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Full-Length Research Article

Assessment of Some Genetic Thrombophilias in Nigerian Patients with Venous Thromboembolism

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Summary: Venous thromboembolism (VTE) is a leading cause of mortality globally, resulting from genetic risk factors and/or acquired risk factors like oral contraceptives, smoking, diabetes, immobilization, cancer, trauma, fracture, and surgical procedures. This study aims to assess the involvement and prevalence of some genetic thrombophilias in Nigerian VTE patients. A total of 107 participants were recruited, comprising 67 individuals with VTE from three tertiary hospitals in Southwest Nigeria and 50 apparently healthy controls. Parameters included the absolute platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, protein C, protein S, and antithrombin levels. The VTE patients had significantly lower mean platelet counts, protein C and S antigenic concentrations, and protein S activity ($p<0.05$), with elevated mean PT and D-dimer levels ($p<0.05$). Protein C antigen and activity levels were reduced in 6.8% and 2.5% of participants, respectively, indicating deficiencies, while protein S antigen and activity were reduced in 1.7% and 0.9%. One (0.9%) participant had reduced antithrombin III level. Seven participants with protein S or C deficiencies experienced recurrent thrombosis. The study identifies type I antithrombin III deficiency and types I and II protein C and S deficiencies as genetic risk factors for VTE. The prolonged PT and elevated D-dimer levels observed in this study challenged the assumption of consistently reduced PT in VTE patients.

Keywords*: Genetic thrombophilia, protein C and S deficiency, Protein S deficiency, antithrombin deficiency, venous thromboembolism.*

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INTRODUCTION

Venous thromboembolism account for a notable incidence of thrombotic complication with genetic and/or acquired risk factors leading to an increasing yearly mortality rate of a 1 in 2 deaths per 1000 individual worldwide (Horner & Mahan, 2017; Wendelboe & Raskob, 2018). Genetic or inherited thrombophilias primarily result from inheritance of genetic mutations; they include antithrombin deficiency, protein C or S deficiency, factor V Leiden mutation (activated protein C resistance), histidine-rich glycoprotein deficiency and prothrombin-related thrombophilia (Dautaj *et al*.,2019), while the secondary (acquired) thrombophilia can be obtained through heparin-induced thrombocytopenia, antiphospholipid antibody syndrome, neoplasia, oral contraceptive use, obesity, smoking and surgery (Dautaj *et al*.,2019). These deficiencies could occur to affect the functionality, concentration of the proteins or both, resulting in their categorization into types based on deficiencies.

Type I protein C deficiency occurs because of reduced level of protein C, while Type II deficiency results from production of an altered molecule with decreasing levels of activity (Gupta & Patibandla, 2023). Type I protein S deficiency is characterized by a quantitative defect that shows low levels of total protein S (TPS) and free protein S (FPS). Type II (also known as type IIb) deficiency occurs when protein S activity is decreased but TPS and FPS antigen levels are normal. Type III (also known as Type IIa) deficiency is characterized by a quantitative defect that shows normal levels of TPS but reduced levels of FPS and protein S activity (Gupta *et al*., 2022). Also, quantitative (type I) or qualitative (type II) antithrombin deficiency is also present. Type II is further classified into two subtypes: type IIa, which is less frequent but more thrombophilic due to mutations in the thrombin-binding site, and type IIb, which is more common but less thrombogenic due to a failure in the heparin-binding region of the AT. There is also a pleiotropic type IIc deficit (Patnaik & Moll,2008).

