

Journal Club: Trends in Incidence and Epidemiologic Characteristics of Cerebral Venous Thrombosis in the United States

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Neurology® 2021;97:144-147. doi:10.1212/WNL.00000000000011760

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Cerebral venous thrombosis (CVT) is rare. Early estimations of its incidence were derived from autopsy series and were extrapolated to be around 0.1 to 0.2 patients with CVT per 100,000 per year.¹ Recently, a cross-sectional study in the Netherlands and a population-based study in Australia found a much higher incidence of up to 1.6 per 100,000 per year.^{2,3} Even higher incidences have been reported in the Middle East.⁴ Wider availability of imaging, technological advances, and a shift in risk factors might explain these differences.²⁻⁴

This Journal Club article reports on a large retrospective cohort study by Otite et al.⁵ conducted in the United States, which confirmed the trend towards an increased incidence of CVT. The authors also shed light on age-, sex-, and race-specific incidence of CVT and risk factor profiles of patients with CVT in a multiethnic population. A clear understanding of the epidemiologic characteristics of CVT has important implications for public health.

Hypothesis and Design

The authors hypothesized that race-, age-, and sex-specific incidence of CVT has increased in the United States over the past decade. Given the lack of recent data on dynamics of demographic and risk factor profiles in multiethnic populations,^{5,6} the authors' primary aims were to determine the current age-, sex-, and race-specific incidence of CVT in the United States, investigate trends in incidence and overall burden of CVT hospitalizations in the United States, and describe trends in the prevalence of CVT risk factors in the United States over the past decade. They conducted a large retrospective cohort study using the State Inpatients Database (SID) of New York and Florida and the National Inpatient Sample (NIS) database in the United States.

Methods

Case Identification for Incident CVT Hospitalizations

The authors used administrative claims data from acute care hospitals contained in the SID of Florida and New York, which covered up to 97% of US community hospital discharges, to identify patients with first-ever CVT between 2006 and 2016. Florida and New York are home to >10% of the total US population and are also demographically diverse.

National Burden of CVT Hospitalizations

To ensure generalizability of the results to the entire United States, data on national trends in the burden of CVT hospitalizations and the epidemiologic characteristics of CVT were acquired from the NIS database, which comprises a 20% stratified sample of all US hospital discharges.

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

US Population Data

Data on age, sex, and race were obtained from the US Census Bureau website.

Outcome Identification

A first-ever CVT was defined as the first hospitalization incorporating a corresponding ICD-9/10 code. A 1-year washout period (2005) was applied to minimize the influence of earlier CVT hospitalizations on study estimates after this year. Relevant risk factors for CVT were defined as already established in the literature and were identified by the Health Care Utilization Project software or the ICD-9/10 codes. Age was stratified according to the following age groups: 18–44, 45–64, and ≥65 years. The nature of the dataset allowed the sex categories of men and women and the racial categories of non-Hispanic White, non-Hispanic Black, African American, Hispanic, and Asian to be differentiated.

Statistical Analysis

Descriptive statistics were used to calculate the annual incidence of CVT in the 2 states studied. Age-stratified and crude estimates by sex and race were also obtained. Similarly, the annual incidence of CVT in the whole United States and in both sex groups was calculated. Joinpoint regression models were applied in this study to assess the trends in the incidence of CVT and in the burden of CVT hospitalizations over time.

Joinpoint regression is a well-known approach used to study potential changes in trends over time that might happen following interventions or changes in external conditions. It can identify if/when changes in population parameters occur. Time and population measures are inputted into the model. For example, it has been applied for analysis of cancer or motor vehicle collision mortality rates and of disease risk. A logistic regression model was used to identify a possible linear trend in the prevalence of each CVT risk factor over time. Each risk factor was used as the dependent variable and the year of discharge as the independent variable, evaluated continuously, with the significance of differences in trend over time assessed using the Wald test. Regression analysis is a statistical technique for estimating the relationships among variables.

Results

Between 2005 and 2016, there were 57,315 weighted admissions of patients with CVT in the United States, representing 0.66% of all adult hospitalizations for any cerebrovascular disease within this period. A cohort of 5,567 patients with CVT was identified. About two-thirds of all patients hospitalized with CVT in the United States were women, but this proportion declined over time, while the proportion of hospitalizations of men increased by 88.6% over time (p -trend <0.001). The mean age of women with CVT steadily increased during the study period (p -trend <0.001). Over time, the proportion of young women with CVT declined significantly, while the proportion

of all other age groups affected increased. The combined proportions (women and men) of elderly patients hospitalized with CVT more than doubled during the study period from 11.2% to over 24%. The age and sex distribution of patients with CVT in Florida and New York were similar to that of the entire United States.

