



OPEN Neutrophil to high-density lipoprotein cholesterol ratio predicts deep venous thrombosis in spontaneous intracerebral hemorrhage

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Deep vein thrombosis (DVT) is a common and serious complication of spontaneous intracerebral hemorrhage (ICH). The timely recognition and treatment of DVT can significantly mitigate several negative consequences. To investigate the association between the neutrophil-to-high-density lipoprotein cholesterol ratio (NHR) and the occurrence of DVT in ICH patients. This multicenter, retrospective cohort study included patients diagnosed with ICH from three hospitals. The primary outcome was the occurrence of DVT. The NHR was calculated using complete blood counts. Receiver operating characteristic (ROC) analysis was performed to determine the optimal NHR threshold for predicting DVT and to compare its predictive performance with that of other biomarkers. Univariate and multivariate logistic regression analyses were conducted to identify factors associated with DVT and to explore clinical complications related to NHR. A total of 5,004 patients were ultimately included in this study, among whom 359 (7.2%) were diagnosed with DVT. The optimal NHR cutoff for predicting DVT was 6.55, based on the Youden Index from the ROC curve, and was used to dichotomize the study population. In multivariable analyses, even after adjustment, a higher NHR was associated with an increased occurrence of DVT (adjusted odds ratio 1.69, 95% confidence interval 1.33–2.16) and its complications. Additionally, ROC analysis showed that NHR had superior predictive ability for DVT compared to single markers. In patients with ICH, a high NHR (≥ 6.55) independently predicts DVT and may serve as a laboratory marker for its occurrence.

Keywords Neutrophil-to-high-density lipoprotein cholesterol ratio, Mortality, Complication, Intracerebral hemorrhage

Abbreviations

ICH	Spontaneous intracerebral hemorrhage
NHR	Lactate dehydrogenase
GCS	Glasgow Coma Scale
ROC	Receiver operating characteristic
AUROC	The area under the receiver operating characteristic curve

Spontaneous intracerebral hemorrhage (ICH) is associated with high mortality and morbidity rates¹, highlighting a significant clinical challenge despite advancements in medical treatment². Effective therapeutic options for ICH remain limited³, emphasizing the need for ongoing research and attention to this serious health issue⁴. ICH patients are particularly susceptible to complications such as deep venous thrombosis (DVT), which can severely impact their recovery and quality of life^{5,6}. If left untreated, lower limb DVT following an ICH episode

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can progress and lead to sudden death due to pulmonary embolism^{7–10}. Despite the critical importance of DVT prevention in ICH patients, data on effective prophylactic measures are scarce¹¹. Therefore, identifying reliable predictors for DVT in ICH patients is essential to improve patient outcomes and guide timely therapeutic interventions¹².

Previous studies have identified several risk factors for predicting DVT, including advanced age, current smoking status, admission Glasgow Coma Scale (GCS) score, National Institutes of Health Stroke Scale (NIHSS) score¹³. Laboratory biomarkers have garnered significant attention due to their practicality, sensitivity, and convenience. However, the limited predictive value of single biomarkers restricts their clinical utility in the early prediction of DVT¹⁴. Therefore, there is a need for more reliable and easily accessible blood markers for the early prediction of DVT and to guide timely therapeutic interventions.

The neutrophil-to-high-density lipoprotein cholesterol ratio (NHR) is a well-established serum marker for inflammation and infection and has demonstrated strong predictive capabilities for metabolic-related diseases, as well as adverse cardiovascular outcomes^{15,16}. However, its potential as a predictor for DVT in patients with ICH has not yet been explored. Therefore, the objective of this multicenter cohort study is to evaluate the association between NHR, which can be easily obtained through routine laboratory tests, and the occurrence of DVT in ICH patients. Our study aims to fill this gap in the literature and provide valuable insights into this topic.

Methods

Study design

Our study was a retrospective, multicenter cohort study involving 5,004 patients diagnosed with ICH. Data were collected from three hospitals: West China Hospital of Sichuan University (December 2010 to August 2019), The First People's Hospital of Longquanyi District Chengdu (December 2016 to November 2020), and the Affiliated Hospital of Chengdu University (August 2012 to November 2020). The study received approval from the institutional review boards of the ethics committees of the three hospitals: West China Hospital (No. 2021–624), The First People's Hospital of Longquanyi District Chengdu (No. AF-AK86 2,022,010), and the Affiliated Hospital of Chengdu University (No. PJ2021-017-03). As this study involved a clinical audit, informed consent was waived. The study adhered to the STROBE criteria and followed the ethical principles outlined in the Declaration of Helsinki 1964.

