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Risk factors and predictors of outcomes in 243 Chinese patients with cerebral venous sinus thrombosis: A retrospective analysis

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ABSTRACT

Objectives: To investigate the risk factors and predictors of outcomes in a cohort of Chinese patients with cerebral venous sinus thrombosis (CVST), so as to provide a reference for customized clinical decision.

Patients and methods: A total of 243 Chinese patients, diagnosed as a first CVST were enrolled in this retrospective study from March 2013 through April 2017. Risk factors and predictors of outcomes for CVST were summarized and analyzed by Chi-square test and logistic regression analysis.

Results: Of the 243 cases, obstetric cause (19.8%) was the leading risk factor for CVST, followed by infection (17.7%) and anemia (17.7%). Gender differences in the risk factors for CVST were analyzed, showing that obstetric cause was the top risk factor in female, while hyperhomocysteinemia (22.3%) was the top risk factor in male. In age subgroups, obstetric cause (26.3%) and anemia (17.6%) were more commonly observed in age ≤ 44 years and age > 44 years subgroup, respectively. The ratio of poor outcomes (mRS = 3–6) in this cohort was 23.0%, and central nervous system (CNS) infection was closely related to poor outcomes at discharge ($p = 0.023$).

Conclusion: The predominant risk factor for CVST, in this Chinese cohort, may still be obstetric cause in female and hyperhomocysteinemia in male. In addition, CNS infection may predict poor outcomes in CVST patients.

1. Introduction

A number of risk factors have been shown to be associated with cerebral venous sinus thrombosis (CVST), posing a huge challenge to the etiological workup. For example, a study from Italy indicated a strong correlation between CVST and oral contraceptive use [1]. In addition, patients with genetic thrombophilia such as prothrombin G20210A mutation display a higher propensity to CVST when compared to other venous thrombosis [2]. Apart from these well-established risk factors, several risk factors have recently been reported in case series, including Behcet's disease, lumbar puncture, paroxysmal nocturnal hemoglobinuria, and methylmalonic aciduria, which further broaden our knowledge of the pathogenesis of CVST [3–7].

The results regarding the prevalence of CVST risk factors are mixing according to previous studies [8–19]. The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), which is by far the largest prospective study, reported that thrombophilia was the strongest risk factor, accounting for 34.1% patients; while infection, pregnancy or puerperium were identified as the most common causes of CVST in other studies from Mexico and Tunisia [9,14,18]. However, it should be noted that few patients from China were analyzed previously, even in the study from ISCVT. Given the disparity in ethnic population and healthcare among different countries, risk factor profiles may vary between Western and Asian populations. Therefore, studies exploring the risk factors for CVST based on regional and racial differences are warranted to further identify the disease. This study aims to investigate the risk factors and predictors of outcomes for CVST in a Chinese cohort, so as to provide a reference for clinicians to prevent CVST and optimize their clinical decisions.

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2. Patients and methods

2.1. Patient enrollment

A total of 243 Chinese patients who were diagnosed as a first CVST in Xuanwu hospital were enrolled consecutively in this study from March 2013 through April 2017. The diagnosis of CVST was based on various imaging modalities including magnetic resonance imaging (MRI), magnetic resonance venography (MRV), computed tomography (CT), computed tomography venography (CTV) and/or digital subtraction angiography (DSA). The inclusion criteria were as follows: 1) patients who fulfilled the diagnostic criteria of CVST, 2) diagnosis of CVST confirmed by at least two imaging modalities, 3) first-onset CVST and 4) patients aged from 18 to 80. The exclusion criteria included: 1) patients who only performed one kind of imaging modalities and 2) patients without complete data except for protein S/C, AT-III (which were only tested in 171 patients for protein S/C and in 182 patients for AT-III).

Subgroup analyses were performed according to genders (female and male) and ages (age $\leq$ 44 years and age > 44 years).

