

CORRESPONDENCE

Open Access



Combination of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio with plasma D-dimer level to improve the diagnosis of deep venous thrombosis (DVT) following ankle fracture

Zhida Gao^{1,2†}, Kuo Zhao^{1†}, Lin Jin^{1†}, Xiaodong Lian¹, Zhiang Zhang¹, Lijie Ma¹ and Zhiyong Hou^{1,3,4,5,6*}

Abstract

Purpose To investigate the relationship between neutrophil to lymphocyte ratio (NLR)/platelet to lymphocyte ratio (PLR) with deep venous thrombosis (DVT) following ankle fracture and the diagnostic ability of combination model.

Method This retrospective study included patients with a diagnosis of ankle fracture who had undergone preoperative Duplex ultrasound (DUS) examination for detecting the possible deep venous thrombosis (DVT). The variables of interest, the calculated NLR and PLR and others (demographics, injury, lifestyles and comorbidities) were extracted from the medical records. Two independent multivariate logistics regression models were used to detect the relationship between NLR or PLR and DVT. If any, combination diagnostic model was constructed and its diagnostic ability was evaluated.

Results There were 1103 patients included, and 92 (8.3%) were found to have preoperative DVT. The NLR and PLR, which had respective optimal cut-off point of 4 and 200, were significantly different between patients with and without DVT either in continuous or categorical variable. After adjustment for covariates, both NLR and PLR were identified as independent risk factors associated with DVT, with odd ratio of 2.16 and 2.84, respectively. The combination diagnostic model, including NLR, PLR and D-dimer, demonstrated to significantly improved the diagnostic performance than any one alone or combined (all $P < 0.05$), and the area under the curve was 0.729 (95% CI 0.701–0.755).

Conclusion We concluded the relatively low incidence rate of preoperative DVT after ankle fracture, and both NLR and PLR were independently associated with DVT. The combination diagnostic model can be considered as a useful auxiliary tool for identifying high-risk patients for DUS examination.

Keywords Ankle fracture, Lymphocyte ratio/platelet to lymphocyte ratio, Combination diagnostic model, Improved diagnostic performance

[†]Zhida Gao, Kuo Zhao and Lin Jin are contributed equally to this work

*Correspondence:

Zhiyong Hou

drzyhou@gmail.com

Full list of author information is available at the end of the article



Introduction

Deep venous thrombosis (DVT) is a prevalent and severe complication in orthopedic trauma, especially in lower extremity fractures. Ankle fracture is among the most common injuries and the preoperative incidence of DVT is greatly varying from 0.28 to 13.7%, primarily attributable to the differences in study design, setting, patient characteristics, screening methods and the prevention strategies [1–4]. DVT was associated with significantly increased risk of adverse events, including pulmonary emboli, atherothrombosis and cardiovascular complications [5, 6]. To date, DVT prophylaxis is not routinely administered in ankle fracture surgery in most institutions, when balancing the risks and benefits. In contrast, identifying individuals at high-risk and establishing tailored early detection and prevention strategies has been consistently the most desirable approach.

The plasma D-dimer test is generally used in various settings as a primary screening test for detection of DVT, pulmonary embolism (PE) or both, due to its ease, high sensitivity and low-cost of operation. However, the low specificity (even < 20% even in elderly patients) will produce a disproportionate number of false positives, and thus recur additional medical resources consumption [7]. During the past decade, efforts to identify a variety of risk factors associated with DVT have been made, and some important factors have been well established such as older age, male gender, higher fracture severity, history of VTE, immobility of injured extremity and et al. [1, 2, 8–10]. Recently, emerging evidences have shown that DVT was associated with inflammatory/immune response to fracture, surgical trauma or systemic chronic conditions in different medical settings [11–13]. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are the typical representatives [14, 15], but their relation to DVT is not always consistent. Considering that these two indexes are readily accessible, low-cost and without requiring additional laboratory test, it is very essential to elucidate their relationship with DVT, and if any, to investigate the potential of combination diagnosis by using NLR/PLR and the D-dimer level. This study therefore, aimed to first, determine whether NLR or PLR was associated with preoperative presence of DVT, and second, if any, to evaluate the diagnostic ability of NLR and/or PLR with plasma D-dimer level.

Materials and methods

Inclusion and exclusion criteria

This study was approved by the ethics committees of the Third Hospital of Hebei Medical University and was performed in accordance with the Helsinki Declaration. Adult patients who had an ankle fracture surgically treated and had a complete preoperative duplex

ultrasound (DUS) screening examination between January 2017 and December 2021 in our institution were included. The exclusions criteria were old fracture (> 21 days after fracture), pathological fracture, open fracture, multiple fractures, polytrauma, abnormal lower limb muscle strength, history of VTE events, thrombophilia or hematological disorders, anticoagulants or glucocorticoids use within 3 months of fracture, anticoagulant medication administered before DUS screening or absence of preoperative DUS examination. According to the Robinov group's criteria, the diagnosis of DVT was made by two ultrasound physicians [16].

