Predictors for outcome and recovery time of cerebral venous thrombosis and ischemic stroke in Suratthani hospital

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Abstract

Background and objective: To study predicting factors for favorable clinical outcome and recovery time of cerebral venous sinus thrombosis (CVST) and acute ischemic stroke (AIS).

Materials and Methods: We performed a retrospective study in Suratthani Hospital, Thailand, between January 2013 and December 2018. All cases of CVST patients were included and compared with random samplings of AIS on the ratio of 1:1 in the same period. Disability at six months or until full recovery and time to recovery were assessed.

Results: 104 patients, there were 52 patients in each group. Mean age was 44 years in CVST patients and 70 years in AIS patients. In CVST group, age < 45 years (aOR = 5.69, 95% CI 1.51–21.39, P = 0.010) was associated to good recovery, whereas age < 65 years (aOR = 23.24, 95% CI 2.36–229.13, P = 0.007), and small vessel type arterial infarction (aOR = 17.49, 95% CI 2.91–105.10, P = 0.002) were predicting factors for good recovery in AIS. The median time to recovery was 60 days and 93 days in CVST and AIS, respectively.

Conclusion: Predictors for favorable outcome in cerebral venous thrombosis patients was age less than 45 years. Predictors for favorable outcome in ischemic stroke patients were age less than 65 years and small vessel subtype.

Keywords: cerebral venous sinus thrombosis, prognosis, recovery time (J Thai Stroke Soc. 2019;18(2):5–14)

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ปัจจัยที่มีผลต่อการรักษาและระยะเวลาในการฟื้นตัวของโรคหลอดเลือดดำและหลอดเลือดแดงในสมองอุดตันในโรงพยาบาลสุราษฎร์ธานี

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บทคัดย่อ

ความเป็นมาและวัตถุประสงค์: เพื่อศึกษาปัจจัยที่มีผลการรักษาและระยะเวลาการฟื้นตัวของโรคหลอดเลือดดำและหลอดเลือดแดงในสมองอุดตัน

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาแบบย้อนหลังในโรงพยาบาลสุราษฎร์ธานี ประเทศไทย ระหว่างเดือนมกราคม พ.ศ. 2556 และ ธันวาคม พ.ศ. 2561 โดยศึกษาในกลุ่มประชากรหลอดเลือดดำในสมองอุดตันทุกราย เปรียบเทียบกับกลุ่มประชากรหลอดเลือดแดงในสมองอุดตัน โดยการสุ่มเลือกแบบหนึ่งต่อหนึ่งในช่วงเวลาเดียวกัน และประเมินการฟื้นตัวที่ 6 เดือนหรือจนกลับมาปกติ ตลอดจนศึกษาระยะเวลาที่ใช้ในการฟื้นตัว

ผลการศึกษา: กลุ่มประชากรทั้งหมด 104 คน แบ่งเป็นกลุ่มหลอดเลือดดำในสมองอุดตันและหลอดเลือดแดงในสมองอุดตันกลุ่มละ 52 คน อายุเฉลี่ย 44 ปีในผู้ป่วยหลอดเลือดดำในสมองอุดตัน และ 70 ปีในผู้ป่วยหลอดเลือดแดงในสมองอุดตัน พบว่า อายุน้อยกว่า 45 ปี (aOR = 5.69, 95% CI 1.51–21.39, P = 0.010) สัมพันธ์กับการฟื้นตัวที่ดีในกลุ่มหลอดเลือดดำอุดตัน ในขณะที่ปัจจัยที่มีผลต่อการฟื้นตัวที่ดีในกลุ่มหลอดเลือดแดงในสมองอุดตัน คือ อายุน้อยกว่า 65 ปี (aOR = 23.24, 95% CI 2.36–229.13, P = 0.007) และหลอดเลือดเส้นเล็กอุดตัน (aOR = 17.49, 95% CI 2.91–105.10, P = 0.002) ระยะเวลามัธยฐานในการฟื้นตัวเท่ากับ 60 วัน และ 93 วัน ในกลุ่มหลอดเลือดดำในสมองอุดตันและหลอดเลือดแดงในสมองอุดตัน ตามลำดับ

สรุป: ปัจจัยที่มีผลต่อการผลการรักษาที่ดีของโรคหลอดเลือดดำในสมองอุดตัน คือ อายุน้อยกว่า 45 ปี ปัจจัยที่มีผลต่อการฟื้นตัวของโรคหลอดเลือดแดงในสมองอุดตันคือ อายุน้อยกว่า 65 ปีและโรคสมองขาดเลือดชนิดหลอดเลือดเส้นเล็กอุดตัน

