

Original Article

Clinical characteristics and risk factors for in-hospital death due to cerebral venous sinus thrombosis in three medical centers over a 10-year period

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Abstract: Objectives: We retrospectively described and analyzed clinical risk factors for in-hospital death due to cerebral venous thrombosis (CVT). Methods: A total of 172 CVT patients were seen over a 10-year period at three medical centers in China. Demographic and clinical characteristics, neuroimaging, treatment, and outcome data were collected and analyzed. Results: The 28-day in-hospital mortality rate was 4.1%. All seven deceased patients died of transtentorial herniation and were more likely to exhibit coma (42.86% vs. 3.64%, $P = 0.003$), intracranial hemorrhage (ICH; 85.71% vs. 36.36%, $P = 0.013$), straight sinus thrombosis (71.43% vs. 26.06%, $P = 0.019$), and thrombosis of the deep cerebral venous system (DVS; 28.57% vs. 3.64%, $P = 0.036$) than surviving patients. Multivariate analysis identified coma (odds ratio [OR], 11.17; 95% confidence interval [CI], 1.85-67.46, $P = 0.009$), ICH (OR, 20.47; 95% CI, 1.11-376.95, $P = 0.042$), and DVS thrombosis (OR, 36.16; 95% CI, 2.66-491.95, $P = 0.007$) as independent acute-phase mortality predictors. Thirty-six patients received endovascular treatment. The Glasgow Coma Scale score increased postoperatively compared with preoperatively ($P = 0.017$). Conclusions: The main cause of 28-day in-hospital CVT-associated death was a transtentorial hernia, and patients with risk factors such as ICH, coma, and DVS thrombosis were more likely to die. Endovascular treatment may be a safe and effective treatment for severe CVT when conventional management is inadequate.

Keywords: Cerebral venous thrombosis, death, endovascular treatment, poor prognosis, risk factors

Introduction

Cerebral venous thrombosis (CVT) is an uncommon type of stroke that represents 0.5-1% of all strokes. It usually affects young to middle-aged adults with a fatality rate of 3-10% in the acute phase [1-4]. Case series from developing countries reported higher rates of early death after CVT [5]. The initial treatment for CVT is systemic anticoagulation, which is associated with improved neurological outcomes [4]. However, with anticoagulation alone, large and extensive thrombi are unlikely to dissolve. Consequently, approximately one-third of patients with severe presentation have a high risk of incomplete

recovery [3, 6, 7]. If this progressive pathogenesis cannot be quickly resolved in severe CVT patients with increased intracranial hemorrhage (ICH), or rapid deterioration of clinical symptoms, or failure of anticoagulant therapy, cerebral hernia soon follows. Accordingly, rapid and effective interventions are urgently needed to save patients' lives. Even if all available treatments are used, the outcome can be poor, and the patient may die. To date, most studies worldwide have focused on the efficacy and safety of treatments for CVT, but few have investigated risk factors for CVT-associated death, particularly in developing countries such as China.

Characteristics of CVT-associated death

In this study, we retrospectively described and analyzed risk factors for CVT-associated death in China to guide the development of future treatment strategies for CVT patients, particularly those with severe presentation.

Methods

Study population

This retrospective study of 172 CVT patients was conducted in three medical centers (Department of Neurology of the Second Affiliated Hospital of Shandong First Medical University, Department of Neurosurgery of Qilu Hospital of Shandong University, and the Affiliated Taian City Central Hospital of Qingdao University) from October 2011 to October 2021. The diagnosis of CVT was confirmed via brain computed tomography venogram (CTV), magnetic resonance venography, and/or digital subtraction angiography.

Treatment methods

After the diagnosis of CVT was confirmed, individualized treatments were administered considering various patient factors. Treatments included systemic anticoagulation, antiplatelet therapy, intravascular techniques, decompressive craniectomy (DC), intracranial hematoma clearance, and brain ventricular drainage. In addition, basic treatments such as appropriate hydration, seizure control, and treatment of elevated intracranial pressure were administered.

