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Post-SARS-CoV-2-vaccination Cerebral Venous Sinus Thrombosis: an analysis of cases notified to the European Medicines Agency

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Abstract

Background: Cerebral venous sinus thrombosis (CVST) has been described after vaccination against SARS-CoV-2. We report clinical characteristics of 213 post-vaccination CVST cases notified to the European Medicines Agency (EMA).

Methods: Data on Adverse Drug Reactions after SARS-CoV-2 vaccination notified until 8 April 2021 under the Medical Dictionary for Regulatory Activities Term 'Central nervous system vascular disorders' were obtained from the EudraVigilance database. We compared post-vaccination CVST to 100 European patients with CVST from before the COVID-19 pandemic derived from the International CVST Consortium.

Results: We identified 213 CVST cases: 187 after AstraZeneca/Oxford (ChAdOx1 nCov-19), vaccination and 26 after a mRNA vaccine (25 Pfizer/BioNTech, BNT162b2 and 1 Moderna, mRNA-1273). Thrombocytopenia was reported in 107/187 CVST cases (57%, 95%CI 50-64%) in the ChAdOx1 nCov-19 group, in none in the mRNA vaccine group (0%, 95%CI 0-13%), and in 7/100 (7%, 95%CI 3-14%) in the pre-COVID-19 group. In the ChAdOx1 nCov-19 group, there were 39 (21%) reported COVID-19 PCR tests performed within 30 days of CVST symptom onset, and all were negative. Of the 117 patients with a reported outcome in the ChAdOx1 nCov-19 group, 44 (38%, 95%CI 29-47%) had died, compared to 2/10 (20%, 95%CI 6-51%) in the mRNA vaccine group and 3/100 (3%, 95%CI 1-8%) in the pre-COVID-19 group. Mortality among patients with thrombocytopenia in the ChAdOx1 nCov-19 group was 49% (95%CI 39-60%).

Conclusions: CVST occurring after ChAdOx1 nCov-19 vaccination has a clinical profile distinct from CVST unrelated to vaccination. Only CVST after ChAdOx1 nCov-19 was associated with thrombocytopenia.

Keywords: COVID-19 vaccine, CVST, thrombocytopenia, EMA

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Introduction

Vaccination against SARS-CoV-2 has been initiated at an impressive speed to lower the global burden of the COVID-19 pandemic. By April 2021, four vaccines were licensed by the European Medicines Agency (EMA) and are currently in use in Europe: a recombinant chimpanzee adenoviral vector from Astra-Zeneca/Oxford (ChAdOx1 nCov-19), a recombinant adenovirus type 26 vector from Janssen/Johnson&Johnson (Ad26.COV2.S) and two messenger RNA-based vaccines, one from Pfizer/BioNTech (BNT162b2) and one from Moderna (mRNA-1273) (1). After vaccination of millions of individuals, several patients were reported who developed cerebral venous sinus thrombosis (CVST) or other thrombotic events, frequently in combination with thrombocytopenia, within 28 days of vaccination (2-6). This condition has been termed vaccine-induced immune thrombotic thrombocytopenia (VITT) and appears to be related to the ChAdOx1 nCov-19 and Ad26.COV2.S vaccines (2, 4, 7).

The number of published post-SARS-CoV-2-vaccination CVST cases is small and there is a possibility of selective reporting of patients with VITT. Also, characteristics of patients who developed CVST after SARS-CoV-2 vaccination have not yet been compared to patients with CVST from before the COVID-19 pandemic. Here, we report clinical data of patients with CVST notified to EMA after SARS-CoV-2-vaccination and compare these with a control group of CVST cases from before the COVID-19 pandemic.

