Cerebrovascular Diseases

Clinical Research in Stroke

Cerebrovasc Dis
DOI: 10.1159/000527155

Received: June 21, 2022
Accepted: September 9, 2022
Published online: December 23, 2022

Predictors of Mortality and Functional Outcome in Pregnancy and Puerperium-Related Cerebral Venous Thrombosis

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Keywords
Cerebral venous thrombosis · Stroke · Pregnancy · Puerperium · Women

Abstract

Introduction: Cerebral venous thrombosis (CVT) associated with pregnancy and puerperium has long been recognized, with poor information in terms of functional outcomes. Our objective was to analyze risk factors, clinical, imaging, and laboratory variables to predict functional outcome and death in this population. ***Methods:*** CVT registries from three referral centers from Pakistan, Turkey, and Mexico, recruiting prospective cases, were combined for CVT associated with pregnancy or puerperium. Datasets and variables were standardized. Demographic characteristics, presentation, risk factors, and functional outcomes in pregnancy/puerperium-related CVT were analyzed. Binary logistic regression was used to assess predictors of outcome. The main outcome was modified Rankin score >2 at 30 days and mortality at 30 days. ***Results:*** Five hundred fifty-three cases (median age 28 years [IQR 23–34]) of CVT associated with pregnancy and puerperium were included; 439 cases (79.4%) happened in the puerperium and 20.6% during pregnancy (53.5% occurred during the first trimester). Anemia (36.7%) and dehydration (22.9%) were the commonest obstetric risk factors identified. Predictors of poor outcome (mRS >2) were encephalopathy (OR 12.8, $p < 0.001$), cases from Mexican origin (OR 3.1, $p = 0.004$), fever/puerperal infection (OR 2.7, $p = 0.02$), and anemia (OR 2.2, $p = 0.01$). Cases from Mexican origin (OR 12.0, $p = 0.003$) and Encephalopathy (OR 7.7, $p < 0.001$), presented with the highest mortality association in the final adjusted model. ***Discussion/Conclusion:*** In CVT associated with pregnancy and puerperium, encephalopathy, fever/puerperal infection, and anemia are associated with bad functional outcomes, meanwhile encephalopathy and cases from Mexican origin with higher mortality in the acute (30-days) of CVT onset. Anemia and infection are potential reversible predictors of poor outcome that clinicians should be aware of in order to prevent poor outcomes in these patients.

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Introduction

Cerebral venous thrombosis (CVT) occurs because of occlusion to the veins and sinuses draining the brain parenchyma. It is considered a relatively rare condition, with yearly incidence of 1.32/100,000 general population in Western Europe and somewhat higher in Asian countries [1]. Despite being uncommon, it constitutes one of the most devastating neurological conditions to affect women in pregnancy and puerperium with incidence ranging between 11.6 per 100,000 deliveries in developed countries [2] and 450 per 100,000 deliveries in India [3].

The association between CVT and pregnancy and puerperium has been long recognized [4], and several studies have reported on clinical features, risk factors, and outcomes of these women [5–7]. The ISCVT reported 17% of the 465 women included to have pregnancy or puerperium-related CVT [8]. The Asian CVT registry from nine countries reported pregnancy and puerperium to account for 143 of the 479 cases of CVT in women (29.8%). A similar percentage was reported from the VENOST study from Turkey, where 216 of 777 women had pregnancy or puerperium related CVT [9]. However, the absolute number of pregnancy and puerperium-related CVT patients included in these studies was relatively small and this aspect was not the main focus of reporting; more importantly, functional outcomes in this specific group have been poorly analyzed. Our objective is to analyze demographic, clinical, and imaging characteristics of CVT during pregnancy and puerperium from three countries: Pakistan, Turkey, and Mexico; and to develop a predictive model for its acute prognosis (functional outcome and death) in these patients.