We used the American Heart Association (AHA)/American Stroke Association (ASA) recommendations for CVT patients on systemic anticoagulants [3]. Heparin was the initial treatment, with a dose of 1 µg/kg intravenous and bolus dosing twice a day. Subsequently, warfarin was maintained for a minimum of 6 months. We monitored the international normalized ratio (INR) and adjusted the dose of warfarin with a target INR of 2-3 to limit the risk of hemorrhage.

When anticoagulant therapy was ineffective or inappropriate in the most severe patients, endovascular treatment (EVT) and/or DC was used. EVT included direct catheter thrombolysis, continuous thrombolysis, balloon-assisted thrombectomy, mechanical thrombectomy, stent retriever thrombectomy, rheolytic catheter thrombectomy and aspiration thrombectomy [8]. The criteria for performing EVT were as follows: (1) rapid deterioration of neurological

function, as manifested by a rapid decline of neurological symptoms after administering systemic anticoagulation; (2) aggravated ICH or severe cerebral edema, presenting a high risk of cerebral hernia; or (3) clinical symptoms of CVT accompanied by sinus venous stenosis that could not be controlled after anticoagulation. DC was performed for patients with cerebral hernias.

Data collection

We collected the following information: demographic data; risk factors for CVT; times of symptom onset, hospital admission, and death; clinical presentation on admission and during the clinical course; neuroimaging findings; individualized treatments, including anticoagulants, EVT, and/or DC; Glasgow Coma Scale (GCS) score on admission; and modified Rankin Scale (mRS) score at discharge. For patients undergoing EVT, preoperative and postoperative GCS scores and mRS scores at 6 and 12 months after surgery were also recorded.

Statistical analysis

Descriptive statistics were calculated to describe characteristics of deceased and surviving CVT patients. For continuous variables, median and interquartile range (IQR) were calculated. For categorical variables, numbers and percentages for each category were tabulated. Comparisons were made between deceased and surviving patients. Univariate analysis was performed with Fisher's exact tests for categorical data and Mann-Whitney U tests for continuous data. We performed logistic regression analysis (with the backward selection method) and calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the retained variables associated ($P < 0.10$) with the outcome of death in univariate analyses. A Wilcoxon's matched-pairs signed-rank test was used to compare preoperative and postoperative GCS scores. A P -value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 25 (Chicago, IL).

Results

Description of deceased patients

The study included 172 patients with CVT, of whom seven (4.1%) died during the acute

Characteristics of CVT-associated death

phase. None of these deaths occurred after discharge. These seven patients consisted of three men and four women, with a median (IQR) age of 42 (27-51) years. The median (IQR) hospitalization period lasted 3 (1-6) days. The median (IQR) GCS score at admission was 9 (4-12). All seven patients died of cerebral herniation, due to either a focal mass effect or multiple lesions and massive edema.

The deceased CVT patients showed several initial symptoms (**Tables 1 and 2**). The most common complaints were headache, followed by coma, seizures, focal motor deficit, nausea/vomiting, limb numbness, dizziness, and sensory aphasia.

Risk factors or comorbidities of the deceased CVT patients included pregnancy/puerperium, anemia, oral contraceptive use, thrombophilia, thyroid disease, hepatitis B, and diabetes mellitus (**Table 3**).

Computed tomography (CT)/magnetic resonance imaging (MRI) revealed parenchymal lesions in all deceased patients. Most patients presented with evidence of ICH, whereas almost half presented with infarcts, and less than one-third presented with thalamic edema. On magnetic resonance venography, thrombi were most frequently localized at the straight sinus, followed by the transverse sinus and superior sagittal sinus. Slightly more than one-quarter of patients had a thrombus in one sinus, almost half had thrombi in three sinuses, and one patient each had involvement of two sinuses or more than three sinuses (**Table 4**).

Regarding treatment methods, all but one deceased patient were treated with anticoagulants (low molecular weight heparin and/or warfarin) in a similar proportion as that among surviving patients. Anticoagulant therapy was administered within 24 hours in two-thirds of patients and after 24 hours in the remaining one-third. Among the deceased patients, one patient developed an intraventricular hemorrhage after administration of anticoagulation therapy. One patient declined to take any anticoagulant medicine and was provided with symptomatic treatment, such as reducing intracranial hypertension, and antiepileptic treatment based on his complaints. One patient underwent DC. No deceased patients received thrombolytic therapy, EVT, or antiplatelet therapy (**Table 5**).

