



Risk factors for early-onset seizures in patients with cerebral venous sinus thrombosis: A meta-analysis of observational studies

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ABSTRACT

Purpose: We conducted a meta-analysis to determine the predictors of early-onset seizure in patients with cerebral venous sinus thrombosis (CVST) and to provide a basis for further clinical trials of prophylactic use of antiepileptic drugs in patients with CVST.

Method: The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Relevant observational studies that investigated risk factors for early-onset seizures after CVST were retrieved from Pubmed and Embase databases. Odds ratios (OR) for early-onset seizures were calculated from the pooled data using the random effects model.

Results: Six observational studies (combined n = 1244) were included in this meta-analysis. Coma [OR, 2.265; 95% confidence interval (CI) 1.251–4.100], mental status (OR, 3.450; 95% CI 1.150–10.356), motor symptoms (OR, 3.726; 95% CI 2.519–5.514), involvement of cortical veins (OR, 3.574; 95% CI 2.521–5.068), supratentorial lesion (OR, 5.041; 95% CI 3.622–7.015), frontal lobe (OR, 3.481; 95% CI 1.703–7.114), parietal lobe (OR, 3.638; 95% CI 1.911–6.925), hemorrhagic lesions (OR, 2.505; 95% CI 1.485–4.225), and pregnancy (OR, 2.054; 95% CI 1.043–4.048) showed a significant association with early-onset seizures.

Conclusion: Involvement of a number of specific cortical regions in the post-CVST phase may induce early-onset seizures, especially in the setting of concomitant hemorrhagic infarct or cortical vein involvement.

1. Introduction

Cerebral venous sinus thrombosis (CVST) is a subtype of cerebral stroke, with an annual incidence of approximately 3–4 cases per million population [1]. Unlike other types of stroke, CVST typically occurs in young adults (mean age at onset: 35 years) [2]. In general, patients with CVST have a fair prognosis. Previous studies have shown that 60–79% of patients achieve good functional outcomes [Modified Rankin Scale (mRS) score 0–1] [3,4]. However, occurrence of seizures in these patients may adversely affect the prognosis; in one study, CVST patients with seizures were found to experience two-fold higher mortality rates as compared to their counterparts who did not develop seizures [5]. In addition, recurrence of seizures can severely affect the patient's self-care ability and quality of life. However, seizures are ubiquitous in patients with CVST, and up to 51.1% patients may develop seizures in the early stage of the disease [5–7]. In previous studies, seizures related to CVST were categorized into two types: early-onset seizures and late-onset seizures [8]. The former type was defined as seizures appearing

before the diagnosis of CVST (patients presenting with seizures) or within 14 days after the diagnosis (acute symptomatic seizures) [9]. The latter type was defined as those occurring beyond 14 days after diagnosis. In previous studies, early-onset seizures (especially status epilepticus) in patients with CVST were associated with poor short-term outcomes, such as higher mortality [10–12]. Since the pathogenetic mechanism of seizures in patients with CVST is not clear, some studies have sought to determine potential predictors of seizures. Some of the identified predictors, include motor or sensory symptoms, parenchymal lesion, cortical vein thrombosis, and intracranial hemorrhage [5–7,12–14]. However, there is no clear consensus on the validity of these predictors. This may be due to the small sample size in these studies, which in turn is attributable to the low incidence rate of CVST. Mehvari et al summarized the risk factors for early-onset seizures in CVST patients [15]; however, the authors did not perform a systematic evaluation of pooled data from previous studies; in addition, their conclusions may have been influenced by confounding factors. Therefore, we performed a meta-analysis to determine the predictors of

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seizures in patients with CVST. To the best of our knowledge, this is the first meta-analytic study on this subject. Our results may provide a basis for further clinical trials of prophylactic antiepileptic therapy in patients with CVST.

2. Methods

The present meta-analysis was conducted according to the Systematic Reviews and Meta-analyses (PRISMA) guidelines [16].

2.1. Literature search

We searched the PubMed and Embase databases to retrieve all relevant studies pertaining to early-onset seizures and CVST that were published as of March 2019. The search strategy was a combination of medical subject headings (MeSH) and free words; combination of different search terms was employed using the Boolean operators "OR" or "AND". Details of the search strategy in PubMed are presented in Table S1 (Supplementary material). In addition, the reference lists of the retrieved articles were manually screened, to identify additional relevant studies.

