

Incidence of deep venous thrombosis (DVT) of lower extremity in patients undergoing surgeries for ankle fractures

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Abstract

Objective To investigate the incidence of postoperative deep venous thrombosis (DVP) in patients undergoing surgeries for ankle fractures and identify the associated risk factors.

Methods This was a retrospective study. A total of 1451 patients undergoing surgery of ankle fractures from January 2016 to June 2019 were included. Their inpatient medical records were inquired for data collection, including demographics, comorbidities, injury and surgery-related data and laboratory biomarkers. DVT of lower extremity was diagnosed by routine doppler examination. Univariate analyses and multivariate logistic regression analyses were used to identify the independent risk factors.

Results Among the 1451 patients, DVT was confirmed in 38 cases, indicating an incidence of 2.6%. DVT involved both the operated and non-operated limbs in 8 patients (21.1%). DVT involved superficial femoral vein in 4 cases (6.6%), deep femoral vein in 2 (3.3%), popliteal vein in 5 (8.2%), posterior tibial vein in 11 (18.0%) and peroneal vein in 39 (63.9%). The median interval between operation and diagnosis of DVT was 7 days. Six risk factors were identified to be independently associated with DVT, including age (10-year increase) (OR, 1.44), preoperative stay (delay of each day) (OR, 1.11), anesthesia (general vs regional) (OR, 3.51), lower hemoglobin level (OR, 2.02), total cholesterol >5.2mmol/L (OR, 3.20) and reduced lymphocyte count (OR, 3.16).

Conclusion These identified factors, although not easily modifiable, do help counsel patients about the risk of DVT and help individualized assessment of the risk factors and accordingly the risk stratification.

Introduction

Ankle fracture is a common fracture type, with an population-based incidence of 37.1/100000 person-years [1], representing 7.6% of all adult fractures [2]. Because of its special anatomical features, most of the ankle fractures involve the articular surface to varying degrees. The relatively thin skin and less soft tissue coverage more likely result in the swelling after fracture, and the post-trauma blood is often at high coagulation state. Moreover, surgical interventions (tissue dissection and stripping) and postoperative long-term immobilization of ankle joint also places regional blood at higher risk of formation of thrombosis. These constitute the theoretical pathological basis for thrombosis formation.

It is well established that deep venous thrombosis (DVT) of lower extremity following major orthopaedic surgeries increased the risk of pulmonary emboli and mortality [3, 4]. By far, studies on DVT mainly focus on hip and knee joint arthroplasties [5, 6], the major orthopedics trauma (hip fracture, spinal injury and others) [7–9], a specific population (elderly, patients with immobilization) [8] or prophylactic drug use (low molecular weight heparin, aspirin) [5, 6, 10, 11]. Specified at ankle fracture, however, there is still scarcity of epidemiologic data. SooHoo et al [12] attempted to evaluate the risk factors associated with DVT following surgical treatment of ankle fractures, but the fewer potential factors included in the multivariate model might compromise the results. Shibuya et al [13] evaluated the incidence of DVT and pulmonary embolism in foot and ankle trauma using the US national trauma data bank, but they did not separate the

ankle fractures out for analysis. Basques et al [14] used ACS-NSQIP database and identified obesity, heart disease, and dependent functional status as independent factors associated with thromboembolic events after ankle fracture surgeries. Despite a national database used in these studies, the variability in data collection among the hospitals would be an issue.

Applicability of these results on DVT in other orthopaedic surgeries or studies with small sample size might be poor, and use of these results might result in a misdirected guidance in constructing a risk prediction model for DVT. Given these, we conducted this retrospective study, using data from inpatient records and laboratory tests, to evaluate the incidence rate of postoperative DVT and identify some risk factors associated with DVT.

Methods

The study was reported in accordance with the STROCSS (Strengthening the Reporting of Cohort Studies in Surgery) guidelines. It was designed as a retrospective study and approved by the ethics committee of the 3rd Hospital of Hebei Medical University.

