

# The study of intermediate-term survival of the patients with cerebral venous sinus thrombosis

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## Abstract

**Objective:** This study aimed to investigate the intermediate survival of patients with cerebral venous sinus thrombosis (CVST). **Methods:** This is a retrospective study recruiting patients with a definite diagnosis of CVST who were referred to teaching hospitals of “Shiraz University of Medical Sciences” from 2007 to 2017. Follow-up phone calls were conducted in March 2019 till June 2019. All-cause mortality, mortality due to CVST, and CVST recurrence were investigated. **Results:** Of the total of 301 patients, 213 (70.8%) were female. Patients’ age ranged from 1 to 95 year with a mean of 39.9 year. Intermediate follow-up (mean 46.9, 95%CI: 43.6-50.2 months) was done. Intermediate term mortality was 12.3%, mostly from CVST, and largely occurred within the first month. Age was a significant risk factor for survival (HR=1.056, 95%CI:1.037-1.075). The difference was not statistically significant in males in comparison to females (HR=1.3, 95%CI:0.67-2.60, P=0.41). Patients with recurrent CVST had a higher risk of mortality (HR=9.14, 95%CI:4.70-17.89, P<0.001). There was statistically higher risk of mortality in patients with deep vein thrombosis (DVT) (HR=8.97, 95%CI: 4.32-18.61, P<0.001). Although the risk of death for patients using oral contraceptives (OCPs) was 16% higher, this was not statistically significant (HR=1.16, 95%CI: 0.52-2.55, P= 0.21).

**Conclusions:** Intermediate-term mortality was 12.3%, and associated with older age, recurrent CVST and DVT. The reasons for these findings need further investigation.

**Keywords:** Cerebral venous sinus thrombosis, age, intermediate survival, mortality

## INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare clinical cause of stroke that can have a high incidence in young adults.<sup>1,2</sup> CVST is more frequent in Asian countries. Most patients with CVST are discharged with favorable outcomes.<sup>3</sup> However, delayed diagnosis of CVST could lead to considerable morbidity and mortality. In an Asian series, death and dependency are observed in 12.7% of the patients.<sup>4</sup>

There is an information gap about the intermediate-term prognosis of patients with CVST. There are few studies on the survival of CVST patients.<sup>5-7</sup> Although CVST is more common in Asian countries<sup>4</sup>, most of the studies are from western countries, while, the demographic and clinical characteristics of CVST in Asian countries are different from West.<sup>3,4,8,9</sup>

We aimed here to investigate all-cause mortality, mortality due to CVST, and CVST recurrence in an Iranian population with CVST.

## METHODS

This is a retrospective study recruiting CVST patients who were referred to teaching hospitals of “Shiraz University of Medical Sciences” from 2007 to 2017. The patients were primarily identified through ICD-10 coding system with diagnostic codes of G08 for “intracranial and intraspinal phlebitis and thrombophlebitis”, O87.3 for “cerebral venous thrombosis in the puerperium”, and I67.6 for “non-pyogenic thrombosis of the intracranial venous system”. The definitive CVST diagnosis was made based on re-evaluation of clinical records and results of the neuroimaging including magnetic

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resonance image (MRI), magnetic resonance venography (MRV), computed tomographic venography (CTV) and conventional angiography. We excluded patients with incomplete medical records. Patients, whose presentations could be better explained by any other neurological diseases according to their referring neurologist, were excluded. Patients with septic CVST were also excluded. The review board waived the need for patient consent.

Follow-up phone calls were conducted in March 2019 till June 2019. All-cause mortality was defined as any cause of death relevant or irrelevant to CVST. Mortality due to CVST was defined as death owing to direct effects of CVST such as brain herniation, status epilepticus, hospital complications, head trauma mediated by seizure, late hemorrhages due to a dural arteriovenous fistula, etc. Data on age, sex, cause of mortality, and CVST recurrence in the patients were extracted from their hospital recordings.

Survival curves (Kaplan-Meier) were obtained using data of death as the endpoint outcome. Cox proportional-hazards regression analysis was used to model the time of death data to identify possible predictors of mortality.

## RESULTS

From 2007 to 2017, 358 CVST patients were documented in the database, 57 patients had missing data. Of the total of 301 patients, 213 (70.8%) were female. Patients' age ranged from 1 to 95 years with a mean of 39.9 (95% Confidence Interval (CI): 38.1-41.6). The mean age of men was 40.3 (95%CI: 36.1-44.1) and that of women was 39.7 (95%CI: 37.9-41.5); the difference was not statistically significant ( $P=0.81$ ). The mean follow-up duration was 46.9 months (95%CI: 43.6-50.2 months). During the follow-up period, 37 (12.3%) patients passed away, 26 deaths (8.6%) were directly resulted from CVST. CVST-related mortality includes 10 brain herniation, 2 status epilepticus, 13 infectious complications, and one late hemorrhage due to dural arteriovenous fistula.