Measurement of biological indicators

Routine blood test was performed immediately after admission and repeated before operation in accordance with the Instruction Manual, by use of a hematology analyzer (UniCel DxH 800; Beckman Coulter, Brea, CA, USA) an automated coagulation analyzer (ACL 700, Beckman Coulter, Brea, CA, USA), respectively. NLR was calculated by dividing the neutrophil count by the lymphocyte count, and PLR was calculated by dividing the platelet count by the lymphocyte count (Fig. 1).

Data collection

Data were collected by inquiring the electronic medical record for the index hospitalization. These included age at the time of surgery, gender, time from injury to DUS examination, body mass index (BMI, calculated by dividing the body weight in kilogram by the height in meter), fracture location (uni-, bi- or tri-malleolar), presence or absence of dislocation/subluxation, injury mechanism (high- or low-energy trauma), smoking status (yes or no), alcohol drinking (yes or no), comorbidities (hypertension, diabetes, cerebrovascular disease, heart disease, living disease), American Society of Anesthesiologists (ASA) classification, lymphocyte count, neutrophil count, platelet count and plasma D-dimer concentration.

Statistical analysis

For continuous variables, Shapiro–Wilk test was used to explore their normally distributed status, based on which, continuous variables were expressed as mean \pm standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for the skewed. Student-*t* test or Mann–Whitney *U* test was performed to compare the between-group difference, as appropriate. Categorical variables were expressed as number and its percentage, and Chi-square or Fisher's exact test was used to compare the between-group difference, as appropriate.

First, receiver operator characteristic (ROC) analysis was performed to determine the optimal cut-off value for NLR, PLR and plasma D-dimer, when Youden index