Inclusion and exclusion criteria

Between January 2016 to June 2019, patients who underwent surgical treatment for acute ankle fractures in our hospital were included. The baseline characteristics and complications during hospitalization were obtained from the patient's medical records. Inclusion criteria were: patients aged 18 years or older, definite diagnosis of ankle fracture, surgical treatment (osteosynthesis) and complete data available in medical records. Exclusion criteria were: pathological (metastatic) or old fracture (> 3 weeks since occurrence), open fracture, concurrent fractures in other locations, conservative treatment, incomplete medical records, current use of heparin, low molecular weight heparin (LMWH) or other anticoagulants due to chronic comorbidities, and preoperative diagnosis of DVT. All the patients were given basic anticoagulant treatment before surgery, including elevation of the affected limb and lower limb intermittent inflatable pressure.

Diagnosis of DVT

DVT was diagnosed in accordance with the Guideline for the Diagnosis and Treatment of Deep Vein Thrombosis (3rd edition) proposed by Chinese Medical Association [15]. Ultrasound report was used to obtain the diagnostic information of DVT. During the postoperative hospitalization stay, in patients with lower limb swelling, pain, tenderness in the rear and/or inner thighs, DVT was confirmed by duplex ultrasound: deep venous lumen obstruction or filling defect. Routine scanning was performed for the femoral common vein, superficial and deep femoral vein, popliteal vein, posterior and anterior tibial vein, and peroneal vein of bilateral lower extremities. Superficial or intermuscular vein thrombosis (soleal or gastrocnemius vein thrombosis) was excluded, due to its relatively less clinical significance [16, 17].

Data collection

Electronic medical records (EMR), picture archiving and communication system (PACS), operation reports were were inquired for relevant data. The demographic data included age, gender, residence (urban or rural), body mass index (BMI), cigarette smoking and alcohol consumption. The co-morbidities included hypertension, diabetes, ischemic heart disease, previous history of any surgery and history of allergies to any medications, all of which were self-reported by patients. Fracture and surgery-related data included: fracture location (uni, bi-or trimalleolar fracture), injury mechanism (low or high-energy trauma), accompanied dislocation, concurrent fractures of other locations, preoperative interval (between fracture occurrence and operation), American Society of Anesthesiologists (ASA) classification, anesthesia type, type of fracture reduction (open or closed), prophylactic use of antibiotics, surgical duration, bone graft, fixation type, intraoperative blood loss, perioperative blood transfusion, and postoperative use of drainage. The BMI (kg/m) was divided using the criteria recommended by the Chinese working group on obesity: normal (18.5-23.9), underweight (<18.5), overweight (24.0-27.9) and obesity (≥ 28.0). Low-energy injury was defined as an injury caused by a fall from a standing height, and others such as fall from a height, motor accidents were high-energy injury.

The biomarkers from preoperative laboratory tests included total protein (TP) level, albumin (ALB) level, fasting blood glucose (FBG) level, preoperative red blood cell (RBC) count, white blood cell (WBC) count, neutrophile (NEUT) count, lymphocyte (LYM) count, neutrophile/lymphocyte rate (NLR), hemoglobin (HGB) level, haematocrit (HCT), platelet (PLT), red blood cell distribution width (RDW), serum total cholesterol (TC) level, triglyceride (TG) level, low density lipoprotein (LDL-C) level, high density lipoprotein (HDL-C) level, very low-density lipoprotein (VLDL) level and D-dimer level. If patients had multiple laboratory tests before when DVT was diagnosed, laboratory tests closest to the diagnostic time point were chosen for data analysis.

Statistical analysis

Continuous variables were expressed by mean and standard deviation (SD), and were evaluated by student-t test or Mann Whitney-*U* test. The categorical data were expressed as number and percentage (%), and were evaluated by chi-square or Fisher's exact test. Multivariate logistics regression model was used to identify the independent risk factors associated with occurrence of DVT, using the stepwise backward elimination method. Variables with $p < 0.10$ were retained in the final model, and the correlation strength is indicated by odd ratio (OR) and 95% confidence interval (95%CI). The statistical test level was set as $p < 0.05$. Hosmer-lemeshow (H-L) test was used to evaluate the fitting degree of the final model, and $p > 0.05$ represented the acceptable result. SPSS23.0 was used to perform all the tests (IBM, armonk, New York, USA).

Results

A total of 1451 patients with 1474 ankle fracture treated surgically were included for data analysis, consisting of 825 males and 626 females, with an average of 43.7 years (Sd, 15.1; range, 18–95; median, 43.0). Unimalleolar fracture accounted for 45.8% (673/1474), followed by trimalleolar fractures (471,

32.0%) and bimalleolar fractures (330, 22.2%). There were 264 (18.1%) fractures that were accompanied by dislocation or subluxation. The total hospitalization stay was 16.3 days in average (Sd, 14.6; median, 13; range, 2 to 137). The average preoperative hospitalization stay was 5.4 days (Sd, 3.5; range, 0–18; median, 5).

