

Risk Factors for Thrombosis in an African Population

Awa O.T. Fall¹, Valérie Proulle², Abibatou Sall¹, Alassane Mbaye³, Pape Samba Ba⁴, Maboury Diao⁵, Moussa Seck¹, Macoura Gadji¹, Sara B. Gning⁴, Saliou Diop¹, Tandakha N.D. Dièye¹, Blaise Félix Faye¹, Doudou Thiam¹ and Marie Dreyfus²

¹Laboratory of Hematology, Cheikh Anta Diop University of Dakar, Senegal. ²Laboratory of Hematology, Bicêtre Hospital of Paris, France.

³Cardiology Department, "Grand Yoff" Hospital of Dakar, Senegal. ⁴Cardiology Department, Dakar Principal Hospital, Senegal.

⁵Cardiology Department, Aristide Le Dantec hospital of Dakar, Senegal.

SUMMARY: Little is known about the biological, epidemiological, and clinical risk factors for thrombosis and venous thromboembolism (VTE) among Black Africans. We undertook a study of the prevalence of VTE risk factors for thrombosis in a Senegalese population.

A three-year cross-sectional and case-control study involving 105 cases and 200 controls was conducted in various hospitals in Dakar (Senegal). Our results demonstrate that oral contraception, immobilization by casts, surgery, and blood group were significantly associated with VTE occurrence. Additionally, 16 cases and 2 controls had protein S (PS) values of less than 48.4% (M-2SD), exhibiting a highly significant difference ($P < 1 \times 10^{-4}$). The number of cases with a low protein C (PC) level was significantly higher than the respective number of controls. Using logistic regression methods, we established a correlation between significantly associated variables and deep venous thrombosis (DVT) occurrence. Age, obesity, sickle cell disease, and PC deficiency were not significantly associated with thrombosis. In contrast, gender, PS deficiency, varicose veins, surgery, non-O blood type, and the presence of anti-phospholipid antibodies were significantly and independently associated with DVT.

These findings are extremely useful for clinical management of patients suffering from DVT and can help to reduce the high recurrence rate observed in our study.

KEYWORDS: risk factors, thrombosis, Africa

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CORRESPONDENCE: awaoumar2000@yahoo.fr

Background and Purpose

In developed countries, venous thromboembolism (VTE) is already a serious public health problem and ranks among the main causes of mortality. Mortality from this disease is also increasing in non-developed countries.¹ Clinical symptoms include recurrent deep venous thrombosis (DVT) sometimes complicated by pulmonary embolism (PE). However, many thromboses remain undetected and clinical investigations often yield unremarkable findings. Nearly one half of TED patients have one or several genetic risk factors.¹

Acquired risk factors also play an important part, whether circumstantial (protracted immobilization, surgery,

pregnancy), iatrogenic (oral contraception, hormone replacement therapy), or disease-related (cancer, immune, or cardiovascular system).

Many studies have shown that concomitance of several risk factors (both genetic and acquired) increases thrombosis risk.¹

VTE prevalence fluctuates between 5 and 15% depending on the geographical region and is believed to decrease along a north-south axis.² VTE is thought to be more frequent in northern Europe than in the Mediterranean region. However, venous VTE prevalence among Black Africans is still unknown, and to our knowledge, no epidemiological,



clinical, or biological studies of risk factors have so far been published.

We undertook a study of VTE risk factors in Dakar hospitals and the contribution of biological risk factors to thrombosis occurrence within a Black African population.

Materials and Methods

Patient populations. We carried out a three-year cross-sectional and case-control study involving 105 cases and 200 controls. The patients included in our study were recruited from the cardiology, internal medicine, neurology, hematology, and respiratory medicine units of five Dakar hospitals. Controls were recruited at the hematology laboratory and blood bank of the Le Dantec Hospital in Dakar.

Inclusion criteria. Only patients aged 15 years or more who fulfilled one of the two following conditions were included in this study:

- they had been admitted into the emergency ward for suspected DVT and/or PE
- or had previously suffered one or several episodes of DVT.

Exclusion criteria. Patients were excluded if:

- imaging did not confirm DVT
- or they were receiving anticoagulant therapy.