The precise prevalence of inherited thrombophilia remains a subject of ongoing investigation as new studies continue to emerge, and this prevalence varies among different racial groups. Additionally, the situation is further complicated by the existence of numerous unidentified

genetic abnormalities, contributing to a significant number of unexplained venous thromboembolism (VTE) cases observed in families where no identifiable genetic defects have been identified (Ashraf *et al*., 2019). Pulmonary embolism has been reported to have an estimated annual incidence of two to three cases per 1000 in the United States population with 7-30 % prevalence in autopsy series (Ashraf *et al*., 2019; Turetz *et al*., 2018), 0.2-6.0% in Asia, 0.14%-61.5% in Africa (Danwang *et al*., 2017) all of which results in high mortality rate if left untreated. Furthermore, the incidence of deep venous thrombosis has been reported as 1 in 1000 yearly in United Kingdom and United state of America population with a resulting mortality rate of 5-10% (Siddiquie *et al*., 2018), Asian countries have reported a 0.15-1.35 % incidence rate in post-operative patients with a population –wide incidence of 15-20%, and Africa reporting 2.4-9.6% prevalence across post-operative and pregnant women (Danwang *et al*., 2017; Adeleye and Ogun, 2016). Despite the reported incidence of venous thromboembolic disorders in Nigeria which ranges from 2.4-9.6 % in post-operative cases and 380- 448 cases per 100,000 pregnant women (Adeleye and Ogun, 2016), there has been dearth of information on the existence and prevalence of genetic thrombophilias. These being significant contributors in the recurrence and complication of the thrombotic conditions; hence there is a need for adequate information that will serve as a guide in proper diagnosis and management of the patients which prompted the need for this study.

MATERIALS AND METHODS

Study Design: This is a descriptive-quantitative, cross-sectional study using convenience sampling technique.

Study Population and Sites: A total of 107 individuals participated in this study, including 67 patients with venous thromboembolism (VTE) comprising 61 individuals with deep vein thrombosis (DVT) and six with pulmonary embolism (PE). These patients were recruited with Ethical approvals from the hematology clinics of three tertiary hospitals in Southwest Nigeria: LAUTECH Teaching Hospital, Osogbo (LTH/EC/2019/05/415); University College Hospital, Ibadan (UI/EC/21/0623); and Federal Teaching Hospital, Ido-Ekiti (ERC/2019/02/13/1015). Informed consent was obtained from all participants. Fifty apparently healthy, age- and sex-matched individuals served as controls. Patients with cancer, liver cirrhosis, pregnancy, or those on anticoagulant therapy were excluded from the study.

Sample and Data Collection: Clinical histories were obtained using a pre-tested, structured, interviewer-administered questionnaire. Five millilitres of blood were collected from each participant: 2 ml dispensed in EDTA bottles for platelet count and 3 ml in trisodium citrate vacutainer tubes, which were centrifuged at 2000g for 15 minutes to isolate platelet-poor plasma. Plasma was stored at -20°C in labeled sterile cryovial tubes for assays, including prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, Protein S, Protein C, and Antithrombin III.

Methods: Platelet counts were measured using a Sysmex KX-2IN autoanalyzer (Sysmex, 1999). PT and APTT assays were performed on a Coagulometer (Unitron Bio Medical, India) using Diagen Diagnostic reagents (UK). D-dimer levels were assessed using Tina-Quant D-dimer Gen 2 reagent on a Cobas C111 analyzer (Roche). Protein C, Protein S, and Antithrombin III antigenic assays were conducted using ELISA (Biorex Diagnostic Reagents, UK), with optical density measured at 450 nm using a microtiter plate reader. Blood pressure was measured using the Oscillometric technique by Bakris *et al*. (2016).

Protein S and Protein C Activity Assays: Protein S activity was measured using a clotting-based assay (Biorex Diagnostic, UK). Two millilitres each of Protein S APTT reagent and calcium chloride were prewarmed in a coagulometer (Unitron Bio Medical, India) at 37°C. A 1:10 dilution of the sample in buffer was prepared, and 500 µL was pipetted into a clean test tube. Fifty microliters each of Protein S-deficient plasma, Protein S activator, and prewarmed APTT reagent were sequentially added to each solution, followed by incubation for 3 minutes. Prewarmed calcium chloride (50 µL) was then added, and the clotting time was recorded. Calibration curves provided by the manufacturer were used to derive Protein S activity from the sample time, following the manufacturer's instructions.
For Protein C assay, samples were diluted in imidazole buffer (1:10), and 100 µL of the diluted sample was mixed with 25 µL each of Protein C activator and APTT reagent sequentially. After 3 minutes of incubation at 37°C, 50 µL of calcium chloride was added, and the clotting time recorded. Protein C concentration was calculated using a standard curve per the manufacturer's guidelines.