Methods

Dataset

Pakistan, located in South Asia, Turkey in Western Asia, and Mexico in North America are all populous countries, classified as lower-middle income (Pakistan) and upper-middle income (Mexico and Turkey) economies. The three countries have maintained registries of long-term consecutive patients for CVT cases, which include prospective case data on demographics, CVT risk factors (including those related to obstetric conditions), radiological and laboratory data, functional outcomes, and other potential risk factors, collected from third-level stroke centers on each country.

Data from Turkey were collected retrospectively and prospectively from 35 centers across the country and consisted of cases presenting between 2000 and 2015 [10]. From Pakistan, six centers contributed data to the Asian CVT registry [11]. Data from Mexico originated from a single tertiary center receiving patients mainly from Mexico City.

Patient Selection

Inclusion criteria were confirmed CVT cases by vascular imaging (CT venography, MR venography, or digital subtraction angiography – DSA), in female cases with the history of concomitant pregnancy, puerperium (defined as 6 weeks after the child's birth), or postabortion; complete information on dataset and medical records of clinical relevant dependent variables in the dataset (acute and/or 30-day modified Rankin score [mRS] and death). Exclusion criteria were female patients with no obstetric related-CVT, relevant incomplete information on the datasets, and presence of alternate diagnosis of cerebrovascular obstetric conditions (ischemic/hemorrhagic stroke).

Outcomes and Clinical Definitions

Functional outcome was assessed using the mRS and categorized as good (mRS 0–2) and bad outcomes (mRS >2), which was evaluated in person by treating physicians (local certified vascular neurologists) during in-hospital period and at discharge. For the purpose of the analysis, there was a composite of discharge and 30-day mRS to include all available cases from the three datasets, defined as "acute mRS." Anemia was defined when hemoglobin/hematocrit values were lower than expected on each pregnancy trimester or postpartum (according to the WHO and the American College of Obstetricians and Gynecologists) [12] and marked as "positive" for the purpose of the analysis.

Clinical syndromes were grouped into isolated intracranial hypertension (presence of headache with or without vomiting and papilledema, with no other clinical findings), focal syndrome (including focal deficit such as paresis, aphasia, sensitive abnormalities, seizures, or a combination of them), encephalopathy (when bilateral and multifocal signs, delirium, or consciousness disturbances [such as stupor/coma] occur), and cranial nerve syndrome (isolated of combined presence of any cranial nerve involvement) [13].

Statistical Analysis

Continuous variables are expressed as means with standard deviations, or median and interquartile ranges, according to their normality distribution. Categorical variables are expressed as counts and percentages. Age was evaluated with a receiver-operating characteristic curve, to extract the best discrimination threshold for death/bad functional outcome for binary regression analysis.

Univariate analysis was performed with Cochran-Mantel-Haenszel test and Yates' correction, for those variables (dichotomic age, risk factors, clinical symptoms, and imaging findings) predefined as predictors of bad functional outcome (mRS >1) and death; a logistic regression analysis was performed including those variables with a p value ≤0.1 in the first part of the model. A Hosmer-Lemeshow Goodness of fit test was used in the adjusted model (backward conditional stepwise). Odds ratio (OR) and 95% confidence interval (95% CI) are provided; p values <0.05 were considered significant. Missing values are reported for each independent variable. All statistical analyses were performed using SPSS version 21.0.

Results

The pooled dataset resulted in 579 female CVT potential study subjects; 26 (4.5%) cases were excluded due to absent information on functional outcomes (22 subjects) and un-