Control group. The control group was recruited from healthy blood donors with no history of thrombosis. The controls over 65 years of age were selected from elderly persons who had been referred to the hematology laboratory for a pre-operative check-up.

Sampling. Sampling was systematically randomized: a blood sample was taken from any patient admitted for suspected DVT or PE before the initiation of anticoagulant therapy and/or six weeks after it ended.

Sample size was 150 cases and 200 controls, but 45 cases were removed for technical reasons (see Findings section).

All samples with low levels of protein S or C and antithrombin, found early after thromboembolic event, had been confirmed at least six weeks after anticoagulation.

Analyses (bioassays). Various tests, assays, and molecular biology investigation techniques were used at the hematology labs of both university hospitals: Le Dantec in Dakar and Bicêtre in Paris.

Blood cell count was performed using automated hematology counters: either KX 21 (Sysmex Laboratories, Kobe, Japan) or ADVIA 60 (Bayer Labs; Germany).

Blood type under the ABO system was determined by both the Beth-Vincent globular and Simonin serum methods.

Sickling test or Emmel test on red cells was assessed as positive whenever the red blood cells trapped between the slide and the cover slip become sickle-shaped 15 minutes after the addition of sodium metabisulfite.

Routine homeostasis testing (QT, ACT, and fibrinogen assay) was performed using automated devices: either STA compact or STA-R type (Diagnostica Stago Labs, France).

Immunoenzymatic detection of anti-phospholipid (APL) antibodies was carried out by means of a single enzyme-linked immune method using microtitration plates coated with a mixture of cardiolipin, phosphatidyl serine, and phosphatidic acid. We used the Asserachrom APA kit (Diagnostica Stago Labs) containing all the required reagents.

Our heparin cofactor assay of antithrombin activity consisted in a qualitative antithrombin assay with an STA compact analyzer (Diagnostica Stago Labs) that applies an amidolytic method on a chromogenic synthetic substrate.

Protein C (PC) anti-clotting activity was determined by means of a PC activity chromometric assay using an STA compact analyzer (Diagnostica Stago Labs).

The **protein S (PS) anti clotting activity assay** performed was a PS chromometric assay based on Factor Va proteolytic degradation.

Screening for presence or absence of lupus anticoagulant (LA) was tested by determining diluted venom Russell time (DRVVT).

Molecular detection of Factor V Q506 and Factor II G20210A mutations was done by PCR Duplex prothrombin 20210 and F V.

Statistical analyses. Result acquisition and analysis were carried out with software such as Epi Data, Epi Info 6, and Stata. Assessment of risks was conducted by performing univariate and bivariate analysis of the cases as compared to the control population by means of odds ratio calculation. A difference in either proportion or mean was considered significant when the 95% confidence interval (CI) did not include 1, or when $P < 0.05$. Multivariate analysis was conducted using Stata software, enabling the actual effect of various risk factors to be measured by logistic regression.

Ethical approval. This study was approved by ethical committee of each of the five hospitals where we recruited patients and controls. All samples were performed after patient consent.

Results

Patients and controls. A total of 150 cases were found but statistical analysis was performed on 105 patients as 45 cases have missing information or technical issues with their samples.

Epidemiological and clinical risk factors.

Age and sex factors. The mean age for cases was 42 years, ranging from 17 to 78 years. The mean age of the control population was 38 years, ranging from 18 to 65 years.

Women were more prone to thrombosis, accounting for 81 of the 105 cases (77%). Women made up 62% (125 of 200) of the control population. This difference was statistically significant ($P = 0.009$).

Clinical locations of thrombosis. Most DVT cases occurred in the lower limbs (71%), predominantly on the left side (58%).

Table 1. Demographics of case and control.

