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Rivaroxaban for Thromboembolism Prophylaxis in Patients with Nephrotic Syndrome: A Single-Arm, Prospective Study

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Key Points

- Limited data on thromboprophylaxis with rivaroxaban in nephrotic syndrome (NS) are available.
- We evaluated the impact of NS on pharmacokinetics of rivaroxaban.
- Hypoalbuminemia was significantly associated with decreased drug concentrations and increased thrombosis risk.
- Dose adjustments based on drug concentrations may be appreciated for thromboprophylaxis in NS patients.

Keywords
Rivaroxaban · Nephrotic syndrome · Thromboprophylaxis · Gene polymorphisms · Pharmacokinetics

Abstract

Introduction: Thromboembolism is a recognized complication of nephrotic syndrome (NS). Evidence supporting the use of rivaroxaban to prevent NS-related thrombosis is limited and controversial. This study aimed to explore the impact of NS on rivaroxaban pharmacokinetics and to collect observational data on the efficacy and safety of rivaroxaban as primary thromboprophylaxis in patients with NS. ***Methods:*** This prospective study analyzed 141 patients with NS who received rivaroxaban (10 mg/day) for thromboprophylaxis. High-performance liquid chromatography-tandem mass spectrometry was used to measure the trough and peak plasma concentrations (C_{trough} and C_{max}) of rivaroxaban. The influence of clinical and genetic factors on these concentrations was examined using multivariate logistic regression. ***Results:*** The median C_{max} and C_{trough} were 68.5 ng/mL (interquartile range [IQR], 31.7–105.5 ng/mL) and 4.4 ng/mL (IQR, 1.2–11.9 ng/mL),

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respectively. The incidence of thromboembolic events (TEs) was 12.8%, while that of bleeding events was 14.2%, although all were classified as minor. Albumin level was the most significant factor affecting C_{max} (ρ = 0.55; $p < 0.001$) and was also significantly associated with TEs (0.81; 0.71–0.91 per 1.0 g/dL increase; $p = 0.001$) and bleeding risks (1.11; 1.03–1.19 per 1.0 g/dL increase; $p = 0.008$). Single nucleotide polymorphisms in the *ABCB1* gene significantly influenced C_{trough} but were not associated with clinical outcomes. ***Conclusion:*** Hypoalbuminemia significantly affects the pharmacokinetics of rivaroxaban in NS patients. A dose-adjustment strategy based on rivaroxaban concentrations, accounting for variable albumin levels, may improve the safety and efficacy of thromboprophylaxis in this population.

Introduction

Nephrotic syndrome (NS) is a significant contributor to end-stage kidney disease, characterized by edema, nephrotic-range proteinuria exceeding 3.5 g/d, and hypoalbuminemia [1]. Its etiology encompasses various glomerular diseases, such as membranous nephropathy, IgA nephropathy, focal segmental glomerulosclerosis, minimal change disease, lupus nephritis [1]. Thromboembolism is a well-documented complication of NS, resulting from urinary loss of natural anticoagulants due to defects in the glomerular filtration barrier [2]. The risk of thromboembolic events (TEs) in NS patients has been estimated at up to 40% [2]. Consequently, thromboprophylaxis is essential for the NS patients to be at high risk for thrombosis. Guidelines commonly recommend low-molecular-weight heparin (LMWH) prophylactic dose and warfarin, although the evidence supporting their use is limited [1, 3, 4].

Rivaroxaban, an oral direct factor Xa inhibitor, is recommended as a first-line therapy in thromboembolic prevention guidelines [5, 6]. Its benefits, including rapid onset and the absence of routine monitoring requirement, make rivaroxaban increasingly preferred for NS patients [7, 8]. However, as a substrate for P-glycoprotein (P-gp) with high protein binding (~95%) and metabolized by the cytochrome P450 (CYP) enzymes 3A4/5 and CYP2J2, rivaroxaban is mainly eliminated renally (~66%) [9]. Therefore, typical pathological states and therapies associated with NS, such as hypoalbuminemia and renal dysfunction, may influence rivaroxaban pharmacological properties. Additionally, genetic polymorphisms in the genes that encode enzymes and transporters involved in rivaroxaban metabolism, such as *ABCB1* (the gene encoding P-gp), *CYP3A4/5* and *CYP2J2*, could potentially affect drug exposure and thus efficacy and safety. However, while the effects of *ABCB1* mutations on rivaroxaban metabolism and clinical outcomes are relatively well-established, the impacts of other genetic variations are less well understood [10–14]. *ABCB1* mutations may lead to decreased clearance, prolonged half-life, and variable drug exposure, resulting in uncertain clinical outcomes [10–14]. Given these uncertainties, the prophylactic use of rivaroxaban in NS patients remains controversial and insufficiently substantiated [15]. This study aimed to explore the impact of NS on rivaroxaban pharmacokinetics and assess the appropriateness of prescribing a fixed dose (10 mg/day) of rivaroxaban as primary thromboprophylaxis for NS patients.

Methods

This prospective study was conducted at the National Clinical Research Center of Kidney Disease, Jinling Hospital, Medical School of Nanjing University, Nanjing, China, from March 2021 to September 2022. The study focused on the patients with NS who were prescribed rivaroxaban (10 mg/day) for primary thromboprophylaxis. The study was approved by the Ethics Committee of Jinling Hospital and complied with the Declaration of Helsinki. All participants provided their written informed consent.

Inclusion and Exclusion Criteria

The eligible participants were Han Chinese, diagnosed with NS, aged ≥18 years, with proteinuria >3.5 g/24 h and serum albumin <25 g/L. Exclusion criteria included comorbidities requiring anticoagulation (e.g., atrial fibrillation, confirmed thrombosis, acquired and inherited hypercoagulation), known bleeding disorders, recent TEs or major bleeding within 6 months before enrollment, history of malignancy, prolonged baseline prothrombin time or activated partial thromboplastin time, platelet count $<100 \times 10^9$/L, concurrent use of other anticoagulants or antiplatelets, significant liver dysfunction (cirrhosis or bilirubin >2 ×, and serum transaminases >3 ×, upper limit of normal) or renal dysfunction (creatinine clearance [CrCl] <15 mL/min), and low medication adherence (Morisky Medication Adherence Scale-8 [MMAS-8] score <6) [16].