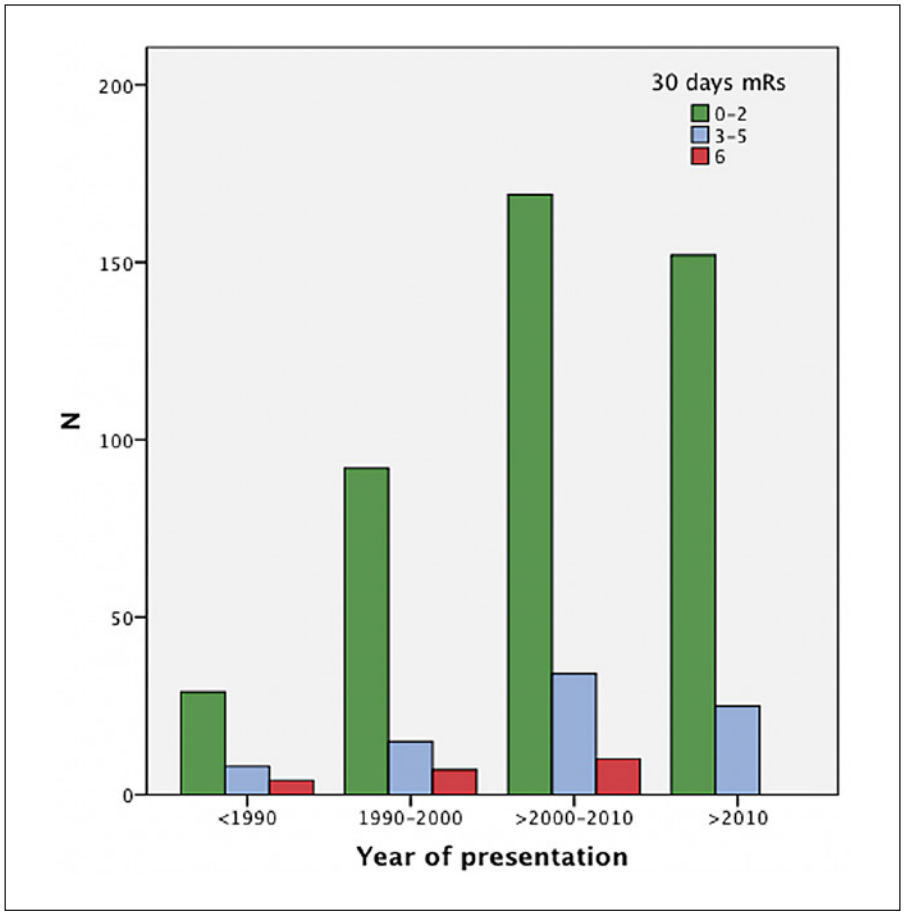

Fig. 1. Thirty-day modified Rankin score categories per period of time.

confirmed relationship between CVT and any obstetric condition (4 subjects). After exclusion, five hundred and fifty-three cases of CVT during pregnancy and puerperium were included in the final analysis. Two-hundred and eight patients (37.6%) were from Mexico, 195 (35.3%) from Turkey, and 150 (27.1%) were from Pakistan. The data spanned over 4 decades, from 1979 to 2018, and each subsequent decade saw an increase in the number of cases (1979–1988 = 33 cases, 1989–1998 = 101 cases, 1999–2008 = 130 cases, and 2009–2018 = 289 cases); Results related to mRS categories per decade are expressed in Figure 1.

Overall, 439 cases (79.4%) happened in the puerperium (only five happened postabortion) and 114 during pregnancy (20.6%). The median age of the entire population was 28 years (interquartile range 23–34 years), with a threshold of 25 years (AUC = 0.36, $p < 0.001$, 95% CI: 0.31–0.41) for mRS = 3–6. The mean duration of puerperium at the time of diagnosis was 9.6 days (standard deviations 7.6). From those cases occurring during pregnancy, 53.5% occurred during the first trimester, 16.6% in the second trimester, and 29.8% in the third trimester. Information from delivery place was available for 307 cases: majority of them delivered in hospital (90.8%), and 28 cases delivered at home.

Risk Factors for CVT

General risk factors assessed in the population are detailed in Table 1; inherited (18.4%, more frequent in puerperium cases [$p = 0.01$]) and acquired (13.4%) thrombophilia were the most common risk conditions presented in the dataset, with known antiphospholipid syndrome and systemic lupus erythematous as the main conditions for acquired cases (8.2 and 3.2% respectively); no relevant associations were found in other risk factors.

