Association of Clinical and Laboratory Variables with In-Hospital Incidence of Deep Vein Thrombosis in Patients with Acute Stroke: A Retrospective Study

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Abstract

Backgrounds: Deep vein thrombosis (DVT) is a serious complication in patients with acute stroke. Early prediction of DVT could enable physicians to perform a proper prevention strategy. We analyzed the association of clinical and laboratory variables with DVT to evaluate the risk of DVT in patients after stroke.

Results: Acute stroke patients admitted to the Changsha Central Hospital between January 2016 and December 2019 with length of stay in hospital ≥ 30 d were included. Clinical and laboratory variables for DVT at baseline were collected, and the diagnosis of DVT was confirmed by ultrasonography. Risk factors were developed by Multivariate logistic regression analysis. A total of 101 patients were included in the study, of which 77.2% (78/101) were diagnosed ischemic stroke and 22.8% (23/101) were confirmed hemorrhagic stroke. The overall incidence of DVT after acute stroke within 30 days was 19.8% (20/101). The level of D-dimer when DVT detected was significantly increased than that on admission. Pulmonary infection and increased muscle tone as independent relevant factors for DVT were confirmed.

Conclusions: Pulmonary infection as a risk factor and increased muscle tone as a protector factor for DVT were identified in patients after stroke and the significant change in level of D-dimer could be a warning for DVT occurrence. It helps with taking early managements to reduce the incidence of DVT in patients after stroke.

Introduction

Stroke is one of the severe cerebral disorders leading to high disability and mortality among hospitalized patients(1), while deep vein thrombosis (DVT) is one of most common and fatal complications in patients after stroke(2). In western countries, the incidence of DVT in acute stroke patients without prophylactic treatment was up to around 80% (3), and DVT still occurred in at 2–3% of patients even receiving comprehensive prophylactic therapy(4, 5). The CLOTS trial, as a largest multicenter observational research with 5632 patients with stroke revealed that the in-hospital incidences of detected DVT within 10 days and within 30 days were 11% and 15%, respectively(6). In Asia, the morbidity of DVT after stroke was less common, which varied in 3–17% (7).

However, the clinical outcomes were confirmed to be improved significantly in DVT patients after stroke including thrombolytic and anti-coagulation therapies(8), there was still lack of explicitness on the timing of thromboprophylaxis in the international guidelines(1). Hence, the risk of developing DVT in every single patient after stroke should be evaluated early so that the benefit and risk of thromboprophylaxis therapy could be comprehensively weighed and analyzed. In this study, we analyzed the association of clinical and laboratory variables with DVT in patients after stroke in order to explore risky factors for predicting in-hospital incidence of DVT.

Methods
Patients

Acute stroke patients admitted to the Changsha Central Hospital between January 2016 and December 2019 with length of stay (LOS) in hospital ≥ 30 d were included. Inclusion criteria were identified as follows: age ≥ 18, radiographical results showing cerebral infarction or cerebral hemorrhage, and length of stay in-hospital ≥ 30d. Exclusion criteria were identified as follows: past medical history of DVT, DVT detected on admission, varicose of lower extremities, malignant tumor and coagulation disorder.

Data collection

Based on electronic health records, the general information of patients was collected, including age, sex and comorbidities (coronary heart disease, rheumatoid heart disease, atrial fibrillation, hypertension, diabetes). The National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), Wells scale and Modified Rankin Scale (MRS) were performed for all the patients when on admission. Laboratory variables while patients admitted in ≤ 24 h were collected including platelet counts, red blood cell volume distribution width (RDW), low density lipoprotein (LDL), D-dimer and fibrinogen (Fbg). Moreover, management therapies including anti-coagulation and rehabilitation were also recorded. When DVT detected in patients by color doppler ultrasonography (CDUS), the clinical variables in 24 hours were collected. The incidence of in-hospital pulmonary infection and in-bed ≥ 3d were recorded. Clinical outcomes were LOS in hospital, in-hospital incidence of pulmonary embolism and in-hospital mortality.

DVT assessment

According to the electronic health record, the DVT assessment was applied with color doppler ultrasonography (CDUS) on the patients while on admission. Common femoral vein and the popliteal vein of patients were examined by CDUS for DVT diagnosis. During the time of in-hospital, CDUS was performed in 2 weeks after admission as well as whenever clinically requested such as swollen or paresthesia of extremities on the basis of electronic health records.

