Original Article

Incidence and Predictive Factors of Lower Extremity Deep-vein Thrombosis in Patients with Neurological Diseases in a Sub-Saharan Tertiary Hospital

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Abstract

Background: Deep-vein thrombosis (DVT) is a major cause of morbidity among patients with neurological disease and is implicated in 50%–90% of pulmonary embolisms (PE). **Aim:** This study aims to identify the incidence and predictive factors of lower extremity (LE) DVT in high-risk neurological patients. **Materials and Methods:** All patients with neurological diseases who were confined to bed for three days or more, or had elevated D-dimer over a 22 months were included in the study. They all had routine mechanical and chemical prophylaxis. Serial color duplex ultrasonography of the LE was performed for all the patients, and the results were used to stratify them into two groups: DVT positive and DVT negative, and their clinical parameters were recorded and utilised for statistical analysis. Multivariate logistic regression analysis was used to determine the predictive risk factors. **Results:** A total of 611 patients were admitted, and 107 met the inclusion criteria. The mean age was 57 ± 17 years, with a male-to-female ratio of 1.7:1. Forty-four (41.4%) patients had DVT (overall incidence was 7.2%). Primary intracranial tumours and craniocerebral trauma accounted for 27.2% and 20.5% of aetiology, respectively. The comparative DVT-positive versus DVT-negative group D-dimer levels were 7.9 versus 4.9 mg/L (P = 0.0065), duration of immobility 65.0 versus 35.3 days (P = 0.0001), and length of hospital (LOH) stay 32.5 versus 18.2 days (P = 0.0001). The proximal LE vessels were involved in 64.2%. The PE risk was 0.98%, with three mortalities. The predictive factors on multivariate logistic regression were elevated D-dimers (odds ratio [OR] 2.02, 95% confidence interval [CI] 1.1–4.45 P = 0.030) and preoperative immobility >seven days ([OR] 2.38, 95% [CL] 1.28–4.39 P = 0.042). Gender, C-reactive protein, Glasgow Coma Scale, comorbidities, LOH, and chronic steroid use were not predictive. **Conclusion:** The overall incidence of DVT and mortality from PE were low among patients with neurological diseases. Most thrombi involved proximal LE veins. Elevated D-dimers and preoperative immobility >seven days were predictive factors for LE DVT.

Keywords: D-dimers, deep-vein thrombosis, lower extremity, Memfys hospital, predictive factors

Introduction

Deep-vein thrombosis (DVT) is a major cause of morbidity in patients with neurological diseases and is reported to be associated with up to 50%–90% of pulmonary embolisms (PE).[1,2] The inherent peculiarities of central nervous system diseases predispose them to a high risk of venous thromboembolism (VTE).[3-6]

The incidence of DVT is estimated to be over 550,000 yearly in the USA and contributes significantly to the financial burden of inpatient care.[5,7,8] There is a paucity of data on the incidence of DVT in Sub-Saharan Africa and more so in high-risk patients with neurological disease.

The current standard for diagnosis of DVT is duplex ultrasonography, which detects the presence of thrombus through direct interrogation of the lower limb veins.[9] The findings are incomplete compression of the vein or absence of flow, which is diagnostic of DVT and has a sensitivity of

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How to cite this article: Campbell FC, Ajare EC, Ndukuba KO, Okwunodulu O, Hart I, Nnama SS, *et al*. Incidence and predictive factors of lower extremity deep-vein thrombosis in patients with neurological diseases in a sub-Saharan Tertiary Hospital. Niger J Med 2023;32:382-7.

Submitted: 31-Jul-2023 **Revised:** 07-Oct-2023
Accepted: 21-Oct-2023 **Published:** 08-Dec-2023

Access this article online

Quick Response Code:

Website: http://journals.lww.com/NJOM

DOI: 10.4103/NJM.NJM_81_23

96.5% and 71.2% for proximal and distal LE DVT respectively and an overall specificity of 94.0.[1,9]

In addition, the serum D-dimers is useful screening tool for VTE with sensitivity and specificity of 99.4% and 38.2%, respectively, at a serum level of 0.5 mg/L.[1,10] It is a breakdown product of blood clots and is commonly elevated in DVT and PE. In high-risk patients, it is recommended that regular screening with serum D-dimers be routinely done and followed by a duplex scan in the subgroup with elevated levels.[11]

Various factors that increase the patient's risk of DVT and PE have been studied.[12-14] Notably are advanced age, presence of intracranial tumours (especially glioma and meningioma), immobility, unconscious state, and prolonged hospital stay. However, their predictive value for DVT are variable and largely inconclusive, and may vary between race and geographical location.[5,12]

Furthermore, despite multimodal prevention strategies, including mechanical and pharmacological methods, many patients with neurologic pathologies still develop DVT and catastrophic PE, negatively impacting outcomes.[6,14] Therefore, identifying the early predictive factors that may facilitate early diagnosis and treatment is imperative.

