Asian Study of Cerebral Venous Thrombosis

Mohammad Wasay, MD, FRCP, FAAN,* Subash Kaul, MD,† Bindu Menon, MD, DM,‡ Alper I. Dai, MD,§ Mohammad Saadatnia, MD,¶ Abdul Malik, MD,‖ Ahmed Khalifa, FRCP,# Afshin Borhani-Haghighi, MD,** Manmohan Mehndiratta, MD, FRCP,†† Maria Khan, FCPS,‡‡ Nimalendu Bikash Bhowmik, MD,§§ and Safia Awan, MSc*

Background/Objective: Most of the studies and registries related to cerebral venous thrombosis (CVT) are reported from European countries and the United States. The objective of the present study is to identify risk factors, presentation, and outcome of CVT in Asian patients. *Methods:* Asian CVT registry is a prospective multinational observational study that included patients (aged > 16 years) with symptomatic CVT. *Results:* Eight hundred and twelve patients (59% women) from 20 centers in 9 Asian countries were included. Mean age of the patients was 31 years. Motor weakness in limbs was present in 325 (40%) patients. One hundred and eighty (22.1%) patients had a normal Glasgow coma scale (GCS) at presentation, and another 529 patients (65%) had GCS between 11 and 14. The rest (103; 13%) had a GCS of less than 10 at presentation. Permanent risk factors were present in 264 (33%) patients, transient in 342 (42%) patients, both in 43 (5%) patients and no risk factors were found in 163 (20%) patients. Anemia was present in 51%, use of oral contraceptive pills (OCP) was present in 12% women and a hypercoaguable state was present in more than 40% of those tested. One hundred and forty-three cases (18%) were in women who were either pregnant (18; 2%) or in the puerperium (up to 6 weeks postpartum; N = 125; 15%). A total of 86 (10.5%) patients were diagnosed with infection in any part of the body. The most common MRI finding was local brain edema or ischemia (53.3%) followed by hemorrhage (26.7%). Twenty-seven patients (3.3%) died during hospital stay. The mRS score at discharge was available for 661 (81%) patients. Of these, 577 (87.3%) had good functional outcome at discharge. Motor weakness at presentation, GCS of 9 or less and mental status disorder were the strongest independent predictors of mortality at last follow-up among patients with CVT. *Conclusions:* Important differences were identified as compared to western data including younger age, high frequency of anemia, low use of OCP, and high frequency of hypercoaguable states. Functional outcome at discharge was good.

Key Words: Cerebral venous thrombosis—sinus thrombosis—hypercoaguable state—MRI—outcome—venous stroke

From the *Department of Medicine, Aga Khan University, Karachi, Pakistan; †Department of Neurology, Nizam Institute of Neurology, Hyderabad, India; ‡Department of Neurology, Apollo Speciality Hospital, Nellore, Andhra Pradesh, India; §Department of Neurology, Gaziantep University, Gaziantep, Turkey; ¶Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran; ‖Liaquat Medical and Dental College, Karachi, Pakistan; #Department of Neurology, Damascus University, Damascus, Syria; **Department of Neurology, Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; ††Department of Neurology, Janakpuri Speciality Hospital, New Delhi, India; ‡‡Department of Neurology, Rashid Hospital, Dubai, UAE; and §§Asghar Ali Hospital, Dhaka, Bangladesh.

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Address correspondence to Mohammad Wasay MD, FRCP, FAAN, Department of Neurology, Aga Khan University, Stadium Road, Karachi 74800, Pakistan. E-mails: mohammad.wasay@aku.edu, mohammadwasay@hotmail.com.

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Introduction

Cerebral venous thrombosis (CVT) is a well-known entity.[1] Two large database of patients with CVT included 624 and 706 cases.[2,3] Most of the studies and registries related to CVT are reported from European countries and the United States.[2-5] A large series of patients recently reported from Turkey (Venost) included patients both from Asian and European parts of country.[6]There are only a few multicenter or multinational studies reported from Asian countries.[7] Recently a single-center retrospective review of 428 patients with CVT was published from India.[8]

CVT is not uncommon in Asia, especially in the south Asian subcontinent including India, Pakistan, and Bangladesh. Pangayara reported from India that CVT accounted for half of the young stroke cases and 40% for strokes in woman.[9] A study of young Asian women with stroke reported a frequency of 20% stroke related to CVT.[10]