2.2. Literature screening

The retrieved articles were screened independently by two reviewers. The titles or abstracts of each article were reviewed in the first round. The full-text of the selected articles were reviewed in the second round. The study selection criteria were: 1) case-control or cohort studies; 2) study population: patients with CVST, regardless of age, gender, or ethnicity; 3) studies that examined the risk factors or predictors of early-onset seizures in patients with cerebral venous sinus thrombosis; 4) primary outcome: seizures appearing before the CVST diagnosis (presenting seizures) or within 14 days after the diagnosis; 5) Availability of valid data [odds ratio (OR) or relative risk (RR), with 95% confidence intervals (CIs)]. No restrictions were imposed with respect to the language of publication and region. Duplicate publications and those that did not qualify the inclusion criteria were excluded. Any disagreement during literature screening was resolved by consensus.

2.3. Data extraction and literature assessment

Two independent reviewers performed data extraction and quality evaluation. A pre-designed standardized form was used to extract relevant data including: 1) first author, year of publication; 2) research details: study type, sample size, study reference period, region, sex ratio, average age. Each study was assessed using the Newcastle-Ottawa Scale (NOS) with respect to a total of 8 items including selectivity, comparability, outcome or exposure in three dimensions. Based on the 8 entries, the possible range of grades was 0–9; a grade of > 6 was considered indicative of high quality.

2.4. Statistic analysis

Stata version 12.0 was used for data analysis. The results of this research are expressed as OR with 95% CI in univariate analysis. The results of the original data provided were singled out. Heterogeneity of entries was tested by the I^2 statistic; $I^2 < 50\%$ was considered indicative of no significant heterogeneity. A random-effects model was used for meta-analysis of all variables.

3. Results of literature screening

A total of 1704 articles were retrieved on database search. After two rounds of screening, 6 studies were included in the meta-analysis (Fig. 1). Of these, three were case-control studies and three were cohort

studies; two studies had excluded acute symptomatic seizures. Characteristics of the included studies are summarized in Table S2 (Supplementary material). In terms of literature quality, according to the NOS scale, three papers were rated as 9 points, two as 7 points, and one as 8 points. The details of literature quality assessment are shown in Table S2 (Supplementary material).

4. Results of data analysis

4.1. Demographic characteristics

Five studies had explored the relationship of age or gender with early seizures. None of these studies found any association of age or gender with increased risk of ES (Fig. 2A-B).

4.2. Clinical symptoms

With respect to clinical syndrome, coma (OR, 2.265; 95% CI, 1.251–4.100), mental status (OR, 3.450; 95% CI 1.150–10.356), and motor symptoms (OR, 3.726; 95% CI 2.519–5.514) were identified as risk factors for seizures (Fig. 3A-G).

4.3. Anatomical and imaging characteristics

Involvement of cortical vein (OR, 3.574; 95% CI 2.521–5.068), supratentorial lesion (OR, 5.041; 95% CI 3.622–7.015), frontal lobe (OR, 3.481; 95% CI 1.703–7.114), parietal lobe (OR, 3.638; 95% CI 1.911–6.925), and hemorrhagic infarct (OR, 2.505; 95% CI 1.485–4.225) were predictors of early-onset seizures (Fig. 4A-L).

4.4. Etiology

With respect to etiology, only pregnancy-induced CVST (OR, 2.054; 95% CI 1.043–4.048) showed a mild association with early-onset seizures. Other common etiological factors such as oral contraceptives, hematological abnormalities, vasculitis, or central nervous system infection were not associated with early-onset seizures in patients with CVST (Fig. 5A-F).

