The Incidence and Characteristics of Venous Thromboembolism in Neurocritical Care Patients: A Prospective Observational Study

Ping Zhang, MD1, Yi Bian, MD2, Feng Xu, MD1, Lifei Lian, MD1, Suiqiang Zhu, MD, PhD1, Zhouping Tang, MD, PhD1, and Furong Wang, MD, PhD1

Abstract
Risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is presumed to be high for neurologic intensive care unit (NICU) patients. However, exact incidences of VTE have yet to be reported. In this prospective observational study, we consecutively enrolled 126 neurocritical care patients who had an NICU stay ≥ 1 week with paralysis and/or unconsciousness. All patients received DVT prevention strategies. Patients were screened for VTE after 1 week of hospitalization, using venous ultrasonography and computed tomography pulmonary angiography. Following 1 week of NICU hospitalization, DVT incidence was 35.7% and PE incidence was 17.5%. Of the DVTs, 75.6% were in the muscular calf vein. Of the PEs, 22.7% were in main pulmonary arteries, while 77.3% were in branches. Approximately 96% of the DVTs and 86% of the PEs were asymptomatic. Approximately 24% of patients with DVT had a concurrent PE, while 50% of PE patients had a DVT. Paralysis, raised D-dimer on admission, and pulmonary infection were found to be independent risk factors for DVT. Paraplegia, femoral vein thrombosis, and pulmonary infection were found to be independent risk factors for PE. Despite active preventive measures, incidences of VTE in NICU patients were high. Most VTEs were asymptomatic, meaning they could have led to a missed diagnosis. Attention should be paid to the VTE events of critically ill neurological patients.

Keywords
neurologic intensive care unit, venous thromboembolism, deep vein thrombosis, pulmonary embolism

Date received: 3 December 2019; revised: 13 January 2020; accepted: 29 January 2020.

Introduction
Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common problem associated with both significant morbidity and mortality. With an estimated annual incidence of 1 to 4 per 1000 persons,1-4 VTE is a leading cause of cardiovascular death.5 Patients admitted to intensive care units (ICUs) are at high risk of VTE. Incidences of DVT and PE in adult ICU patients have been reported to be 20 per 1000 patients,6 although this number does not take into account undiagnosed or asymptomatic VTEs. Patients in neurologic intensive care units (NICUs) tend to be bedridden and to have long-term stays, while many have varying degrees of paralysis and coma. The risk of VTE in NICU patients is presumed to be high. Blood stasis caused by paralysis and prolonged coma may be the main cause for this. Additionally, endothelial dysfunction and clotting system abnormalities, which may be a result of cerebrovascular diseases, malignancies, or inflammatory diseases of the nervous system, also contribute to the high risk of VTE.7 However, exact incidences of DVT and PE in adult NICU patients have not yet been reported.

In 2016, the Neurocritical Care Society (NCS) announced evidence-based guidelines concerning VTE prophylaxis for neurocritical care patients. This was the first statement to...
provide guidance about VTE, specifically for NICU patients. Nevertheless, many points of this guideline are not yet supported by solid and high-quality evidence. Thus, it is crucial to investigate the incidence and characteristics of VTE in adult NICU patients.

Therefore, in this study, we aimed to investigate the incidence and characteristics of VTE—including DVT and PE—in NICU patients as well as to determine risk factors for VTE in these patients.

Patients and Methods

Study Design and Setting

Patients admitted to the NICU of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China, between April 1, 2018, and January 31, 2019, were enrolled in this prospective observational study. The NICU has 18 beds for neurological patients who are critically ill. Patients with brain trauma are not routinely accepted. This study is aligned with the principles of the 1964 Declaration of Helsinki and its later amendments and was approved by the institutional review board of the hospital (no. TJ-IRB20180702). All patients (or their relatives) gave written informed consent.

Study Population

Consecutive patients who met both of the following criteria were included: (1) length of NICU stay ≥1 week and (2) being bedridden due to paralysis and/or unconsciousness ≥1 week. Exclusion criteria were as follows: (1) unstable vital signs, (2) unable to wean from mechanical ventilation, (3) renal insufficiency, (4) hypersensitivity to iodinated contrast media, (5) patient or relatives could not give informed consent, and (6) study examinations could not be completed for any reason.