Methods

Data selection

The European Medicine Agency (EMA) granted the authors research access to the EudraVigilance database (8). EMA is the official institution of the European Economic Area (EEA) that regulates all drug-related activities within the European Union and one of its duties is to collect data on Adverse Drug Reactions (ADRs) (9, 10). EudraVigilance is a passive pharmacovigilance system hosted and maintained by EMA in which all reported suspected ADRs are collected from the marketing authorisation holders and national competent authorities (10). Following approval by EMA of a formal request by the authors (submitted 1 April 2021), a level 2A output was provided of Individual Case Safety Report (ICSR) data with a Medical Dictionary for Regulatory Activities High Level Group Term (MedDRA HLGT, version 24.0) 'Central nervous system vascular disorders', for which suspected ADRs were collected according to the European legislation, for each of the four SARS-CoV-2 vaccines approved by EMA (ChAdOx1 nCov-19, BNT162b2, mRNA-1273, and Ad26.COV2.S). The data extracted include the suspected adverse events reported to the EudraVigilance post-marketing module between 24 December 2020 and 8 April 2021 from the EEA and the United Kingdom, as well as any suspected serious ADR's within and outside of the EEA (8) .

Cases with the following "Reaction Preferred Terms" (RCPT) of the Medical Dictionary for Regulatory Activities were considered to have CVST: "cerebral venous thrombosis", "cerebral venous sinus thrombosis", "jugular vein thrombosis", "superior sagittal sinus thrombosis", "transverse sinus thrombosis" and "cavernous sinus thrombosis". In addition, we screened cases with a RCPT that could potentially indicate CVST (see Table S1 in the appendix). Clinical data of each case with one of the RCPTs which could indicate a CVST were independently screened by two of three investigators (KK, MSK, and TH), using information from the reported Data Elements available (see Table S2 in the appendix). Cases that were marked as "potential CVST" by at least one of the investigators were adjudicated by a senior vascular neurologist (JMC), who made the final decision on whether or not to classify the case as CVST. After identification of the CVST cases, duplicates and cases that were reported from countries outside the European continent were excluded.

We considered the following variables as traditional CVST risk factors: cancer, hormone replacement therapy or oral contraceptive use, genetic thrombophilia and any concomitant infection. Thrombocytopenia was defined as a platelet count of $<150 \times 10^3/\mu L$. Cases were considered to have thrombocytopenia if platelet counts $<150 \times 10^3/\mu L$ were reported in the "Result Unstructured Data" (F.r.3.4) (see Table S2 in the appendix) or if there was RCPT "thrombocytopenia" reported.

We compared CVST reported in patients who received an adenovirus based vaccine (ChAdOx1 nCov-19 and Ad26.COV2.S) to patients who received a mRNA vaccine (BNT162b2 and mRNA-1273). However, because there were no CVST cases after the Ad26.COV2.S vaccine reported from European countries

during the study period, this vaccine was disregarded from the analysis. We additionally compared post-vaccination CVST cases to a control group of CVST patients diagnosed prior to the COVID-19 pandemic. Data for this control sample were derived from the international CVST consortium, which is an academic collaboration established in 2015 with the aim to perform clinical research on CVST (11-14). CVST patients from three participating European hospitals (see Table S4 in the appendix) – all with symptom onset between 1 January 2015 and 31 December 2017 were used as a control sample. Each centre obtained permission from their ethical review board for the collection of observational data. Written patient informed consent was obtained if required under applicable national laws.

Statistical analysis

We performed a descriptive analysis, calculating median and interquartile range for continuous variables, and counts and percentages for categorical variables. We calculated 95% confidence intervals (95%CI) for the following variables that were hypothesized to be different between the cases after adenovirus-based vaccination and the two other groups: thrombocytopenia, concomitant venous thromboembolic events (VTE), and mortality. Confidence intervals were calculated using Wilson's method using the Hmisc package in R Studio 4.0.3.

Results

Out of 2517 individual cases with at least one neurovascular ADR recorded in the EudraVigilance database, we identified 213 CVST cases from 18 European countries (Figure 1). Of these, 187 occurred after ChAdOx1 nCov-19 vaccination and 26 after vaccination with a mRNA vaccine (25 BNT162b2 and 1 mRNA-1273). In the control group there were 100 pre-COVID-19 CVST patients from the three European hospitals with symptom onset between 1 January 2015 and 31 December 2017.