Of the 1451 patients, 38 developed a postoperative DVT, indicating an incidence rate of 2.6%. There was no thrombosis found in anterior tibial or femoral common vein. At the other 5 veins, a total of 61 clots were found, representing an average of 1.61 (range, 1 to 5) for each patient. DVT involved both the operated and non-operated limbs in 8 patients (21.1%). DVT involved only the non-operated limb in 5 patients (13.2%). The detailed DVTs involving veins were as follows: 4 in superficial femoral vein, 2 in deep femoral vein, 5 in popliteal vein, 11 in posterior tibial vein, and 39 in peroneal vein. The interval between operation and diagnosis of DVT ranged from 1 to 26 days, with median at 7 days.

Table 1 presented the univariate analyses results. It was different between DVT and non-DVT patients in term of age both in continuous ($p < 0.001$) and categorical variable ($p = 0.001$), diagnosis of diabetes mellitus, anesthesia type, preoperative stay, ASA classification, intraoperative bleeding, TP (< 60 g/L), ALB (< 35 g/L), TC (> 5.2 mmol/L), LYM ($< 1.1 \times 10^9$ /L), RBC count, HGB level, HCT, PDW, RDW and D-Dimer level. DVT was associated with a significantly increased hospitalization stay of 6.9 days (23.0 vs 16.1 days).

Table 1
univariate analyses of risk factors associated with DVT following ankle fracture surgeries

Variables	Number (%) of DVT (n = 38)	Number (%) of non-DVT (n = 1413)	P
Gender (male)	19 (50.0)	806 (57.0)	0.387
Age (years)	55.6 ± 14.6	43.4 ± 15.0	< 0.001
18–44	11 (28.9)	764 (54.1)	0.001
45–64	18 (47.4)	515 (36.4)	
65 or older	9 (23.7)	134 (9.5)	
Living place			0.789
Rural	23 (60.5)	777 (55.1)	
Urban	15 (39.5)	635 (44.9)	
BMI (kg/m ²)	24.5 ± 3.6	25.9 ± 4.1	0.181
18.5–23.9	11 (28.9)	414 (29.3)	
<18.5	2 (5.3)	25 (1.8)	
24.0-27.9	18 (47.4)	608 (43.0)	
≥28.0	7 (18.4)	366 (25.9)	
Cigarette smoking	9 (23.7)	212 (15.0)	0.142
Alcohol consumption	11 (28.9)	387 (27.4)	0.832
Diabetes mellitus	12 (31.6)	179 (12.7)	0.001
Hypertension	9 (23.7)	183 (13.0)	0.054
Chronic heart disease	3 (7.9)	65 (4.6)	0.343
History of allergies to any medications	8 (21.1)	202 (14.3)	0.243
History of any surgery	5 (13.2)	109 (7.7)	0.218

Abbreviation and Notes: DVT: deep venous thrombosis; BMI, body mass index; ASA, American Society of Anesthesiologists; RBC, red blood cell, reference range: Female, 3.5-5.0*10¹²/L; males, 4.0-5.5*10¹²/L. HGB, hemoglobin, reference range: Females, 110–150 g/L; males, 120–160 g/L; FBG, fasting blood glucose; HCT, haematocrit, 40–50%; WBC, white blood cell; NEUT, neutrophile; LYM, lymphocyte; PLT, platelet, 100–300*10⁹/L; TP, total protein; ALB, albumin; RDW, red cell distribution width; PDW, platelet distribution width; TC, total cholesterol; TG, triglyceride, LDL-C, low density lipoprotein; HDL-C, high density lipoprotein; VLDL, very low-density lipoprotein.