All participants received positive DVT prevention measures, including intermittent pneumatic compression (IPC) and passive limb exercises. Regarding those critically ill patients who were immobile due to neurologic injury, the plan for chemical DVT prophylaxis was determined based on the NCS who were immobile due to neurologic injury, the plan for passive limb exercises. Regarding those critically ill patients (6) study examinations could not be completed for any reason. Patient or relatives could not give informed consent, and (4) hypersensitivity to iodinated contrast media, (3) renal insufficiency, (2) unable to wean from mechanical ventilation, (1) unstable vital signs, (5) patient or relatives could not give informed consent, and (6) study examinations could not be completed for any reason.

All participants received positive DVT prevention measures, including intermittent pneumatic compression (IPC) and passive limb exercises. Regarding those critically ill patients who were immobile due to neurologic injury, the plan for chemical DVT prophylaxis was determined based on the NCS who were immobile due to neurologic injury, the plan for passive limb exercises. Regarding those critically ill patients (6) study examinations could not be completed for any reason. Patient or relatives could not give informed consent, and (4) hypersensitivity to iodinated contrast media, (3) renal insufficiency, (2) unable to wean from mechanical ventilation, (1) unstable vital signs, (5) patient or relatives could not give informed consent, and (6) study examinations could not be completed for any reason.

Data Collection

The following information was collected from medical records: sex, age, date of admission, primary diagnosis, comorbidities and complications, degree of paralysis, Glasgow Coma Scale (GCS) score, plasma homocysteine level, serum d-dimer levels both on admission and after 1 week of NICU hospitalization, treatments, and prognosis. Assessment and grading of VTE risk was carried out using the Caprini scoring system. In this system, 0 to 1 indicates low risk, 2 moderate risk, 3 to 4 higher risk, and 5 or more highest risk of VTE.

Measurements of DVT and PE

Patients were screened for VTE on days 7 to 10 of hospitalization. The symptoms of DVT such as limb swelling and pain were observed and recorded. Color Doppler venous ultrasonography of the extremities was used for DVT diagnosis. Patients were also observed for respiratory and circulatory signs of a PE. Computed tomography pulmonary angiography (CTPA) was used for PE diagnosis.

Statistical Analysis

Measurement data are expressed as mean ± standard deviation, while enumeration data are expressed as count and percentage. In the univariate analysis of risk factors, Student t test was used to evaluate measurement data, while Pearson χ² test, Continuity Correction, or Fisher exact test was used for analysis of enumeration data. Variables with a value of P < .1 were included in the multivariate analysis. Logistic regression (enter method) was applied for multivariate analysis, where P < .1 indicated statistical significance. All analyses were performed using SPSS version 19.0 software (2010, IBM SPSS Statistics for Windows, IBM Corp, Armonk, New York).

Results

Patient General Characteristics

A total of 126 NICU patients were included in this study. Mean patient age was 54 years (range: 16-90) and there were 85 males and 41 females. The most common admission diagnoses were intracerebral hemorrhage (ICH), ischemic stroke, and intracranial infection. Ninety-one (72.2%) patients developed 1 or more complications during their NICU stay. Sixty-five (51.6%) had comorbidities, which were primarily chronic diseases. Most (83.3%) patients had varying degrees of paralysis, with coma being commonly presented. The GCS score of patients ranged from 5 to 15, with a mean of 11. Based on GCS score, 24.6% of patients had severe coma (GCS 3-8). Caprini scores ranged from 1 to 15, with a mean of 9. Approximately 95% of patients had a Caprini score ≥3. Patient data are summarized in Table 1.

Deep Vein Thrombosis

After 1 week of NICU hospitalization, the use of ultrasonography revealed DVT in 45 patients, meaning DVT incidence was 35.7%. Approximately 76% of the DVTs were located in the muscular calf vein, while 11% were in the femoral vein and 2% in the iliac vein (iliofemoral DVT). Other veins in which DVT was located included superficial femoral, posterior tibial, fibular, popliteal, internal jugular, subclavian, axillary, and brachial. Approximately 13% of DVTs were related to central venous catheterization. It is noteworthy that just 2 DVT patients had symptoms such as limb swelling and pain. The
other 95.6% were asymptomatic. Some 24.4% of DVT patients had a concurrent PE. The characteristics of DVT are summarized in Table 2.

### Pulmonary Embolism

After 1 week of NICU hospitalization, PE was diagnosed in 22 patients by CTPA, meaning there was an incidence of 17.5%.

Some 22.7% of PEs were located in the main pulmonary arteries, while the rest (77.3%) were in the pulmonary artery branches. Similar to the DVTs, most PEs (86.4%) were asymptomatic; only 3 (13.6%) patients presented with respiratory system and/or circulatory system symptoms, including dyspnea, hypoxemia, and severe arrhythmia. Of the PE patients, 50% had a concurrent DVT. The characteristics of PE are listed in Table 2.

