeutic PT-INR controls and increases the risk of bleeding. Our results suggest that close observation of serum albumin levels would help to prevent excessive warfarin control and bleeding events in clinical practice.

## 5. Study limitations

The sample size was small and the observational period was short, both of which could limit the likelihood of detecting small effects or significant relationship from the data. For this reason, large-scale, multicenter studies for longer follow-up period are required. The study does not consider patients with valvular heart disease because the target therapeutic range is different. We were unable to control variables such as antiplatelet pharmacotherapy, thrombocytopenia, endothelial dysfunction, and fibrinolysis that may precipitate hemorrhagic events. We did not collect data on other possible confounding variables such as patients' education, socioeconomic status, and distance from the hospital, all of which may be associated with the quality of anticoagulation. Although the cutoff value of 3.6 mg/dl of serum albumin levels is predictive for MB, the ROC curve still showed low accuracy (AUC = 0.65). Low serum albumin levels which increase bleeding risk may vary among individuals and are likely affected by age, gender, body weight, concomitant drugs, underlying diseases, and so on. In this study, eligible patients had a variety of background characteristics in the general anticoagulation population. Nor did we examine genetic polymorphisms such as VKORC1 and CYP2C9 which are known to influence the inter-individual variability and risk of bleeding in patients receiving warfarin [20]. We considered neither strokes nor recurrent venous thromboembolic events, and therefore the examination of definitive outcomes is limited to major hemorrhage.

## 6. Conclusion

Among AF patients on warfarin, low levels of serum albumin increase the likelihood of supratherapeutic PT-INR control and increase the risk of MB. Serum albumin levels can be a clinical surrogate marker that can help physicians optimize warfarin control to prevent MB.

## Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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