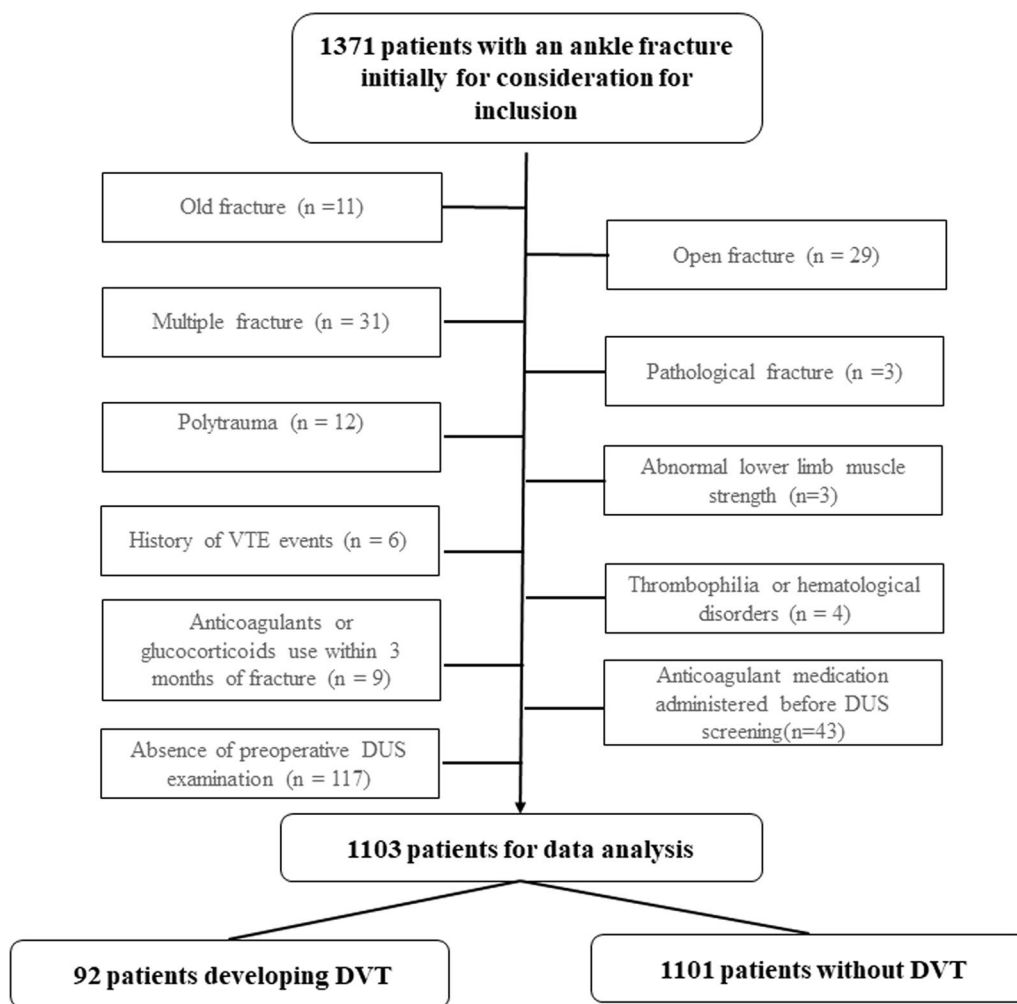


Fig. 1 The flowchart of this study

(= sensitivity + specificity - 1) was maximum. Based on the cut-off value, these three indexes were dichotomized as low versus high, respectively. The area under the ROC curve (AUC) was used to quantify the diagnostic ability, which ranged from 0 to 100%, with higher representing better ability. To investigate whether NLR in dichotomous variable was independently associated with preoperative DVT, multivariate logistic regression models were constructed, when adjusting for all the covariates (not including PLR) using the “enter” method, namely the “total adjusted model”, did as the same for PLR. The association magnitude was indicated by odd ratio (OR) with 95% confidence interval (95% CI). The goodness-of-fit of the model was evaluated by Hosmer–Lemeshow (H–L) test, with $P > 0.05$ suggestive of an acceptable result. The above analyses were performed using SPSS 23.0 (IBM, Armonk, New York, USA).

If the association of NLR and/or PLR with preoperative DVT demonstrated to be significant, another multivariate

logistic regression model adjusted for NLR and/or PLR and D-dimer was constructed, forming the combination diagnostic model and the C-statistic (equivalent to the AUC) was used to evaluate the diagnostic performances of this combination diagnostic model. Comparisons of diagnostic performances between D-dimer alone, combination with PLR and/or NLR in diagnosing preoperative DVT were performed by using the MedCalc software (MedCalc 19.2.1; MedCalc, Mariakerke, Belgium).

The $P < 0.05$ was set as significance level for all the analyses.

Results

There were 1103 patients included in this study, including 657 males and 446 females, with an average age of 42.8 ± 14.2 years (range, 18–84). Among them, 92 were found to have preoperative DVT detected by DUS, suggesting an incidence rate of 8.3% (95% CI 6.7–10.0%). A total of 142 thrombi were found, indicating an average

of 1.54 for each patient with DVTs; most of thrombi (92.3%, 131) were located distal to the popliteal veins, and over 80% (81.7%, 116/142) at the injured limb.

There were significant differences between patients with and without DVT in terms of age (48.6 ± 14.7 vs 42.3 ± 14.0), male gender (70.7% vs 58.6%), prevalence of hypertension (19.6% vs 12.3%), injury mechanism (65.5% vs 35.5%), lymphocyte count (1.3 ± 0.6 vs 1.6 ± 0.7), NLR (5.7 ± 3.1 vs 4.7 ± 3.2), PLR (225.7 ± 125.4 vs 167.1 ± 80.9), and D-dimer concentration (2.6 ± 5.8 vs 0.8 ± 1.5), with all *P* values less than 0.05 (Table 1).

The NLR was 4.77 ± 3.19 (range 0.35–34.36), with 5.7 ± 3.1 in DVT group and 4.7 ± 3.2 in non-DVT group, and the difference was significant ($P=0.004$). The optimal cut-off point for NLR was 4 (AUC, 0.616; 95% CI 0.557–0.674; $P<0.001$) and the proportion of $NLR \geq 4$ was 69.6% (64/92) in patients with DVT and 48.7% (492/1011) in those without, with a significant difference ($P<0.001$) (Fig. 2). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for NLR was 69.6%, 51.3%, 11.5%, and 94.9%. The total adjusted logistic regression model showed $NLR \geq 4$ was significantly associated with the increased risk of

Table 1 Univariate analysis of variables between DVT and non-DVT group

Variables	Number (%) of patients without DVT (n = 1011)	Number (%) of patients with DVT (n = 92)	<i>P</i>
Age (years)	42.3 ± 14.0	48.6 ± 14.7	< 0.001
Sex (male)	592 (58.6)	65 (70.7)	0.024
BMI (kg/m ²)	25.6 ± 3.9	26.0 ± 3.0	0.667
< 28.0	877 (86.7)	79 (85.9)	0.813
≥ 28.0	134 (13.3)	13 (14.1)	
Fracture location			
Unimalleolar	427 (42.2)	44 (47.8)	0.583
Bimalleolar	244 (24.1)	20 (21.7)	
Trimalleolar	340 (33.6)	28 (30.4)	
Dislocation/subluxation	193 (19.1)	23 (25.0)	0.171
Hypertension	124 (12.3)	18 (19.6)	0.045
Diabetes mellitus	146 (14.4)	20 (21.7)	0.061
Cerebrovascular disease	9 (0.9)	2 (2.2)	0.235
Heart disease	36 (3.6)	3 (3.3)	0.881
Liver disease	22 (2.2)	4 (4.3)	0.189
Smoking	250 (24.7)	25 (27.2)	0.604
Alcohol drinking	280 (27.7)	32 (34.8)	0.148
Injury mechanism			0.001
Low-energy	652 (64.5)	43 (46.7)	
High-energy	359 (35.5)	49 (53.3)	
ASA classification			0.122
I	180 (17.8)	13 (14.1)	
II	715 (70.7)	62 (67.4)	
III–IV	116 (11.5)	17 (18.5)	
Lymphocyte	1.6 ± 0.7	1.3 ± 0.6	< 0.001
Neutrophile	6.4 ± 2.7	6.4 ± 2.1	0.982
Platelet	239.2 ± 80.0	259.8 ± 101.1	0.060
NLR	4.7 ± 3.2	5.7 ± 3.1	0.004
≥ 4	492 (48.7)	64 (69.6)	< 0.001
PLR	167.1 ± 80.9	225.7 ± 125.4	< 0.001
≥ 200	253 (25.0)	47 (51.1)	< 0.001
D-dimer	0.8 ± 1.5	2.6 ± 5.8	0.004
≥ 0.80	259 (25.6)	54 (58.7)	< 0.001

