Cerebral venous thrombosis in Argentina: clinical presentation, predisposing factors, outcomes and literature review

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Background: Cerebral venous thrombosis (CVT) is a rare medical condition that primarily affects young adults. The clinical spectrum is broad and its recognition remains a challenge for clinicians. Limited information is available on CVT in Argentina. Our goal was to report the results of the first National registry on CVT in Argentina and to compare clinical presentation, predisposing factors and outcomes with other international registries. *Material and method:* The Argentinian National Registry on CVT (ANR-CVT) is a multicenter retrospective cohort study comprising patients aged 18 and older with a diagnosis of CVT from January 2015 to January 2019. We evaluated demographics, predisposing factors, clinical presentation, and radiological characteristics (e.g. number of involved sinuses, venous infarction or hemorrhage on CT and MRI scans at admission), therapeutic interventions and functional outcomes at discharge and at 90 days. Our results were compared to a literature review of CVT registries. *Results:* Overall, one hundred and

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sixty-two patients met the inclusion criteria. The mean age was 42 (±17) years; 72% were women. Seventy percent of patients were younger than 50 years. The most common presenting symptom was headache (82%). The transverse sinus was the most common site of thrombosis (70%) followed by the sigmoid sinus (46%). The main predisposing factor in women was contraceptive use (44%), 3% of the events occurred during pregnancy and 9% during the puerperium. Participants 50 years and older had a higher frequency on malignancy related (7.5% vs. 30%, $p = 0.0001$) and infections (2% vs. 11%, $p = 0.001$). The modified Rankin Scale (mRS) ≤2 at discharge was 81% and the rate of mortality at discharge was 4%. At 90 days, the mRS≤2 was 93%. When the ANR-CVT was compared with larger registries from Europe and Asia, the prevalence of cancer among patients with CVT was two to five-fold higher (15% vs. 7% and 3%, respectively; $p = 0.002$ and $p < 0.001$). Anticoagulation rates at discharge were also higher (94%) compared to registries from Asia (ASCVT − 68%) or Turkey (VENOST − 67%). *Conclusion:* Participants in the first ANR-CVT had a low mortality and disability at 90 days. Clinical and radiological characteristics were similar to CVT from other international registries with a higher prevalence of cancer. There was a high variability in treatment adherence to guidelines as reflected by anticoagulation rates (range 54.5%-100%) at discharge.

Keywords: Argentine—cerebral veins—cerebral venous sinus thrombosis—cerebrovascular disease—outcome—registry—stroke

1. Introduction

Cerebral venous thrombosis (CVT) is an uncommon medical condition that primarily affects young individuals. Previous studies suggest an annual incidence rate of 1-12/1,000,000 cases, representing 0.5% to 3% of all stroke.[1-4] CVT is more common in childbearing women, usually associated with a transient prothrombotic state (e.g. pregnancy, puerperium, exposure to oral contraceptives).[5]

Most common clinical presentation among patients with CVT include headaches, seizures, impaired consciousness and focal neurological signs. A high level of suspicion is required to make the diagnosis given the commonalities to the clinical presentation in other neurological conditions (e.g. stroke, meningitis, encephalopathies, etc.). Approximately 5% of individuals have a more insidious course not having most common neurological manifestations, making the diagnosis challenging. [1,2]

To date, the largest multicenter CVT studies are from Turkey, Asia, Europe and the ISCVT (International). Limited information is available of CVT in Argentina and South America. Our intention was to evaluate most common factors and features of CVT in our population given differences in ethnic backgrounds and the prevalence of risk factors (for CVT) compared to other registries.

We performed the Argentinian National Registry on CVT (ANR-CVT), a multicenter cohort study, aiming to evaluate demographics, predisposing factors, clinical presentation, radiological characteristics, therapeutic interventions and modified Rankin Scale (mRS) at discharge and at 90 days in CVT patients. Our results were compared to a literature review of CVT registries.

2. Methods

We are first reporting the results of the Argentinian National registry on CVT (ANR-CVT), a multicenter retrospective cohort study. Patients over 18 years old with confirmation of cerebral venous thrombosis in either computed tomography (CT) with venography (CTV), magnetic resonance (MR) with venography (MRV) or cerebral digital subtraction angiography (DSA) were included in this study. The reporting period comprised eligible participants from January 1st, 2015 to January 31st, 2019. The information was collected by a standardized data collection form from 23 participating stroke centers from Argentina. CVT cases were identified by multiple searches in hospital registries and neurology divisions databases. We included all patients with a diagnosis of CVT irrespective of the admission setting from all participating institutions. In other words, patients with CVT admitted to the stroke unit, neurology ward, internal medicine ward, intensive care unit (ICU), or obstetrics and gynecology (OBG) wards were included in our study. Taking into account extrapolated data from a survey carried out by the Stroke Study Group - Argentine Neurological Society in 2017 (where the data showed that 72 centers in Argentina had the capacity to manage acute stroke), we could estimate that we have obtained information from one-third of the centers in the country with stroke experience.

As an inclusion criteria, the patient must be over 18 years-old at the time of the clinical event. Those with incomplete data or incomplete diagnosis were excluded. Demographic data, predisposing factors, clinical presentation, diagnostic imaging, affected cerebral venous sinuses, treatment and functional outcome at discharge and at 90 days measured by modified Rankin Scale were analyzed. The mRS was

evaluated by a vascular neurology physician during an outpatient visit 90 days after admission or, if that was not possible (i.e.: long distance from the institution), patients were contacted by telephone.

A comparative analysis of the data obtained by sex and age (≤ 50 vs > 50 years) was performed. The cut-off point to define young patients was considered ≤ 50 years.

Among predisposing factors, those with a known relationship to CVT were evaluated (exposure to oral contraceptives, pregnancy, puerperium, obesity, infections, active malignancy and thrombophilia, among others). The association with: antiphospholipid antibodies, factor V Leiden, hyperhomocysteinemia, methylenetetrahydrofolate reductase gene (MTHRF) mutation, PAI 4G/5G mutation, prothrombin 20210 gene mutation, altered protein S and protein C and resistance to activated protein C were obtained when available.

We defined a priori group age (≤ 50 vs > 50 years) and sex group comparisons as these were common factors reported in previous studies. Similarly, the prevalence of thrombophilia as an association with CVT was also defined a priori.

The study was approved by the Ethics Committee of each center. The data obtained by each center coordinator was included in a standardize case-review form.

3. Literature review

3.1. Data sources

We conducted a literature search of MEDLINE, Scielo and Lilacs, from January 2000 to December 2019, using a combination of MeSH terms as major subjects, including: "cerebral sinus", "cerebral venous", "cerebral vein", "dural sinus" AND "Thrombosis", 'Sinus AND Thrombosis" and "Intracranial AND thrombosis", "CVT", "registry" and "study" (or their equivalents in Spanish to include Latin Americans databases). Duplicate results were excluded.