Comparisons between deceased and surviving patients

To identify the predictors of CVT-associated death, we compared demographic data, clinical characteristics, neuroimaging findings, comorbidities, and treatments between the seven deceased patients and 165 surviving patients.

In univariate analysis, coma (42.86% vs. 3.64%; $P = 0.003$), ICH (85.71% vs. 36.36%; $P = 0.013$), straight sinus thrombosis (71.43% vs. 26.06%; $P = 0.019$), and deep cerebral venous system (DVS) thrombosis (28.57% vs. 3.64%; $P = 0.036$) were associated with a higher risk of death after CVT (**Table 2**). Within the study sample, no significant differences between deceased and surviving patients were found for sex, age, time from symptom onset to admission, or number of sinuses involved. There were also no significant differences in treatment methods or comorbidities.

The sample size of this study was small and did not meet the requirements of 10 events per variable in logistic regression analysis. However, considering that CVT is rare and that the results of logistic regression analysis were interpretable, we nevertheless present the results. Binary logistic analysis indicated that coma (OR, 11.17; 95% CI, 1.85-67.46, $P = 0.009$), ICH (OR, 20.47; 95% CI, 1.11-376.95, $P = 0.042$), and DVS thrombosis (OR, 36.16; 95% CI, 2.66-491.95, $P = 0.007$) were independent predictors of in-hospital death after CVT.

Demographic characteristics, EVT type, and prognosis of patients who underwent EVT

Of the 172 patients, 36 (male, 16; female, 20) underwent EVT and/or DC, with a median (IQR) age of 33 (27-46) years. Before EVT, 19 (52.8%) patients manifested ICH, whereas 17 (47.2%) patients did not.

In terms of EVT type, mechanical thrombectomy was applied in 33 patients, direct catheter thrombolysis in 33 patients, stent retriever thrombectomy in 21 patients, continuous thrombolysis in 18 patients, balloon-assisted thrombectomy in 4 patients, and sinus venous stenting in 4 patients. Five patients underwent EVT and DC.

The mean GCS score of the 36 patients with ICH was 12.33 (SD = 3.83; range 3-15) before operation and 13.89 (SD = 3.83; range 7-15)

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Table 1. Summary of patients who died during hospitalization for CVT

No	Sex/age (y)	Symptoms/signs until admission	Risk factors/comorbidity	Onset to admission	Admission to death	GCS score at admission	Hemorrhage and/or infarction	Location of CVT	DC	Anticoagulation	EVT	Antiplatelet therapy	Cause of death
1	M/42	Headache, limb numbness and weakness, focal motor deficits, coma and seizure	No	6 days	1 day	4	(B) parietal lobe, (L) frontal lobe hem and SAH	SSS/SS/(R) TS	No	No	No	No	Herniation (hem)
2	F/19	Dizziness, focal motor deficits and unconsciousness	Miscarriage	1 day	1 day	9	(R) temporal, parietal lobe hem and inf, and thalamic edema	DVS/SS/(R) SiS	No	Yes	No	No	Herniation (inf, hem, and edema)
3	F/34	Headache with nausea and vomiting, coma	Pregnancy, hyperhomocysteinemia	6 days	1 day	7	(L) frontal and parietal lobe hem and inf	SSS/(L) TS/(L) SiS/SS	No	Yes	No	No	Herniation (hem and inf)
4	M/70	Somnolence and lags in response	Diabetes mellitus	3 months	7 days	10	Intraventricular hem, thalamic edema	SS	No	Yes	No	No	Herniation (hem and edema)
5	M/27	Headache with nausea and vomiting, focal motor deficits and seizure	Hepatitis B	9 days	3 days	15	(L) frontal, temporal, parietal lobe and intraventricular hem, SAH	SSS/(L) TS	No	Yes	No	No	Herniation (hem)
6	F/51	Headache, limb numbness and weakness, seizure and coma	OC for dysfunctional uterine bleeding, anemia	5 days	6 days	3	venous inf, thalamic edema	SS/DVS/ISS	No	Yes	No	No	Herniation (inf and edema)
7	F/48	Headache, abnormal consciousness	Hyperthyroidism, severe anemia	3 days	3 days	12	(L) frontal, temporal and parietal lobe hem	(L) TS	Yes	Yes	No	No	Herniation (hem)

