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Sex differences in cerebral venous sinus thrombosis after adenoviral vaccination against COVID-19

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Abstract

Introduction: Cerebral venous sinus thrombosis associated with vaccine-induced immune thrombotic thrombocytopenia (CVST-VITT) is a severe disease with high mortality. There are few data on sex differences in CVST-VITT. The aim of our study was to investigate the differences in presentation, treatment, clinical course, complications, and outcome of CVST-VITT between women and men.

Patients and methods: We used data from an ongoing international registry on CVST-VITT. VITT was diagnosed according to the Pavord criteria. We compared the characteristics of CVST-VITT in women and men.

Results: Of 133 patients with possible, probable, or definite CVST-VITT, 102 (77%) were women. Women were slightly younger [median age 42 (IQR 28–54) vs 45 (28–56)], presented more often with coma (26% vs 10%) and had

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a lower platelet count at presentation [median (IQR) 50x10^9/L (28–79) vs 68 (30–125)] than men. The nadir platelet count was lower in women [median (IQR) 34 (19–62) vs 53 (20–92)]. More women received endovascular treatment than men (15% vs 6%). Rates of treatment with intravenous immunoglobulins were similar (63% vs 66%), as were new venous thromboembolic events (14% vs 14%) and major bleeding complications (30% vs 20%). Rates of good functional outcome (modified Rankin Scale 0-2, 42% vs 45%) and in-hospital death (39% vs 41%) did not differ.
Discussion and conclusions: Three quarters of CVST-VITT patients in this study were women. Women were more severely affected at presentation, but clinical course and outcome did not differ between women and men. VITT-specific treatments were overall similar, but more women received endovascular treatment.

Keywords
VITT, CVST, sex differences

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Introduction

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare but severe adverse reaction after adenoviral vaccination for SARS-CoV-2.[1] It may cause thromboses at multiple sites and in multiple vascular beds, cerebral venous sinus thrombosis (CVST) being the most frequent and strongly associated with mortality.[2] Previous reports on VITT have shown conflicting results, with some reporting a higher frequency in women,[3–5] while others found no difference in frequency of VITT in women and men.[2,6] However, reports on patients with CVST associated with VITT (CVST-VITT) consistently found a higher proportion of affected women than men.[7,8]

There is a lack of data about the clinical characteristics of CVST-VITT in women compared to men. The aim of this study was to compare the presentation, treatment, clinical course, complications, and outcome of CVST-VITT in women and men.

Methods

We used data from an ongoing international registry on CVST-VITT, details of which have been reported previously.[9] In short, this is a registry-based study. Investigators were asked to report consecutive patients who developed CVST within 28 days of any SARS-CoV-2 vaccination.

Data were collected using a standardized electronic case report form (Castor EDC, Ciwit B.V., Amsterdam, The Netherlands). The ethical review committee of the Academic Medical Center in Amsterdam approved this observational cohort study. Each center was responsible for obtaining permission from local authorities if required by national and local law. The study was endorsed by the European Academy of Neurology and European Stroke Organisation.

We included patients reported until January 10, 2023 with possible, probable, or definite CVST-VITT according to the criteria proposed by an expert hematology panel by the British Society for Haematology as described by Pavord et al.[2] For the assessment of anti-platelet factor 4 (anti-PF4) antibodies, we accepted all types of tests, as reported by the investigators. In all cases, CVST was confirmed radiologically or at autopsy, and symptom onset was within 28 days of SARS-CoV-2 vaccination. Coma was defined as Glasgow Coma Scale score <9 points. Non-haemorrhagic lesions were defined as edema or venous infarction. Major bleeding was defined according to International Society of Thrombosis and Haemostasis criteria.[10] For outcome analysis, we dichotomized the modified Rankin Scale at discharge in 0–2 (favorable outcome) and 3–5 (poor outcome). The VITT-specific treatments included immunomodulatory treatment such as intravenous immunoglobulins or plasma exchange, avoidance of heparins, and avoidance of platelet transfusions, unless required for surgery.[11] Female specific risk factors for CVST were defined as oral contraceptive use, pregnancy, or recent childbirth. Conventional risk factors for CVST were defined as infection, previous venous thromboembolism, genetic or acquired thrombophilia, or cancer within the past 10 years. For thrombus load, the number of sinuses or veins that were thrombosed were added.[12]

Data analysis

We used descriptive statistics for baseline characteristics, treatment, complications during hospitalization, and outcome. We used Mann–Whitney U test, Chi-square, Fisher's exact, or Fisher-Freeman-Holton test, as appropriate, to determine significance and considered a two-sided probability value below 0.05 as significant. Confidence intervals were calculated using Wilson's method. The number of missing values for each variable is reported. Analyses were performed with IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, N.Y., USA).