Antithrombin III Activity Assay: Antithrombin III activity was measured using a chromogenic method with reagents from Coamatic Chromogenix, Diapharma, UK. Plasma was diluted 1:9 in heparin buffer, and 200 µL of the diluted sample was incubated with 200 µL of Factor Xa reagent at 37°C for 90 seconds. Chromogen S-2765 (200 µL) was added, and absorbance was measured spectrophotometrically at 405 nm. Results were read against a standard curve prepared according to manufacturer's instruction to determine antithrombin activity.

Data Analysis: Data were analyzed using IBM SPSS version 25.0. Categorical variables were summarized using frequencies and proportions, while continuous variables were summarized using means and standard deviations. Chi-square tests assessed associations between categorical variables, and t-tests analyzed continuous variables. Statistical significance was determined at $p < 0.05$.

RESULTS

Table 1 represents the demographic features of all the participants; the mean±standard deviation (SD) age for the test subjects and controls is 43.32±15.16 and 40.12±11.41 with a t-value of 1.687 and no significant difference ($p>0.05$) observed among the two groups.

Table 1:
The Sociodemographic Characteristics of the test and control subjects.

Characteristics	Test	Control	X^2 value	p-value	t-value
Age group (years)	**Frequency (%)**	**Frequency (%)**			
≤20	1(1.5)	1 (2)	0.299	0.061	
21-30	5(7.5)	7(14.0)			
31-40	25(37.3)	22(44.0)			
41-50	9(13.4)	11(22.0)			
> 50	27(40.2)	9(18.0)			
Age (mean±SD years)	43.32±15.16	40.12±11.41		0.091	1.687
Blood Pressure (mean±SDmmHg)					
Systolic	123.98±10.10	121.59±8.69		0.061	1.063
Diastolic	80.30±6.39	77.56±4.46		0.001*	3.516
Sex					
Male	34(50.7)	24(48.0)	0.180	0.671	
Female	33(49.2)	26(52.0)			

* Statistically significant at p≤0.05
LTH- LAUTECH Teaching Hospital; UCH- University College Hospital (UCH); FETHI- Federal Teaching Hospital, Ido-Ekiti, Nigeria.

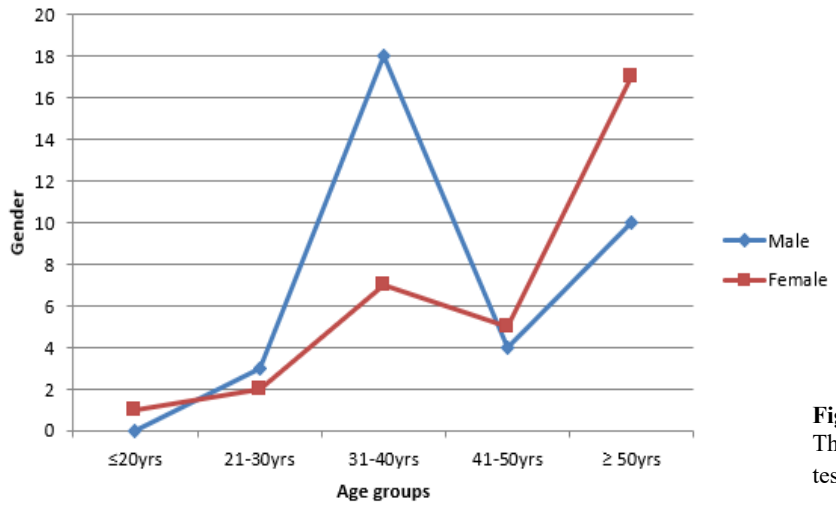

Figure 1:
The age group distribution across the gender of the test and control participants

