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Risk factors of preoperative deep vein thrombosis in patients with non-traumatic osteonecrosis of the femoral head

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Abstract

Purpose This study aims to identify independent risk factors for preoperative lower extremity deep venous thrombosis (DVT) in patients with non-traumatic osteonecrosis of the femoral head (NONFH), and to develop a prediction nomogram.

Methods Retrospective analysis of prospectively collected data on patients presenting with non-traumatic osteonecrosis of the femoral head between October 2014 and April 2019 was conducted. Duplex ultrasonography (DUS) was routinely used to screen for preoperative DVT of bilateral lower extremities. Data on demographics, chronic comorbidities, preoperative characteristics, and laboratory biomarkers were collected. Univariate analyses and multivariate logistic regression analyses were used to identify the independent risk factors associated with DVT which were combined and transformed into a nomogram model.

Result Among 2824 eligible patients included, 35 (1.24%) had preoperative DVT, including 15 cases of proximal thrombosis, and 20 cases of distal thrombosis. Six independent risk factors were identified to be associated with DVT, including Sodium ≤ 137 mmol/L (OR = 2.116, 95% confidence interval [CI]: 1.036–4.322; $P = 0.040$), AGE ≥ 49 years (OR = 7.598, 95%CI: 1.763–32.735; $P = 0.008$), D-Dimer > 0.18 mg/L (OR = 2.351, 95%CI: 1.070–5.163; $P = 0.033$), AT III ≤ 91.5% (OR = 2.796, 95%CI: 1.387–5.634; $P = 0.006$), PLT ≥ $220.4*10^9$ /L (OR = 7.408, 95%CI: 3.434–15.981; $P = 0.001$) and ALB < 39 g/L (OR = 3.607, 95%CI: 1.084–12.696; $P = 0.042$). For the nomogram model, AUC was 0.845 (95%CI: 0.785–0.906), and C-index was 0.847 with the corrected value of 0.829 after 1000 bootstrapping validations. Moreover, the calibration curve and DCA exhibited the tool's good prediction consistency and clinical practicability.

Conclusion These epidemiologic data and the nomogram may be conducive to the individualized assessment, risk stratification, and development of targeted prevention programs for preoperative DVT in patients with NONFH.

Keywords Deep vein thrombosis, Non-traumatic osteonecrosis of the femoral head, Epidemiology, Risk factors, Nomogram

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Introduction

Non-traumatic osteonecrosis of the femoral head (NONFH) is a type of avascular necrosis that has been identified as the result of disruption or reduction of blood flow to marrow and bone [1, 2]. Steroid-induced or alcoholic-induced osteonecrosis could cause hypercoagulability of the blood and patients often have prolonged immobility of the affected limb and soft tissue damage, especially in the late stages [3–5]. Consequently, there may be higher odds of deep vein thrombosis (DVT) in this specific population. However, the fact that most preoperative DVTs are asymptomatic [6] makes it difficult to alert the treating surgeons of the DVT risk, and more likely that they are inadequately identified and inappropriately treated. Furthermore, there remains the risk of the thrombus propagating to the proximal veins and subsequently causing PE risk, especially in the setting of hip surgical trauma [7–9]. Thus it is essential to identify the incidence and risk factors of preoperative DVT in NONFH patients.

To date, there are numerous studies that focus on the clinical manifestations and complications following NONFH, such as joint mobility impairment, hip-spine syndrome, and secondary osteoarthritis [10–12], but none focused on preoperative DVT in a specific population of NONFH patients. To our best knowledge, only one study focused on the NONFH population in a retrospective cohort of 1514 patients and reported an incidence of 1.19% for preoperative DVT [13], the study did not further discuss the associated risk factors. The data such as patient comorbidity characteristics and lifestyle information were not incorporated, leaving a substantial residual confounding effect. Furthermore, all data in that study had been registered with codes, therefore further classification of disease status was impracticable. Indeed, assessing risk factors independently significantly impedes the accurate determination of DVT likelihood in patients. Furthermore, the persistent deficiency of comprehensive research and the lack of authoritative guidelines for the prevention of preoperative DVT in NONFH have created an urgent clinical need for an effective decision-making tool.

Given that, we designed this study with the aim to identify the incidence rate and independent risk factors associated with preoperative DVT in patients with NONFH, based on which, to develop a risk prediction model.

Materials and methods

Patients

Patients with NONFH admitted to The Third Hospital of Hebei Medical University between October 2014 and April 2019 were initially deemed eligible for inclusion in this study. The inclusion criteria were: (1) age≥18 years; (2) meeting the definite diagnostic criteria in the 2019 guideline for NONFN [14]; (3) experiencing both hematological test and duplex ultrasonography (DUS) examination preoperatively. Exclusion criteria were: (1) combine with any type of malignancy; (2) incomplete case data; (3) history of DVT and/or PE events; (4) lower limb surgery within one year; (5) antithrombotic drugs used within three months (such as aspirin, heparin, low molecular weight heparin, etc.). This cross-sectional study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University and all procedures were carried out in accordance with the principles of the Declaration of Helsinki and compliance with the guidelines of the Strengthening the Reporting of Surgical Cohort Studies (STROCSS). All participants gave informed consent for the possible use of clinical data.

All data for this cross-sectional study were collected retrospectively from the Surgical Site Infection in Orthopaedic Surgery (SSIOS) database. The SSIOS database is a prospectively manually maintained database of all the data on hospitalized patients who experience orthopedic surgeries in the 3rd Hospital of Hebei Medical University; the primary purpose of this data is to study incisional infections in orthopedic surgery; data are collected manually by 230 standardized trained investigators and updated annually; this was described in detail in the previous study [15–22].

According to the requirements for developing the clinical prediction model, the sample size should be at least 10 times the number of variables [23]. In our study, there were 30 variables, and the sample size should be at least 300, therefore our sample size is adequate.