Review of CVT cases from Asian and other developing countries is suggestive of differences in risk factors profile and outcome in these patients as compared to European studies. One of the largest cohort of CVT patients from Europe (ISCVT; n = 624) reported that 50% of these cases were related to oral contraceptive pills, 6% were associated with pregnancy and 14% with puerperium.[2] Venost reported gynecological causes (puerperium: 18%, OCP: 14%, and pregnancy: 9%) as most common cause of CVT, 26% had prothrombotic states, 9% had Bachets disease, 8% had infections, and 5% had malignancy.[6]

A study of 182 adult patients with CVT from the USA reported 7% associated with pregnancy and puerperium and 5% related to OCP use.[4] A study from Pakistan (109 patients with CVT) reported that 17% were due to pregnancy and puerperium and 5% related to OCP use.[7] Cantu from Mexico reported 59% cases due to pregnancy/puerperium.[11]

We believe that risk factors, presentation, and outcome of CVT in Asian countries may be different from those in European and North American patients. The objective of the present study is to identify risk factors, presentation, and outcome of CVT in Asian patients. This study may help planning future case-control studies and randomized controlled trials related to CVT.

Subjects and Methods

Study Design and Enrollment

The Asian CVT registry is a prospective multinational observational study that included patients (aged > 16 years) with symptomatic CVT.

Data were collected from 20 centers (14 public and 6 private hospitals) in 9 Asian countries (a list of all participating centers with principal investigators and number of patients enrolled is provided in Appendix 1). All participating centers provided data on consecutive cases diagnosed at their institutions and performed at least a 6-month follow-up evaluation. All data sheets with baseline and follow-up data were entered and analyzed at the coordinating center at the Aga Khan University, Karachi. All participating investigators were neurologists. Patients were enrolled not only from neurology services but also Medicine, Obstetrics and Gynecology, and other services. For standardization we followed the methodology adopted by the International study of Cerebral Venous thrombosis (ISCVT) investigators.[2]

Patient enrollment started in July 2009 and continued until July 2012 (3 years). Follow-up was completed in July 2013.

Case Definition and Ascertainment

Patients were only included in study if they had a diagnosis of CVT, proven by MRI, MRV, contrast-enhanced CT and CT venography or conventional cerebral venography, according to established criteria.[12]

All patients underwent a history and a complete physical and neurological examination and a neuroimaging study. Confirmation of cases and review of imaging were done by local participating center.

Baseline Data

Following data were recorded in a prespecified data sheet: demographic data; dates of onset of symptoms, of hospital admission, and of confirmation of the diagnosis by imaging (considered as day 0); symptoms and signs from onset to diagnosis; Glasgow coma scale (GCS) score on admission and during the clinical course; imaging methods used; location of the thrombus; and number, location, and size of any parenchymal brain lesions. Presenting symptoms were recorded as isolated intracranial hypertension, headache (type, duration, and location), seizures, vomiting, and papill-edema with/without visual loss, sixth and other cranial nerve paresis, other neurological symptoms or signs and other presenting syndromes. Confusion or psychosis at presentation was labeled as mental status disorder. Dehydration was diagnosed based on clinical signs and symptoms. A number of predisposing conditions for CVT were evaluated in these patients. We divided predisposing conditions in 4 categories: permanent, transient, both, and none. Permanent risk factors included hypercoaguable states and malignancies while transient predisposing factors included pregnancy/puerperium, anemia, infections, drugs, systemic inflammatory diseases, and dehydration. A number of tests were performed to identify hypercoagulable states in these patients including Protein C, S and antithrombin III deficiency, Factor V mutation, antiphospholipid antibodies, prothrombin gene mutation, and serum and urine homocystiene levels.

The choice of treatment was left to the treating physician, but all treatments were systematically recorded.

Follow-Up

Follow-up visits were performed at 1 month, 6 months, and 12 months, and yearly thereafter, by direct interview and observation by the local investigators. Follow-up data included: disability (according to modified Rankin Score [mRS], death, recurrent symptomatic sinus thrombosis (new symptoms with new thrombus on repeated venogram or MRI), other thrombotic events, seizures, headaches, severe visual impairment (quantified with an optometric chart as $< 4/10$), pregnancy, abortion, and current antithrombotic and other treatments.

Outcome

Outcome was classified according to the Modified Rankin Score (mRS): complete recovery (mRS 0-1); partial recovery, independent (mRS 2); dependent (mRS 3-5); and death (mRS 6). Primary outcome was death or dependence (mRS > 2) at the end of the follow-up period. Secondary outcomes were death and death or dependence at 6 months.