Regarding CVT risk factors, the proportion of hospitalizations of women during pregnancy and puerperium decreased by over 50% over time in the United States as a whole but remained the most frequent risk factor for CVT. The proportion of hospitalizations of patients with comorbid cancer and CNS trauma increased significantly over time in both sexes (all p -trends <0.001). The findings for Florida and New York were again very similar to that of the entire United States.

Annual age- and sex-standardized incidence of CVT in the 2 selected states in cases/million population ranged from 13.9 to 20.2, but incidence was significantly higher in women. The incidence of CVT increased over the study period, but the rate of increase was 4-fold more rapid in men and increased in all age groups. The increase in incidence in women was driven by middle-aged and elderly women. The sex ratio in elderly patients with CVT was evenly distributed. The national burden of hospitalizations of patients with CVT increased consistently throughout the study period. Incidence also differed by race (Black > White > Asian).

A sensitivity analysis restricted to the period from 2006 to 2014 did not lead to any relevant differences in the findings.

Interpretation

The study by Otite et al.⁵ has contributed to the literature by describing the current incidence of CVT in the United States and highlighting demographic changes in this disease.

The strengths of this study are the population-based dataset with details on ethnic background and the large sample size, which allowed for meaningful subgroup analyses. In addition, the authors provided national estimates of the burden of risk factors.

The main limitation of the study is the potential underdetection/underestimation bias. Several aspects of the study could contribute to this potential bias. First, patients with asymptomatic or mild CVT were probably not hospitalized. Second, codes used for CVT diagnosis have only modest sensitivity. Third, a small proportion of patients may have been misdiagnosed when they initially presented at the emergency department. Also, cumulative incidence calculations assumed a closed population, which may have contributed not only to potential underdetection but also to overdetection/overestimation. A further contribution to overdetection/overestimation is possible from patients who were counted more than once or who were hospitalized for non-CVT-related illness. Moreover, hospitalizations with missing

tracking variables as well as missing information on age or sex and patients who were nonresidents of the state in which they were hospitalized were excluded. This bias might decrease the validity of the study. Finally, the generalizability of the data to the whole United States is somewhat limited, since the CVT population selected represents a selection bias.

This study used claims data, which raises the following concerns: that health care providers might upcode diagnoses in claims, that claims data consist of standardized but non-homogeneous information, that duration of follow-up is usually restricted, and that validation studies concerning claims are scarce. Major benefits of claims data include the review of a large number of patients treated by different health care providers and their high external validity, as there is no reimbursement without submitting data.

Based on the literature, we would have expected oral contraceptive use to be a far greater CVT risk factor and this raises the question of whether it was underreported in this cohort.^{7,8} Furthermore, the formulations of oral contraceptives used likely varied among the population under study and over time. In addition, transgender individuals taking oral contraceptives were probably neglected in the population analyzed. Also, hormone replacement therapy is a well-known risk factor for CVT but was not identified as such in this study.⁸ An increase in intake of hormone replacement therapy in middle-aged and elderly women might partially explain the increase in incidence of CVT in those women over time.

Changes in prevalence of known CVT risk factors, like the increased number of traumas of the CNS and emerging or unknown CVT risk factors, might help to explain the disproportionate increase in the pace of CVT detection over time in men.

Compared to European data, arterial hypertension and diabetes mellitus were found more often in this cohort, which might reflect the higher prevalence of these vascular risk factors in the US population.^{8,9}

Information on hypercoagulable disorders in the study patients, for example, factor V Leiden or prothrombin gene mutation, was not available although thrombophilia is one of the most common CVT risk factors.⁸

Thus, there might have been both underascertainment and overascertainment bias concerning risk factors.

The analysis of trends was based on the implicit assumption of unchanged coding practices over time but the study period overlapped with the changeover from ICD-9 to ICD-10 utilization. ICD-10 goes along with higher positive predictive values of CVT.¹⁰

Whether the overall increase in CVT incidence seen in this study constitutes a true increase resulting from changing risk factors or

an artifactual increase resulting from better detection remains an open question even though the authors provided some explanations supporting the first hypothesis. Importantly, the improvement not only in radiologic but also in clinical detection may have occurred disproportionately in different demographic groups over time. Overall, more women were affected by CVT than men, but these differences were not seen in elderly patients in this cohort, which is in line with previous findings.⁷

The study has made an important contribution to the field of cerebrovascular diseases and has highlighted the changing trends in demographic characteristics of patients with CVT. Its crucial findings were the doubling of the incidence of CVT hospitalizations in the elderly and the increased age- and sex-standardized incidence of CVT in Black patients.

Inequity plays an important role in cerebrovascular health and should be a focus in future cohort studies as well as prospective multiethnic studies in this field.

Acknowledgment

The authors thank Susan E. Kaplan for proofreading the manuscript.

Study Funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Neurology 2021;97:144-147 Published Online before print March 3, 2021
DOI 10.1212/WNL.00000000000011760

This information is current as of March 3, 2021

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