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Effect of mild-to-moderate COVID-19 on the incidence and risk factors for deep vein thrombosis in patients with hip fracture: a retrospective study

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Abstract

Purpose This retrospective study aimed to investigate the effect of mild-to-moderate COVID-19 on the risk of deep vein thrombosis (DVT) in patients with hip fractures. Hip fractures are common in the elderly, and previous research has shown that they accounted for 58.3% of traumatic fractures in older inpatients during the COVID-19 pandemic in China. Meanwhile, the relationship between COVID-19 and DVT is complex. Some studies have reported that the incidence of DVT in critically ill COVID-19 patients can be as high as 46%, and 20% in those with moderate-to-severe cases. However, the impact of mild-to-moderate COVID-19 on DVT risk in hip fracture patients remains unclear.

Methods Adult patients who underwent surgery for hip fractures between December 8, 2022, and January 9, 2023, were included in the study. All patients were tested for SARS-CoV-2 nucleic acid and were assessed for DVT preoperatively using doppler ultrasonography (DUS). Logistic regression was used to identify risk factors for DVT.

Results The records of 98 patients with hip fractures, were included in the analysis, of whom 63 were SARS-CoV-2 positive and 35 were SARS-CoV-2 negative. Pre-operative DUS showed that 36/98 patients (37%) had DVT, including 25/63 (40%) patients with COVID-19, and 11/35 (31%) patients without COVID-19. Multivariable logistic regression analysis showed that pre-operative leukocyte count and platelet-to-lymphocyte ratio (PLR) were independent risk factors for DVT, whereas mild-to-moderate COVID-19 was not an independent risk factor for DVT. In patients with hip fractures, COVID-19 did not significantly increase the risk of DVT.

Conclusions Therefore, in patients with hip fractures, DVT prevention measures should be implemented routinely, regardless of COVID-19 status.

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Keywords COVID-19, Deep vein thrombosis, Hip fracture, Risk factors, SARS-CoV-2

Introduction

An outbreak of cases of "pneumonia of unknown origin" in Wuhan, China in December 2019 [1] was subsequently identified as being caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was named coronavirus disease (COVID-19) by the World Health Organization (WHO) [2]. In China, according to the Diagnosis and Treatment Plan for Novel Coronavirus Pneumonia (10th edition) issued by the National Health Commission [3], COVID-19 is clinically classified according to the following criteria: (1) Mild: upper respiratory tract infection manifesting as dry throat, sore throat, cough, and fever; (2) Moderate: continued fever for > 3 days or cough, and shortness of breath, but respiratory rate < 30 breaths/min, SPO_2 > 93% at rest, and imaging showed characteristic pneumonia manifestations of COVID-19; (3) Severe: adults with any of the following that cannot be explained by anything other than COVID-19: respiratory distress with respiratory rate ≥ 30 breaths/min, SPO_2 ≤ 93% at rest, PaO_2/FiO_2 ≤ 300 mmHg, progressive exacerbation of clinical symptoms with marked progression of > 50% of the lesion within 24–48 h on lung imaging; (4) Critical: patients with any of the following conditions: respiratory failure requiring mechanical ventilation, shock, or other organ failure requiring admission to an intensive care unit (ICU). The precise mechanism underlying the development of deep vein thrombosis (DVT) in patients with COVID-19 remains unclear; however, it is thought to be influenced by Virchow's triad, which includes hypercoagulability, blood stasis, and endothelial injury.