Statistical Analysis

Descriptive results are presented as median and mean $\pm$ standard deviation for quantitative variables and number (percentage) for qualitative variables. Differences in proportions were assessed by using the chi-square test or Fisher exact test where appropriate. For contrasts of continuous variables, one-way analysis of variance, and independent sample *t* test were used to assess the difference of means. Univariable analyses were performed to examine associations between independent variables and mortality. Multivariable analysis was conducted to identify factors associated with poor outcome. All *P* values were based on 2-sided tests and significance was set at a *P*value less than .05. The analyses were performed using SPSS (Statistical Package of Social Sciences) version 19.

RESULTS

Eight hundred and twelve patients from 20 centers in 9 Asian countries were included in this analysis. Mean age of the patients was 31 years (range 16 to 85; median 32 years). Fifty-nine percent (n = 479) were women. Two-thirds of the patients were from India and Pakistan. Mean duration between symptom onset and diagnosis was 10 days (1-60 days). Median duration was 11.4 days.

Presenting Signs and Symptoms

Headache was the most common presenting symptom, present in 90% of our patients. In more than half of these patients, headache duration was more than a week before hospital presentation. The most common location for the headache was frontal and it was diffuse in almost 40% of patients. In 81% of patients it was associated with vomiting.

GCS was abnormal in 632 (78%) subjects. One hundred and eighty (22.1%) patients had a normal GCS at presentation, and another 529 patients (65%) had GCS between 11 and 14. The rest (103; 13%) had a GCS of less than 10 at presentation.

Seizures were another common presentation, reported in 360 patients (44%). A total of 77.5% of these patients had generalized seizures with 3 patients presenting as status epilepticus.

Visual symptoms were present in 225 (28%) patients and these included blurring of vision (149; 18%), diplopia (33; 4%), and transient visual obscurations (26; 3%). Seventeen patients (2%) had loss of vision at presentation. Papilledema was present in 462 patients (57%).

Cranial nerve involvement was found in 109 (13%) patients. Central facial nerve involvement was the most common found in 66 (8%) patients, followed by abducens palsy in 60 (7%) patients. Motor weakness in limbs was present in 325 (40%) patients.

Predisposing Conditions

Permanent risk factors were present in 264 (33%) patients, transient in 342 (42%) patients, both in 43 (5%) patients, and no risk factors were found in 163 (20%) patients. A total of 649 (80%) patients had one or more predisposing factors for CVT out of which 204 (31%) had single predisposing factor, 364 (56%) had 2 risk factors, and 81(12%) had 3 or more risk factors.

One hundred and forty-three cases (18%) were in women who were either pregnant (18; 2%) or in the puerperium (up to 6 weeks postpartum; N = 125; 15%). Among those pregnant, the mean duration of pregnancy was 27 weeks at the time of diagnosis. For those diagnosed with CVT in the puerperium, the mean time between child birth and diagnosis was 19 days. Additional conditions like fever and dehydration were found in 26 (18% of all pregnancy/puerperium) and 24 (17%) of these women respectively in puerperium and pregnancy.

A total of 86 (10.5%) patients were diagnosed with infection in any part of the body. The most common location of infections was in contiguous sites: 9 had meningitis, 17 had mastoiditis, and another 37 had sinusitis. Nine patients were diagnosed with urinary tract infections and another 3 had sepsis.

Twenty-four patients (3%) had concomitant malignancies, 10 with hematological, and the rest with solid tumors. Among the solid tumors lung cancer was the commonest, found in 4 subjects, followed by ovarian and tongue (2 each). Among hematological malignancies included lukemias, lymphoma, and multiple myeloma.

Protein C, S, and antithrombin III deficiencies were tested in a large majority of cases, and each deficiency was identified in close to 40% of those tested. Table 1

provides details of other conditions predisposing to hypercoagulability in these patients.

Other medical conditions which may be associated with CVT were present in 101 patients (12%). These included dehydration (69; 8%), systemic lupus erythematosis (18; 2%), inflammatory bowel disease (10; 1%), and nephrotic syndrome (4; .5%). Fifty-nine women (12% of 479 women in this study) were taking oral contraceptive pill at the time of diagnosis.

Diagnostic Findings

MRI and MRV were performed in 686 patients. Three patients had MRI alone, another 8 had CT venography, and 115 had contrast-enhanced CT alone. The most common MRI finding was an area of hypodensity on T1-weighted images suggesting local brain edema or ischemia (53.3%) followed by hemorrhage (26.7%). Diffuse cerebral edema was seen in 97 (14.3%) patients. Focal or gyral enhancement was seen in postcontrast MR imaging in 58 (7%) of patients. Among patients who underwent CT imaging, only 10% had areas of hypointensity, and another 9.6% had hemorrhage.

