Multiple Health Care Encounters Prior to Diagnosis of Cerebral Venous Thrombosis

Lily W. Zhou, MD, MS*; Vanessa Dizonno, MSc; Jennifer Mandzia, MD, PhD; Mohammed A. Almekhlafi, MD, MSc; Fouzi Bala, MD, MSc; Ibrahim Alhabli, MD; Maria Karina Villaluna, RN, CCRP, CNN; Princess King-Azote, MD, FPNA, CCRP; Namali Ratnaweera, MSc; Stephen C. Van Gaal, MD, MSc; Laura K. Wilson, MD; Brett R. Graham, MD; Luciano A. Sposato, MD, MBA; Dylan Blacquiere, MD, Msc; Mark I. Boulos, MD; Brian H. Buck, MD; Celine Odier, MD; Kanjana S. Perera, MD; Aleksandra Pikula, MD; Aleksander Tkach, MD; George Medvedev, MD; Michael D. Hill, MD, MSc; Thalia S. Field, MD, MHSc on behalf of the SECRET and TOP-SECRET investigators

*Corresponding Author. E-mail: lily.zhou@vch.ca.

Study objective: Cerebral venous thrombosis symptom onset can be insidious and without focal deficits. We performed a planned analysis of care-seeking patterns prior to diagnosis in a Canadian randomized trial examining treatment and prognosis of cerebral venous thrombosis and its companion prospective observational registry to examine whether time to diagnosis or multiple health care encounters prior to diagnosis were associated with 180-day outcomes.

Methods: Adults within 14 days of diagnosis of a new symptomatic cerebral venous thrombosis were included. We examined timing from symptom onset to diagnosis and the number of health care encounters for cerebral venous thrombosis symptoms prior to diagnosis. We explored associations between multiple care encounters prior to diagnosis with patient demographics, baseline clinical and radiologic features, and 180-day outcomes.

Results: Of 102 patients (median age 45 [interquartile range {IQR} 31.0 to 61.0] years, 68.6% women), 40 (39%) had multiple health care encounters for their cerebral venous thrombosis symptoms prior to diagnosis. The median time from symptom onset to diagnosis was 4 (IQR 1 to 8) days. Women had a longer time from symptom onset to diagnosis compared with men (median 5 days [IQR 2 to 8 days] versus 2 days [IQR 1 to 4.5 days]), difference 3 days, 95% confidence interval [CI] 1 to 5 days) and were almost twice as likely as men to have had multiple health care encounters prior to diagnosis (46% versus 25%, difference 21%, 95% CI, 2 to 40). Time from symptom onset to diagnosis and number of health care encounters prior to diagnosis were not associated with adverse 180-day outcomes.

Conclusion: Women were more likely to have multiple health care encounters prior to cerebral venous thrombosis diagnosis. However, this was not associated with worse outcomes. [Ann Emerg Med. 2026;87:477-483.]

Please see page 478 for the Editor's Capsule Summary of this article.

Keywords: Cerebral venous thrombosis, Diagnosis delays, Patient-reported outcomes, Functional outcomes.

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INTRODUCTION

Study Objective

Cerebral venous thrombosis refers to thrombosis of the cerebral venous sinuses or veins. Younger women are more often affected due to cerebral venous thrombosis's association with oral contraception and the postpartum period.[1] Diagnosis of cerebral venous thrombosis can be delayed due to its often-insidious symptom onset, frequent absence of focal neurologic features, and distinct demographic profile compared with other stroke types. In contrast to ischemic stroke, in which diagnosis often occurs within 8 hours of symptom onset in patients who present to hospital, average time from cerebral venous thrombosis symptom onset to diagnosis is 4 to 9 days.[2-6] It is not known whether multiple health care encounters prior to diagnosis impacts patient-reported outcomes related to common cerebral venous thrombosis sequelae, including headache and reduced quality of life.

We describe prevalence of multiple health care encounters prior to diagnosis in cerebral venous thrombosis patients, association with functional outcomes, and patient-reported outcome measures (PROMs) in a Canadian randomized trial and parallel registry.

Editor's Capsule Summary

What is already known on this topic

Those with cerebral vein thrombosis often have vague symptoms and a delayed diagnosis.

What question this study addressed

What are the observed number of health care encounters, time to diagnosis, and functional outcomes for a cohort of patients in whom cerebral vein thrombosis is ultimately diagnosed?

What this study adds to our knowledge

In an analysis of a Canadian multisite trial of those with cerebral vein thrombosis, 39% experienced more than one health care encounter prior to diagnosis, with a median time to diagnosis of 4 days, women having more encounters and longer time to diagnosis. The delay was not associated with adverse clinical outcomes.