Patients with critical COVID-19, especially those who are bedridden, obese, or have concurrent infections, are at high risk of developing venous thromboembolism (VTE) [4–6]. VTE, comprising DVT and pulmonary embolism (PE), is a severe problem in patients surgically treated for trauma and orthopedic conditions [7, 8]. Most studies of VTE have focused on patients undergoing hip and knee arthroplasty. The incidence of hip fractures, which include femoral neck, intertrochanteric, and subtrochanteric fractures, is high among older adults, and is associated with significant morbidity and mortality. According to Zhu et al. [9], hip fractures accounted for the largest proportion (58.3%) of traumatic fractures in older patients admitted to hospitals in China during the COVID-19 pandemic. However, the authors did not report the outcomes associated with hip fractures. Although several studies have addressed the association between COVID-19 and hip fractures, most previous studies have focused on cases of severe COVID-19. However, there is a lack of studies of hip fractures in patients with mild-to-moderate COVID-19. This study aimed to investigate the incidence and risk factors for DVT in patients with hip fractures and mild-to-moderate COVID-19 and to compare them with patients with hip fractures without COVID-19.

Methods

Study design and participants

After ethics committee approval, a retrospective review of institutional databases was performed in Xi'an Honghui Hospital. We conducted a study on the data in the database using a retrospective cohort study. This single-center, retrospective, observational study analyzed data on 98 patients admitted to Honghui Hospital in Xian, China, with hip fractures from December 8, 2022, to January 9, 2023. We were able to obtain information which was capable of identifying individual participants either during the data collection process or after its completion. COVID-19 diagnosis was based on the WHO and Chinese national diagnostic criteria [3, 10]. The inclusion criteria were (1) age ≥ 18 years, and (2) a hip fracture. The exclusion criteria were (1) missing information on body mass index (BMI), (2) no prophylactic anticoagulation, (3) no pre-operative doppler ultrasonography (DUS), (4) old injury, (5) polytrauma, and (6) high-energy fractures. The diagnosis of hip fracture was identified based on the diagnosis codes in the hospital discharge registry. COVID-19 was diagnosed based on a positive SARS-CoV-2 nucleic acid test result. The calculation of the sample size was carried out according to the sample size formula,

$$n = \frac{\left(z_{\alpha/2} + Z_{\beta}\right)^2 \times \left(P_1 \times \left(1 - P_1\right) + P_2 \times \left(1 - P_2\right)\right)}{\left(P_1 - P_2\right)^2}$$

Chemical thromboprophylaxis using subcutaneous low-molecular-weight heparin (LMWH) (enoxaparin at a prophylactic dose) was routinely administered during hospitalization. LMWH was stopped 12 h before surgery and restarted 12 h after surgery. After discharge, oral rivaroxaban was administered for 35 days as thromboprophylaxis. An inferior vena cava filter was placed in patients with contraindications to chemical anticoagulation therapy. During hospitalization, patients underwent routine VTE screening using DUS. If there was clinical suspicion of PE, they underwent spiral computed tomography to confirm the diagnosis. Proximal DVT or PE can be confirmed at any time from injury to hospital discharge via radiographic methods and was defined as clinically important venous thromboembolism. The deep veins below the knee, including peroneal veins,

posterior tibial veins, anterior tibial veins, and gastrocnemius muscle veins were defined as distal deep veins [11]. The greater saphenous, popliteal, and femoral veins were defined as proximal deep veins. All DUS procedures were performed by a certified ultrasonographer and interpreted by an experienced attending radiologist.

We confirm that all study protocols were approved by the Xi'an Honghui Hospital Research Ethics Committee on May 6, 2024 (No.202405005). We confirmed that all methods were carried out in accordance with relevant guidelines and regulations. Upon receiving approval from the Xi'an Honghui Hospital Research Ethics Committee, the requirement for informed consent was waived due to the retrospective nature of the study.

Data collection

Data were collected on age; sex; comorbidities; BMI; smoking and drinking habits; time of injury; time of admission; time of surgery; time from injury to admission; time from injury to surgery; mechanism of injury (low-energy injury, high-energy injury); associated injuries (head, chest, abdomen, other orthopedic injuries); site of fracture (neck of femur, trochanter); VTE prophylaxis; duplex ultrasound for assessment of DVT (if performed); location of DVT; chronic disease history (hypertension, diabetes, stroke, coronary artery disease); D-dimer, fibrinogen, hemoglobin, glutamic-pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), and uric acid (UA) levels; leucocyte count; hematocrit; neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV).