The superior sagittal sinus was the most common site for thrombosis, found in 568 patients (69.9%) using all modalities. This was followed by transverse (215; 26.5%) and sigmoid sinuses (96; 11.8%). Cavernous sinus was involved in only 8 patients. Twenty-eight patients had deep CVT (3.4%).

Treatment

Out of 812 patients, 783 (96%) received anticoagulation (372: unfractionated heparin; 375: low molecular weight heparin (LMWH); and 36: both). None of the patients was treated with thrombolysis or endovascular intervention.

Table 1. *Prothrombotic/hematological workup*

Procoagulant State (number undergoing testing)	Number with abnormal results (%)
Protein C (526)	215 (40.9%)
Protein S (518)	215 (41.5%)
Anti-thrombin III (508)	187 (36.8%)
Prothrombin G20210A (32)	3
Factor V Leiden mutation (175)	
Heterozygous	71 (40.6%)
Homozygous	22 (12.6%)
Antiphospholipid antibodies (225)	45 (20%)
Elevated Homocysteine level (495)	184 (37.2%)
Sickle cell anemia	7
Iron deficiency anemia (756)	383 (50.7%)
Polycythemia	12
Thrombotic thrombocytopenic purpura	3

Surgical intervention was done in 16 (2%) patients, including decompression, intraventricular drain, and shunt placement. A total of 553 (68%) were discharged on warfarin anticoagulation, and 207 (25%) on one or more antiplatelet drugs. Majority of patients that did not receive anticoagulation were due to various reasons which included hematuria, gastrointestinal bleeding, postpartum hemorrhage, neurosurgical intervention and CVT related to infections, pregnancy, and malignancy.

Decision of treatment with unfractionated heparin (UFH) or LMWH was the attending physician's choice. We compared both groups to identify differences and outcomes. Patients treated with LMWH were more often females, had more frequently visual symptoms, low GCS (<9), and more seizures. Patients treated with UFH were more often males, with higher frequencies of hemorrhagic infarcts and thrombophilia. Complications were not different in 2 groups. There was no difference in baseline characteristics and outcome among 2 groups on direct comparison.

Outcomes

A number of in-hospital complications were observed in our patients (Table 2). Seizures were the most common and occurred in 10% of the patients. Twenty-two patients (2.7%) required mechanical ventilation and 16 patients (2%) required surgical intervention, mainly decompression surgery.

Twenty-seven patients (3.3%) died during hospital stay. Causes of death included herniation, sepsis or infection, cardiac causes, and pulmonary embolism. The mRS score at discharge (excluding death or mRS = 6) was available for 661 (81%) patients. Of these, 577 (87.3%) had good functional outcome at discharge, defined as mRS of 2 or less (Fig 1).

Thirty-day follow-up was available for 633 of the 785 discharge cases (80.6%). Another 16 patients had died at this time, bringing the total 30-day mortality to 43 (5%). The follow-up rate further dropped at 6 months and 1 year, (418 and 230). Another 15 and 10 patients respectively had died during this period. Out of all available follow-up, 68 (8%) died at 1-year follow-up (Fig 1).

After 1 year recurrent CVT was observed in 9 (1%) patients and 71 (9%) continued to have seizures despite antiepileptic treatment. Out of the 230 patients available for 1-year follow-up, 109 (48%) were taking warfarin. Patients receiving antiepileptic drugs or anticoagulation were more likely to return for follow-up after 1 year.

Predictors of Outcome

Cox regression analysis was done to identify predictors of mortality at last follow-up. We compared our outcome predictors to predictive model suggested by Koopman et al.[13] Motor weakness at presentation, GCS of 9 or less and mental status disorder were the strongest independent predictors of mortality at last follow-up among patients with CVT.