GCS, Glasgow Coma Scale; DC, decompressive craniectomy; EVT, endovascular treatment; M, male; F, female; OC, oral contraceptives; L, left; R, right; B, bilateral; hem, hemorrhagic; inf, infarct; SAH, subarachnoid hemorrhage; SSS, superior sagittal sinus; ISS, inferior sagittal sinus; TS, transverse sinus; SiS, sigmoid sinus; SS, straight sinus; DVS, deep cerebral venous system.

Characteristics of CVT-associated death

Table 2. Comparison of demographic and clinical characteristics between surviving and deceased CVT patients

Parameters	Surviving patients (n = 165)	Deceased patients (n = 7)	P-value
Demographic data			
Age, median (IQR), years	32 (25-44)	42 (27-51)	0.230
Men, n (%)	75 (45.45)	3 (42.86)	> 0.999
Onset of symptoms to admission, median (IQR), days	10 (5-30)	6 (3-9)	0.144
Clinical characteristic, n (%)			
Headache	143 (86.67)	5 (71.43)	0.253
Seizures	51 (30.91)	3 (42.86)	0.679
Coma on admission (GCS < 9)	6 (3.64)	3 (42.86)	0.003
Focal motor deficit	28 (16.97)	3 (42.86)	0.112
Nausea/vomiting	37 (22.42)	2 (28.57)	0.658
Limb numbness	13 (7.88)	2 (28.57)	0.116
Dizziness	16 (9.70)	1 (14.29)	0.524
Dysarthria/aphasia	8 (4.85)	1 (14.29)	0.318
Blurred vision/hemianopia/blindness	19 (11.52)	0 (0.00)	> 0.999

CVT, cerebral venous thrombosis; IQR, interquartile range; GCS, Glasgow Coma Scale. P-values reflect Fisher's exact test or Mann-Whitney U-test, as appropriate.

Table 3. Comparison of neuroimaging findings between surviving and deceased CVT patients

Parameters	Surviving patients (n = 165)	Deceased patients (n = 7)	P-value
Parenchymal lesions, n (%)			
Venous infarction	46 (28.48)	3 (42.86)	0.408
Intracranial hemorrhage	60 (36.36)	6 (85.71)	0.013
Bilateral parenchymal lesions	11 (6.67)	1 (14.29)	0.403
Number of sinuses involved, n (%)			
One sinus	36 (21.82)	2 (28.57)	0.651
Two sinuses	59 (35.76)	1 (14.29)	0.424
Three sinuses	46 (27.88)	3 (42.86)	0.408
More than three sinuses	24 (14.55)	1 (14.29)	> 0.999
Site of sinus/vein occlusion, n (%)			
Transverse sinus	125 (75.76)	4 (57.14)	0.369
Sigmoid sinus	97 (58.79)	2 (28.57)	0.136
Superior sagittal sinus	88 (53.94)	3 (42.86)	0.708
Straight sinus	43 (26.06)	5 (71.43)	0.019
Confluence of sinuses	17 (10.30)	0 (0.00)	> 0.999
Inferior sagittal sinus	11 (6.67)	1 (14.29)	0.403
DVS	6 (3.64)	2 (28.57)	0.036

CVT, cerebral venous thrombosis; DVS, deep cerebral venous system.

after operation (**Figure 1**). Wilcoxon's matched-pairs signed-rank test showed a significant difference in GCS score before and after operation ($Z = -2.383$, $P = 0.017$). Neurological deficits were categorized as mild, moderate, or severe, which corresponded to an mRS score of

1-2, 3-4, and 5, respectively. The ratios of good prognosis ($mRS \leq 2$) at discharge and at 6 and 12 months after discharge were 69.4% (25/36), 77.8% (28/36), and 83.3% (30/36), respectively. No patients who underwent EVT died during the 12-month follow-up.