3.2. Study selection

Candidate articles reporting cerebral venous thrombosis were included if they met the following inclusion criteria: First, at least more than ten patients reported. Second, basic information about demographics, predisposing factor, diagnosis methods and treatment should be easily available. Third, patients should be older than 18 years. Fourth, at least one outcome measure (death in hospitalization, disability al discharge, etc.) should be reported. Fifth, the study was written in English or Spanish.

We analyzed the original data as reported by the authors (in text and/or tables). When data was not available, we tried to complete it from others sources (e.g., additional files). We excluded the study if raw data was not available. We excluded isolated case reports. We also excluded from our sample other types of publications (e. g. review articles, letters to Editors).

3.3. Data extraction

Two reviewers (MJA, CC) assessed the abstracts to determine eligibility. Information was extracted in a data collection form, including: country of origin, year of publication, type of registry (retrospective, prospective), demographics (age, sex), symptoms, CVT predisposing factors (e.g., prothrombotic state, infections, malignancy, etc.), cerebral venous sinus involved, treatment (e.g., anticoagulation, decompressive surgery, etc.) and outcomes (e.g., death, disability at discharge, CVT recurrence, etc.).

3.4. Statistical analysis

Continuous data were summarized as mean (± standard deviation) or median (minimum - maximum) considering their distribution. Categorical data were presented as frequency and percentage. An independent t-test was used to compare groups for continuous variables. Categorical data were analyzed using Pearson's chi-square or statistical likelihood ratio test. The collected data was analyzed with SPSS v.22.

4. Results

One hundred and sixty-two patients met the inclusion criteria.

Seventy-two percent of the patients were women (n=117) (female/male ratio 2.6). Women with CVT were younger than men [mean age: 39.5 (±17) vs 47.5 (±18); $p < 0.01$]. Overall, 114 patients (70%) were under 50 years of age. Demographic characteristics, clinical presentation, diagnostic methods, number of affected cerebral venous sinus and associated brain lesions are shown in Table 1. Most patients were assessed in tertiary stroke care centers from largest cities in Argentina (e.g. City of Buenos Aires, La Plata, Córdoba, Rosario and Tucumán), comprising 83% of all CVT reported during the study period.

The median time since symptoms onset to the initial medical assessment was 4 days (range: 0-74 days). Headache was the most frequent presenting symptom in both women and men (85% vs. 75%; $p = 0.14$), and 44 patients (27%) presented with isolated headache. No significant differences were found in the clinical presentation by sex or age group. Fifteen patients (9.3%) were in coma and 12 patients (7.4%) had a decreased level of consciousness (stupor or drowsiness) on admission or during hospital stay.

Radiological characteristics: The diagnosis of CVT was confirmed by computed tomography (CT) + CT angiography in 26 patients (16%), by magnetic resonance imaging (MRI) + MR angiography in 83 patients (51%) and in 38 patients (23%) by DSA. The remaining 9% of patients required a combination of diagnostic tests to confirm the diagnosis.

The most commonly affected location was the transverse sinus (70%, with 54% left side involvement) followed by sigmoid sinus (46%, with 61% involvement

Table 1. *Demographic, clinical and radiological characteristics (n = 162)*

		Gender		Total		
		Male $n = 45$	Female $n = 117$		p	*95% CI*
Age, n (%)	18 to 50 years	24 (53)	90 (77)	114 (70)	**0.0045**	(0.0789 - 0.3929)
	> 50 years	21 (47)	27 (23)	48 (30)	**0.0045**	
Clinical manifestation, n (%)	Headache	33 (75)	100 (85)	133 (82)	NS	
	Decreased visual acuity	7 (18)	16 (15)	23 (14)	NS	
	Diplopia	8 (18)	15 (13)	23 (14)	NS	
	Aphasia	8 (18)	16 (14)	24 (15)	NS	
	Dysarthria	6 (13)	12 (10)	18 (11)	NS	
	Motor symptoms	13 (29)	35 (30)	48 (30)	NS	
	Sensory deficit	4 (9)	22 (19)	26 (16)	NA	
	Seizure	11 (24)	29 (25)	40 (25)	NS	
	Intracranial hypertension	18 (40)	25 (21)	43 (27)	**0.04**	(0.0345 - 0.3381)
	Sensory impairment	5 (11)	22 (20)	27 (17)	NA	
	Others*	6 (13)	18 (15)	24 (15)	NS	
	ICU admission	19 (42)	53 (45)	72 (44)	NS	
	Mechanical ventilation	6 (13)	13 (11)	19 (12)	NS	
Diagnostic imaging, n (%)	Angio-CT	6 (13)	20 (17)	26 (16)	NS	
	Angio-MRI	24 (53)	59 (50)	83 (51)	NS	
	Digital angiography	9 (20)	29 (25)	38 (23)	NS	
	Two or more methods	6 (13)	9 (8)	15 (9)	NS	
Number of affected sinus, n (%)	1 or 2	25 (56)	64 (55)	89 (55)	NS	
	3 or 4	13 (29)	43 (37)	56 (35)	NS	
	> 4	7 (16)	8 (7)	15 (9)	NS	
Brain involvement, n (%)	SAH	9 (20)	28 (24)	37 (23)	NS	
	Venous infarct	13 (29)	40 (34)	53 (33)	NS	
	ICH	15 (33)	30 (26)	45 (28)	NS	

* Others: hemianopia, tinnitus, cranial nerve involvement, photophobia, phonophobia.
ICU: Intensive care unit, **SAH**: Subarachnoid hemorrhage, **ICH**: Intracerebral hemorrhage
NA: not applicable. NS: not significant

of the left side) (Figure 1). In 95% of cases thrombosis was located in superficial venous system (superior and inferior sagittal sinus, transverse or lateral sinus, straight sinus, sigmoid sinus and cortical veins). Twenty-four patients (15%) had bilateral compromise of venous sinus.

Venous infarction was identified in 53 patients (33%), subarachnoid hemorrhage (SAH) in 37 (23%), intracerebral hemorrhage (ICH) in 45 (28%) and subdural hematoma (SDH) in 8 (5%). Forty-one percent of the patients did not show any lesions.

Factors associated with CVT and related complications: Overall, the most common identified factors associated with CVT were exposure to oral contraceptives (31%) and thrombophilia (28%) (Table 2).