VARIABLES	CAS (N = 105)	TEMOINS (N = 200)	p	OR	IC à 95%
Sex					
Females n(%)	82 (77%)	125 (62,5%)*	0.009		
Males n(%)	23 (23%)	75 (37,5%)			
Age					
≤40 yrs n(%)	55 (54%)	118 (59%)	0.33		
>40 yrs n(%)	50 (46%)	82 (41%)			
mean (yrs)	42	38,6			
Iterative fetal loss	21	18	0,006	2,53	1,22–5,27
Sickle cell disease or trait	14	13	0,043	2,21	0,93–5,95
Smoking	12	12	0,09	2	0,8–5,02
OCP	13	1	< 10⁴	28	4–1212
Cancer	4	0	0,013		
Tuberculosis	2	0	0,1		

We also observed 17 cases of PE, four of which were associated with DVT of the left lower limb (LLL) at the time of diagnosis; ten cases of cerebral venous thrombosis (CVT); three cases of retina central vein thrombosis, and two of upper limb thrombosis (ULDVT).

A total of 42 cases were included because of recurrent thrombotic events. Recurrence mainly involved the initial thrombosis site (66%). In two patients, the recurrence affected the opposite limb. Two patients experienced multiple recurrence of thrombosis that might be described as true thromboembolic disease. Fourteen patients had a family history of DVT.

Additional findings. Other signs of thrombotic disease were iterative fetal losses (IFL). Apart from cases of LL thrombophlebitis or PE, 21 women suffered obstetrical accidents such as IFL. This accounted for a quarter of the female case population, ie a significantly higher proportion than in the female control population ($P = 0.006$).

Four patients suffered a kidney disease-related failure associated with DVT as a result of thrombosis of renal vessels. No control suffered any kidney disease.

Sickle cell disease was diagnosed (both homozygote and heterozygote) in 14 patients and 13 individuals in the

control group, with a significant difference between the two populations ($P = 0.043$).

Other risk factors for thrombosis. Some risk factors related to patient background were significantly associated with DVT risk: oral contraceptives, immobilization by casts, surgery, and ABO blood group. There was no association with other factors such as smoking or obesity (Table 1).

Biological risk factors.

PS. 16 cases and 2 controls had PS values below 48.4% (M-2SD); the difference was significant ($P < 0.01$).

The free antigen assay performed on 11 patients confirmed decreased SP anti-clotting activity.

PC. The number of cases with a low PC rate was significantly greater than the number of controls exhibiting a comparable decrease (nine compared to five subjects) with $P = 0.015$ (cut off value = 54%).

Antithrombin. A decreased antithrombotic rate (<76%) was found in only two cases and one control. The difference between the two populations was not significant ($P = 1.39$).

No factor II or V mutation was observed either among patients or controls (Table 2).

Table 2. Biological abnormalities predisposing to thrombosis.

VARIABLES	CASES (N = 105)	CONTROLS (N = 200)	OR	95% CI	p
AT deficiency (≤76%)	2	1	3.86	0.27–108.92	1.39
PS deficiency (≤48%)	16	2	17	3.72–14.81	< 1 × 10⁴
PC deficiency (≤54%)	9	5	3.69	1.07–14.36	0.015
20210A mutation	0	0	ND	ND	ND
FVL	0	0	ND	ND	ND

**Table 3.** Results of screening for anti phospholipid antibodies.

VARIABLES	CASES	CONTROLS	OR	IC AT 95%	P
Anti phospholipids					
(+)	19	5	4.43	1.47–14.25	0.025
(–)	79	92			
Lupus anticoagulant					
(+)	13	28	0.86	0.4–1.85	0.69
(–)	92	171			

APL. We were able to investigate APLs in only 98 cases and 97 controls. These antibodies were found in 18 of the 98 cases and 5 of the 97 controls tested. The relative risk connected with their presence was close to 4; OR = 4.43 with a 95% CI of between 1.45 and 14.39.

Lupus anticoagulant or lupus antibody (LA). This antibody was discovered mainly among controls (14% as compared to 12% among cases). The difference is not significant (OR = 0.86 with a 95% CI ranging between 0.4 and 1.85) (Table 3).

The presence of APL antibody and/or LA, in addition to limb DVT was associated with some thrombotic manifestations at other sites:

- Stroke: 2 cases
- Myocardial infarction: 2 cases
- IFL: 5 cases
- Kidney disease involving acute kidney failure related to renal vein thromboses: 2 cases.

Risk factors significantly responsible for the occurrence of DVT were often associated among cases but rarely in controls.