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Table 4. Comparison of risk factors between surviving and deceased CVT patients

Parameters	Surviving patients (n = 165)	Deceased patients (n = 7)	P-value
Comorbidity/risk factors, n (%)			
Malignancy	3 (1.82)	0 (0.00)	> 0.999
Pregnancy/puerperium ^a	34 (37.78)	2 (50.00)	0.636
OC ^a	14 (15.56)	1 (25.00)	0.507
Thrombophilia	65 (39.39)	1 (14.29)	0.252
Anemia	13 (7.88)	2 (28.57)	0.116
Infections of the head or neck	21 (12.73)	0 (0.00)	0.600
Dehydration	10 (6.06)	0 (0.00)	> 0.999
Operation history	3 (1.82)	0 (0.00)	> 0.999
Thyroid disease	3 (1.82)	1 (14.29)	0.154
Hepatitis B	6 (3.64)	1 (14.29)	0.256
Diabetes mellitus	5 (3.03)	1 (14.29)	0.224

^aWomen only; OC, oral contraceptives.

Table 5. Comparison of treatment between surviving and deceased CVT patients

Parameters	Surviving patients (n = 165)	Deceased patients (n = 7)	P-value
Treatment, n (%)			
Anticoagulation	132 (80)	6 (85.71)	0.245
EVT	36 (21.82)	0 (0.00)	0.347
Antiplatelet therapy	8 (4.85)	0 (0.00)	> 0.999
DC/IHC/BVD	7 (3.64)	1 (14.29)	0.256

EVT, endovascular treatment; DC, decompressive craniectomy; IHC, intracranial hematoma clearance; BVD, brain ventricular drainage.

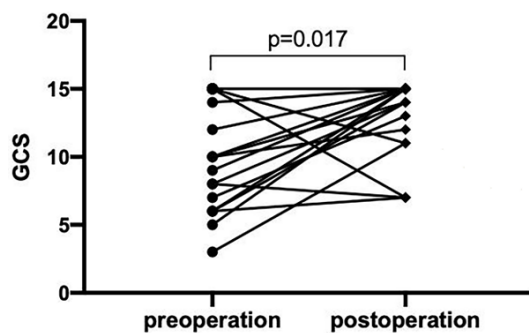


Figure 1. Preoperative and postoperative Glasgow Coma Scale (GCS) scores for patients receiving endovascular treatment.

Illustrative cases

Case 4

A 70-year-old man was admitted to the hospital with somnolence and lags in response over the past 3 months. He was initially misdiagnosed as having a thalamus tumor at his local hospital. Seven days before his death, MRI and CTV

revealed a straight sinus thrombosis. Systemic anticoagulation was performed for 6 days with a target INR of 2-3 until his sudden and unexpected death on the 7th day. CT showed intraventricular hemorrhage (**Figure 2**).

Case 17

A similar case to Case 4 was rescued by aggressive treatments. This second patient was a 23-year-old woman who was pregnant and had been vomiting for 3 days. She presented at the hospital in a comatose state with a GCS score of 6 (E1V1M4). CT showed left thalamic edema, and CTV revealed straight sinus thrombosis (**Figure 3**). Emergency endovascular techniques were performed under general anesthesia. Intraoperative digital subtraction angiography showed partial recanalization of the straight sinus after mechanical thrombectomy and direct catheter thrombolysis. Fourteen days after the procedure and receipt of systemic anticoagulation, straight sinus patency was normalized, and the patient was discharged without any neurological deficits.