Procedures

After at least 7 days of rivaroxaban therapy, peripheral venous blood samples were collected within 30 min before and 2–4 h after drug administration to measure plasma concentrations and genotypes.

Study Outcomes

The primary outcome was the pharmacokinetic parameters of rivaroxaban in patients with NS. The secondary outcome was a composite of the incidence and severity of clinical outcomes, including TEs and bleeding.

TEs encompassed both asymptomatic or symptomatic arterial and venous thromboembolism, such as deep vein thrombosis, renal vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, and peripheral arterial disease. The probability of TEs was initially assessed using the Wells rule (scoring: active cancer, bedridden or major surgery, calf swelling, collateral superficial veins, entire leg swollen, localized tenderness along the deep veins, pitting edema, paralysis or paresis, and previous TE scored 1; alternative diagnosis of TE scored -2; a score ≥1 indicated a medium to high probability of TE) [17] and D-dimer testing at baseline and subsequent visits. Patients with a Wells score ≥1, a positive D-dimer, or typical clinical signs and symptoms underwent further diagnostic evaluation. This included complete compression ultrasound, renal vein and pulmonary artery computed tomography angiography, and brain magnetic resonance imaging as indicated. Patients with positive imaging findings were diagnosed with TEs.

Bleeding events were categorized according to the criteria of the International Society on Thrombosis and Hemostasis (ISTH) [18, 19] as follows. Major bleeding is defined clinically overt and associated with one or more of the following: a decrease in hemoglobin of 2 g/dL, the requirement for transfusion of 2 units of packed red blood cells, bleeding at critical sites (intracranial, intraspinal, intraocular, retroperitoneal, or pericardial), or contributing to death. Clinically relevant nonmajor bleeding is overt bleeding that does not meet the criteria for major bleeding but requires medical intervention, unscheduled physician contact, interruption or discontinuation of anticoagulation, or causes significant discomfort or impairs daily activities. Minor bleeding is defined as clinically overt bleeding that does not meet the criteria for major bleeding or clinically relevant nonmajor bleeding. The locations of thrombosis and bleeding and the timing of these events were recorded.

Covariates

Baseline characteristics included demographic information (e.g., age, sex, height, weight, body mass index [BMI], and histologic subtypes) along with relevant laboratory markers and concomitant medications. Histological diagnoses were verified based on kidney biopsy reports. Biochemical analyses were conducted using automated and standardized clinical assays. Thrombosis risk was assessed using the Padua Prediction Score: active cancer, previous VTE, reduced mobility, and known thrombophilic conditions scored 3; recent trauma and/or surgery scored 2; and factors such as age ≥70 years, heart/respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, BMI ≥30 kg/m^2, or ongoing hormonal treatment scored 1, with a total score ≥4 indicating a high risk of TEs [20].

Bleeding risk was evaluated using the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Score: anemia and severe renal disease scored 3; age ≥75 years scored 2; and prior bleeding or hypertension scored 1, with scores ≥5 indicating a high risk of bleeding [21]. The BMI was calculated as weight [kg]/[height (m)]^2. CrCl was estimated using the Cockcroft-Gault formula: [(140-age) × weight (kg) × (0.85 if female)]/[72 × serum creatinine] [6].

Follow-Up

The patients were evaluated at baseline and subsequently every 3 months at our center, with additional monthly follow-ups by telephone and WeChat after local medical center evaluations. During each follow-up, drug exposure was estimated from dispensation data, including package size, product strength, and dispensation date. Follow-up continued from the initiation of rivaroxaban until its discontinuation for any reason.

Blood Sample Processing

Blood samples were collected in tubes containing 3.2% sodium citrate (1:9 *v/v*) and mixed by inverting the for 8–10 min. The samples were centrifuged at 3900 rpm for 10 min at room temperature. Plasma was separated and stored at −80°C until analysis.

Plasma Rivaroxaban Quantification

The rivaroxaban plasma concentration was determined using high-performance liquid chromatography-tandem mass spectrometry. An Agilent 1260 high-performance liquid chromatography system coupled with an API-4000 mass spectrometer was employed.

Chromatographic separation achieved on an Agilent Zorbax Eclipse Plus C18 column (3.5 μm, 2.1 × 100 mm) kept at 40°C. The mobile phase consisted of a mixture of 10 mM ammonium acetate buffer (A, 0.1% formic acid) and acetonitrile (B, 0.1% formic acid) at a 0.4 mL/min flow rate. The gradient elution program was as follows: 0–0.5 min, 80% A; 0.5–1.0 min, 80–20% A; 1.0–3.0 min, 20% A; 3.0–3.1 min, 20–80% A; and 3.1–6.0 min, 80% A. Rivaroxaban and the internal standard rivaroxaban-d4 (Zhenzhun, Shanghai, China) were ionized using an electrospray source in positive ionization mode and detected in multiple-reaction monitoring mode, with mass-to-charge ratio (*m/z*) transitions of 436.3→145.0 for rivaroxaban and 440.3→145.0 for rivaroxaban-d4 (shown in online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000540107).

Genetic Analysis

Genomic DNA was extracted from peripheral whole blood using the Wizard Genomic DNA Purification Kit (Promega, Madison, USA). Single nucleotide polymorphisms (SNPs) were genotyped using pyrosequencing with PyroMark Q24 (Qiagen, Hilden, Germany). Details are shown in online Supplementary Table S1.

Genotyping was repeated in 20% of the patients to ensure quality, yielding consistent results. We confirmed that all SNPs were in Hardy-Weinberg equilibrium and that the imputation quality was sufficient (info score >0.85) [22].

Statistical Analysis

Continuous variables were presented as means with standard deviations or medians with interquartile ranges (IQRs) based on the distribution. Categorical variables were reported as frequencies and percentages. Baseline characteristics and outcomes were compared using the Mann-Whitney U or Kruskal-Wallis test for continuous variables and the χ^2 or Fisher's exact test for categorical variables. The allele frequencies of genetic polymorphisms were assessed f or Hardy-Weinberg equilibrium using χ^2 tests or Fisher's exact tests. Kaplan-Meier estimates were used to generate cumulative risks and describe the time to thromboembolic and bleeding events.