How this is relevant to clinical practice

Delayed diagnosis and repeat care episodes in those with cerebral vein thrombosis are common and an opportunity for future care.

METHODS

We performed a planned analysis examining care-seeking patterns in adults in whom cerebral venous thrombosis is diagnosed and who are enrolled in the study of rivaroxaban for cerebral venous thrombosis (SECRET) trial or the TOP-SECRET registry. SECRET was a phase II, prospective, open-label, blinded-end point 1:1 randomized controlled trial enrolling patients from 12 comprehensive Canadian stroke centers. Diagnosis of disease was done in the emergency setting for all patients. Methods and primary trial results have been published.[7] Briefly, the trial studied patients aged 18 years and older within 14 days of cerebral venous thrombosis diagnoses (confirmed on computed tomography/magnetic resonance [CT/MR] venography). Participants were randomized to a minimum of 6 months of rivaroxaban 20 mg daily versus standard-of-care anticoagulation (warfarin or low-molecular weight heparin). The parallel registry, TOP-SECRET, enrolled patients presenting within the same timeframe who declined randomization or who did not otherwise meet inclusion criteria for SECRET. All 102 participants underwent the same follow-up assessments over 12 months. The study received approval from the Research Ethics Board at the University of British Columbia and all participating sites.

Patient demographics, number of health care encounters for cerebral venous thrombosis-associated symptoms, timing from symptom onset to diagnosis, and symptoms and signs at diagnosis were collected from all participants. The variable related to the number of health care encounters prior to diagnosis was patient-reported and specific to symptoms related to the current diagnosis of cerebral venous thrombosis. Outcome measures were the modified Rankin Scale (mRS and primary outcome), and PROMs (secondary outcomes), including Euro Quality of Life-5 Dimensions-5 levels (EQ-5D-5L) and Visual Assessment Scale (EQ-VAS), Patient Health Questionnaire (PHQ-9), Headache Impact Test (HIT), and Fatigue Assessment Scale (FAS). Proxy data were permitted for the mRS but not for the PROMs. Non-mRS missing data were excluded from analysis without imputation or last timepoint carried forward.

We described patient demographics, clinical variables, and neuroimaging data of patients who recieved a diagnosis of CVT at their first encounter versus those requiring more encounters. The 95% confidence interval (CI) in the difference of the median time to presentation by sex was obtained through the percentile method from the ordered bootstrap distribution (2.5 and 97.5 percentile. We used univariable and multivariable logistic regression to examine odds ratios for repeated encounters prior to diagnosis by sex, controlling for age, presentation with isolated headache, and relevant past medical history.

Finally, we performed linear or ordinal regressions to examine the association between one or more encounters prior to diagnosis on 180-day functional and patient-reported outcomes, controlling for age and sex. Outcomes with significant deviation from normality were log-transformed prior to regression. No adjustment was made for multiple testing. Statistical analyses were performed using STATA/BE 17 (StataCorp LLC, College Station, TX). Deidentified participant data are available on request following an approved proposal and signed data access agreement.

RESULTS

A total of 102 patients were recruited from March 2019 to October 2021 (median age 45 [IQR 31.0-61.0] years, 70/102 women); 53 from SECRET and 49 from the registry. One patient from the registry was excluded because of missing baseline data regarding the timing of symptom onset.

More than one-third of patients (40/102, 39%) had more than or equal to one health care encounter prior to cerebral venous thrombosis diagnosis (Table 1). The median time from symptom onset to diagnosis was 4 days (IQR 1 to 8 days) (Figure 1, Table E1, available at

Table 1. Baseline characteristics and outcomes in patients with single and multiple health care encounters prior to cerebral venous thrombosis diagnosis.

