Thrombosis and Bleeding in Patients with Vaccine-Induced Immune Thrombotic Thrombocytopenia: A Systematic Review of Published Cases

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Abstract

Introduction Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a highly prothrombotic reaction to COVID-19 (coronavirus disease 2019) adenoviral vector vaccines. Its distinct bleeding and thrombotic patterns compared with other platelet consumptive disorders remain unclear.

Methods We performed a systematic review of the literature (PubMed and Embase) up to July 31, 2022, including case reports and case series providing nonaggregate data of VITT patients. Accurate VITT diagnosis required fulfillment of the following criteria: (1) endorsement by the authors, (2) consistent vaccine type and timing, (3) presence of thrombocytopenia and thrombosis, (4) detection of anti-platelet factor 4 antibodies. Data are presented as frequencies with 95% confidence intervals (CIs) calculated with the exact binomial method.

Results We retrieved 143 eligible studies, describing 366 patients. Of 647 thrombotic events, 53% (95% CI: 49–56) were venous thromboses at unusual sites and 30% (95% CI: 27–34) were cerebral venous sinus thromboses (CVSTs). The ratio of venous-to-arterial events was 4.1. Thromboses in most sites were associated with at least another thrombotic event, with the exception of CVST and CNS arterial thrombosis (isolated in 49 and 39% of cases, respectively). Bleeding occurred in 36% (95% CI: 31–41) of patients; 68% (95% CI: 59–75) of bleeding events were intracranial hemorrhages (ICHs). Overall mortality was 24% (95% CI: 19–29), and 77% (95% CI: 58–90) in patients with isolated CVST complicated by ICH.

Conclusion VITT displays a venous-to-arterial thrombosis ratio comparable to heparin-induced thrombocytopenia. However, VITT is characterized by a higher prevalence of CVST and ICH, which contribute to the increased bleeding frequency and mortality.

Keywords
- adenovirus
- platelet
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- thrombosis

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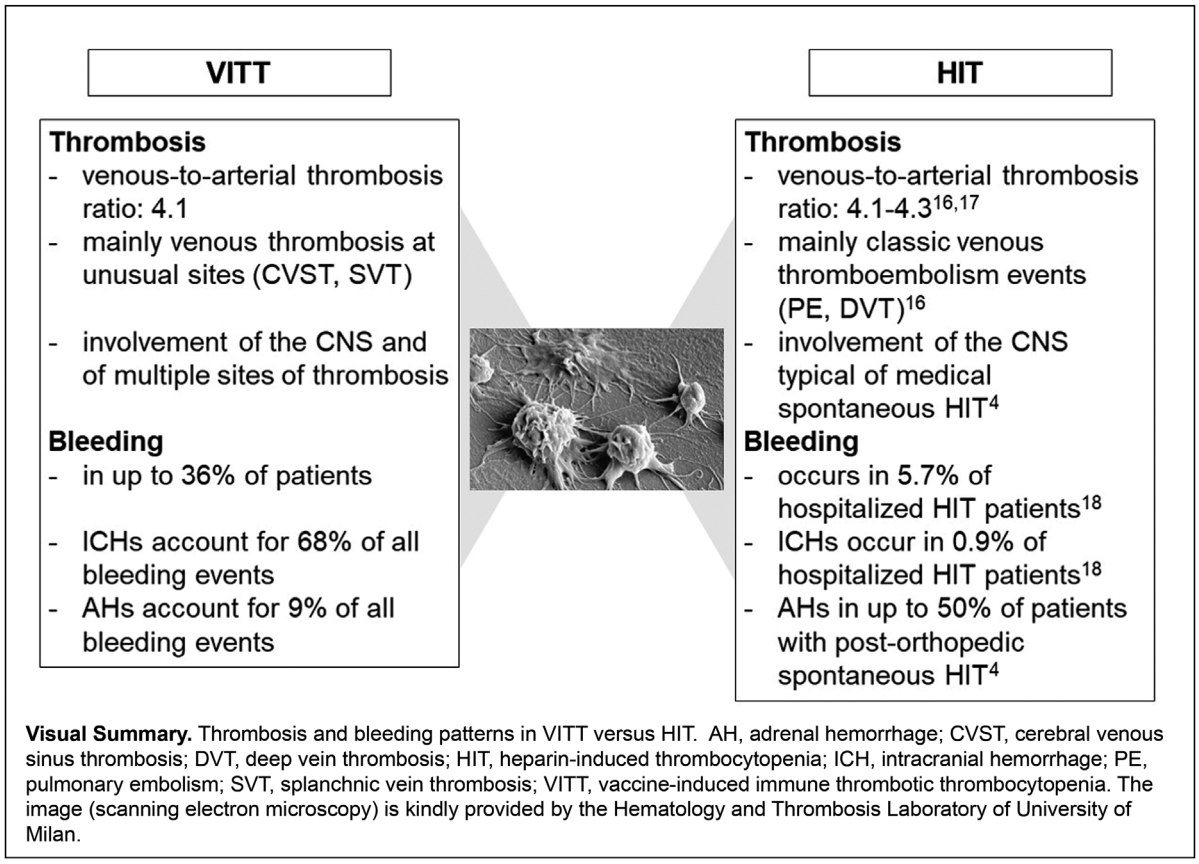

