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Original Article

Analysis of immune cells and risk factors related to lower limb deep vein thrombosis in patients with cerebral infarction

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Abstract: To explore the characteristics of hematologic indicators and related risk factors of lower extremity deep vein thrombosis (LDVT) in patients with cerebral infarction. Methods: This study retrospectively analyzed data from 174 patients with cerebral infarction admitted to The Rehabilitation Department of Shanghai Fifth Rehabilitation Hospital and Shanghai First People's Hospital from June 2022 to June 2023. Based on the results of lower limb venous color Doppler ultrasound examinations, patients were divided into two groups: the LDVT group (35 cases) and the non-LDVT group (139 cases). We compared the clinical data and hematologic indicators (D-dimer value, fibrinogen, white blood cells, platelets, uric acid, creatinine, etc.) of the two groups to identify the risk factors of cerebral infarction complicated with LDVT. Results: Statistical analysis revealed that the D-dimer values of the LDVT group were significantly ($P<0.05$) higher than those of the non-LDVT group. The uric acid value of the LDVT group was significantly lower than that of the non-LDVT group, with statistical significance ($P<0.05$). The Brunnstrom staging in the LDVT group was significantly different from that in the non-LDVT group ($P<0.05$). Meanwhile, binary logistic regression analysis showed that LDVT complicated with cerebral infarction was associated with D-dimer level [OR=1.302, 95% CI (1.077, 1.575)], uric acid level [OR=0.995, 95% CI (0.990, 1.000)], and Brunnstrom staging [OR=3.005, 95% CI (1.312, 6.880)]. Conclusion: D-dimer value, uric acid value, and Brunnstrom stage I to II are closely related to the occurrence of LDVT in patients with cerebral infarction. High D-dimer value, low uric acid value, and Brunnstrom stage I to II are independent risk factors for LDVT in cerebral infarction. Early assessment of D-dimer value, uric acid value, and Brunnstrom stage of cerebral infarction should be considered in clinical practice.

Keywords: Cerebral infarction, lower limbs, deep vein thrombosis, blood indicators

Introduction

Cerebral infarction can lead to functional impairments, such as hemiplegia, aphasia, dysphagia, and decreased level of consciousness [1]. Annually, 2 million new patients with stroke are diagnosed in China [2], and nearly half of the patients are at risk of LDVT [3]. LDVT poses a high risk of pulmonary embolism, and previous studies have shown that 35.1% of patients with LDVT experience pulmonary embolism [4]. In severe cases, it can threaten the patient's life [5]. Therefore, early detection and treatment of LDVT is critical.

Recent studies have found that deep vein thrombosis is related to immune response. Through immune mechanisms, immune dysfunction can increase the risk of deep vein thrombosis. As the main immune cells, white blood cells participate in the initiation and spread of thrombosis [6]. There is a lack of risk assessment for cerebral infarction complicated with LDVT in clinical practice.

Therefore, this study collected relevant hematologic indicators and clinical data from patients with cerebral infarction to identify the risk factors of cerebral infarction complicated with LDVT.

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Materials and methods

Case selection, data collection, and grouping

Inclusion criteria were as follows: 1) those who meet the diagnostic criteria for cerebrovascular diseases revised by the 4th National Conference on Cerebrovascular Diseases [7], and were confirmed to have cerebral infarction and lower limb dysfunction through cranial imaging examination; 2) 30 years old ≤ Age ≤90 years old; 3) 1 week ≤ disease course ≤3 months; 4) within 3 days of admission, the patient underwent lower limb venous ultrasound, routine biochemistry and blood test, and complete coagulation tests; 5) stable vital signs; and 6) signed informed consent form was provided.

Exclusion criteria were as follows: 1) Hemorrhagic cerebrovascular disease; 2) Incomplete clinical data; 3) Patients with serious illnesses, those taking special medications such as hormones, and those with severe organ dysfunction; 4) Severe cerebral infarction complicated with intracranial hypertension or severe consciousness disorders; and 5) Hematologic diseases.

From June 2022 to June 2023, 174 patients with recovery after stroke who were initially hospitalized in the Rehabilitation Department of Shanghai Fifth Rehabilitation Hospital and Shanghai First People's Hospital and met the above criteria were included. They were divided into the LDVT group and the non-LDVT group based on the presence or absence of LDVT. This study was approved by the Ethics Committee of Shanghai First People's Hospital ([2023] 094).