คำสำคัญ: หลอดเลือดดำในสมองอุดตัน, การพยากรณ์โรค, ระยะเวลาในการฟื้นตัว (J Thai Stroke Soc. 2019;18(2):5–14)

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease with diverse clinical manifestations that often affects young adults. The most common clinical manifestations are headache, seizures, altered consciousness, and focal neurological signs. A prior study reported that 50% of CVST patients had poor prognosis.[1] Mortality of CVST is lower than in arterial stroke[2] and depends on a prognostic factor such as early treatment to correct causes of disease and good medical care. Positive prognostic factors that affect the outcome of CVST in previous studies were modified Rankin scale (mRS) ≤ 2,[3] involvement of lateral sinus,[4] unfavorable functional outcome associated with National Institutes of Health Stroke

Scale score > 2 at admission, low education level,[5] signs of mass effect on imaging, clinical deterioration after admission,[6] age > 37 years, male[7] and presence of hemorrhagic infarction.[4] Hypercoagulable state, the number of involved venous sinuses, or intracranial hemorrhage and seizures are not associated with prognostic outcome.[3]

CVST is more difficult to diagnose than arterial stroke. Delay in hospital admission and delay of diagnosis are important factors that may postpone CVST treatment. Previous studies reported median admission delay of 4 days, with two-thirds of the patients admitted within 7 days and 75% within 13 days.[8] The median time between diagnosis and death was 5 days, and the median time between symptom onset and death was 13 days.[9]

The purpose of this study is to assess the predicting factors of favorable outcome and time to recovery in venous and arterial ischemic stroke patients.

Methods

We conducted a period retrospective study in Suratthani Hospital, Thailand from January 2013 to December 2018. The study was approved by the Suratthani Hospital Institutional Review Board. The eligibility inclusion criteria were: (1) adult-onset, age more than 15 years (2) diagnosis of CVST or acute ischemic stroke (AIS) base on clinical presentation and confirmed by computed tomography (CT), or magnetic resonance imaging (MRI), or CT and computed tomography venography (CTV), or MRI and MR venography (MRV). Exclusion criteria was hemorrhagic stroke, except in CVST. Medical records written by neurologists or junior medical officers were reviewed to collect demographic, imaging, and outcome data. We compared difference of demographic, imaging, and outcome data between CVST (cases) and AIS (control) group.

We categorized arterial stroke as small intracranial vascular lesion (perforating artery and small vessel) and large vascular lesion (major vessel and the main branch of major vessel). Patients were followed up at least 6 months or until recovery. Patients who died during hospitalization were analyzed (mRS = 6), however there was no death observed during follow-up.

The outcome was classified according to modified Rankin Scale (mRS) into independence (mRS ≤ 2) and disability (mRS > 2). Time to recovery was defined as the time between hospital admission and the time the patients get back to their independence in daily activities or mRS ≤ 1 for the first time of record.

Statistical analysis

Stata program was used for data analysis. Categorical variables were presented as percentages and were compared by using Fisher's exact test. Continuous variables were presented as mean, standard deviation (SD) and were compared by using the two-sample t-test. Shapiro-Wilk test was used for normal distribution testing. Non-parametric continuous variables were presented as interquartile ranges (IQRs) and were compared using the Wilcoxon rank-sum test. All proportions and P-values were calculated based on variables with no missing data. The logistic regression analysis was carried out to determine the factors associated outcome of CVST and AIS. Odds ratio (OR) and 95% confidence intervals (CI) were estimated. We selected variables at $P < 0.1$ on univariate analysis, as well as those considered prior associated factor based on previous literature for the final multivariate logistic regression model, $P < 0.05$ was statistically significant. Parametric survival

analysis and log-normal regression statistics were used for plotting the survival curve.

Results

The study included a total of 104 patients, 52 of which were CVST and the remainder were AIS. CVST group were significant younger, included more female and had less severe stroke on admission. The median time from symptom onset to admission, time to diagnosis from admission and length of stay were delayed in CVST patients (all P < 0.001). However, mRs at discharge and complications of treatment between two groups were not significantly different. (Table 1)

Table 1. *Clinical characteristics of CVST and AIS in Suratthani Hospital, Thailand, January 2013 – December 2018 (n=104)*