Diagnosis and management of DVT

Criteria for the diagnosis of DVT by DUS were incompletely compressible vein, insufficient flow augmentation to veins of foot and calf after compression, lack of respiratory vibration in the superior knee vein segment, and filling defect or obstruction of the lumen. The vein involved can be any one or any combination (common femoral vein, superficial femoral vein, deep femoral vein, popliteal vein, anterior tibial vein, posterior tibial vein, or peroneal vein). Thrombosis solely located in intramuscular veins (e.g. flounder or gastrocnemius veins) was excluded from this study because they were considered less clinically significant [24]. According to institutional policy, patients with non-traumatic femoral head necrosis are required to undergo duplex ultrasound (DUS) for bilateral limb deep vein thrombosis on admission. The diagnosis of DVT was identified and reviewed by ultrasonographers with more than 5 years of experience using standardized procedures with the same set of instruments, and in case of disagreement, reviewed by a senior chief ultrasonographer [25]. For patients with positive DUS results, the therapeutic doses of anticoagulant drugs (e.g. enoxaparin sodium

injection, 100 AxaIU/kg, twice daily) were prescribed, and for patients at high risk of thrombosis, such as the elderly, we would inject prophylactic doses of blood-thinning drugs (e.g. enoxaparin sodium injection, 4000 AxaIU, once daily). For patients who have to wait a long time for surgery, we usually instruct patients to drink more water and move the affected limb appropriately, and the intermittent pneumatic pressure pumps were used to drive the blood circulation of lower extremities to prevent thrombosis.

Data collection

All data were extracted from the patient's inpatient medical records. We reviewed the previous medical records of all patients meeting the criteria and collected general information on the patients from four aspects: demographics, chronic comorbidities, preoperative characteristics, and laboratory biomarkers. Demographics included gender, age, and body mass index (-BMI). Chronic comorbidities included hypertension, diabetes, cardiovascular disease, pulmonary disease, liver disease, kidney disease, peripheral vascular disease (PVD), and a history of surgery, all of which were self-reported by the patient. Preoperative characteristics included the American Society of Anesthesiologists (ASA) classification, the site of the lesion, and the stage of the Association Research Circulation Osseous (ARCO) [14, 26]. Laboratory biomarkers included albumin, Antithrombin III (ATIII), aspartate transaminase/alanine transaminase (AST/ALT), high-sensitivity C-reactive protein (HCRP), lactate dehydrogenase (LDH), high-density lipoprotein cholesterol (HDL-C), sodium concentration (Na+), white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), the count of platelet (PLT), D-Dimer, fibrinogen, and mean platelet volume (MPV). If the patient underwent multiple hematologic tests before the diagnosis of DVT, we selected the one which was closest to the diagnosis. We subsequently observed and analyzed the relationship between the above data and lower extremity DVT formation. The Harris hip score (HHS) for hip function were measured before surgery.

Statistics

SPSS version 26.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. Continuous data were presented as mean±standard deviation (SD) when in the normal distribution, otherwise as the median and inter-quartile range (IQR). Kolmogorov–Smirnov test was performed to evaluate the normality of the continuous variables, and the Student t-test or Mann–Whitney test was used for normally or non-normally distributed data according to the results. Categorical variables were expressed as numbers and percentages (%), and analyzed by chi-square or Fisher's exact test.

Plasma D-dimer and ALB can reflect the development of DVT, but their elevated levels can also be affected by other factors, such as inflammation, so we decided to use the Youden-index to determine the optimal cut-off point. The same method was applied to determine the demarcation point for AGE, Sodium, AT III, and PLT.

All variables with $P<0.05$ in univariate analysis were entered into multivariate logistics regression analysis and screened by the backward stepwise regression elimination method to identify the independent risk factors for DVT. The selected predictors were entered into R software (Version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria) for further analysis, and the "rms" package was used to construct the nomogram. The value of the C-index and the area under the receiver operating characteristic curve (AUC) were positively correlated with the discriminant ability and predictive accuracy of the nomogram. The calibration curve was used to evaluate the agreement between diagnosed thrombosis and predicted thrombosis. The clinical application value of the nomogram model was evaluated by DCA. Finally, to further verify the prediction performance of the model, we used the Bootstrap method for internal verification, and calculate the modified C-index through 1000 repeated sampling. Significance levels were set at 0.05 for all analyses [27, 28].

Result

Demographic data

As shown in Fig. 1, a total of 3364 patients with NONFH were selected. According to the selection criteria, 2824 patients were retained for analysis, including 1973 males and 851 females with a mean age of 49.87 years (SD: 13.346; median: 51). The number of patients with lower extremity DVT at preoperative DUS screening was 35, with a positive rate of 1.24%, including 15 cases of proximal thrombosis and 20 cases of distal thrombosis. There were 13 cases of ipsilateral thrombus with unilateral necrotic location, 6 cases of contralateral thrombus with unilateral necrotic location, 3 cases of bilateral thrombus with unilateral necrosis, 11 cases of unilateral thrombus with bilateral necrosis, and 2 cases of bilateral thrombus with bilateral necrosis. In detail, DVTs involved femoral common vein in 5 patients, superfcial femoral vein in 11, deep femoral vein in 1, popliteal vein in 7, posterior tibial vein in 15, and peroneal vein in 17 patients.

Univariate logistic regression analysis and multivariate logistic regression analysis of DVT

There were significant differences between patients with and without DVT in age, history of hypertension, history of surgical trauma (not within one year before