This study aims to determine lower extremity (LE) DVT incidence and predictive factors among patients with neurological diseases managed in Memfys Hospital, Enugu, Nigeria.

Materials and Methods

This retrospective observational study was conducted in Memfys Hospital, a private Hospital in Enugu, and referral centre for managing major neurologic and neurosurgical diseases in southeast Nigeria. Relevant information of patients admitted over the study period between January 2020 and October 2021 were retrieved from the inhospital database after obtaining ethical clearance from the institutional review board. We included all patients with neurological diseases with elevated D-dimers (>0.5 mg/L) or were confined to bed for three days or more. All patients had serial color duplex ultrasonography (CDUS) of the LE. Exclusion criteria include patients with incomplete medical records and age <18. In addition, patients with previous LE DVT or a history of coagulation disorders or atrial fibrillation which may be confounding were excluded from the study. Figure 1 shows a flow chart depicting the recruitment method and exclusion criteria.

According to Memfys Hospital protocol, while on admission, they all had routine mechanical prophylaxis with compressive stockings and intermittent pneumatic compression till discharge. Patients who had surgical intervention were commenced on chemical prophylaxis (subcutaneous enoxaparin 40 IU daily) 48–72 h postoperatively.

Patients with ischemic stroke and other neurologic diseases were commenced on chemical prophylaxis according to the hospital protocol on the day of admission; however, this was delayed until 48–72 h in patients with hemorrhagic stroke. Patients diagnosed with DVT were treated using the American Society of Haematology guidelines for the management of VTE.[15]

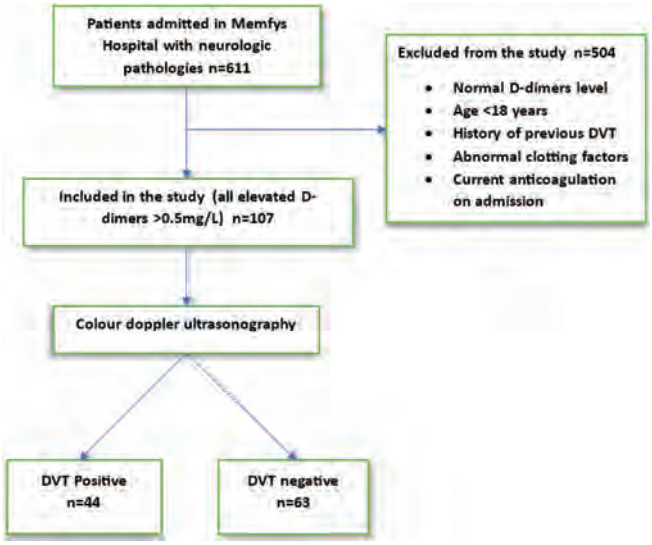

Figure 1: Flow chart showing patient recruitment

The recruited patients were divided into two groups: those with LE venous thrombus confirmed by CDUS as the DVT-positive group and those without thrombus as the DVT-negative group. The patients' clinical parameters, including age, sex, comorbid illness, hospital stay, duration of preoperative immobility, Glasgow coma score, steroid use, C-reactive protein (CRP), serum D-dimer levels, and type of surgery, were analysed.

D-dimer estimation was performed with an ichroma™ machine manufactured by Boditech© Medical incorporated in Korea. Internal and external quality control was done periodically as recommended by the manufacturer. Doppler ultrasonography of the LE using the GE vivid ultrasound machine with a 7.5 Hz linear transducer was performed by the same radiology team [Figure 2]. The iliac, common femoral, superficial, and deep-femoral veins were classified as proximal LE veins, whereas the popliteal, tibial, fibula, and soleal veins were distal vessels. The veins that displayed lack of flow or demonstrated thrombus, evidenced by incomplete compressibility, were flagged as containing DVT and recorded. The cohort with positive DVT had serial CDUS until the resolution of DVT was confirmed. Each patient was counted once, irrespective of the number of positive CDUS performed.