Table 2 shows gender differences of CVT. The most common factor associated with CVT in women was the exposure to oral contraceptives (44%), followed by transient hypercoagulable states related to pregnancy (3%) and puerperium (9%). Three of the four CVT cases during pregnancy occurred in the third trimester and 90% of CTV postpartum cases occurred within the first 4 weeks of the puerperium. In patients with contraceptive use, 16 (31.4%) had positive thrombophilia test. The most common predisposing factor for CVT in men was thrombophilia (36%).

The analysis of predisposing factors by age group revealed a higher prevalence of cancer among those patients over 50 years compared to their younger counterparts (30.0% vs. 7.5%, $p < 0.001$) and infections (11.0% vs. 2.0%, $p < 0.001$) (Table 2). Cancer types included solid tumors (n = 13), haematological (n = 10) and central nervous system (n = 2).

Treatment: A total of 153 patients (94%) received anticoagulation treatment at discharge. The most common medication used was acenocoumarol (vitamin K antagonist), followed by low molecular weight heparin. The average time between the onset of symptoms and the start of treatment was 8 days (95% CI 6-10 days).

Endovascular treatment (mechanical thrombectomy/thromboaspiration) was performed in 8 patients (5%). Hemicraniectomy was performed in 2 patients (1.2%) and ventricular shunt in 3 (2%).

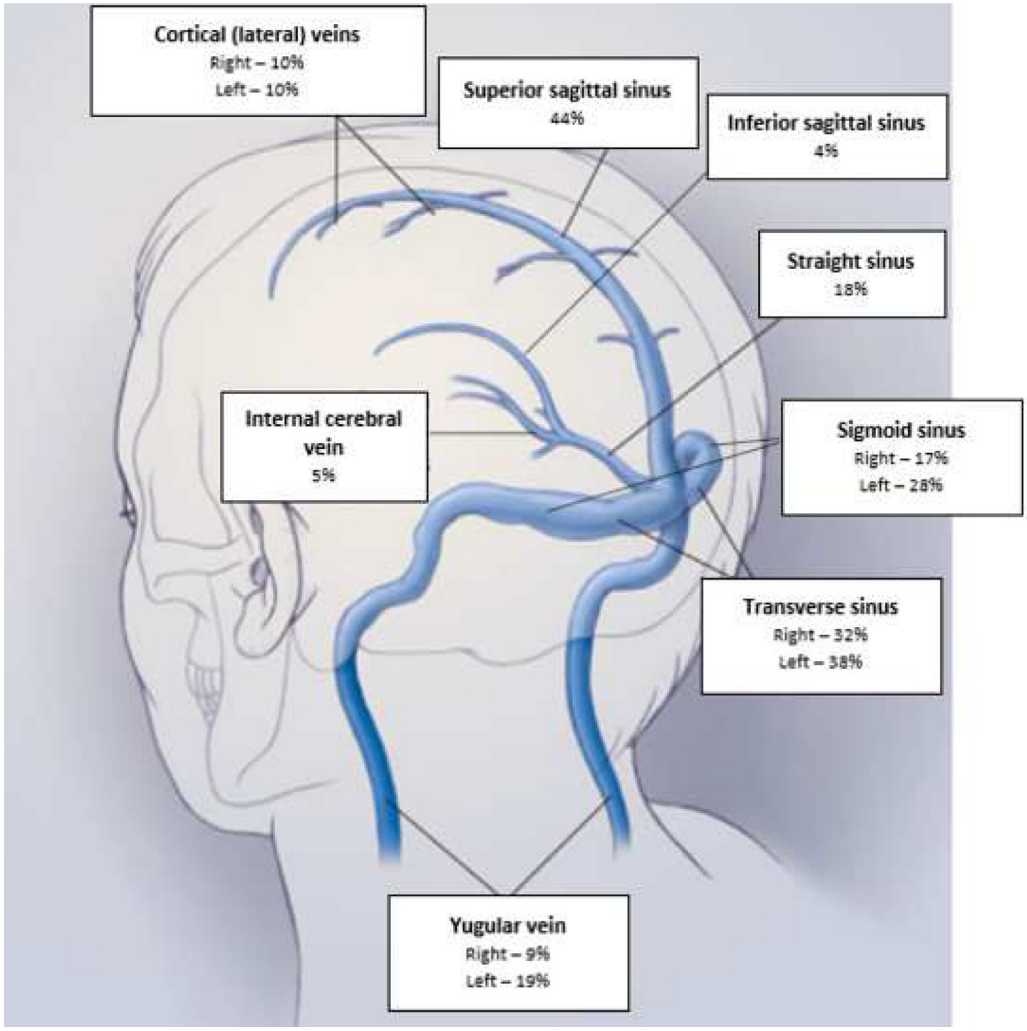

Figure 1. ***adapted from:*** *Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005; 352(17): 1791-8.*

Outcome measures: Functional outcomes at discharge were available in 161 patients, of whom 131 (81%) achieved functional independence (mRS 0-2) at hospital discharge, 24 (15%) were dependent (mRS 3-5) and 6 (4%) died. Follow-up data at 90 days were obtained from 137 patients (85%). During this period, 128 patients (93%) were functional independent (mRS 0-2), whereas 3 more patients died, with an overall mortality at 90 days of 6% (Figure 2). In 7 patients (4%), recurrence of CVT was identified in the follow-up period, most commonly observed among those age 50 years and older (10% vs. 2%, $p = 0.03$).

5. Discussion

CVT is challenging medical condition representing approximately 1% of all strokes.[6]

We reported the results of the first ANR-CVT describing baseline characteristics, clinical presentation, predisposing factors, imaging findings, treatment and outcome measures.

We found that CVT primarily affects young individuals under the age of 50 years and women. The median time since symptoms onset to the initial medical assessment was 4 days. Headache was the most frequent presenting symptom. The most affected sinus was the transverse sinus (70%) followed by sigmoid sinus (46%). Overall, the most common identified predisposing factors were exposure to oral contraceptives (31%) and thrombophilia (28%). We found a higher prevalence of cancer among patients over 50 years. The great majority of patients received anticoagulation treatment. Four out of five patients achieved functional independence (mRS 0-2) at discharge with a low mortality rate (4%). We also observed a low recurrence rate (4%).