The distribution of the age group within the test subjects shows participants above fifty years with the highest population frequency followed closely by those in their thirties and those below twenty years with the lowest frequency.
The diastolic blood pressure in the test group is significantly higher than that of the control group ($p<0.05$) while no difference exists in the systolic blood pressure. In addition, the gender frequency in Table 1 revealed no significant difference ($p>0.05$) among the gender when compared across each group of the participants.

Figure 1 displayed line plot of the age group distribution across the gender of the subject participants where the male individuals within age group 31years to 40 years had the significantly highest frequency compared to their female counter parts and other groups ($p<0.05$), they were followed by the female in those above 50 years and the male below 20 years had the lowest frequency.

The case participants portray all the subjects with pulmonary embolism as females, their clinical history showed approximately 3%, 34% and 7% of those with deep venous thrombosis had experienced miscarriage, hypertension and smoking ($p<0.05$) (Figure 2a); while Figure 2b shows 3, 5 and 2 individuals out of the 6 with pulmonary embolism have histories of miscarriage, hypertension and smoking respectively. From the questionnaire administered, all the subjects had history of lower limb pain, none of the female participants was pregnant at the time of sample collection as they tested negative to serum human chorionic gonadotrophin (HCG) antigen test while all those with pulmonary embolism had experienced chest pain at a time.

Table 2 displayed the mean ± SD of all parameters assessed between the test and control participants. In the table the absolute platelet count was significantly lower in the tests than in the control ($p<0.05$) whereas the PCV and APTT were also lower in the test group but not statistically significant ($p>0.05$). The mean ± SD prothrombin time was significantly prolonged in the test subjects, the D-dimer was higher as well in the same group ($p<0.05$). In addition, the mean ± SD protein C and S antigenic concentrations and protein S activity level were significantly reduced in tests compared with the controls ($p<0.05$) while protein C activity level which was also lower in the test was not statistically significant ($p>0.05$). The table further reveals lower values of antithrombin III antigenic and activity level among the tests than the controls but at an insignificant statistical level ($p>0.05$).

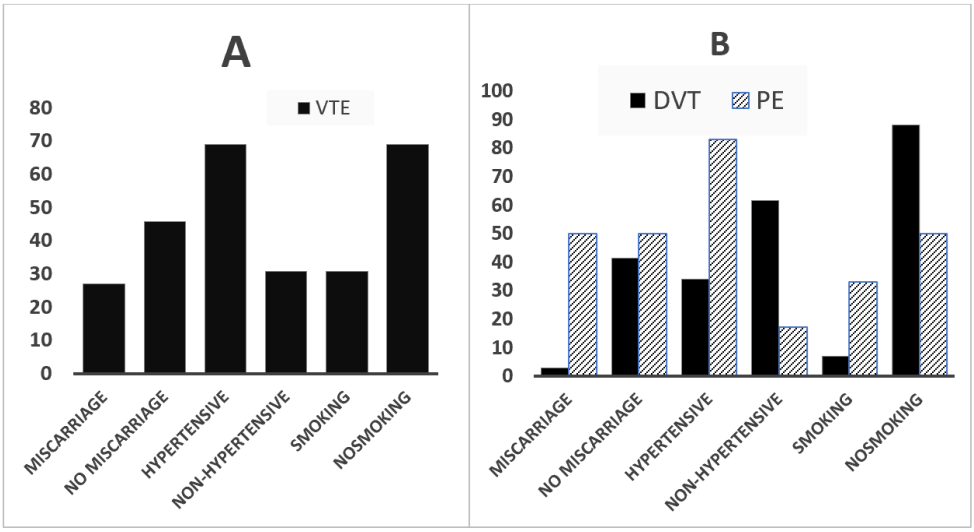

Figure 2:
(a) Distribution by Clinical History of test subjects with Venous Thromboembolism type (b) Distribution by Clinical History of test subjects with Deep Vein thrombosis (DVT) and Pulmonary Embolism (PE)

Table 2:
Mean ± SD of PCV, Absolute platelet count and other basic coagulation parameters in Tests and Controls.