Risk factors for thromboembolic and bleeding events were investigated using multivariate logistic regression. Variables anticipated to influence outcomes were initially included in the models, irrespective of their statistical significance. Backward elimination, based on the likelihood ratio, was utilized to refine the model until no variables were further excluded. Adjusted results were presented as odds ratios with 95% confidence intervals (CIs) in a forest plot. The Spearman coefficient was used to explore the correlations between the rivaroxaban trough or peak concentrations (C_{max}) and demographic characteristics.

A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY, USA).

Results

Patient Characteristics

Of the 516 patients with NS screened, 141 first used rivaroxaban (10 mg/day) to prevent NS-related thrombosis were included (shown in online suppl. Table S2). Most exclusions were due to other indications for anticoagulation (shown in online suppl. Fig. S2). All included patients completed the study with a median follow-up of 200 days (IQR, 72–283 days). Follow-up usually ended after discontinuing rivaroxaban, when physicians deemed NS remission and reduced TE risk, with most patients exhibiting increased albumin levels to 30–35 g/L. Allele frequencies distributions were in Hardy-Weinberg equilibrium (Fisher's exact test, $p > 0.05$).

Primary Outcome – Pharmacokinetics

A total of 231 plasma concentrations were analyzed, including 127 trough concentrations (C_{trough}) and 104 C_{max}. The steady-state median C_{trough} was 4.4 ng/mL (IQR, 1.2–11.9 ng/mL) and the median C_{max} was 68.5 ng/mL (IQR, 31.7–105.5 ng/mL) for our patients (shown in Fig. 1). They were characterized by hypoalbuminemia with the median serum albumin of 21.3 (16.5–24.1) g/L, while that were within the normal range (35–50 g/L) for the general patients with approved indications in clinical trials.

For the steady-state median C_{trough}, there was no significant difference among the patients who experienced TEs, bleeding or without outcomes (shown in Fig. 2a). However, the median C_{max} in patients with TEs (37.1 ng/mL; IQR, 22.9–55.1 ng/mL) was much significantly lower than in those with minor bleeding (136.0 ng/mL; IQR, 112.1–191.5 ng/mL, $p < 0.001$) and those without any outcomes (68.5 ng/mL; IQR, 28.2–90.6 ng/mL, $p = 0.047$). In addition, the median C_{max} of bleeding patients was significantly higher compared to patients without outcomes ($p < 0.001$) (shown in Fig. 2b).