5. Discussion

The present meta-analysis included six studies with a combined study population of 1244 patients with CVST. The reference periods of these studies ranged from 1972 to 2015 and these studies were conducted in India, Iran, Portuguese, India, Canada, and many other countries. Out of the 1244 patients, 532 patients (42.77%) developed presenting or acute symptomatic seizures; this further confirms the high incidence of early-onset seizures in CVST patients. Early-onset seizures are liable to aggravate edema, hemorrhage, and intracranial hypertension in the acute phase of CVST, which may worsen the prognosis. In previous studies by Ferro and Masuhr, early-onset seizures (especially status epilepticus) were found to be an important cause of disability and mortality among CVST patients [12,13]. This prompted a series of studies to identify potential predictors of early-onset seizures in these patients. However, due to the low incidence of CVST and the difficulty in diagnosis, the sample size in previous studies was largely inadequate. In the present meta-analysis, we identified some risk factors for early-onset seizures using a relatively large sample size. None of the demographic characteristics were found to be associated with early-onset seizures. In terms of clinical symptoms, coma, mental status, and motor symptoms showed a significant association with early-onset seizures. In terms of anatomical lesion and imaging features, involvement of cortical veins, supratentorial lesion, frontal lobe, parietal lobe, and hemorrhagic lesions were associated with a significantly increased risk of early-onset seizures. In terms of etiology, only pregnancy-related CVST showed a mild association with early-onset seizures; however,

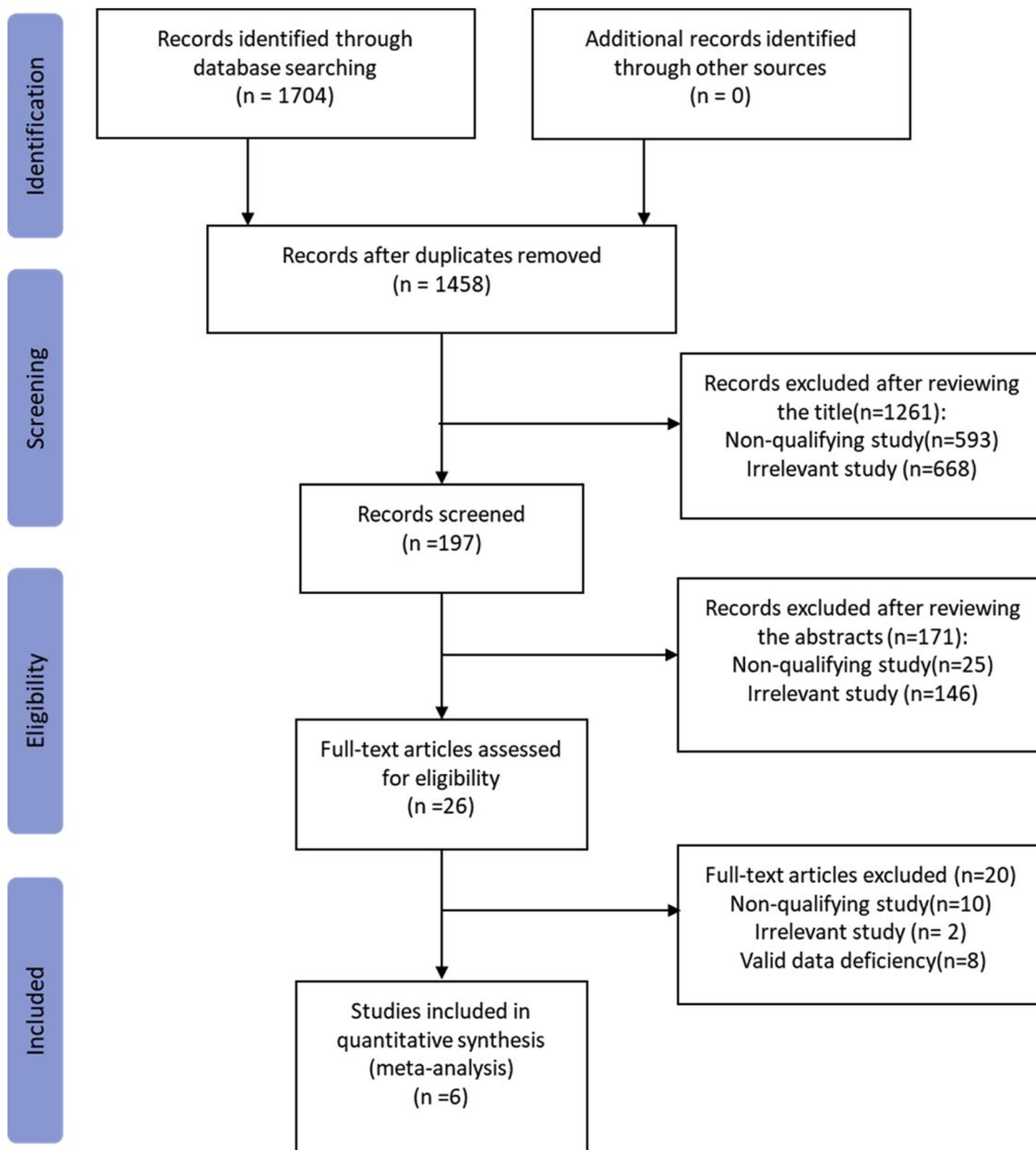
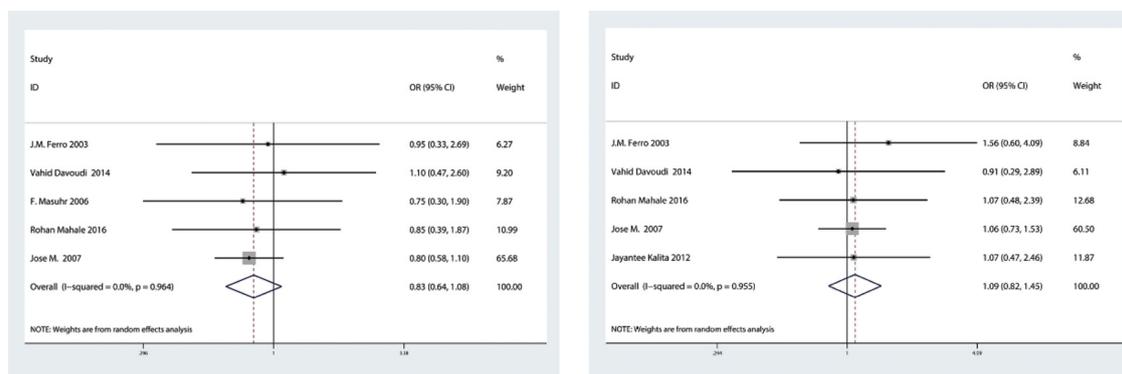