DVT—deep venous thrombosis, BMI—body mass index, ASA—American Society of Anesthesiologists, NLR—neutrophil to lymphocyte ratio, PLR—platelet to lymphocyte ratio

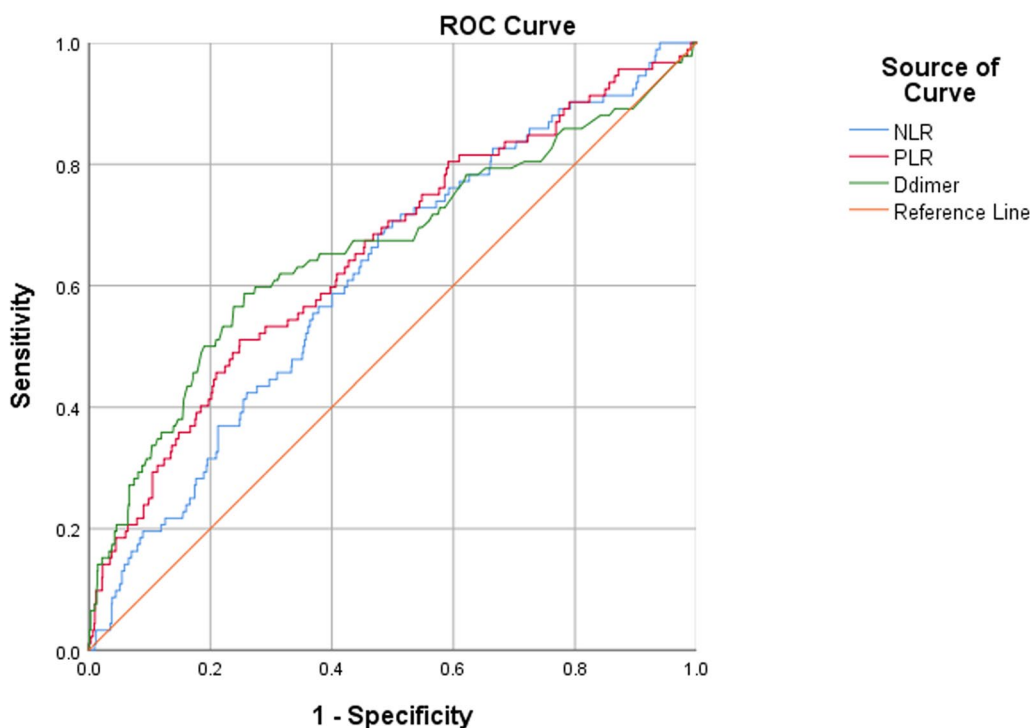


Fig. 2 The ROC curve and analysis for NLR, PLR, and D-dimer, respectively. The optimal cut-off point for NLR, PLR, and D-dimer was 4, 200 and 0.8 mg/L, with respective AUC being 0.616 (95% CI 0.557–0.674; $P < 0.001$), 0.653 (95% CI 0.591–0.714; $P < 0.001$), and 0.660 (95% CI 0.631–0.688; $P < 0.001$)

DVT, with OR value of 2.16 (95% CI 1.34–3.49; $P = 0.002$) (Table 2). The PLR was 172.00 ± 86.97 (range, 13.0–660.0), with 225.7 ± 125.4 in DVT group and 167.1 ± 80.9 in non-DVT group, and the difference was significant ($P < 0.001$). The optimal cut-off point for PLR was 200 (AUC, 0.653; 95% CI 0.591–0.714; $P < 0.001$) and the proportion of $PLR \geq 200$ was 51.1% (47/92) in patients with DVT and 25.0% (253/1011) in those without, with a significant difference ($P < 0.001$) (Fig. 2). Also, the total adjusted logistic regression model showed the significant relation between $PLR \geq 200$ and DVT, with OR value of 2.84 (95% CI 1.80–4.47; $P < 0.001$) (Table 3). The sensitivity, specificity, PPV, and NPV for PLR was 51.1%, 75.0%, 15.7%, and 94.4%. D-dimer level, which was determined to be with an optimal cut-off point of 0.80 (AUC, 0.660; 95% CI 0.631–0.688; $P < 0.001$), demonstrated to be significantly associated with DVT in both multivariate logistic regression models for NLR and PLR (Table 2s and 3). Figure 3 depicts the AUC, which represented the diagnostic performance in DVT, for four indexes, D-dimer alone (0.660; 95% CI 0.631–0.688), NLR + D-dimer (0.704; 95% CI 0.676–0.731), PLR + D-dimer (0.711; 95% CI 0.683–0.737), and NLR + PLR + D-dimer (0.729; 95% CI 0.701–0.755). The results showed the combination model with D-dimer, NLR, and PLR included exhibited