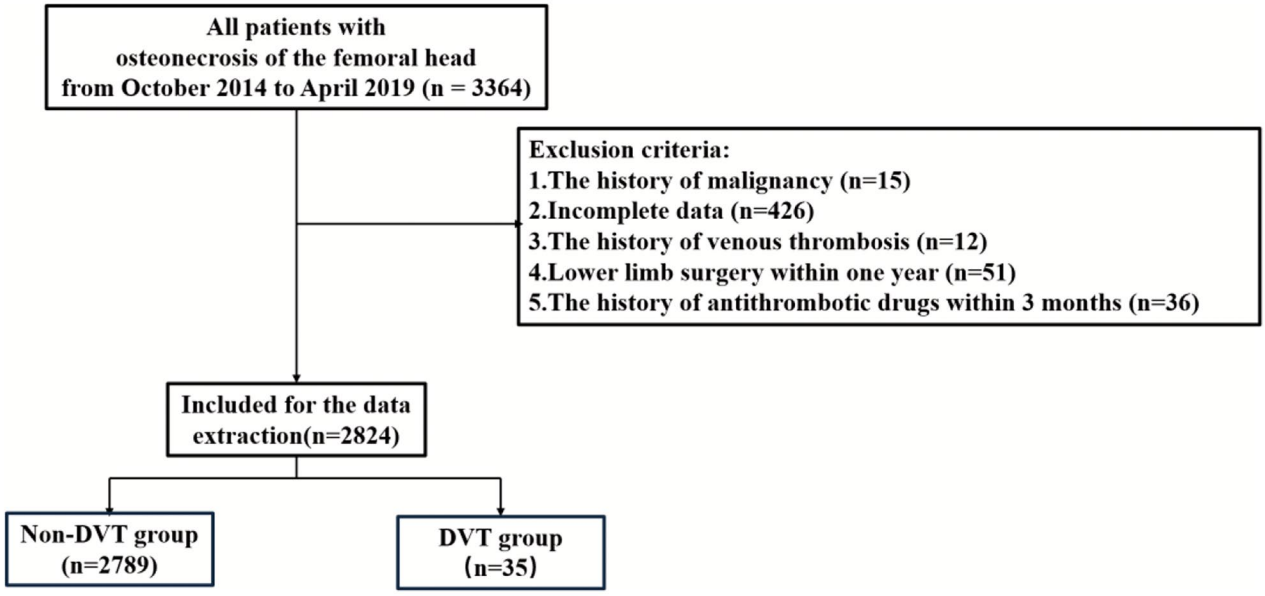

Fig. 1 Patients selection flowchart

surgery), ASA classification, site of lesion, ARCO stage, ALB, AT III, Sodium concentration, PLT and D-Dimer (all $P<0.05$). There were no significant differences in gender, BMI, previous history of diabetes, cardiovascular disease, pulmonary disease, liver disease, kidney disease, PVD, AST/ALT, HCRP, LDH, HDL-C, WBC, RBC, hemoglobin, hematocrit, MCV, FIB, Harris score and MPV ($P>0.05$), details of which are recorded in Table 1. All variables with $P<0.05$ in univariate analysis were calculated with the best cutoff value and replaced in binary logistic regression for analysis, totaling 10 variables in the form of categorical variables in Table 2, binary logistic regression indicated Sodium ≤ 137 mmol/L, AGE ≥ 49 years, ALB < 39 g/L, AT III ≤ 91.5%, D-Dimer > 0.18 mg/L and PLT ≥ $220.4*10^9$ /L were independent risk factors for the development of DVT in patients with NONFH. The H-L test showed good applicability of the final model ($X^2=9.731$, $P=0.284$).

Nomogram for DVT

These six predictors were substituted into a binary logistic regression analysis and transformed the results into the nomogram that could be used to predict the risk of preoperative DVT (Fig. 2), and further evaluated the reliability and performance of the nomogram. The AUC of the prediction model was 0.845 (95% CI: 0.785–0.906) (Fig. 3), with a specificity of 68.6% and a sensitivity of 85.0%, indicating the model has a strong discriminatory ability. The C-index for the nomogram was 0.847, and the corrected value was 0.829 after 1000 bootstrap validations, which indicated the good refinement of the model. Moreover, the calibration curve (Fig. 4) showed that the predicted probability of deep vein thrombosis in patients with femoral head necrosis by the nomogram was in good agreement with the actual probability. DCA of nomogram showed that compared to no intervention, using DVT prediction nomogram can bring positive net benefit when the threshold probability was in the range of 1-16% (Fig. 5). Finally, the performance of the ROC, calibration curve and decision curve analysis showed good consistency in the comparison of the training and validation cohorts.

As shown in Fig. 2, a nomogram was established that contained 6 covariates. When using the nomogram, the subject's age was positioned on the corresponding variable axis at first; next, draw a vertical line to the "Points" axis to obtain the corresponding score (when age = 45, the corresponding score was 40). Repeat the above process to obtain the scores of each covariable, and add them up to obtain the total score. Find the corresponding point of the total score on the "Total Points" axis and make a vertical line to the "Risk of DVT" axis to obtain the likelihood of developing DVT.

Discussion

The present study investigated the association between NONFH and unprovoked DVT and produced several striking clinical findings. Our findings suggested that Sodium ≤ 137 mmol/L, AGE ≥ 49 years, ALB < 39 g/L, AT III ≤ 91.5%, PLT ≥ $220.4*10^9$/L, and D-Dimer > 0.18 mg/L are independent risk factors for DVT in patients with NONFH. To our knowledge, this is the largest sample size study available to assess the epidemiological

Table 1 Univariate analysis of variables with interest between DVT and Non-DVT patients

Variables	Patients with DVT ($n=35$)	Patients without DVT ($n=2789$)	*P*
Sex (M/F)	26/9	1947/842	0.544
Hypertension, n (%)	15 (42.9)	612 (21.9)	0.003*
Diabetes, n (%)	3 (8.6)	193 (6.9)	0.702
Cardiovascular disease, n (%)	3 (8.6)	199 (7.1)	0.736
Pulmonary disease, n (%)	2 (5.7)	39 (1.4)	0.091
Liver disease, n (%)	1 (2.9)	79 (2.8)	1.000
Kidney disease, n (%)	1 (2.9)	91 (3.2)	1.000
PVD, n (%)	2 (5.7)	33 (1.2)	0.069
History of surgery, n (%)	17 (48.6)	898 (32.2)	0.040*
ASA, n (%)			0.005*
I-II	26 (74.3)	2489 (89.2)	
≥III	9 (25.7)	300 (10.8)	
Site, n (%)			0.041*
Bilateral	13 (37.1)	1519 (54.5)	
Unilateral	22 (62.9)	1270 (45.5)	
ARCO, n (%)			0.148
I-II	6 (17.1)	804 (28.8)	
III	12 (34.3)	1033 (37.1)	
IV	17 (45.6)	952 (34.1)	
AGE (y)	61.23 ± 9.70	49.45 ± 13.68	< 0.001*
BMI (kg/m^2)	26.51 ± 4.03	25.35 ± 3.57	0.059
ALB (g/L)	34.63 ± 4.10	37.35 ± 5.44	0.003*
AT III (%)	96.43 ± 14.73	102.91 ± 17.64	0.031*
AST/ALT	1.43 ± 0.77	1.25 ± 0.64	0.103
HCRP (mg/L)	41.36 ± 34.07	43.23 ± 42.13	0.793
LDH (U/L)	185.21 ± 36.28	181.73 ± 52.96	0.699
HDL-C (mmol/L)	1.01 ± 0.26	1.05 ± 0.28	0.376
Sodium (mmol/L)	136.97 ± 3.46	138.51 ± 3.73	0.015*
WBC (10^9/L)	8.56 ± 2.06	8.82 ± 2.67	0.557
RBC (10^{12}/L)	3.77 ± 0.56	3.89 ± 0.64	0.269
HGB (g/L)	114.71 ± 18.47	120.48 ± 19.92	0.088
HCT (%)	34.40 ± 5.46	35.91 ± 5.89	0.131
MCV (fl.)	91.39 ± 7.28	92.45 ± 5.40	0.253
PLT (10^9/L)	244.91 ± 61.93	209.67 ± 67.22	0.002*
D-Dimer (mg/L)	0.24 (0.77)	0.15 (0.19)	< 0.001*
FIB (g/L)	3.71 ± 0.88	3.49 ± 0.92	0.144
MPV (fl.)	8.31 ± 0.86	8.52 ± 0.98	0.235
Harris score	60.88 ± 0.33	60.97 ± 0.10	0.927