Outcomes and exposures

The main outcome was the incidence of pre-operative DVT (distal and proximal) and the main exposures of interest were pre-operative risk factors for DVT in patients with hip fractures and mild-to-moderate COVID-19 with pharmacological prevention.

Statistical analysis

Continuous variables were reported as means and standard deviations. We divided the patients into the DVT group and the non-DVT group for comparison, evaluate the distribution differences of each variable between the two groups and calculate the standardized mean difference. $p < 0.01$ was considered statistically significant. After performing univariate logistic regression analysis, the included variables were selected as predictors using stepwise binary logistic regression analysis with forward selection (likelihood ratio - LR). Then, multivariable logistic regression analysis was performed to identify independent risk factors for DVT in patients with hip fractures. Two-tailed P values < 0.05 were defined as statistically significant. The data were analyzed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The multivariable logistic regression equation is:

$$logit[\pi(X)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_P X_P.$$

Results

Patient characteristics

Over the study period, 179 patients met the inclusion criteria, of whom 81 were excluded according to the exclusion criteria (29 without BMI data, 7 without chemical thromboprophylaxis, 13 without pre-operative DUS, 2 with old injury, 26 with polytrauma, and 4 with high-energy fractures) (Fig. 1). The sample size calculated according to the sample size formula is 439. Finally, we analyzed the data of 98 patients with hip fracture, 36 with DVT and 62 without DVT. All patients received VTE pharmacologic thromboprophylaxis prescribed with LMWH during hospitalization, which was appropriate and consistent with the current institutional and national guidelines [12]. The mean age was 78.7 ± 8.9 years (range: 53–95 years), 34 patients were male, and 64 were female. Patient characteristics are shown in Table 1. Of the 98 patients, 63 had mild-to-moderate COVID-19 according to the tenth edition of the diagnosis and treatment plan criteria issued by the National Health Commission [3], and 35 patients did not have COVID-19. The mean time from injury to admission was 4.5 ± 6.3 days, and the mean length of hospital stay was 10.0 ± 6.9 days (Table 1).

Incidence of DVT

Pre-operative bilateral lower extremity deep vein ultrasound results showed that 36 patients (37%) had DVT. Of the 36 patients, 17 had bilateral thrombosis and 19 had unilateral thrombosis; 7 had combined distal and proximal thrombosis 28 had distal thrombosis alone, and 1 had proximal thrombosis alone. The incidence of DVT was 25/63 (40%) in patients with COVID-19, and 11/35 (31%) in patients without COVID-19.

Risk factors for DVT

Using univariate logistic regression analysis, we identified four potential preoperative venous thrombosis factors in patients with hip fractures: the pre-operative fibrinogen level, pre-operative leukocyte count, pre-operative NLR, and pre-operative PLR.

Multivariable logistic regression analysis ($logit[\pi(X)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_P X_P$) showed that pre-operative leukocyte count (odds ratio [OR]: 1.294, 95% confidence interval [CI]: 1.017–1.645, $P = 0.036$) and pre-operative PLR (OR: 1.006, 95% CI: 1.001–1.011, $P = 0.024$) were significantly associated with pre-operative DVT (Table 2).