Within 3 days of admission, we conducted lower limb deep vein color Doppler ultrasound examination on 174 patients with cerebral infarction to determine the presence of LDVT. Diagnostic criteria were as follows [8]: 1) solid echo found in the venous lumen of the lower limb; 2) partial compression or inability to compress the venous lumen after probe pressure; 3) lack of color blood flow and pulse Doppler ultrasound blood flow at the site of thrombosis; 4) the patient's blood flow spectrum did not change with breathing; 5) the diameter of collateral veins widened. In total, 174 patients with cerebral infarction were divided into the LDVT (35 cases) and non-LDVT groups (139 cases) based on the results of color Doppler ultrasound of deep veins of lower limbs. We also measured the effect of antiplatelet therapy.

Data collection and research methods

According to the results of lower limb ultrasound, patients were divided into two groups, namely the LDVT and non-LDVT groups. Clinical data of the two groups of patients were collected, including gender, course of disease, age, history of smoking, hypertension, drinking, hyperlipidemia, and diabetes, consciousness disorder, dysphagia, speech disorder, hemiplegia, muscle tone, antiplatelet therapy, etc. In addition, data on indicators, such as hemoglobin, albumin, fibrinogen, white blood cells, fasting blood glucose, neutrophil percentage, globulin, platelet count, creatinine, calcium, sodium, uric acid, D-dimer, neutrophil count, eosinophil count, lymphocyte count, monocyte count, etc., were detected in the venous blood in the morning the next day of admission.

Statistical analysis

Data were analyzed using SPSS 22.0 software. Age, gender, course of disease, history of smoking, hypertension, drinking, hyperlipidemia, and diabetes, consciousness disorder, dysphagia, speech disorder, hemiplegia, muscle tension, antiplatelet therapy, Brunnstrom staging, etc. of the two groups were compared using χ^2 test. Hemoglobin, albumin, fibrinogen, white blood cell count, fasting blood glucose, percentage of neutrophils, globulin, platelet count, creatinine, calcium, sodium, uric acid, D-dimer, neutrophil count, eosinophil count, lymphocyte count, and monocyte count were compared using independent sample t-test in the presence of normal distribution, or using rank sum test and binary logistic regression in the absence of normal distribution. $P<0.05$ indicated independent variables in univariate analysis, and $P<0.05$ indicated statistical significance.

Result

Clinical data of the two groups

There was no significant difference between the two groups in terms of gender, course of disease, age, history of smoking, hypertension,

Table 1. Comparison of basic data between the two groups of patients

Basic data		LDVT group	Non-LDVT group	*P* value
Number of cases/case		35	139	
Age/Year		70.77±1.73	69.71±0.89	>0.05
Gender	Male	19	87	>0.05
	Female	16	52	
Disease duration/month		1.33±0.58	1.50±0.71	>0.05
Smoking history	Yes	10	47	>0.05
	No	25	92	
History of drinking	Yes	7	26	>0.05
	No	28	113	
History of hypertension	Yes	27	115	>0.05
	No	8	24	
History of hyperlipidemia	Yes	0	3	>0.05
	No	35	136	
History of diabetes	Yes	15	56	>0.05
	No	20	83	
Disturbance of consciousness	Yes	2	8	>0.05
	No	33	131	
Hemiplegic side to side	Left side	21	70	>0.05
	Right side	13	62	
	Bilateral	1	7	
Speech disorders	Yes	17	50	>0.05
	No	18	89	
Hypermyotonia	Yes	7	37	>0.05
	No	28	102	
Dysphagia	Yes	3	14	>0.05
	No	32	125	
Brunnstrom staging	Stages I-II	16	16	<0.05
	Stages III-VI	19	19	
Antiplatelet therapy	Yes	26	104	>0.05
	No	9	35	

drinking, hyperlipidemia, and diabetes, consciousness disorder, dysphagia, speech disorder, hemiplegia, muscle tension, and antiplatelet therapy (P>0.05).

Brunnstrom staging was significantly different between the two groups (P<0.05) (**Table 1**).

Analysis of hematologic indicators

Hemoglobin, albumin, fibrinogen, white blood cell count, fasting blood glucose, neutrophil percentage, globulin, platelet count, creatinine, calcium, sodium, neutrophil count, eosinophil count, lymphocyte count, and monocyte count were not significantly (P>0.05) different between the two groups. D-dimer and uric acid values were compared between the two groups, and differences were significant (P<0.05) (**Table 2**).

