International Journal of Biomedical and Clinical Research
2026 Volume 6, Issue 5
DOI: 10.59657/2997-6103.brs.26.128

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Research Article

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Evaluation of D-Dimer, Thrombin-Antithrombin Complex, Prothrombin Fragment 1+2, and Factor V Leiden Mutation in Deep Vein Thrombosis Patients Attending Federal Teaching Hospital Owerri

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Abstract

Deep vein thrombosis (DVT) is a prominent part of venous thromboembolism (VTE) and a major cause of death and illness around the world because of problems including pulmonary embolism and post-thrombotic syndrome. D-dimer is commonly employed in the diagnostic assessment of DVT; nevertheless, its restricted specificity necessitates the investigation of supplementary biomarkers that more precisely indicate thrombin production and coagulation activity. The thrombin–antithrombin complex (TAT) and prothrombin fragment 1+2 (F1+2) serve as sensitive markers of active thrombin generation, whereas the Factor V Leiden mutation constitutes a significant hereditary thrombophilia risk factor. Information about the integrated assessment of these markers, especially concerning sex-based correlations, is still scarce in sub-Saharan Africa. This case-control study examined plasma D-dimer, TAT, F1+2, and the prevalence of the Factor V Leiden mutation in DVT patients at Federal Teaching Hospital Owerri. One hundred Doppler-verified DVT patients and one hundred age-matched ostensibly healthy controls were enlisted. We used enzyme-linked immunosorbent assay (ELISA) to find the plasma levels of D-dimer, TAT, and F1+2. We used polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) to find the Factor V Leiden mutation. We used the right parametric and non-parametric tests to do the statistical analyses, and $p < 0.05$ was regarded significant. Patients with DVT had markedly higher concentrations of D-dimer, TAT, and F1+2 in comparison to controls ($p < 0.001$). The average biomarker values in male DVT patients were much greater than those in female DVT patients ($p < 0.05$). The Factor V Leiden mutation was found in 8% of cases and 2% of controls, with a greater rate in men. In patients with DVT, there were positive relationships between sex and biomarker levels. The results show that DVT patients have a lot of coagulation and thrombin production, especially men. The joint examination of biochemical and genetic markers could enhance risk stratification, illness severity assessment, and clinical management of DVT in Nigerian populations.

Keywords: D-dimer; thrombin-antithrombin complex; prothrombin fragment 1+2; factor V Leiden mutation; deep vein thrombosis; Owerri

Introduction

Deep vein thrombosis (DVT) is a prevalent and potentially fatal disorder marked by the development of thrombi within the deep venous system, predominantly in the lower limbs. It is a key sign of venous thromboembolism (VTE) and a major cause of death and disease around the world, especially when it is made worse by pulmonary embolism or chronic post-thrombotic syndrome [1]. In numerous low- and middle-income nations, including Nigeria, the actual prevalence of DVT is probably underestimated owing to insufficient epidemiological data and diagnostic difficulties [2].

Virchow's triad, which includes endothelial damage, venous stasis, and hypercoagulability, is the traditional way to describe how DVT happens. These interconnected pathways result in the overproduction of thrombin and the synthesis of fibrin, ultimately leading to the development of intravascular clots. Duplex Doppler ultrasonography is still the best way to make a diagnosis, although laboratory biomarkers are very important for screening, early identification, risk assessment, and keeping an eye on how well a treatment is working [3].

D-dimer, a breakdown product of cross-linked fibrin, is commonly utilized because it is very good at ruling out DVT. Nevertheless, its specificity is constrained, as heightened levels are noted in various physiological and pathological circumstances, including pregnancy, infection, cancer, trauma, and inflammatory states [4]. As a result, depending only on D-dimer could lead to false positives and further imaging tests. This constraint has led to a growing interest in markers that more directly show how thrombin is made [5].

The thrombin-antithrombin complex (TAT) is made when thrombin binds to its natural inhibitor, antithrombin. This is a very sensitive way to measure thrombin activity in vivo. Prothrombin fragment 1+2 (F1+2) is also released when prothrombin is turned into thrombin, which shows that the coagulation cascade is activated. High levels of TAT and F1+2 mean that thrombin is still being made, which could give doctors useful information about how active and severe the disease is in people with DVT [6].

In addition to acquired risk factors such surgery, immobilization, cancer, and hormonal therapy, hereditary thrombophilia's play a big role in increasing the risk of thrombotic events. The Factor V Leiden mutation (G1691A) causes resistance to activated protein C and makes thrombin levels go up. It is acknowledged as the predominant hereditary thrombophilia within Caucasian demographics [7]. Historically deemed uncommon in African communities, recent findings indicate it may be under acknowledged, especially in individuals with unexplained or recurring thrombosis [8].