*$P < 0.05$ was considered statistically significant

Abbreviations PVD: Peripheral vascular disease; ASA: American Society of Anesthesiologists; ARCO: Association Research Circulation Osseous; BMI: Body mass index; ALB, Albumin; AT III: Antithrombin III; AST: Aspartate transaminase; ALT: Alanine transaminase; HCRP: High-sensitivity C-reactive protein; LDH: Lactate dehydrogenase; HDL-C: High-density lipoprotein cholesterol; WBC: White blood cell; RBC: Red blood cell, reference range: Female, 3.5–5.0×10^{12}/L; males, 4.0–5.5×10^{12}/L; HGB: Hemoglobin, reference range: Females, 110–150 g/L; males, 120–160 g/L; HCT: Hematocrit, reference range: Females, 35–45%; males, 40–50%; MCV: Mean corpuscular volume; PLT: Platelet; FIB: Fibrinogen; MPV: Mean platelet volume

Table 2 The logistic regression analysis on the risk factors of DVT in patients with NOFNH

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Hypertension	2.668 (1.358–5.242)	0.004*	2.010 (0.993–4.068)	0.052
History of surgery	1.989 (10.20-3.877)	0.044*	1.630 (0.804–3.304)	0.175
ASA				
I-II	-	-	-	-
≥III	2.872 (1.333–6.187)	0.007*	1.701 (0.755–3.830)	0.200
Site				
Bilateral	-	-	-	-
Unilateral	0.494 (0.248–0.985)	0.045*	0.537 (0.263–1.096)	0.088
AGE (≥ 49years)	12.334 (2.954–51.500)	0.001*	7.598 (1.763–32.735)	0.008*
ALB (< 39 g/L)	5.888 (1.799–19.278)	0.003*	3.607 (1.084–12.696)	0.042*
AT III (≤ 91.5%)	2.648 (1.354–5.178)	0.004*	2.796 (1.387–5.634)	0.006*
Sodium (≤ 137mmol/L)	2.752 (1.393–5.435)	0.004*	2.116 (1.036–4.322)	0.001*
D-Dimer (> 0.18 mg/L)	4.273 (1.995–9.153)	< 0.001*	2.351 (1.070–5.163)	0.033*
PLT (≥ 220.4*10^9/L)	4.035 (1.930–8.434)	< 0.001*	7.408 (3.434–15.981)	< 0.001*

*$P < 0.05$ was considered statistically significant

Abbreviations HR: Hazard ratio; CI: Confidence interval; ASA: American Society of Anesthesiologists; ALB, Albumin; AT III: Antithrombin III; Na+: Sodium concentration; PLT: Platelet

characteristics of preoperative lower extremity DVT in patients with NONFH.

Our statistics showed that the overall incidence of preoperative deep vein thrombosis in NONFH patients was 1.24%, which is similar to the 1.19% incidence found by Sung et al. in Taiwan [13]. However, this rate is slightly lower than the incidence of preoperative thrombosis reported for degenerative diseases (3.1-6.1%) [29, 30]. Potential reasons for this discrepancy may relate to patient inclusion criteria and the diagnosis of lower extremity DVT. Yao and Sato included patients with both femoral head necrosis and osteoarthritis of the hip and considered intermuscular vein thrombosis as a positive finding, which likely increased the reported incidence of lower extremity DVT. Although the incidence of DVT in our study aligns with previous research on ONFH patients, the differences observed in other patient groups highlight the need for tailored DVT prophylaxis and risk assessment for patients with ONFH.

Our study found that age ≥ 49 years enhances the probability of preoperative DVT in patients with NONFH by 7.598 times (95%CI 1.763–32.735). Increasing age leads to the loss of functional tissue cells and a continuous decrease in the ability of tissue self-renewal and