Patient selection

All patients diagnosed with spontaneous ICH were included in the study. Diagnosis of ICH was confirmed at admission through computed tomography (CT) or magnetic resonance imaging (MRI), and intraoperative diagnosis by a neurosurgeon during hospitalization. Only patients aged 18 years and older were included. Exclusion criteria were as follows: (1) ischemic stroke with hemorrhagic transformation, trauma, cerebral aneurysm, arteriovenous malformations, brain tumor bleeding, hemorrhagic disorders due to coagulation abnormalities, and other conditions distinct from primary ICH; (2) DVT before admission; (3) patients whose serum NHR levels were not obtained within 24 h of admission.

Data collection

We collected the following baseline information: demographic variables (age and sex); physiological indicators (body mass index and systolic blood pressure); lifestyle history (smoking and alcohol consumption); relevant comorbidities (hypertension, diabetes, and chronic kidney disease); treatment details at baseline (antithrombotic therapy); hematoma characteristics (including size and location); and the GCS score at admission. Additionally, baseline laboratory parameters, defined as the first available results within the first 7 days of admission, included NHR, albumin, lymphocyte count, glucose, leukocyte count, platelet count, and APTT. Admission NHR, given its early predictive value and clinical feasibility, was used, and its optimal cutoff value was determined through ROC curve analysis and the Youden index.

Outcomes

The primary outcome was the occurrence of DVT. DVT was diagnosed based on clinical evaluation and confirmed by imaging. Specifically, if a patient developed signs or symptoms suggestive of DVT (such as limb swelling, pain, or Homans' sign), Doppler ultrasound of the lower extremities was performed to confirm the presence of thrombosis. All DVT diagnoses, including clinical presentation and imaging confirmation, were documented in the electronic medical record and served as the basis for outcome determination.

Given the high risk of rebleeding and the complexity of anticoagulation management in patients with ICH, all participating centers adopted a cautious and standardized approach to DVT prevention. Upon admission, patients without contraindications were started on mechanical prophylaxis measures, including but not limited to graduated compression stockings, intermittent pneumatic compression devices, and other standard supportive modalities. Pharmacological prophylaxis with low-molecular-weight heparin was reserved for a small proportion of patients and initiated only when imaging confirmed stability and there was no evidence of ongoing hemorrhage.

Additionally, we evaluated several secondary outcomes, which were categorized into three main groups: (1) mortality-related outcomes, such as 30-day, 90-day, and 180-day mortality, as well as overall survival; (2) infectious complications, including hospital-acquired infections, pneumonia, intracranial infections, urinary tract infections, and bloodstream infections; (3) other clinical complications, including acute kidney injury (AKI) and seizures. The date of death was obtained from the Chinese Hukou System. Hospital-acquired infections were defined as infections occurring after 48 h of hospital admission and included all of the aforementioned infection types. AKI was defined based on KDIGO criteria—specifically, a rise in serum creatinine ≥ 0.3 mg/dL within 48 h or ≥ 1.5 times baseline within one week, consistent with stage 1 AKI¹⁷.

Statistical analysis

Continuous variables were presented as means and standard deviations and were compared using the Student's *t*-test and the Mann–Whitney *U*-test. Categorical data were analyzed by calculating frequencies or percentages and compared using the chi-square test or Fisher's exact test. All available demographics, baseline variables, and laboratory tests were selected as factors in logistic regression models based on prior studies and clinical expertise. Univariate logistic regression models were conducted separately to analyze the association between each factor and the outcomes. Factors with *P*-values less than 0.05 in univariate analysis were included as confounders in the multivariable logistic regression analysis. ROC curves were used to compare the predictive abilities of NHR and other biomarkers (including albumin, lymphocytes, neutrophils, white blood cells, platelets, glucose, high-density lipoprotein, and activated partial thromboplastin time) for DVT. ROC curves were also used to evaluate the discriminative ability of admission NHR, maximum NHR, and median NHR in predicting the occurrence of DVT within 7 days.

Further subgroup analyses were conducted based on age (≤ 65 years and > 65 years), sex (male and female), smoking status, alcohol consumption, hypertension, diabetes, hematoma location (infratentorial and supratentorial), hematoma volume (≤ 30 ml and > 30 ml), presence of intraventricular hematoma, and GCS scores to explore the heterogeneity of outcomes. All factors were selected based on clinical advice, prior studies, and a review of risk scores. All statistical analyses were performed using R software (version 4.2.1; Foundation for Statistical Computing). A *P*-value of less than 0.05 was considered statistically significant, and all *P*-values were two-sided.

Results

A total of 5,004 patients from West China Hospital, The First People's Hospital of Longquanyi District Chengdu, and The Affiliated Hospital of Chengdu University, who were diagnosed with ICH and were over 18 years old, were included in the study. Patients with conditions other than primary ICH and those without NHR measurements at admission were excluded.