Visual Summary. Thrombosis and bleeding patterns in VITT versus HIT. AH, adrenal hemorrhage; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; ICH, intracranial hemorrhage; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; VITT, vaccine-induced immune thrombotic thrombocytopenia. The image (scanning electron microscopy) is kindly provided by the Hematology and Thrombosis Laboratory of University of Milan.

Background

The development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines has significantly contributed to the reduction of global morbidity and mortality from coronavirus disease 2019 (COVID-19). Notably, the ChAdOx1 nCov-19 vaccine, utilizing a replication-deficient simian adenovirus vector, has emerged as the most widely distributed vaccine worldwide, accounting for a staggering 3 billion doses administered. Impressively, this vaccine is estimated to have saved approximately 6.3 million lives globally within the first year of its deployment.[1] Vaccine-induced immune thrombotic thrombocytopenia (VITT) was first identified in February 2021 in recipients of ChAdOx1 nCov-19[2] and is caused by platelet-activating antibodies against platelet factor 4 (PF4).[3] The pathomechanism is similar to that of heparin-induced thrombocytopenia (HIT), but occurs in the absence of heparin exposure, similarly to spontaneous HIT.[4] The syndrome is associated primarily with adenoviral vector vaccines against SARS-CoV-2 (ChAdOx1 nCoV-19 and Ad26.COV2.S)[5] and is characterized by moderate-to-severe thrombocytopenia, which is frequently accompanied by thrombotic events.[6] Thrombosis can be either arterial or venous and is often located in unusual sites, with cerebral venous sinus thrombosis (CVST) and splanchnic vein thrombosis (SVT) among the most frequent events.[4] Although high-income countries have mainly used mRNA vaccines for COVID-19 vaccination campaigns, adenoviral vector vaccines have been extensively employed and are currently in use by developing countries due to their favorable storage profile.[7–9] VITT diagnosis is supported by diagnostic tests designed to detect anti-PF4 platelet-activating antibodies. These include enzyme-linked immunosorbent assays (ELISAs), which represent the screening test for the syndrome,[2,3,7] and platelet activation tests, which are useful confirmation tests.[2,3] Definitive VITT diagnosis requires specific criteria,[10] based on the current understanding of VITT clinical presentation and pathophysiology. However, the ratio of venous-to-arterial thrombotic events, their co-association, the frequency of bleeding, and how thrombosis and bleeding patterns compare with HIT remain unclear. Therefore, we performed a systematic review of the literature to investigate thrombotic and bleeding manifestations in patients with an accurate diagnosis of VITT.

Materials and Methods

PubMed and Embase were searched by two researchers (C.A. and B.P.) with a predefined research string [((((thrombosis) OR (thrombotic)) AND (vaccine)) AND (thrombocytopenia OR thrombocytopaenia)]. Our research was restricted to articles written in English, published from January 1, 2020, until July 31, 2022.