2.2. Data collection

Following data from the database were analyzed: demographic data, symptoms and signs, past medical history, CVST risk factors, the time from initial symptoms occurred to diagnosis confirmed, mRS at both admission and discharge, laboratory findings, neuroimaging presentations, location of occluded sinus, more than 3-month (if available) functional outcomes, and treatments. All patients enrolled underwent the following basic laboratory tests upon admission, including complete blood count, serum chemistries, hyperhomocysteinemia, coagulation studies, thyroid function tests, serum tumor markers, serologies (HIV, syphilis), C-reaction protein, erythrocyte sedimentation rate, antinuclear and antineutrophil cytoplasmic antibodies as well as anti-cardiolipin antibodies. Lumbar punctures were performed in almost all patients except for those who were under life-threatening condition at admission. CSF analysis (presence of cells, protein and glucose levels, Gram stain, fungal and bacterial smear, virus antibodies, immunoglobulins and oligoclonal bands) was examined. Since some thrombophilia screening tests (genetic tests in particular) were not widely carried out in early years, protein S and C were only tested in 171 patients and AT-III in 182 patients.

2.3. Follow-up

Follow-up were performed mainly by direct interview and telephone interviews.

2.4. Treatment and outcome

All patients were administered enoxaparin at 100 IU/kg subcutaneously twice a day when in hospital. Endovascular treatment would be considered if clinical conditions deteriorated despite anticoagulation. Endovascular techniques in our hospital include direct catheter thrombolysis and mechanical thrombectomy. The choice of techniques was based on interventionalists' assessment. Oral anticoagulants were initiated immediately after discharge for a minimum of 3–6 months, while the selection of anticoagulant (vitamin K antagonist or non-vitamin K antagonist oral anticoagulant) would be left to the physicians based on the individualized condition of each patient.

The modified Rankin Scale (mRS) was evaluated at both discharge and outpatient follow-up to measure the clinical outcomes. The mRS = 0–2 was defined as relatively favorable outcomes (independency), whereas mRS = 3–6 was poor (dependency or death).

2.5. Statistical analysis

All statistical analyses were conducted using SPSS Version 19.0 (SPSS, Inc., Chicago, IL). Continuous data were presented as mean $\pm$ SD when following a Gaussian distribution; otherwise median (IQR) was used. Chi-square or Fisher exact test as appropriate for categorical data and *t*-test for continuous data were performed to test the hypothesis. A logistic regression model analysis was established to identify prognostic factors for poor clinical outcomes (mRS = 3–6) in this study. Only factors that were closely correlated to the dependent variate (with $p < 0.1$ in Chi-square test) could be involved in the regression model. Results were displayed as odd ratio (OR) and 95% confidence interval (95%CI), and p-value < 0.05 was considered as statistical significance.

3. Results

3.1. Baseline characteristics

Data from 243 eligible Chinese patients were involved in the final analysis. Patients enrolled in this cohort were from 23 provinces (Supplementary material Fig. 1), which covered 71% of regions in China. Han nationality accounted for 95% of the patients, while ethnic minorities accounted for 5%. The mean age of the overall population was 36 $\pm$ 13 years, and 131 (54.3%) patients were female. The median onset-to-door time was 8 days. Headache (90.1%) was the most common symptom, followed by focal neurological deficits (30.5%), seizure (30.5%), visual impairment (24.3%), and consciousness disorder (14.0%). Neuroimaging demonstrated that the lateral sinus (81.1%) was the most commonly involved sinus, followed by the sagittal sinus (76.5%), the sigmoid sinus (59.3%), the straight sinus (22.6%), the cortical veins (10.3%), the jugular veins (10.3%), and the cerebral deep venous system (2.5%). In this study, 208 (85.6%) patients had multi-sinus involvement and 134 (55.1%) had brain parenchymal lesions, including ischemic lesions (33.7%) and brain hemorrhage (21.4%).

3.2. Risk factors for CVST

The prevalence of risk factors for CVST was detailed in Supplementary material Table 1. The top three risk factors for CVT (in descending order of prevalence) were obstetric cause (19.8%), infection (17.7%), anemia (17.7%). Others included hyperhomocysteinemia (14.4%), antiphospholipid and anticardiolipin antibodies (10.3%), oral contraceptive uses or hormone replacement therapy (HRT) (9.5%), and thyroid diseases (9.5%), etc. Multiple factors were identified in approximately 50.2% of all patients and also took up the largest proportion in each subgroup. Among them, the coexistence of prothrombotic conditions and hematologic disorders was the most common condition.