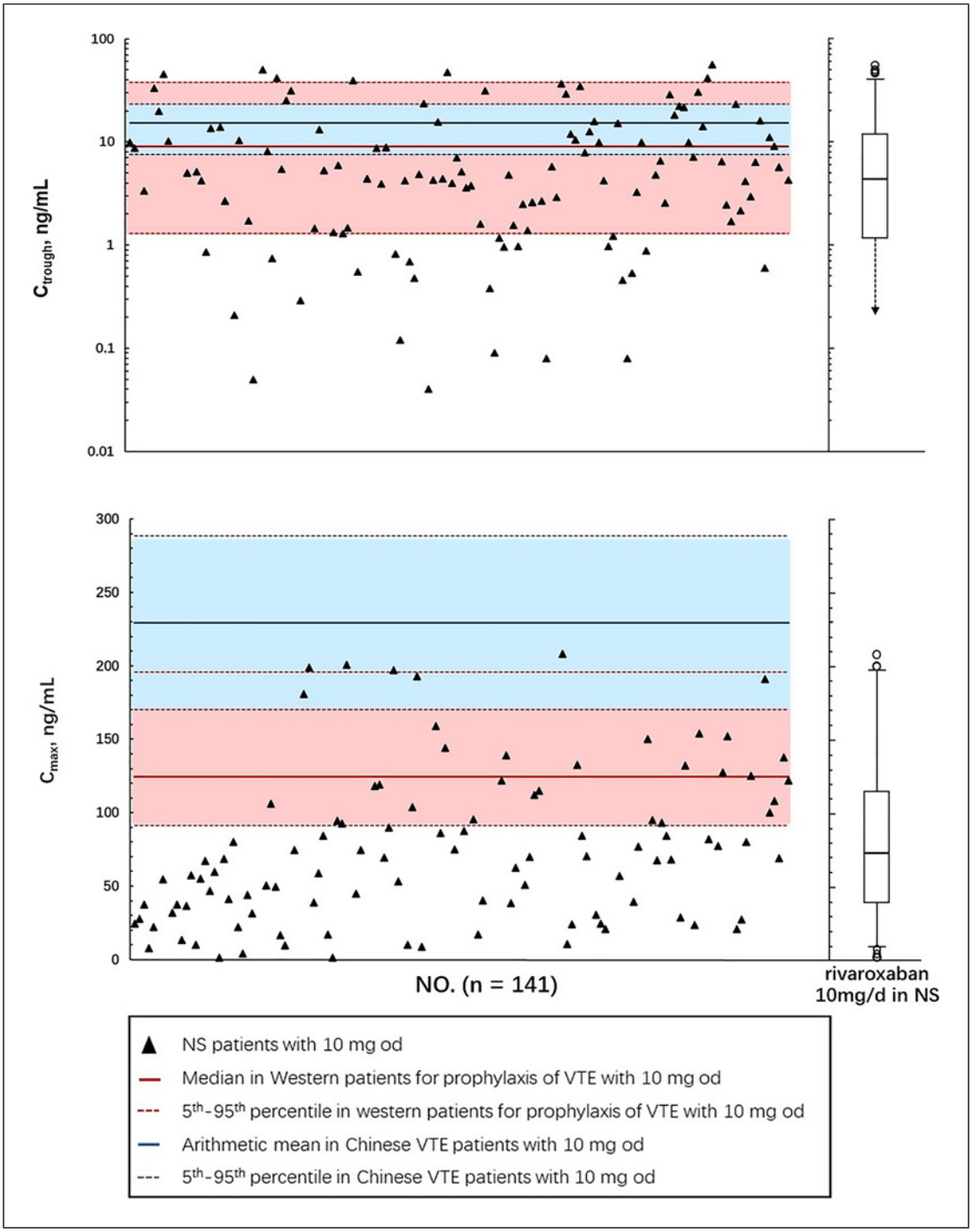


Fig. 1. Pharmacokinetic data for the patients with NS receiving rivaroxaban (10 mg/day) relative to general patients. The median C_{trough} was 4.4 ng/mL (IQR, 1.2–11.9 ng/mL) for NS patients, while that were 9 ng/mL (95% CI, 1–38 ng/mL) and 15.4 ng/mL (95% CI, 7.6–23.2 ng/mL) for general Western patients on thromboprophylaxis and Chinese VTE patients who received 10 mg/day, respectively. The median C_{max} was 68.5 ng/mL (IQR, 31.7–105.5 ng/mL) for NS patients, while that were 125 ng/mL (95% CI, 91–196 ng/mL) and 229.2 ng/mL (95% CI, 170–288 ng/mL) for general Western patients on thromboprophylaxis and Chinese VTE patients who received 10 mg/day, respectively. IQR, interquartile range; NS, nephrotic syndrome; VTE, venous thromboembolism; C_{trough}, trough concentrations; C_{max}, peak concentrations.

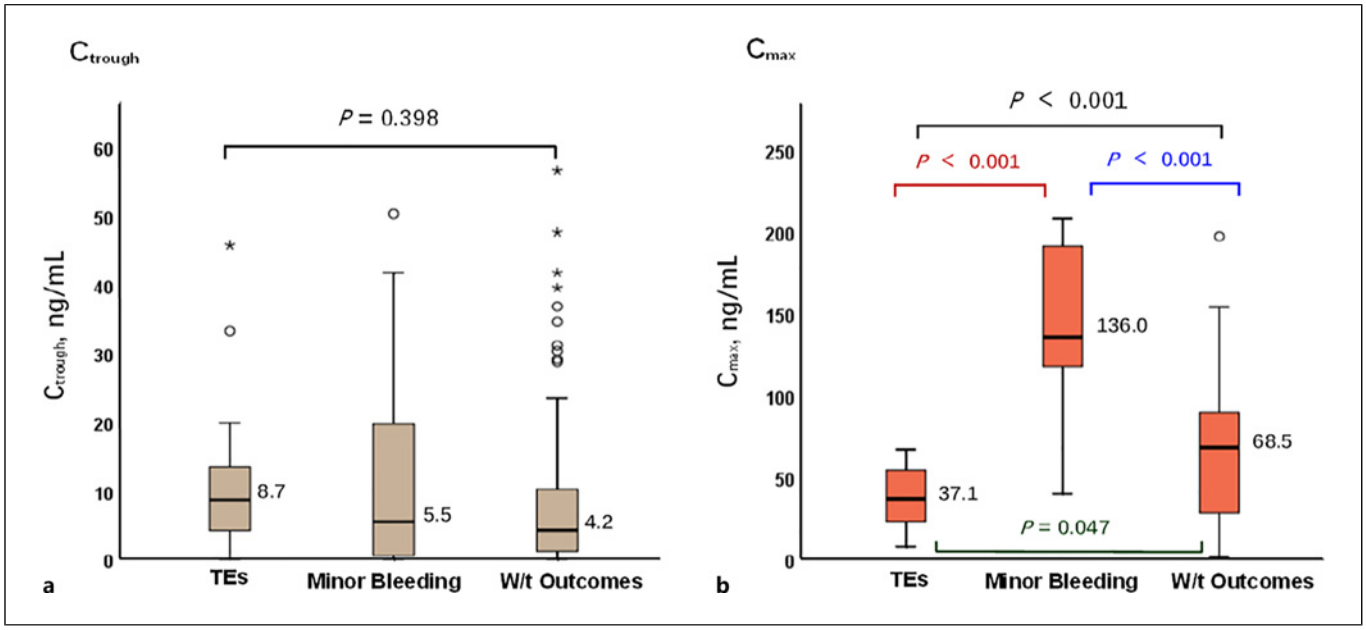


Fig. 2. Boxplots describing plasma concentrations among patients with TEs, minor bleeding or without outcomes. **a** C_{trough}. **b** C_{max}. *p* value among 3 groups showed in black; *p* value between TEs and minor bleeding showed in red; *p* value between TEs and W/t outcomes showed in green; *p* value between minor bleeding and W/t outcomes showed in blue. TEs, thromboembolic events; W/t, without; C_{trough}, the trough concentrations; C_{max}, the peak concentrations; circles, discrete value; stars, extreme value.

Analysis of Factors Influencing Plasma Concentrations

Factors influencing C_{max}

The analysis identified five factors significantly affecting the C_{max} of rivaroxaban in patients with NS (shown in Fig. 3). Age and albumin levels positively influence C_{max} values. In contrast, weight and CrCl had a negative impact. Additionally, patients who received concurrent tacrolimus therapy exhibited significantly lower median C_{max} (47.3 ng/mL; IQR, 26.2–81.1 ng/mL) compared to those who did not receive tacrolimus (76.1 ng/mL; IQR, 38.2–122.8 ng/mL).

Factors Influencing C_{trough}

Four factors significantly influenced the C_{trough} of rivaroxaban in patients with NS (shown in Fig. 4). BMI was identified as a weak negative factor. Genotypes of the *ABCB1* gene had a significant impact.

ABCB1 c.1236C>T: A significant difference in the median C_{trough} was observed between carriers of the CC genotype (9.1 ng/mL; IQR, 2.3–17.0 ng/mL) and those with TT genotype (3.6 ng/mL; IQR, 1.0–8.4 ng/mL).

ABCB1 c.2677A>G: Patients with the AA genotype showed a significantly lower median C_{trough} (2.6 ng/mL; IQR, 0.7–8.0 ng/mL) compared to AG carriers (6.2 ng/mL; IQR, 2.3–15.7 ng/mL).