Specific obstetric-related factors presented with anemia (36.7%) as the commonest risk factor identified (more frequent in puerperium cases ($p < 0.001$)). Fever/puerperal infection (11.0%), dehydration (22.9%), previous abortion (14.1%), and preeclampsia (10.0%) were other frequent risk factors in datasets that collected information on them, but important missing values were present in these variables (see Table 1).

Table 1. Clinical, imaging, laboratory, and functional characteristics of pregnancy and puerperium-related CVT[a]

	Pregnancy, *n* = 114 (%)	Puerperium, *n* = 439 (%)	Total, *N* = 553 (%)	*p* value
Demographics				
Age, median years (IQR)	28 (23–34)	30 (25–34)	28 (23–34)	0.07*
Country				
• Pakistan	6 (5.3)	144 (32.8)	150 (27.1)	<0.001
• Mexico	42 (36.8)	166 (37.8)	208 (37.6)	
• Turkey	66 (57.9)	129 (29.4)	195 (35.3)	
General risk factors[a]				
Known blood hypertension	5/48 (10.4)	2/310 (0.6%)	7/358 (2.0)	<0.001
Active smoking	2/114 (1.8)	14/439 (3.2)	16/553 (2.9)	0.41
Inherited thrombophilia	12/114 (10.5)	90/439 (20.5)	102/553 (18.4)	0.01
Acquired thrombophilia	9/82 (11.0)	30/209 (14.4)	39/291 (13.4)	0.44
• Known antiphospholipid syndrome	3/42 (7.1)	14/166 (8.4)	17/208 (8.2)	0.78
• Known systemic lupus erythematous	4/114 (3.4)	12/381 (3.1)	16/495 (3.2)	0.83
Obstetric-related factors[a]				
Fever/puerperal infection	5/76 (6.6)	50/424 (11.8)	55/500 (11.0)	0.18
Previous abortion	10/48 (20.8)	39/299 (13.0)	49/347 (14.1)	0.15
Anemia	16/114 (14.3)	187/439 (42.6)	203/553 (36.7)	<0.001
Preeclampsia	6/48 (12.5)	25/262 (9.5)	31/310 (10.0)	0.53
Associated dehydration	2/5 (40.0)	22/100 (22.0)	24/105 (22.9)	0.35
Clinical syndrome[a]				
• Isolated intracranial hypertension	3/114 (2.6)	28/439 (6.4)	31/553 (5.6)	0.12
• Focal syndrome	64/114 (56.1)	324/439 (73.8)	388 (70.2)	<0.001
• Encephalopathy	21/114 (18.4)	88/439 (20.0)	109/553 (19.7)	0.70
• Cranial nerve palsy	9/114 (7.9)	25/439 (5.7)	34/553 (6.1)	0.38
Laboratory[a]				
Protein C or S deficiency	6/114 (5.3)	39/439 (8.9)	45/553 (8.1)	0.21
Hyperhomocysteinemia	0	37/212 (17.5)	37/277 (13.4)	<0.001
Antithrombin III deficiency	0	27/249 (10.8)	27/328 (8.2)	0.002
V Leyden factor mutation	5/62 (8.1)	12/146 (8.2)	17/208 (8.2)	0.97
Antiphospholipid antibodies				
• Lupus anticoagulant	3/77 (3.9)	6/190 (3.2)	9/267 (3.4)	0.76
• Anticardiolipin	5/61 (8.2)	17/120 (14.2)	22 (12.2)	0.24
• Beta2 glycoprotein	2/13 (15.4)	4/32 (12.5)	6/45 (13.3)	0.79
Prothrombin mutation	1/55 (1.8)	4/124 (3.2)	5/179 (2.8)	0.59
Imaging characteristics[a]				
Venous infarction	42/114 (36.8)	212/436 (48.6)	254/550 (46.2)	0.02
Hemorrhagic infarction	38/114 (33.3)	152/439 (34.6)	190/553 (34.4)	0.84
Deep venous system	7/44 (15.9)	25/289 (8.7)	32/333 (9.6)	0.13
Transverse sinus	49/112 (43.8)	168/427 (39.3)	217/539 (40.3)	0.39
Superior sagittal sinus	62/112 (55.4)	296/427 (69.3)	358/539 (66.4)	<0.001
Sigmoid/jugular vein	8/110 (7.3)	26/418 (6.2)	34/528 (6.4)	0.69
Functional outcome				
Good functional outcome (mRS = 0–2)	95/114 (83.3)	355/439 (80.9)	450/553 (81.4)	0.54
Death	3/114 (2.6)	18/439 (4.1)	21/553 (3.8)	0.46