We included case reports and case series providing non-aggregate data of the clinical course of patients with an accurate diagnosis of VITT. We considered VITT diagnosis accurate if all of the following were met: (1) VITT diagnosis was supported by the authors, (2) symptoms manifested 4 to

42 days after adenoviral vector vaccine administration, (3) thrombocytopenia (defined as a platelet count $< 150 \times 10^9$/L) and at least one thrombotic event were present, and (4) diagnosis was confirmed by at least one laboratory test (either ELISA or functional platelet activation test) detecting anti-PF4 antibodies. We excluded studies or single patients of eligible studies if: (1) diagnosis of VITT was not supported by all of the criteria listed above, (2) patients' clinical features were absent, unclear, or presented in aggregate, (3) diagnostic test results were unclear, (4) patients had already been described in other eligible studies, and (5) diagnostic tests were performed on biological specimens collected *postmortem*. Eligibility assessment was performed at the title and/or abstract level by two reviewers (C.A. and B.P.), who independently assessed each study. Disagreements were solved by consensus or by a third reviewer (S.B.). Four reviewers (C.A., B.P., B.C., and E.P.) extracted the following relevant data from eligible studies: subject characteristics, study site, study period, patient demographics and clinical features, diagnostic tests performed and relative methods, diagnostic test results, and diagnostic test interpretation. Data conversions were performed to ensure homogeneity of laboratory results across studies (i.e., platelet counts, D-dimer levels). Retrieved data were recorded in a Microsoft Excel datasheet for subsequent analyses. We categorized thrombotic events into two types (venous and arterial) and into four categories: classic venous thromboembolism (VTE), venous thrombosis at unusual sites, cardio/cerebral arterial thrombosis, and aortic/peripheral artery thrombosis. Classic VTE events include deep vein thrombosis (DVT) in the upper and lower extremities, pulmonary embolism (PE), and/or superficial vein thrombosis. Venous thrombosis at unusual sites events include CVST, SVT, jugular vein thrombosis (JVT), and other sites of venous thrombosis. Cardio/cerebral arterial thrombosis includes arterial thrombosis of the central nervous system (CNS) and/or myocardial infarction (MI).

Continuous variables were described as means ± standard deviation or medians with ranges and interquartile ranges, according to their distribution. Categorical variables were described as proportions and percentages, with 95% confidence intervals (CIs) calculated with the exact binomial method. We performed a meta-analysis of the data using the random intercept logistic regression model and logit transformation, using the I^2 statistic as a measure of heterogeneity using R Core Team software, 2023. The results of this systematic review were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The study protocol was not registered.

Results

Study Selection

We retrieved 2,157 studies. Following the exclusion of 887 duplicates and 846 results at the title or abstract level, 424 full-text studies were evaluated for eligibility and 143 studies were included in the final analysis (►**Fig. 1**). The eligible studies provided data regarding 366 VITT patients, 647 thrombotic events, and 140 bleeding events. The details of all eligible studies can be found in ►**Supplementary Table S1** (available in the online version).

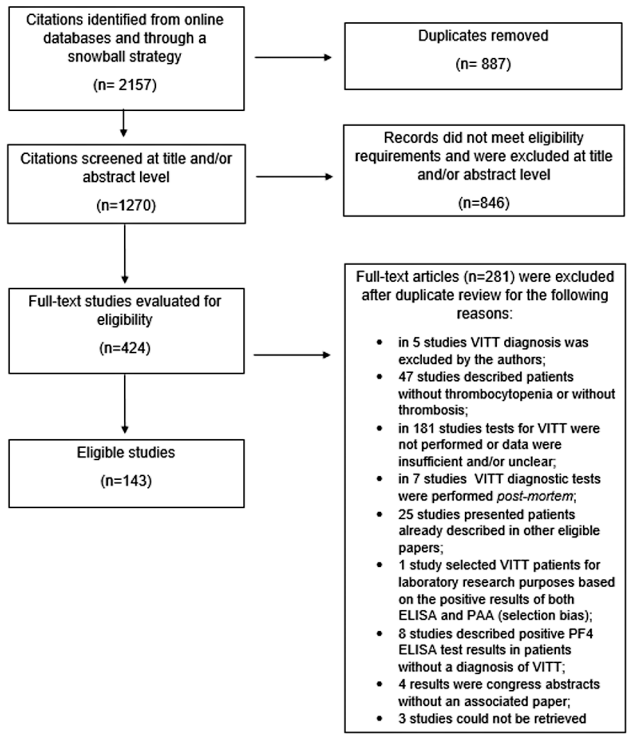

Fig. 1 Flowchart of study selection. VIIT, Vaccine-induced Immune Thrombotic Thrombocytopenia; PF4, Platelet Factor; ELISA, Enzyme-linked Immunosorbent Assay.