Of the CVST-related mortality group, 8 (9.1%) patients were male and 18 (8.5%) patients were female. There was no significant difference between CVST-related mortality in sex groups ( $P=0.5$ ). The mean age of the CVST-related mortality group was 50.8 years (95%CI: 41.7-59.9) in comparison to alive patients 38.8 (95%CI: 37.1-40.5). This difference was statistically significant ( $P<0.001$ ). CVST-related mortality among <18, 19-45, 46-65 and >65 year-groups

were 20%, 3.7%, 12.3%, 42.8% respectively ( $P<0.001$ ). Mean hospital stay in CVST-related mortality patients was significantly longer than alive patients (16.9 vs. 9.6 days,  $P=0.019$ ).

As shown in Figure 1, the overall cumulative survival rate for all-cause mortality was 91.4% (90.9% for men and 91.5% for women) at one month, 88.4% (86.4% for men and 89.2% for women) at 3 months and 87.7% (85.2% for men and 88.7% for women) at 12 months. There was no statistically significant difference between sex groups (Log-rank  $P=0.41$ )

Figure 2 exhibits the survival function curves of the patients based on age groups. The results represent that 1, 3 and 12 months' cumulative survival rate was significantly different between <18, 19-45, 46-65, and >65 year-groups (Log-rank  $P<0.0001$ ).

In the Cox proportional hazard model, the results of the univariate analysis showed that age was a significant risk factor for survival (HR=1.056, 95%CI: 1.037-1.075). Mortality was significantly higher in the >45 age group in comparison to <45 group (HR=4.99, 95%CI: 2.50-9.94,  $P<0.001$ ).

Although the risk of death was 30% higher in male patients, the difference was not statistically significant (HR=1.3, 95%CI: 0.67-2.60,  $P=0.41$ ). Patients with recurrent CVST (4 patients; 1.3%) had a higher risk of mortality in comparison patients without recurrent CVST (HR=9.14, 95%CI:4.70-17.89,  $P<0.001$ ). In addition, there was a statistically higher risk of mortality in patients with deep vein thrombosis (DVT) (16 patients; 5.3%) (HR=8.97, 95%CI: 4.32-18.61,  $P<0.001$ ). Although the risk of death for patients using OCP was 16% higher, this increment was not statistically significant (HR=1.16, 95%CI: 0.52-2.55,  $P=0.21$ ).

## DISCUSSION

In this study, we investigated the intermediate-term survival of CVST patients in an Iranian population. Similar to previous studies<sup>10</sup>, the majority of the patients were female (70.8%). Intermediate follow-up of the patients showed that age is a significant risk factor for survival. Mortality was significantly higher in the age of over 45 years. Our finding also indicated that patients with recurrent CVST as well as patients with DVT had a higher risk of mortality.

There are few studies on the long-term outcome of CVST. For instance, English *et al.* (2009) evaluated clinical presentation and long-term

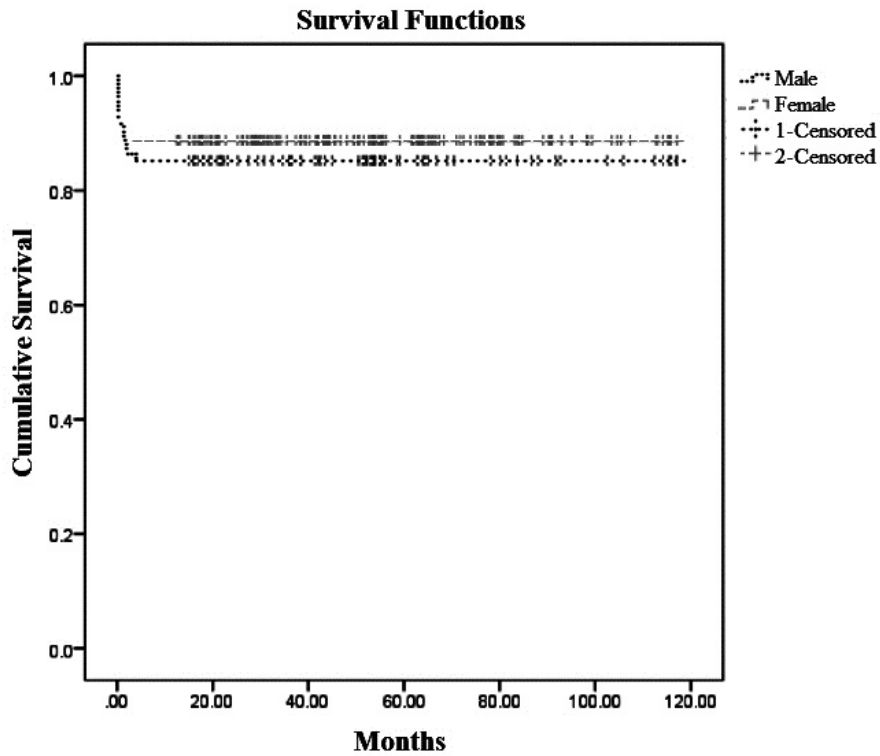


Figure 1. Kaplan-Meier curve showing the survival function of the patients with CVST based on gender