IQR, interquartile range; mRS, modified Rankin score. **p* value by the U-Mann Whitney Wilcoxon test. [a]Counts and percentages presented according to missing values on each single variable.

In-Hospital Laboratory Workup

The mentioned measured laboratory tests were concomitant with the acute index CVT; due to institutional policies and the behavior of some of these thrombophilic factors, they were not systematically measured in all patients. Among inherited thrombophilias, protein C or S deficiency was reported in 8.1% of women tested; meanwhile, hyperhomocysteinemia was present in 13.4% of cases (more frequent in puerperium, $p < 0.001$). Of those women tested for acute antiphospholipidic antibodies, 13.3% were positive for beta-2 glycoprotein, 12.2% for anticardiolipin, and 3.4% for lupus anticoagulant. Antithrombin III deficiency was positive only in puerperium cases that were tested (8.2%) (see Table 1 for further information).

Table 2. Bad functional status (mRS >2) risk at discharge/30 days in obstetric CVT cases

	mRS 3–6 *n* = 103 (%)	uOR (CI 95%)[a]	*p* value	aOR (CI 95%)[b]	*p* value
Mexico	48/103 (46.6)	1.6 (1.0–2.4)	0.03	3.1 (1.4–6.6)	0.004
Age ≤25	53/103 (51.5)	1.8 (0.3–0.7)	<0.001	0.7 (0.3–1.2)	0.19
Fever/puerperal infection	21/86[c] (24.4)	3.6 (1.9–6.6)	<0.001	2.7 (1.1–6.2)	0.02
Anemia	54/93[c] (58.1)	2.3 (1.7–4.2)	<0.001	2.2 (1.2–4.2)	0.01
Anticoagulation	25/103 (24.3)	1.7 (1.1–2.9)	0.02	1.6 (0.8–3.1)	0.17
Encephalopathy	52/103 (50.5)	7.0 (4.3–11.3)	<0.001	12.8 (6.4–25.5)	<0.001
Focal syndrome	90/103 (87.4)	3.5 (1.9–6.5)	<0.001	1.2 (0.5–2.6)	0.71
Hemorrhagic lesion	50/103 (48.5)	2.1 (1.3–3.2)	0.001	1.4 (0.7–2.6)	0.25
Isolated intracranial hypertension	0	0.8 (0.7–0.9)	0.006	–	–

mRS, modified Rankin score; uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval. [a]Cochran-Mantel-Haenszel test. [b]Hosmer-Lemeshow Goodness of fit test: $\chi^2 = 23.9$, df = 8, *p* value = 0.002 (dependent variable = mRS >2). [c]Missing values at the independent variable.

Clinical and Radiological Findings

Focal clinical syndrome (with 53.3% of cases with seizures and 48.8% with motor weakness) was the most common presentation overall (70.2% of cases, more frequent in puerperium [$p < 0.001$]), followed by encephalopathy in 19.7% of cases (mainly due to stupor/coma in all of them). Imaging analysis revealed most of the cases related to superior sagittal sinus (66.4%) and transverse sinus (40.3%) thrombosis, with only 9.6% deep venous system thrombosis cases. Hemorrhagic parenchymal lesions were present in 34.4% cases, and venous infarction in 254 cases (46.2%). Brain edema/midline shift was recorded in 35/345 cases (10.1%). More details are provided in Table 1.

