

Risk factors in women with cerebral venous thrombosis treated with oral anticoagulants at Bach Mai National Institute Of Neuroscience

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ABSTRACT

This study aimed to describe risk factors in women with cerebral venous thrombosis (CVT) treated with oral anticoagulants and to compare women within and beyond reproductive age. This retrospective cross-sectional study at Bach Mai National Institute of Neuroscience included women with CVT admitted from January 2022 to December 2024 and maintained on rivaroxaban or vitamin K antagonists. Of 167 women (mean age 44.0 ± 14.5 years), 77.7% were aged 18-50. Sex-specific risk factors were present in 34.7%, all aged 18-50; oral contraceptive use was the most common (24.6%). Anemia was found in 26.3%, reduced natural anticoagulant activity ($< 60\%$) in 22.2%, and positive antiphospholipid antibodies in 3.6%. No identifiable risk factor was more frequent in women over 50 than in those aged 18-50 (51.4% vs. 26.4%, $p = 0.004$). In women with CVT receiving oral anticoagulation, oral contraceptives and pregnancy-related conditions were the main risk factors at reproductive age, whereas no risk factor was identified in half of those over 50, warranting a more comprehensive etiological evaluation.

Keywords: cerebral venous thrombosis, women, risk factors, oral contraceptives, oral anticoagulants.

Abbreviations: CVT, cerebral venous thrombosis; ISCVT, International Study on Cerebral Vein and Dural Sinus Thrombosis; VENOST, multicenter Turkish study of cerebral venous thrombosis; SD, standard deviation; IQR, interquartile range; OR, odds ratio; Hb, hemoglobin; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

1. INTRODUCTION

Cerebral venous thrombosis (CVT) is an uncommon type of stroke, but its epidemiology differs from that of arterial stroke: the disease typically affects young people and predominantly women. In the International Study on Cerebral Vein and Dural Sinus Thrombosis

(ISCVT) of 624 patients, women accounted for 74.5%, and among women under 50 years of age, oral contraceptive use reached 54.3%.¹ Sex-specific risk factors such as oral contraceptives, pregnancy, the puerperium, and hormone replacement therapy frequently coexist with an underlying prothrombotic state: according to de Bruijn et al., oral contraceptives increase the risk of CVT approximately 13-fold, and when combined with an inherited prothrombotic abnormality, the risk rises approximately 30-fold compared with women without either factor.²

The risk factor profile in women is heterogeneous. An analysis of women in the ISCVT showed that 65% had at least one sex-specific risk factor, and the absence of such factors was an independent predictor of poor outcome.³ Among the 777 women in the VENOST study, those without reproductive health-related risk factors were significantly older (43.2 ± 13 vs. 34 ± 9 years) and more frequently had malignancy.⁴ The risk factor profile also varies across regions: in the Asian CVT registry, anemia was present in 51% of patients, whereas oral contraceptive use was found in only 12% of women and the puerperium in 15%.⁵

In Vietnam, studies on CVT have mainly described both sexes together, with risk factors in women presented only as a subgroup. At Bach Mai Hospital, Trinh Tien Luc reported oral contraceptive use in 38.1% and the postpartum period in 21.4% of 84 female patients.⁶ Few studies in Vietnam have comprehensively described the groups of risk factors in women, compared women within and beyond reproductive age, or focused on patients receiving long-term oral anticoagulation - a group in whom identifying risk factors directly influences the duration of treatment and counseling on contraception and future pregnancy.

Therefore, we conducted this study to describe the characteristics of risk factors in women with cerebral venous thrombosis treated with oral anticoagulants at Bach Mai National

Institute of Neuroscience and to compare these factors between women within and beyond reproductive age.

II. SUBJECTS AND METHODS

2.1. Participants

The study subjects were female patients enrolled in the research project "Prognostic factors and treatment outcomes of cerebral venous thrombosis with rivaroxaban and vitamin K antagonists" who met the following criteria.

Inclusion criteria:

- Patients aged ≥ 18 years with a confirmed diagnosis of CVT based on clinical and imaging findings (brain magnetic resonance imaging with magnetic resonance venography).
- Receiving maintenance anticoagulation with rivaroxaban or a vitamin K antagonist.
- Able to be followed up for at least 6 months after treatment.