We conducted a literature review and compared our results with CVT registries from around the world (Tables 3 and 4) .[3,6,8-30]

We found in Pubmed 79 case reports from South America, but no registry data. In Scielo and Lilacs we found registries from Colombia[8], Brazil[9] and Uruguay.[10] The VENOST study[7] was the largest worldwide CVT

Table 2. *Predisposing factors according to sex and age group (n=162)*

		Gender		Total			Age group			
		Male ***n* = 45**	**Female** ***n* = 117**		***p***	***95% CI***	**≤50** ***n* = 114**	**>50** ***n* = 48**	***p***	***95% CI***
Obesity, n (%)		14 (31)	22 (19)	36 (22)	NS		22 (21)	14 (32)	NS	
Cancer, n (%)		9 (20)	16 (14)	25 (15)	NS		8 (7.5)	17 (39)	**0.0001**	(0.1622 - 0.4058)
Rheumatic diseases, n (%)		1 (2)	3 (3)	4 (2)	NA		4 (4)	-	NA	
Trombophilia (n= 141), n (%) *		16 (36)	29 (25)	45 (28)	NS		33 (31)	12 (27)	NS	
	Antiphospholipid antibodies	5 (16)	7 (6)	13 (8)	NS		7 (7)	4 (9)	NA	
	Factor V Leiden	5 (16)	2 (2)	7 (4)	**0.01**	(0.0241 - 0.1639)	4 (4)	3 (7)	NA	
	Hyperhomocysteinemia	-	1 (1)	1 (0.6)	NA		1 (1)	-	NA	
	MTHRF mutation	-	1 (1)	1 (0.6)	NA		1 (1)	-	NA	
	PAI 4G/5G	2 (6)	5 (4)	7 (4)	NA		6 (6)	1 (2)	NA	
	Prothrombin 20210 mutation	-	3 (3)	3 (2)	NA		2 (2)	1 (2)	NA	
	Low C Protein	2 (6)	-	2 (1)	NA		-	2 (5)	NA	
	Low S Protein	1 (3)	5 (4)	6 (4)	NA		6 (6)	-	NA	
	Activated protein C resistance	-	2 (2)	2 (1)	NA		2 (2)	-	NA	
Contraceptives, n (%)		-	51 (44)	51 (31)	NA		50 (47)	1 (2)	**0.0001**	(0.2611 - 0.5744)
Pregnancy, n (%)		-	4 (3)	4 (2)	NA		4 (4)	-	NA	
Puerperium, n (%)		-	10 (9)	10 (6)	NA		10 (9)	-	NA	
Infection, n (%)		3 (7)	4 (3)	7 (4)	NA		2 (2)	5 (11)	**0.0001**	(0.0181 - 0.1552)
Hormonal replacement, n (%)		-	3 (3)	3 (2)	NA		2 (2)	1 (2)	NA	
Cocaine use, n (%)		1 (2)	-	1 (1)	NA		1 (0.9)	-	NA	
Chronic alcoholism, n (%)		1 (2)	-	1 (1)	NA		-	1 (2)	NA	
CNS tumor (compression), n (%)		-	1 (1)	1 (1)	NA		1 (0.9)	-	NA	
Autoimmune hepatitis, n (%)		-	1 (1)	1 (1)	NA		-	1 (2)	NA	
Undetermined etiologies, n (%) **		4 (8)	8 (7)	12 (11)	NA		8 (9)	3 (6)	NA	
Unknown etiology, n (%)		4 (9)	5 (4)	9 (6)	NA		8 (7.5)	1 (2)	NA	

MTHFR: Methylenetetrahydrofolate reductase, **PAI**: Plasminogen tissue activator inhibitor type 1 gene, **CNS**: Central nervous system.
NA: not applicable. NS: not significant
Note: *In 21 patients (13%), no information on thrombophilias was available. Positive thrombophilia was considered according to the cut-off point of each institution.
** Undetermined etiologies: Lumbar puncture, trauma, surgery, central catheter.

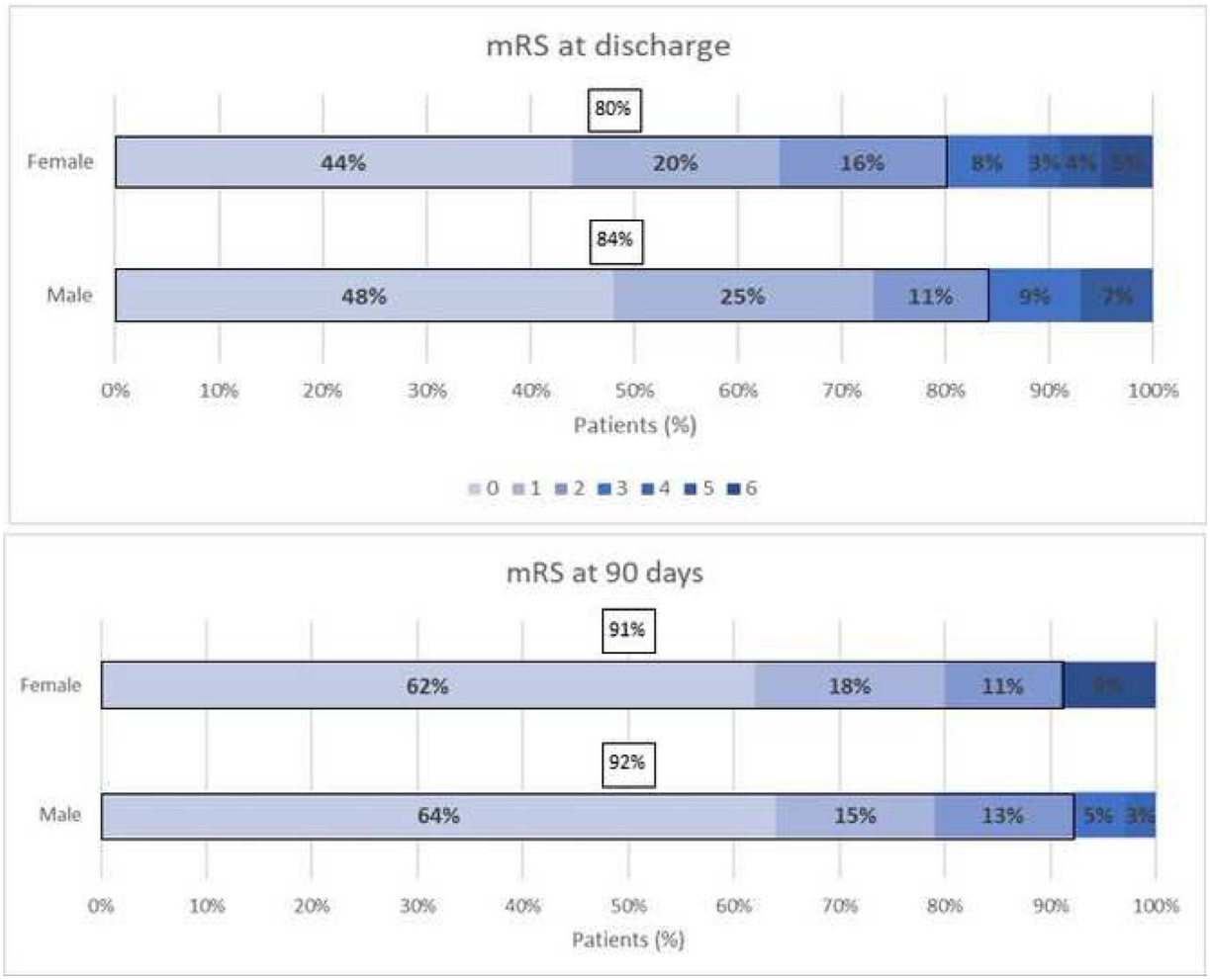

Figure 2. ***Disability assessed by modified Rankin Scale (mRS) at discharge and at 90 days grouped by sex*** *The trends did not show significant differences between groups and functional outcome. At discharge p = 0.6 and at 90 days p = 1. *The black box shows the percentage of patients with good functional outcome (defined as mRS ≤2)*

registry, comprising 1114 patients receiving care at 25 hospitals in Turkey.

