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

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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 $\geq$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

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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

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provide guidance about VTE, specifically for NICU patients.[7] 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 $\geq$1 week and (2) being bedridden due to paralysis and/or unconsciousness $\geq$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 VTE prophylaxis guideline.[7] Considering the associated risk from bleeding due to standard VTE prophylaxis and existing bleeding contraindications (such as stress ulcer bleeding or hemorrhagic conversion of strokes), individualized timing and administration of chemical DVT prophylaxis via subcutaneous low-molecular-weight heparin (LMWH) was determined by a clinical team of trained neurologists.

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.[8] 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 $\pm$ 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 χ^2 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 regression) 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 $\geq$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

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)
Angiitis	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)
Quadriparesis	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)
$\geq$3	120 (95.2)
Plasma HCY, n (%)	
Normal	83 (65.9)
Hyperhomocysteinemia	43 (34.1)
NICU mortality, n (%)	2 (1.6)

Abbreviations: COPD, chronic obstructive pulmonary disease; CVST, cerebral venous sinus thrombosis; GBS, Guillain-Barre syndrome; GCS, Glasgow Coma Scale; HCY, homocysteine; ICH, intracerebral hemorrhage; MG, myasthenia gravis; MODS, multiple organ dysfunction syndrome; NICU, neurologic intensive care unit; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

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%.

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.

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

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
Quadriparesis	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	56.1 ± 12.0	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

Abbreviations: DVT, deep venous thrombosis; GCS, Glasgow Coma Scale; HCY, homocysteine; ICH, intracerebral hemorrhage; MODS, multiple organ dysfunction syndrome.

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: CI, confidence interval; OR, odds ratio.

Table 5. Univariate Analysis of Risk Factors of Pulmonary Embolism.

Variables	PE (+), n = 22	PE (−), n = 104	*P* Value
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
Quadriplegia	8 (36.4%)	22 (21.2%)	.128
Quadriparesis	2 (9.1%)	9 (8.7%)	1.000
Paraplegia	2 (9.1%)	1 (1.0%)	.079
Severe coma (GCS ≤ 8)	6 (27.3%)	25 (24.0%)	.749
Caprini score ≥3	21 (95.5%)	99 (95.2%)	1.000
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%)	.460
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%)	22 (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%)	1.000
Diabetes	3 (13.6%)	8 (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.

examination should extend from the proximal deep vein trunk to the distal branches in order to avoid a missed diagnosis. In our study, more than 75% of DVTs occurred in the muscular calf veins. Muscular calf vein thrombosis (MCVT) is considered a peripheral type of DVT. The thrombus forms and locates in the venous plexus of the gastrocnemius and soleus. Authors have previously reported that calf vein thrombosis accounted for 50% of all DVTs in the lower extremities, while MCVT accounted for 50% of the calf vein thrombosis.[11] In our study with NICU patients, the proportion of MCVT was much higher. Muscular calf vein thrombosis can further extend into the deep vein trunk and so form a more severe DVT. Additionally, they are a common source of pulmonary thrombosis.[12-14] In our study, 31.8% of PEs were associated with isolated MCVT.

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,[15] 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.[6] 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.[7] 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."[7] However, this recommendation is only supported by a small number of low-quality studies.[16-19] 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.

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Declaration of Conflicting Interests

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