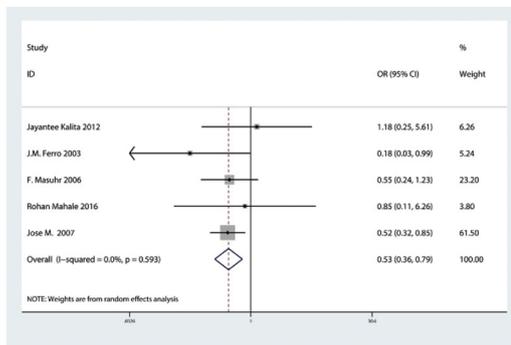
Fig. 1. Schematic illustration of the literature search and study selection criteria.



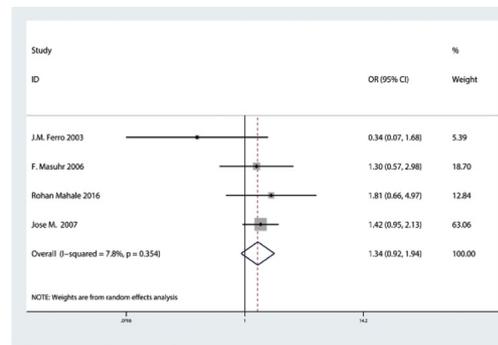
(A) age

(B) gender

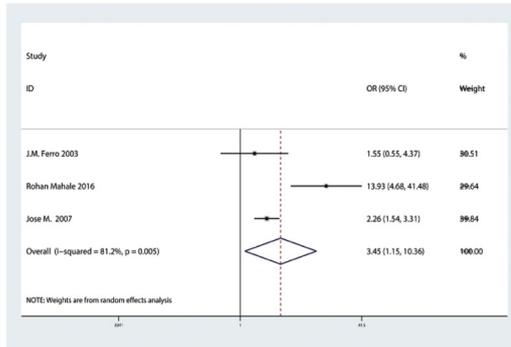
Fig. 2. Forest plot of demographic characteristics.