Variables	Number (%) of DVT (n = 38)	Number (%) of non-DVT (n = 1413)	P
Injury mechanism (high-energy)	10 (26.3)	284 (20.1)	0.347
Fracture location			0.757
Unimalleolar	17 (44.7)	656 (45.8)	
Bimalleolar	7 (18.4)	323 (22.5)	
Trimalleolar	14 (36.8)	454 (31.7)	
Accompanied dislocation or subluxation	9 (23.7)	258 (17.9)	0.361
Preoperative stay	7.7 ± 3.2	5.3 ± 3.6	< 0.001
Total hospital stay	23.0 ± 7.8	16.1 ± 14.7	0.004
Anesthesia (general)	19 (50.0)	271 (19.2)	< 0.001
ASA class			0.033
I	4 (10.5)	250 (17.7)	
II	25 (65.8)	1011 (71.5)	
III or above	9 (23.7)	152 (10.8)	
Operation timing			0.293
Day	38 (100)	1373 (97.2)	
Night	0	40 (2.8)	
Type of fracture reduction			0.780
Closed	1 (2.6)	49 (3.5)	
Open	37 (97.4)	1364 (96.5)	
Fixation type			
Screw or pins only	0	73 (5.2)	0.150

Abbreviation and Notes: DVT: deep venous thrombosis; BMI, body mass index; ASA, American Society of Anesthesiologists; RBC, red blood cell, reference range: Female, $3.5-5.0 \times 10^{12}/L$; males, $4.0-5.5 \times 10^{12}/L$. HGB, hemoglobin, reference range: Females, 110–150 g/L; males, 120–160 g/L; FBG, fasting blood glucose; HCT, haematocrit, 40–50%; WBC, white blood cell; NEUT, neutrophile; LYM, lymphocyte; PLT, platelet, $100-300 \times 10^9/L$; TP, total protein; ALB, albumin; RDW, red cell distribution width; PDW, platelet distribution width; TC, total cholesterol; TG, triglyceride, LDL-C, low density lipoprotein; HDL-C, high density lipoprotein; VLDL, very low-density lipoprotein.

Variables	Number (%) of DVT (n = 38)	Number (%) of non-DVT (n = 1413)	P
Plate and screws	38 (100)	1340	
Bone grafting	2 (5.3)	52 (3.7)	0.611
Intraoperative bleeding	254.2 ± 349.6	167.1 ± 213.9	0.014
Perioperative blood transfusion (yes)	3 (7.9)	44 (3.1)	0.101
Surgical duration	134.9 ± 74.4	130.7 ± 58.2	0.664
TP (< 60 g/L)	12 (31.6)	245 (17.3)	0.023
ALB (< 35 g/L)	10 (26.3)	171 (12.1)	0.009
Intraoperative prophylactic use of antibiotics	38 (100)	1332 (94.3)	0.129
Postoperative use of antibiotics	36 (94.7)	1304 (92.3)	0.575
FBG (> 6.1 mmol/L)	15 (39.5)	398 (28.2)	0.127
TC (> 5.2 mmol/L)	13 (34.2)	237 (16.8)	0.005
TG (> 1.7 mmol/L)	7 (18.4)	270 (19.1)	0.915
LDL-C (> 3.37 mmol/L)	11 (28.9)	250 (17.7)	0.075
HDL-C (< 1.1 mmol/L)	12 (31.6)	511 (36.2)	0.561
VLDL (> 0.78 mmol/L)	6 (15.8)	263 (18.6)	0.659
WBC (> 10*10 ⁹ /L)	8 (21.1)	373 (26.4)	0.460
NEUT (> 6.3* 10 ⁹ /L)	17 (44.7)	603 (42.7)	0.726
LYM (< 1.1*10 ⁹ /L)	20 (52.6)	273 (19.3)	< 0.001
RBC (< lower limit)	15 (39.5)	271 (19.2)	0.002
HGB (< lower limit)	15 (39.5)	269 (19.0)	0.002

Abbreviation and Notes: DVT: deep venous thrombosis; BMI, body mass index; ASA, American Society of Anesthesiologists; RBC, red blood cell, reference range: Female, 3.5-5.0*10¹²/L; males, 4.0-5.5*10¹²/L. HGB, hemoglobin, reference range: Females, 110–150 g/L; males, 120–160 g/L; FBG, fasting blood glucose; HCT, haematocrit, 40–50%; WBC, white blood cell; NEUT, neutrophile; LYM, lymphocyte; PLT, platelet, 100–300*10⁹/L; TP, total protein; ALB, albumin; RDW, red cell distribution width; PDW, platelet distribution width; TC, total cholesterol; TG, triglyceride, LDL-C, low density lipoprotein; HDL-C, high density lipoprotein; VLDL, very low-density lipoprotein.