We carried out a comparative analysis with registries from across the globe. Our findings showed similarities in demographics when compared to CVT registries. CVT was predominant in women (72%), occurring more frequently during childbearing age.[6,11,31,32] The mean age in our study was 42 ± 17 years, similar to North American and European studies,[13] but higher than South American and Asiatic publications;[8-10] this could be a possible explanation for the low rate of CVT in pregnancy (3%) and puerperium (9%) in our study. Headache was the most frequent presenting symptom (82%) as in most studies (70 to 90%).[11,13,15,16,33,34] Overall, demographic data and clinical presentation was very similar to ISCVT and CEVETIS. Regarding male proportion (28%), it was similar to ISCVT, South America, Europe, Turkey and two African registries. There was up to 10-20% more males reported in registries from Canada, USA and Asia.

The most frequently affected sinus was the transverse sinus (70%), followed by the sigmoid sinus (46%). We observed no major regional differences in the affected sinuses across studies. We found that 33% of patients had venous infarcts at the time of diagnosis and 56% had hemorrhagic lesions (SAH 23%, SDH 5% and ICH 28%). We found a high association with CVT and SAH compared to most registries. ICH could be observed in 27% of patients from Asia (ASCVT and VENOST) and 28% in Europe (CEVETIS). In about 45% of patients we did not find alterations in parenchyma, similar to other registries. [23,35-37]

The main differences that we found were regarding predisposing factors. A recent meta-analysis on CVT described that hematological etiologies were the most common ones in Africa, Asia, and South America, while systemic etiologies were the most common ones in Australia, Europe, and North America.[6] We also observed country differences in the use of contraceptives among patients with CVT. For example, 44% of our patients had exposure to contraceptives, compared to lower rates in Asian (11 to 14%) and Mexican (14 to 18%) studies. We also found a higher prevalence of cancer (15%) in comparison with most series across the world.[6,38] Patients with

Table 3. *Comparative table of the main variables in CVT registries around the globe. Data from our population is presented in the last row*

Continent	Global	Asia								Asia/Europe		Europe	Africa				Oceania	North America		South America					
Country		Asia[#]	China	Saudi Arabia	India	Irán	Japón	India	Pakistan	Turkey	Turkey	Europe	Tunisia	Morocco	Tunisia	Sudan	Australia	Mexico	Mexico	Canada	USA	USA	USA	Colombia	Brazil	Argentina[&]
Study	ISCVT	ASCVT						NIZAM		VENOST		CEVETIS						NINN	RENAMEVASC							
Year of publication	2004	2019	2019	2019	2019	2016	2014	2012	2008	2017	2017	2012	2017	2014	2013	2008	2016	2018	2012	2017	2017	2009	2008	2012	2010	
Number of patiens	624	812	243	26	71	151	22	428	109	1144	50	706	160	30	41	15	105	343	59	40.7	152	61	182	38	15	162
Mean age (years)	37	31	36	29.4	36.6	37	50.1	31.3	35	n/a	34.6	40	37.3	29	38	33.9	49	29	31	41	42	40	38	n/a	36	42
Female (%)	74.5	59	54.3	57.7	40.8	78.1	59.1	46.3	53	68	78	73.7	83.1	67	68	80	52	83.9	85	55	69	67	60	76	73	72
Headache (%)	88.8	90	90.1	65.4	66.2	85.4	59.1	88.3	81	87.2	96	n/a	71.3	80	83	100	n/a	n/a	91.5	75	85.7	82	71	n/a	100	82
Seizures (%)	39.3	44	30.5	26.9	46.5	21.2	27.3	45.2	39	23.7	34	n/a	32.5	33	29	20	n/a	n/a	20.3	25	13.6	31	32	18	33	25
Predisposing factor																										
Pregnancy / puerperium (%)	20.1	18	19.8	3.8	9.8	12.3	4.5	9.8	31	27	34	7.8	38.6	33	38	6.6	5	52.2	56.5	7.5	16.2	23	7	24	20	12
Use of oral contraceptives (%)	54.3	12	9.5	23	24.1	55.1	4.5	11.4	12	14	16	39.4	23.5	n/a	11	20	31	14.1	18	25	35.2	45	5	3	40	44
Infections (%)	12.3	11	17.7	15.3	22.5	9.9	-	2	18	8	4	8.3	8.7	26	34	13.33	n/a	n/a	n/a	n/a	6.6	16	1	3	n/a	4
Cancer (%)	7.4	3	n/a	-	5.6	5.3	-	1	4	5	6	7.4	3.7	3	7	-	n/a	n/a	-	15	3.3	13	7	3	n/a	15
Trombophilias (%)	34.1	48	10.3	23	44.7	14.6	59.1	34	34	27	38	41.1	16.2	13	56	26.6	n/a	3	n/a	7.5	31.1	30	21	24	13	28
Cerebral venous sinus																										
Multiple sinuses involvement (%)	n/a	n/a	85.6	80.3	n/a	41.7	45.4	n/a	50	18	8	n/a	71.25	n/a	46	20	57	n/a	n/a	n/a	83.7	69	n/a	40	50	44
Superior sagittal sinus (%)	62	69.9	76.5	57.7	70.8	48.3	63.6	54.3	71	38.9	66	37.8	65	50	51	40	16	n/a	78	n/a	57.1	51	n/a	40	53	44
Transverse sinus (%)	85.9[1]	26.5	81.1	73	68.2	45.7	54.5	47.7	47	73.4	62	71.7	60.6[1]	50[1]	56	n/a	11	n/a	15.3	n/a	86.4	69	n/a	56	73	70
Sigmoid sinus (%)	85.9[1]	11.8	59.3	57.7	43.6	15.2	n/a	20.6	31	39.8	36	n/a	60.6[1]	50[1]	20	26.6	9	n/a	n/a	n/a	61.9	31	n/a	24	20	46
Deep sinus (%)	10.9	3.4	2.5	n/a	12.7	7.3	n/a	5.8	3	n/a	n/a	n/a	5	7	5	20	1	n/a	3.4	n/a	5.4	5	n/a	15	n/a	5
ICH in CT/MRI (%)	39	27	21.4	40	52	20.5	50	58	34	21.1	30	27.9	38.1	39.3	10	n/a	n/a	38.4	n/a	32.5	43.2	44	28	68	n/a	51
Anticoagulation at discharge (%)	83.3	68	n/a	88.5	n/a	n/a	54.5	92.5	67	66.7	96	88.8	98.1	90	100	n/a	n/a	71.1	81	90	100	84	68	93	80	94
Decompresive surgery /Shunt/ ICH evacuation (%)	3	2	n/a	n/a	4.2	4	n/a	3.7	4	n/a	n/a	n/a	1.25	0	n/a	n/a	n/a	n/a	3.4	-	n/a	5	8	0	0	3