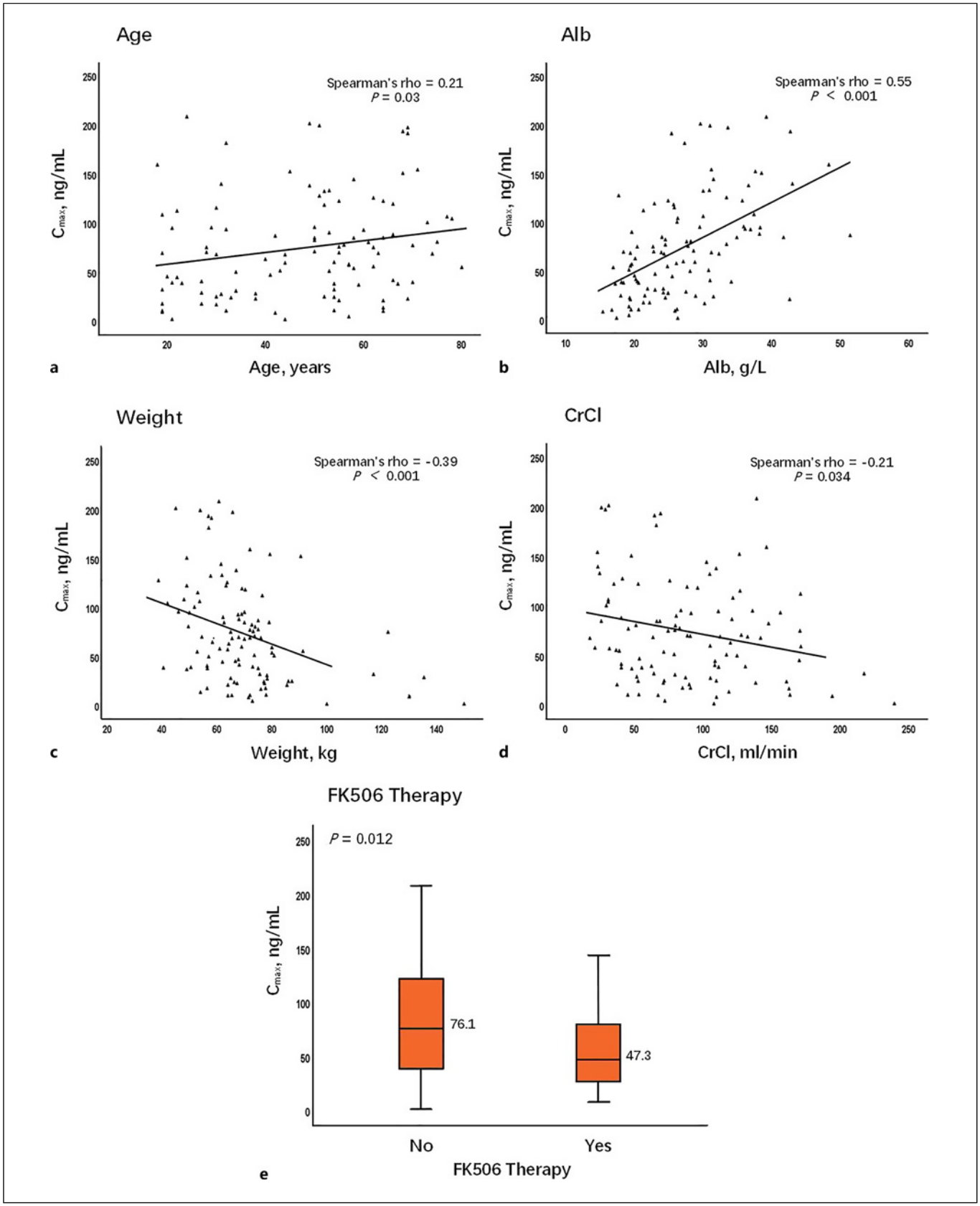
ABCB1 c.3435 C>T: CC carriers had a much lower median C_{trough} (2.5 ng/mL; IQR, 0.6–4.6 ng/mL) compared to TT (5.7 ng/mL; IQR, 1.9–15.5 ng/mL) and CT carriers (5.1 ng/mL; IQR, 1.2–13.8 ng/mL).

Other theoretical factors that influence rivaroxaban pharmacokinetics did not demonstrate a statistically significant impact on the drug concentrations in our patients.

Secondary Outcome – Clinical Outcomes

Incidence and Timing of TEs and Bleeding

The incidence of TEs was 12.8%, including deep vein thrombosis, pulmonary embolism, renal vein thrombosis, and cerebral infarction. The median time to occurrence of TEs was 44.5 days (IQR, 24.5–126.5 days), typically within the first 6 months after diagnosis. In contrast, bleeding episodes were observed in 20 patients (14.2%), all classified as minor (e.g., epistaxis, gingival hemorrhage, menorrhagia, and subcutaneous hemorrhage), and did not require medical intervention. The median time to bleeding was significantly later at 256.0 days (IQR, 162.0–292.8), predominantly after the first 6 months of diagnosis (shown in Fig. 5).



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Six cases involved membranous nephropathy with thrombosis at multiple sites. Two patients experienced minor bleeding at more than two sites (shown in Table 1).

Risk Factors for TEs and Bleeding

Five factors were significantly related to the clinical outcomes. Albumin level was a key determinant, inversely correlated with thrombosis risk and positively with bleeding risk. The increase in age was a significant risk factor for TEs. At the same time, the absence of tacrolimus therapy served as a protective factor (shown in Fig. 6a). Regarding bleeding events, a BMI ≥24 kg/m^2 and Padua scores ≥4 points were associated with reduced risk (shown in Fig. 6b). Other potential factors, including histologic subtypes, the use of glucocorticoids, statins, and *ABCB1* genotypes, did not statistically affect clinical outcomes.

Discussion

This study investigated the impact of NS on the pharmacokinetics of rivaroxaban. Our observational data indicated that NS patients generally exhibit lower plasma concentrations of rivaroxaban compared to the patients with other approved indications for the drug, particularly in terms of peak plasma concentrations. A key pathological feature of NS, hypoalbuminemia, was identified as a significant factor in reducing these concentrations.