Parameters (Mean ± SD)	Tests	Controls	T -value	p-value
Absolute Platelet Count (X 10^9/L)	196.90±66.40	329.04±93.66	11.509	0.001*
Prothrombin Time (seconds)	21.55±11.82	14.37±3.02	5.880	0.001*
APTT (seconds)	39.85±14.47	41.69±5.18	1.198	0.233
D-dimer (µg FEU/mL)	1.06±0.55	0.41±0.05	11.836	0.001*
Protein C Antigen (ug/ml)	4.19±1.00	4.88±0.51	6.143	0.001*
Protein C Activity (U/ml)	1.32±0.50	1.34±0.30	0.293	0.770
Protein S Antigen (ug/ml)	20.86±6.53	25.60±6.62	5.096	0.001*
Protein S Activity (%)	112.53±22.61	119.93±13.53	2.809	0.005*
Antithrombin III Antigen (g/L)	0.61±0.62	0.65±0.63	0.482	0.630
Antithrombin III Activity (%)	93.65±13.69	97.19±15.55	1.709	0.089

*- Statistically significant at p≤0.05
Mean ± SD – Mean ± Standard deviation; PCV- Packed cell volume; APTT- Activated partial thromboplastin time.

Table 3:
Prevalence of Some Genetic Thrombophilia markers among the test and control participants

	Variable	Tests (%) (n-67)	Controls (%) (n-50)	X^2 value	p-value
Platelet (X10^9/L)	160-400 (Normal)	48(41.0)	50(42.7)	64.471	0.001*
	<160 (Reduced)	19(16.22)	0		
PT (seconds)	14-16 (Normal)	32(27.3)	50(42.7)	53.193	0.001*
	>16 (Prolonged)	27(23.1)	0		
	<14 (Reduced)	8(6.8)	0		
APTT (seconds)	28-41 (Normal)	27(23.1)	49(41.8)	43.690	0.001*
	>41 (Prolonged)	8(6.8)	1(0.9)		
	<41 (Reduced)	32(27.3)			
D-dimer (µgFEU/mL)	<0.48 (Normal)	7(6.0)	50(42.7)	124.832	0.001*
	>0.48 (Increased)	60(51.2)			
Protein C Antigen (ug/ml)	3.9- 4.9 (Normal)	59(50.4)	50.0(42.7)	18.579	0.001*
	<3.9 (Reduced)	8(6.8)	0		
Protein C Activity (U/ml)	0.9-1.33 (Normal)	64(54.6)	50 (42.7)	20.930	0.001*
	<0.9 (Reduced)	3(2.5)	0		
Protein S Antigen (ug/ml)	15-25 (Normal)	65(55.5)	50 (42.7)	5.799	0.055
	<15 (Reduced)	2(1.7)	0		
Protein S Activity (%)	65-120 Normal	66(56.3)	50(42.7)	3.047	0.218
	<65 (Reduced)	1(0.9)	0		
AT III Antigen (g/L)	0.3-0.65 Normal	64(54.6)	50(42.7)	1.005	0.605
	>0.65 (Increased)	2(1.7)	0		
	<0.3 (Reduced)	1(0.9)	0		
AT III Activity (%)	Normal (75-110)	100(100.0)	50(42.7)		

*- Statistically significant at p≤0.05
PT- Prothrombin Time; APTT- Activated partial thromboplastin time, AT III- Antithrombin III.