Characteristics	CVST (n = 52)	AIS (n = 52)	P value
Age, years	44 (30–52)	70 (60–79)	< 0.001
Age, < 45 years	32 (64)	3 (1)	< 0.001
Sex			0.028
Male	16 (36)	28 64)	
Female	36 (60)	24 (40)	
mRS* on admission			0.037
1	0	0	
2	5 (10)	0	
3	22 (42)	20 (38)	
4	13 (25)	23 (44)	
5	12 (23)	9 (17)	
Onset symptoms, hours, median	72 (24–168)	5 (3–13.5)	< 0.001
Time to diagnosis, hours, median	48 (24–48)	1 (1.0–1.0)	< 0.001
Length of stay, days, median	6 (5–8.5)	3 (2–9.0)	< 0.001
Complication			
Seizure	2 (4)	0	0.50
Status epilepticus	4 (8)	0	0.12
Intracranial hemorrhage	5 (10)	1 (2)	0.11
Pneumonia	7 (13)	5 (10)	0.76
Urinary tract infection	0	4 (8)	0.12
Upper gastrointestinal bleeding	0	3 (6)	0.24
Surgical treatment	4 (8)	2 (4)	0.68
mRS* on discharge			0.070
1	2 (4)	0	
2	21 (40)	13 (25)	
3	13 (25)	19 (37)	
4	6 (12)	14 (27)	
5	4 (8)	1 (2)	
6	6 (12)	5 (10)	

**mRS = modified Rankin scale*

CT or MRI of brain was abnormal in all CVST patients. In CVST patients, the most common involved sinus was the transverse sinus, appearing on 30% of CT-brain or CTV technique. Transverse sinus (51%) and sagittal sinus (51%) were the most commonly involved sinus thrombosis on MRI-brain or MRV technique. For some patients who had both imaging modalities (CT and MRI); 61% had transverse sinus thrombosis, and 57.5% had sagittal sinus thrombosis. Six patients (12%) did not have any abnormal lesion on CT brain. In AIS group, 31 patients (60%) affected medium to large vessel. The most common area of infarction was the branch of middle cerebral arterial found in 21 patients (40%) in this study. (Table 2)

Table 2. *Imaging finding of CVST and AIS*

Imaging findings	CVST (n = 52)	AIS (n = 52)
CT Brain (± CTV) findings		
Transverse sinus thrombosis	15 (30)	0
Sagittal sinus thrombosis	10 (20)	0
Hemorrhagic infraction	20 (40)	2 (4)
Focal hypodensity	32 (64)	28 (55)
Unremarkable study	6 (12)	0 (0)
Middle cerebral infarction (M1)	0	6 (12)
MCA branch infarction	0	21 (40)
Anterior cerebral infarction	0	1 (2)
Posterior cerebral infarction	0	2 (4)
Internal carotid infarction	0	1 (2)
Small vessel infarction	0	19 (37)
MRI brain (± MRV) findings		
Transverse sinus thrombosis	18 (51)	0
Sagittal sinus thrombosis	18 (51)	0
Cortical vein thrombosis	3 (9)	0
Deep vein thrombosis	2 (6)	0
Cavernous sinus thrombosis	2 (6)	0
Hemorrhagic infraction	15 (43)	2 (4)
Focal acute infarction	28 (80)	1 (2)
Middle cerebral infarction (M1)	0	1 (2)
Posterior cerebral infarction	0	1 (2)
Brain stem infarction	0	2 (4)

CT = Computed Tomography, CTV = Computed Tomography Venography, MCA-M1 = middle cerebral infarction segment 1, MRI = Magnetic resonance tomography, MRV = Magnetic Resonance Venography