### Venous Thromboembolism in Severe ICH Patients

Intracerebral hemorrhage patients are at high risk of VTE. Treating ICH patients with a VTE is complex as anticoagulant therapy increases the risk of recurrent bleeding and hematoma enlargement. Therefore, a subgroup analysis of ICH patients was carried out. There were 57 severe ICH patients in the study, with a mean age of 55 years and a male to female ratio of 40:17. Among these, 59.6% (34/57) of the hematomas were located in the basal ganglia or lobes, while 21.1% (12/57) were in the brainstem, 12.3% (7/57) were in the ventricular system, 5.3% (3/57) were in the cerebellum, and 1.8% (1/57) were in the subdural space. More than half of the ICH patients underwent

---

**Table 1. Patient General Characteristics.**

| Variables                  | Patients |
|----------------------------|----------|
| Age, years                 | 54 (16-90) |
| Ratio, male/female         | 85/41    |
| Admission diagnosis, n (%) |          |
| ICH                        | 57 (45.2) |
| Ischemic stroke            | 39 (31.0) |
| Intracranial infection     | 17 (13.5) |
| Ischemic hypoxic cerebropathy | 3 (2.4)  |
| GBS                        | 2 (1.6)  |
| SAH                        | 2 (1.6)  |
| Status epilepticus         | 2 (1.6)  |
| Multiple system atrophy    | 1 (0.8)  |
| CVST                       | 1 (0.8)  |
| TBI                        | 1 (0.8)  |
| MG                         | 1 (0.8)  |
| Complications, n (%)       |          |
| Pulmonary infection        | 81 (64.3) |
| Epilepsy                   | 7 (5.6)  |
| Gastrointestinal bleeding  | 13 (10.3) |
| Electrolyte imbalance      | 7 (5.6)  |
| MODS                       | 4 (3.2)  |
| Angitis                    | 6 (4.8)  |
| Others                     | 23 (18.3) |
| Comorbidities, n (%)       |          |
| Hypertension               | 55 (43.7) |
| Atrial fibrillation/flutter| 5 (4.0)  |
| Diabetes                   | 11 (8.7) |
| Hepatitis B                | 7 (5.6)  |
| Coronary heart disease     | 4 (3.2)  |
| COPD                       | 5 (4.0)  |
| Paralysis, n (%)           |          |
| Hemiplegia                 | 61 (48.4) |
| Quadriplegia               | 30 (23.8) |
| Quadriaparesis             | 11 (8.7) |
| Paraplegia                 | 3 (2.4)  |
| GCS score, n (%)           |          |
| 9-15                       | 95 (75.4) |
| 3-8                        | 31 (24.6) |
| Caprini score, n (%)       |          |
| 0-2                        | 6 (4.8)  |
| ≥3                         | 120 (95.2) |
| Plasma HCY, n (%)          |          |
| Normal                     | 83 (65.9) |
| Hyperhomocysteinemia       | 43 (34.1) |
| NICU mortality, n (%)      | 2 (1.6)  |

**Table 2. Incidence and Characteristics of Deep Venous Thrombosis and Pulmonary Embolism at 1 Week of Neurologic Intensive Care Unit Hospitalization.**

| Variables                          | Patients |
|------------------------------------|----------|
| DVT incidence at 1 week            | 45/126 (35.7%) |
| Location of DVT                    |          |
| Femoral vein                       | 5/45 (11.1%) |
| Iliac vein                         | 1/45 (2.2%) |
| Superficial femoral vein           | 1/45 (2.2%) |
| Posterior tibial vein              | 3/45 (6.7%) |
| Fibular vein                       | 1/45 (2.2%) |
| Popliteal vein                     | 1/45 (2.2%) |
| Muscular calf vein                 | 34/45 (75.6%) |
| Internal jugular vein              | 1/45 (2.2%) |
| Subclavian vein                    | 1/45 (2.2%) |
| Axillary vein                      | 2/45 (4.4%) |
| Brachial vein                      | 3/45 (6.7%) |
| Central venous catheter            | 6/45 (13.3%) |
| Symptoms of DVT                    |          |
| Symptomatic                        | 2/45 (4.4%) |
| Asymptomatic                       | 43/45 (95.6%) |
| Concurrent with PE                 |          |
| With PE                            | 11/45 (24.4%) |
| Without PE                         | 34/45 (75.6%) |
| PE incidence at 1 week             | 22/126 (17.5%) |
| Location of PE                     |          |
| Main pulmonary artery              | 5/22 (22.7%) |
| Pulmonary artery branch            | 17/22 (77.3%) |
| Symptoms of PE                     |          |
| Symptomatic                        | 3/22 (13.6%) |
| Asymptomatic                       | 19/22 (86.4%) |
| Concurrent with DVT                |          |
| With DVT                           | 11/22 (50.0%) |
| Without DVT                        | 11/22 (50.0%) |

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism.