Sex-related disparities in thrombotic risk and recurrence have been recorded, with males frequently exhibiting elevated recurrence rates and potentially increased coagulation activation. However, there have been few research in Nigeria that looked at differences in thrombin production indicators and genetic propensity between men and women with DVT [9,10].

Due to the scarcity of local data, this study sought to assess D-dimer, TAT, F1+2, and the Factor V Leiden mutation in Doppler-verified DVT patients at Federal Teaching Hospital Owerri, and to identify sex-related disparities in these biochemical and genetic markers. The results are anticipated to augment comprehension of thrombosis pathogenesis in Nigerian patients and facilitate enhanced diagnostic and risk stratification methodologies.

Materials and Methods

Study Design and Population

This hospital-based case-control study was conducted among adult patients attending the Hematology and Radiology Units of Federal Teaching Hospital Owerri, Nigeria.

A total of 200 participants were enrolled and categorized into two groups:

Cases: One hundred (100) patients with Doppler ultrasonography-confirmed deep vein thrombosis (DVT), comprising 56 males and 44 females.

Controls: One hundred (100) apparently healthy, age-matched individuals without clinical or radiological evidence of DVT, comprising 54 males and 46 females.

Inclusion Criteria

- Adults aged 18-70 years
- First episode of DVT confirmed by Doppler ultrasonography

Exclusion Criteria

- Current or recent anticoagulant therapy
- History of malignancy
- Pregnancy
- Recent surgery
- Acute infection

Ethical Considerations

Ethical approval was obtained from the Federal Teaching Hospital Owerri Ethics Committee. Written informed consent was obtained from all participants prior to enrollment, in accordance with the principles of the Declaration of Helsinki.

Laboratory Methods

Sample Collection and Processing

Five milliliters (5 mL) of venous blood were collected aseptically from each participant into tubes containing 3.2% sodium citrate as anticoagulant. Samples were centrifuged at 3000 rpm for 15 minutes to obtain platelet-poor plasma. The plasma was aliquoted and stored at -80°C until analysis.

Biochemical Assays

Plasma levels of coagulation biomarkers were determined as follows:

D-dimer: Quantitative enzyme-linked immunosorbent assay (ELISA) kit (DRG International Inc., USA).

Thrombin-Antithrombin Complex (TAT): Sandwich ELISA method (Abcam®, Cambridge, UK).

Prothrombin Fragment 1+2 (F1+2): Competitive ELISA method (Siemens Healthineers®, Germany).

All assays were performed according to the manufacturers' instructions, and quality control procedures were strictly adhered to.

Molecular Analysis

Detection of Factor V Leiden mutation (G1691A) was carried out using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique. DNA extraction and amplification were performed using reagents supplied by Thermo Fisher Scientific®, USA. Amplified products were subjected to restriction enzyme digestion and analyzed

by agarose gel electrophoresis for genotype determination.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages. Independent sample t-test was used for comparison of means between two groups. Chi-square test was used to compare categorical variables. Pearson correlation analysis was applied to assess associations between sex and biomarker levels among DVT patients. Statistical significance was set at $p < 0.05$.

Results

Table 1: Baseline Characteristics of Study Participants.

Parameter	DVT (n=100)	Controls (n=100)	p-value
Age (years)	47.6 ± 12.3	46.8 ± 11.9	0.74
Male/Female	56/44	54/46	0.76

There was no statistically significant difference in age or sex distribution between DVT patients and controls ($p > 0.05$).

Table 2: Comparison of Biomarkers Between DVT Patients and Controls.

Parameter	DVT Patients	Controls	p-value
D-dimer (µg/mL)	4.82 ± 1.39	0.42 ± 0.16	<0.001
TAT (µg/L)	28.9 ± 9.6	4.5 ± 2.1	<0.001
F1+2 (nmol/L)	3.11 ± 0.81	0.58 ± 0.20	<0.001

DVT patients demonstrated significantly elevated levels of D-dimer, TAT, and F1+2 compared to controls ($p < 0.001$ for all parameters).

Table 3: Sex-Based Comparison of Biomarkers Among DVT Patients.

Parameter	Males (n = 56)	Females (n = 44)	p-value
D-dimer (µg/mL)	5.12 ± 1.41	4.43 ± 1.28	0.018
TAT (µg/L)	30.4 ± 9.2	26.9 ± 8.7	0.041
F1+2 (nmol/L)	3.28 ± 0.82	2.89 ± 0.76	0.027

Male DVT patients had significantly higher levels of all three biomarkers compared to female patients ($p < 0.05$).

Table 4: Distribution of Factor V Leiden Mutation.

Group	Mutation Present	Wild Type	p-value
DVT Patients	8 (8%)	92 (92%)	0.042
Controls	2 (2%)	98 (98%)	—

Factor V Leiden mutation was significantly more prevalent among DVT patients compared to controls ($p = 0.042$).

Table 5: Correlation Between Sex and Biomarkers in DVT Patients.