Management and Functional Outcomes

Treatment was initiated with heparin in 351 patients (65.7%), 100 (18.7%) received antiplatelets, whereas 83 patients were not given any medications. Most patients (98%) started on antiplatelets were from Mexico and 78 of these had been treated before 1998, reflecting a change in practice in more recent years. Fifteen patients underwent thrombolysis and six had decompressive surgery. Discharge medication data were available for 457 patients and of these 343 (75.0%) were on oral anticoagulation. Only 13 patients were discharged on direct oral anticoagulants.

Acute good functional outcome (mRS 0–2) was present in 81.4% cases at discharge/30 days (combined) in the entire dataset, with no differences among pregnancy and puerperium; death was present in 21 in-patients (3.8%), most of them from the Mexico dataset (18 cases). No deaths were reported in the outcomes from Turkey.

On univariate analysis, predictors for bad functional outcome (mRS >2) included younger patients (≤25 years) (OR 1.8, $p < 0.001$), Mexican origin (OR 1.6, $p = 0.03$), puerperal infection/fever (OR 3.6, $p < 0.001$), dehydration (OR 6.5, $p < 0.001$), anemia (OR 2.7, $p < 0.001$), focal syndrome (OR 3.5, $p < 0.001$), encephalopathy (OR 7.0, $p < 0.001$), anticoagulation (OR 1.7, $p = 0.02$), and hemorrhagic lesion at the index imaging study (OR 2.1, $p = 0.001$); isolated intracranial hypertension syndrome behave as a good functional outcome predictor (OR 0.8, $p = 0.06$). When performing the logistic regression analysis, in the final model dehydration was excluded due to the amount of missing values in the entire dataset, which affected negatively the final model; therefore cases from Mexican origin (OR 3.1 [95% CI: 1.4–6.6], $p = 0.004$), fever/puerperal infection (OR 2.7 [95% CI: 1.1–6.2], $p = 0.02$), anemia (OR 2.2 [95% CI: 1.2–4.2], $p = 0.01$), and encephalopathy (OR 12.8 [95% CI: 6.4–25.5], $p < 0.001$) remained as the strongest associated variables (see Table 2).

When analyzing predictors of mortality, unadjusted association analysis showed younger age (≤25 years) (OR 3.5, $p = 0.003$), Mexican origin cases (OR 10.8, $p < 0.001$), anemia (OR 3.9, $p = 0.003$), focal syndrome (OR 4.2, $p = 0.04$), encephalopathy (OR 3.9, $p = 0.001$), superior sagittal sinus thrombosis (OR 5.0, $p = 0.02$), and hemorrhagic lesion at the index imaging study (OR 3.2, $p = 0.007$) as the strongest associated variables; venous infarction (OR 0.3, $p = 0.03$) appeared protective for acute death. When adjusted logistic regression analysis was performed, en-

Table 3. Mortality risk at discharge/30 days in obstetric CVT cases

	Death $n = 21$ (%)	uOR (CI 95%)[a]	*p* value	aOR (CI 95%)[b]	*p* value
Mexico	19/21 (90.5)	10.8 (3.1–37.1)	<0.001	12.0 (2.3–62.4)	0.003
Age ≤25	14/21 (66.7)	3.5 (1.4–8.5)	0.003	0.5 (0.2–1.5)	0.23
Anemia	14/21 (66.7)	3.9 (1.5–10.5)	0.003	2.1 (0.7–6.1)	0.19
Encephalopathy	10/21 (47.6)	3.9 (1.6–9.6)	0.001	7.7 (2.6–22.7)	<0.001
Focal syndrome	19/21 (90.5)	4.2 (0.9–18.2)	0.04	1.2 (0.2–6.7)	0.85
Superior sagittal sinus	19/21 (90.5)	5.0 (1.1–21.7)	0.02	2.8 (0.5–14.3)	0.20
Hemorrhagic lesion	13/21 (61.9)	3.2 (1.3–8.0)	0.007	1.1 (0.2–4.7)	0.90
Venous infarction	5/21 (23.8)	0.3 (0.1–0.9)	0.03	0.2 (0.1–1.2)	0.09

uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval. [a] Cochran-Mantel-Haenszel test. [b] Hosmer-Lemeshow Goodness of Fit test: $\chi^2 = 18.7$, df = 8, *p* value = 0.016 (dependent variable = dead).

cephalopathy (OR 7.7 [95% CI: 2.6–22.7], $p = <0.001$) and Mexican origin cases (OR 12.0 [95% CI: 2.3–62.4], $p = 0.003$) presented with the highest risk association in the final model (see Table 3).

Discussion

The present study reports on predictors of functional outcome and mortality in a pooled analysis of CVT related to pregnancy and puerperium. Our results depict an increasing recognition of CVT over time with puerperium presenting with the highest number of cases. In our final adjusted model, encephalopathy was the strongest risk factor for death and bad functional outcome. Other significant predictors for these outcomes were anemia, fever/puerperal infection, and country of origin.

Our data spanned over 4 decades, and there was an almost 10-fold increase in the number of cases collected between the first and last decades. An increase in the incidence of CVT has been reported previously [14, 15]. Although this was not the main intent of the registry, these increases in number may reflect better diagnostic modalities and recognition of milder cases [16]. A shift in the risk factors may be another reason for this observation. When analyzing country of origin, a trend in Mexican cases in terms of bad functional outcome and death was observed, although we are aware of the bias of this finding: most of the older cases come from the Mexican registry, even with cases older than 1990, when no guidelines for this condition were created and also most of the registered deaths are from Mexico, so an increase in the association odds was expected.

It has long been recognized that women in reproductive age group are at higher risk of stroke, and this risk is primarily attributable to pregnancy and puerperium-related CVT [17, 18]. Most of the cases in our dataset occurred in early puerperium, with a mean duration 9.6 days from delivery. This is supported by earlier publications [18–20]. In a previous report, 34% cases occurred in week 1, and 59% in weeks 2 and 3 postpartum [17]. Another study reported >50% of their patients presenting within 10 days postpartum [21]. In addition, we also found the first trimester to be a high-risk period, where almost 50% of pregnancy CVT was seen, as reported by Cantu-Brito et al. [22] as well. Previous reports suggest that women who have had CVT early on in their pregnancy tend to have another underlying mechanism for their hypercoagulable state such as antiphospholipid antibodies [23] and Factor V Leiden mutation, but we found no such association in our patients. Also, in low- and low-middle income countries, healthcare pregnancy programs for unemployed women could be limited, and in some regions absent; this could explain worse outcomes when more complicated obstetric cases presented in younger women; also, anemia is more frequent in younger obstetric patients, and as a covariate could be related to our finding; this should be explored in future prospective CVT registries.

Encephalopathy (which we defined as either multifocal or diffuse brain dysfunction evident by multifocal signs and/or reduction in consciousness) came out as the strongest predictor for both bad functional outcome and death. Brain dysfunction associated with CVT has been variably measured in previous studies [11, 24]. Moreover, this association has been seen in CVT irrespective of the underlying etiology (obstetric, immune mediated, infective, or neoplastic).

Dehydration also seems to stand out. Although the information was available for only 105 cases, almost one quarter were found to have this risk factor, compared to 38% in the study by Liu et al. [25] and 9.4% in a recent study by Sarathchandran et al. [26]. A major limitation of this variable in our analysis was a lack of standard definition used for its measurement and the number of cases with missing variables. However, the association found in univariate analysis warrants further prospective studies with standard measurement to better understand its impact on outcomes in obstetric CVT.