Figure 1 shows the ROC curves of admission, maximum, and median NHR within the first 7 days of hospitalization for predicting DVT. Due to its practicality and early availability, admission NHR was chosen as the primary variable for analysis. An NHR value of 6.55 at admission was identified as the optimal threshold for distinguishing patients with DVT. Based on this value, patients were divided into two groups: a lower NHR group (< 6.55) and a higher NHR group (≥ 6.55). The higher NHR group comprised 2,584 patients, while the lower NHR group comprised 2,420 patients. Table 1 shows the comparison of patient demographics, medical history,

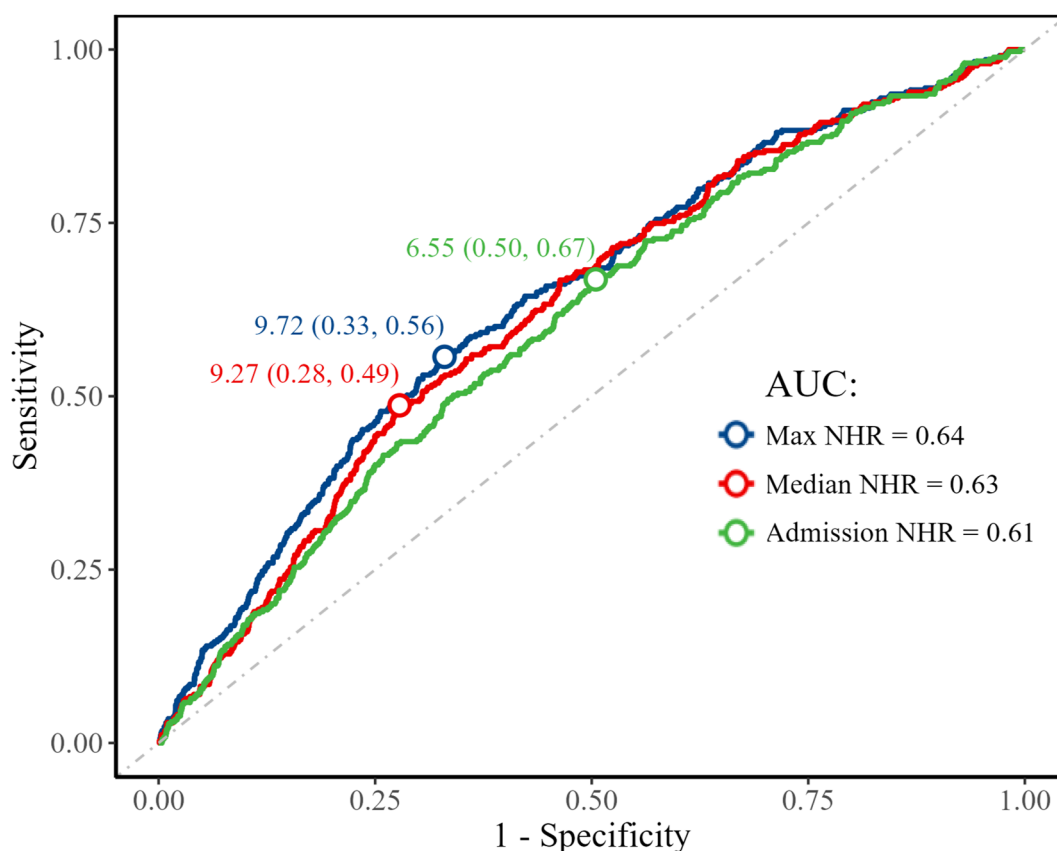


Fig. 1. Receiver operating characteristic curve analysis of different NHR measures for predicting deep venous thrombosis. NHR, neutrophil-to-high-density lipoprotein cholesterol ratio.