Table 2. *In-hospital complications observed in CVT patients*

In-hospital complications	Number (%)
Seizures	83 (10.2)
Progressive coma	36 (4.4)
Deep venous thrombosis	28 (3.4)
Aspiration pneumonia	26 (3.2)
Visual loss	23 (2.8)
New infarct	17 (2.1)
Gastro-intestinal bleeding	14 (1.7)
Extension of hemorrhage	10 (1.2)
New intracerebral hemorrhage	9 (1.1)
Mechanical ventilator need	22 (2.7)

Type of Heparin

Out of 783 patients treated with anticoagulation 372 (48%) received UFH, 375 (48%) received LMWH, and 36 (4%) received both. There was no difference in baseline characteristics and outcome (mortality) among 2 groups on direct comparison.($P = .35$)

Hemorrhage and Ischemic Infarcts

Out of 812 subjects, 692 (85%) had infarcts (hemorrhagic: 202, 29% and nonhemorrhagic: 490, 71%). Patients with hemorrhagic infarcts were more likely to have a low GCS (<9) and superior sagittal sinus thrombosis. Patients with hematologic disorders were more likely to have a lesion (hemorrhage or nonhemorrhage) on imaging. Mortality and disability were high in patients with hemorrhagic lesions but these were not statistically significant ($P = .11$).

Discussion

This study represents largest data of patients with CVT especially from Asian countries. It is the first prospective, multinational and multicenter data from 9 Asian countries. Asian countries, especially south Asia, are considered to be highest prevalent areas for CVT.[14] We compared findings of this study to the ISCVT, CEVETIS, and Venost, which included predominantly European patients NIZAM institute study representing Indian patients (Table 3).[2,3,6]

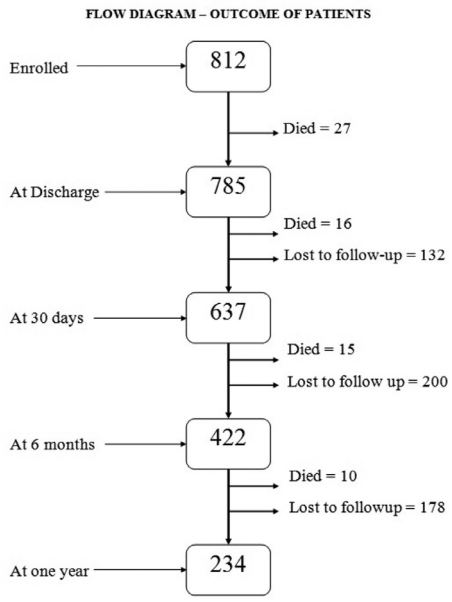

Figure 1. *Flow chart; outcome of patients.*

Our patients had CVT at a much younger age as compared to ISCVT, CEVETIS, and Venost (31 years vs 39-41 years). In a recent CVT study from India the mean age was 32 years.[8] CVT was more common in women in our study (59%), but the frequency is low as compared to ISCVT, CEVETIS, and Venost (73%-75% and 67%). A study of CVT patients from USA showed mean age of 38 years and a female preponderance (60%).[4] Recent study from India[8] showed a male preponderance (53%). These findings suggest that CVT in Asian countries occurs at a younger age as compared to Europe and the USA and that the percentage female patients is lower. One possible explanation is sampling bias. It is well established that in these developing countries gender differences are present in stroke care and outcome.[15,16] This gender difference in developing Asian countries may be related to access of care. Stroke in women is poorly reported from South Asia though it is leading cause of death in women above age 60 years in this region.[17]

These findings are contrary to the common belief in this region that CVT is largely a women disease mostly related to pregnancy and puerperium. CVT is a frequent cause of stroke in young Asian women and probably the most common cause of stroke in pregnancy in Asia.[18] In VENOST study 27% were due to pregnancy and puerperium.

Mean delay from symptom onset to diagnosis was 10 days (as compared to 7 days in ISCVT). This could be related to awareness and availability of diagnostic facilities. About two-thirds patients are from South Asia, where the number of neurologists and diagnostic facilities is less as compared to Europe.

Headache was the most common presenting symptom, as identified in previous studies. There was no association of headache with presence of hemorrhage, and no relation between lateralization/localization of headache and sinus involvement. These findings are consistent with previous studies.[19]

Papilledema was present in 57% patients as compared to 28% in ISCVT. This could be an important indicator for imaging in resource limited settings. Very high frequency of papilledema may reflect more parenchymal involvement and longer duration of thrombosis. Papilledema with headache may sometimes be mistaken for idiopathic intracranial hypertension. A young patient especially woman with headache, papilledema, and seizure or focal neurological deficit should prompt any physician to consider CVT.[20] Public and physicians awareness may play a key role in early identification and treatment of these patients.