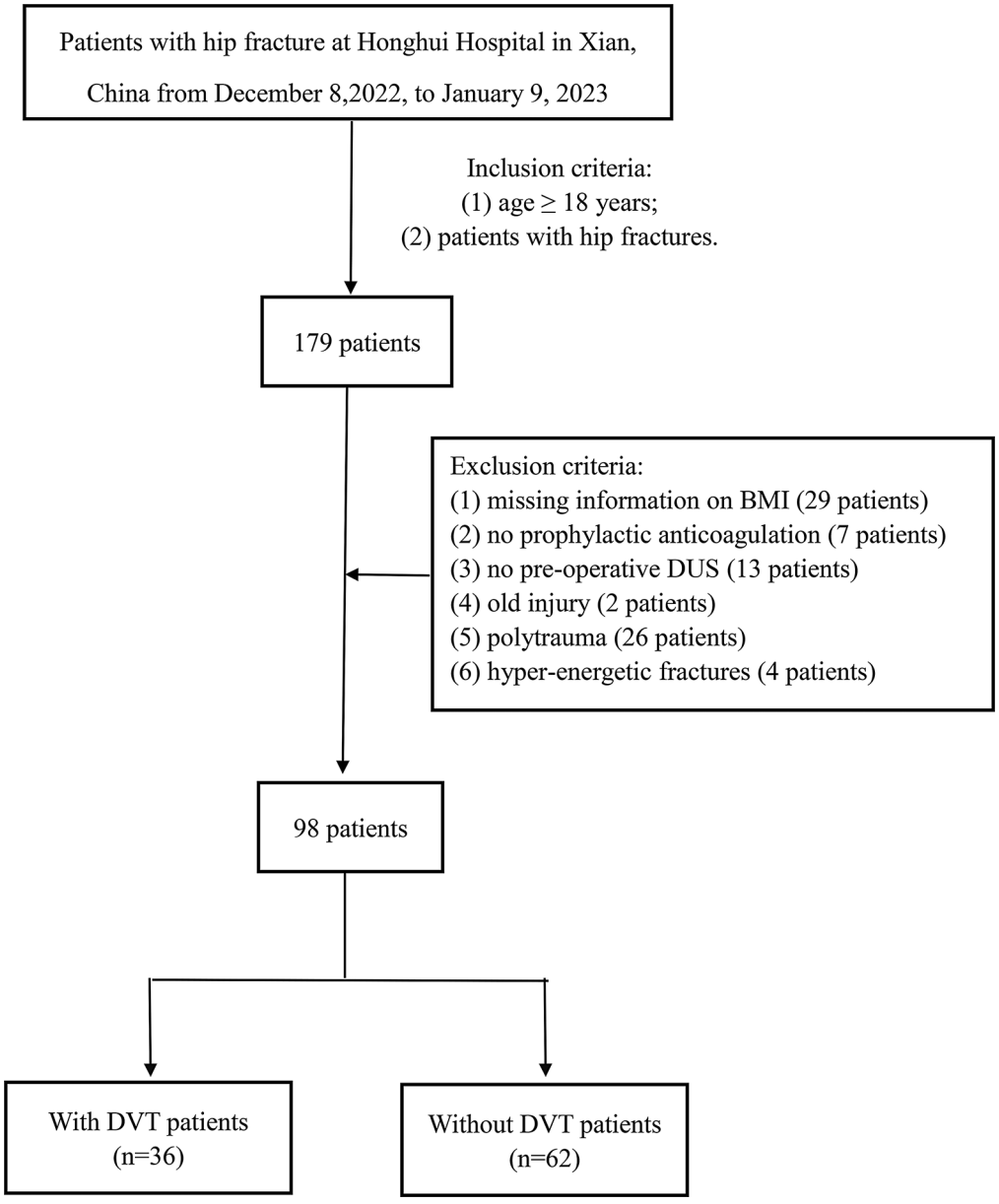

Fig. 1 Flowchart of the study population

Mild-to-moderate COVID-19 was not an independent risk factor for pre-operative DVT (unadjusted OR: 1.435, 95% CI: 0.599–3.440, $P = 0.418$; and adjusted OR: 1.058, 95% CI: 0.384–2.917, $P = 0.913$) (Table 2).

Discussion

This study aimed to assess the pre-operative incidence of DVT and identify pre-operative risk factors among patients with hip fractures and mild-to-moderate COVID-19, particularly when pharmacological prevention is used. VTE is the third most common complication after hip fracture [13]. The incidence of DVT ranges from 40 to 80% in patients undergoing major orthopedic procedures, and the incidence of clinical PE ranges from 4 to 10% [14]. Surgery-related factors affect the incidence of DVT after hip fracture surgery [15]. Because surgery is an important risk factor for DVT, this study focused on pre-operative indicators in patients with hip fracture.