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

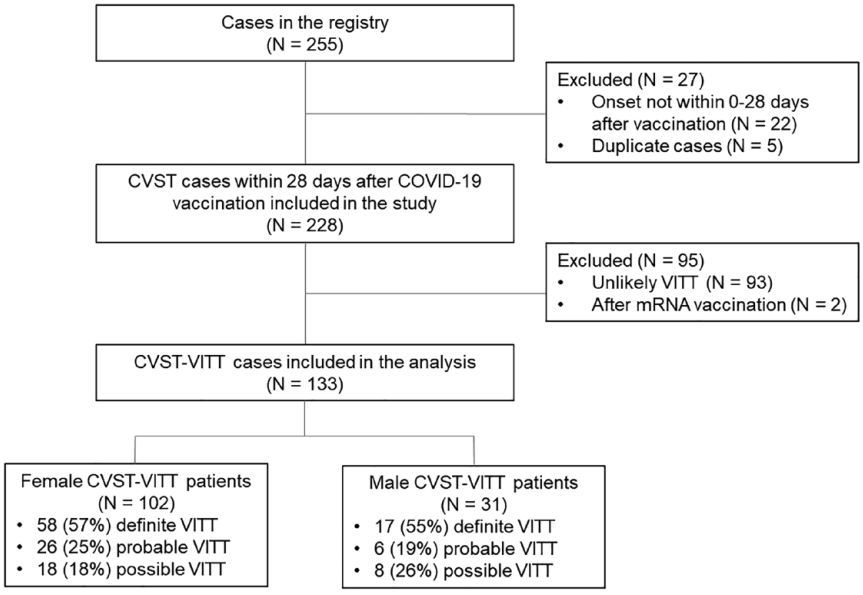

Figure 1. Flowchart of patient selection.
CVST: cerebral venous sinus thrombosis; VITT: vaccine-induced immune thrombotic thrombocytopenia.

Results

Of the 255 patients entered in the registry, 22 were excluded due to onset of symptoms more than 28 days after, or prior to vaccination, 5 were duplicates, 93 had unlikely VITT, and 2 had VITT after mRNA vaccination, leaving 133 cases for analysis (Figure 1).

Of the 133 included cases, 102 (77%) were women and 31 (23%) were men. Women were slightly younger than men (median age 42 [IQR 28–54] vs 45 [28–56], respectively). The time from vaccination to symptom onset (9 days [IQR 7–11] vs 10 days [7–11]) and from symptom onset to diagnosis (3 days [IQR 2–6] vs 3 days [1–6]) was similar in women and men. At the time of CVST-VITT diagnosis, 14/102 (14%) women had an intake of oral contraceptives and one was pregnant. Conventional risk factors for CVST did not differ between women and men (Table 1).

More women presented with coma (26% [95%CI 18–35] vs 10% [3–26]) and in women the platelet count at presentation was lower (50×10^9/L [IQR 28–79] vs 68 [30–125], $p = 0.049$). More women had thrombosis in the deep venous system (14% [95%CI 8–22] vs 0% [0–11], $p = 0.039$). The thrombus load and presence of haemorrhagic and non-haemorrhagic lesions did not differ between the groups.

The nadir of platelet count was lower in women than in men (median [IQR]: 34 [19–62] vs 53 [20–92]). During hospitalization, occurrence of new venous thromboembolism (14% [95%CI 8–22] vs 14% [6–31]) and bleeding complications (36% [95%CI 27–46] vs 27% [14–44]) had similar proportions in both women and men.

More women received endovascular treatment than men (15% [95%CI 9–23] vs 6% [2–21]). The proportions of VITT-specific treatments such as any immunomodulatory treatment (65% [95%CI 55–74] vs 76% [58–88]), any non-heparins as first anticoagulants (59% [95%CI 48–68] vs 68% [49–82]) or platelet transfusions (24% [95%CI 17–33] vs 28% [15–46]) were similar.