We measured trough and peak concentrations of rivaroxaban for all enrolled NS patients. Notably, the median C_{max} of our patients was 68.5 ng/mL (IQR, 31.7–105.5 ng/mL), while that were 125 ng/mL (95% CI, 91–196 ng/mL) for general Western patients on thromboprophylaxis and 229.2 ng/mL (95% CI, 170–288 ng/mL) for Chinese VTE patients who received the same dose [23, 24]. The decrease of C_{max} in NS patients was also reported in a phase Ia trial of another high protein-binding oral factor Xa inhibitor, apixaban, which has about 87% protein binding. In this trial, the C_{max} was reduced by 9.6% in general NS patients compared to healthy controls, with a reduction of 18.7% in patients with severe NS [25]. Additionally, the decrease in D-dimer levels 24 h after apixaban administration was significantly lower in NS patients than in healthy controls, suggesting a reduced response to apixaban among this group [25]. Given these observations, direct oral anticoagulants with high protein binding might require a dose increase beyond standard recommendations to achieve adequate therapeutic concentrations in NS patients [26, 27].

Our findings indicate that albumin level is the primary factor influencing the C_{max} of rivaroxaban in NS patients. Specifically, their decreased albumin levels caused a decrease in rivaroxaban C_{max}, contrary to the observations in non-NS populations [28, 29]. Similarly, an open-label pharmacokinetic study of apixaban in NS patients demonstrated that albumin levels were positively correlated with C_{max} and $AUC_{0\text{-}24}$ but negatively correlated with drug clearance [25]. This relationship is likely due to hypoproteinemia in NS patients, caused by macroproteinuria, leading to more significant urinary loss of the protein-bound drug fraction and consequently to more rapid clearance of high protein-binding anticoagulants [25]. As a result, drug concentrations may drop below the levels required for effective thromboprophylaxis, potentially reducing the efficacy of such anticoagulants. This problem parallels the challenges observed in NS patients treated with warfarin, which is also highly protein-bound (99%). Hypoproteinemia in NS patients has been shown to triple the clearance rate of warfarin compared to controls, significantly shortening its elimination half-life [30]. However, unlike rivaroxaban, warfarin therapy can be adjusted based on the international normalized ratio to ensure safety and efficacy. Considering these dynamics, a dose-adjustment regimen based on rivaroxaban pharmacokinetic parameters may be necessary to ensure effective thromboprophylaxis in NS patients.

Beyond albumin levels, factors that traditionally affect the pharmacokinetics of rivaroxaban in the general population also influenced its C_{max} in NS patients. Advanced age was associated with increased C_{max}, while reduced renal function and increased body weight negatively impacted C_{max} [31, 32]. Intriguingly, concomitant use of tacrolimus significantly reduced the C_{max} of rivaroxaban. A similar decrease in drug exposure was observed in a study in which healthy volunteers received concurrent administration of apixaban and tacrolimus [33]. However, the mechanism requires further investigation. Although the association between *ABCB1*-related SNPs and rivaroxaban pharmacokinetic outcomes has been established in general populations [10–14], this

Fig. 3. a Age. **b** Albumin. **c** Weight. **d** CrCl. **e** FK506 treatment. NS, nephrotic syndrome; CrCl, creatinine clearance; FK506, tacrolimus; C_{max}, peak concentrations.