Statistical analysis

Results were presented as mean ± standard deviation and frequencies (%) for continuous and categorical variables. Similarly, a Chi-squared/Fisher's test or independent Student's *t*-test was used to compare the categorical and continuous variables respectively. Multivariate logistic regression analysis was performed to determine the independent risk factors for DVT in both the DVT and non-DVT groups. All *P* values were

two-sided. $P < 0.05$ was considered statistically significant. All analyses were performed by IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA).

Results

Over the study period, 611 patients with neurological diseases were admitted of which 107 met the inclusion criteria and were included in the analysis [Figure 1].

The mean age was 57 ± 17 years, with a male-to-female ratio 1.7:1. Forty-eight (44.8%) patients had comorbidities, with hypertension accounting for 69.1%. There was no statistically significant difference between the presence of comorbidity and the risk of LE DVT in the study ($P = 0.694$) [Table 1].

The incidence of DVT among the study population was 41.1%; however, the overall incidence among all admitted patients was 7.2%. The proximal LE vessels were involved in 64.2%, with the femoral veins accounting for 60.2% of the DVT. There was an almost equal distribution of DVT between the left and right lower limbs, whereas five patients had bilateral DVT [Figure 3]. In addition, clinical features suggestive of DVT were seen in 23.5% of patients with Doppler-confirmed DVT.

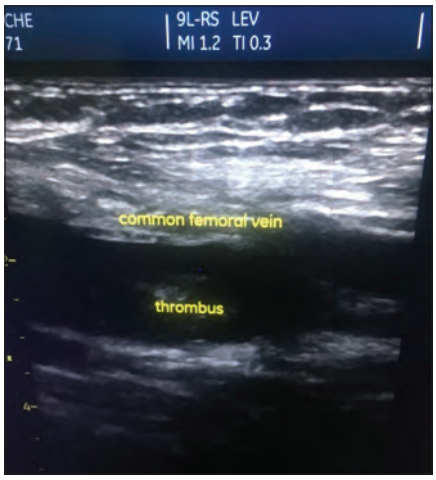

Figure 2: Doppler ultrasound image demonstrating the left common femoral vein with a thrombus. The vessel was poorly compressible

The diagnosis of patients with LE DVT is shown in Table 2. Intracranial tumours (meningioma and glioma accounting for 63.6%) and craniocerebral trauma accounted for 47.8% of the LE DVT recorded in the study.

Comparing the biochemical and clinical parameters of both groups, the D-dimer level, duration of immobility, and length of hospital (LOH) stay showed statistical significance [Table 2]. Other parameters tested, including age, sex, presence of comorbidity, chronic steroid use (more than one month), CRP, and Glasgow Coma Scale (GCS), were not statistically significant risk factors for lower limb DVT and were not predictive on logistic regression [Tables 2 and 3]. In addition, high D-dimer level >5 mg/L and duration of immobility >seven days were predictive factors for LE DVT using multivariate logistic regression analysis [Table 3].

Six patients had clinically suspected PE; however, only three were confirmed with computed tomography pulmonary angiography. There were three mortalities from suspected PE, with a mortality rate of 2.8% in the high-risk cohorts. In addition, the overall PE risk was 0.98%.

Discussion

Central nervous system pathologies are most often associated with variable decrease in mobility and primary or secondary hypercoagulable state, which increase the risk of developing VTE according to Virchow's triad.[6,16] This results in significant morbidity and negatively impacts patient outcomes.

Table 1: Comparison of clinical/biochemical factors between deep-vein thrombosis positive and deep-vein thrombosis negative groups