	Total	1 Encounter	>1 Encounter
Characteristics	**N=102**	**N=62**	**N=40**
Age, y (median, IQR)	45.0 (31.0-61.0)	47.0 (35.0-63.0)	39.5 (27.5-58.0)
Sex, women (%)	68.6	61.3	80.0%
Ethnicity (missing=3) (%)			
East Asian	11.8	11.3	12.5
Indigenous	2.9	3.2	2.5
Other	7.8	6.5	10.0
South Asian	6.9	6.5	7.5
White	67.6	67.7	67.5
Past medical history (%)			
History of VTE	14.7	16.1	12.5
History of stroke or TIA	4.9	3.2	7.5
History of cancer	6.9	8.1	5.0
History of migraine	11.8	8.1	17.5
Sex specific risk factors in women participants (n=70), %			
Pregnant	1.4	2.6	0
Postpartum	1.4	2.6	0
Oral contraceptive	44.3	42.1	46.9
Hormone replacement therapy	4.3	7.9	0
Presenting clinical features (%)			
NIHSS>0 (missing=3)	35.4	39.0	30.0
Seizure	35.3	43.5	22.5
Focal weakness	35.3	40.3	27.5
Isolated headache	23.5	19.4	30.0
Baseline noncontrast CT abnormality (missing=15)	51.7	51.0	52.8
Hemorrhage	40.0	37.9	43.2
Venous infarct	24.1	25.5	22.2
Midline shift	11.6	11.8	11.4
180-day mRS (missing=8)			
0	28.4	32.3	22.5
1	45.1	38.7	55.0
2	17.6	19.4	15.0
6	1.0	1.6	0.0
180-day EQ-5D (median, IQR, missing=16)	0.9 (0.8-0.9)	0.9 (0.8-0.9)	0.9 (0.9-0.9)
180-day EQ-VAS (mean, SD, missing=16)	80.0 (70.0-90.0)	80.0 (67.5-90.0)	80.0 (75.0-85.0)
180-day PHQ-9 (median, IQR, missing=17)	3.0 (0.0-6.0)	3.0 (0.0-6.5)	3.0 (1.0-6.0)
180-day HIT-6 (mean, SD, missing=17)	44.0 (36.0-56.0)	40.0 (36.0-56.0)	48.0 (38.0-56.0)
180-day FAS (median, IQR, missing=17)	19.0 (13.0-24.0)	19.0 (12.0-25.5)	18.0 (16.0-21.0)

TIA, transient ischemic attack; *NIHSS,* National Institute of Stroke Scale.

http://www.annemergmed.com). For encounters where initial diagnosis of cerebral venous thrombosis was not made, 20% were to a family physician, 28% to emergency departments (EDs), 6% to neurologists, and 7% to another specialty or non-MD health care provider (hematology, otolaryngology, audiology, ophthalmology/optometry). Multiple encounters were almost twice as common for women (46% versus 25%, difference 21%,

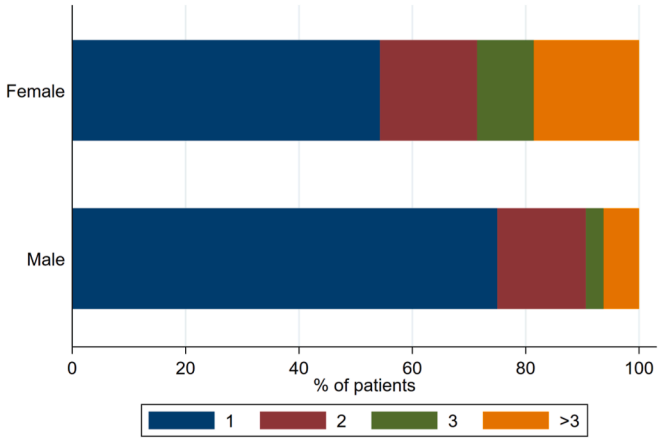

Figure 1. Number of health care encounters related to cerebral vein thrombosis diagnosis.

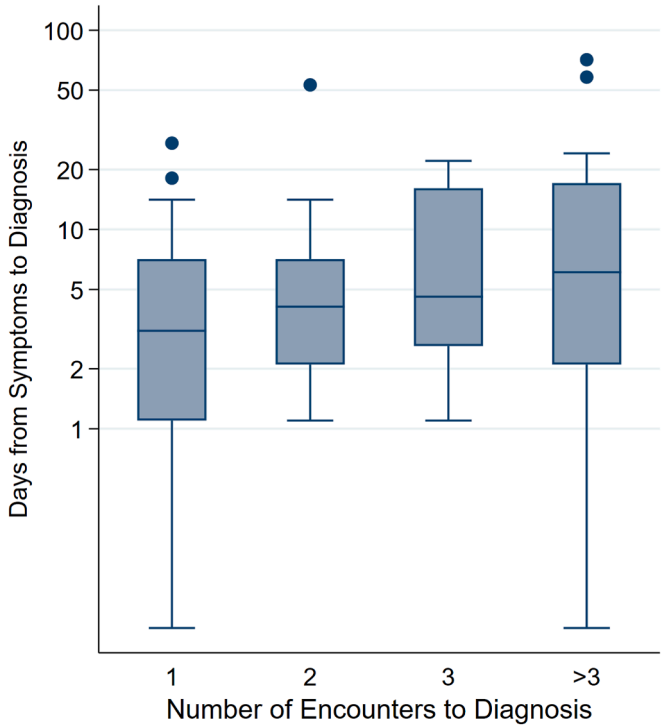

Figure 2. Days from symptom onset to diagnosis by number of encounters to diagnosis.