Patient Population

VITT patients' clinical characteristics are summarized in ►**Table 1**. Of the 366 eligible patients, 321 (88%, 95% CI: 84–91) had been vaccinated with ChAdOx1 nCoV-19, while 45 (12%, 95% CI: 9–16) had received Ad26.COV.2. In all patients for whom this information was available (229/229, 100%, 95% CI: 98–100), VITT occurred after the administration of the first dose of the involved adenoviral vector vaccine. The majority of cases (268/333, 80%) occurred in patients under 60 years. There was only a slight predominance of female patients (179/332, 54%, 95% CI: 48–59). The median time of symptom onset since vaccination was 9 days (range: 2–31). Most patients had a platelet count nadir below 50×10^9/L (149/236, 63%, 95% CI: 57–69). An elevation of the D-dimer above 500 mcg/L was found in almost all patients (212/214, 99%, 95% CI: 97–100). Outcomes were known for 290 patients; 69 (24%, 95% CI: 19–29) died. Meta-analyzed data were overall congruent (patients with platelet count nadir $<50 \times 10^9$/L, 65%, 95% CI: 56–72; mortality 13%, 95% CI: 7–25), although distorted by the small sample size of eligible studies and by the low frequency of events (►**Supplementary Table S2**, available in the online version).

All eligible patients had at least one thrombotic event, as documented thrombosis was part of our inclusion criteria. The proportion of patients with any bleeding event was 36% (131/366, 95% CI: 31–41).

Table 1 Clinical characteristics of eligible patients with vaccine-induced immune thrombotic thrombocytopenia

Patient characteristics	Total number of patients, $N = 366$	95% CI[a]
Type of vaccine, *n*/*N* (%)		
ChAdOx1 nCoV-19	321/366 (88)	84–91
Ad26.COV.2	45/366 (12)	9–16
Vaccine dose, *n*/*N* (%)		
First dose	229/229 (100)	98–100
Age, *n*/*N* (%)		
≤39 y	130/333 (39)	34–45
40–59 y	138/333 (41)	36–47
≥60 y	65/333 (20)	15–24
Sex, *n*/*N* (%)		
Male	153/332 (46)	41–52
Female	179/332 (54)	48–59
Time since symptom onset[b]		
Median days (range); number of patients	9 (2–31); 207	NA
Platelet count nadir, *n*/*N* (%)		
$< 50 \times 10^9$/L	149/236 (63)	57–69
$50–99 \times 10^9$/L	68/236 (29)	23–35
$100–149 \times 10^9$/L	19/236 (8)	5–12
D-dimer, *n*/*N* (%)		
> 500 mcg/L	212/214 (99)	97–100
> 10,000 mcg/L	149/214 (70)	63–76
Death, *n*/*N* (%)	69/290 (24)	19–29

Abbreviations: CI, confidence interval; NA, not applicable.
[a]95% confidence intervals were calculated using the exact binomial method.
[b]Four patients with otherwise compatible clinical presentation displayed a symptom onset within 4 days from vaccination.

Table 2 Thrombotic events in eligible patients with vaccine-induced immune thrombotic thrombocytopenia

Thrombosis according to site	Total number of events, $N = 647$	95% CI[a]
Venous thrombosis, *n*/*N* (%)		
DVT	59/647 (9)	7–12
PE	122/647 (19)	16–22
Total classic VTE events	181/647 (28)	25–32
CSVT	196/647 (30)	27–34
SVT	93/647 (14)	12–17
JVT	33/647 (5)	4–7
Others	18/647 (3)	2–4
Total venous thrombosis events at unusual sites	340/647 (53)	49–56
Total venous thrombotic events	521/647 (81)	77–84
Arterial thrombosis, *n*/*N* (%)		
CNS	46/647 (7)	5–9
AMI	15/647 (2)	1–4
Peripheral artery	22/647 (3)	2–5
Aorta	21/647 (3)	2–5
Others	22/647 (3)	2–5
Total arterial events	126/647 (19)	16–23

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CNS, central nervous system; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis (upper and lower extremities); JVT, jugular vein thrombosis; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; VTE, venous thrombo-embolism.
[a]95% confidence intervals were calculated using the exact binomial method.