Characteristics	Overall (n = 5,004)	Lower NHR (<6.55, n = 2,420)	Higher NHR (≥ 6.55, n = 2,584)	P
Demographics				
Age, year, mean (SD)	56.75 (14.58)	58.50 (14.69)	55.10 (14.28)	<0.001
Female, n (%)	1,769 (35.4)	968 (40.0)	801 (31.0)	<0.001
Smoking, n (%)	1,338 (26.7)	586 (24.2)	752 (29.1)	<0.001
Alcohol, n (%)	1,605 (32.1)	751 (31.0)	854 (33.0)	0.134
Medical history, n (%)				
Hypertension	3,615 (72.2)	1,682 (69.5)	1,933 (74.8)	<0.001
Diabetes	553 (11.1)	248 (10.2)	305 (11.8)	0.088
Chronic kidney disease	147 (2.9)	75 (3.1)	72 (2.8)	0.568
Hematoma characteristics, n (%)				
Size of hematoma, cm, mean (SD)	22.40 (27.32)	17.84 (23.59)	26.74 (29.81)	<0.001
Infratentorial hematoma, n (%)	994 (19.9)	438 (18.1)	556 (21.5)	0.003
Intraventricular hematoma, n (%)	1,045 (20.9)	415 (17.1)	630 (24.4)	<0.001
Glasgow coma score, n (%)				
3–8	1,689 (33.8)	448 (18.5)	1,241 (48.0)	<0.001
9–15	3,282 (65.6)	1,959 (81.0)	1,323 (51.2)	
SBP, mean (SD)	159.04 (31.83)	155.26 (29.28)	162.57 (33.68)	<0.001
Antithrombotic therapy, n (%)	413 (8.3)	228 (9.4)	185 (7.2)	<0.001
Laboratory tests				
Albumin, g/L, mean (SD)	38.20 (6.07)	39.14 (5.16)	37.31 (6.70)	<0.001
Lymphocyte, 10 ⁹ /L, mean (SD)	1.10 (0.66)	1.15 (0.61)	1.06 (0.69)	<0.001
Neutrophil, 10 ⁹ /L, mean (SD)	8.95 (5.01)	6.02 (2.43)	11.69 (5.25)	<0.001
White blood cell, 10 ⁹ /L, mean (SD)	10.91 (10.46)	7.79 (4.01)	13.84 (13.39)	<0.001
Platelets, 10 ⁹ /L, mean (SD)	162.38 (73.48)	154.02 (64.29)	169.21 (79.44)	<0.001
Glucose, mmol/L, mean (SD)	7.47 (3.14)	6.73 (2.59)	8.16 (3.44)	<0.001
High-density lipoprotein, mmol/L, mean (SD)	1.27 (0.45)	1.46 (0.45)	1.09 (0.37)	<0.001
Activated partial thromboplastin time, s, mean (SD)	28.81 (8.49)	28.19 (7.34)	29.37 (9.37)	<0.001

Table 1. Baseline characteristics of the patients by neutrophil-to-high density lipoprotein cholesterol ratio. SD, standard deviation; NHR, neutrophil-to-high-density lipoprotein cholesterol ratio.

and other factors between the two groups. Specifically, a higher NHR was generally associated with younger age and male sex, and was more likely to be observed in patients with a history of smoking and hypertension, lower GCS scores, higher systolic blood pressure, and larger hematoma volumes. Additionally, NHR levels were significantly associated with hematoma location.

The overall DVT rate in the entire plation was 7.2% (n = 359). Patients with a higher NHR had a mortality rate of 9.3% (n = 240), compared to 4.9% (n = 119) in patients with a lower NHR ($P < 0.001$). Logistic regression analysis showed that age, GCS score, hematoma size and location, history of diabetes, chronic kidney disease, and antithrombotic therapy were independent risk factors for the development of DVT. The adjusted OR for the association between NHR level and DVT was 1.69 (95% CI: 1.33–2.16), as shown in Table 2. This finding was consistent with the associations observed for AKI (adjusted OR: 1.84; 95% CI: 1.52–2.22; $P < 0.001$), hospital-acquired infections (adjusted OR: 1.63; 95% CI: 1.43–1.86; $P < 0.001$), pneumonia (adjusted OR: 2.03; 95% CI: 1.78–2.31; $P < 0.001$), intracranial infection (adjusted OR: 2.28; 95% CI: 1.50–3.47; $P < 0.001$), urinary tract infection (adjusted OR: 1.44; 95% CI: 1.19–1.74; $P < 0.001$), and bloodstream infection (adjusted OR: 2.04; 95% CI: 1.44–2.91; $P < 0.001$). Moreover, NHR was also found to be significantly associated with both short- and long-term mortality in patients with ICH, such as 30-day mortality (adjusted OR: 1.50; 95% CI: 1.21–1.86) and long-term mortality (adjusted OR: 1.41; 95% CI: 1.18–1.69).

The restricted cubic spline (RCS) demonstrated the association between NHR and the risk of DVT (Fig. 2). As NHR increased, the OR showed a slight upward trend, suggesting a potential positive dose–response relationship between NHR and DVT risk. This relationship appeared to be non-linear ($P = 0.37$). ROC curve analysis was conducted to assess the predictive value of NHR and other laboratory indicators for DVT (Fig. 3). Among all variables, NHR had the highest area under the curve (AUC = 0.61), followed by albumin (Alb, AUC = 0.60), high-density lipoprotein (HDL, AUC = 0.59), lymphocytes (Lymph, AUC = 0.56), glucose (Glu, AUC = 0.56), neutrophils (Neut, AUC = 0.56), white blood cells (WBC, AUC = 0.55), activated partial thromboplastin time (APTT, AUC = 0.53), and platelets (Plt, AUC = 0.53). These results indicate that NHR has relatively superior discriminatory power compared to the other parameters.