95% CI 2 to 40) (Figure 2). Women also had a longer time from symptom onset to diagnosis (median 5 days [IQR 2 to 8 days] versus 2 days [IQR 1 to 4.5 days], difference 3 days, 95% CI 1 to 5 days). The unadjusted odds of multiple versus single encounters for cerebral venous thrombosis diagnosis for women versus. men were 2.53 (95% CI 1.00 to 6.39). The directionality and magnitude of the effect remained similar with adjustment for age, presentation with isolated headache, and past medical history (Table 2).

Those diagnosed on their initial encounter were more likely to present with seizures (44% versus 22%, difference 22%, 95% CI 3 to 40). There were no differences with regard to presentation with focal weakness or isolated headache, and there were no differences in rates of abnormal findings on noncontrast head CT. Those with single versus multiple encounters prior to diagnosis did not have differences in 180-day outcomes (mRS, EQ-5D-5L, ED-VAS, PHQ-9, HIT, or FAS; Table 1, Figure E1, available at http://www.annemergmed.com). These results did not change after adjustment for age and sex (Table E2, available at http://www.annemergmed.com).

LIMITATIONS

This cohort had an underrepresentation of severely affected patients, so our findings may not be generalizable to patients with very severe cerebral venous thrombosis, such as those requiring surgical decompression or endovascular therapy (less than 10% in a recent large registry).[5] Some participants had missing outcome data at 6 months (n=8 for 6-month mRS; n=16-17 for patient-reported outcomes), which may have biased our findings. We did not capture the duration from symptom onset to the first health care encounter. Thus, we do not know what proportion of diagnostic delay was due to delays from patients seeking care. We also lack information on symptoms endorsed at preceding nondiagnostic encounters. This information would be valuable to inform future strategies for frontline provider education. Additionally, the number of previous encounters was collected from patients, with possible recall errors or misattribution of unrelated symptoms to the cerebral venous thrombosis.

DISCUSSION

In this Canadian study conducted at tertiary stroke centers, 40% of cerebral venous thrombosis patients experienced multiple health care encounters for their cerebral venous thrombosis symptoms prior to diagnosis. Women more frequently had multiple encounters. These findings complement recent work using Canadian health services data showing a high proportion (58%) of individuals with more than or equal to one health care encounter within the 7 days prior to their cerebral venous thrombosis hospitalization; women were likelier to experience multiple encounters.[8] A previous US study examining ED encounters prior to cerebral venous thrombosis hospitalization found that 3.6% had previous ED encounters.[9] This rate is much lower than in our study, suggesting that counting ED visits alone may underrepresent the prevalence of repeat health care presentations prior to diagnosis. Further, the use of

Table 2. Odds of diagnosis with multiple versus single health care encounters, women versus men, crude and multivariable logistic regression.

Characteristics	OR For Women Sex, 95% CI	Other Model Parameters
Sex	2.53 (1.00-6.39)	Pseudo $R^2 = 0.030$
Sex adjusted for age (>45 y)	2.45 (0.96-6.22)	Age, OR 0.75 (0.33-1.70) Pseudo $R^2 = 0.034$
Sex adjusted for age (>45 y) and Sex*age interaction	2.38 (0.64-8.88)	Age, OR 0.75 (0.33-1.70) Sex*Age Interaction, OR 0.94 (0.15-6.07) Pseudo $R^2 = 0.034$
Sex adjusted for age (>45 y) and isolated headache on presentation	2.63 (1.02-6.97)	Age, OR 0.80 (0.34-1.83) Isolated headache, OR 1.93 (0.74-5.07) Pseudo $R^2 = 0.047$
Sex adjusted for age, isolated headache, and history of prior venous thromboembolism, stroke/TIA, migraine, or cancer	3.08 (1.09-8.68)	Age, OR 0.70 (0.28-1.72) Isolated headache, OR 2.08 (0.77 - 5.64) History of VTE, OR 0.49 (0.11 - 2.12) History of stroke/TIA, OR 8.3 (0.81 -85) History of cancer, OR 0.46 (0.07 - 3.11) History of migraine, OR 2.64 (0.71-9.80) Pseudo $R^2 = 0.091$

OR, Odds ratio; *TIA*, transient ischemic attack; *VTE*, venous thromboembolism.

International Classification of Diseases diagnosis codes to identify preceding diagnoses of seizure and headache in the US study may have yielded lower sensitivity for delayed diagnosis.