Multivariate logistic regression analysis

Logistic regression analysis was conducted using single factors with statistically significant differences in clinical data and hematologic indicators, including D-dimer, uric acid value, and Brunnstrom stage, as independent variables. The results showed that D-dimer and Brunnstrom stage were risk factors for LDVT among patients with cerebral infarction (P< 0.05) (**Table 3**).

Discussion

Stroke is the second leading cause of death worldwide, second only to ischemic heart dis-

Table 2. Comparison of hematologic indicators between the two groups

Hematologic indicators	LDVT group	Non-LDVT group	T/Z	*P* value
D-Dimer (mg/L)	2.74±0.70	0.97±0.11	-3.687	<0.05
Globulin (g/L)	26.20±0.74	26.21±0.36	-0.289	>0.05
Hemoglobin (g/L)	124.49±2.68	129.34±1.47	-1.104	>0.05
Leukocyte ($\times10^9$/L)	7.26±0.40	7.25±0.22	-0.107	>0.05
Uric acid (μmol/L)	270.51±74.08	307.57±7.91	-2.183	<0.05
Platelet ($\times10^9$/L)	243.57±13.57	237.89±6.00	0.413	>0.05
Albumin (g/L)	39.18±1.24	39.69±0.33	-1.076	>0.05
Neutrophil ratio (%)	69.70±1.61	66.84±0.78	1.630	>0.05
Creatinine (μmol/L)	70.83±3.83	74.45±2.64	-0.576	>0.05
Fibrinogen (g/L)	4.16±0.21	4.07±0.09	-0.466	>0.05
Urea (mmol/L)	6.27±0.37	6.28±0.23	-0.113	>0.05
Fasting blood glucose (mmol/L)	6.51±0.40	6.33±0.24	-0.820	>0.05
Calcium (mmol/L)	2.26±0.22	2.42±0.14	-0.941	>0.05
Sodium (mmol/L)	140.55±0.42	140.29±0.33	-0.098	>0.05
Neutrophils ($\times10^9$/L)	5.18±0.38	4.96±0.2	0.501	>0.05
Eosinophils ($\times10^9$/L)	0.15±0.02	0.24±0.04	-1.17	>0.05
Lymphocytes ($\times10^9$/L)	1.47±0.1	1.59±0.05	-1.075	>0.05
Monocytes ($\times10^9$/L)	0.44±0.03	0.47±0.02	-0.908	>0.05

Table 3. Multivariate logistic regression analysis

Argument	B	SE	Wald	P	OR (95%) CI
Uric acid (μmol/L)	-0.005	0.003	4.012	0.045	0.995 (0.990-1.000)
D-Dimer (mg/L)	0.264	0.097	7.412	0.006	1.302 (1.077-1.575)
Brunnstrom Staging (stages I-II:stages III-VI)	1.100	0.423	6.777	0.009	3.005 (1.312-6.880)

ease. It is also the third leading cause of disability [9]. Complications of cerebral infarction include joint contracture, infection, LDVT, gastrointestinal bleeding, pressure sore, etc. LDVT, as a serious complication of cerebral infarction, has a high incidence rate. In the absence of timely detection and treatment, LDVT can be fatal among patients with stroke. In this study, 35 out of 174 patients developed LDVT, accounting for 20.11%. Thrombosis predominantly occurred in the deep femoral vein, popliteal vein, posterior tibial vein, and intermuscular vein. The study showed that approximately one-third of intermuscular vein thrombosis progressed to proximal vein thrombosis, and intermuscular vein thrombosis is an important source of pulmonary embolism [10]. Patients with cerebral infarction and hemiplegia are at a higher risk of LDVT [11]. Therefore, it is crucial to identify the risk factors of LDVT among patients with cerebral infarction and adopt preventive measures. Previous studies have shown that the activation of white blood cells can trigger the coagulation cascade, inducing a prothrombotic state and deep vein thrombosis. This experiment did not find significant differences in the number of white blood cells, neutrophils, lymphocytes, monocytes, and eosinophils between the two groups, which might be due to insufficient sample size. In this study, univariate analysis showed that the incidence of LDVT is closely related to D-dimer value, uric acid value, and Brunnstrom staging among patients with cerebral infarction. Logistic multivariate result analysis showed that high D-dimer value, low uric acid value, and Brunnstrom stage I-II were independent risk factors for LDVT in cerebral infarction.