---

Some 22.7% of PEs were located in the main pulmonary arteries, while the rest (77.3%) were in the pulmonary artery branches. Similar to the DVTs, most PEs (86.4%) were asymptomatic; only 3 (13.6%) patients presented with respiratory system and/or circulatory system symptoms, including dyspnea, hypoxemia, and severe arrhythmia. Of the PE patients, 50% had a concurrent DVT. The characteristics of PE are listed in Table 2.
surgery, including microinvasive craniopuncture therapy (52.6%), ventricular drainage (7.0%), and craniotomy evacuation of the hematoma (3.5%).

In this subgroup, DVT incidence at 1 week was 31.6% (18/57), with 77.8% (14/18) of DVTs located in the muscular calf vein. Other locations were the femoral (11.1%), superficial femoral (5.6%), posterior tibial (11.1%), popliteal (5.6%), internal jugular (5.6%), and brachial (5.6%) veins. Most (88.9%) DVTs were asymptomatic. Of the 18 patients with a DVT, 5 (27.8%) had a concurrent PE.

After 1 week of NICU hospitalization, PE incidence in severe ICH patients was 12.3% (7/57). Approximately 14% of the PEs were in the main pulmonary arteries, while the remainder (85.7%) were in the pulmonary artery branches. Only 1 patient with PE presented with dyspnea and cardiac arrest; all others were asymptomatic. Approximately 71% of the PE patients also had a DVT.

**Risk Factors for VTE**

Results of the univariate analysis of DVT risk factors are summarized in Table 3. Demographic data and the distribution of most variables were similar in patients with and without a DVT. The percent of patients with paralysis, raised d-dimer on admission, and pulmonary infection were significantly higher in the DVT group than in those without a DVT. In the multivariate logistic regression analysis, paralysis, raised d-dimer on admission, and pulmonary infection were found to be independent risk factors for DVT in NICU patients (Table 4).

In the univariate analysis of PE risk factors, percent of patients with paraplegia, femoral vein thrombosis, posterior tibial vein thrombosis, and pulmonary infection were significantly higher in the PE group (Table 5). Use of multivariate logistic regression analysis revealed that paraplegia, femoral vein thrombosis, and pulmonary infection were independent risk factors for PE in NICU patients (Table 6).

**Discussion**

Patients with neurological conditions such as paralysis and unconsciousness, especially those hospitalized in the NICU, have multiple VTE risk factors. Authors of previous studies have shown that DVT incidence in stroke patients is as high as 30% to 40%,9 which is higher than for general surgical patients and similar to patients receiving knee or hip arthroplasty.10 This is the first prospective observational study to report incidences of DVT and PE in a single-center NICU. According to our results, VTE incidence in NICU patients after 1 week of hospitalization is very high (35.7% with DVT and 17.5% with PE).

Diagnosis of DVT is usually informed by clinical symptoms and venous ultrasonography. Typical symptoms include swelling and pain in affected limbs, tortuous dilation of superficial veins, and Homan sign. Since coma and aphasia are common in NICU patients, the lack of self-reported symptoms contributed to the very low proportion of symptomatic DVTs in this study. Thus, venous ultrasonography, which is noninvasive, repeatable, and accurate, is necessary for DVT diagnosis. Ultrasound