Variables	Number (%) of DVT (n = 38)	Number (%) of non-DVT (n = 1413)	P
HCT (< lower limit)	22 (57.9)	563 (39.8)	0.025
PLT (> 300*10 ⁹ /L)	6 (15.8)	256 (18.1)	0.713
PDW (> 18.1%)	2 (5.3)	18 (1.3)	0.037
RDW (> 16.5%)	4 (10.5)	52 (3.7)	0.031
D-Dimer (> 0.3 mg/L)	30 (81.1)	860 (60.9)	0.013
Abbreviation and Notes: DVT: deep venous thrombosis; BMI, body mass index; ASA, American Society of Anesthesiologists; 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; FBG, fasting blood glucose; HCT, haematocrit, 40–50%; WBC, white blood cell; NEUT, neutrophile; LYM, lymphocyte; PLT, platelet, 100–300*10 ⁹ /L; TP, total protein; ALB, albumin; RDW, red cell distribution width; PDW, platelet distribution width; TC, total cholesterol; TG, triglyceride, LDL-C, low density lipoprotein; HDL-C, high density lipoprotein; VLDL, very low-density lipoprotein.			

In the multivariate model, the above-mentioned 17 variables together with hypertension ($p = 0.054$) and elevated LDL-C level ($p = 0.075$) were entered. Finally, six risk factors were identified to be associated with DVT, including age (10-year increase), preoperative stay (delay of each day), anesthesia (general vs regional), lower LGB level, TC > 5.2 mmol/L and reduced LYM count (Table 2). As for other variables, we did not find the independent effect on DVT. The H-L test demonstrated the good fitness of the final model ($\chi^2 = 8.216$, $p = 0.413$; Nagelkerke $R^2 = 0.220$).

Discussion

There remain scarce of epidemiologic data the DVT following surgery of ankle fractures. In this retrospective study, we evaluated the incidence rate of DVT during hospitalization period and identified some independent associated risk factors. Inclusion of a large sample participants and multiple potential variables involving clinics, operation and laboratory tests is the major advantage. This study may help counseling patients about the risk of DVT and help orthopedic surgeons in treatment decision making, DVT risk evaluation and stratification and taking targeted preventive measures.

Most of previous studies focused on the preoperative DVT, and only a very few studies focused on the postoperative DVT and reported the greatly varied results. Shibuya [13] et al reported the incidence rate of acute DVT was 0.28% in 75664 patients with foot and ankle trauma, using data from the national trauma data bank. SooHoo et al [12] used California discharge database including 57183 patients undergoing surgical treatment of ankle fractures, and found the extremely low incidence rate of DVT, that was 0.05%. In other studies with relatively small sample (100 to 2347), authors reported the comparable rates, 3.5% for DVT following surgical treatment [16] and 5.0% after plaster cast [18], which were consistent with ours

(2.6%). These reported greatly varied figures for DVT in a specified ankle trauma population reflected the importance of study design, data resources, and also the differences in race and ethnics.

In this study, patients with DVT had a significant increased age of 12.2 years (55.6 vs 43.4) than those without DVT, and every increase of 10-years was associated with a 44% increased risk of DVT. Consistent with ours, the previous studies had demonstrated the similar dose-dependent effect of age on the occurrence of DVT following surgery of ankle trauma. Shibuya et al [13] found a converted a 20% increased risk of DVT with every 10-year increment. Similarly, Stavem et al [19] found the significant result when age used in a continuous variable in the multivariate model. This can be explained by the vascular aging with age, such as damaged vascular endothelial cell and decreased fibrinolytic function and lower limb vein valve function [20]. However, it was not easy to confirm the cut-off value of age above which the risk of DVT was significantly increased, especially in context of racial and ethnic differences. SooHoo et al [12] found age of 50–75 rather than > 75 years was associated with increased risk of DVT compared to those aged 50 years and younger. In another study, Duan et al [20] used 40 years as the cut-off value and identified the independent effect of the advanced age on DVT occurrence. In this study, we divided the age into 3 groups based on the traditional criteria proposed by WHO, but did not find the positive result in the multivariate model. It is possible that individual variation in vascular aging and sensitivity to thrombosis development should be a more worthy contributor than age itself.