Clinical variable	Total	DVT positive	DVT negative	*t*-score/χ^2	*P*
Sex, *n* (%)					
Male	68 (100)	25 (36.8)	43 (62.2)	1.463	0.307
Female	39 (100)	19 (48.7)	20 (51.3)		
Comorbidity, *n* (%)					
Yes	48 (100)	21 (43.7)	27 (56.3)	0.248	0.694
No	59 (100)	23 (38.9)	36 (61.0)		
Chronic steroid use, *n* (%)					
Yes	13 (100)	8 (61.5)	5 (38.5)	2.548	0.138
No	94 (100)	36 (38.3)	58 (61.7)		
Age (years)	58.4±17.1	61.4±17.5	55.5±16.7	1.7631	0.0808
D-dimers (mg/L)	6.4±5.6	7.9±6.6	4.9±4.5	2.778	0.0065*
CRP (mg/L)	100.9±95.6	118.0±82.8	83.8±108.5	1.262	0.2125
Duration of immobility (days)	50.2±14.5	65.0±22.8	35.3±6.1	9.582	0.0001*
LOH (days)	25.35±4.1	32.5±5.6	18.2±2.6	17.739	0.0001*
GCS score	13.25±1.6	13.5±1.5	13.0±2.0	1.404	0.163

*Statistically significant $P<0.05$. DVT: Deep-vein thrombosis, CRP: C-reactive protein, GCS: Glasgow Coma Scale, LOH: Length of hospital

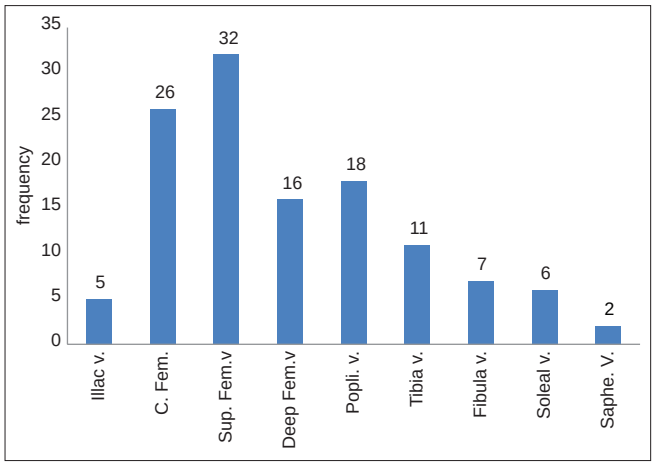

Figure 3: Anatomic distribution of lower limb deep-vein thrombosis. Most clots involved the proximal lower extremity vessels(64.2%)

A combination of chemical and mechanical prophylaxis is currently recommended as the standard of care to prevent DVT and PE, although a significant proportion of patients still develop these complications despite all preventive strategies.[6,17,18] Early identification of relevant predictive factors may enable prompt diagnosis, intervention, and possibly improved outcomes. To the best of our knowledge, this is the first study in the subregion that evaluated the incidence and predictive factors of LE DVT among patients with neurological diseases.

The overall risk of DVT in this study was 7.2% and falls within the reported incidence of 1.7%–34% in patients with neurological diseases.[4,6,12,14,19] Henwood *et al*.[20] and Rethinasamy *et al*.[4] reported overall DVT incidence of 9.7% and 10.3%, respectively, with both studies having similar methodology as this index study. On the contrary, a very low incidence of 1.7% was reported in a large-scale multicentre study involving over a million patients extracted from the American College of Surgeons' neurosurgical database for cranial and spinal procedures.[12] Indeed, the study population, methodologies, and means of diagnosis could explain the wide discrepancies in the reported incidence.

Considering the high risk of DVT in neurosurgical patients, regular clinical and radiological surveillance, biochemical testing, and proactive treatment are advocated to reduce associated morbidity and mortality. Unfortunately, positive clinical features are poor markers of VTE.[21] Only one in four patients with thrombus demonstrated by CDUS in our series had clinical features suggestive of DVT. This aligns with the literature which suggests the use of more sensitive and specific biochemical markers like D-dimers or interval LE Doppler ultrasound to detect DVT reliably, especially in high-risk patients.[10,11,20,22] There was no relationship found in the study between the presence of comorbidities and the occurrence of DVT and PE. This is at variance with increased risk noted in patients with cardiopulmonary diseases, obesity, diabetes, and renal diseases.[8,23]

Table 2: Diagnosis of the patients with lower extremity deep-vein thrombosis

Diagnosis	Frequency, *n* (%)
Craniocerebral trauma	9 (20.5)
Rupture intracranial aneurysm	6 (13.6)
Primary intracranial tumours	12 (27.3)
Ischemic stroke	8 (18.2)
Hemorrhagic stroke	3 (6.8)
Others	6 (13.6)
Total	44 (100)