Statistics

Statistical results were showed in mean ± standard deviation for normal data, while for non-normal data, interquartile range (IQR) and median were utilized. Categorical data were showed as percentage and number. The comparison between two groups was performed with chi-squared test or Mann–Whitney U-test. Variables that were significant different in two groups on univariate analysis were further analyzed in multivariate logistic regression. Statistical analysis was performed using SPSS software (version 26) and two-sided P values of less than 0.05 were defined statistically significant.

Results
General characteristics of the patients

A total of 122 patients with diagnosis of acute stroke were enrolled and 21 were excluded on the basis of exclusion criteria (Fig. 1). Finally, 101 patients were included in the study, of which 77.2% (78/101) were diagnosed ischemic stroke, 22.8% (23/101) were confirmed hemorrhagic stroke, 66% (67/101) were male and median age was 66 (66.0 ± 16.2). There were 20 patients in DVT group and 81 patients in non-DVT group, respectively. The general characteristics of the patients were demonstrated in Table 1. There were no significant differences in proportion of subtypes of stroke, sex, age, comorbidities (coronary heart disease, rheumatoid heart disease, atrial fibrillation, hypertension, diabetes) between two groups. Lab variables (platelet counts, RDW, LDL, fibrinogen (Fbg), management (anti-coagulation, rehabilitation therapy) and clinical outcomes were no significant different between two groups. None of the patients had in-hospital pulmonary embolism. In DVP group, the proportion of increased muscle tone was significant lower than that in non-DVT group (10% vs 67.8%, P = 0.002), while there was no significant difference in muscle strength between two groups. The incidence of pulmonary infection was significantly higher in DVT group than non-DVT group (85% vs 60.4%, P = 0.044). The level of D-dimer and Wells scale were also significant different (P < 0.05).
| Characteristic                              | Total (n = 101) | DVT (n = 20) | Non-DVT (n = 81) | P-value |
|--------------------------------------------|----------------|-------------|-----------------|--------|
| Gender                                     |                |             |                 |        |
| Male, n(%)                                 | 67 (66.3)      | 11 (55.0)   | 56 (69.1)       | 0.292  |
| Female, n(%)                               | 34 (33.7)      | 9 (45.0)    | 20 (30.9)       |        |
| Age (years, mean ± sd)                     | 66.0 ± 16.2    | 65 ± 16.4   | 66 ± 16.3       | 0.684  |
| Ischemic stroke, n(%)                      | 78 (77.2)      | 15 (75.0)   | 63 (77.8)       | 0.938  |
| Hemorrhagic stroke n(%)                    | 23 (22.8)      | 4 (20.0)    | 19 (23.4)       | 0.626  |
| Comorbidities                              |                |             |                 |        |
| Coronary heart disease, n(%)               | 23 (22.7)      | 8 (40.0)    | 15 (18.5)       | 0.070  |
| Rheumatoid heart disease, n(%)             | 6 (5.9)        | 1 (5.0)     | 5 (6.1)         | 1.000  |
| Arial fibrillation, n(%)                   | 19 (18.8)      | 7 (35.0)    | 12 (21.4)       | 0.055  |
| Hypertension, n(%)                         | 83 (82.1)      | 18 (90.0)   | 65 (80.2)       | 0.514  |
| Diabetes, n(%)                             | 15 (14.8)      | 2 (10.0)    | 13 (16.0)       | 0.729  |
| In-hospital complications                   |                |             |                 |        |
| In-bed ≥ 3d, n(%)                          | 85 (84.1)      | 17 (85.0)   | 68 (83.9)       | 1.000  |
| Pulmonary infection, n(%)                  | 66 (65.3)      | 17 (85.0)   | 49 (60.4)       | 0.044  |
| Central venous catheter, n(%)              | 6 (5.9)        | 2 (10.0)    | 4 (4.9)         | 0.340  |
| Increased muscle tone n(%)                 | 40 (39.6)      | 2 (10.0)    | 38 (67.8)       | 0.002  |
| Muscle strength (grade, mean ± sd)         | 2.4 ± 1.6      | 2.8 ± 1.7   | 2.4 ± 1.6       | 0.332  |
| Lab findings                               |                |             |                 |        |
| Platelet (10^9/L, mean ± sd)               | 189.3 ± 57.7   | 182 ± 50.5  | 191 ± 59.5      | 0.512  |
| RDW(%, mean ± sd)                          | 14.6 ± 12.3    | 13.7 ± 2.1  | 14.9 ± 1.5      | 0.704  |
| LDL (mmol/L, mean ± sd))                   | 2.0 ± 1.2      | 1.9 ± 1.2   | 2.0 ± 1.1       | 0.813  |
| D-dimer (mg/L, mean ± sd)                  | 1.6 ± 3.3      | 3.1 ± 5.3   | 1.3 ± 2.4       | 0.021  |
| Fbg (mg/L, mean ± sd)                      | 2.9 ± 1.3      | 2.5 ± 1.1   | 3.0 ± 1.3       | 0.068  |