The median age of our population was 28 years, and most of the women were less than 40 years of age (89.5%). Increasing age has been recognized as a risk factor for CVT [2]. Contrary to this finding, we found younger age (≤25 years) presented with a tendency for poor functional outcome and death. Factors that predispose younger females to CVT might be responsible for this.

Another risk factor that stands out in terms of frequency in this cohort of obstetric patients is anemia. Earlier studies have identified it as an important risk factor associated with all CVT [27, 28] specially the one associated with pregnancy and puerperium [17]. A case-control study by Coutinho et al. [27] found that women with CVT had 3.6 times higher odds of being anemic, and hemoglobin as a continuous variable was inversely related to CVT diagnosis. In addition, anemia has been associated with worse clinical outcomes as well as mortality in previous studies. Liu et al. [29] report a 3.6-fold higher risk of mRS 3–6 and a 5.5 times higher risk of mortality in CVT patients with anemia. In our cohort of obstetric CVT, despite the fact that anemia was not validated in the final model as the highest association variable for bad functional outcome and death, it remained as an important associated factor, which should be explored in terms of not the presence of hemoglobin decrease, but also hematologic intrinsic effects in hemostasis and thrombi formation, which was not explored in our study. Protein C/S deficiency and hyperhomocysteinemia were other frequently identified risk factors present in one-fifth of our tested patients, a finding contrasting VENOST study [30], but similar to a report by Klai et al. [31].

The 1-month outcomes we observed in this cohort of pregnancy and puerperium-related CVT varied significantly between countries. Turkey reported no deaths, whereas Mexico presented most of the mortality. Good functional outcomes (mRS 0–2) were reported significantly more frequently from Turkey compared to the other two countries. These differences may be accounted for by a more advanced healthcare system that exists in Turkey compared to the other two countries, which allows for early identification of the condition, but this finding should also be analyzed cautiously, as Mexican cohort presents a wider timeline of recruitment, with cases treated under antiplatelet therapy (before year 2000), which could explain some of the functional outcomes.

Limitations

There are several limitations we need to acknowledge. First, the data span over 4 decades, and many factors would have changed over time, including methods of testing for various risk factors, methods of diagnosing CVT, and importantly treatment modalities. However, most of the data, >50%, are from the last decade and, therefore, may be generalizable to CVT cases we are observing nowadays. Second, differences also exist across the three countries in terms of resources, and health systems which would have impacted not just assessment of risk factors but also outcomes. Third, although registries try to maintain data on all consecutive cases, it is difficult to be certain that all patients were included over such a long span of time. The absence of mortality in data from Turkey may indicate some selection bias over the years. Fourth, functional follow-up information is based in the acute setting of the CVT, as data for the 3-6-12 months were not consistent among the centers, or not available for all cases; therefore, this should be taken into account in terms of external validation. Lastly, it is registry-based data and carries all the limitations attributable to retrospective reviews of such datasets, including missing data. Thus, we consider a major limitation since many variables had substantial amounts of missing data, and complete data might have resulted in different results.

Statement of Ethics

Ethics Committee from each center approved their respective CVT dataset according to local and international research legislations; no informed consent was necessary as the information was extracted from the retrospective database, but patients gave consent when included on each country's study. Data collection at Aga Khan University was approved by AKU Ethics Review Committee (873-Med/ERC-07).

Conflict of Interest Statement

None of the authors report any conflicts of interest.

Funding Sources

No funding was received by any authors during the conduct, data collection, or write-up of the study.

Author Contributions

Maria Khan, FCPS, MSc, Antonio Arauz, MD, PhD, and Mohammad Wasay, MD, FRCP, FAAN: concept, data collection, data analysis, manuscript writing, and manuscript review.

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Taskin Duman, MD: data collection, data analysis, manuscript writing, and manuscript review. Vanessa Cano-Ningenda, MD: data collection and manuscript review.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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