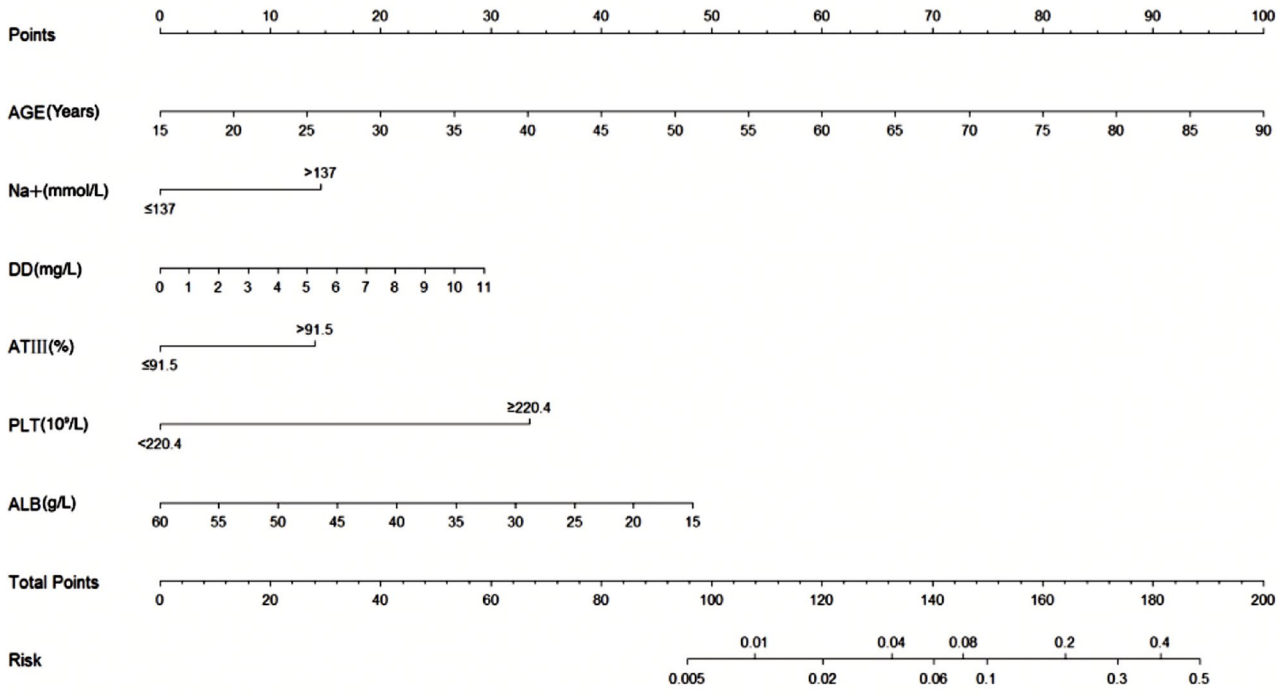

Fig. 2 Nomogram for predicting preoperative DVT in patients with NONFH. The sum of the scores of each predictor (D-dimer, Albumin, AGE, PLT, Sodium, and AT III) corresponds to the risk of DVT

maintenance resulting in femoral head vascular aging characterized by smooth muscle cells and progressive endothelial dysfunction [31–33]. Meanwhile, in our experimental group data, the proportion of patients with hypoproteinemia in the thrombus group was 19/35 and the antithrombin III (ATIII) was low in the thrombus group, leading to a decrease in plasma colloid osmotic pressure, an increase in blood hematocrit, and an increase in blood viscosity, combined with the immobility of the limb for long periods, therefore the blood in the limb is in a relatively stagnant state, which becomes a contributing factor to the formation of DVT [34, 35]. Therefore, clinical patients aged≥49 years should be encouraged to be active or use intermittent pneumatic pumps to promote blood circulation, while doing comprehensive preoperative education and adequate preoperative preparation such as comprehensive examination or drug prevention, and timely supplementation of albumin for patients with hypoproteinemia.

Sodium imbalance, either hypernatremia or hyponatremia, is associated with an increased risk of venous thromboembolism and even death, the association that has been confirmed in a cohort study using a large administrative database [36]. Some studies had shown that hyponatremia leads to subtle neurological damage, which further exacerbates motor dysfunction [37], as well as abnormal bone tissue morphology and reduced bone mineral density (BMD) [38]. Another study suggested that lower sodium concentrations imply remediation of systemic fluid and serum sodium balance after ONFH due to vascular endothelial dysfunction, thus reflecting a secondary state of blood hypercoagulation subsequently affecting thrombus formation [39]. Hyponatremia was present in 37.1% (13/35) of the patients in the experimental group and the optimal cut-off value derived from the roc curve was 137 mmol/L. Sodium concentration as a routine post-admission test is less expensive and takes less time to perform, allows for easy construction of nomogram, and can be easily used to identify patients at risk of DVT.

The functions of platelet adhesion, activation, and aggregation play a crucial role in thrombosis formation and become the basis for the pathogenesis of thrombotic disease [40, 41]. Many studies had demonstrated that platelet activation and elevated counts reflect a hypercoagulable state of the blood [42, 43], and it had been shown that circulating platelet-derived particles may be a potential cause of thrombosis in patients with NONFH [44]. Our data showed that patients with platelet counts higher than $220.4*10^9$ /L have a greater likelihood of thrombosis and patients with abnormally high counts should be treated promptly and symptomatically.

D-Dimer is the simplest fibrin degradation product and the most commonly used indicator of the function of

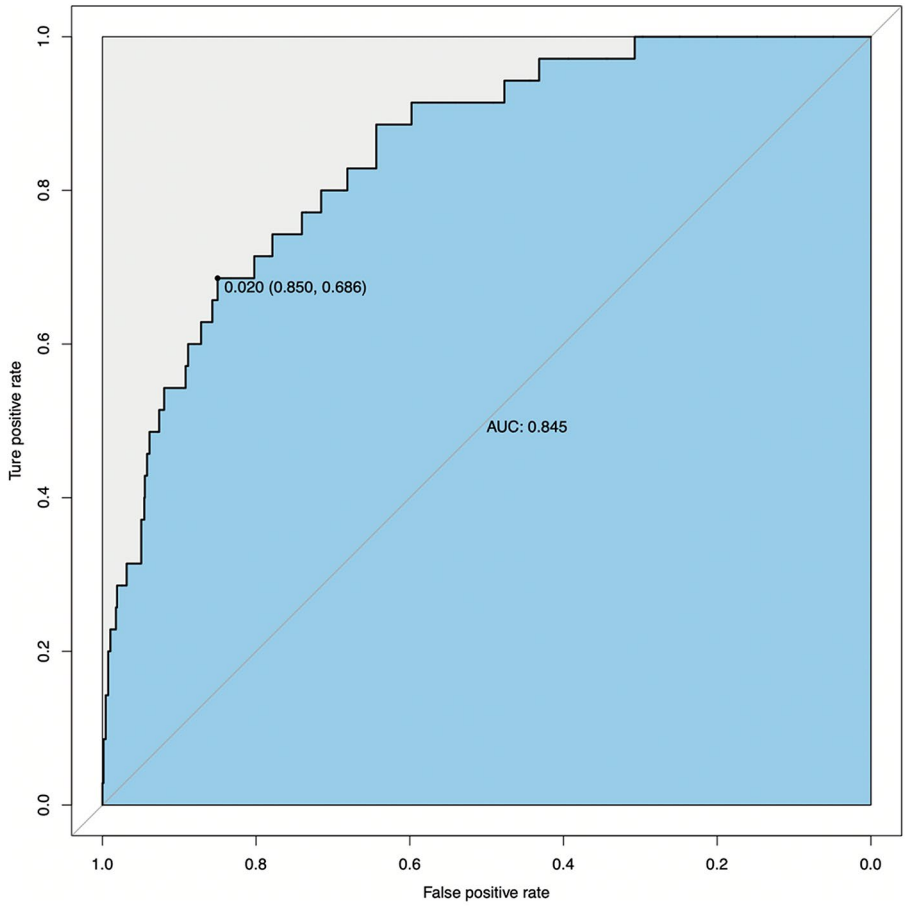

Fig. 3 The receiver operating characteristic curve (ROC) of the nomogram. The area under the curve (AUC) was positively correlated with the predictive accuracy of the nomogram