Some notable results on the prevalence of indicative parameters of genetic thrombophilias in this study indicate a significant difference in the distribution of the test participants when compared with controls ($p<0.05$) in the platelet values, PT, APTT and D-dimer which displayed the prevalence of baseline genetic thrombophilias among the test and control participants (Table 3). The test subjects with reduced absolute platelet count are significantly lesser in distribution and percentage than those with normal platelet values, this occurrence is also observed in the distribution based on PT level where those with reduced values where significantly lower in number than those with prolonged and normal PT values. Test subjects with prolonged PT values (41%) are closer in distribution to those with normal values (47%). However, subjects with prolonged APTT level are significantly lower in distribution than those with reduced and normal values in which the latter groups do not differ excessively amongst themselves. Notably, the D-dimer level is increased in majority of the test subjects with 89% of the entire test population having higher level of the marker.

The protein C and protein S antigen and activity levels all have frequencies and percentages of test participants with reduced values at both significant ($p>0.05$) and insignificant statistical differences ($p<0.05$). Importantly, 6.8% and 2.5% of the entire study population, had reduced protein C antigen and activity levels respectively; while 1.7% and 0.9% had reduced protein S antigen and activity levels. From the population with reduced protein S and C parameters, 7 subjects had recurrent thrombotic condition. Also, antithrombin III antigen assessment had one (0.9%) individual with reduced level while all other participants had normal activity level of the marker.

DISCUSSION

The association of genetic thrombophilias with mortality is often underreported in Africa due to under-diagnosis and limited resources. Despite scarce studies in this region, some have identified these disorders even in unsuspecting populations (Adeyemo *et al*., 2012; Abdi and Osman, 2017). Participants in this study had a mean age above 40 years, reflecting age as a thromboembolism risk factor linked to thickened venous valves with aging (Yusuf *et al*., 2013). While some research suggests venous thromboembolism (VTE) incidence rises after 60 years (Yusuf *et al*., 2013; White *et al*, 2021), others highlight age as a key factor from 40 years onward, especially in younger hospitalized populations17,18. This study observed a high VTE incidence in individuals over 40 years, suggesting an earlier onset in the studied region which is likely influenced by lifestyle, reduced mobility, and genetic factors diminishing fibrinolytic activities.

Notably, males aged 31–40 years formed the largest group, suggesting a higher risk in this age range, potentially linked to lifestyle-related factors. Despite controls for age and sex, no significant differences were noted between genders, possibly due to both experiencing acquired and genetic VTE risk factors. While reproductive hormonal changes have been linked to thromboembolism in females, studies show males may face greater recurrence and severity of thrombotic events (Olié *et al*., 2012; Bamisaye *et al*., 2021; Albertsen *et al*., 2022; Pastori *et al*., 2023) thus aligning with this study where males aged 31–40 years had the highest VTE occurrence.

This study revealed that most participants exhibited normal systolic blood pressure, suggesting there was no significant association identified between elevated systolic blood pressure and the development or severity of VTE in the absence of other risk factors. However, lower systolic blood pressure has been linked to VTE risk, aligning with Virchow's triad, where circulatory stasis triggers endothelial hypoxemia, promoting adhesion molecule expression and activation of the extrinsic coagulation pathway (Ghouse *et al*., 2023). Diastolic blood pressure in our VTE participants was significantly higher than in controls, this is consistent with Anders *et al*. (2010), who associated high diastolic pressures with increased VTE risk. Furthermore, this study found deep venous thrombosis (DVT) as the predominant form of VTE, with pulmonary embolism (PE) observed in 9% of cases, aligning with reports that PE complicates 30-40% of DVT cases (García-Fuster *et al*., 2014; Center for Disease and Control, 2023). The PE cases were associated with smoking and miscarriage histories which emphasizes their role as risk factors. Notably, some DVT cases lacked identifiable risk factors, indicating a potential role of genetic predispositions or other contributors (Ageno *et al*., 2008; Zhang *et al*., 2016; Pastori *et al*., 2023).