Variable	R-value	p-value
Sex vs D-dimer	0.31	0.004
Sex vs TAT	0.27	0.011
Sex vs F1+2	0.29	0.007

Sex showed a positive and statistically significant correlation with biomarker levels among DVT patients.

Discussion

This study shows that DVT patients had far more active coagulation and thrombin production than healthy controls. The markedly increased concentrations of D-dimer, thrombin–antithrombin complex (TAT), and prothrombin fragment 1+2 (F1+2) in these patients indicate persistent fibrinogenesis and continuous thrombin activity. D-dimer, a byproduct of fibrin breakdown, shows that the clot is still breaking down after fibrin has been stabilised. TAT and F1+2, on the other hand, show that thrombin is being made and the coagulation cascade is being activated. The simultaneous increase of these biomarkers enhances their collective diagnostic significance and corroborates their function as sensitive indications of active thrombosis [11].

The results are consistent with the pathophysiological model delineated by Virchow's triad, wherein hypercoagulability is pivotal in thrombus development. Increased TAT and F1+2 levels specifically highlight heightened procoagulant activity

at an earlier phase of the coagulation pathway, prior to fibrinolysis. Their substantial increase in DVT patients indicates that these markers may enhance D-dimer testing by offering insights on thrombin generation intensity, thereby refining the evaluation of disease activity and severity [12].

A significant finding in this study is the sex-based disparity in biomarker levels among DVT patients. Male patients demonstrated markedly elevated levels of D-dimer, TAT, and F1+2 in comparison to females, indicating enhanced thrombin production and clot turnover. This increased coagulation activation in guys may partially elucidate the elevated recurrence rates and suboptimal clinical outcomes often observed in men with venous thromboembolism. The positive connection between sex and biomarker levels reinforces the findings of sex-specific variation in thrombotic activity [13].

Hormonal factors may play a role in these disparities. Oestrogen has been demonstrated to possess anticoagulant and vasoprotective properties by modulating coagulation factors and augmenting fibrinolytic activity. Consequently, premenopausal women may gain advantages from a comparatively protective hormonal profile. In contrast, males do not possess this hormonal modulation, which may make them more likely to produce more thrombin during thrombotic events [14,15].

Along with biological characteristics, lifestyle and environmental factors may make guys in this situation more likely to have blood clots. Occupational immobility, extended sitting, smoking behaviours, and delayed health-seeking behavior-factors more prevalent among males in numerous Nigerian communities-may increase hypercoagulability and venous stasis. These integrated biological and behavioural aspects may elucidate the elevated biomarker levels and potentially increased disease severity noted in male DVT patients [16].

Another important result is that 8% of DVT patients had the Factor V Leiden mutation, mostly in men. While historically deemed uncommon in African populations, its occurrence in this cohort contests that presumption and indicates potential under-diagnosis [17]. The Factor V Leiden mutation makes activated protein C less effective, which keeps thrombin levels high and raises the risk of blood clots. The greater incidence in cases relative to controls underscores its contributory role in illness vulnerability. These results highlight the potential significance of targeted genetic screening, especially in individuals with idiopathic, early-onset, or recurrent DVT [18].

The lack of substantial sex differences in biomarker levels within the control group signifies that the identified inequalities are disease-specific rather than intrinsic physiological abnormalities. This reinforces the notion that male sex may correlate with heightened coagulation activation during active thrombosis, rather than indicating inherent biological disparities [19].

The study collectively advocates for an integrated biochemical and genetic methodology to comprehend DVT in Nigerian patients. Evaluating both thrombin production markers and hereditary thrombophilia may yield a more thorough assessment of thrombotic risk, disease activity, and future recurrence.

Conclusion

Patients with DVT at Federal Teaching Hospital Owerri have much higher levels of D-dimer, thrombin-antithrombin complex, and prothrombin fragment 1+2. This means that their blood is actively clotting and making thrombin. These increases are more noticeable in male patients, which suggests that there are differences in thrombotic intensity based on sex. The Factor V Leiden mutation increases thrombotic risk in certain people, especially males, and may be more common in this group than previously thought.

A combined biochemical and genetic assessment technique, with careful consideration of sex-specific characteristics, may enhance diagnostic accuracy, risk classification, and individualized management of DVT in Nigerian communities.

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Cite this article: Iheanacho MC, Amadi UV, Ogunnaya FU. (2026). Evaluation of D-Dimer, Thrombin-Antithrombin Complex, Prothrombin Fragment 1+2, and Factor V Leiden Mutation in Deep Vein Thrombosis Patients Attending Federal Teaching Hospital Owerri, *International Journal of Biomedical and Clinical Research*, BioRes Scientia Publishers. 6(5):1-5. DOI: 10.59657/2997-6103.brs.26.128

Article History: **Received:** February 19, 2026 | **Accepted:** March 25, 2026 | **Published:** March 30, 2026