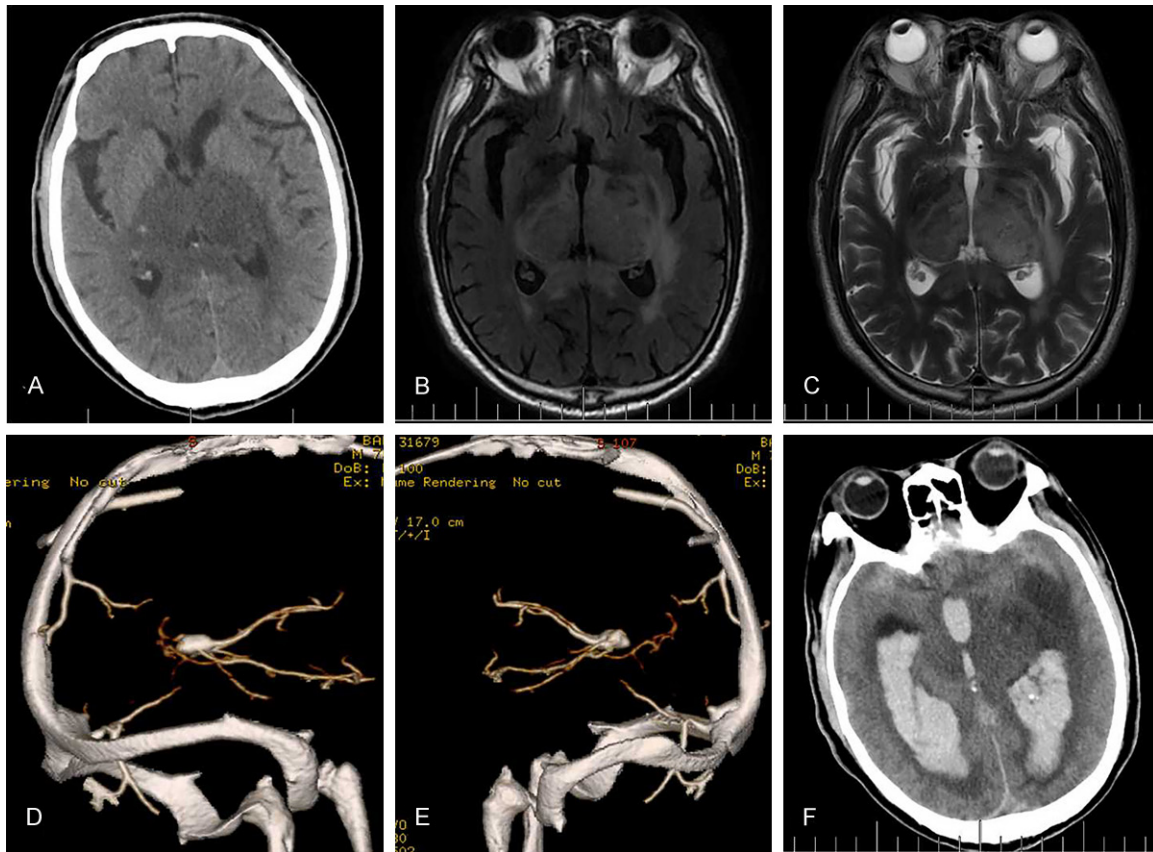


Figure 2. In Case 4, a 70-year-old man was admitted to the hospital with somnolence and lags in response lasting 3 months. A-C. Computed tomography and magnetic resonance imaging showed bilateral thalamic edema, initially misdiagnosed as a thalamus tumor. D, E. Computed tomography venography image revealed cerebral venous thrombosis in the straight sinus. F. Computer tomography image showed intraventricular hemorrhage after 7 days of anticoagulation.

Discussion

CVT is an uncommon and frequently unrecognized type of stroke that affects approximately five people per million annually. In contrast to most previous studies that focused on treatment, we summarized the clinical details of CVT-associated death in the present study. Patients with risk factors identified by multivariate analysis, such as ICH, coma, and thrombosis of the DVS, were more likely to die after CVT. The main cause of 28-day in-hospital CVT-associated death was a transtentorial hernia. GCS score increased after EVT as compared with before operation, and no patients who underwent EVT died. Thus, EVT may be a safe and effective treatment option when other treatments fail in patients with CVT.