Table 2 Relationship between NLR and preoperative DVT investigated by total adjusted multivariate logistic regression model

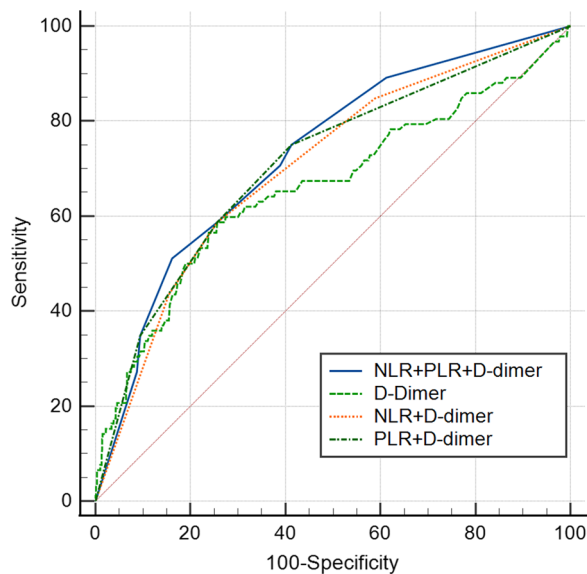
Variables	OR and 95% CI	P
NLR	2.16 (1.34–3.49)	0.002
Age	1.04 (1.02–1.05)	<0.001
Gender (male vs female)	1.95 (1.08–3.53)	0.027
Obesity (BMI ≥ 28.0 kg/m ²)	1.22 (0.61–2.41)	0.573
Smoking	0.78 (0.42–1.43)	0.414
Alcohol drinking	1.32 (0.74–2.35)	0.350
Time from fracture to DUS examination	1.16 (1.10–1.23)	<0.001
Fracture type		
Unimalleolar	Reference	
Bimalleolar	0.82 (0.44–1.50)	0.508
Trimalleolar	0.80 (0.45–1.41)	0.432
Dislocation/subluxation	1.27 (0.72–2.22)	0.410
Mechanism (high- versus low-energy)	1.45 (0.88–2.37)	0.144
Hypertension	1.33 (0.70–2.53)	0.378
Diabetes mellitus	1.46 (0.80–2.69)	0.220
Cerebrovascular disease	0.81 (0.15–4.50)	0.811
Heart disease	1.32 (0.43–8.91)	0.090
Liver disease	2.16 (0.66–7.09)	0.205
D-dimer (> 0.80 mg/L)	2.90 (1.77–4.74)	<0.001

NLR—neutrophil to lymphocyte rate, BMI—body mass index, OR—odd ratio, CI—confidence interval

Table 3 Relationship between PLR and preoperative DVT investigated by total adjusted multivariate logistic regression model

Variables	OR and 95% CI	P
PLR	2.84 (1.80–4.47)	<0.001
Age	1.04 (1.02–1.05)	<0.001
Gender (male vs female)	2.12 (1.21–3.76)	0.027
Obesity (BMI \geq 28.0 kg/m ²)	1.23 (0.62–2.45)	0.558
Smoking	0.76 (0.42–1.41)	0.387
Alcohol drinking	1.30 (0.73–2.32)	0.380
Time from fracture to DUS examination	1.15 (1.08–1.22)	<0.001
Fracture type		
Unimalleolar	Reference	
Bimalleolar	0.83 (0.45–1.53)	0.551
Trimalleolar	0.83 (0.47–1.49)	0.538
Dislocation/subluxation	1.33 (0.76–2.33)	0.316
Mechanism (high- versus low-energy)	1.38 (0.84–2.26)	0.202
Hypertension	1.37 (0.72–2.60)	0.342
Diabetes mellitus	1.43 (0.78–2.63)	0.247
Cerebrovascular disease	0.87 (0.16–4.84)	0.872
Heart disease	1.29 (0.41–8.84)	0.088
Liver disease	2.01 (0.61–6.59)	0.251
D-dimer (> 0.80 mg/L)	2.91 (1.79–4.76)	<0.001

PLR—platelet to lymphocyte rate, BMI—body mass index, OR—odd ratio, CI—confidence interval

**Fig. 3** Depicted the ROC curve and analysis for D-dimer, NLR + D-dimer, PLR + D-dimer, and NLR + PLR + D-dimer, with the latter one having the significantly higher diagnostic performance

the significantly better diagnostic performance, compared to any other one, single or combined (Table 4). Particularly, compared to the use of D-dimer alone, the

combination model showed the significantly larger AUC, with an absolute difference of 0.069 ($P=0.003$). The sensitivity, specificity, PPV, and NPV for D-dimer was 58.7%, 74.4%, 17.2%, and 95.2%.