In women and men, functional outcome at discharge for modified Rankin Scale (mRS) 0–2 (41/98 [42%, 95%CI 33–52] vs 13/29 [45% 28–62]), mRS 3–5 (19/98 [19%, 95%CI 13–28] vs 4/29 [14% 5–31]) and in-hospital mortality (38/98 [39%, 95%CI 30–49] vs 12/29 [41% 26–59]) did not differ (Figure 2). Also there were no differences regarding the discharge disposition.

In an exploratory analysis of cases who were comatose and had a severe thrombocytopenia (platelet count $< 50 \times 10^9$/L) at presentation, 20/133 (15%) patients were selected. Of these, 19 were women and one was a man. The male patient had a recent lumbar puncture, but no other risk factors for CVST. Of the female patients, two used prothrombotic medication (one of which oral contraceptives), one patient was pregnant, one patient had a history of autoimmune disease, and one patient was obese without oral contraceptive use. The other patients had no known risk factors for CVST.

Discussion

The main findings of our analysis of sex differences in our multicenter cohort study are: (1) three quarters of CVST-VITT patients were women, (2) women were slightly younger and women appeared to be more severely affected at presentation with higher frequency of coma and lower admission platelet counts, and (3) VITT-specific treatments,

Table 1. Patient characteristics of female and male CVST-VITT patients.

	Female CVST-VITT patients (*N* = 102)	Male CVST-VITT patients (*N* = 31)	*P* value
Baseline characteristics, n/N (%)			
Age at diagnosis, median (IQR), years	42 (28–54)	45 (28–56)	0.731
Conventional CVST risk factors			
Oral contraceptive use	14/102 (14)	N/A	
Pregnancy	1/102 (1)	N/A	
Recent delivery[†]	0/102	N/A	
Infection	4/102 (4)	3/31 (10)	0.353*
Previous VTE	2/102 (2)	0/31	>0.999*
Thrombophilia	1/102 (1)	1/31 (3)	0.413*
Cancer[††]	3/102 (3)	2/31 (6)	0.331*
SARS-CoV-2 vaccine			0.160*
ChAdOx1 nCoV-19	91/102 (89)	24/31 (77)	
Ad26.COV2.S	5/102 (5)	5/31 (16)	
BBIBP-CorV	3/102 (3)	1/31 (3)	
Sinovac	3/102 (3)	1/31 (3)	
Time from vaccination to symptom onset, median (IQR), days	9 (7–11)	10 (7–11)[a]	0.893
Time from symptom onset to diagnosis, median (IQR), days	3 (2–6)	3 (1–6)[b]	0.858
Focal neurologic deficits at presentation	57/99 (58)	17/31 (55)	0.788
Coma at presentation (GCS < 9)	25/97 (26)	3/30 (10)	0.069
Seizure at presentation	15/100 (15)	5/31 (16)	>0.999*
Concomitant VTE at presentation[†††]	23/97 (24)	6/29 (21)	0.734
Splanchnic vein thrombosis	9/97 (9)	2/29 (7)	>0.999*
Deep vein thrombosis	4/97 (4)	1/29 (3)	>0.999*
Pulmonary embolism	14/97 (14)	3/29 (10)	0.760*
Pelvic vein thrombosis	5/97 (5)	0/29	0.589*
Other thrombosis	1/97 (1)	0/29	>0.999*
Laboratory data, n/N (%)			
Thrombocytopenia at any time during admission	100/102 (98)	30/31 (97)	0.552*
Platelet count at presentation, median (IQR), $\times 10^9$/L	50 (28–79)	68 (30–125)	**0.049**
Platelet count nadir, median (IQR), $\times 10^9$/L	34 (19–62)	53 (20–92)	0.163
Anti-PF4 antibodies			0.891*
Positive	72/102 (71)	22/31 (71)	
Negative	8/102 (8)	3/31 (10)	
Not tested or unknown	22/102 (22)	6/31 (19)	
D-dimer level >4 µg/mL FEU			
>4 µg/mL FEU	82/102 (80)	24/31 (77)	
2–4 µg/mL FEU	8/102 (8)	4/31 (13)	
<2 µg/mL FEU	3/102 (3)	1/31 (3)	
Not tested or unknown	9/102 (9)	2/31 (6)	
INR, median (IQR)	1.1 (1.1–1.3)[c]	1.2 (1.1–1.3)[d]	0.291
aPTT, median (IQR), seconds	29 (25–34)[e]	30 (26–34)[f]	0.402
Hemoglobin level, median (IQR), mmol/L	7.9 (7.5–8.5)[g]	9.1 (7.9–9.7)[h]	<**0.001**
Baseline imaging, n/N (%)			
Thrombosis location[†††]			
Superior sagittal sinus	53/102 (52)	17/31 (55)	0.779
Transverse or sigmoid sinus	80/102 (78)	23/31 (74)	0.621
Straight sinus	20/102 (20)	2/31 (6)	0.084
Deep venous system[‡]	14/102 (14)	0/31	**0.039***
Thrombus load, median (IQR)[‡‡]	3 (2–4)[i]	2 (1–4)	0.239
Intracranial hemorrhagic lesion	68/99 (69)	20/31 (65)	0.665