---

**Table 3. Univariate Analysis of Risk Factors of Deep Venous Thrombosis.**

| Variables                        | DVT (+), n = 45 | DVT (-), n = 81 | P Value |
|----------------------------------|----------------|----------------|---------|
| Male sex                         | 27 (60.0%)     | 58 (71.6%)     | .183    |
| Age ≥ 60                         | 17 (37.8%)     | 26 (32.1%)     | .519    |
| ICH                              | 18 (40.0%)     | 39 (48.1%)     | .379    |
| Ischemic stroke                  | 13 (28.9%)     | 26 (32.1%)     | .709    |
| Intracranial infection           | 7 (15.6%)      | 10 (12.3%)     | .613    |
| Complications and comorbidities  | 38 (84.4%)     | 69 (85.2%)     | .911    |
| Paralysis                        | 41 (91.1%)     | 62 (76.5%)     | .043    |
| Hemiplegia                       | 19 (42.2%)     | 42 (51.9%)     | .300    |
| Quadriplegia                     | 14 (31.1%)     | 16 (19.8%)     | .151    |
| Quadriaparesis                   | 5 (11.1%)      | 6 (7.4%)       | .707    |
| Paraplegia                       | 3 (6.7%)       | 0 (0%)         | .081    |
| Severe coma (GCS ≤ 8)            | 13 (28.9%)     | 18 (22.2%)     | .405    |
| Caprini score ≥ 3                | 43 (95.6%)     | 77 (95.1%)     | 1.000   |
| Caprini score ≥ 5                | 40 (88.9%)     | 72 (88.9%)     | 1.000   |
| Caprini score ≥ 9                | 23 (51.1%)     | 43 (53.1%)     | .832    |
| Hyperhomocysteinemia             | 15 (33.3%)     | 28 (34.6%)     | .889    |
| Raised d-dimer at admission      | 41 (91.1%)     | 62 (76.5%)     | .043    |
| Raised d-dimer at 1 week         | 43 (95.6%)     | 77 (95.1%)     | 1.000   |
| Symptomatic of DVT               | 2 (4.4%)       | 0 (0%)         | .126    |
| Complications                    | 37 (82.2%)     | 54 (66.7%)     | .062    |
| Pulmonary infection              | 35 (77.8%)     | 46 (56.8%)     | .018    |
| Tracheotomy                      | 6 (13.3%)      | 7 (8.6%)       | .600    |
| Epilepsy                         | 3 (6.7%)       | 4 (4.9%)       | 1.000   |
| Gastrointestinal bleeding        | 5 (11.1%)      | 8 (9.9%)       | 1.000   |
| Electrolyte imbalance            | 5 (11.1%)      | 2 (2.5%)       | .105    |
| MODS                             | 1 (2.2%)       | 3 (3.7%)       | 1.000   |
| Others                           | 10 (22.2%)     | 13 (16.0%)     | .390    |
| Comorbidities                    | 21 (46.7%)     | 44 (54.3%)     | .410    |
| Hypertension                     | 19 (42.2%)     | 36 (44.4%)     | .810    |
| Atrial fibrillation/flutter       | 2 (4.4%)       | 3 (3.7%)       | 1.000   |
| Diabetes                         | 4 (8.9%)       | 7 (8.6%)       | 1.000   |
| Hepatitis B                      | 1 (2.2%)       | 6 (7.4%)       | .417    |
| Coronary heart disease           | 2 (4.4%)       | 2 (2.5%)       | .940    |
| Age                              | 56 (71.5%)     | 53.4 ± 13.7    | .271    |
| GCS score                        | 11.3 ± 3.4     | 11.5 ± 2.8     | .812    |
| Caprini score                    | 8.7 ± 3.1      | 8.5 ± 2.9      | .821    |
| Plasma HCY                       | 14.9 ± 6.0     | 16.3 ± 12.2    | .479    |
| d-Dimer at admission             | 6.3 ± 11.8     | 5.5 ± 15.3     | .780    |
| d-Dimer at 1 week                | 4.4 ± 8.6      | 4.1 ± 9.0      | .880    |

**Table 4. Multivariate Logistic Regression Analysis of Risk Factors of Deep Vein Thrombosis.**

| Variables                        | P Value | OR (95% CI)  |
|----------------------------------|---------|--------------|
| Paralysis                        | .055    | 3.162 (0.976-10.236) |
| Raised d-dimer at admission      | .090    | 2.785 (0.852-9.106)  |
| Pulmonary infection              | .058    | 2.290 (0.972-5.395)  |

**Abbreviations:** DVT, deep venous thrombosis; GCS, Glasgow Coma Scale; HCY, homocysteine; ICH, intracerebral hemorrhage; MODS, multiple organ dysfunction syndrome.
Table 5. Univariate Analysis of Risk Factors of Pulmonary Embolism.