Discussion

Given the clinical importance of DVT in short- and long-term prognosis, there has been increasing number of studies focusing on identification of the acquired or inherited risk factors, helping to adopt the optimal preventive strategies in high-risk individuals. Recently, increasing evidences have demonstrated the close link between inflammation and thrombosis, [14, 17–19], which, however, was not well studied in orthopedic trauma field. Thus, the present study was specifically designed to investigate the association of NLR or PLR with preoperative DVT in the setting of a very common fracture type, ankle fracture. We found that elevated NLR and PLR were independently associated with 2.16- and 2.84-fold increased risk of DVT, respectively; also, the combination diagnostic model, including NLR, PLR, and D-dimer, demonstrated to significantly improve the diagnostic performance compared to D-dimer use alone or combined with PLR or NLR ($P < 0.05$).

The ultrahigh sensitivity of D-dimer is helpful in excluding acute DVT or PE, but the limited specificity does not allow diagnostic confirmation, especially in those hospitalized patients [15]. Thus, adding markers to form a practical combination diagnostic model is highly desirable to improve the diagnostic accuracy. During the past decade, more attention has been given to the correlation of inflammatory factors (NLR/PLR) with prognosis (morbidity and mortality) after surgically treated fractures [20–22]. However, few linked them to the thrombosis after fracture. In a retrospective of 1179 tibial plateau fractures, Liu et al. [23] found NLR and PLR were significantly different between patients with and without preoperative DVT in the univariate analysis, but either was no more significant after adjustment for other covariates; instead, the platelet and neutrophil count were identified as independent factors for DVT [23]. In this study, we found both NLR and PLR were independently associated with 2.16-fold and 2.84-fold increased risk of preoperative DVT after ankle fractures, possibly suggesting the fracture locations also contribute a role in risk of DVT.

In previous studies, researchers examined the referral intervals of the PLR and NLR in the population of adult physical examinees. Meng et al. [24] reviewed the data of 24,029 healthy physical examinees in Henan China, and reported the NLR of 1.72 (1.39–2.17) for males and 1.71 (1.35–2.18) for females and PLR of 102 (85–124) for males and 115 (95–140) for females. In another study covering 38,176 adults without any disease

Table 4 Comparison of diagnostic performance by AUC among different markers or combined

Pairwise comparisons	Absolute difference in AUC	Z statistic	P
D-dimer versus D-dimer + NLR	0.044	1.959	0.050
D-dimer versus D-dimer + PLR	0.051	2.285	0.022
D-dimer versus D-dimer + NLR + PLR	0.069	2.938	0.003
D-dimer + NLR versus D-dimer + NLR + PLR	0.024	2.235	0.025
D-dimer + PLR versus D-dimer + NLR + PLR	0.018	2.013	0.044
D-dimer + NLR versus D-dimer + PLR	0.007	0.378	0.705

PLR—platelet to lymphocyte rate, NLR—neutrophil to lymphocyte rate, AUC—area under the curve

and ostensibly healthy in Wuhan China, Fei et al. [25] reported the comparable results, NLR of 1.67 (1.33–2.11) and PLR of 113 (93–137) for males, 1.68 (1.32–2.14) and 124 (102–150) for females, respectively. Similar results were also reported in other studies [26–28]. In contrast, our reported results (NLR, 4.77; PLR, 172) that were 2.8 times and 1.6 times the normal referral value reflected the systemic immune/inflammatory response to fracture trauma (especially the vascular damage around the fracture), which might largely explain the association with DVT identified herein.

The potential pathophysiological mechanisms underlying the association between NLR/PLR are not fully elucidated. In an in vivo, a cross talk was identified between neutrophils, platelets and monocytes, and neutrophil provided the initiating stimuli for formation of thrombus and platelets contributed to the propagation and progression of DVT [29]. In addition, the neutrophils get entrapped in the growing thrombus, enabling recruitment of other cells active in the coagulation cascade via the release of neutrophil extracellular traps (NETs), especially when blood flow is minimal in venous valves [30]. In other animal studies, NK cell-dependent IFN- γ production demonstrated to play a crucial role in formation of NETs by neutrophils for thrombus development [31].

The identified association of PLR/NLR with DVT and the established combination diagnostic model can be used as auxiliary screening tools in management of ankle fractures. For example, they can be used to identify those who carry higher risk of preoperative DVT, and thus prompt and targeted preventive measures can be administered before DUS is arranged, resembling the “empirical prevention.” Because, in most large hospitals, DUS examination is not readily accessible. On the other hand, for patients at low-risk of DVT, e.g., with NLR, NLR and D-dimer level less than the cut-off value, routine chemoprophylaxis or DUS screening is not necessarily prescribed.