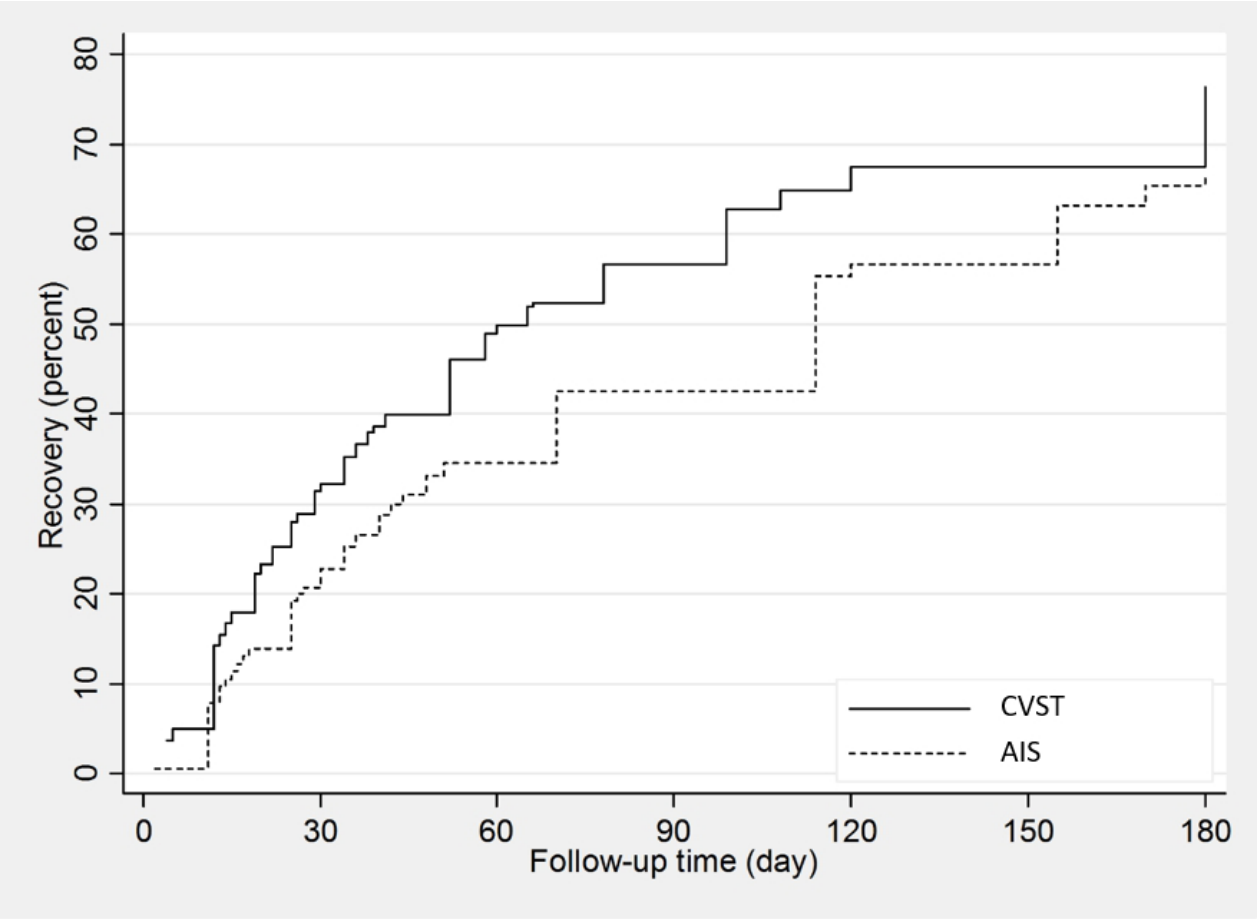
The relative risk factors to predict recovery within 180 day were age < 45 years (adjusted odds ratio (aOR) = 5.84, 95% CI 1.76–19.42, P = 0.004), and mRS on admission ≤ 3 (aOR = 8.6, 95% CI 3.05–24.32, P < 0.001). In subgroup analysis, significant predicting factor of recovery in CVST group was age < 45 years (aOR = 5.69, 95% CI 1.51–21.39, P = 0.010). In AIS subgroup, the significant predicting factors to recovery were age < 65 years (aOR = 23.24, 95% CI 2.36–229.13, P = 0.007), and small vessel subtype (aOR = 17.49, 95% CI 2.91–105.10, P = 0.002). (Table 3)

***Table 3**. Predictive factor for recovery time within 180 days*

Predicting Factor Recovery < 180 days	OR (95% CI)	P-value	aOR (95% CI)	P-value
All				
Male	1.58 (0.71–3.54)	0.264	2.48 (0.90– 6.86)	0.080
Age < 45 years	4.63 (1.7–12.57)	0.003	5.84 (1.76–19.42)	0.004
Time to diagnosis < 48 hours	1.75 (0.7–4.33)	0.230	1.10 (0.33–3.67)	0.873
mRS on admission				
4–5	1			
2–3	9.09 (3.47–23.84)	0.001	8.6 (3.05– 24.32)	<0.001
Status epilepticus, no complication,	4.69 (0.47–46.73)	0.187	3.62 (0.28–46.49)	0.323
Type of stroke				
AIS	1			
CVST	1.62 (0.74–3.57)	0.232	2.06 (0.11–2.16)	0.341
CVST group*				
Male	1.9 (0.51–7.11)	0.335		
Age ≤ 45 years	6.5 (1.84– 22.92)	0.004	5.69 (1.51–21.39)	0.010
Others venous infarction	1			
Lateral sinus thrombosis	1.4 (0.43–4.5)	0.573	1.04 (0.26–4.14)	0.954
AIS group#				
Male	1.83 (0.61–5.51)	0.285		
Age < 65 years	12.69 (2.49– 64.58)	0.002	23.24 (2.36–229.13)	0.007
Large vessel infarction	1		1	
Small vessel infarction	18.9 (0.01–0.27)	<0.001)	17.49 (2.91–105.10)	0.002