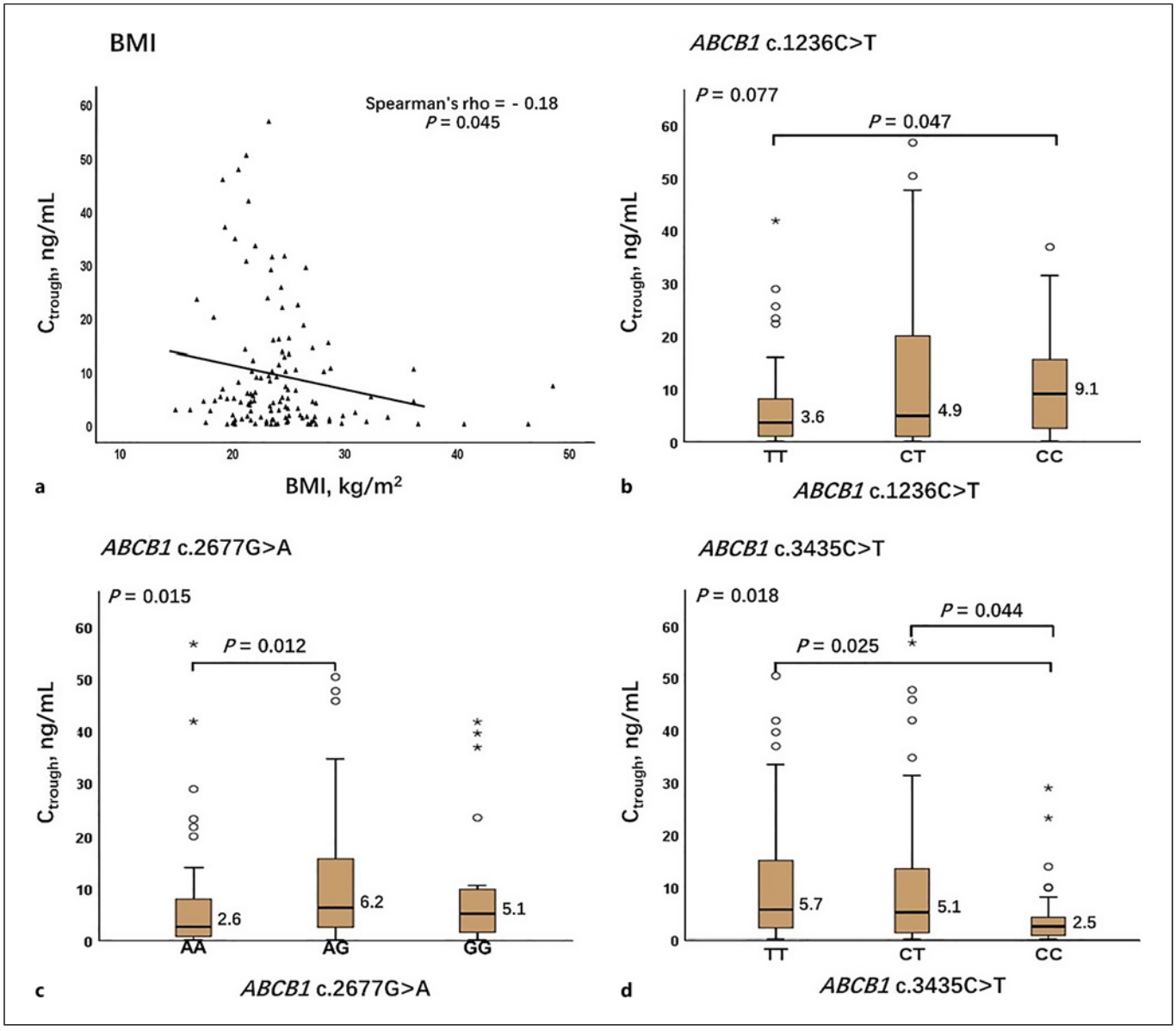

Fig. 4. Factors influencing through concentrations in NS patients. **a** BMI. **b** *ABCB1* c.1236C>T. **c** *ABCB1* c.2677G>A. **d** *ABCB1* c.3435C>*T*. NS, nephrotic syndrome; BMI, body mass index; C_{trough}, trough concentrations; circles, discrete value; stars, extreme value.

relationship remains unclear in NS patients. In this study, we examined the correlation between *ABCB1* polymorphisms and rivaroxaban concentrations in NS patients for the first time. Similar to findings in general populations [10–14], *ABCB1* variants were found to significantly impact rivaroxaban C_{trough} in NS patients, although their effects on C_{max} were not statistically significant.

Our observational data indicated a 12.8% incidence of TE, most of which were serious and exacerbated the primary disease, which typically occurred within the first 6 months of diagnosis. The incidence of bleeding was 14.2%, characterized exclusively by minor events after the first 6 months of diagnosis. The incidence of TE in our cohort exceeded that reported in phase III trials of rivaroxaban for thromboprophylaxis [34–36] and was higher than the rates observed in NS patients treated with LMWH or warfarin [3–5]. For example, an uncontrolled study reported a thrombosis rate of only

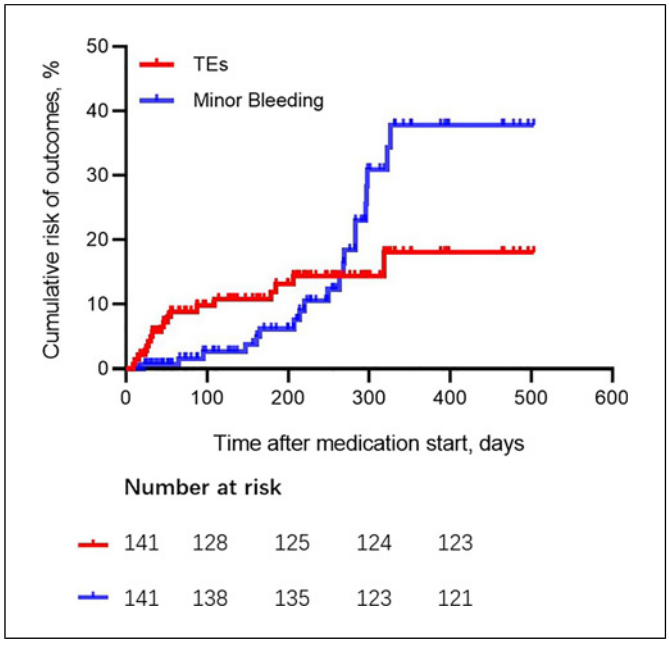

Fig. 5. Cumulative incidence of outcomes. The median time to TEs was 44.5 days (IQR, 24.5–126.5) and to bleeding was 256.0 days (IQR, 162.0–292.8). Red color indicates cumulative of TEs; blue color indicates cumulative of bleeding. TEs, thromboembolic events.

Table 1. Outcomes in study patients

Variable	All patients (n = 141), n (%)
TEs	18 (12.8)
Pulmonary embolism	6 (4.3)
Deep vein thrombosis	9 (6.4)
Renal vein thrombosis	5 (3.5)
Cerebral infarction	4 (2.8)
Minor bleeding	20 (14.2)
Epistaxis	7 (5.0)
Gingival hemorrhage	2 (1.4)
Menorrhagia	3 (2.1)
Subcutaneous hemorrhage	11 (7.8)

1.39% in NS patients receiving prophylactic doses of LMWH [3], and no NS-related thrombosis was documented in a retrospective study of warfarin-treated patients [4]. Even among NS patients without prophylactic anticoagulation, the incidence of TE was lower at 11.4% [4], suggesting a potentially less effective thromboprophylaxis profile for rivaroxaban in this specific patient population.

Certain factors influencing rivaroxaban concentrations in NS patients are also closely associated with treatment outcomes. Advanced age not only contributed to increased peak rivaroxaban concentrations but was also closely related to higher thrombosis risk [31, 37]. In contrast, a higher BMI ≥24 kg/m^2 led to decreased C_{trough} and was associated with a reduced risk of bleeding [38, 39]. The concomitant use of tacrolimus, while increasing the risk of TE, may do so by lowering the C_{max} of rivaroxaban. Furthermore, the enhancement of platelet aggregation mediated by tacrolimus could also be a contributing factor to the increased risk of TEs [40].

In patients with NS, reduced albumin levels not only predict an increased risk of TE but also significantly impact the pharmacokinetics of rivaroxaban, particularly its C_{max}. During the initial diagnostic phase, extremely low albumin levels contribute to reduced drug efficacy, leading to a higher incidence of TEs within the first 100 days despite prophylactic dosing. As disease remits and albumin levels increase, the risk of TEs decreases, correlating with increased rivaroxaban concentrations and a subsequent increase in minor bleeding events after 200 days. In a retrospective real-world study of 999 rivaroxaban users, haplotypes of *ABCB1* genes were identified as potential factors affecting TEs [10]. However, in our cohort, while *ABCB1* polymorphisms were associated with rivaroxaban C_{trough}, they did not correlate significantly with TE risk, suggesting that haplotypes should be considered as an additional important genetic factor in the future exploration of TE risk factors.