Exclusion criteria:

- Severe underlying diseases affecting prognosis (end-stage cancer, severe hepatic or renal failure, etc.).
- Pregnant or breastfeeding women.
- Non-adherence to treatment or loss to follow-up.

2.2. Methods

Study design, setting, and time. This was an observational, retrospective, cross-sectional descriptive study using data at the time of diagnosis, conducted at Bach Mai National Institute of Neuroscience, Bach Mai Hospital, in patients admitted from January 1, 2022 to December 31, 2024.

Sampling. Consecutive (total) sampling was applied, including all eligible female patients during the study period.

Study groups. Patients were divided into two groups according to age at admission: within reproductive age (18-50 years) and beyond reproductive age (over 50 years). The cut-off of

50 years was chosen to correspond with the age grouping used in the VENOST study.⁷ In addition, patients were classified into those with and without sex-specific risk factors.

Variables and definitions. Risk factors were collected from medical records using a standardized case report form and categorized according to the classification of the ISCVT.¹ Sex-specific risk factors comprised oral contraceptive use, pregnancy-related conditions (delivery, miscarriage, curettage, or induced abortion preceding the onset of CVT, as recorded in the medical history), and hormone replacement therapy, adapted from the definition used by Coutinho et al.³

Protein C activity, protein S activity, and antithrombin III activity were measured once at the time of diagnosis on an ACL TOP 750 analyzer at Bach Mai Hospital. Activity was considered reduced when it was < 60%; in addition, the proportion of patients with activity below the laboratory reference limits was reported. Genetic testing for factor V Leiden and the prothrombin G20210A mutation was not performed routinely and was available only in a subset of patients at the discretion of the treating physician. Antiphospholipid antibodies were considered positive when at least one of anti-phospholipid, anti-cardiolipin, or anti- β_2 glycoprotein I antibodies (IgM or IgG) was positive; lupus anticoagulant was reported separately because of possible false-positive results during anticoagulant therapy. Other risk factors included malignancy, anemia (hemoglobin < 120 g/L at admission), thrombocytosis (platelet count > 450×10^9 /L or a history of thrombocytosis), systemic disease (with an established clinical diagnosis), Graves' disease, renal disease, ear, nose, and throat infection, meningitis, mechanical factors (traumatic brain injury, craniomaxillofacial surgery), and a history of venous thrombosis. Conditions recorded only as "other" without further specification were not counted as risk

factors. The number of risk factors per patient (0, 1, ≥ 2) included sex-specific risk factors, positive antiphospholipid antibodies, and the other risk factors listed above, excluding reduced activity of natural anticoagulants and lupus anticoagulant; patients in whom no factor was identified were classified as having no identifiable risk factor.

Data analysis. Data were analyzed using SPSS 20.0 software. Continuous variables were presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR) depending on their distribution and were compared between the two groups using the t-test or the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and were compared using the χ^2 test, or Fisher's exact test when expected frequencies were less than 5. Comparisons were not performed for factors that are age-dependent by definition. Percentages were calculated based on patients with available data. A p-value < 0.05 was considered statistically significant. The study was reported in accordance with the STROBE guidelines.

2.3. Ethical considerations

The study was approved by the Biomedical Research Ethics Committee of Bach Mai Hospital (Certificate No. 52/BM-HĐĐĐ dated February 1, 2026). Because of the retrospective design using anonymized medical records, the requirement for informed consent was waived.

III. RESULTS

A total of 167 female patients met the inclusion criteria. Age was available for 166 patients: the mean age was 44.0 ± 14.5 years (median 41; IQR 34-49.8; range 18-89). Of these, 129 patients (77.7%) were aged 18-50 years, with a mean age of 37.6 ± 7.8 years, and 37 patients (22.3%; Figure 1) were over 50 years, with a mean age of 66.2 ± 9.9 years. Genetic testing was available in 20 patients, none of whom carried factor V Leiden or the prothrombin G20210A mutation.