In terms of gender, we found that gender-specific risk factors (obstetric cause, oral contraceptive use and HRT) may explain a high rate of CVST in female (36.6%), including 3 patients with high-risk pregnancy (2.3%), 39 patients in puerperium (29.8%), 6 patients with abortion history (4.6%), and 26 patients with history of oral contraceptive use or HRT (19.8%). By contrast, the most common risk factor for CVST in male was hyperhomocysteinemia (22.3%). In regards to other risk factors, no statistical difference was found between the two gender subgroups (male vs. female) except for thrombocythemia (2.7% vs. 9.2%, $p = 0.036$), anemia (4.5% vs. 29.0%, $p < 0.001$), hyperhomocysteinemia (22.3% vs. 7.6%, $p = 0.001$) and thyroid diseases (1.8% vs. 16.0%, $p < 0.001$). Besides, in this cohort of CVST, protein S (which was tested in 171 patients) deficiency deserved more attention due to a high proportion (55.0%), especially in female patients (female vs. male, 67.6% vs. 36.2%, $p < 0.001$). Notably, it was found that in the female subgroup, protein S deficiency occurred in 61% of patients who were pregnant or have recently given birth and 72.1% of non-

pregnant women. In comparison, only 36.2% of male had the evidence of protein S deficiency, the ratio of which was significantly lower than that of pregnant and puerperal female or non-pregnant female ($p = 0.012$ and $p < 0.001$, respectively).

For age subgroups, obstetric cause was the leading risk factors in the patients aged ≤ 44 years rather than those aged > 44 years (26.3% vs. 3.0%, $p < 0.001$). Infection was the leading risk factor in the age > 44 years subgroup (23.5%), even though the frequency of infection between the two age subgroups did not reach statistical difference. In addition, Malignancy was more often seen in the age > 44 years subgroup than in the age ≤ 44 years subgroup (7.4% vs. 1.7%, $p = 0.07$).

3.3. Risk factors for the prognosis

At discharge, 77.0% patients showed favorable outcomes, while the poor outcome rate and the death rate were 23.0% and 2.8%, respectively.

Central nervous system (CNS) infection exhibited a significant correlation with poor outcomes at discharge ($p = 0.023$). Other clinical variables strongly related to poor outcomes at discharge included neurological deficits ($p < 0.001$), seizure ($p < 0.001$), consciousness disorder ($p < 0.001$), deep cerebral venous thrombosis ($p = 0.027$), inferior sagittal sinus thrombosis ($p = 0.014$), brain hemorrhage ($p < 0.001$), subarachnoid hemorrhage ($p < 0.001$), ischemic brain lesions ($p = 0.002$) and herniation ($p < 0.001$). According to multivariate analyses, the independent predictors of dependency and death at discharge were: neurological deficits (OR, 3.59; 95%CI, 1.52–8.45; $p = 0.003$), consciousness disorder (OR, 5.20; 95%CI, 1.92–14.08; $p = 0.001$), herniation (OR, 23.64; 95%CI, 2.21–252.78; $p = 0.009$), brain hemorrhage (OR, 3.15; 95%CI, 1.20–8.23; $p = 0.02$), and inferior sagittal sinus thrombosis (OR, 5.48; 95%CI, 1.20–25.07; $p = 0.028$)(see Table 1).

Outpatient follow-up information was available for 159 patients (65.4%). The median outpatient follow-up period was 18 months (interquartile range [IQR]: 12–36). Overall, 91.8% of patients were recovered well (mRS = 0–2), and 6.9% remained dependent (mRS = 3–5). Only 2 patients died after discharge.