This was the first study to specifically investigate the association of NLR/PLR with the preoperative DVT in ankle fracture, and the strengths included strict screening criteria, multiple variables for adjustment and

establishment of a combination diagnostic model. Several limitations should also be noted. First, the retrospective design had the inherent limitation in data collection, especially in terms of self-reported comorbidities, body mass and height, lifestyles. However, the primary variables (neutrophil, lymphocyte, platelet count) were hardly affected. Second, although we adjusted for the time from injury to DUS examination, the dynamic change over time for NLR/PLR was not investigated, and should be a future research direction. Third, fracture severity, surrounding soft-tissue damage, degree of vascular injury and immobility of affected limb almost certainly impact the risk of DVT, but relevant data were unavailable or could not be measured. Fourth, the single-center study in a tertiary university-affiliated hospital might have affected the results, because patients transferred were more likely medically unstable or had a complex fracture type. Thus, the generalizability may be less to other settings.

In conclusion, preoperative DVT incidence was 8.3% after ankle fracture. We identified both NLR and PLR as independent risk factors associated with preoperative DVT, with OR of 2.16 and 2.84, respectively. The combination diagnostic model, including PLR, NLR with D-dimer, demonstrated better diagnostic performance than use of D-dimer alone, and could be considered as an auxiliary tool for identifying high-risk patients for subsequent DUS examination. Future studies are warranted for elucidating the dynamic change of PLR/NLR over time after injury and the possible underlying mechanism.

Abbreviations

NLR	Neutrophil to lymphocyte ratio
PLR	Platelet to lymphocyte ratio
DVT	Deep venous thrombosis
PE	Pulmonary embolism
VTE	Venous thrombus embolism
DUS	Duplex ultrasound
ASA	American Society of Anesthesiologists
BMI	Body mass index
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval
ROC	Receiver operator characteristic

AUC Area under the curve
OR Odd ratio
H–L Hosmer–Lemeshow

Acknowledgments

We are grateful to Y.Y. of the Department of Orthopedics, and to X.Z. of the Department of statistics and applications for their kind assistance.

Author contributions

HZ conceived the idea for the study. GZ, ZK, and JL collected the relevant data. ZZ prepared the figures and tables. ML performed the statistical analyses. All the authors interpreted the data and contributed to preparation of the manuscript. GZ, ZK, and JL contributed equally to this manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 82202683).

Availability of data and materials

All the data will be available upon motivated request to the corresponding author of the present paper.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committees of the Third Hospital of Hebei Medical University.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Orthopaedic Surgery, Third Hospital of Hebei Medical University, Shijiazhuang 050051, Hebei, People's Republic of China. ²Department of Orthopaedic Surgery, Shijiazhuang People's Hospital, Shijiazhuang 050051, Hebei, People's Republic of China. ³Key Laboratory of Biomechanics of Hebei Province, Shijiazhuang 050051, Hebei, People's Republic of China. ⁴Orthopaedic Research Institution of Hebei Province, Shijiazhuang 050051, Hebei, People's Republic of China. ⁵NHC Key Laboratory of Intelligent Orthopaedic Equipment, The Third Hospital of Hebei Medical University, Shijiazhuang, People's Republic of China. ⁶Department of Orthopaedic Trauma Center, The 3rd Hospital of Hebei Medical University, No 139 Ziqiang Road, Shijiazhuang 050051, Hebei, People's Republic of China.