Median age was 46 (IQR 32-56), 56 (IQR 36-81), and 45 (IQR34-55) for the ChAdOx1 nCov-19, mRNA vaccine, and pre-COVID-19 groups, respectively. In the ChAdOx1 nCov-19 vaccine, mRNA vaccine, and pre-COVID-19 groups, there were 138 (75%), 20 (77%) and 66 (66%) women (Table 1). Median interval between first reported administration of SARS-CoV-2 vaccine and CVST symptom onset was 9 days (IQR 5-13) in the ChAdOx1 nCov-19 group and 7 days (IQR 2-21) in the mRNA vaccine group. In the mRNA vaccine group, there were two patients who developed CVST 2 and 13 days after the second vaccination with BNT162b2 vaccine.

A traditional CVST risk factor was reported in 20 (11%) and 4 (15%) cases in the ChAdOx1 nCov-19 and mRNA vaccine groups, respectively, whereas a CVST risk factor was identified in 64 (64%) patients in the pre-COVID-19 cohort group (Table 1). Among patients with thrombocytopenia in the ChAdOx1 nCov-19 group, 10 (9%) had an additional risk factor reported (see Table S3 in the appendix).

Thrombocytopenia was reported in 107/187 cases (57%, 95%CI 50-64%) in the ChAdOx1 nCov-19 group, none in the mRNA vaccine group (95%CI 0-13%), and 7/100 (7%, 95%CI 3-14%) in the pre-COVID-19 CVST group. Among patients with thrombocytopenia in the ChAdOx1 nCov-19 vaccine group, the median of the lowest reported platelet count was $31x10^3/\mu L$ (IQR 17-64, reported in 57/107 cases, 53%). Antibodies against platelet factor 4 were reported to be present in 15 cases in the ChAdOx1 nCov-19 group and in none in the mRNA vaccine group. There was no information on the number of patients tested for these antibodies.

In 22 patients (12%, 95%CI 8-17%) in the ChAdOx1 nCov-19 vaccine group a concomitant VTE in addition to CVST was reported, compared to none in the mRNA vaccine group (95%CI 0-13%) and 9 (9%, 95%CI 5-16%) in the pre-COVID-19 group (Table 1). Of the 107 patients with thrombocytopenia in the ChAdOx1 nCov-19 vaccine group, a concomitant VTE was reported in 19 (18%, 95%CI 12-26%) (see Table S3 in the appendix).

A COVID-19 PCR test performed within 30 days from CVST symptom onset was reported in 39 (21%) cases in the ChAdOx1 nCov-19 vaccine group and in 6 (23%) in the mRNA vaccine group (Table 1). All reported COVID-19 PCR tests were negative in both groups.

Of the 117 patients with a reported outcome in the ChAdOx1 nCov-19 vaccine group, 44 (38%, 95%CI 29-47%) had died, compared to 2/10 (20%, 95%CI 6-51%) in the mRNA vaccine group and 3 (3%, 95%CI 1-8%) in the pre-COVID-19 group. Among patients with thrombocytopenia in the ChAdOx1 nCov-19 vaccine group, 39/79 (49%, 95%CI 39-60%) patients with reported outcome died (see Table S3 in the appendix).

Discussion

Using the EMA pharmacovigilance database and pre-COVID-19 CVST cases as a historical control group, we found that CVST reported after ChAdOx1 nCov-19 vaccination: (1) was notified more frequently than after the BNT162b2 and mRNA-1273 vaccines; (2) was associated in approximately half of patients with thrombocytopenia, with no thrombocytopenia reported for any patient following a mRNA vaccine; (3) was associated with positive anti-platelet factor 4 antibodies in some patients; (4) was accompanied in 1/8 patients by other concomitant venous thrombotic events; (5) was associated with a high mortality rate, both when compared to CVST after mRNA vaccines or historical CVST controls, and (6) was infrequently associated with traditional CVST risk factors, which were present in two thirds of historical CVST controls.

The confirmation that CVST arising after vaccination with the ChAdOx1 nCov-19 vaccine has distinct features further supports causality in this association, together with the consistent temporal sequence, and the identification of a putative pathophysiological mechanism (2-4).