Abbreviations: DVT = Deep Vein Thrombosis, RDW = Red blood cell volume distribution width, LDL = low density lipoprotein, Fbg = fibrinogen, GCS = Glasgow Coma Scale, NIHSS = National Institutes of Health Stroke Scale, MRS = Modified Rankin Scale
| Characteristic       | Total (n = 101) | DVT (n = 20) | Non-DVT (n = 81) | P-value |
|---------------------|----------------|--------------|------------------|---------|
| **Scoring system**  |                |              |                  |         |
| GCS                 | 11.6 ± 3.5     | 11.5 ± 3.5   | 11.6 ± 3.5       | 0.927   |
| NIHSS               | 16.9 ± 10.2    | 19.7 ± 10.6  | 16.2 ± 10.1      | 0.181   |
| MRS                 | 4.1 ± 1.3      | 4.2 ± 1.4    | 4.1 ± 1.3        | 0.905   |
| Wells               | 0.43 ± 0.64    | 0.7 ± 0.7    | 0.4 ± 0.6        | 0.031   |
| **Management**      |                |              |                  |         |
| Anti-coagulation n(%)| 8(7.9)         | 1(5.0)       | 7(8.6)           | 1.000   |
| Rehabilitation therapy n(%) | 101(100.0) | 20(100.0) | 81(100.0) | 1.000   |
| **Clinical outcomes**|               |              |                  |         |
| Pulmonary embolism n(%) | 0(0.0)        | 0(0.0)       | 0(0.0)           | 1.000   |
| Length of stay in hospital(days) | 79.0 ± 60.2 | 73.7 ± 37.6 | 80.3 ± 64.7 | 0.666   |
| In-hospital mortality, n(%)   | 1(0.9)        | 0(0.0)       | 1(1.2)           | 1.000   |

Abbreviations: DVT = Deep Vein Thrombosis, RDW = Red blood cell volume distribution width, LDL = low density lipoprotein, Fbg = fibrinogen, GCS = Glasgow Coma Scale, NIHSS = National Institutes of Health Stroke Scale, MRS = Modified Rankin Scale

**Multiple logistic regression analysis for in-hospital incidence of DVT**

Two independent variables were identified by multivariate logistic regression analysis in (Table 2). Pulmonary infection was a risk factor for in-hospital incidence of DVT (Odds Ratio(OR) = 5.4, 95%CI: 1.10-26.65, P = 0.037), while increased muscle tone was negative parallel with in-hospital incidence of DVT (OR = 0.11, 95%CI = 0.02–0.58, P = 0.010).
Table 2
Multiple logistic regression analysis for in-hospital incidence of DVT

|                          | OR  | 95% CI    | p-value |
|--------------------------|-----|-----------|---------|
| Coronary heart disease   | 2.4 | 0.48–12.24| 0.288   |
| Atrial fibrillation      | 2.5 | 0.49–13.2 | 0.265   |
| Fbg                      | 0.6 | 0.34–1.13 | 0.116   |
| D-dimer                  | 1.2 | 0.91–1.47 | 0.231   |
| Increased muscle tone    | 0.11| 0.02–0.58 | 0.010   |
| Wells score              | 2.0 | 0.86–4.62 | 0.106   |
| Pulmonary infection      | 5.4 | 1.10–26.65| 0.037   |

Abbreviations: DVT = Deep Vein Thrombosis, Fbg = fibrinogen

Analysis of the relevance between DVT and increased muscle tone

In non-DVT group, the incidence of increased muscle tone was significantly higher than that in DVT group (67.8% vs 10%, P = 0.002) (Fig. 2). Non-parametric correlation analysis showed that there was a negative correlation between DVT and increased muscle tone (R = -0.703, P = 0.031). Compared the time when DVT detected and when muscle tone increased, the average days from admission to when DVT detected were significantly longer than the time from admission to when muscle tone increased (17.7 vs 9.9, P < 0.001) (Fig. 3).