| Variables                        | PE (+) | PE (-) | P  |
|----------------------------------|--------|--------|----|
| Age ≥ 60                         | 7 (31.8%) | 36 (34.6%) | .802 |
| ICH                              | 7 (31.8%) | 50 (48.1%) | .164 |
| Ischemic stroke                  | 7 (31.8%) | 32 (30.8%) | .923 |
| Intracranial infection           | 5 (22.7%) | 12 (11.5%) | .293 |
| Complications and comorbidities  | 20 (90.9%) | 87 (83.7%) | .388 |
| Paralysis                        | 17 (77.3%) | 86 (82.7%) | .769 |
| Hemiplegia                       | 6 (27.3%) | 55 (52.9%) | .029 |
| Quadruplegia                     | 8 (36.4%) | 22 (21.2%) | .128 |
| Quadriplegia                     | 2 (9.1%) | 9 (8.7%) | 1.000 |
| Paraplegia                       | 2 (9.1%) | 12 (11.5%) | .079 |
| Severe coma (GCS ≤ 8)            | 6 (27.3%) | 25 (24.0%) | .749 |
| Caprini score ≥ 3                | 21 (95.5%) | 99 (95.2%) | .125 |
| Caprini score ≥ 5                | 17 (77.3%) | 95 (91.3%) | .125 |
| Caprini score ≥ 9                | 12 (54.5%) | 54 (51.9%) | .823 |
| Hyperhomocysteinemia             | 9 (40.9%) | 34 (32.7%) | .293 |
| Raised d-dimer at admission      | 20 (90.9%) | 83 (79.8%) | .357 |
| Raised d-dimer at 1 week         | 21 (95.5%) | 99 (95.2%) | .958 |
| Symptomatic of DVT               | 1 (4.5%) | 1 (1.0%) | .320 |
| DVT (+)                          | 11 (50.0%) | 34 (32.7%) | .124 |
| Trunk of deep vein               | 3 (13.6%) | 9 (8.7%) | .746 |
| Branch of deep vein              | 8 (36.4%) | 25 (24.0%) | .232 |
| Femoral vein                     | 3 (13.6%) | 2 (1.9%) | .037 |
| Iliac vein                       | 0 (0.0%) | 1 (1.0%) | 1.000 |
| Superficial femoral vein         | 0 (0.0%) | 1 (1.0%) | 1.000 |
| Posterior tibial vein            | 2 (9.1%) | 1 (1.0%) | .079 |
| Fibular vein                     | 0 (0.0%) | 1 (1.0%) | 1.000 |
| Popliteal vein                   | 1 (4.5%) | 0 (0.0%) | .175 |
| Muscular calf vein               | 8 (36.4%) | 26 (25%) | .275 |
| Internal jugular vein            | 0 (0.0%) | 1 (1.0%) | 1.000 |
| Subclavian vein                  | 0 (0.0%) | 1 (1.0%) | 1.000 |
| Axillary vein                    | 0 (0.0%) | 2 (1.9%) | 1.000 |
| Brachial vein                    | 0 (0.0%) | 3 (2.9%) | 1.000 |
| Central venous catheter          | 2 (9.1%) | 4 (3.8%) | .618 |
| Complications                    | 19 (86.4%) | 72 (69.2%) | .103 |
| Pulmonary infection              | 18 (81.8%) | 63 (60.6%) | .059 |
| Tracheotomy                      | 1 (4.5%) | 12 (11.5%) | .553 |
| Epilepsy                         | 3 (13.6%) | 4 (3.8%) | .191 |
| Gastrointestinal bleeding        | 2 (9.1%) | 11 (10.6%) | 1.000 |
| Electrolyte imbalance            | 0 (0.0%) | 7 (6.7%) | .459 |
| MODS                             | 1 (4.5%) | 3 (2.9%) | .541 |
| Others                           | 1 (4.5%) | 21 (21.2%) | .126 |
| Comorbidities                    | 9 (40.9%) | 56 (53.8%) | .270 |
| Hypertension                     | 8 (36.4%) | 47 (45.2%) | .448 |
| Atrial fibrillation/flutter       | 1 (4.5%) | 4 (3.8%) | .100 |
| Diabetes                         | 3 (13.6%) | 7 (7.7%) | .630 |
| Hepatitis B                      | 1 (4.5%) | 6 (5.8%) | 1.000 |
| Coronary heart disease           | 0 (0.0%) | 4 (3.8%) | 1.000 |
| COPD                             | 0 (0.0%) | 5 (4.8%) | .586 |
| Age                              | 55.4 ± 10.8 | 54.1 ± 13.6 | .681 |
| GCS score                        | 10.9 ± 3.1 | 11.5 ± 3.0 | .347 |
| Caprini score                    | 8.3 ± 3.5 | 8.6 ± 2.8 | .635 |
| Plasma HCY                       | 16.8 ± 8.1 | 15.5 ± 10.9 | .604 |
| d-Dimer at admission             | 12.2 ± 23.1 | 4.4 ± 11.0 | .018 |
| d-Dimer at 1 week                | 7.3 ± 11.0 | 3.6 ± 8.2 | .074 |

Abbreviations: COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; GCS, Glasgow Coma Scale; HCY, homocysteine; ICH, intracerebral hemorrhage; MODS, multiple organ dysfunction syndrome; PE, pulmonary embolism.