Nevertheless, investigations for potential alternate causes are necessary to establish causality. COVID-19 itself is associated with an increased risk of CVST (15, 16), and therefore the hypothesis of mild or undiagnosed SARS-CoV-2 infection has been suggested as a possible contributing factor for the post-vaccination CVST cases. However, the current data make this hypothesis unlikely, since none of the patients with post-vaccination CVST tested positive for SARS-CoV-2 infection.

The features of CVST occurring after the mRNA vaccines should also be noted. Besides the lower frequency, we found no differences in the clinical profile when compared with historical controls. This suggests absence of an association, as CVST can occur by chance in the month following vaccination due to the background incidence. CVST can occur by chance either in association with any of the established risk factors or in the absence of any identified precipitant for CVST, as it has been previously described in about 15% of patients in the pre-COVID-19 era (17).

Another important finding was the identification of CVST in 21 subjects (of whom 13 had thrombocytopenia) above the age of 60 after the ChAdOx1 nCov-19 vaccine. Although this is somehow in disagreement to past reports (2, 3), it should be noted that because of the small sample size and absent denominator, no robust conclusions regarding incidence by age groups can be drawn, especially since the age and sex distribution of persons receiving each type of vaccine in Europe is not yet exactly known, and in several

European countries the ChAdOx1 nCov-19 vaccine was initially used predominantly in persons under 65, whereas the mRNA vaccines were mostly administered in the elderly. The fact that Health Care Workers, where women are more frequent than males, had priority for vaccination, may contribute to explain the female predominance, on CVST after both COVID-19 vaccines. Given the small sample size and wide confidence intervals, no firm conclusions can be drawn from the mortality rate of CVST after mRNA vaccines.

Our study has some strengths in comparison with previous reports of CVST after anti-SARS-CoV-2 vaccines. It used a centralized European pharmacovigilance database that includes several hundreds of notified cases irrespective of the applied vaccine. This allowed us to describe CVST cases occurring after any type of vaccine, irrespective of platelet count values. We centrally reviewed not only cases reported as CVST, but also cases signalled as intracerebral haemorrhages or thrombocytopenia, who could have CVST as a secondary diagnosis. Additionally, we used a historical control group of CVST, registered in the International CVST consortium database in the last years before the COVID-19 pandemic.

The study also has several limitations. First, the main purpose of the European pharmacovigilance database is to register and signal unexpected adverse events, not previously detected in the clinical trials that were used to register those vaccines. These notifications are often focused on the adverse effect and generally do not provide detailed clinical information necessary for further research on the topic, resulting in a large number of notifications with missing information and limiting the number of variables that can be analysed. Especially data on traditional risk factors and frequency of positive PF4 antibodies should be interpreted with caution. Second, despite the broadness of the EudraVigilance database, there is still a possibility of selective or underreporting, since there is no method to determine with certainty if all CVST cases that occurred after SARS-CoV-2 vaccination were notified to EMA. Selective reporting could have also been influenced by the widespread media attention, particularly focused on the ChAdOx1 nCov-19 vaccine. Selective reporting of more severe cases is a possibility, whereas less severe cases might not have been diagnosed, recognized as an ADR or reported. Third, higher mortality in CVST vaccine associated cases, may be partly explained by less experience in managing CVST in centres notifying ADRs, in comparison with the three high-volume academic centres participating in the registry. Additionally, at the time of the inaugural reports of CVST after vaccination, there was limited experience in treating CVST with thrombocytopenia. Fourth, diagnosis and quality of information were not centrally validated, and thus accuracy of the diagnoses is unknown. Fifth, we could not analyse CVST occurring after the Ad26.COV2.S vaccine, because no cases were reported in European countries during the study period. Finally, we did not calculate the absolute risk of CVST occurring after SARS-CoV-2 vaccination, as the detailed information on the denominator, namely the number of vaccinated Europeans by age and sex strata, was not available, but is likely to be different between the two types of vaccines.

Despite the robust information on the profile of CVST occurring after the different SARS-CoV-2 vaccines in the present study, further prospective registries with more detailed information on clinical, imaging and laboratory results and outcome are needed (14).