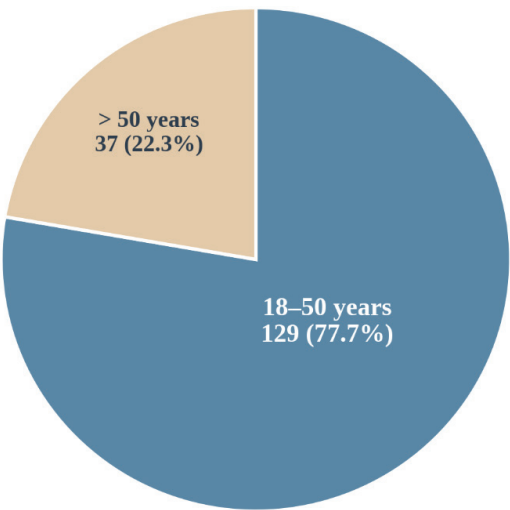


Figure 1. Distribution of age groups in the study population (n = 166)

Comment: Most patients (77.7%) were within reproductive age.

Table 1. Sex-specific risk factors by age group

Factor	Overall (n = 167)	18-50 years (n = 129)	> 50 years (n = 37)
Oral contraceptive use	41 (24.6)	41 (31.8)	0
Pregnancy-related condition (postpartum, miscarriage, curettage, or induced abortion)	19 (11.4)	19 (14.7)	0
Hormone replacement therapy	1 (0.6)	1 (0.8)	0
≥ 1 sex-specific risk factor	58 (34.7)	58 (45.0)	0

Age was missing for 1 patient, who was included only in the Overall column.

Comment: Sex-specific risk factors were present in 34.7% of patients, all of whom were in the 18-50 group (45.0% of this group). Oral contraceptive use was the most common factor (24.6%), followed by pregnancy-related conditions (11.4%).

Table 2. Coagulation test results at diagnosis by age group

Test, n/N (%)	Overall	18-50 years	> 50 years	p
Reduced protein C activity	17/167 (10.2)	13/129 (10.1)	4/37 (10.8)	1.000
Reduced protein S activity	21/158 (13.3)	18/123 (14.6)	3/34 (8.8)	0.570
Reduced antithrombin III activity	9/167 (5.4)	6/129 (4.7)	3/37 (8.1)	0.419
Reduction of ≥ 1 of the 3 factors (< 60%)	37/167 (22.2)	29/129 (22.5)	8/37 (21.6)	0.912
Reduction of ≥ 1 of the 3 factors (laboratory reference limits)	96/167 (57.5)	73/129 (56.6)	22/37 (59.5)	0.756
≥ 1 positive antiphospholipid antibody	6/167 (3.6)	4/129 (3.1)	2/37 (5.4)	0.616
Lupus anticoagulant positive/suspected	17/165 (10.3)	14/127 (11.0)	2/37 (5.4)	0.528

Age was missing for 1 patient, who was included only in the Overall column.

Comment: Reduced activity of at least one of the three natural anticoagulants was found in 22.2% of patients and in 57.5% when laboratory reference limits were applied, with no difference between the two age groups under either definition. Antiphospholipid antibodies were positive in 3.6% of patients.

Table 3. Other risk factors by age group

Factor	Overall (n = 167)	18-50 years (n = 129)	> 50 years (n = 37)	p
Anemia (Hb < 120 g/L)	44 (26.3)	32 (24.8)	11 (29.7)	0.547
Thrombocytosis	17 (10.2)	13 (10.1)	4 (10.8)	1.000
Renal disease	7 (4.2)	6 (4.7)	1 (2.7)	1.000
History of venous thrombosis	7 (4.2)	5 (3.9)	2 (5.4)	0.654
Systemic disease	6 (3.6)	5 (3.9)	1 (2.7)	1.000
Traumatic brain injury / craniomaxillofacial surgery	6 (3.6)	4 (3.1)	2 (5.4)	0.617
Ear, nose, and throat infection	2 (1.2)	2 (1.6)	0	1.000
Malignancy	1 (0.6)	1 (0.8)	0	1.000
Meningitis	1 (0.6)	1 (0.8)	0	1.000
Graves' disease	1 (0.6)	1 (0.8)	0	1.000

Age was missing for 1 patient, who was included only in the Overall column.