The subgroup analysis further demonstrates the association between NHR distribution across different clinical factors and event occurrence (Fig. 4). The results show that in most subgroups, no significant interaction was observed between NHR levels and event occurrence ($P > 0.05$). However, in the subgroups of age, alcohol use, and chronic kidney disease, the effect of NHR levels on the occurrence of DVT showed significant differences

Outcomes	Events, n (%)	Unadjusted		Adjusted	
		OR (95% CI)	P	OR (95% CI)	P
Primary outcome					
Deep Vein Thrombosis	240 (9.3)	1.98 (1.58–2.48)	<0.001	1.69 (1.33–2.16)	<0.001
Complications					
Seizures	65 (2.5)	1.33 (0.91–1.95)	0.141	1.39 (0.92–2.11)	0.115
Acute Kidney Injury	572 (22.1)	2.42 (2.07–2.84)	<0.001	1.84 (1.52–2.22)	<0.001
Hospital-acquired infections	1,192 (46.1)	2.09 (1.86–2.35)	<0.001	1.63 (1.43–1.86)	<0.001
Pneumonia	1,232 (47.7)	2.46 (2.18–2.76)	<0.001	2.03 (1.78–2.31)	<0.001
Intracranial infection	113 (4.4)	3.41 (2.30–5.07)	<0.001	2.28 (1.50–3.47)	<0.001
Urinary tract infection	364 (14.1)	1.61 (1.35–1.92)	<0.001	1.44 (1.19–1.74)	<0.001
Bloodstream infection	141 (5.5%)	2.85 (2.05–3.98)	<0.001	2.04 (1.44–2.91)	<0.001
Mortality					
Mortality at 30 days	429 (27.6)	2.27 (1.87–2.74)	<0.001	1.50 (1.21–1.86)	<0.001
Mortality at 90 days	493 (31.7)	2.28 (1.90–2.73)	<0.001	1.50 (1.22–1.85)	<0.001
Mortality at 180 days	541 (34.7)	2.31 (1.94–2.75)	<0.001	1.58 (1.29–1.93)	<0.001
Mortality at 1 year	591 (38.0)	2.21 (1.87–2.61)	<0.001	1.56 (1.28–1.90)	<0.001
Mortality at 2 years	658 (42.3)	2.06 (1.76–2.42)	<0.001	1.46 (1.21–1.76)	<0.001
Mortality at 3 years	698 (44.8)	2.02 (1.72–2.36)	<0.001	1.46 (1.22–1.76)	<0.001
Mortality at 4 years	718 (46.1)	1.90 (1.63–2.22)	<0.001	1.40 (1.16–1.68)	<0.001
Mortality at 5 years	744 (47.8)	1.88 (1.61–2.18)	<0.001	1.40 (1.17–1.68)	<0.001
In-hospital mortality	294 (12.5)	2.77 (2.21–3.47)	<0.001	1.57 (1.22–2.02)	0.001
Long-term mortality	782 (50.2)	1.83 (1.57–2.13)	<0.001	1.41 (1.18–1.69)	<0.001

Table 2. Comparison of unadjusted and risk-adjusted outcomes by neutrophil-to-high density lipoprotein cholesterol ratio. Hospital-acquired infections (≥ 48 h after admission), including pneumonia, intracranial, urinary tract, and bloodstream infections. OR, odds ratio; CI: confidence interval.

($P < 0.05$), suggesting that these factors may exacerbate the risk of DVT in the high NHR group, particularly among individuals who are younger, have alcohol consumption habits, and have chronic kidney disease.

Discussion

In this study, we found a strong association between elevated NHR levels and the risk of developing DVT in patients with ICH. Patients with admission NHR levels above 6.55 had a significantly higher likelihood of DVT. This association followed a clear linear dose–response pattern, as confirmed by RCS analysis. Moreover, elevated NHR levels were also significantly linked to other complications, such as AKI and various infections, including pneumonia, urinary tract infections, and bloodstream infections, as well as increased short- and long-term mortality. Subgroup analyses further revealed that in certain subgroups—specifically younger patients, individuals with a history of alcohol use, and those with chronic kidney disease—the association between elevated NHR levels and DVT was significantly stronger.

DVT prevention is explicitly recommended for patients with ICH in clinical guidelines from multiple countries^{3,18,19}. Studies have shown that the median time from ICH onset to DVT diagnosis is 7 days, suggesting that earlier prevention may be critical²⁰. Therefore, this study aimed to evaluate the predictive value of the NHR at admission for the development of DVT, in order to facilitate early identification of high-risk patients and guide timely clinical interventions. Previous studies have demonstrated that NHR can predict early hematoma expansion and poor outcomes in patients with ICH^{21,22}. For example, Yu et al.²³ reported that a higher NHR is associated with an increased risk of acute ischemic stroke. Similarly, Liu et al.²⁴ found that elevated NHR levels are predictive of adverse cardiovascular outcomes in individuals with pre-diabetes. Our study is the first to investigate the association between NHR levels and the occurrence of DVT in patients with ICH. The findings are consistent with these studies, demonstrating that elevated NHR levels are significantly associated with DVT and other adverse outcomes in patients with ICH.