Table 3. *Comparison to regional and western data*

	ASCVT	VENOST	CEVETIS	ISCVT	NIZAM
Region	Asia	Turkey	Europe	Europe	India
Number of patients	812	1144	706	624	428
Mean age (y)	31		40	37	31
Female (%)	59	68	74	75	46
Pregnancy/puerperium (%)	18	27	8	19	10
OCP (%)	12	14	39	54	11
Infections (%)	11	8	8	12	2
Malignancy (%)	3	5	7	7	1
Thrombophilia (%)	48	27	52	74	34
Hemorrhage on CT/MRI (%)	27	21	28	39	58
Received LMWH/UFH treatment (%)	96	83	84	98	98
Received long-term anticoagulation (%)	68	67	83	n/a	n/a
Surgery done (%)	2	n/a	n/a	3	4
Death at discharge (%)	3.3	n/a	n/a	4.3	7.7
Disability (mRS 3-5) at discharge (%)	13	n/a	11	7	25
Mortality at 6 months (%)	n/a	n/a	2.8	6.8	n/a

Seizures and ischemic infarcts were more common and hemorrhage was less common as compared to European data. Overall frequency of parenchymal disease and subnormal GCS was more common in our patient population as compared to previous studies.

There were a number of notable differences in predisposing factors in our patient population as compared to European and North American studies. Anemia (51%) was extremely common as compared to ISCVT (9%) and Venost (3%) while use of oral contraceptive pills (12%) was uncommon as compared to ISCVT (54%). Use of contraception is low (5.5%) in these countries especially Pakistan.[21] Most of CVT in Asian patients is related to thrombophilia and pregnancy/puerperium. Use of OCP was present in 11%-12% women as compared to 54% in ISCVT patients (Table 3). An association between iron deficiency anemia and venous thromboembolism is well known though mechanism poorly understood.[22]

Comprehensive work up for hypercoaguable states was not done in all patients. Protein C and S deficiency and hyperhomocystinemia were more common among those tested as compared to previous studies. These findings should be interpreted carefully as most of these tests were done in the acute phase. It is suggested that these patients should have a repeat test after 3 months but it was not done in almost all cases. Frequencies of pregnancy/puerperium, malignancy, and infection were similar to previous reports. Retrospective review of a large sample of CVT patients from India showed anemia and hyperhomocystenemia to be the most common risk factors.[8] Anemia is very common in Asia especially South Asian countries. Prevalence of anemia in women of reproductive age is more than 50% and in children is 32% in Pakistan.[23,24] This is probably why anemia-related CVT is more common in Asian patients.

Although 96% patients received anticoagulation (UFH or LMWH) in the acute stage, only 68% were discharged on anticoagulation (warfarin). Patients with pregnancy/puerperium, malignancy, surgical intervention, and infections less often received anticoagulation at discharge. This could be due to physicians awareness, availability of long-term anticoagulation monitoring facilities, physicians comfort level with anticoagulation especially warfarin etc. The frequency of anticoagulation is comparable to Venost study where 67% received long-term anticoagulation.

Overall outcome was better than in the ISCVT. Only 3.3% died and 87% had good functional outcome at discharge. This is much better than our reported data from 2008[7] with mortality of 6% and poor functional outcome in 40%. Due to large number of dropouts at long-term follow-up it is hard to comment on long-term outcome. Mortality was 8% after 1 year in our study but it may be higher than this. Stroke treatment and rehabilitation facilities and follow-up mechanism are poor in South Asian countries. Despite these shortcomings, outcome was good. Early diagnosis and aggressive management especially endovascular thrombolysis may further reduce this mortality and disability. Endovascular thrombolysis was almost nonexistent in these developing Asian countries. This modality may have a role in patients not responding to conventional anticoagulation, but there is so far no evidence from randomized trials.[25,26]

Data from ISCVT reported better safety and efficacy of LMWH as compared to UFH.[27]Our study findings suggest no difference in outcome of both treatment groups.

Strengths of this study include the large sample size, multicenter and multinational data collection, and decent data quality. Development of a network of Asian stroke centers, research infrastructure and collaboration are long-term benefits of this study.

South Asia is probably the hardest hit region in world related to stroke, especially CVT. Lack of Asian or African data was a limitation of ISCVT. This study helps to fill

this information gap. Lack of central imaging review, non-uniformity of work up, and large number of dropouts at follow-up are major limitations of our study. CVT in children is not uncommon in our part of world. This study did not include children but this gap can be filled in the future following our model of collaborative research.

Future interventions to reduce the burden of CVT in this region may involve better treatment of anemia, identification, and treatment of young high-risk patients with hypercoaguable states, hyper homocystinemia, antiphospholipind antibodies etc. and prompt and adequate treatment of infection, dehydration, and hypercoaguable states in puerperium.