Table 6. Multivariate Logistic Regression Analysis of Risk Factors of Pulmonary Embolism.

| Variables                        | P Value | OR (95% CI) |
|----------------------------------|---------|-------------|
| Paraplegia                       | .084    | 11.099 (0.726-169.604) |
| Femoral vein thrombosis          | .031    | 9.570 (1.235-74.150)   |
| Pulmonary infection              | .066    | 3.241 (0.927-11.332)   |

Abbreviations: CI, confidence interval; OR, odds ratio.

Pulmonary embolism is one of the leading causes of sudden death in acute stroke patients. However, PE can easily be misdiagnosed. A low-risk PE, defined as an acute PE with the absence of the clinical markers of adverse prognosis which define massive or submassive PE, can be asymptomatic or only lead to mild symptoms, which can be misdiagnosed as a severe pulmonary infection. In our study, 86.4% of PE patients had no definite symptoms, and diagnosis was made by CTPA. Compared to venous ultrasonography, CTPA is not routinely performed unless there is a strong suspicion of PE. This might be why screening with CTPA resulted in a much higher incidence of PE than in previous studies. In our study, 77.3% of PEs occurred in the pulmonary artery branches. Patients did not have any clinical symptoms and were labeled as low-risk PE. Although relatively “low risk,” these PEs are still at high risk of developing into a massive or submassive PE. In the current study, 24.4% of DVT patients had a PE, indicating that DVT patients are at high risk of developing PE. In contrast, 50% of PE patients had a DVT, reminding us that only screening for a PE in DVT patients may lead to missed diagnosis.

In a subgroup analysis of severe ICH patients, the incidence and characteristics of DVT and PE at 1 week of hospitalization were similar to the whole NICU group. The NCS VTE prophylaxis guidelines recommend use of IPC and/or graduated elastic compression stockings for severe ICH patients severe ICH. They also suggest “using prophylactic doses of subcutaneous unfractionated heparin or LMWH to prevent VTE in patients with stable hematomas and no ongoing coagulopathy, starting within 48 hours after hospital admission.” However, this recommendation is only supported by a small number of low-quality studies. The safety of anticoagulant in ICH patients...
as well as its most suitable time, drug, and dose has always been controversial.20 Thus, compliance with VTE prevention in the real world is insufficient. Authors of a study investigating nationwide trends of DVT prophylaxis after ICH in the United States reported that fewer than 20% of patients received anticoagulation, and the time of initiation was less than 48 hours in fewer than 50%.21 In our study, LMWH was used for VTE patients with stable hematomas and no active bleeding. Neither extension of hematomas nor increased mortality was observed.

Both paralysis and pulmonary infection are independent risk factors for DVT and PE in NICU patients. Paralysis is commonly seen in patients with neurological diseases, while pulmonary infection is a ubiquitous complication of ICU patients. It has been suggested that ventilator-associated pneumonia occurs in as many as 30% of ICU patients requiring mechanical ventilation.22 D-Dimer is an important exclusion indicator for VTE.23 However, an elevated d-dimer level was detected in more than 90% of NICU patients in this study, indicating a relatively low specificity. It should be noted that the Caprini scoring system did not have a predictive value for VTE in the NICU patients. According to the Caprini score, more than 95% of patients were at higher/highest risk of VTE, thus revealing a weak distinguishing ability. The Caprini risk assessment model was established and validated with general surgery patients, with no critically ill patients included.24,25 Therefore, an appropriate VTE risk assessment tool is needed for neurocritical care patients.

Our study has several limitations. First, it is a single-centered observational study with a limited sample size. Second, selection bias exists due to the disease spectrum of patients in our NICU. Traumatic brain injury patients are not routinely admitted to our neurology ICU. Third, some unstable and critically ill patients were not included, as per the exclusion criteria. Thus, the true incidence of PE may be underevaluated. Fourth, due to the complicated disease condition and contraindications as well as differing opinions of the attending neurologists, the strategy for chemical DVT prophylaxis was highly individualized. Finally, for patients who were unable to undergo CTPA, other diagnostic methods for PE, such as ventilation-perfusion scan and transesophageal echocardiography, were not carried out.

Conclusions

Our study is the first to include incidences of DVT and PE in a single-center NICU. Even with preventative measures, VTE incidence in these NICU is very high. Most VTEs are asymptomatic, which could lead to a missed diagnosis. Researchers should pay attention to VTE events in critically ill neurological patients.

Authors’ Note

This study complied with the principles of the 1964 Declaration of Helsinki and its later amendments, and was approved by the institutional review board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (no. TJ-IRB20180702). All patients (or relatives) provided written informed consent.