Analysis of the changes in laboratory variables when DVT detected

Compared the levels of laboratory variables in patients with DVT between the time on admission and the time when DVT detected, the level of D-dimer when DVT detected was significantly increased than that on admission (P < 0.001) (Table 3).
Table 3
Comparison laboratory variables in different time

|                          | At admission | At Time when DVT detected | p-value |
|--------------------------|--------------|----------------------------|---------|
| Platelet (10^9/L, mean ± sd) | 182 ± 50.5   | 172 ± 30.5                 | 0.483   |
| RDW(%,mean ± sd)          | 13.7 ± 2.1   | 13.9 ± 4.9                 | 0.658   |
| LDL (mmol/L, mean ± sd)   | 1.9 ± 1.2    | 1.8 ± 1.3                  | 0.337   |
| D-dimer(mg/L, mean ± sd)  | 3.1 ± 5.3    | 13.6 ± 1.7                 | < 0.001 |
| Fbg(mg/L, mean ± sd)      | 2.5 ± 1.1    | 2.8 ± 0.9                  | 0.198   |

Abbreviations: DVT = Deep Vein Thrombosis, RDW = Red blood cell volume distribution width

Discussion

Risk factors for DVT in patients after acute stroke varied in different clinical researches. The typical factors included older age, medical history of DVT, increased body mass index (BMI), malignant tumor, pulmonary infection, increased level of some laboratory variables (9–13). In our study, pulmonary infection and increased muscle tone were identified as independent factors associated with in-hospital incidence of DVT in patients after acute stroke.

In our multiple logistic regression model, patients with pulmonary infection experienced an increased risk of DVT. A higher risky relevance of pulmonary infection with DVT was also demonstrated in other researches (14, 15). A research on the psychiatric inpatients revealed that the average in-hospital incidence of DVT was up to 10%, while the DVT risk in the group with pulmonary infection was significantly increased (16). In addition, a clinical case review showed that patients died secondary to staphylococcal community-acquired pneumonia had higher risk of DVT (14). Research clarified that some pathogens, especially bacteria had surface proteins and exotoxins leading to damaging endothelial cells, activating coagulation pathway and forming micro-thrombosis and DVT (17).

Immobility was a major risk factor for DVT in neurological diseases (4, 18). An observational research analyzed 542 stroke patients with DVT and found that DVT occurred in 73% of patients with weaker muscle strength while only 11% of patients with stronger were diagnosed with DVT (19). Our study showed that there was no difference in muscle strength between DVT-group and non-DVT group. The difference could be partly explained by the different samples and subtypes of the patients. In our study, ischemic stroke accounted for 77.2%, while others were hemorrhagic stroke patients. Some researches on different subtypes of stroke clarified that patients with hemorrhagic stroke had significantly higher risk of DVT due to lower rate of antithrombotic management and more severe neurological disability in patients with hemorrhagic stroke compared with patients with ischemic stroke (20).
Although muscle strength was not linked with DVT in our study, muscle tone was identified as a negative relevant factor with the incidence of DVT and patients with increased muscle tone were less likely to developing DVT. Among patients with stroke, increased muscle tone and muscle spasms of lower extremities usually develop gradually within several months (21), which theoretically resulted in emptying of veins in lower extremities by enhancing the capability of the calf muscle pump. Previous studies observed some vascular changes with a generalized atrophy of the arteries and decreased blood flow in the paralyzed lower extremities, which could adjust the lower oxygen supply to match the decreased activity of the paralyzed muscles (22). With blood stasis reduced in extremities, the risk of DVT was decreased. Moreover, clinical observations suggested that increased muscle tone was a protective factor against DVT in neurological disorders (19, 23). Increased muscle tone in stroke patients at the initial stage indicated the gradual emergence of active exercise, which could lead to increase the cerebral blood flow in the injured site and promote the recovery of motor function and intelligence, resulting in blood flow velocity of hemiplegic extremities increased and the occurrence of DVT decreased (24, 25).