These findings highlight important differences as compared to western data including younger age, high frequency of anemia, low use of OCP, high frequency of hypercoaguable states, and a longer diagnosis delay. Despite low number of diagnostic and treatment facilities in this part of world, overall outcome was good. Identification of high-risk patients, early diagnosis and aggressive management may further improve outcome.

Acknowledgments

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Conflict of Interest

None.

Author's Contribution

Mohammad Wasay: Literature search, study design, protocol writing, collaboration, data collection, data analysis, data interpretation, manuscript writing, manuscript review; Subash Kaul: Study design, data collection, data analysis, data interpretation, manuscript writing, manuscript review; Bindu Menon: Data collection, data analysis, data interpretation, manuscript writing, manuscript review; Alper I. Dai: Data collection, data analysis, data interpretation, manuscript writing, manuscript review; Mohammad Saadatnia: Collaboration, data collection, data analysis, data interpretation, manuscript writing, manuscript review; Abdul Malik: Data collection, data analysis, data interpretation, manuscript writing, manuscript review; Ahmed Khalifa: Data analysis, data interpretation, manuscript writing, manuscript review; Afshin Borhani: Data collection, data analysis, data interpretation, manuscript writing, manuscript review; Manmohan Mehndiratta: Data collection, data analysis, data interpretation, manuscript writing, manuscript review; Maria Khan: Data analysis, data interpretation, manuscript writing, manuscript review; Bhowmik Bikash: Data collection, data analysis, data interpretation, manuscript writing, manuscript review; Safia Awan: Study design, protocol writing, data analysis, data interpretation, manuscript writing, manuscript review.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.06.005.

Appendix 1: Participating Centers

Pakistan

1. Aga Khan University (PI; M Wasay); private hospital; number of patients = 129
2. Shifa International (Maimoona Siddiqi); private hospital; number of patients = 19
3. PIMS, Islamabad (Mohammad Tariq); government hospital; number of patients = 37
4. Liaquat National hospital (Abdul Malik); private hospital; number of patients = 57
5. Ziauddin Medical University (Bashir Soomro); private hospital; number of patients = 38
6. Shaheed Benazir Bhutto Medical university (Alam Ibrahim Siddiqi); government hospital; number of patients = 25

India

7. Nizam Institute of Neurology, Hyderabad, India (PI; Subash Kaul); government hospital; number of patients = 107
8. G B pant Hospital, New Delhi, India (PI-MM Mehndiratta); government hospital; number of patients = 32
9. Vellore medical college, Vellore, India (PI; P Muthu); government hospital; number of patients = 39
10. Simhapuri Hospital, Nellore, Andhra Pradesh (PI; Bindu Menon); government hospital; number of patients = 64
11. Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India (PI; Sri Nawas): government hospital; number of patients = 31

Singapore

12. Raffles Neuroscience Centre, Raffles Hospital, Singapore (PI; Narayanaswamy Venketasubramanian); government hospital; number of patients = 4

Turkey

13. Gaziantep University, Gaziantep, Turkey (PI; Alper Dai); government hospital; number of patients = 51

Iran

14. Isfahan University of Medical sciences (PI; Mohammad Saadatnia); government hospital; number of patients = 48
15. Tehran University of medical sciences (PI; Farzad Fatehi); government hospital; number of patients = 28