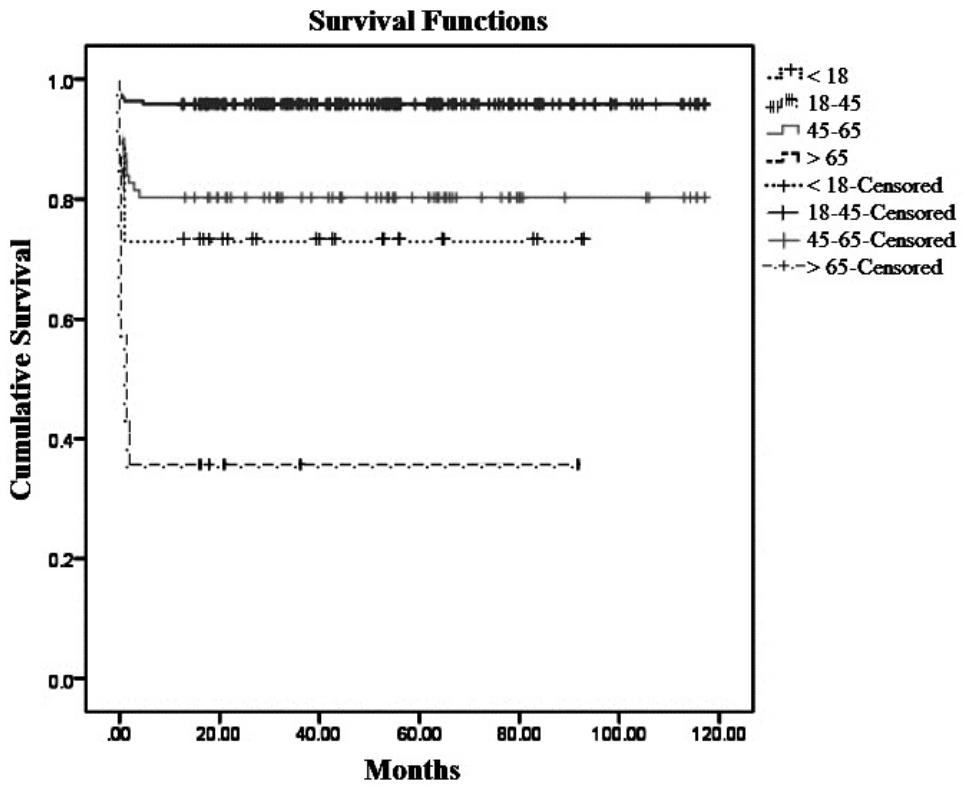


Figure 2. The survival function curve of the patients with CVST based on age groups using Kaplan-Mir method

outcomes of CVST in North American from a single center.<sup>7</sup> In parallel with our study, the majority of their patients were young women. Besides, they showed that in a mean follow-up of 54 months, 90% of patients had the desired long-term outcome. The rate of mortality in their study was 9%. However, it should be noted that although all patients in our study were Asian, their study patients were ethnically diverse (12% Asian, 57% Caucasians, 17% Hispanics, and 12% African-American). A similar result indicating that most patients with CVST had favorable clinical outcomes, but with shorter follow-up time, was also reported in Lee *et al.* study. They described management and outcome of CVST in a single-institution cohort. They identified 41 patients with CVST that the number of women was more than twice that of men. However, female gender and favorable admission examination were reported as predictors of a favorable outcome. While older age was not statistically significant in their study, it was as predictors of an unfavorable outcome.<sup>10</sup> In addition, Preter *et al.* (1996) evaluated long-term prognosis in 77 patients with CVT (64% female) during a mean follow-up time of 77.8 months.<sup>5</sup> In comparison to their study, the sample size of our study was larger but the mean follow-up time was shorter. Further, the incidence of recurrence CVT in their study was higher (11.7% vs. 1.3%).

However, similar to their study, recurrent CVT had a higher risk of mortality in the current study. It should be considered that their study was dated from 1975 to 1990, while we studied the patients from 2007 to 2017. It seems that increased quality of medical and hospital care has led to improved outcomes in the mid-term or long-term. Further, the survival of the patients with CVST in our series is in accordance with a large prospective cohort study of International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). In this international study that registered 624 CVST patients, the mean age was 39 years, women consisted of 75% of patients, and the rate of mortality was 8%. Also, 2.2% of patients had a recurrent CVST.<sup>8</sup> However, the mean length of follow-up was 18.6 months which was shorter than our study. Our results indicated that while the majority of the patients were women, the risk of death was 30% higher in male patients. However, this difference was not significant. Further, some studies reported male patients had a worse outcome<sup>10,11</sup> and the mortality rate was relatively higher in male patients.<sup>12</sup>

In the current study, extreme age but not sex was determinant of intermediate prognosis. However, Ruiz-Sandoval JL *et al.* reported that

only age <40 years was associated with loss of disability in a Cox proportional hazards model.<sup>13</sup>

The main limitation of this study was the lack of evaluation of important determinant factors such as etiologic causes and patterns of involvement of different sinuses and veins. This was due to a phone-call follow-up and incomplete medical records. Our study shows that intermediate term mortality of CVST is 12.3%, and is associated with older age, recurrent CVST and DVT. The reasons for these findings need further investigation.

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## DISCLOSURE

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Conflicting interest: None

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