Since early in the COVID-19 pandemic, studies have indicated an increased risk of VTE and arterial thromboembolism in patients with COVID-19, including an increased risk of DVT, PE, ischemic stroke, myocardial infarction, and peripheral arterial thromboembolism [16]. Liao et al. [17] reported a significant increase in the risk of VTE among patients with COVID-19. Furthermore, the estimated mortality rate among patients with COVID-19 and PE is approximately 45%, indicating a poor prognosis [17]. In a small study of 25 patients with

Table 1 Demographic and clinical characteristics of patients with hip fracture (preoperative) ($\bar{x} \pm s, n$)

	All patients (*N* = 98)	Patients with DVT (*N* = 36)	Patients without DVT (*N* = 62)	*P* value
Age (years)	—	79.2 ± 7.8	78.4 ± 9.4	0.674
Sex				0.829
Male	34(35%)	12(33%)	22(35%)	
Female	64(65%)	24(67%)	40(65%)	
BMI	—	20.2 ± 4.0	21.2 ± 3.4	0.125
COVID-19				0.417
Yes	63(64%)	25(69%)	38(61%)	
No	35(36%)	11(31%)	24(39%)	
Smoking				0.978
Yes	11(11%)	4(11%)	7(11%)	
No	87(89%)	32(89%)	55(89%)	
ETOH				0.187
Yes	1(1%)	1(3%)	0(0%)	
No	97(99%)	35(97%)	62(100%)	
Time from injury to the admission	—	6.0 ± 7.1	3.7 ± 5.6	0.074
Laboratory parameters				
D-Dimer	—	5.2 ± 6.4	3.4 ± 3.2	0.083
Fibrinogen	—	4.4 ± 1.3	3.9 ± 1.2	0.040*
Leucocyte count	—	8.1 ± 3.4	6.7 ± 2.2	0.029*
Hematocrit	—	32.9 ± 4.1	31.8 ± 5.2	0.273
Hemoglobin	—	110.2 ± 13.6	107.8 ± 16.9	0.460
Neutrophil to lymphocyte ratio (NLR)	—	11.1 ± 11.7	5.5 ± 3.3	0.003*
Platelet to lymphocyte ratio (PLR)	—	327.5 ± 182.4	213.1 ± 103.7	< 0.001*
Mean platelet volume (MPV)	—	10.1 ± 1.4	10.4 ± 1.2	0.305
Glutamic-pyruvic transaminase	—	20.9 ± 13.9	24.6 ± 18.0	0.246
Glutamic oxaloacetic transaminase	—	27.6 ± 12.5	31.2 ± 18.9	0.266
Uric acid	—	241.4 ± 94.6	263.5 ± 116.0	0.310
Medical history				
Hypertension	55(56%)	23(64%)	32(52%)	0.238
Diabetes	22(22%)	10(28%)	12(19%)	0.335
Obsolete cerebral infarction	43(44%)	19(53%)	24(39%)	0.176
Coronary artery disease	30(31%)	12(33%)	18(29%)	0.656
Site of fracture				0.680
Neck of femur	38(39%)	13(36%)	25(40%)	
Trochanter	60(61%)	23(64%)	37(60%)	

* A p value < 0.05 was considered statistically significant

COVID-19, Longchamp et al. [18] highlighted the importance of lower extremity thrombosis as a primary factor contributing to the risk of PE in this patient population, and the authors found an overall prevalence of proximal DVT of 24% in patients with PE. Another study found that the incidence of DVT was high (46%) in patients with critical COVID-19 [19], and 20% in patients with moderate-to-severe COVID-19 [20]. One study found a low prevalence (4%) of newly detected asymptomatic DVT in patients with COVID-19 who did not require ICU admission [21]. Zhu et al. [9] reported that hip fracture accounted for the majority (58.3%) of traumatic fractures in older adults presenting to a hospital in China during the COVID-19 pandemic; however, the study did not report the outcomes associated with hip fractures.