the anticoagulation and fibrinolytic systems in humans. Phillip et al. [45] reported that the degree of abnormally elevated D-dimer was positively correlated with the probability and size of thrombosis; nevertheless, it had also been suggested that D-dimer is less specific in predicting human thrombosis due to its susceptibility to trauma, pregnancy, the release of bleeding inflammatory factors and comorbidities [46]. Our statistics showed that the mean value of D-dimer was higher in the thrombus group (0.54) than in the control group (0.27), however, our data yielded an optimal cut-off value of 0.18 mg/L by Youden's index, which is different from the commonly used clinical standard of >0.5 mg/L. The adjusted value significantly improves the sensitivity from 25.7 to 74.3% compared to the conventional value. We suggested that the onset of NONFH is a chronic long-term outcome in patients without significant bleeding or stress, resulting in insignificant D-dimer elevations and that most patients who develop thrombosis do not reach the commonly used clinical cutoff value of 0.5 for D-Dimer. This result suggests to clinicians that in patients with nontraumatic femoral head necrosis, even if the D-Dimer examined is <0.5, there is still a risk of DVT so DVT cannot be excluded on this basis.

It is crucial to acknowledge that clinical practice often involves numerous, interconnected factors in individual patients, which can synergistically elevate the risk of DVT. This indicates that patients presenting with multiple coexisting risk factors constitute a high-risk group, necessitating preoperative optimization and heightened surveillance. Aggressive ultrasound screening is recommended and targeted prophylaxis based on routine anticoagulation may be considered.

Limitation

This study still has some limitations. First, this study has limitations immanent in retrospective single-center studies. Although we tried to involve as many potential risk factors as possible in our analysis, other confounding factors may contribute to preoperative DVT, and further prospective findings are needed to validate our conclusions, further subgroup analyses or propensity score matching can reduce population heterogeneity, and multicenter prospective cohort studies in the future

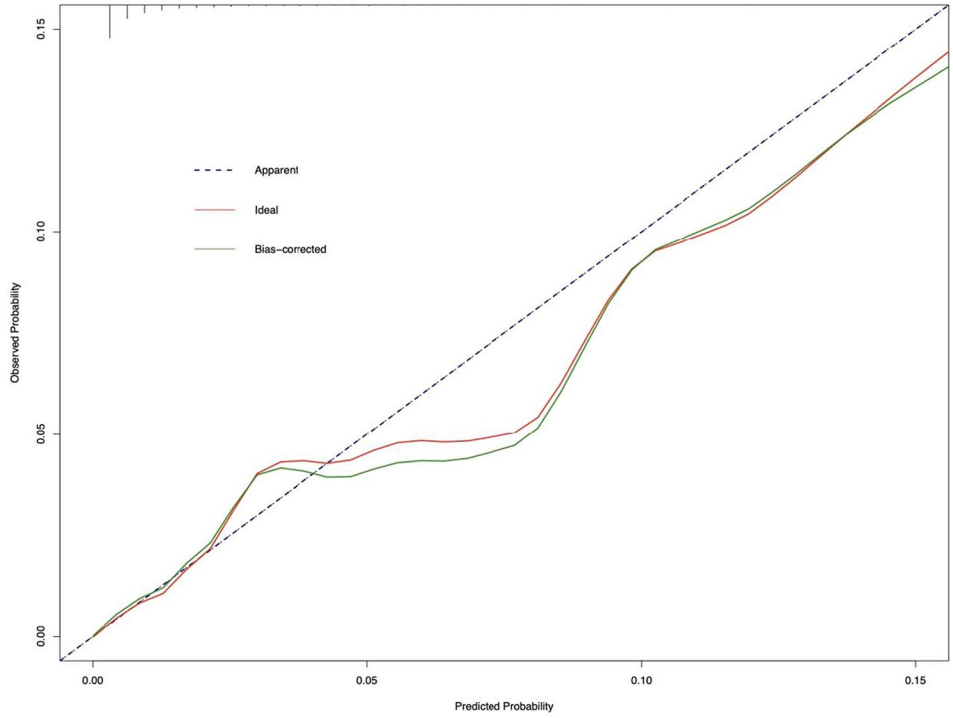

Fig. 4 The calibration curves of the nomogram. In the calibration curve, the higher the overlap between the predicted curve and the ideal curve, the better the consistency between the predicted probability and the true probability