There are three known risk factors that can affect venous thrombosis, namely endothelial injury, hypercoagulable state, and slow blood flow [12]. Plasma D-dimer is elevated after fibrinolysis, helping diagnose thrombotic diseases [13-15]. The sensitivity of D-dimer for diagnosing deep vein thrombosis is 85% to 95%, and

its specificity is 25% to 50% [16]. Some scholars believe that the combination of D-dimer and FDP or CRP can increase diagnostic efficiency. Consistent with previous studies, this study indicated that there is a significant difference in D-dimer values between the LDVT group and the non-LDVT group, suggesting that D-dimer has good predictive value for LDVT.

Uric acid is the main antioxidant molecule in plasma and is necessary and sufficient for inducing type 2 immune response [17]. Some studies suggested that hyperuricemia can promote coagulation [18], while this study drew the opposite conclusion. Uric acid can promote plasma oxidative stress, inflammatory response, and endothelial dysfunction. As an effective antioxidant, uric acid can remove peroxynitrite, hydrogen peroxide, superoxide anions, hydroxyl radicals, etc. High levels of uric acid enhance this effect, while low levels of uric acid reduce nitric oxide synthesis and increase oxidative stress, which may lead to endothelial dysfunction [19]. The plasma concentration of uric acid is approximately 15-450 μM. It is 10 times higher than ascorbic acid, but uric acid levels rapidly decrease after acute ischemic stroke (AIS). This decrease is associated with poorer outcomes of stroke [20]. Low levels of uric acid undermine its antioxidant activity and lead to endothelial dysfunction, which in turn leads to thrombosis. In addition, decreased cellular levels of UA may be related to the deletion and mutation of UA transporter 1 (encoded by the SLC22A12 gene), which affects its expression in the kidneys and blood vessels [17, 21]. The specific mechanism still needs further investigation.

In patients with cerebral infarction and hemiplegia, Brunnstrom staging can reflect the functional status of the hemiplegic side. The lower the staging, the worse the functional status. Brunnstrom staging stage I is mainly characterized by the absence of voluntary movement and no movement of the lower limbs. Patients with Brunnstrom stage II have very little free lower limb movement. Brunnstrom stage III can cause spontaneous coordinated movement, resulting in coordinated flexion of the lower limbs. In Brunnstrom stage IV and above, there is a separation movement, indicating the gradual return to normal movement patterns [22]. This study showed a statistically significant difference in Brunnstrom staging between the LDVT group and the non-LDVT group, suggesting a higher risk of LDVT among patients with cerebral infarction and Brunnstrom stages I-II. Considering its association with low physical activity, more preventive measures should be adopted against LDVT in patients with cerebral infarction and Brunnstrom stages I-II.

There are also limitations to this study, such as incomplete risk factors and small sample size. In addition to the risk factors identified in this study, other factors of LDVT have been discovered in previous studies. For example, Jimenez *et al.* [23] found that feeding rats with iron-deficient foods increased platelet count and induced thrombus formation, and iron replacement therapy reversed these changes. Rinaldi *et al.* [24] suggested that the neutrophil-to-lymphocyte ratio (NLR) can serve as a supplementary diagnostic tool for ruling out DVT based on D-dimer, especially among patients with low clinical suspicion. Bhargava *et al.* [25] found that renal transplantation surgery is a moderate risk factor for venous thromboembolism in clinical practice.

In summary, plasma D-dimer value, uric acid value, and Brunnstrom stage are significantly correlated with LDVT complicated by cerebral infarction. High D-dimer value, low uric acid value, and Brunnstrom stage I were independent risk factors for LDVT among patients with cerebral infarction in this study. In clinical practice, early assessment of D-dimer value, uric acid value, and Brunnstrom stage should be conducted to determine the risk of LDVT among patients with LDVT. Similarly, relevant therapeutic interventions should be actively conducted. Reducing D-dimer levels in the lower limb on the hemiplegic side and maintaining normal uric acid levels are preventive measures that can prevent LDVT among patients with cerebral infarction.

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Disclosure of conflict of interest

None.

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