n/a: data not available. [#]Several Asian countries. [&]Data of the present work.

1. Informed combined as ''lateral sinus''

Table 4. *Comparative table of the main variables in CVT registries around the globe. Data from our population is presented in the last row*

Continent	Global	Asia								Asia/Europe		Europe	Africa				Oceania	North America						South America		
Country		Asia[#]	China	Saudi Arabia	India	Irán	Japón	India	Pakistan	Turkey	Turkey	Europe	Tunisia	Morocco	Tunisia	Sudan	Australia	Mexico	Mexico	Canada	EEUU	EEUU	EEUU	Colombia	Brazil	Argentina[&]
Study	ISCVT	ASCTV						NIZAM		VENOST		CEVETIS						NINN	RENAMEVASC							
Year	2004	2019	2019	2019	2019	2016	2014	2012	2008	2017	2017	2012	2017	2014	2013	2008	2016	2018	2012	2017	2017	2009	2008	2012	2010	
Death in hospitalization (%)	4.3	3.3	2.8	n/a	5.6	11.3	-	7.7	6.4	-	4	n/a	3.7	10	7.3	13.3	9	7.3	3.4	5	9.9	1	13	-	-	4
Disability (mRS 3-5) at discharge (%)	14.6	13	23	n/a	25.4	14.5	13.6	25.7	39.4	10	n/a	7.1	n/a	27	10	40	n/a	30	33.9	20	30	19	25	n/a	13	15
CVT recurrence (%)	2.2	1	n/a	n/a	n/a	4	n/a	5.1	n/a	n/a	n/a	4.4	1.2	n/a	2.5	n/a	n/a	3.5	n/a	n/a	n/a	n/a	4	n/a	-	4

n/a: data not available. [#]Several Asian countries. [&]Data of the present work.
1. Informed combined as ''lateral sinus''

cancer are particularly vulnerable to hypercoagulability either related to the underlying malignancy or treatment complications.[39]

A few studies reported age cut off points when analyzing CTV predisposing factors. A study from México[3] used 40 years, a study from China[28] used 44 years and a study from Turkey[7] used 18-36, 37-50 and 51+ years. For age subgroups, the obstetric causes were more frequent in younger patients, whereas infection and malignancy were more often seen in older patients.

The use of anticoagulation treatment in different parts of the world was recently published.[6] They found that it varied between the continents and was surprisingly low at 57% in South American countries. In our registry, anticoagulation treatment at discharge was 94%, with a higher rate compared to some series from Asia or North America. According ISCVT,[11] more than 80% of the patients were treated with anticoagulants, indicating a consensus on the efficacy and safety of anticoagulation in CVT. Personal beliefs regarding the benefits of this therapy for CVT or knowledge to action gaps could explain the difference in some regions. Further studies would be needed to explain this phenomenon (Figure 3).

Only the treatment at discharge was collected in our study. In Argentina, as recommended in the latest guideline,[40] the standard treatment scheme starts in the acute stage with heparin (mostly LMWH), followed by VKA agents at discharge to prevent recurrent CVT and other venous thromboembolic events. Some patients were discharged early or derived to rehabilitation centers, and acenocoumarol treatment was started in the follow up. In some patients with malignancy related CVT, the treating physician might had opted for heparin at discharge.

The comparison of outcome measures among CVT registries is highly variable. For example, we observed a 4% mortality rate at discharge, whereas other registries reported no deaths (VENOST, Turkey) up to 13.3% in Sudan. Similar variability was observed in functional status at discharge. In addition, we observed a 15% disability at discharge, whereas the ISCVT reported 7% reaching it highest prevalence in Pakistan (39.4%) or Sudan (40%). Given methodological differences and lack of patient-level data a reliable statistical comparison was not possible.

After CVT, the risk of venous thrombotic events is estimated at 2% to 3% for a new CVT and 3% to 8% for extracranial events. Venous thrombosis after CVT is more frequent among men and in patients with polycythemia/thrombocythemia. Cancer/malignant hemopathies, and unknown CVT causes were found to be at higher risk of recurrence.[41,42] We had a 4% of patients with CVT recurrence, quite similar to the reviewed registries with follow up information (from 1% to 5.1%). Is important to remark that follow-up time differs in every study, therefore we can only make an estimation.

Our study has limitations that deserve comment. First, as in many multicenter studies, we cannot rule out the