Risk factors for CVT are either acquired or genetic [3]. The obstruction of blood flow from a

clot in the veins of the head leads to blood backflow and increased blood pressure in the blood vessels preceding the obstruction [9]. The goals of CVT therapy are to re-establish circulation distal to the occlusion as early as possible, to prevent further development of thrombus, to treat the underlying cause, and to prevent recurrence [10, 11]. Although systemic anticoagulation and endovascular techniques can reduce the mortality associated with CVT, approximately 3-15% of patients die in the acute phase of the disorder. Most early deaths are a consequence of the CVT itself. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), 3.4% of patients died within 30 days of symptom onset [4]. In a study from the United States, an even higher mortality rate (13%) was reported [3]. Case series from developing countries also report higher rates of early death [5, 12].

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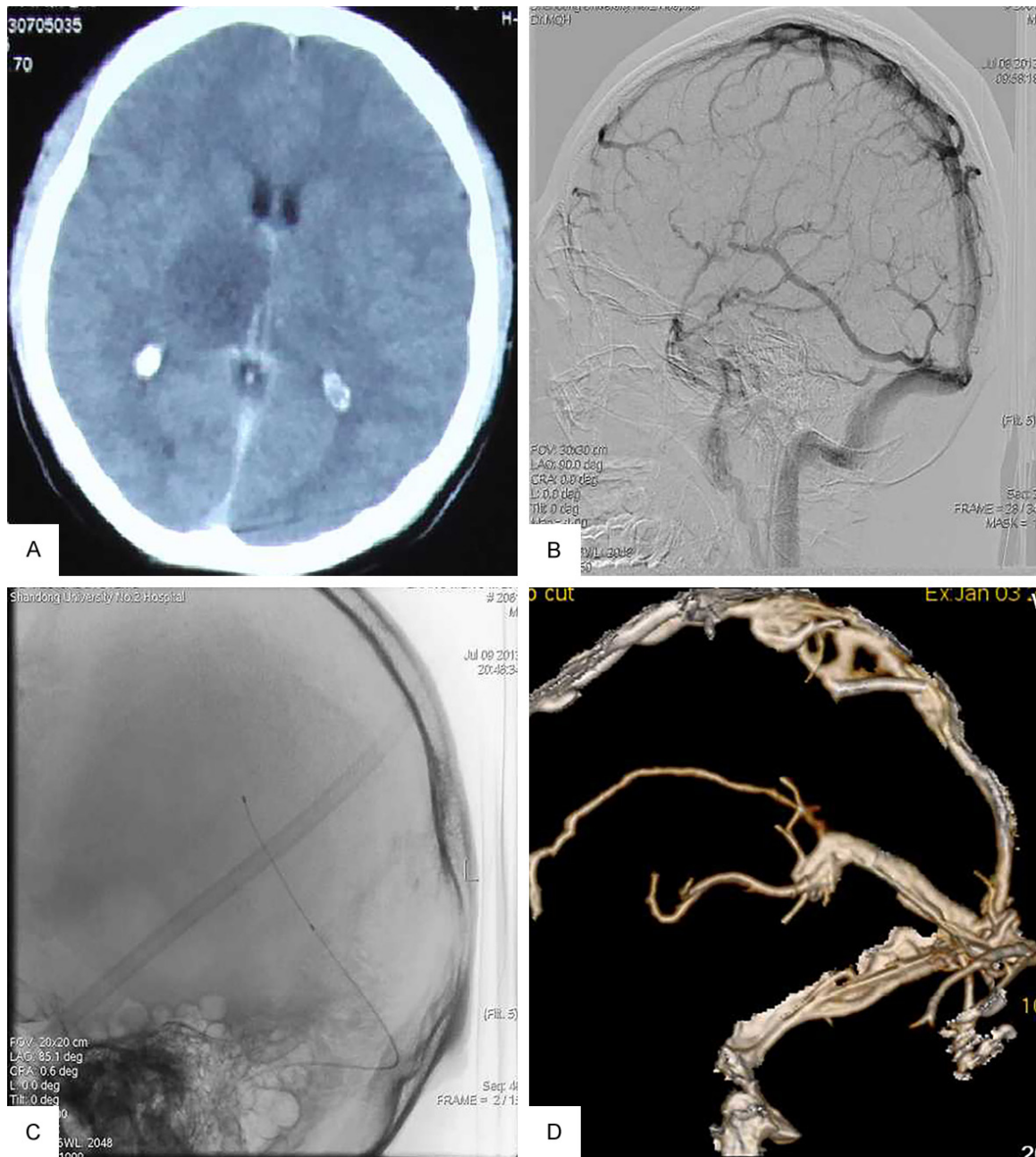