Several potential mechanisms may explain the association between NHR levels and DVT in ICH patients. First, the inflammatory response following ICH can activate the coagulation cascade, increasing the risk of thrombosis, and may also exacerbate endothelial injury, further promoting a pro-thrombotic state^{25,26}. Second, neutrophils release extracellular traps that serve as both a scaffold and a prothrombotic stimulus by capturing platelets, red blood cells, and plasma proteins, while histones within NETs directly trigger platelet activation and aggregation, thereby promoting blood clot formation^{27,28}. HDL-C not only reduces platelet sensitivity to aggregation stimuli but also inhibits the formation of neutrophil extracellular traps, thereby reducing thrombosis formation^{29,30}. Moreover, they are all closely related to the coagulation cascade^{31,32}. These mechanisms underscore the potential value of the NHR in predicting DVT in this patient population.

Our study has several strengths. Firstly, the large sample size of 5,004 patients from multiple centers enhances the generalizability of our findings. Secondly, we utilized both univariate and multivariate analyses to adjust for

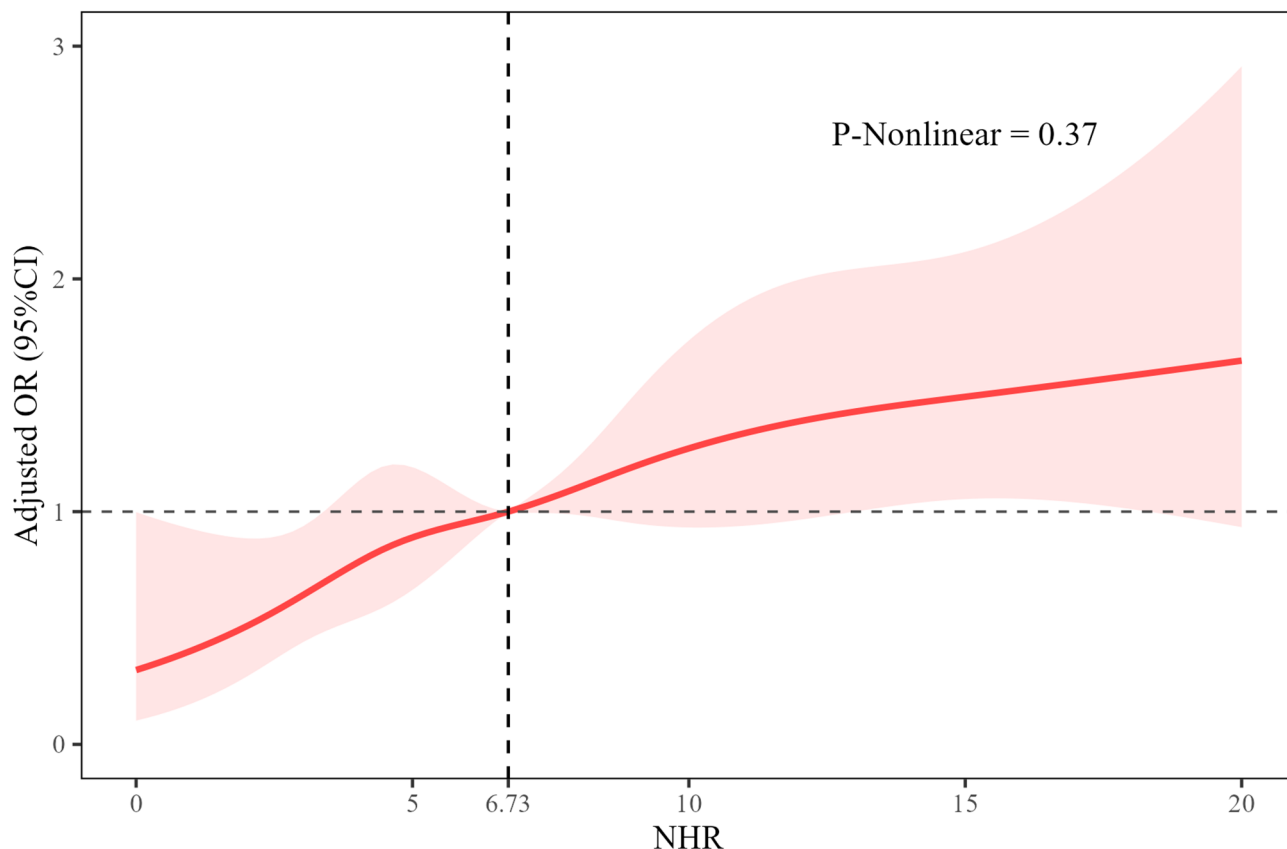


Fig. 2. Restricted cubic spline analysis of the association between neutrophil-to-high-density lipoprotein cholesterol ratio and deep venous thrombosis. NHR, neutrophil-to-high-density lipoprotein cholesterol ratio; OR, odds ratio; CI: confidence interval.