Comment: Anemia was the most common factor in this group (26.3%), followed by thrombocytosis (10.2%). Each of the remaining factors was found in fewer than 5% of patients, with no difference between the two age groups.

Table 4. Number and combination of risk factors by age group

Factor	Overall (n = 167)	18-50 years (n = 129)	> 50 years (n = 37)	p
No identifiable risk factor	53 (31.7)	34 (26.4)	19 (51.4)	0.004
1 risk factor	82 (49.1)	67 (51.9)	14 (37.8)	0.130
≥ 2 risk factors	32 (19.2)	28 (21.7)	4 (10.8)	0.139
Sex-specific risk factor with antiphospholipid antibodies	1 (0.6)	1 (0.8)	0	1.000

Age was missing for 1 patient, who was included only in the Overall column.

Comment: No risk factor was identified in 31.7% of patients; this proportion in the over-50 group (51.4%) was nearly twice that in the 18-50 group (26.4%), $p = 0.004$.

Table 5. Comparison between patients with and without sex-specific risk factors

Characteristic	Present (n = 58)	Absent (n = 109)	p
Age (years), mean ± SD	35.4 ± 7.3	48.6 ± 15.3	< 0.001
Any other risk factor	14 (24.1)	56 (51.4)	< 0.001

Characteristic	Present (n = 58)	Absent (n = 109)	p
Reduction of ≥ 1 natural anticoagulant (< 60%)	11 (19.0)	26 (23.9)	0.469
≥ 1 positive antiphospholipid antibody	1 (1.7)	5 (4.6)	0.666
Systemic disease	0	6 (5.6)	0.092
Anemia	11 (19.0)	33 (30.3)	0.114
Malignancy	0	1 (0.9)	1.000

Any other risk factor: antiphospholipid antibodies, malignancy, anemia, thrombocytosis, systemic disease, Graves' disease, infection, mechanical factors, or history of venous thrombosis.

Comment: Patients with sex-specific risk factors were significantly younger (35.4 ± 7.3 vs. 48.6 ± 15.3 years, $p < 0.001$). Patients without sex-specific risk factors more often had other risk factors (51.4% vs. 24.1%, $p < 0.001$) and tended to have systemic disease and anemia more frequently, although the latter differences were not statistically significant.

IV DISCUSSION

Most women in our study were of reproductive age, consistent with large cohorts: the median age in the ISCVT was 37 years,¹ and 83.4% of the 777 women in the VENOST study were aged 50 years or younger.⁴ The mean age of our patients was higher than that reported by Trinh Tien Luc at the same center (36.7 ± 12.2 years),⁶ possibly because pregnant or breastfeeding women were excluded from our study, reducing the number of young patients with pregnancy-related CVT.

Oral contraceptive use was the most frequent sex-specific risk factor in our cohort. Its frequency (24.6% overall and 31.8% among women aged 18-50 years) was lower than in the ISCVT, in which 54.3% of women under 50 used oral contraceptives,¹ and than the 38.1% reported among female patients by Trinh Tien Luc,⁶ but higher than among all

women in the VENOST study (13.9%)⁴ and in the Asian CVT registry (12%).⁵ These differences may reflect variations in contraceptive practices across populations as well as differences in study design and inclusion criteria, and support the routine assessment of oral contraceptive use in all young women with CVT.

Pregnancy-related conditions in our study are not directly comparable with the puerperium as defined in other studies, which accounted for 13.8% of women under 50 in the ISCVT,¹ 18.3% of women in the VENOST study,⁴ and 15% in the Asian registry (up to 6 weeks postpartum),⁵ because our variable combined the postpartum period with miscarriage, curettage, and induced abortion and the interval to CVT onset was not available. Moreover, the frequency of pregnancy-related factors is likely underestimated, because the inclusion criteria required maintenance oral anticoagulation and excluded pregnant or breastfeeding women, who are usually treated with low-molecular-weight heparin.

Reduced activity of natural anticoagulants was common and did not differ between age groups, irrespective of the cut-off applied. Trinh Tien Luc also reported high proportions of reduced protein C, protein S, and antithrombin III (18.3%, 24.2%, and 12.4%, respectively).⁶ Such proportions far exceed the expected prevalence of inherited deficiencies and should not be interpreted as inherited thrombophilia.