The median time between symptom onset and diagnosis in our cohort was 4 days. This timeframe is similar to diagnostic delays in ACTION-cerebral venous thrombosis (n=935; median time to diagnosis 4 days, IQR 1 to 10 days), a large international retrospective cohort study of patients with cerebral venous thrombosis hospitalized between 2015 and 2020.[5] These timeframes are shorter, however, than those in historical observational cohorts,[4,6] which may be explained by increases in the routine use of noninvasive vascular imaging (CT or MR venography), which are the standard of practice for cerebral venous thrombosis diagnosis.[9] Unlike other studies, we did not find that presenting with an isolated headache was associated with a longer time to diagnosis.[5,10]

Our findings of longer duration from symptom onset to diagnosis in women are consistent with other stroke and cardiovascular literature.[11] The directionality of this relationship remained after adjustment for age and past medical history and highlights that, particularly in younger women, cerebral venous thrombosis should be included in the differential diagnosis in the appropriate clinical context, and appropriate investigations, including vascular neuroimaging, should be pursued.

We did not find any associations between time to diagnosis and adverse clinical outcomes at 6 months, including on PROMs (EQ-5D, ED-VAS, PHQ-9, HIT, or FAS). Our findings are consistent with previous studies that did not find an association between diagnostic delay and outcomes in cerebral venous thrombosis.[4,5,8,10] This lack of association between delayed diagnosis and outcomes in cerebral venous thrombosis is likely because the natural history of the disease is favorable overall and, in our cohort, also likely reflects the high proportion of patients who had mild symptoms at baseline.[7] Prompt diagnosis of cerebral venous thrombosis is still important as it reduces the burden of health care utilization and impacts patient experience.[12] Further, a minority of cerebral venous thrombosis patients develop serious adverse sequelae, including intracerebral hemorrhage, coma, status epilepticus, or death. Acknowledging that cerebral venous thrombosis is a rare disease, future multicenter work should focus on diagnostic delays and outcomes in this severely affected group of cerebral venous thrombosis patients to identify opportunities for quality improvement.

The broadly accepted definition of medical error from the United States National Academies of Sciences, Engineering, and Medicine is "the failure to establish an accurate and timely explanation of the patient's health problem."[13] Diagnosis of cerebral venous thrombosis can be challenging for a variety of reasons. Symptoms of headache and vision changes are common in cerebral venous thrombosis but are nonspecific and have a broad differential diagnosis. Cerebral venous thrombosis can be overlooked in the differential diagnosis for these common complaints due to its relative rarity.[14] In patients presenting with headache and vision changes, in addition to arranging follow-up and instructing patients on when to seek reassessment, it is

prudent to consider cerebral venous thrombosis within the differential and to review for symptoms of elevated intracranial pressure (vision changes with new/different headache pain which worsens with straining, lying down or Valsalva), thrombosis risk factors (eg, use of oral contraceptives, peripartum or malignancy status) and a personal/family history of thrombosis may be helpful alongside the use of appropriate neurovascular imaging (CT or MR venography) in addition to parenchymal imaging. Multiple presentations for persistent symptoms also warrant a reconsideration of the underlying diagnosis.

In conclusion, within our cohort, time to diagnosis and multiple encounters prior to diagnosis were not associated with adverse functional or PROMs at 180 days in patients with cerebral venous thrombosis. Our findings may be due to relatively short times to diagnosis in a cohort with milder clinical presentations.

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Author affiliations: From the Division of Neurology (Zhou, Dizonno, Villaluna, Azote, Ratnaweera, Gaal, Wilson, Medvedev, Field), University of British Columbia; Department of Clinical Neurological Sciences (Mandzia, Sposato), Western University; Department of Clinical Neurosciences (Almekhlafi, Hill), University of Calgary; Diagnostic and Interventional Neuroradiology Department (Bala), University Hospital of Tours, France; Alberta Children's Hospital (Alhabli), Calgary; University of Saskatchewan College of Medicine (Graham); University of Ottawa (Blacquiere), Medicine, Ottawa; Faculty of Medicine (Boulos), University of Toronto; Division of Adult Neurology (Buck), Department of Medicine, Edmonton, University of Alberta Hospital; Centre Hospitalier de l'Universite de Montreal (Odier), Montreal; Faculty of Health Sciences and Medicine (Perera), University of Toronto, Faculty of Medicine (Pikula), McMaster University; Southern Medical Program (Tkach), the University of British Columbia Okanagan.

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Data sharing statement: Deidentified participant data will be available, once planned subanalyses are complete, on request following an approved proposal and with a signed data access agreement. Requests should be emailed to the corresponding author.

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