4. Discussion

To the best of our knowledge, this is the first retrospective study investigating the risk factors and outcomes of CVST in Chinese patients based on a relatively large sample size. To date, the majority of studies regarding CVST were conducted in Europe or other regions of Asia such as Pakistan and India [8–10,13,16]. Characteristics and risk factors for the CVST and outcomes in Chinese have yet to be fully described. Given the presence of regional, racial and lifestyle disparities among different countries, it is imperative to explore the risk factors and outcomes of Chinese patients with CVST. Results in this study are considered representative due to the large sample size and wide distribution of patients from the majority of provinces in China, which may, at least partially, help to improve CVST prevention and treatment in China.

Baseline characteristics of this cohort are generally in consistent with what has been previously reported in other studies [9]. However, only 53.9% of the patients in the present study were female and this ratio apparently differs from prior reports with a clear predominance in female, implying that some Chinese men may be more vulnerable to CVST than expected. Additionally, low prevalence of oral contraceptive use in Chinese women and advancement in pregnancy health care may contribute to the indistinctive gender predilection of CVST in China [20].

The prevalence of risk factors was not entirely in accordance with the data from other countries [9,10,16,18,19]. The most frequently identified risk factors in our study were obstetric causes, instead of oral contraceptive use or thrombophilia in whites. The proportion of oral contraceptive use and HRT in Chinese female patients with CVST (18.3%) was considerably lower in comparison to the findings reported in Western CVST studies (35.2%–55%) [8,9,19]. Possible explanation for the discrepancy, on the one hand, is due to a less widespread use of oral contraceptives among Chinese compared to Westerners. Based on the survey data from the United Nations, only 1.2% women of 15–49 years old in China are estimated to choose oral contraceptives as a major contraceptive method, which is much lower than ratios (17.7%–44.8%) prevailing in developed countries [20]. On the other hand, due to the high birth rate in developing countries, pregnancy and puerperium are thought to be the stronge risk factors in these countries [10,14,18]. This can be demonstrated by the fact that a declining trend in the proportion of pregnancy and puerperium was observed in parallel with the growing standard of living and medical services, when comparing CVT data from different countries.

Of note, 171 patients underwent protein S test at admission, in which 55.0% were found with the levels of protein S below the normal range, which was similar to the ratio (57.1%) of protein S deficiency reported in a Indian cohort but is significantly higher than the ratios reported in other studies (3–5%) [10,11,16,18,19]. Clinical diagnosis of hereditary protein S deficiency mainly relies on a combination of history of thrombosis and thrombophilia tests (including genetic tests). However, laboratory tests for protein S may be inaccurate due to a number of reasons. For instance, the plasma levels of protein S may transiently decrease during several specific conditions such as acute thrombosis and pregnancy [21]. Furthermore, vitamin K antagonists may influence the assessment of protein S level in plasma [22]. Lacking of repeated protein S tests at non-acute phase in our study may overestimate the real prevalence of protein S deficiency. Thus, data regarding protein S deficiency among Chinese CVST patients still needs further evaluation. However, no statistical difference was observed in our study between pregnant and non-pregnant female ($p = 0.238$) with respect to the prevalence of protein S deficiency, indicating that

Table 1
Predictors for CVST outcomes.

Clinical Features	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
CNS infection	6.01	1.39–26.01	0.018	2.68	0.39–18.51	0.32
neurological deficits	7.06	3.68–13.55	< 0.001	3.59	1.52–8.45	0.003
seizure	5.11	2.71–9.64	< 0.001	1.97	0.82–4.78	0.13
consciousness disorder	11.15	4.97–25.04	< 0.001	5.20	1.92–14.08	0.001
deep cerebral venous thrombosis	7.12	1.27–39.94	0.027	3.60	0.27–47.85	0.33
inferior sagittal sinus thrombosis	3.67	1.23–10.97	0.22	5.48	1.20–25.07	0.03
brain hemorrhage	6.03	3.08–11.82	< 0.001	3.15	1.20–8.23	0.02
subarachnoid hemorrhage	5.59	2.02–15.48	0.001	1.27	0.29–5.54	0.75
ischemic brain lesions	2.58	1.40–4.75	0.002	1.95	0.80–4.81	0.15
herniation	40.44	5.05–323.92	< 0.001	23.64	2.21–252.78	0.01