potential confounders, providing robust evidence for the independent predictive value of NHR. Thirdly, the practical application of NHR, derived from routine blood tests, makes it an accessible and cost-effective tool for clinicians. There are several limitations to this study that should be acknowledged. First, its retrospective design may have introduced selection bias and unmeasured confounding variables. Second, the use of electronic medical records for data collection may be associated with reporting bias. Third, the study population consisted exclusively of patients from China, which may limit the generalizability of the findings to other populations. Despite these limitations, our results suggest that measuring the NHR at baseline may have clinical relevance in identifying ICH patients at higher risk of DVT and in guiding more personalized prophylactic strategies. Nevertheless, further prospective, multicenter studies with larger and more diverse populations are needed to validate the findings of this study.

Conclusions

An NHR exceeding 6.55 was established as an independent predictor of DVT in patients with ICH. Furthermore, NHR emerged as an independent predictor of various clinical complications, particularly infectious ones. Due to its ease of measurement and cost-effectiveness, NHR may prove to be a valuable tool for prognostication in ICH patients.

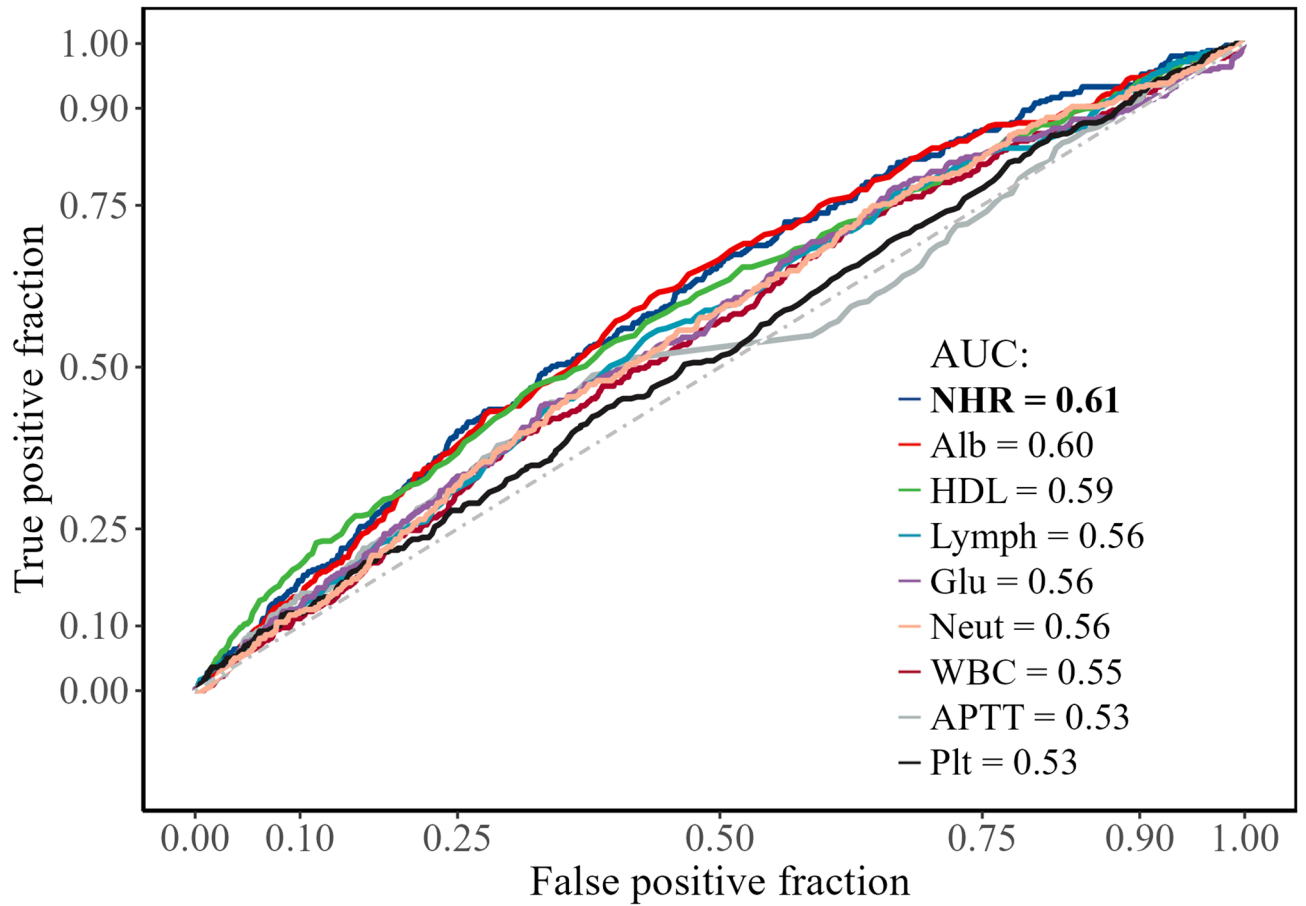


Fig. 3. Receiver operating characteristic curve analysis of different biomarkers for predicting deep venous thrombosis. NHR, neutrophil-to-high-density lipoprotein cholesterol ratio; Alb, albumin; HDL, high-density lipoprotein cholesterol; Lymph, lymphocyte; Glu, glucose; Neut, neutrophil; WBC, white blood cell count; APTT, activated partial thromboplastin time; Plt, platelet count.