Interestingly, we compared the laboratory variables in different times and found that the level of D-dimer was significantly higher when DVT detected than that on admission, which suggested that dynamically testing D-dimer could be a predictive method for DVT. D-dimer as a sensitive marker for thrombus formation, was an indicator for predicting DVT in different disorders (12, 15, 26). In the current studies, D-dimer demonstrated a sensitivity of 85%-95% and a specificity of 25%-50% for DVT (27, 28). Baseline levels of D-dimer varied in different age due to variability in the inflammatory and immune response dependent on age (29) and the elders were more likely to suffering from stroke, which could explain why the specificity of a standard D-dimer cut-off at 500ug/L for DVT prediction in elderly patients with stroke was comparatively low. A systemic review indicated that utility of an age-adjusted D-dimer cut-off (patient’s age*10)ug/L) for elderly patients for ruling out DVT was recommended (30). The average levels of D-dimer when DVT detected were about 4-fold as the levels of that on admission in our study, which suggested that the gradually increased level of d-dimer was associated with DVT.

The strength of this study is that it concludes that pulmonary infection as a risk factor and increased muscle tone as a protector factor for DVT, which enables physicians to take early managements to reduce the incidence of DVT such as paying more attention to the patients with pulmonary infection and taking more effective therapies to improve muscle tone of patients. In addition, the significant change in level of D-dimer could be a warning for DVT occurrence so that dynamically monitoring the level of D-dimer is of importance in patients after stroke.

There were some limitations. First, due to relatively small samples, we didn’t divide the cohort into several subtypes groups such as ischemic stroke, hemorrhagic stroke and traumatic brain injury. Further study with larger samples and more subtypes needs to be explored. Second, because it was a retrospective research, the time when DVT detected by CDUS might be delayed compared to the actual time when DVT developed. Further prospective research should be performed to validate our conclusions. Moreover, bias couldn’t be avoided. Caution should be needed while our findings is interpreted in other multiple-center cohort studies. Third, although venography was the gold standard for diagnosing DVT, serial
compression ultrasonography as the reference test was applied in our study for detecting DVT owing to its non-invasiveness. It might be not as perfectly accurate as venography.

**Conclusion**

Pulmonary infection as a risk factor and increased muscle tone as a protector factor for DVT were identified in patients after acute stroke and the significant change in level of D-dimer could be a warning for DVT occurrence.

**List Of Abbreviations**

DVT=deep vein thrombosis, LOS=length of stay, NIHSS =National Institutes of Health Stroke Scale, GCS=Glasgow Coma Scale, MRS=Modified Rankin Scale, RDW=red blood cell volume distribution width, LDL=low density lipoprotein, Fbg=fibrinogen, CDUS=color doppler ultrasonography, IQR= interquartile range, OR=Odds Ratio, BMI=body mass index

**Declarations**

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**Ethics approval and consent to participate**

Ethics approval was provided by the Medical Ethics Committee of Changsha central Hospital. Due to the nature of retrospective study, informed consent was waived.

**Availability of data and materials**

Datasets used and/or analyzed in the present study were availed by the corresponding author on reasonable request.

**Author contributions**
The manuscript writing and patient's data recording were done by Yucai Huang and Ning Ding. Kun Song, Wen Peng and Yang Zhou assisted in information collection. Changluo Li and Ning Ding analyzed and interpreted the patients' general indices. The final manuscript was read and ratified by all authors.

**Disclosure Statement**

There are no real or apparent conflicts of interest to disclose.

**Consent for publication**

Not applicable

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Figures
Figure 1

Flow chart for patients enrollment and study design.
Figure 2

Comparison muscle tone between DVT and non-DVT groups (10% vs 67.8%, P=0.002)

| muscle tone increased | DVT group | non-DVT group |
|-----------------------|-----------|---------------|
|                       | 2         | 38            |

Figure 3

Comparison the time between when DVT detected and when muscle tone increased (17.7 vs 9.9, P<0.001)