Few studies have explored the association between mild-to-moderate COVID-19 and the occurrence of DVT among patients with hip fractures. Zhang et al. [22] studied 143 patients with COVID-19 from January 29, 2020, to February 29, 2020, and found that COVID-19 is an additional risk factor for DVT in hospitalized patients. The severity of the COVID-19 (moderate versus mild) was independently associated with the incidence of VTE [23]. Clavijo et al. [24] reported that mild COVID-19 might be an independent risk factor for VTE. In contrast to other reports, a study of the results from patients tested for SARS-CoV-2 in the emergency department showed no association between vascular thrombosis and COVID-19 test positivity [25], consistent with the findings of our study.

Data for this study were collected from December 8, 2022, to January 9, 2023, during a period in which the SARS-CoV-2 Omicron variant was the predominant variant worldwide. The infectivity of the Omicron variant is estimated to be more than 10-fold higher than that of the original virus and approximately twice as high as that of the Delta variant [26, 27]. The Omicron variant is more highly transmissible than other variants [27–29]. Patients with previous COVID-19 are at a significant risk of reinfection with the Omicron variant, indicating higher transmissibility [30]. However, the Omicron variant appears to cause less severe disease, and Omicron variant infections are associated with a lower risk of hospitalization and mortality [31]. A study conducted in South Africa [32] found that the most confirmed cases of Omicron variant infection were asymptomatic or mild, and no deaths were reported. Vaccination is the best way to prevent COVID-19, especially serious disease, although the neutralizing activity against Omicron variants triggered by vaccines is substantially reduced [31]. All patients in our study received at least one dose of COVID-19 vaccine, and most had received two doses. In a study of patients hospitalized with COVID-19, 75% of the patients with Omicron variant infections were unvaccinated, suggesting that existing vaccines may be protective against the Omicron variant [29]. Chenchula et al. [33] reviewed the results of 27 studies and found that booster doses of

Table 2 Risk factors of DVT

Risk factors	Univariate OR	*P* value	Multivariate OR	*P* value
Age (years)	1.010(0.964,1.059)	0.670	—	—
Sex	1.100(0.462,2.66)	0.829	—	—
COVID-19	1.435(0.599,3.440)	0.418	1.058(0.384,2.917)	0.913
Smoking	1.018(0.277,3.749)	0.978	—	—
Drinking	0(0,0)	1	—	—
Site of fracture	0.837(0.358,1.954)	0.680	—	—
Hypertension	0.603(0.260,1.401)	0.239	—	—
Diabetes	0.624(0.238,1.636)	0.338	—	—
Coronary artery disease	0.818(0.338,1.980)	0.656	—	—
Obsolete cerebral infarction	0.565(0.246,1.296)	0.178	—	—
BMI	0.924(0.822,1.040)	0.190	—	—
Time from injury to the surgery	1.062(0.992,1.136)	0.083	—	—
D-Dimer	1.092(0.987,1.208)	0.087	—	—
Mean platelet volume (MPV)	0.838(0.598,1.174)	0.303	—	—
Hemoglobin	1.010(0.984,1.037)	0.456	—	—
Hematocrit	1.050(0.963,1.146)	0.271	—	—
Glutamic-pyruvic transaminase	1.015(0.989,1.043)	0.252	—	—
Glutamic oxaloacetic transaminase	1.015(0.988,1.043)	0.270	—	—
Uric acid	1.002(0.998,1.006)	0.308	—	—
Fibrinogen	1.427(1.006,2.022)	0.046*	1.321(0.884,1.973)	0.175
Leucocyte count	1.220(1.039,1.432)	0.015*	1.294(1.017,1.645)	0.036*
Neutrophil to lymphocyte ratio (NLR)	1.183(1.071,1.307)	0.001*	1.027(0.907,1.163)	0.679
Platelet to lymphocyte ratio (PLR)	1.007(1.003,1.010)	0.001*	1.006(1.001,1.011)	0.024*

*A p value < 0.05: Risk factors with statistical significance are shown

COVID-19 vaccine were effective against the Omicron variant, reduced mortality and hospitalization rates, and the incidence of serious complications. These findings support our conclusion that mild-to-moderate COVID-19 is not an independent risk factor for DVT in patients with hip fractures.