Oral contraceptives. A model that considered only females found that taking oral contraceptives was significantly associated with DVT independently of the following variables: SP, non-O blood group, and surgery (Table 4).

Discussion

Several lines of evidence support the existence of VTE in Africa, particularly in Senegal. The risk factors for Black Africans and Caucasians are similar. However, a detailed study determining the risk factors of VTE disease in African

populations was yet to be conducted. We undertook a study to assess the various clinical, epidemiological, and/or biological risk factors for thrombosis in a Black African population of patients having experienced one or several episodes of DVT. The recurrence rate of DVT in our patients is 40% with 42 patients having already experienced at least one previous thrombotic event, independently of the initial location of the previous DVT. This rate is higher than in the Caucasian population, where it ranges from 7 to 12.9%.^{3–6} Although 40% of our patients enrolled in this study had developed recurrent thrombosis, we were unable to precisely determine the time interval between the thrombotic events. A number of health issues that arise in non-developed countries, such as inadequate clinical care, failure to assess biological risk factors, and the financial burden of covering all the medical tests may be at the root of this higher rate of recurrence. Our study uncovered risk factors that are generally accepted as significantly associated with DVT occurrence.

Epidemiological and clinical risk factors associated with DVT. 13% of female patients and one female in the control group were taking oral contraceptives (Stediril (50 µg ethinyl-oestradiol) or Adepal (30 µg levonorgestrel-ethinylestradiol)). Oral contraceptive regimens are therefore highly associated with DVT at a rate greater than that given by the WHO (28 vs 4). Among them, seven had LLDVT, four had a PE, and two had a brain VT with a central retina vein thrombosis.

Our study also showed that DVT was significantly associated with female gender (OR = 2.21), with women accounting for 77% of our case patient cohort. These results differ from Anderson, Nordstrom, and Sluis, who find identical thrombosis incidence in both sexes.^{7–9} However, there were far more males than females in the blood donor population (4:1). Hence, the higher proportion of women in the case patient population.

Surgery contributes to DVT occurrence and associated bed confinement worsens blood stasis.¹⁰ Among our patients, 12% suffered a DVT event in the aftermath of an operation or following plaster cast immobilization. The surgery consisted either in cesarean sections (10 cases), where the hormonal context added hyper-coagulability to the surgical risk, or varicocelelectomy (two cases). The prevalence of post surgery thrombosis is lower in Senegal than for Caucasians (12 vs 30%). In Chinese populations, the risk of DVT following surgery and where no preventive measures are taken is practically nonexistent (<1%).¹¹ Studies carried out on Black populations living in the USA or in Africa found a similar lower prevalence.^{12–14}

Non-O blood grouping presents a relative risk close to 3 in our study (68.9% of non-O blood group patients compared to 44.5% in controls). Our results are consistent with those of Wautrecht and Dentali.^{15,16} This relationship is partially explained by the effects of blood group type on the concentrations of both factor VIII and the von Willebrand factor.

Table 4. Risk factors significantly associated with thrombosis.

VARIABLES	OR	95% CI	P
Female	2.21	1.13–4.34	0.021
Varicose veins	32.3	2.31–452.3	0.042
Surgery	3.07	1.07–8.76	0.008
Non-O blood type	2.8	1.5–5.3	<1 × 10⁻⁴
PS	28	3.2–245.3	<1 × 10⁻⁴
aCL	5.75	1.9–17.44	0.002

Our risk factor modeling establishes that a non-O erythrocyte phenotype is an independent risk factor for DVT occurrence in the Senegalese population.

Can sickle cell disease be considered a DVT risk factor among Senegalese people despite the conflicting findings? S hemoglobin (S Hb) was found in 8% of case patients compared to 6.5% of controls, with a statistically significant difference ($P = 0.043$) and an estimated risk of 2.24. Of the 22 individuals, both cases and controls, with S Hb, 9 (41%) had DVT, regardless of their particular carrier status. DVT prevalence among people with sickle cell anemia remains poorly studied and the few studies there are show a higher prevalence than in the general population.^{17,18} Among the factors that are thought to predispose to thrombosis during sickle cell disease, we noted APL antibodies and low PS and PC.^{19,20} However, these results have not been confirmed either by a study conducted in Cote d'Ivoire²¹ or by ours.