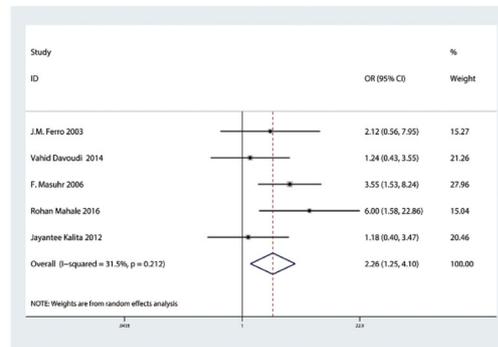
(A) headache



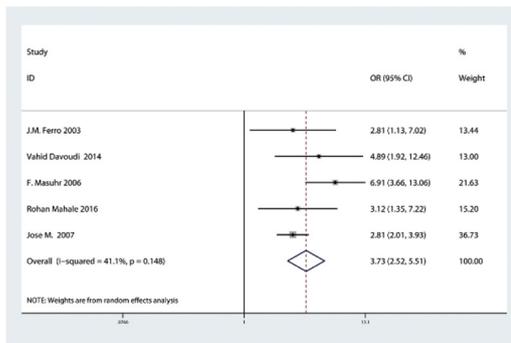
(B) aphasia



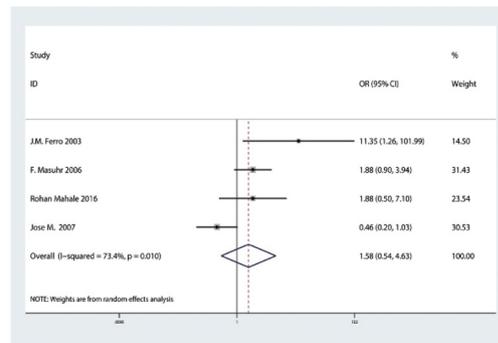
(C) mental status



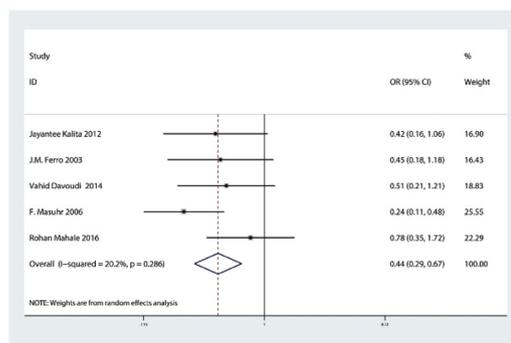
(D) coma



(E) motor symptom



(F) sensory symptom



(G) cranial hypertension symptom

Fig. 3. Forest plot of clinical symptoms.



Fig. 4. Forest plot of anatomical correlates and imaging characteristics.

there was some inconsistency among the included studies in this respect. Besides, we conducted sub-group analyses by disaggregating Asian population and American-European population to identify any potential differences between different populations. Detailed results of the sub-group analyses are shown in Table S3 (supplemental materials). Our results showed no significant difference between different populations, which is also supported by previous studies conducted in United States and China [17,18].

Among these risk factors, some are intrinsically related, such as the clinical symptoms and anatomical location of the lesions: involvement