**analysis only CVST group; #analysis only AIS group*

Figure 1. *Recovery time of CVST and AIS*



Patients in both groups tend to have early recovery. (Figure 1) The median time to recovery was 60 days and 93 days in the CVST and AIS group, respectively. (Table 4)

Table 4. *Median time recovery of CVST and AIS*

Type of stroke	Median survival time (days)
CVST	60
AIS	93

Discussion

Cerebral venous thrombosis was a rare important cause of stroke in younger patients, affecting more women than men. The most common symptoms are headache, seizures and focal neurological deficits. In previous studies published in 2014 and 2016, there were 3.7–5.3 times more female than male[10, 11] and the mean age was 30–41 years[12–16] which is consistent with CVST group in our study. However, there is a higher occurrence among men and higher median age in AIS group. Previous studies reported transverse sinus is the most common site of involvement that found in 61%[17]–78.4%[10] of cases. We found transverse sinus involvement in our research was 61% of all CVST.

Normal CT brain in patients with clinical suspicion of stroke either CVST or AIS may require further investigation because CT Brain could exhibit normal finding in early cerebral venous sinus thrombosis, particularly small vessel cerebral infarction and early infarction. Our study

found that 12% of CT brains were normal in CVST group.

Risk factors for favorable outcome were identified in previous studies including mRS ≤ 2,[3] involvement of lateral sinus.[4] On the other hand, unfavorable functional outcome was associated with National Institutes of Health Stroke Scale score > 2 at admission, low education level,[5] signs of mass effect on imaging, clinical deterioration after admission,[6] age > 37 years old, male sex[7] and the presence of hemorrhagic infarction.[4] Our study found favorable outcome in younger patients (age < 45 years in CVST and age < 65 years in AIS).

Prior studies mentioned low mRS 0–1 as a good functional outcome[5, 7] and found mRs ≤ 3 showed significant related with recovery time. Most patients in our study involved moderate to severe clinical presentation and only 5 cases with mild impairment. Early diagnosis and therapy had contributed to a decrease in mortality in cerebral venous thrombosis.[15]

Most patients in our study revealed good recovery outcome is associated with baseline mRs ≤ 3 and small vessel subgroup in arterial stroke. Other risk factors such as male gender, delayed diagnosis and status epilepticus as a complication did not show significant difference in recovery in both groups. Previously, lateral sinus was strong predictor of outcome in CVST.[4] Our study showed that among 31 patients who had lateral sinus thrombosis, the recovery was not significantly better than other sinus involvement. We included a total of 44 male patients, 16 of which are in CVST group and 28 patients are in AIS group. Male gender was an unfavorable predictor of functional outcome compared with hazard risk of 1.6 in the previous study. However, our study showed 2.48 times the odds of favorable outcome in male for both groups. However, male population was found less in CVST, which may not be concluded, have to wait for further study.

Previous studies showed a median admission delay of 4 days, and 75% of admission was extended within 13 days.[8, 9] Additionally, the delayed diagnosis before the patient received neurological attention correlated to prolonged duration of hospitalization.[18] This study found time to onset and time to diagnosis were significantly delayed in CVST group. The median time to onset was 72 hours and the time to diagnosis was 48 hours. Delayed time to hospital and delayed time to diagnosis may be due to some patients having a subacute onset of symptoms, mild symptoms and no neurological deficits. Early diagnosis in this study was not associated with delayed recovery. A possible explanation may be that the median time to diagnosis was within 2 days, which was faster than previous studies. In AIS group, diagnoses were made within the first day because most patients presented with obvious symptoms and signs of focal neurological deficit.

Venous infarct had a more favorable outcome than arterial group, although this was statistically insignificant. Median time to recovery was shorter in CVTS. A possible reason for this was that arterial infarcts were associated with parenchymal lesions. However, neurological deficits in venous group may be due to increased intracranial pressure rather than the parenchyma.

Status epilepticus (SE) was associated with discharge and long-term outcome of post stroke.19 Our study was limited to demonstrate the relation due to small number of patients with SE.

Conclusion

Prognostic factors affecting the recovery of stroke include age of the patients and the severity of disease. In arterial ischemic stroke, small vessel subtype also was a good prognostic factor. Cerebral venous sinus thrombosis patients tend to have a shorter recovery time than arterial stroke.

Originality and body of knowledge

We demonstrated age and stroke severity at admission as different prognostic factors associated with favorable outcome. However, further studies are needed to confirm this finding.

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