Figure 3. In Case 17, a 23-year-old woman presented with vomiting for 3 days. Her Glasgow Coma Scale score was 6 (E1V1M4). (A) Computed tomography revealed right thalamic edema. (B) Digital subtraction angiography showed cerebral venous thrombosis in the straight sinus. (C) Mechanical thrombectomy by a microguide wire resulted in (D) complete recanalization of the straight sinus.

CVT is a potentially life-threatening condition if it remains undiagnosed. The outcome can range from total recovery to death. Currently, its diagnosis is still frequently missed or delayed because of the wide spectrum of clinical symptoms and the often subacute or lingering onset of the condition [13]. Patients with CVT often present with slowly progressing symp-

toms. The median delay from the onset of symptoms to hospital admission is 4 days and from symptom onset to diagnosis is 7 days [3, 4]. In animal experiments, Wang et al. found that thrombocalcification occurs in the second week in rats [14]. As anticoagulation may not work well in patients with chronic thrombosis, early recognition of the condition is crucial.

Characteristics of CVT-associated death

EVT may be considered in patients with absolute contraindications for anticoagulation therapy or failure of initial treatments [3]. CVT patients can undergo rapid recanalization of occluded sinuses via EVT between 88 and 244 hours after CVT [15, 16]. This is in stark contrast to the several days or even weeks needed if occluded sinuses are treated with heparin [17]. A recent systematic review assessed 185 patients who underwent mechanical thrombectomy and noted that, in severe cases, venous anticoagulation may not be the treatment of choice; instead, intrathrombolysis and/or mechanical thrombolysis may be indicated [18]. EVT is reported as an effective and safe procedure for potentially catastrophic hemorrhagic CVT [19].

In our study, all seven deceased patients had one or more factors associated with a poor prognosis listed in the AHA/ASA statement, such as thrombosis of the straight sinus, ICH and/or infarction on admission as seen on CT/MRI, a GCS score of 9, mental status disturbance, an age of ≥ 37 years, and male sex [3]. Of all clinical signs reported for CVT, coma on admission is the most consistent and strongest predictor of a poor outcome [4, 18]. In severe cases with impending herniation, a craniectomy can be used as a life-saving intervention. If patients deteriorate despite adequate anticoagulation, and if other causes of deterioration have been ruled out, thrombolysis may be a therapeutic option in selected cases, possibly those without a large ICH and threatening herniation [20]. In our study, Patient in Case 1 (Table 1) had no opportunity to receive aggressive treatments for his cerebral hernia and unstable condition. In the treatment of Case 4 (Table 1), misdiagnosis and/or inappropriate treatment strategies may have been involved. The elderly man presented with somnolence and lags in response lasting for 3 months, and a systemic anticoagulant was not only unable to dissolve the hardened and calcified thrombi but also increased the risk of ICH (Figure 2). Although there was no unique cause of death for CVT, the data in Tables 2, 3 and 5 suggest that patients with risk factors such as ICH, coma, and DVS thrombosis are more likely to die. Some deceased patients may have had the option to undergo EVT and/or DC, such as the patient in Case 17 (Figure 3), who had a similar presentation as Case 4 but survived. In the

present study, data from the 36 patients who underwent EVT suggest that EVT is a safe and valid treatment that may increase the chance of survival.

As this study had a small sample size, the results may not be sufficiently robust, and their reliability needs to be confirmed by further research. In the future, we will explore the implications of our study findings in the field of CVT management.

Conclusions

CVT patients with risk factors such as ICH, coma, and thrombosis of the DVS are more likely to die. When CVT patients do not respond well to anticoagulant therapy, if their condition deteriorates rapidly, or if extensive sinus thrombosis occurs, EVT may be a safe and effective treatment.

Disclosure of conflict of interest

None.

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