Table 3: Multivariate logistic regression analysis of variables in both groups

Clinical variable	*n*	OR	95% CI	*P*
Age	107	2.70	0.29–25.23	0.384
D-dimers >5 mg/L	107	2.02	1.09–4.45	0.030*
CRP	107	1.509	0.16–14.08	0.718
LOH	107	1.35	0.82–22.06	0.781
Duration of immobility >seven days	107	2.38	1.28–4.39	0.042*
Chronic steroid use	107	0.69	0.44–1.09	0.190
Comorbidity	107	1.12	0.50–2.49	0.781

*Statistically significant $P<0.05$. CRP: C-reactive protein, OR: Odds radio, CI: Confidence interval, LOH: Length of hospital

The predictive value for DVT increases with higher values of D-dimer.[1,10] However, the threshold D-dimer level that serves as the minimum benchmark to predict DVT is unclear.[1,4,10,24,25] Ma *et al*.[24] and Prell *et al*.[25] in their studies opined that values of 1.08 mg/L and ≥2 mg/L were predictive of the presence of DVT, whereas others advocated for an even greater value as the cutoff predictive D-dimer level at the cost of larger false negativity.[4] A low cutoff value (≥0.5 mg/L) was utilised in this study to increase the sensitivity and minimise the false negative rate.

In this study, more than two-thirds of the thrombus involved the proximal LE veins (the iliac, common femoral, superficial, and deep-femoral veins). These thrombi are more dangerous as they are often clinically silent compared to calf thrombus, usually of larger size and solid consistency and are more prone to embolisation. There is no clear definition of the proximal and distal LE DVT cutoff point, and their prevalence varies in the literature.[9,22,24,26,27] El-Menyar *et al*. reported proximal LE vein involvement in 95% of their retrospective analysis.[26] They also noted that proximal DVT was more associated with polytrauma, prolonged hospitalisation, immobility, major surgery, and malignancy. In contrast to their findings, Ouriel *et al*. noted more distal LE DVT in their series; however, they utilised LE contrast venogram, which is known to be more sensitive in identifying the calf and foot thrombus.[27]

Intracranial tumours and craniocerebral trauma were the most common underlying pathology among the high-risk cohort with LE DVT in this study, which is in tandem with most literature reports.[5,28,29] This may be related to the increased production of

tissue factor and tissue factor-bearing micropeptides commonly elaborated by brain tumours or following trauma. These potent procoagulants possess platelet aggregation activity capable of initiating and propagating thrombus through the extrinsic pathway.[5,29]

PE is a significant cause of death in patients with neurological diseases, and incidence varies based on the diagnostic modality employed.[6,8,12,28] Six of our patients had clinically suspected PE; however, only three were confirmed with computed tomography pulmonary angiography. The cardiopulmonary collapse in PE is often rapid, and it may be impossible to perform a diagnostic investigation before the patient's demise. The overall PE risk was 0.98% among our patient population, and the mortality rate was 2.8% among the high-risk cohorts with elevated D-dimers. Some studies have reported PE as the cause of mortality in up to 8.4% of patients with brain tumours autopsy series.[30,31]

It was noted that only D-dimer levels >5 mg/L and long duration of immobility were predictive of LE DVT among all the factors evaluated using multivariate logistic regression analysis. The patient's age, sex, comorbidities, GCS score, long-term steroid use, and LOH stay were not predictive. A similar study indicated that hypertension, high postoperative D dimer level, female sex, and lower GCS (score < 5) were independently associated with LE DVT after brain and spine surgery.[14] Rolston *et al*. found ventilator dependence, immobility, chronic steroid use, malignancy, and sepsis as independent predictors in the analysis of more than a million patients.[12] Although predictive risk factors differ between various studies, this nonuniformity may be related to variability in study methodology, statistical models utilised in the analysis, clinical diagnosis, and observer bias. However, the presence of malignancy, immobility, sepsis, and high D-dimer levels were commonly reported predictive risk factors in these studies.[1,12-14,24] It is imperative to have high surveillance for these factors and initiate prompt definitive investigation and early treatment to reduce morbidity and improve outcomes.

Conclusion

The overall incidence of DVT and mortality from PE seemed low among patients with neurological diseases in this study. In addition, most thrombi involved the proximal LE vessels. Elevated D-dimers and preoperative immobility >seven days were predictive factors independently associated with LE DVT. We advocate surveillance of these factors in patients with central nervous system diseases to enable early detection and prompt intervention to reduce morbidity and improve overall outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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