(continued)

Table 1. (Continued)

	Female CVST-VITT patients (*N* = 102)	Male CVST-VITT patients (*N* = 31)	*P* value
Non-hemorrhagic lesions	28/96 (29)	7/29 (24)	0.597
Treatment data, n/N (%)			
Any anticoagulant treatment	87/101 (86)	28/31 (90)	0.761*
Non-heparin received as first anticoagulant	51/87 (59)	19/28 (68)	0.384
Any immunomodulatory treatment	65/100 (65)	22/29 (76)	0.272
Intravenous immunoglobulin	63/100 (63)	19/29 (66)	0.804
Plasma exchange	6/100 (6)	0/29	0.336*
Corticosteroids	32/100 (32)	7/29 (24)	0.417
Eculizumab	2/100 (2)	0/29	>0.999*
Rituximab	1/100 (1)	0/29	>0.999*
Platelet transfusion	24/100 (24)	8/29 (28)	0.694
Endovascular treatment	15/101 (15)	2/31 (6)	0.358*
Decompressive neurosurgery	27/101 (27)	8/31 (26)	0.919
Intensive care unit admission	79/99 (80)	25/31 (81)	0.918
Clinical events during admission, n/N (%)			
New VTE	13/96 (14)	4/28 (14)	>0.999*
Splanchnic vein thrombosis	5/96 (5)	1/28 (4)	>0.999*
Deep vein thrombosis	4/96 (4)	2/28 (7)	0.617*
Pulmonary embolism	4/96 (4)	3/28 (11)	0.190*
Pelvic vein thrombosis	2/96 (2)	0/28	>0.999*
Other thrombosis	1/96 (1)	1/28 (4)	0.402*
Bleeding complication	35/98 (36)	8/30 (27)	0.359
Major bleeding‡‡‡	29/96 (30)	6/30 (20)	0.276
Discharge data, n/N (%)			
Duration hospital admission, median (IQR), days	8 (3–17)[j]	6 (2–14)[k]	0.560
Discharge disposition			0.780*
Home	44/101 (44)	11/29 (38)	
Rehabilitation center	16/101 (16)	6/29 (21)	
Other hospital	3/101 (3)	0/29	
Deceased	38/101 (38)	12/29 (41)	
mRS score at discharge			0.790
mRS 0–2	41/98 (42)	13/29 (45)	
mRS 3–5	19/98 (19)	4/29 (14)	
mRS 6 (dead)	38/98 (39)	12/29 (41)	

aPTT: activated partial thromboplastin time; CVST: cerebral venous sinus thrombosis; FEU: fibrinogen equivalent units; GCS: Glasgow Coma Scale; INR = international normalized ratio; IQR: interquartile range; mRS: modified Rankin Scale; PF4: platelet factor 4; VITT: vaccine-induced immune thrombotic thrombocytopenia; VTE: venous thromboembolism.

†within 12 weeks; ††in the past 10 years; †††multiple possible; ‡vein of Galen, internal cerebral veins, basal vein of Rosenthal, or inferior sagittal sinus; ‡‡ thrombus load: number of thrombosed sinus/veins (superior sagittal sinus, transverse sinus, sigmoid sinus, torcula, straight sinus, deep venous system, cavernous sinus, cortical vein, cerebellar vein, jugular vein); ‡‡‡according to the International Society of Thrombosis and Haemostasis (ISTH) criteria.