of the cerebral cortex is likely to cause coma, altered sensorium, or corresponding focal neurological deficits. Similarly, cortical involvement may also induce seizures. Involvement of cortical vein is liable to stimulate the cerebral cortex directly through exudates because of the anatomical proximity; in addition, the cortical vein and the superior sagittal sinus (SSS) drain blood from the supratentorial parenchyma, especially the motor and sensory cortex. Involvement of these two structures may aggravate cortical edema because of blocked superficial medullary vein and poor venous outflow [18,19]. However, temporal lobe, which is closely related to epilepsy, was not found to be associated with early-onset seizures in patients with CVST. This may be due to the fact that temporal lobe is associated with more insidious and difficult to diagnose types of seizures as compared to generalized seizures. The predominant seizure type reported in the six studies was primarily generalized (from onset or secondarily) seizures; these accounted for 72.7% (95% CI, 55.0%–90.4%, detailed information shown in Table S4) on pooled analysis using the random effect model. This is consistent with our hypothesis that other types of seizures are neglected. Of note, F. Masuhr 2006 reported a high proportion (54.7%) of Todd's paresis, which may contribute to a study on the mechanism of this special type of seizure [5]. Further studies are required to focus on this aspect. In addition, some authors have suggested that thrombus occurring within the superior sagittal sinus (SSST) may also be associated via a mechanism of altered intracranial pressure dynamics [20]: SSS plays an important role in CSF absorption; SSST may seriously affect CSF absorption, increase intracranial pressure, and consequently induce seizures. Furthermore, increased intracranial pressure has a greater impact in the acute stage, which implies that this is a greater risk factor for early-onset seizures than late-onset seizures. Besides, animal experiments have shown that seizures can be induced by extravasation of serum-derived components in the setting of impaired blood-brain barrier [21]. The association between hemorrhagic lesions and seizures is likely attributable to the stimulation of cerebral cortex by the exudation of hemosiderin and its metabolites post hemorrhage [22,23]. The association between pregnancy and post-CVST seizures was not consistent across multiple studies and is a factor that warrants further study. In this regard, it is noteworthy that pregnancy itself may also cause seizures. The gestation period represents a state of immune tolerance to the half-allogeneic fetus, which may induce epilepsy through autoimmune mechanisms [24]. To summarize, post-CVST cortical involvement due to various factors may be one of the causes of early-onset seizures, especially in the setting of hemorrhagic infarct or cortical vein involvement.

A key limitation of this study is that the current definition of early-onset seizures is not uniform. Two studies [Ferro et al (2008) and Kalita et al (2012)] included only acute symptomatic seizures to calculate the OR, while the remaining four studies included both presenting and acute symptomatic seizures. In the present meta-analysis, the random effect model was used for meta-analysis of all ORs. This may have helped minimize the influence of the difference between the two to some extent; however, the effect of this difference on our results cannot be ruled out. Essentially, we found no differences between acute symptomatic seizures and presenting seizures. Owing to the advances in imaging technology and growing recognition of CVST among clinicians, there has been a gradual decline in the diagnosis of presenting seizures and a concomitant increase in the diagnosis of acute symptomatic seizures. In addition, only observational studies were included in this study, and the sample size was relatively insufficient. The number of included studies with respect to some special variables was too small to allow assessment of publication bias. Besides, due to the lack of uniform standards and/or detailed information, some potential risk factors were not included in the meta-analysis. In particular, we could not assess multiple sinus involvement. In the six included studies, three pertained to multiple sinus involvement, while one [Vahid Davoudi (2014)] pertained to all sinuses, one [J.M. Ferro (2003)] included the cortical vein, and one [Rohan Mahale (2016)] included multiple sinuses. Thus,