Abbreviations: OR, Odds ratio; CI, Confidence interval; CNS, Central nervous system.

pregnancy may not remarkably affect protein S assessment. Interestingly, it was also found that compared to male, protein S deficiency was more prevalent in female whether the patient is pregnant or not, indicating that protein S deficiency may have synergistic effects in female population. These findings may have profound social significance in today's China. In the wake of the implementation of two-child policy, China is bracing for a baby boom, with estimates of 90 million Chinese couples now eligible to have a second child. Therefore, enhancing early recognition of suspected CVST in pregnant women and providing prompt treatment would be an increasingly critical aspect of CVST management in China. Moreover, for CVST patients with obstetric causes, dynamic workup for thrombophilia after pregnancy should be considered to promote CVST prevention.

This study also focused on several potential risk factors mainly reported in case reports including nephrotic syndrome, thyroid disease, thrombocythemia and JAK2 mutations. Although a cause-and-effect relationship has not been fully demonstrated, high frequencies of these risk factors were demonstrated in the previous CVST studies [9,18]. In this study, JAK2 mutations were identified in 12 CVST patients, accounting for 5% of the enrolled patients who had JAK2 mutations tested (prevalence of JAK2 mutation in a general population in China was approximately 1%) [23]. Previous studies reveals that JAK2 mutation may promote the activation of leukocytes and platelets, which may help explain a higher prevalence of JAK2 mutation in CVST patients [24]. Moreover, Coutinho et al. reported a strong association between anemia and CVST (patients vs. controls, 27% vs. 6.5%; adjusted OR, 4.4; 95%CI, 2.8 to 6.9) [25]. Similarly, the ratio of anemia in CVST patients from our study is higher than that in general population (17.7% vs. 14.0%) [26]. Hence, clinicians should be aware of the importance of hematologic abnormalities correction during CVST prevention and management.

The overall outcomes of our study are favorable, with 77.0% patients being independent (mRS = 0–2) at discharge and 91.8% patients reporting independency at the end of follow-up. The mortality rate was 3.7%, which is near the bottom of the previously reported range (3%–15%) [9,11]. Taken together, our study shows that the outcome of CVT in China is favorable. CNS infection was found to be highly associated with poor outcomes at discharge, which may help to predict or identify the potentially severe cases at an early stage. Differ from a prior study, our study failed to observe a significant association between poor prognosis and malignancy [9]. It may be due to the types of malignant tumors found in our study, which were all solid tumors in distant sites with low potential of inducing poor outcomes in CVST. For example, it has been proposed that hematologic malignancies and CNS tumors are more likely to be linked with poor outcomes of CVT, whereas, these malignancies were absent in this cohort of CVST patients [27].

There are also some limitations in our study. First of all, selection bias was unavoidable. Secondly, some of the screening tests such as the evaluation of protein S and protein C levels were only performed at admission, and no dynamic follow-up data were obtained. Accordingly, the prevalences of protein S deficiency, protein C deficiency and AT deficiency were hardly available. Genetic tests for inherited thrombophilia were only carried out in a small portion of patients. Last but not least, the width of 95% CI of OR of some variables such as herniation was wide, which may attribute to the small sample size and variability of the patients. Although the poor outcomes of CVST patients with herniation have been found in previous studies, the actual OR value need to be calculated with a larger sample size.

5. Conclusions

Our study reveals that the predominant risk factors for the CVST in Chinese in the past 5 years may still be obstetric causes in female and hyperhomocysteinemia in male. CNS infection may help predict poor outcomes of CVST. Therefore, improving obstetric management and controlling CNS infection as well as hyperhomocysteinemia may be non-negligible aspects of CVST prevention and treatment. These findings should be further verified by future well-designed clinical trials in China.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Ethic Committee (Xuanwu Hospital, Capital Medical University) and adhered to the tenets of the Declaration of Helsinki.

Declaration of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.105384.

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