Received: 10 February 2023 Accepted: 8 May 2023

Published online: 16 May 2023

References

- Jupiter DC, Saenz F, Mileski W, Shibuya N. Acute deep venous thrombosis and pulmonary embolism in foot and ankle trauma in the National Trauma Data Bank: an update and reanalysis. *J Foot Ankle Surg.* 2019;58(6):1152–62.
- Luo Z, Chen W, Li Y, et al. Preoperative incidence and locations of deep venous thrombosis (DVT) of lower extremity following ankle fractures. *Sci Rep.* 2020;10(1):10266.
- Yi X, Zhu J, Wei M, et al. Risk factors of venous thrombosis in patients with ankle fractures. *Int Angiol J Int Union Angiol.* 2014;33(4):324–8.
- Duan Lianjie PH, Shilei W, Chen C, Xiantie Z, Jiaguo Z. Analysis of the incidence and related factors of preoperative thrombosis in patients with ankle fractures. *Electr J Foot Ankle Surg.* 2018;5(2):18–22.
- Lapidus LJ, Ponzer S, Elvin A, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. *Acta Orthop.* 2007;78(4):528–35.
- Kremers BMM, Birocchi S, van Oerle R, et al. Searching for a common thrombo-inflammatory basis in patients with deep vein thrombosis or peripheral artery disease. *Front Cardiovas Med.* 2019;6:33.
- Gómez-Jabalera E, Bellmunt Montoya S, Fuentes-Camps E, Escudero Rodríguez JR. Age-adjusted D-dimer for the diagnosis of deep vein thrombosis. *Phlebology.* 2018;33(7):458–63.
- Ba B, Cp M, Ns G, Dd B, Jn G. Risk factors for thromboembolic events after surgery for ankle fractures. *Am J Orthop.* 2015;44(7):E220–224.
- Zixuan L, Chen W, Li Y, et al. Incidence of deep venous thrombosis (DVT) of the lower extremity in patients undergoing surgeries for ankle fractures. *J Orthop Surg Res.* 2020;15(1):294.
- Shibuya N, Frost CH, Campbell JD, Davis ML, Jupiter DC. Incidence of acute deep vein thrombosis and pulmonary embolism in foot and ankle trauma: analysis of the National Trauma Data Bank. *J Foot Ankle Surg.* 2012;51(1):63–8.
- Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. *Nat Rev Cardiol.* 2021;18(9):666–82.
- Xue J, Ma D, Jiang J, Liu Y. Diagnostic and prognostic value of immune/inflammation biomarkers for venous thromboembolism: is it reliable for clinical practice? *J Inflamm Res.* 2021;14:5059–77.
- Farah R, Nseir W, Kagansky D, Khamisy-Farah R. The role of neutrophil-lymphocyte ratio, and mean platelet volume in detecting patients with acute venous thromboembolism. *J Clin Lab Anal.* 2020;34(1):e23010.
- Buxhofer-Ausch V, Steurer M, Sormann S, et al. Influence of platelet and white blood cell counts on major thrombosis: analysis from a patient registry in essential thrombocythemia. *Eur J Haematol.* 2016;97(6):511–6.
- Wang KL, Chu PH, Lee CH, et al. Management of venous thromboembolisms: part I: the consensus for deep vein thrombosis. *Acta Cardiol Sin.* 2016;32(1):1–22.
- Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg.* 1972;104(2):134–44.
- Riva N, Donadini MP, Ageno W. Epidemiology and pathophysiology of venous thromboembolism: similarities with atherothrombosis and the role of inflammation. *Thromb Haemost.* 2015;113(6):1176–83.
- Heestermans M, Salloum-Asfar S, Salvatori D, Laghmani EH, Luken BM, Zeerleder SS, Spronk HMM, Korporaal SJ, Wagenaar GTM, Reitsma PH, van Vlijmen BJM. Role of platelets, neutrophils, and factor XII in spontaneous venous thrombosis in mice. *Blood.* 2016; 127(21):2630–2637. *Blood.* 2018;131(26):2996.
- Pfeiler S, Stark K, Massberg S, Engelmann B. Propagation of thrombosis by neutrophils and extracellular nucleosome networks. *Haematologica.* 2017;102(2):206–13.
- Wang Z, Wang H, Yang L, Jiang W, Chen X, Liu Y. High platelet-to-lymphocyte ratio predicts poor survival of elderly patients with hip fracture. *Int Orthop.* 2021;45(1):13–21.
- Zhou J, Fu J, Zhao Q, Lin S, Zhu H. Effect of neutrophil-to-lymphocyte ratio on short-term prognosis of elderly patients with hip fracture. *Am J Transl Res.* 2021;13(8):9122–8.
- Chen YH, Chou CH, Su HH, et al. Correlation between neutrophil-to-lymphocyte ratio and postoperative mortality in elderly patients with hip fracture: a meta-analysis. *J Orthop Surg Res.* 2021;16(1):681.
- Liu D, Zhu Y, Chen W, et al. Relationship between the inflammation/immune indexes and deep venous thrombosis (DVT) incidence rate following tibial plateau fractures. *J Orthop Surg Res.* 2020;15(1):241.
- Meng X, Chang Q, Liu Y, et al. Determinant roles of gender and age on SII, PLR, NLR, LMR and MLR and their reference intervals defining in Henan, China: a posteriori and big-data-based. *J Clin Lab Anal.* 2018;32(2):e22228.
- Fei Y, Wang X, Zhang H, Huang M, Chen X, Zhang C. Reference intervals of systemic immune-inflammation index, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume to platelet ratio, mean platelet volume and red blood cell distribution width-standard deviation in healthy Han adults in Wuhan region in central China. *Scand J Clin Lab Invest.* 2020;80(6):500–7.
- Luo H, He L, Zhang G, et al. Normal reference intervals of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and systemic immune inflammation index in healthy adults: a large multi-center study from Western China. *Clin Lab.* 2019. <https://doi.org/10.7754/Clin.Lab.2018.180715>.
- Wang J, Zhang F, Jiang F, Hu L, Chen J, Wang Y. Distribution and reference interval establishment of neutral-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) in Chinese healthy adults. *J Clin Lab Anal.* 2021;35(9):e23935.

28. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes*. 2017;10(1):12.
29. von Brühl ML, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med*. 2012;209(4):819–35.
30. Kimball AS, Obi AT, Diaz JA, Henke PK. The emerging role of NETs in venous thrombosis and immunothrombosis. *Front Immunol*. 2016;7:236.
31. Bertin FR, Rys RN, Mathieu C, Laurance S, Lemarié CA, Blostein MD. Natural killer cells induce neutrophil extracellular trap formation in venous thrombosis. *J Thromb Haemost*. 2019;17(2):403–14.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