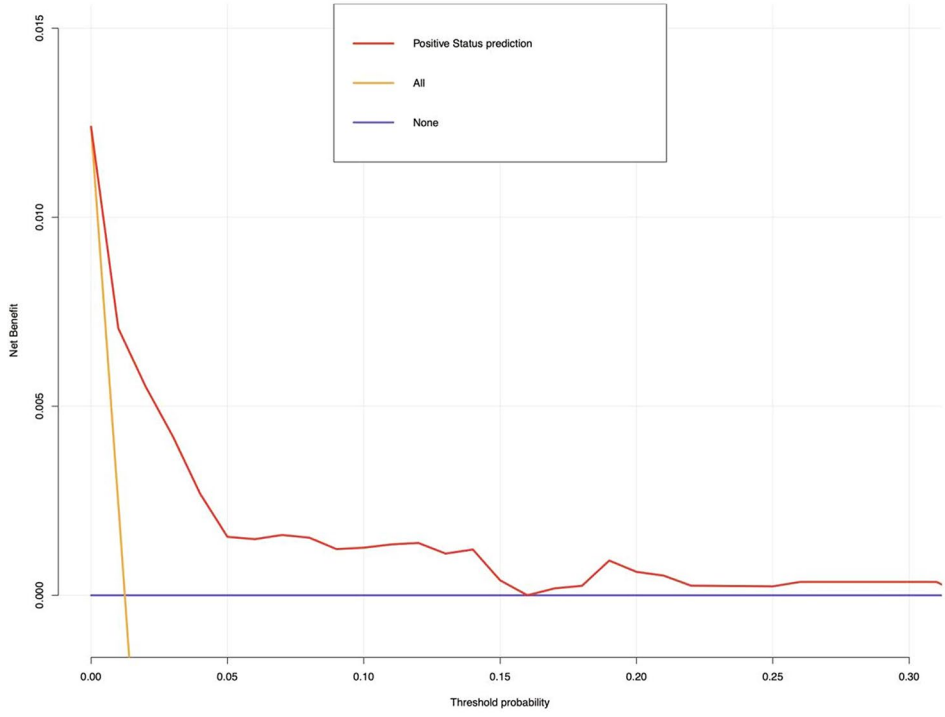

Fig. 5 The decision curve analyses (DCA) of the nomogram. The X-axis represents the threshold probability and the Y-axis represents the net benefit. The red line represents the nomogram, The blue line assumed that no patient has DVT before surgery, while the orange line represented the assumption that all patients have preoperative DVT. The range of threshold probabilities representing positive net benefit is obtained according to the corresponding points of the intersection of the red line with the orange line and blue line on the X-axis

can be more predictive for establishing casual association and reduce heterogeneity in study design. Second, due to incomplete data collection, some indicators were not included and more data support is needed. Third, the nomogram we performed was only internally validated and not externally validated, further external validation is needed to confirm the reliability of the results.

Conclusion

In summary, Sodium≤137 mmol/L, AGE≥49 years, ALB<39 g/L, AT III≤91.5%, PLT≥220.4*10^9 /L, D-Dimer>0.18 mg/L were identified as independent risk factors for the development of preoperative DVT in patients with NONFH. Clinicians should focus on patients with one or more of these risk factors on preoperative examination and prioritize their receipt of ultrasound. For patients with one or more of these factors present on routine preoperative examination, clinicians can employ the nomogram to identify the risk of preoperative DVT in hospitalized patients with NONFH so that early intervention and treatment can be made as necessary to prevent catastrophic consequences caused by the further development of thrombosis.

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Author contributions
YzZ designed the study; TyW and ChsL searched for relevant studies and abstracted the data; XqC and ZhbY analyzed and interpreted the data; DwW wrote the manuscript and YbZh approved the final version of the manuscript. No organization sponsored the research.

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Data availability
All the data used are available from the corresponding author on motivated requests.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of the Third Hospital of Hebei Medical University. All procedures were performed according to the principles of the Declaration of Helsinki and in accordance with the guidelines of Strengthening the Reporting of Surgical Cohort Studies (STROCSS). Patients involved in this study were informed and consented. All data were anonymized by removing sensitive personal information to protect privacy.

Additional information
No additional information is available for this paper.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. DiGiovanni CW, Patel A, Calfee R, Nickisch F. Osteonecrosis in the foot. J Am Acad Orthop Surg. 2007;15(4):208–17.
2. Lafforgue P. Pathophysiology and natural history of avascular necrosis of bone. Joint Bone Spine. 2006;73(5):500–7.
3. Chang C, Greenspan A, Gershwin ME. The pathogenesis, diagnosis and clinical manifestations of steroid-induced osteonecrosis. J Autoimmun. 2020;110:102460.
4. Gold EW, Cangemi PJ. Incidence and pathogenesis of alcohol-induced osteonecrosis of the femoral head. Clin Orthop Relat Res 1979(143):222–6.
5. Zhao D-W, Yu M, Hu K, Wang W, Yang L, Wang B-J, Gao X-H, Guo Y-M, Xu Y-Q, Wei Y-S, et al. Prevalence of nontraumatic osteonecrosis of the femoral head and its Associated Risk factors in the Chinese Population: results from a nationally Representative Survey. Chin Med J (Engl). 2015;128(21):2843–50.
6. Wakabayashi H, Hasegawa M, Niimi R, Sudo A. Clinical analysis of preoperative deep vein thrombosis risk factors in patients undergoing total hip arthroplasty. Thromb Res. 2015;136(5):855–8.
7. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):eS278–325.
8. Anderson FA, Zayaruzny M, Heit JA, Fidan D, Cohen AT. Estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism. Am J Hematol. 2007;82(9):777–82.
9. Kearon C. Natural history of venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I22–30.
10. Zhou Q, Cai Y, Jiang Y, Lin X. Exosomes in osteoarthritis and cartilage injury: advanced development and potential therapeutic strategies. Int J Biol Sci. 2020;16(11):1811–20.
11. Wei Q, He W, Zhang Q, Chen Z, Zheng Y, Lin T. [Clinical significance of different imaging manifestations of osteonecrosis of femoral head in the peri-collapse stage]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2021;35(9):1105–10.
12. Gómez-Hoyos J. Editorial Commentary: hip-spine syndrome: when the hip does not move, the Spine Labors Double. Arthroscopy. 2021;37(5):1510–1.
13. Sung PH, Chiang HJ, Yang YH, Chiang JY, Chen CJ, Yip HK, Lee MS. Nationwide study on the risk of unprovoked venous thromboembolism in non-traumatic osteonecrosis of femoral head. Int Orthop. 2018;42(7):1469–78.
14. Zhao D, Zhang F, Wang B, Liu B, Li L, Kim S-Y, Goodman SB, Hernigou P, Cui Q, Lineaweaver WC, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). J Orthop Translat. 2020;21:100–10.
15. Cheng X, Liu Y, Wang W, Yan J, Lei X, Wu H, Zhang Y, Zhu Y. Preoperative risk factor analysis and dynamic online Nomogram Development for Early Infections Following Primary Hip Arthroplasty in geriatric patients with hip fracture. Clin Interv Aging. 2022;17:1873–83.
16. Zhang K, Zhu Y, Tian Y, Tian M, Li X, Zhang Y. Role of a new age-adjusted D-dimer cutoff value for preoperative deep venous thrombosis exclusion in elderly patients with hip fractures. J Orthop Surg Res. 2021;16(1):649.
17. Tian Y, Zhu Y, Zhang K, Tian M, Qin S, Li X, Zhang Y. Incidence and risk factors for postoperative pneumonia following surgically treated hip fracture in geriatric patients: a retrospective cohort study. J Orthop Surg Res. 2022;17(1):179.
18. Wang Z, Zheng Z, Ye P, Tian S, Zhu Y, Chen W, Hou Z, Zhang Q, Zhang Y. Treatment of tibial plateau fractures: a comparison of two different operation strategies with medium-term follow up. J Orthop Translat. 2022;36:1–7.
19. Zhu Y, Li J, Zhao K, Zhang J, Chen W, Zhang Y. The Hoffa-like fracture of the tibial plateau: a clinical study. Int Orthop. 2022;46(6):1387–93.
20. Wang Y, Deng X, Wang Z, Zhu Y, Chen W, Zhang Y. Total hip arthroplasty or hemiarthroplasty for femoral neck fractures in elderly patients with neuromuscular imbalance. Aging Clin Exp Res. 2022;34(11):2825–33.
21. Zhao K, Zhang J, Wang Z, Wang Y, Li J, Hou Z, Zhang Y, Chen W, Zhang Q. Multiplanar fracture reducer versus manual traction in the treatment of tibial shaft fractures with intramedullary nails. Int Orthop. 2022;46(4):911–7.
22. Zhu J, Hu H, Deng X, Cheng X, Li Y, Chen W, Zhang Y. Risk factors analysis and nomogram construction for blood transfusion in elderly patients with femoral neck fractures undergoing hemiarthroplasty. Int Orthop. 2022;46(7):1637–45.

23. Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, Moons KGM, Collins G, van Smeden M. Calculating the sample size required for developing a clinical prediction model. BMJ. 2020;368:m441.
24. Bikdeli B, Caraballo C, Trujillo-Santos J, Galanaud JP, di Micco P, Rosa V, Cusidó GV, Schellong S, Mellado M, Del Valle Morales M, et al. Clinical presentation and short- and long-term outcomes in patients with isolated distal deep vein thrombosis vs proximal deep vein thrombosis in the RIETE Registry. JAMA Cardiol. 2022;7(8):857–65.
25. Needleman L, Cronan JJ, Lilly MP, Merli GJ, Adhikari S, Hertzberg BS, DeJong MR, Streiff MB, Meissner MH. Ultrasound for lower extremity deep venous thrombosis: multidisciplinary recommendations from the Society of radiologists in Ultrasound Consensus Conference. Circulation. 2018;137(14):1505–15.
26. Cao H, Guan H, Lai Y, Qin L, Wang X. Review of various treatment options and potential therapies for osteonecrosis of the femoral head. J Orthop Translat. 2016;4:57–70.
27. Bantis LE, Nakas CT, Reiser B. Construction of confidence intervals for the maximum of the Youden index and the corresponding cutoff point of a continuous biomarker. Biom J. 2019;61(1):138–56.
28. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ. 2015;350:g7594.
29. Sato K, Date H, Michikawa T, Morita M, Hayakawa K, Kaneko S, Fujita N. Preoperative prevalence of deep vein thrombosis in patients scheduled to have surgery for degenerative musculoskeletal disorders. BMC Musculoskelet Disord. 2021;22(1):513.
30. Yao Y, Chai S, Qiao L, Jiang Q, Xu R. An analysis of the prevalence and risk factors of deep vein thrombosis in non-fracture patients awaiting total hip arthroplasty: a retrospective study of 1244 cases. J Orthop Surg Res. 2024;19(1):84.
31. Matthews C, Gorenne I, Scott S, Figg N, Kirkpatrick P, Ritchie A, Goddard M, Bennett M. Vascular smooth muscle cells undergo telomere-based senescence in human atherosclerosis: effects of telomerase and oxidative stress. Circ Res. 2006;99(2):156–64.
32. Camici GG, Savarese G, Akhmedov A, Lüscher TF. Molecular mechanism of endothelial and vascular aging: implications for cardiovascular disease. Eur Heart J. 2015;36(48):3392–403.
33. Carrington JL. Aging bone and cartilage: cross-cutting issues. Biochem Biophys Res Commun. 2005;328(3):700–8.
34. Berlyne GM, Kwan T, Li J, Caruso C. Oedema protein concentrations for differentiation of cellulitis and deep vein thrombosis. Lancet. 1989;2(8665):728–9.
35. Heijboer H, Brandjes DP, Büller HR, Sturk A, ten Cate JW. Deficiencies of coagulation-inhibiting and fibrinolytic proteins in outpatients with deep-vein thrombosis. N Engl J Med. 1990;323(22):1512–6.
36. Temraz S, Tamim H, Mailhac A, Taher A. Could sodium imbalances predispose to postoperative venous thromboembolism? An analysis of the NSQIP database. Thromb J. 2018;16:11.
37. Moritz ML, Ayus JC. The pathophysiology and treatment of hyponatraemic encephalopathy: an update. Nephrol Dial Transpl. 2003;18(12):2486–91.
38. Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, Resnick HE. Hyponatremia-induced osteoporosis. J Bone Min Res. 2010;25(3):554–63.
39. Ayus JC, Negri AL, Kalantar-Zadeh K, Moritz ML. Is chronic hyponatremia a novel risk factor for hip fracture in the elderly? Nephrol Dial Transpl. 2012;27(10):3725–31.
40. Phillippe HM. Overview of venous thromboembolism. Am J Manag Care. 2017;23(20 Suppl):S376–82.
41. Koupenova M, Kehrel BE, Corkrey HA, Freedman JE. Thrombosis and platelets: an update. Eur Heart J. 2017;38(11):785–91.
42. Chirinos JA, Heresi GA, Velasquez H, Jy W, Jimenez JJ, Ahn E, Horstman LL, Soriano AO, Zambrano JP, Ahn YS. Elevation of endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. J Am Coll Cardiol. 2005;45(9):1467–71.
43. Warny M, Helby J, Birgens HS, Bojesen SE, Nordestgaard BG. Arterial and venous thrombosis by high platelet count and high hematocrit: 108 521 individuals from the Copenhagen General Population Study. J Thromb Haemost. 2019;17(11):1898–911.
44. Kang P, Shen B, Yang J, Pei F. Circulating platelet-derived microparticles and endothelium-derived microparticles may be a potential cause of microthrombosis in patients with osteonecrosis of the femoral head. Thromb Res. 2008;123(2):367–73.
45. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, Kovacs G, Mitchell M, Lewandowski B, Kovacs MJ. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349(13):1227–35.
46. Sugimoto E, Kuroda T, Fujita Y, Namba Y, Mitani S. D-dimer testing cannot rule out thromboembolism after major lower extremity arthroplasties and thromboprophylaxis treatment. J Anesth. 2015;29(5):686–9.

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