16. Shiraz university of medical sciences (PI; Afshin Borhani:); government hospital; number of patients = 36

Saudi Arabia

17. King Fahd Medical City (KFMC) (PI: Fehmi Alsinani); government hospital; number of patients = 4

UAE

18. Rashid Hospital, Dubai, UAE (PI; Mohammad Saadah); government hospital; number of patients = 29

Syria

19. Damascus University, Damascus, Syria (PI - Ahmed Khalifa); government hospital; number of patients = 29

Bangladesh

20. BIRDEM, Dhaka, Bangladesh (PI; Bhowmik Bikash N); private hospital; number of patients = 5

References

1. Bousser MG. Ferro JM cerebral venous thrombosis: an update. Lancet Neurol 2007;6:162-170.
2. Ferro JM, Canhão P, Stam J, et al. 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.
3. Dentali F, Poli D, Scoditti U, et al. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study. J Thromb Haemost 2012;10:1297-1302. https://doi.org/10.1111/j.1538-7836.2012.04774.x.
4. 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. https://doi.org/10.1016/j.jstrokecerebrovasdis.2007.10.001.
5. Wasay M, Dai AI, Ansari M, et al. Cerebral venous sinus thrombosis in children: a multicenter cohort from the United States. J Child Neurol 2008;23:26-31.
6. Duman T, Uluduz D, Midi I, et al. A multicenter study of 1144 patients with cerebral venous thrombosis: the VENOST study. J Stroke Cerebrovasc Dis 2017;26:1848-1857. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.04.020. Epub 2017 Jun 2.
7. Khealani BA, Wasay M, Saadah M, et al. Cerebral venous thrombosis: a descriptive multicenter study of patients in Pakistan and Middle East. Stroke 2008;39:2707-2711.
8. 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;60:154-159.
9. Panagariya A, Maru A. Cerebral venous thrombosis in pregnancy and puerperium—a prospective study. J Assoc Phys India 1997;45:857.
10. Wasay M, Kaul S, Menon B, et al. Ischemic stroke in young Asian women: risk factors, subtypes and outcome. Cerebrovasc Dis 2010;30:418-422.
11. Cantu C, Barinagarrementeria F. Cerebral venous thrombosis associated with pregnancy and puerperium: review of 67 cases. Stroke 1993;24:1880-1884.
12. Wasay M, Azeemuddin M. Neuroimaging of cerebral venous thrombosis. J Neuroimaging 2005;15:118-128.
13. Koopman K, Uyttenboogaart M, Vroomen PC, et al. Development and validation of a predictive outcome score of cerebral venous thrombosis. J Neurol Sci 2009;276:66-68. https://doi.org/10.1016/j.jns.2008.08.033.
14. Wasay M, Khatri IA, Kaul S. Stroke in South Asian countries. Nat Rev Neurol 2014;10:135-143.
15. Mehndiratta P, Wasay M, Mehndiratta MM. Implications of female sex on stroke risk factors, care, outcome and rehabilitation: an Asian perspective. Cerebrovasc Dis 2015;39:302-308.
16. Wang Z, Li J, Wang C, et al. Gender differences in 1-year clinical characteristics and outcomes after stroke: results from the China National Stroke Registry. PLoS One 2013;8:e56459.
17. Vibha, Laskar AR. Women's health: beyond reproductive years. Indian J. Public Health 2011;55:247-251.
18. Khan M, Wasay M, Menon B, et al. Pregnancy and puerperium-related strokes in Asian women. J Stroke Cerebrovasc Dis 2013;22:1393-1398.
19. Wasay M, Kojan S, Dai AI, et al. Headache in Cerebral Venous Thrombosis: incidence, pattern and location in 200 consecutive patients. J Headache Pain 2010;11:137-139.
20. Wasay M, Saadatnia M, Venketasubramanian N, et al. Predictors of cerebral venous thrombosis and arterial ischemic stroke in young Asian women. J Stroke Cerebrovasc Dis 2012;21:689-694.
21. Agha S. Intentions to use contraceptives in Pakistan: implications for behavior change campaigns. BMC Public Health 2010;10:450. https://doi.org/10.1186/1471-2458-10-450.
22. Hung SH, Lin HC, Chung SD. Association between venous thromboembolism and iron-deficiency anemia: a population-based study. Blood Coagul Fibrinolysis 2015;26:368-372. https://doi.org/10.1097/MBC.0000000000000249.
23. Soofi S, Khan GN, Sadiq K, et al. Prevalence and possible factors associated with anaemia, and vitamin B_{12} and folate deficiencies in women of reproductive age in Pakistan: analysis of national-level secondary survey data. BMJ Open 2017;7:e018007. https://doi.org/10.1136/bmjopen-2017-018007.
24. Habib MA, Black K, Soofi SB, et al. Prevalence and predictors of iron deficiency anemia in children under five years of age in pakistan, a secondary analysis of national nutrition survey data 2011-2012. PLoS One 2016;11:e0155051. https://doi.org/10.1371/journal.pone.0155051.
25. Wasay M, Bakshi R, Kojan S, et al. Nonrandomized comparison of local urokinase thrombolysis versus systemic heparin anticoagulation for superior sagittal sinus thrombosis. Stroke 2001;32:2310-2317.
26. Siddiqui FM, Banerjee C, Zuurbier SM, et al. Mechanical thrombectomy versus intrasinus thrombolysis for cerebral venous sinus thrombosis: a non-randomized comparison. Interv Neuroradiol 2014;20:336-344.
27. Coutinho JM, Ferro JM, Canhão P, et al. Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. Stroke 2010;41:2575-2580. https://doi.org/10.1161/STROKEAHA.110.588822.