Acknowledgments

The authors thank all the included patients and their families, physicians, nurses, paramedics, and all staff.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Natural Science Foundation of China (grant nos. 81671064 and 81371222) and the Hubei Provincial Natural Science Foundation of China (grant no. 2018CFB115).

ORCID iD

Furong Wang https://orcid.org/0000-0001-8693-7301

References

1. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(23 suppl 1):I4-I8.
2. McRae S. Treatment options for venous thromboembolism: lessons learnt from clinical trials. Thromb J. 2014;12(1):27.
3. Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. Am J Hematol. 2011;86(2):217-220.
4. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98(4): 756-764.
5. Goldhaber SZ. Evolving concepts in thrombolytic therapy for pulmonary embolism. Chest. 1992;101(4 suppl):183S-185S.
6. Patel R, Cook DJ, Meade MO, et al. Burden of illness in venous thromboembolism in critical care: a multicenter observational study. J Crit Care. 2005;20(4):341-347.
7. Nyquist P, Bautista C, Jichici D, et al. Prophylaxis of venous thrombosis in neurocritical care patients: an evidence-based guideline: a statement for healthcare professionals from the Neurocritical Care Society. Neurocrit Care. 2016;24(1):47-60.
8. Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA Jr, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg. 2010;251(2):344-350.
9. Turpie AG. Prophylaxis of venous thromboembolism in stroke patients. Semin Thromb Hemost. 1997;23(2):155-157.
10. Kelly J, Rudd T, Lewis RR, Hunt BJ. Mortality from pulmonary embolism after acute stroke: can we do better? Age Ageing. 2002;31(3):159-161.
11. Galanaud JP, Sevestre MA, Genty C, et al. Comparison of the clinical history of symptomatic isolated muscular calf vein thrombosis versus deep calf vein thrombosis. J Vasc Surg. 2010;52(4):932-938, 938 e931-932.
12. Gillet JL, Perrin MR, Allaert FA. Short-term and mid-term outcome of isolated symptomatic muscular calf vein thrombosis. J Vasc Surg. 2007;46(3):513-519. discussion 519.
13. Kret MR, Liem TK, Mitchell EL, Landry GJ, Moneta GL. Isolated calf muscular vein thrombosis is associated with pulmonary embolism and a high incidence of additional ipsilateral and contralateral deep venous thrombosis. J Vasc Surg Venous Lymphat Disord. 2013;1(1):33-38.
14. Lautz TB, Abbas F, Walsh SJ, et al. Isolated gastrocnemius and soleal vein thrombosis: should these patients receive therapeutic anticoagulation? Ann Surg. 2010;251(4):735-742.
15. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123(16):1788-1830.
16. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 1991;54(5):466-467.
17. Orken DN, Kenangil G, Ozkurt H, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. Neurologist. 2009;15(6):329-331.
18. Wasay M, Khan S, Zaki KS, et al. A non-randomized study of safety and efficacy of heparin for DVT prophylaxis in intracerebral haemorrhage. J Pak Med Assoc. 2008;58(7):362-364.
19. Tetri S, Hakala J, Juvela S, et al. Safety of low-dose subcutaneous enoxaparin for the prevention of venous thromboembolism after primary intracerebral haemorrhage. Thromb Res. 2008;123(2):206-212.
20. Paciaroni M, Agnelli G, Venti M, Alberti A, Acciarresi M, Caso V. Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: a meta-analysis of controlled studies. J Thromb Haemost. 2011;9(5):893-898.
21. Prabhakaran S, Herbers P, Khoury J, et al. Is prophylactic anticoagulation for deep venous thrombosis common practice after intracerebral hemorrhage? Stroke. 2015;46(2):369-375.
22. Wallace FA, Alexander PD, Spencer C, Naisbitt J, Moore JA, McGrath BA. A comparison of ventilator-associated pneumonia rates determined by different scoring systems in four intensive care units in the North West of England. Anaesthesia. 2015;70(11):1274-1280.
23. Iorio A, Douketis JD. Ruling out DVT using the Wells rule and a D-dimer test. BMJ. 2014;348:g1637.
24. Pannucci CJ, Barta RJ, Portschy PR, et al. Assessment of post-operative venous thromboembolism risk in plastic surgery patients using the 2005 and 2010 Caprini risk score. Plast Reconstr Surg. 2012;130(2):343-353.
25. Pannucci CJ, Bailey SH, Dreszer G, et al. Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. J Am Coll Surg. 2011;212(1):105-112.