Deficiencies of these proteins may be inherited or acquired;⁸ at the time of diagnosis, their activity may be reduced by consumption during thrombus formation and by heparin or vitamin K antagonist therapy, and protein S activity is also physiologically lower with oral contraceptive use and after delivery. Confirmation of a true deficiency therefore requires repeat testing after the acute phase and after discontinuation of anticoagulation.

In the ISCVT, inherited or acquired thrombophilia was found in 34.1% of patients,¹ a proportion much higher than that of prothrombotic abnormalities in our cohort (positive antiphospholipid antibodies in 3.6%, and no factor V Leiden or prothrombin G20210A mutation among the 20 patients tested), largely because of the limited availability of genetic testing. Case-control studies have demonstrated a synergistic effect between oral contraceptives and prothrombotic conditions: the risk of CVT increases approximately 30-fold when both are present² and nearly 150-fold in carriers of the prothrombin G20210A mutation who use oral contraceptives.⁹ The rarity of this combination in our study more likely reflects incomplete thrombophilia screening than a true absence of this interaction.

Anemia was the most common risk factor outside the sex-specific group. Anemia was also frequent in the Asian CVT registry (51%),⁵ suggesting that it is a relevant risk factor in Asian populations. However, because hemoglobin was measured at admission and iron status was not assessed, anemia in our study may partly reflect acute illness rather than a pre-existing condition. Malignancy was rare in our cohort, in contrast to the VENOST study, in which 7% of women without reproductive health-related factors had malignancy;⁴ this is consistent with the exclusion

of end-stage cancer in our study.

The proportion of patients with no identifiable risk factor was higher than in the overall ISCVT cohort of both sexes (12.5%)¹ and in the Asian registry (20%),⁵ which may be partly explained by incomplete thrombophilia testing and by conditions recorded without specification. The most notable finding of our study is that this proportion was nearly twice as high in women over 50 as in younger women. In young women, hormonal and pregnancy-related factors accounted for a large proportion of cases, whereas in women beyond reproductive age, no cause could be identified in half of the patients with the available investigations. This suggests that a more comprehensive etiological evaluation, including screening for occult malignancy, systemic disease, and thrombophilia, may be warranted in this group.

Women with sex-specific risk factors were younger than those without, consistent with the VENOST study (34 ± 9 vs. 43.2 ± 13 years),⁴ whereas women without sex-specific risk factors more often had other risk factors. Coutinho et al. reported that 65% of women in the ISCVT had sex-specific risk factors, compared with about one-third in our study, and that the absence of these factors was an independent predictor of poor outcome (OR 3.7).³ Women without sex-specific risk factors may therefore represent a heterogeneous group in whom other underlying causes should be actively sought; whether this group also has different outcomes in our population requires further analysis.

This study has several limitations. It was a retrospective, single-center study without a control group; therefore, it could only describe the frequency of risk factors and could not assess the strength of their associations. The sample

included only patients receiving maintenance oral anticoagulation and followed up for 6 months and excluded pregnant or breastfeeding women and those with end-stage cancer; thus, the proportions of pregnancy-related factors and malignancy may be underestimated. Pregnancy-related conditions were recorded as a combined variable without timing. Coagulation tests were performed only once, the timing of blood sampling in relation to anticoagulant therapy was not standardized, and genetic testing was available in only a small number of patients. The small size of the over-50 group also reduced the ability to detect differences between age groups. Prospective, multicenter studies that include women irrespective of the anticoagulant used, apply a standardized thrombophilia work-up after the acute phase and discontinuation of anticoagulation, and include a control group are needed to confirm these findings.

V CONCLUSION

In women with cerebral venous thrombosis treated with oral anticoagulants, most patients were of reproductive age. In this group, oral contraceptive use and pregnancy-related conditions were the main identifiable risk factors, whereas anemia was the most common factor outside the sex-specific group. In women over 50 years of age, no risk factor could be identified in half of the patients. Oral contraceptive use and obstetric history should therefore be routinely assessed in all young women with CVT, while women over 50 or without sex-specific risk factors may require a more comprehensive etiological evaluation.

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