Thrombotic Events

In our patient population, 647 thrombotic events were described (►**Table 2**). Most events were venous (521/647, 81%, 95% CI: 77–84). Classic VTE events accounted for 28% of all events (181/647, 95% CI: 25–32), with 59 DVTs and 122 PEs. Conversely, there were 340 venous thromboses at unusual sites (53% of all thrombotic events, 95% CI: 49–56). The most common sites for venous thrombosis at unusual sites were CVST (196/647, 30%, 95% CI: 27–34) and SVT (93/647, 14%, 95% CI: 12–17). One-hundred and twenty-six arterial thromboses were described, and accounted for 19% of all thrombotic events (95% CI: 16–23). The most common site of arterial thrombosis was the CNS (46/647, 7%, 95% CI: 5–9). The ratio of venous-to-arterial thrombotic events was 4.1 (521/126). The ratio of patients with venous thrombosis and arterial thrombosis was 3.8 (329/86).

►**Table 3** shows the co-association of thrombotic events. For each site of thrombosis, the frequency of isolated events ranged from 0% for JVT (95% CI: 0–11) and aortic thrombosis (95% CI: 0–16) to 49% for CVST (95% CI: 42–56). The frequency of association of arterial thrombotic events with venous thrombotic events ranged from 14% (95% CI: 3–36) for aortic thrombosis to 53% (95% CI: 27–79) for MI, whereas venous thrombotic events were less frequently associated with arterial thrombotic events (frequency ranging from 3 to 8%). The combination of multiple categories of thrombotic events was relatively frequent, ranging from 19% (95% CI: 10–31) for DVT to 62% (95% CI: 38–82) for aortic thrombosis. The commonest isolated thrombotic events were CVST (49%, 95% CI: 42–56) and CNS arterial thrombosis (39%, 95% CI: 25–55). The meta-analyzed data were predominantly consistent (proportion of venous events, 89%, 95% CI: 80–90; CVST, 29% of all thrombotic events, 95% CI: 25–34; isolated CVST, 47%, 95% CI: 38–57), notwithstanding the aforementioned biases (►**Supplementary Tables S3** and **S4**, available in the online version).

Bleeding Events

In our patient population, 140 bleeding events were reported (►**Table 4**). Most bleeding events were intracranial hemorrhages (ICHs), accounting for 68% (95% CI: 59–75) of all

Table 3 Association of thrombotic events in eligible patients with vaccine-induced immune thrombotic thrombocytopenia

Type of thrombosis[a]	Category of thrombosis[b]	Site of thrombosis	Isolated event, *n*/*N* (%, 95% CI[c])	Events associated with any other event of the same type		Events associated with any other event of a different type, *n*/*N* (%, 95% CI)	Combination of multiple categories of thrombotic events[d], *n*/*N* (%, 95% CI)
				Events associated with any other event in the same category, *n*/*N* (%, 95% CI)	Events associated with any other event in a different category, *n*/*N* (%, 95% CI)		
Venous thrombosis	Classic VTE	DVT	13/59 (22, 12–35)	18/59 (31, 19–44)	14/59 (24, 14–37)	3/59 (5, 1–14)	11/59 (19, 10–31)
		PE	29/122 (24, 17–32)	18/122 (15, 9–22)	42/122 (34, 26–44)	8/122 (7, 3–13)	25/122 (20, 14–29)
	Venous thrombosis at unusual sites	CVST	96/196 (49, 42–56)	31/196 (16, 11–22)	20/196 (10, 6–15)	6/196 (3, 1–7)	43/196 (22, 16–28)
		SVT	20/93 (22, 14–31)	17/93 (18, 11–28)	12/93 (13, 7–21)	7/93 (8, 3–15)	37/93 (40, 30–50)
		JVT	0/33 (0, 0–11)	16/33 (48, 31–66)	0/33 (0, 0–11)	1/33 (3, 0–16)	16/33 (48, 31–66)
Arterial thrombosis	Cardio/cerebral thrombosis	CNS	18/46 (39, 25–55)	0/46 (0, 0–8)	4/46 (9, 2–21)	14/46 (30, 18–46)	10/46 (22, 11–36)
		Myocardial infarction	3/15 (20, 4–48)	0/15 (0, 0–22)	0/15 (0, 0–22)	8/15 (53, 27–79)	4/15 (27, 8–55)
	Aortic/peripheral artery thrombosis	Peripheral thrombosis	1/22 (5, 0–23)	3/22 (14, 3–35)	2/22 (9, 1–29)	4/22 (18, 5–40)	12/22 (55, 32–76)
		Aortic thrombosis	0/21 (0, 0–16)	3/21 (14, 3–36)	2/21 (10, 1–30)	3/21 (14, 3–36)	13/21 (62, 38–82)

Abbreviations: CI, confidence interval; CNS, central nervous system; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis (upper and lower extremities); JVT, jugular vein thrombosis; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; VTE, venous thrombo-embolism.