In conclusion, analysis of the EMA pharmacovigilance database shows that CVST occurring after the ChAdOx1 nCov-19 vaccine has a clinical profile that is different from patients with CVST unrelated to vaccination. CVST after ChAdOx1 nCov-19 is associated with thrombocytopenia in approximately half of reported patients and has a high mortality rate. CVST cases occurring after mRNA vaccines were similar to pre-COVID-19 CVST cases, pointing towards background incidence rather than association with the vaccine.

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Not applicable.

Author contributions

Conceptualization: MA, JMC and JMF. Data curation: KK, MRH, MSK and SMS. Formal analysis: KK and MSK. Investigation: KK, MRH, MSK, TH, SH, SMS, MML, JAKH, TT, JP, DAS, SM, MA, JMC, JMF. Project administration: KK, MRH, MSK. Resources: MA, JP, JMC, JMF. Supervision: MA, JMC and JMF. Validation and visualization: KK and MSK. Writing, original draft: KK, MRH, DAS, MA, JMC and JMF. Writing, review& editing: KK, MRH, MSK, TH, SH, SMS, MML, JKH, EL, KJ, TT, JP, DAS, SM, MA, JMC, JMF.

KK and JMC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interest

All authors have completed the ICMJE uniform disclosure form.

KK, MSK, TH, SMS, MML, KJ, and JAKH have nothing to disclose.

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DAS reports travel support from Boehringer Ingelheim, DSMB participation for the SECRET trial, and being a member of the ESO Executive Committee.

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Statement of Ethics

The corresponding author affirms that this research complies with internationally-accepted standards for research practice and reporting.

Data Availability Statement

Deidentified participant data from the EudraVigilance database are not publicly available, but upon official request (outlined in the methods) may be obtained from the European Medicine Agency. Data from the international CVST consortium are available upon reasonable request from the corresponding author.

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Tables

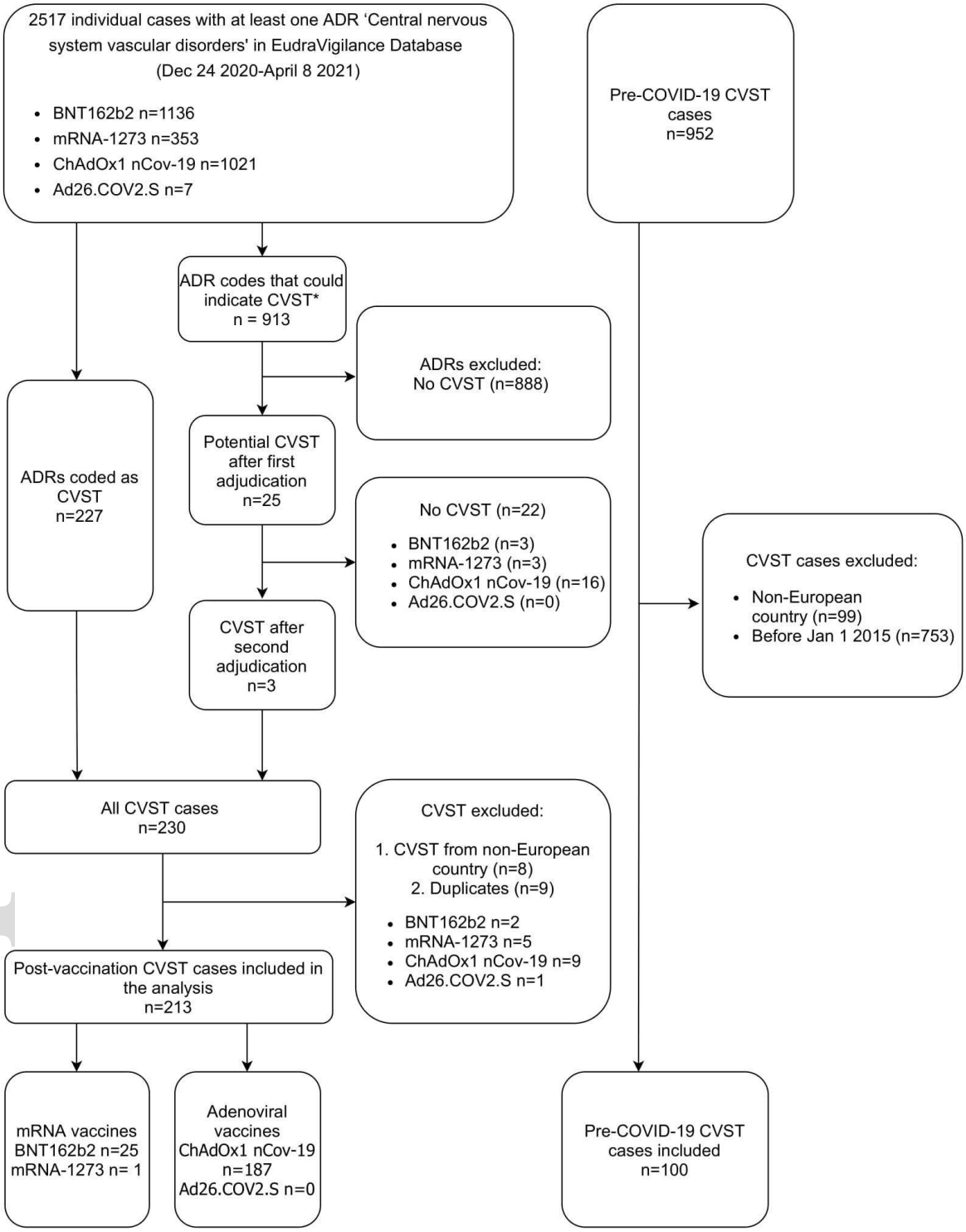
Table 1. Comparison of CVST cases after ChAdOx1 nCov-19, mRNA vaccines and pre-COVID-19 CVST cases from the International CVST Consortium