This study represented the largest prospective analysis that examined the effects of NS on the pharmacokinetics of rivaroxaban and provided observational data on its use for thromboprophylaxis in NS patients. Hypoproteinemia is the predominant pathological factor influencing the concentrations of rivaroxaban, and subsequently impacting the clinical outcomes in this population. Additionally, the *ABCB1* gene polymorphisms were also significant factors influencing the drug concentrations in NS patients, but no genetic association was observed with treatment outcomes. However, due to the main limitation of its single-arm design, the efficacy and safety of rivaroxaban in preventing NS-related thrombosis still need to be determined. This limitation and the absence of quantified pharmacodynamic parameters, such as D-dimer and anti-Xa activity, must be considered when interpreting these preliminary data. Furthermore, the homogeneity of our study population, all of whom were Han Chinese, and the focus on a single-center design may limit the generalizability of our findings. Not all potentially impactful SNPs were covered by our genotyping, which could introduce bias.

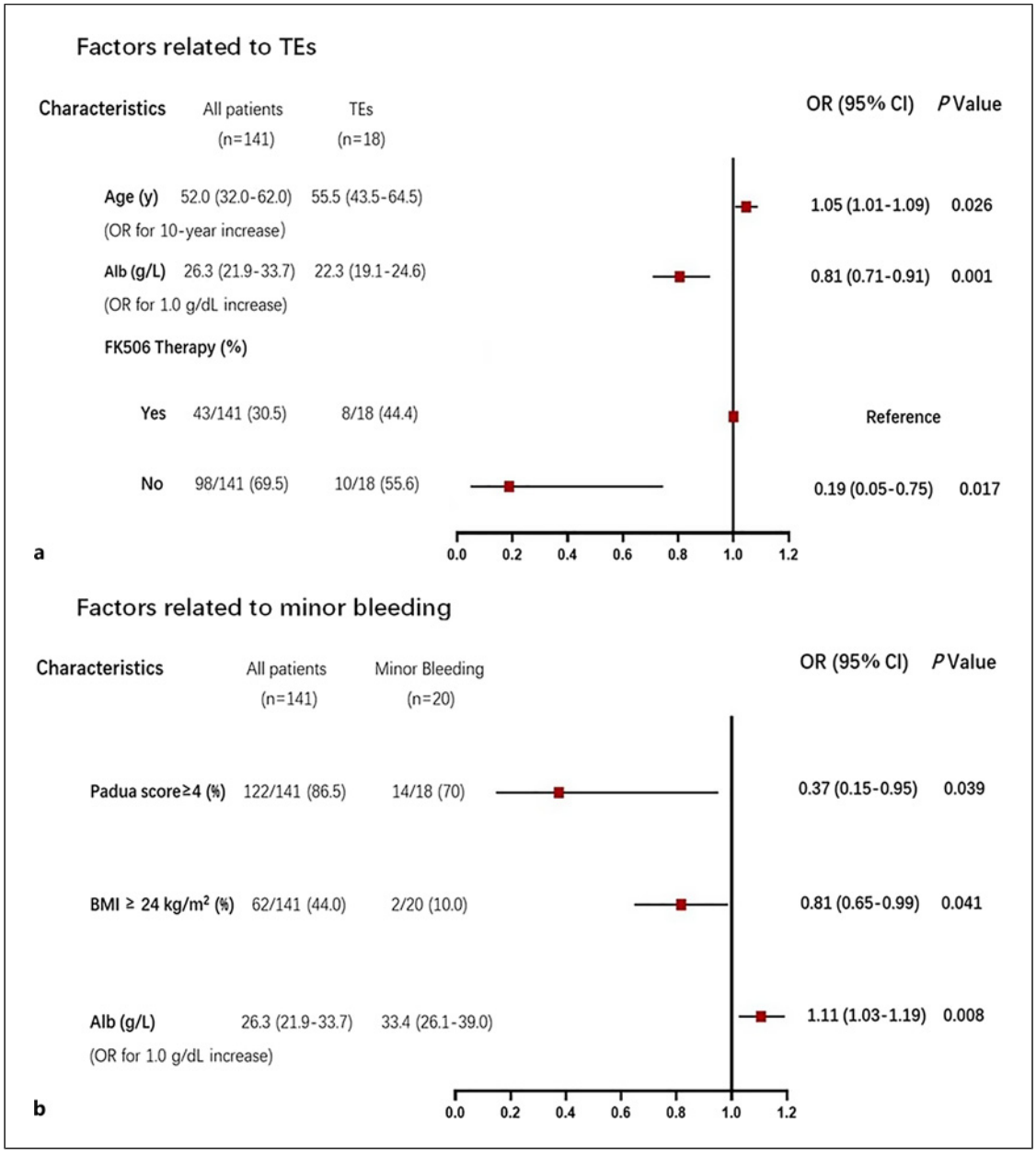

Fig. 6. Forest plot of factors related to outcomes. **a** Factors related to TEs. **b** Factors related to minor bleeding. TEs, thromboembolic events; Alb, albumin; FK506, tacrolimus; BMI, body mass index.

Hypoalbuminemia significantly affects both the incidence of TEs and the pharmacokinetics of rivaroxaban in NS patients. The high protein-binding nature of rivaroxaban results in substantial urinary loss and decreased efficacy. Given the variability in albumin levels between individuals and across different disease stages, a fixed dose of rivaroxaban (e.g., 10 mg/day) may not be optimal for all NS patients. A dose-adjusted regimen, tailored according to drug concentration measurements, could improve the efficacy of rivaroxaban in this population.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Jinling Hospital, Approval No. was 2021DZGZR-YBB-094, and the blood samples for the determination of concentration and genotyping were obtained after written informed consent.

Conflict of Interest Statement

The authors have no competing interests to declare that are relevant to the content of this article.

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Author Contributions

All authors contributed to the study conception and design. M.W., X.W., L.W., and Z.G. participated in the design of the study, recruited patients, performed the statistical analyses, and revised the final version of the manuscript. Y.T., L.Z., J.Z., and H.X. participated in the design of the study, recruited patients, and helped write the manuscript. Q.Z., Y.C., and S.W. participated in the detection of plasma concentrations and genotyping. Z.C., G.Z., and Q.S. participated in the design of the study, wrote the manuscript, and obtained funds. All authors read and approved the final manuscript for submission.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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