[a]Type of thrombosis: thrombotic event involving the venous or arterial district.

[b]Category of thrombosis: sum of thrombotic events here classified as classic venous thromboembolic events (including deep vein thrombosis in upper and lower extremities, pulmonary embolism, and/or superficial vein thrombosis), venous thrombosis at unusual sites (comprehensive of cerebral sinus vein thrombosis, splanchnic vein thrombosis, jugular vein thrombosis), cardio/cerebral arterial thrombosis (including central nervous system thrombosis and myocardial infarction), and aortic/peripheral artery thrombosis (comprehensive of peripheral artery thrombosis and aortic thrombosis).

[c]95% confidence intervals were calculated using the exact binomial method.

[d]Includes multiple combination of thrombotic events involving different thrombosis categories: for example, a pulmonary embolism associated with a thrombosis in unusual site and an arterial thrombosis, or a pulmonary embolism associated with a deep venous thrombosis and a splanchnic vein thrombosis.

Table 4 Bleeding events in eligible patients with vaccine-induced immune thrombotic thrombocytopenia

Bleeding events	Total number of bleeding events, $N = 140$, n/N (%)	95% CI[a]
ICH	95/140 (68)	59–75
Skin	15/140 (11)	6–17
Adrenal gland	12/140 (9)	5–14
GIH	4/140 (3)	1–7
Other	14/140 (10)	6–16
Cases of ICH associated with CVST	79/95 (83)	74–90

Abbreviations: CI, confidence interval; CVST, cerebral venous sinus thrombosis; GIH, gastrointestinal hemorrhage; ICH, intracranial hemorrhage.
[a]95% confidence intervals were calculated using the exact binomial method.

bleeding events, followed at a distance by skin bleeding (11%, 95% CI: 6–17) and adrenal gland hemorrhage (9%, 95% CI: 5–14). Most—albeit not all—cases of ICH occurred in association with documented CVST (79/95, 83%, 95% CI: 74–90). Meta-analyzed data were overall congruent (ICH, 70% of all events, 95% CI: 54–83; ICH associated with CVST, 83%, 95% CI: 74–90), although distorted by the abovementioned biases (►**Supplementary Table S5**, available in the online version).

Mortality According to Thrombosis Site

►**Table 5** shows eligible patients' mortality according to thrombosis site (including only classic VTE, CVST, SVT, and arterial thrombosis). The mortality of patients with isolated events ranged from 5% (95% CI: 1–18) for isolated classic VTE to 37% (95% CI: 26–48) for isolated CVST. Notably, despite the limitations of the small sample size, the mortality of isolated CVST complicated by ICH was remarkably higher than that of isolated CVST noncomplicated by ICH (77 vs. 23%). Throughout all thrombosis sites, except for CVST, patients with more than one thrombosis had a higher mortality compared with patients with isolated thrombosis. Meta-analyzed data were overall congruent (mortality of isolated CVST: noncomplicated by ICH, 23%, 95% CI: 12–42; complicated by ICH, 77%, 95% CI: 59–88), although distorted by the abovementioned biases (►**Supplementary Table S6**, available in the online version).

Table 5 Mortality according to thrombosis site in eligible patients with vaccine-induced immune thrombotic thrombocytopenia[a]

Thrombosis site	Mortality, n/N (%)	95% CI[b]
Classic VTE[c]	17/113 (15)	9–23
Isolated	2/38 (5)	1–18
Associated with any other thrombosis	15/75 (20)	12–31
CVST	50/163 (31)	24–38
Isolated	30/82 (37)	26–48
Complicated with ICH	23/30 (77)	58–90
Noncomplicated with ICH	7/30 (23)	10–42
Associated with any other thrombosis	20/81 (25)	16–36
Complicated with ICH	13/20 (65)	41–85
Noncomplicated with ICH	7/20 (35)	15–59
SVT	16/75 (21)	13–32
Isolated	2/16 (13)	2–38
Associated with any other thrombosis	14/59 (24)	14–37
Arterial thrombosis	21/72 (29)	19–41
Isolated	6/28 (21)	8–41
Associated with any other thrombosis	15/44 (34)	20–50

Abbreviations: CI, confidence interval; CVST, cerebral venous sinus thrombosis; ICH, intracranial hemorrhage; SVT, splanchnic vein thrombosis; VTE, venous thrombo-embolism.
[a]Only patients with available information on mortality were included in this analysis.
[b]95% confidence intervals were calculated using the exact binomial method.
[c]Including deep vein thrombosis in upper and lower extremities, pulmonary embolism, and/or superficial vein thrombosis.