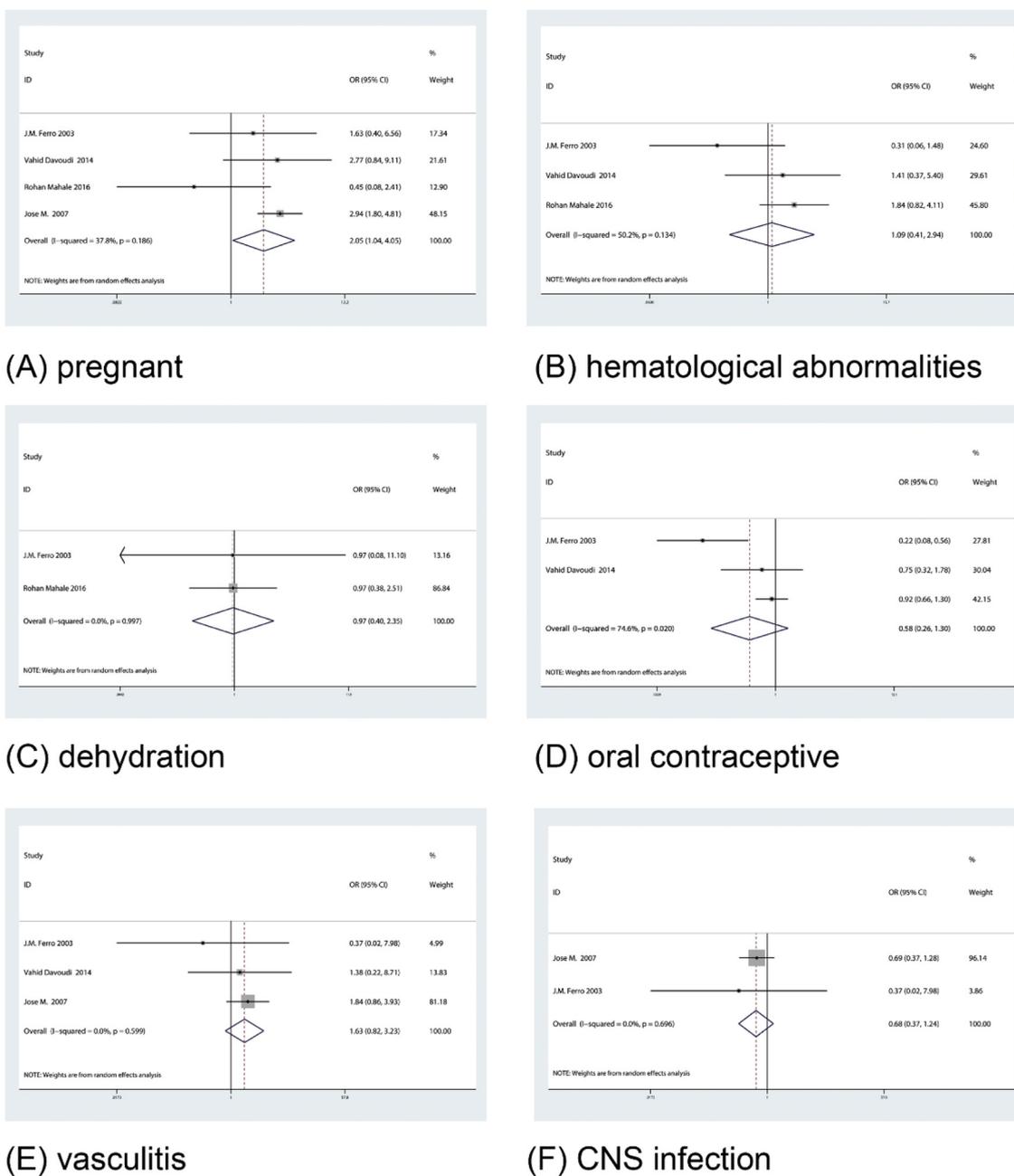


Fig. 5. Forest plot of etiology.

it was difficult to conduct meta-analysis in this respect. However, we tried to pool the results and obtained some interesting findings. Results reported by Vahid Davoudi (2014) and Rohan Mahale (2016) suggest that multiple sinus involvement maybe a strong risk factor [OR: 3.26 (95% CI, 0.52–20.67) and 2.42 (95% CI, 1.03–5.70) respectively]. Conversely, the OR value in the study by J.M. Ferro 2003 was 0.13 (95% CI, 0.05–0.31). More research is needed to draw any definitive conclusions in this regard. These shortcomings may limit the generalizability of our findings. Further well-designed large sample size studies are required to provide more definitive evidence.

6. Conclusion

Post-CVST cortical involvement may be one of the causes of early-onset seizures, especially in the setting of hemorrhagic infarct or cortical vein involvement. Patients with CVST who present with coma, altered sensorium, dysphasia, and those with imaging signs of cortical

vein involvement, supratentorial lesions, frontal lobe or hemorrhagic lesions are more likely to experience early-onset seizures. It is worth considering clinical trials of prophylactic antiepileptic therapy in patients with CVST.

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Ethical approval

This article does not contain any data from any of the authors' studies of human participants or animals.

Declaration of Competing Interest

The authors declare no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.seizure.2019.09.006>.