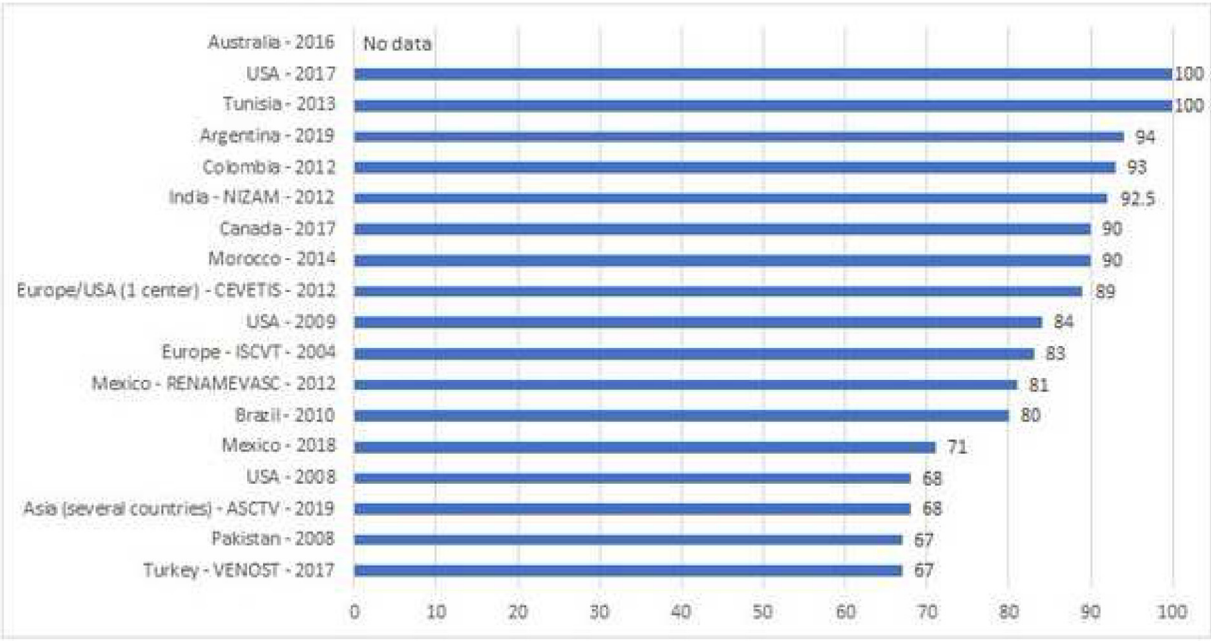

Figure 3. *Comparison of anticoagulation rates at discharge among different CVT registries*

possibility that differences in data collection, completion of investigations and treatment decisions may have influenced our results. Second, we were unable to determine the time of the CVT diagnosis with brain imaging. Third, loss of follow up represented 7% at 90-days. Fourth, given that the decision to proceed with more comprehensive investigations were at the discretion of the treating physician, 13% (n = 21) of the patients have limited information on thrombophilias. We do not have specific information regarding the total number of patients tested for elevated homocysteine and MTFRH mutations, commonly completed in academic centers. The low prevalence of these conditions in CVT and our low sample size might reflect an underestimation of the true prevalence of hyperhomocysteinemia and MTFRH mutation in our study. Finally, our study may not represent the totality of patients with CVT in Argentina as oligosymptomatic patients may have been missed when presenting to other institutions.

Despite these limitations, our study is the first comprehensive report of the Argentinian National multicenter registry on CVT. Our findings are useful for increase public and physician's awareness and planning resources for the optimal management of CVT in Argentina. A recent article about continental disparities in CVT,[6] with data from 7048 patients from all over the world, showed that some continents like South America had limited number of published data compared to other continents like Asia and Europe. Our literature review highlighted similarities and differences in baseline characteristics, clinical presentation, most common predisposing factors, treatment and outcomes between our study and CVT registries from across the globe.

Our results are the starting point for the publication of the first best practice guidelines for the diagnosis and management of CVT in Argentina.

Furthermore, the comparison with other registries is a call for international collaborations as joint efforts to improve our understanding on regional differences in the diagnosis and management of CVT.

Declaration of Competing Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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Appendix: Complete list of other authors and participating centers

The following centers and investigators participated in the ANR-CVT. The number of patients included at each center is given in parentheses:

FLENI, Ciudad Autónoma de Buenos Aires (29, Ameriso S., Alet M. and Pujol-Lereis V.); Hospital Británico, Ciudad Autónoma de Buenos Aires (24, Bonardo P., Bandeo L., González F., Pacio G. and Saucedo M.); Hospital Italiano de Buenos Aires, Ciudad Autónoma de Buenos Aires (14, Cea C. and Zurrú M.); Clínica La Sagrada Familia. Ciudad Autónoma de Buenos Aires (13, Ciardi C., Chasco M. and Cirio J.); HIGA Gral. San Martín de La Plata, Buenos Aires (9, Montes M. and Tumino L.);

Sanatorio de la Trinidad Mitre, Ciudad Autónoma de Buenos Aires (9, Persi G.); Hospital Cullen, Santa Fe (8, Galindo A., Martínez C. and Noguera M.); Hospital San Bernardo, Salta (7, Orzuza G.); Hospital Julio Cecilio Perrando, Chaco (6, Cuculic M.); CEMIC, Ciudad Autónoma de Buenos Aires (6, Romano M.); Hospital Lagomaggiore, Mendoza (5, Giner F.); Sanatorio de los Arcos, Ciudad Autónoma de Buenos Aires (5, Gómez-Schneider M. and Piedrabuena M.); Hospital Provincial del Centenario, Santa Fe (4, Martínez-Lorezín R.); Complejo Médico Policial Churruca-Visca, Ciudad Autónoma de Buenos Aires (4, Povedano G.); Hospital General de Agudos J. M. Ramos Mejía, Ciudad Autónoma Buenos Aires (3, Lepera S. and Rey R.); Hospital Dr. Guillermo Rawson, San Juan (3; Lucato D. and Quiroga-Narváez J.); Hospital César Milstein, Ciudad Autónoma de Buenos Aires (3, Esnaola M.); Clínica Regional del Sud, Córdoba (2, Viglione J.); IMAC - Instituto Médico de Alta Complejidad, Salta (2; Alemán A.); Hospital Ángel Cruz Padilla, Tucumán (2, Cossio J.); Hospital Dr Arturo Oñativia, Buenos Aires (1, Isaac C.); Hospital SAMIC de Alta Complejidad Gobernador Cepernic - Presidente Kirchner, Santa Cruz (1, Sabio R.); Neuromadryn, Chubut (1, García-Pérez F.).