Conversely, other classical clinical risk factors such as age,²² tobacco smoking, cancer,²³ and tuberculosis^{24–26} were not significantly associated with DVT in our population study.

Biological risk factors associated with DVT. In our study, APL antibodies were significantly associated with DVT. Nearly 20% of patients tested carry the antibodies as compared with only 15% of the controls, with a DVT occurrence risk four times greater when this antibody is present. According to the literature, anti-cardiolipin antibody (ACL) prevalence varies between 58 and 65%.²⁷ Unfortunately, we were unable to repeat these analyses on our patients since it was a case-control study. Therefore, anti-phospholipids syndrome can only be suspected in our patients suffering from DVT who carry ACL.

The same applies to LA. 13 individuals carried LAs (12% among cases and 14% in controls). The presence of LA was not significantly associated with DVT occurrence. This finding contradicts Galli's work,²⁸ who funded a DVT risk more strongly associated with LA than with ACL. The noteworthy presence of LA in the control population should be monitored for possible pathogenic effects. LA and/or ACL antibodies were observed in six patients. This association is significantly correlated to the occurrence of IFL.

A decreased PS level was found to be a significant risk factor associated with DVT occurrence among Senegalese people with 16 case patients (15% prevalence) versus only two in the control group. In our study, low PS increases the DVT risk by a factor of more than 15 times. This observed risk is higher than the one reported in literature, which ranges from 1.5 to 10.^{29–31} We acknowledge a slight overestimation in our population study because of the frequent association of this deficiency with other clinical and biological risk factors. We were able to complete the characterization of deficiencies found for only 11 patients: two had a type I quantitative deficiency, two had a type II functional deficiency, and seven had a type III free fraction deficiency. Determining whether this deficiency is either constitutional or acquired has still to

be determined through family surveys and molecular biology analyses after full characterization of the deficiencies. The prevalence of the decreased PS rate was 1% in a population of 200 healthy blood donors. The prevalence rate found in our control group was comparable to the one reported in several European studies, ranging from 0.7 to 2.4%.³² However, it is lower than the prevalence rate found for a population originating from Asia (1 to 4%).³³ A molecular study conducted in Scotland found an even lower prevalence rate of between 0.16 and 0.21%.³⁴ In the population of DVT patients, this prevalence increases to 3% for a Caucasian population, and up to 20%^{35,36} for a population of Asian patients. The few studies carried out on Black population are not exhaustive and concern Black people who live either in Europe or America. PS deficiency prevalence among those Black patients suffering from DVT varies between 3 and 30%.^{29,37}

Other biological abnormalities that are generally considered to be significantly associated with DVT occurrence—eg inflammatory syndrome, myeloproliferative syndrome, antithrombin deficiency, and both factor II and V mutations—are not found to be significant in our study.

Conclusions

From our modeling of risk factors, we were able to establish, for the first time, that female gender, varicose veins, surgery, non-O blood type, a decreased PS level, the presence of ACL antibodies, and oral contraception are factors truly associated with DVT risk in the Senegalese population. The other risk factors studied lose their significance when they are included in a model that takes into account each risk factor's actual weight. Upon completion of this work, our study had identified a risk factor (acquired or hereditary, significant or non-significant) in 94 of the case patients (50%).

On this basis, we can define the patient-at-risk categories to which thrombosis prevention strategy should be offered. Advice should be given about situations such as protracted immobilization, long distance travel, and surgery. A prevention strategy should be routine for women, particularly those who take oral contraceptives, for subjects suffering from varicose veins and those who are of a non-O-blood type.

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Author Contributions

Conceived and designed the experiments: AOTF, MDr. Analyzed the data: AOTF, MDr. Wrote the first draft of the manuscript: AOTF, MDr. Contributed to the writing of the manuscript: AOTF, MDr. Agree with manuscript results and conclusions: AOTF, VP, AS, AM, PSB, MDi, MS, MG, SBG, SD, TNDD, BFF, DT, MDr. Made critical revisions



and approved final version: AOTF, VP, AS, AM, PSB, MDi, MS, MG, SBG, SD, TNDD, BFF, DT, MDr. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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