The VTE group exhibited significantly reduced mean platelet counts compared to controls ($p<0.05$) which suggests impaired clot formation potentially contributing to the condition. Variable platelet counts in thrombotic crises have been documented in VTE conditions (Di Micco *et al*., 2018; Lim *et al*,2019; Bamisaye *et al*., 2020). Prolonged prothrombin time in the VTE participants indicates clotting factor consumption during thrombotic episodes, while the non-significant APTT difference suggests controlled intrinsic pathway involvement. Elevated D-dimer levels observed reflect active fibrinolysis, though D-dimer are nonspecific markers of various conditions (Wypasek and Undas, 2018; Bamisaye *et al*., 2020).

Protein C and S antigen levels, along with Protein S activity, were significantly reduced in the VTE group. Protein S, in conjunction with protein C, inhibits coagulation; its decreased activity suggests a type II deficiency, disrupting coagulation and elevating VTE risk (Fasola *et al*.,2021).

Notably, this study found that 6.8% and 2.5% of participants exhibited reduced level of protein C antigen and activity, indicating the presence of type I and type II protein C deficiencies in the region. These findings highlight the existence of genetic thrombophilia associated with protein C deficiencies, thereby emphasising the need to investigate specific gene mutations. A case study of a patient with a portal vein thrombus linked to gastro-oesophageal reflux affirmed the presence of type II protein C deficiency in the studied region. Corroborating studies by Okoye *et al*. (2019) found a 29.4% prevalence of the protein C deficiencies which are the type I and 27.35% type II, while Imoru *et al*. (2015) reported 29% among Nigerian women with a history of miscarriage. A Benin Republic study also found a 9.5% prevalence among individuals with venous thrombophilia, challenging prior assumptions of rarity in Africa (Houenassi *et al*., 2011).

Furthermore, the Type I deficiency of protein S was identified in 1.7% of participants, with type II protein S deficiency found in 0.9% which is consistent with previous studies in Nigeria where reduced free protein S has been linked to HIV (44.5%), miscarriages (1.3%), and ischemic stroke (6%) in Black Africans (Bello *et al*., 2021). Contrastingly, a local study reported non-association between deficiencies of protein C and S with preeclampsia, suggesting limited relevance to this condition (Okoye *et al*., 2017).

Additionally, one participant (0.9%) with recurrent venous thrombosis exhibited reduced antithrombin III (AT III) antigen levels, indicating type I deficiency, while all participants showed normal AT III activity levels, ruling out types II and III deficiencies. Similar studies in Nigeria have observed lower antithrombin values in 14% of sickle cell anemia cases and among blood donors (Onyemelukwe and Jibril,1992; Osunkalu *et al*., 2015), supporting the presence of type I AT III deficiency in this region.

In conclusion, this study revealed the prevalence of types I and II protein C as well as protein S deficiencies with type I antithrombin III deficiency which are genetic thrombophilias and genetic risk factors for venous thromboembolism (VTE). The patients often presented with prolonged prothrombin time and elevated D-dimer levels, contradicting assumptions of consistently reduced prothrombin time in VTE cases. Also, VTE occurs irrespective of age or gender in this region. Further research is recommended to identify the specific gene mutations and conduct genomic studies to improve management and treatment strategies which was a limitation of the study.

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Authors' contributions

Conceptualization: E.O.B and E.O.O; Methodology, E.O.B., PO and E.O.O.; Software, E.O.B.; Validation, E.O.B and E.O.O; Formal Analysis, E.O.B. and P.O; Investigation, E.O.B, P.O. and E.O.O; Resources, E.O.O.; Data Curation, E.O.B, P.O. and E.O.O; Writing, Review and Editing, E.O.B, P.O. and E.O.O; Supervision, E.O.O.

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