Missing values: [a]Two missing values; [b]Two missing values; [c]Fifteen missing values; [d]Seven missing values; [e]Twenty missing values; [f]Seven missing values; [g]Nine missing values; [h]Three missing values; [i]One missing value; [j]Three missing values; [k]Three missing values.

*Fisher's exact test or Fisher-Freeman-Holton Test. Significant *p* values are in bold.

complications during hospitalization, clinical outcome, and in-hospital mortality did not differ between sexes.

The higher proportion of women with CVST-VITT is in-line with previous reports.[7,8] A direct pathophysiological link between female sex and risk of CVST-VITT cannot be inferred from our observational study. Furthermore, we cannot rule out a selection bias, for example because healthcare workers, which comprise predominantly women, were more likely to be vaccinated against COVID-19 in an early stage before restrictions on adenoviral COVID-19 vaccinations were widely implemented.[13–15] In addition, there might have been a higher awareness of CVST-VITT in female patients since the majority of patients in reports on CVST-VITT were women and might therefore be more likely to undergo investigations in case of suspicion of CVST. In general, women are more likely to suffer from

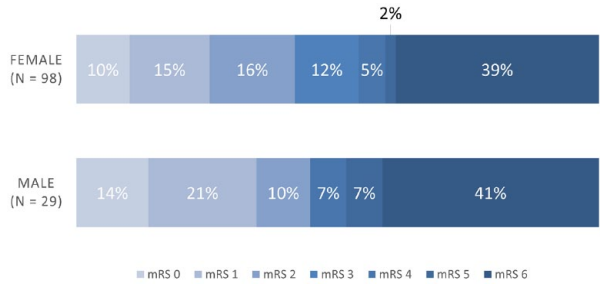

Figure 2. Modified Rankin Scale (mRS) score of women and men with cerebral venous sinus thrombosis due to vaccine-induced immune thrombotic thrombocytopenia (CVST-VITT) at discharge. There are four missing values in the female group and two missing values in the male group.

autoimmune disease given the more pronounced immune response to antigens and vaccines with higher antibody production and stronger T-cell activation, which could at least partially explain these findings.[16,17] Compared to historical CVST cohorts, a lower proportion of women with CVST-VITT had women-specific risk factors.[9]

In our study, the higher proportion of women with coma and lower platelet count at presentation is not explained by a delayed recognition and diagnosis. The number of days between vaccination to symptom onset and symptom onset to diagnosis was similar in both sexes. The higher proportion of women with thrombosis in the deep venous system might explain the higher rate of coma at presentation.[18,19] Additionally, the lower platelet count at admission and the lower nadir during hospitalization in women might reflect a more severe disease. However, the cerebral venous sinus thrombus load and haemorrhagic lesions at presentation, the new thromboses and bleeding rates during hospitalization as well as outcome were similar in both women and men. This could partially be explained by the similar VITT-specific treatments in both groups, especially the treatment with intravenous immunoglobulins (IVIG).[11] IVIG was previously shown to be effective in CVST-VITT.[1,11] The higher proportion of women treated with endovascular treatment might be explained by the more severe clinical presentation.

Our study has several limitations. First, the overall number of patients was low, precluding detection of significant differences, robust statistical comparisons and outcome analyses. Second, there was no central adjudication of reported data, as they have been collected from clinical routine records. Third, local funding and ethical constraints may have influenced the decision to participate in the study, and hence affected the actual consecutiveness of participating centers and reported cases.

In conclusion, in this international cohort, more women than men were reported with CVST-VITT. More women presented with more severe thrombocytopenia and coma compared to men and the nadir platelet count was lower in women. VITT-specific treatments were overall similar. Despite the more severe clinical presentation in women, clinical course and outcome did not differ between women and men.

**The Thrombosis with Thrombocytopenia Syndrome Study Group

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Informed consent

Not applicable

Ethical approval

The ethical review committee of the Academic Medical Center in Amsterdam approved this study. Each center was responsible for obtaining permission from local authorities if required by national and local law.

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Data sharing

The de-identified, individual participant data that underlie the results reported in this article can be made available to investigators whose proposed use of the data has been approved by the International Cerebral Venous Thrombosis Consortium Leadership. Proposals should be directed to the study's Principal Investigator (Dr. Jonathan Coutinho, email: j.coutinho@amsterdamumc.nl).

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