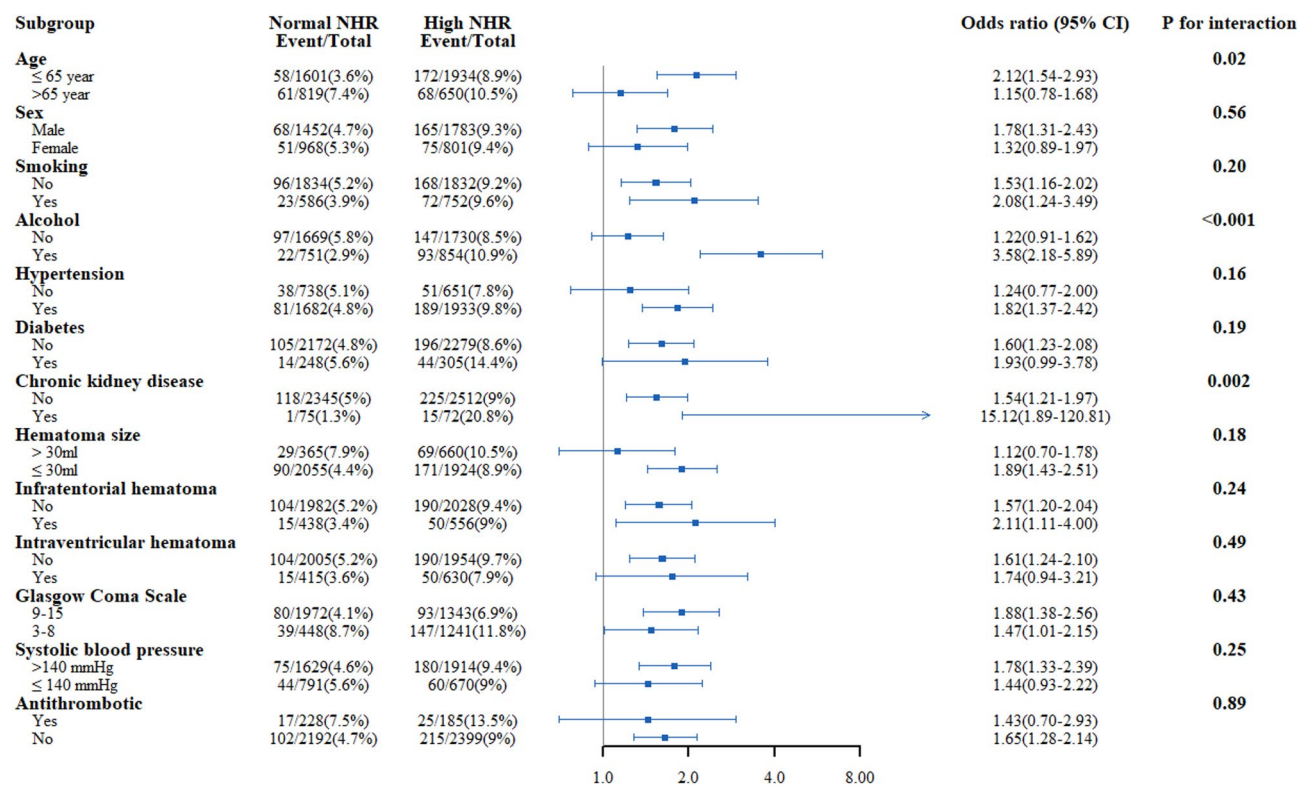


Fig. 4. Subgroup analysis of the association between neutrophil-to-high-density lipoprotein cholesterol ratio and deep venous thrombosis.

Data availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Author contributions

Study concept and design: YZ, FF Acquisition, analysis, or interpretation of data: WX, JW, PW, XC, LP, JH, YF, and FF Statistical analysis: WX, YX Drafting of the manuscript: WX, PW Critical revision of the manuscript for important intellectual content: All authors.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

The ethics committee of West China Hospital (No. 2021-624). The ethics committee of Affiliated Hospital of Chengdu University (No. PJ2021-017-03). The ethics committee of The First People's Hospital of Longquanyi District Chengdu (No. AF-AK-2022010). The committee waived the requirement for informed consent because the data were analyzed anonymously.

Additional information

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