The general anesthesia as an independent risk factor for DVT have been extensively reported in major surgeries, including hip fracture repairs and joint replacement [21, 22]. In a meta-analysis of 21 randomized trials in total hip or knee [23] replacement demonstrated that general anesthesia was significantly associated with 2.48-fold increased risk of DVT, compared to regional anesthesia. However, specified at ankle fractures, general anesthesia as an independent factor for DVT was firstly reported in this study. This could be explained by the fact that, compare to general anesthesia, regional anesthesia allowed early mobility and improved the postoperative functional outcome and pain relief following surgical repair of ankle fractures [24]. In this study, the mean preoperative stay was 7.7 days in patients with DVT and 5.3 days in those without DVT ($p < 0.001$), and each extra day was associated with a 11% increased risk of DVT. However, the role of prolonged preoperative stay in development of DVT might be complex and should be treated dialectically. In fact, there were multiple factors that could affect the preoperative hospital stay, such as severity of trauma, number and severity extent of comorbidities or the availability of operation room [25]. Also, the prolonged preoperative stay means the longer-duration immobilization of injured limb, which is a most common cause for DVT [26]. The relationship between preoperative stay and DVT occurrence require further studies to investigate, especially in setting of adjustment for confounding factors as many.

The other 3 factors identified in this study were all from laboratory test: HGB level, TC level, and LYM count, and their relation to DVT had been discussed in the literature [27–31]. These biomarkers are more likely indication of a low immune, systematic inflammation and anemia status, but the stress effects from trauma cannot be ruled out [32]. In a study of humeral, femoral, and tibial diaphyseal fractures, authors observed significant changes of haematology panel biomarkers for any fracture location,

compared to the controls [33]. In our study, if patients had multiple laboratory tests before when DVT was diagnosed, laboratory tests closest to the diagnostic time point were chosen for data analysis. Therefore, in consideration of the changes of biomarkers after trauma, our results could present more value in predicting DVT occurrence, compared to the commonly used admission biomarkers.

Several challenges and limitations in this study should be noted. Firstly, the retrospective design of this study compromised the accuracy in data collection, especially for those comorbidities self-reported by patients. For patients with incomplete or non-available data in medical records, we had to exclude them and in theory it was randomized. Secondly, we could not include some factors that potentially affect the occurrence of DVT, such as immobilisation duration of the injured limb and prophylactic use of antithrombotic agents [16]. Thirdly, all DVTs were diagnosed during hospitalisation, because DVT was not our routine follow-up content. Therefore, the incidence of DVT in this study was underestimated.

In summary, among the hospitalized patients undergoing surgery of ankle fractures, the incidence rate of postoperative DVT was 2.6%. Patients with DVT had a prolonged 1-week hospitalization stay than those without DVT. Age, prolonged preoperative stay, general anesthesia (vs regional), lower HGB level, hyperlipidaemia and reduced LYM count were identified as independent risk factors associated with DVT. Although most of them are not easily modifiable, they do help counsel patients about the risk of DVT and help individualized assessment of the risk factors and accordingly the risk stratification.

Abbreviations

DVT: deep venous thrombosis

BMI: body mass index

EMR: electronic medical records

ASA: American Society of Anesthesiologists

SD: standard deviation

OR: odd ratio

RBC, red blood cell

HGB, hemoglobin

ALB, albumin;

FBG, fasting blood glucose

HCT, haematocrit

WBC, white blood cell

NEUT, neutrophile

LYM, lymphocyte

PLT, platelet

TP, total protein

PDW, platelet distribution width

RDW, red cell distribution width

TC, total cholesterol;

TG, triglyceride,

LDL-C, low density lipoprotein cholesterol;

HDL-C, high density lipoprotein cholesterol;

VLDL, very low-density lipoprotein cholesterol.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the 3rd hospital of Hebei Medical University. Informed consent was obtained from all the participants.

Consent for publication

Written informed consent was obtained from each patient to authorize the publication of their data.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions: Yanbin Zhu and Fengqi Zhang designed the study; Yansen Li and Weili Zhang inquired the EMR for data on variables of interest; Xiaomeng Wang and Wei Chen searched relevant literature and analyzed and interpreted the data; Zixuan Luo and Xiaomeng Wang wrote the manuscript and Yanbin Zhu approved the final version of the manuscript.

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