References

- [1] Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005;352:1791–8.
- [2] Capecchi M, Abbattista M, Martinelli I. Cerebral venous sinus thrombosis. *J Thromb Haemost* 2018;16:1918–31.
- [3] Salottolo K, Wagner J, Frei DF, Loy D, Bellon RJ, McCarthy K, et al. Epidemiology, endovascular treatment, and prognosis of cerebral venous thrombosis: US Center Study of 152 Patients. *J Am Heart Assoc* 2017;6.
- [4] Ferro JM, Canhão P, Stam J, Boussier MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004;35:664–70.
- [5] Masuhr F, Busch M, Amberger N, Ortwein H, Weih M, Neumann K, et al. Risk and predictors of early epileptic seizures in acute cerebral venous and sinus thrombosis. *Eur J Neurol* 2006;13:852–6.
- [6] Kalita J, Chandra S, Misra UK. Significance of seizure in cerebral venous sinus thrombosis. *Seizure* 2012;21:639–42.
- [7] Ferro JM, Correia M, Rosas MJ, Pinto AN, Neves G. Seizures in cerebral vein and dural sinus thrombosis. *Cerebrovasc Dis* 2003;15:78–83.
- [8] Chen Z, Churilov L, Chen Z, Naylor J, Koome M, Yan B, et al. Association between implementation of a code stroke system and poststroke epilepsy. *Neurology* 2018;90:e1126–33.
- [9] Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia* 2010;51:671–5.
- [10] Jalili M, Ghourchian S, Shahidi GA, Rohani M, Rezvani M, Zamani B. A study of factors associated with cerebral venous thrombosis. *Neurol Sci* 2013;34:321–6.
- [11] Canhao P, Ferro JM, Lindgren AG, Boussier MG, Stam J, Barinagarrementeria F. Causes and predictors of death in cerebral venous thrombosis. *Stroke* 2005;36:1720–5.
- [12] Ferro JM, Canhao P, Boussier MG, Stam J, Barinagarrementeria F. Early seizures in cerebral vein and dural sinus thrombosis: risk factors and role of antiepileptics. *Stroke* 2008;39:1152–8.
- [13] Mahale R, Mehta A, John AA, Buddaraju K, Shankar AK, Javali M, et al. Acute seizures in cerebral venous sinus thrombosis: What predicts it? *Epilepsia Res* 2016;123:1–5.
- [14] Davoudi V, Keyhanian K, Saadatnia M. Risk factors for remote seizure development in patients with cerebral vein and dural sinus thrombosis. *Seizure* 2014;23:135–9.
- [15] Mehvari HJ, Saadatnia M, Tabrizi N. Seizure in cerebral venous and sinus thrombosis. *Epilepsia Open* 2018;3:316–22.
- [16] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- [17] Wasay M, Bakshi R, Bobustuc G, Kojan S, Sheikh Z, Dai A, et al. Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. *J Stroke Cerebrovasc Dis* 2019;17:49–54.
- [18] Ding H, Xie Y, Li L, Chu H, Tang Y, Dong Q, et al. Clinical features of seizures after cerebral venous sinus thrombosis and its effect on outcome among Chinese Han population. *Stroke Vasc Neurol* 2017;2:184–8.
- [19] Liang J, Chen H, Li Z, He S, Luo B, Tang S, et al. Cortical vein thrombosis in adult patients of cerebral venous sinus thrombosis correlates with poor outcome and brain lesions: a retrospective study. *BMC Neurol* 2017;17:219.
- [20] Onder H. Cerebral venous sinus thrombosis complicated by seizures. *J Thromb Thrombolysis* 2018;46:77–8.
- [21] Seiffert E, Dreier JP, Ivens S, Bechmann I, Tomkins O, Heinemann U, et al. Lasting blood-brain barrier disruption induces epileptic focus in the rat somatosensory cortex. *J Neurosci* 2004;24:7829–36.
- [22] Küçükkaya B, Aker R, Yüksel M, Onat F, Yalçın AS. Low dose MK-801 protects against iron-induced oxidative changes in a rat model of focal epilepsy. *Brain Res* 1998;788:133–6.
- [23] Willmore LJ. Post-traumatic seizures. *Neurol Clin* 1993;11:823–34.
- [24] La Rocca C, Carbone F, Longobardi S, Matarese G. The immunology of pregnancy: regulatory T cells control maternal immune tolerance toward the fetus. *Immunol Lett* 2014;162:41–8.