Variable	ChAdOx1 nCov-19 vaccine n=187	mRNA vaccines n=26	pre-COVID-19 CVST cases n=100
Age categories			
Age 0-29	25/124 (20%)	1/22 (5%)	19/100 (19%)
Age 30-59	78/124 (63%)	10/22 (45%)	62/100 (62%)
Age ≥60	21/124 (17%)	11/22 (50%)	19/100 (19%)
Female	138/184 (75%)	20/26 (77%)	66/100 (66%)
Male	46/184 (25%)	6/26 (23%)	34/100 (34%)
Any CVST risk factor reported[a]	20/187 (11%)	4/26 (15%)	64/100 (64%)
Oral contraceptive use reported[b]	16/79 (20%)	1/7 (14%)	30/56 (54%)
Thrombocytopenia reported[c]	107/187 (57%) 95%CI (50-64%)	0/26 (0%) 95%CI (0-13%)	7/100 (7%) 95%CI (3-14%)
Concomitant VTE reported	22/187 (12%)[d] 95%CI (8-17%)	0/26 (0%) 95%CI (0-13%)	9/100 (9%)[e] 95%CI (5-16%)
COVID-19 PCR test performed[f]	39/187 (21%)	6/26 (23%)	NA
Mortality	44/117 (38%) 95%CI (29-47%)	2/10 (20%) 95%CI (6-51%)	3/100 (3%) 95%CI (1-8%)

CVST: cerebral venous sinus thrombosis, VTE: venous thromboembolic events, PCR: polymerase chain reaction; [a] Risk factors included: cancer, hormone replacement therapy or oral contraceptive use, genetic thrombophilia, any concomitant infection; [b] Percentage of women under the age of 60; [c] Thrombocytopenia was defined as a platelet count of <150 x10^3/µL; [d] Concomitant VTEs: splanchnic vein thrombosis (n=11), pulmonary embolism (n=9), deep vein thrombosis (n=4), pelvic/renal vein thrombosis (n=3), vena cava thrombosis (n=1), retinal thrombosis (n=1), unknown (n=1). A total of 30 VTEs reported in 22 patients. [e] For the control group we defined all VTEs occurring within a range of ±30 days from the CVST symptom onset as concomitant VTEs; [f] COVID-19 PCR test performed within a range of ±30 days from the CVST symptom onset. All reported tests were negative.

Figures

Figure 1. Selection of CVST cases in the EudraVigilance database



* See Table S1 in the appendix for the full list.
ADR: Adverse drug reaction. CVST: cerebral venous sinus thrombosis

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