References

1. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-2236.
2. Saposnik G, Barinagarrementeria F, Jr Brown RD, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association / American Stroke Association. Stroke 2011;42:1158-1192.
3. Ruiz-Sandoval JL, Chiquete E, Bañuelos-Becerra LJ, et al. Cerebral venous thrombosis in a Mexican multicenter registry of acute cerebrovascular disease: the RENAMEVASC study. J Stroke Cerebrovasc Dis 2012;21:395-400.
4. Ferro JM, Canhão P. Cerebral venous sinus thrombosis: update on diagnosis and management. Curr Cardiol Rep 2014;16:523.
5. Karnad DR, Guntupalli KK. Neurologic disorders in pregnancy. Crit Care Med 2005;33:S362-S371.
6. Maali L, Khan S, Qeadan F, et al. Cerebral venous thrombosis: continental disparities. Neurol Sci 2017;38(11):1963-1968.
7. Taskin D, Derya U, Ipek M, et al. A Multicenter Study of 1144 Patients with Cerebral Venous Thrombosis: The VENOST Study. J Stroke Cerebrovasc Dis 2017:1848-1857.
8. Amaya González P, Ramírez S, Rodríguez J. Cerebral venous thrombosis, clinical description of a series of cases in adults from Bogotá-Colombia. Neurol Colomb Act 2012;vol.28(n.2):pp.70-pp75.
9. Pereira Christo P, Martins G, Pereira Gomes A. Cerebral venous thrombosis: Study of fifteen cases and review of literature. Associacao Medica Brasileira Magazine 2010;56:288-292.
10. Stevenazzi M, Díaz L. Cerebral venous thrombosis. Arch Med Interna 2012;34(2):43-46.
11. Ferro JM, Canhão P, Stam J, et al. ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004;35:664-670.
12. Narayan D, Kaul S, Ravishankar K, et al. Risk factors, clinical profile, and long-term outcome of 428 patients of cerebral sinus venous thrombosis: insights from Nizam's Institute Venous Stroke Registry, Hyderabad, India. Neurol India 2012;60(2):154-159.
13. Capecchi M, Abbattista M, Martinelli I. Cerebral venous sinus thrombosis. J Thromb Haemost 2018;16(10):1918-1931.
14. Wasay M, Bakshi R, Bobustuc G, et al. Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. J Stroke Cerebrovasc Dis 2008;17:49-54.
15. Sidhom Y, Mansour M, Messelmani M, et al. Cerebral venous thrombosis: clinical features, risk factors, and long-term outcome in a Tunisian cohort. J Stroke Cerebrovasc Dis 2014;23:1291-1295.
16. Khealani BA, Wasay M, Saadah M, et al. Cerebral venous thrombosis: a descriptive multicenter study of patients in Pakistan and the Middle East. Stroke 2008;39:2707-2711.
17. Wasay M, Kaul S, Menon B, et al. Asian Study of Cerebral Venous Thrombosis. J Stroke Cerebrovasc Dis 2019;28(10):104247.
18. Dentali F, Poli D, Scoditti U, et al. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. J Thromb Haemost 2013;11(2):399.
19. Devasagayam S, Wyatt B, Leyden J, et al. Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought: A Retrospective Population-Based Study. Stroke 2016;47(9):2180-2182.
20. Arauz A, Marquez-Romero JM, Barboza MA, et al. Mexican-National Institute of Neurology and Neurosurgery-Stroke Registry: Results of a 25-Year Hospital-Based Study. Front Neuro 2018;9:207.
22. Anderson D, Kromm J, Jeerakathil T. Improvement in the Prognosis of Cerebral Venous Sinus Thrombosis over a 22-Year Period. Can J Neurol Sci 2018;45(1):44-48.
22. Salottolo K, Wagner J, Frei DF, et al. Epidemiology, Endovascular Treatment, and Prognosis of Cerebral Venous Thrombosis: US Center Study of 152 Patients. J Am Heart Assoc 2017;6(6):e005480.
23. English JD, Fields JD, Le S, et al. Clinical presentation and long-term outcome of cerebral venous thrombosis. Neurocrit Care 2009;11(3):330-337.
24. Ramrakhiani N, Sharma DK, Dubey R, et al. Clinical Profile, Risk Factors and Outcomes in Patients with Cerebral Venous Sinus Thrombosis: A Study from Western India. J Assoc Physicians India 2019;67(9):49-53.
25. Shahid R, Zafar A, Nazish S, et al. Etiologic and Clinical Features of Cerebral Venous Sinus Thrombosis in Saudi Arabia. J Neurosci Rural Pract 2019;10(2):278-282.
26. Ghiasian M, Mansour M, Mazaheri S, et al. Thrombosis of the Cerebral Veins and Sinuses in Hamadan, West of Iran. J Stroke Cerebrovasc Dis 2016;25(6):1313-1319.
27. Idris MN, Sokrab TE, Ibrahim EA, et al. Cerebral venous thrombosis. Clinical presentation and outcome in a prospective series from Sudan. Neurosciences 2008;13:408-411.
28. Pan L, Ding J, Ya J, et al. Risk factors and predictors of outcomes in 243 Chinese patients with cerebral venous sinus thrombosis: A retrospective analysis. Clin Neurol Neurosurg 2019;183:105384.
29. Sassi SB, Touati N, Baccouche H, et al. Cerebral Venous Thrombosis: A Tunisian Monocenter Study on 160 Patients. Clin Appl Thromb Hemost 2017;23(8):1005-1009.

30. Shindo A, Wada H, Ishikawa H, et al. Clinical features and underlying causes of cerebral venous thrombosis in Japanese patients. Int J Hematol 2014;99(4):437-440.
31. Ashjazadeh N, Borhani Haghighi A, Poursadeghfard M, et al. Cerebral venous-sinus thrombosis: a case series analysis. Iran J Med Sci 2011;36:178-182.
32. Poungvarin N, Prayoonwiwat N, Ratanakorn D, et al. Thai venous stroke prognostic score: TV-SPSS. J Med Assoc Thai 2009;92:1413-1422.
33. Geisbüsch C, Lichy C, Richter D, et al. Clinical course of cerebral sinus venous thrombosis. Data from a monocentric cohort study over 15 years. Nervenarzt 2014;85:211-220.
34. Wang B, Peng C, Zhou MK, et al. Clinical characteristics and prognosis of patients with cerebral venous sinus thrombosis in southwest China. Sichuan Da Xue Bao Yi Xue Ban 2014;45:515-518.
35. Chen HM, Chen CC, Tsai FY, et al. Cerebral sinovenous thrombosis. Neuroimaging diagnosis and clinical management. Interv Neuroradiol 2008;11(14 Suppl 2):35-40.
36. Wang JW, Li JP, Song YL, et al. Clinical characteristics of cerebral venous sinus thrombosis. Neurosciences (Riyadh) 2015;20:292-295.
37. Kumral E, Polat F, Uzunkprü C, et al. The clinical spectrum of intracerebral hematoma, hemorrhagic infarct, non-hemorrhagic infarct, and non-lesional venous stroke in patients with cerebral sinus-venous thrombosis. Eur J Neurol 2012;19:537-543.
38. Bushnell C, Saposnik G. Evaluation and management of cerebral venous thrombosis. Continuum (Minneap Minn) 2014;20:335-351.
39. Raizer JJ, DeAngelis LM. Cerebral sinus thrombosis diagnosed by MRI and MR venography in cancer patients. Neurology 2000;54(6):1222-1226.
40. Ferro JM, Bousser MG, Canhão P, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - Endorsed by the European Academy of Neurology. Eur Stroke J 2017;2(3):195-221.
41. Palazzo P, Agius P, Ingrand P, et al. Venous Thrombotic Recurrence After Cerebral Venous Thrombosis: A Long-Term Follow-Up Study. Stroke 2017;48(2):321-326.
42. Miranda B, Ferro JM, Canhão P, et al. Venous thromboembolic events after cerebral vein thrombosis. Stroke 2010;41(9):1901-1906.