Leukocytes participate in the pathophysiology of thrombosis. Studies of the study of the composition of thrombus, have shown that approximately 30% of the lymphocytes are monocytes and 70% are neutrophils [34, 35]. When monocytes are activated, they expose transcription factors that activate the exogenous coagulation pathway, release cytokines that activate endothelial cells, and promote the expression of adhesion molecules [36, 37]. In patients with hip fractures, a high monocyte count is an independent risk factor for DVT [38]. Neutrophils contribute to DVT propagation by binding directly to factor XII (FXII) and releasing neutrophil extracellular traps that support the activation of FXII [34, 39]. The leukocyte count has been reported to be an independent risk factor for VTE [40], which is consistent with our findings.

PLR initially served as a systemic inflammatory biomarker for predicting cancer [41, 42]. PLR has recently been used as a predictor of several diseases [42, 43]. PLR is an inexpensive, simple, and practical index, and findings show that it exhibits moderate diagnostic accuracy and may be a helpful biomarker for the diagnosis of DVT [44]. Gao et al. [45] identified PLR as an independent risk factor associated with DVT following ankle fracture. In addition, PLR has potential diagnostic value in patients with spontaneous DVT [46]. One study found that the perioperative PLR was an independent risk factor for DVT after total joint arthroplasty (TJA) [47]. However, a study by Farah et al. [40] found that the PLR was not an independent risk factor for VTE.

This study has some limitations. First, it is based on a retrospective analysis of medical records, which may have introduced bias. The period of data collection is the outbreak period of covid-19, so more patients with hip fractures are infected with SARS-CoV-2. Second, the study was conducted at a single center, potentially reducing the diversity of the patient population and limiting the generalizability of the findings. Third, the SARS-CoV-2 variant was not determined, so it is unclear whether the patients were infected with the Omicron or Delta variant, or mixed variants. This may affect the generalizability of our findings, as different variants exhibit distinct characteristics and transmission patterns. Fourth, the sample size calculated according to the sample size formula is 439, but our actual sample size is only 98, which may have an impact on our research. Although the sample size is small, due to the fact that the p - value of COVID – 19 in the multivariate logistic regression analysis is greater than 0.05 and relatively high, the reliability of the final result remains relatively high.

Conclusion

Patients with hip fractures and mild-to-moderate COVID-19 had a high incidence of DVT despite the use of universal guideline-recommended pharmacologic thromboprophylaxis. In patients with hip fractures, the pre-operative leukocyte count and an elevated pre-operative PLR were independent risk factors for DVT; however, mild-to-moderate COVID-19 was not an independent risk factor for DVT. In patients with mild-to-moderate COVID-19 complicated by hip fracture, the impact of COVID-19 on the development of DVT is minimal. This assessment aligns with the current WHO COVID-19 guidelines, which recommend using a focused approach to managing the risk of thrombosis and the importance of paying attention to other potential contributory factors.

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Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by H.L., J.X., Z.S., Z.F., H.W, S.L., Q.Y., H.F., S.H. and N.Y. Study design were performed P.W. by and K.Z. The first draft of the manuscript was written by H.L. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
We confirm that all study protocols were approved by the Xi'an Honghui Hospital Research Ethics Committee on May 6, 2024 (No.202405005). We confirmed that all methods were carried out in accordance with relevant guidelines and regulations. Upon receiving approval from the Xi'an Honghui Hospital Research Ethics Committee, the requirement for informed consent was waived due to the retrospective nature of the study, and our research adhered to the Declaration of Helsinki.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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