Discussion

Our study provides insight into the specific thrombotic and bleeding manifestations of VITT. In VITT, CVST, PE, and arterial CNS thrombosis are the most frequent venous and arterial thrombotic events, and, for most thrombotic sites, at least another thrombotic event is present in four out of five cases. Bleeding is prevalent, affecting 36% of patients with VITT, and ICH accounts for 68% of all bleeding events. Few systematic reviews of the literature have described thrombosis and bleeding patterns in VITT, and none have compared them to those of HIT and assessed the patterns of co-association of thrombotic events. To this end, we performed this systematic review, including only case reports and case series providing nonaggregate data of patients with an accurate diagnosis of VITT.

VITT is a rare condition, thus there are few reports of longitudinal patient cohorts. One of the largest VITT cohorts, including 220 definite or probable VITT cases identified up to June 6, 2021, in the United Kingdom, has been described by Pavord and colleagues.[11] In this cohort, the most common sites of thrombosis were CVST (110/220, 50%) and DVT and/or PE (82/220, 37%); arterial thrombosis occurred in 47 patients (21%), thrombosis of two or more vascular beds in 64 (29%), and ICH in 47 (21%). The data from Pavord et al's cohort study are consistent with our findings. Descriptions of long-term outcomes of VITT patients have emphasized the high in-hospital mortality of patients with VITT-related CVST (43/107, 40%) and the lack of further thrombotic events in

most patients while on anticoagulation.[12,13] Two systematic reviews provided results on thrombosis and bleeding frequencies that are overall consistent with ours (proportion of patients with CVST ranging from 54 to 59.4%[14,15]; mortality between 32 and 36.5%[14,15]; bleeding in 32.8% of patients[15]). However, in one study ($n = 664$ patients, scientific database search up to October 4, 2021), there was no predefined definition of VITT as part of the inclusion criteria,[14] and in the other ($n = 64$ patients, scientific database search up to June 24, 2021) all cases of documented thrombosis and/or bleeding after ChAdOx1 nCoV-19 were included.[15]

For our systematic review, we used a stringent definition of "accurate VITT diagnosis." Moreover, we performed a literature search up to July 31, 2022. It is likely that the inclusion of later descriptions of VITT is responsible for the lower mortality (24%, 95% CI: 19–29) observed in our patient population. In addition, in our study we elected to evaluate the co-association of thrombotic events and to perform meaningful comparisons with other platelet disorders, particularly HIT, but also thrombotic thrombocytopenic purpura (TTP) and immune thrombocytopenia (ITP). First, we found that, in VITT, the ratio of venous-to-arterial thrombotic events is 4.1. Strikingly, such a ratio is 4.1 to 4.3 in HIT.[16,17] However, compared with HIT, in VITT there is a greater proportion of venous thromboses at unusual sites, with CVST being the most frequent thrombotic event (30% of all thrombotic events in our patient population, 95% CI: 27–34), and a greater proportion, among arterial events, of stroke (37% of all arterial events). In a series of 65 HIT patients with thrombosis, 61 patients had DVT, 32 had PE, and only 2 patients had thrombotic stroke.[16] Notably, in medical spontaneous HIT, CVST and stroke are common occurrences.[4] Second, in our VITT patient population, 36% (131/366, 95% CI: 31–41) of patients experienced bleeding. This figure is considerably higher compared with reported bleeding rates in hospitalized patients with TTP, HIT, and ITP (13.7, 5.7, and 11.5%, respectively).[18] The higher frequency of bleeding in VITT patients is driven by the higher rate of ICH. In our patient population, 26% (95/366) of patients had an ICH, mostly associated with CVST (79/95, 83%, 95% CI: 74–90). Conversely, the rate of CNS bleeding in hospitalized patients with TTP, HIT, and ITP was 1.1, 0.9, and 1.0%, respectively.[18] Therefore, in VITT, bleeding occurs frequently, although mainly as a consequence of thrombosis. In fact, another common site of bleeding in our patient population was the adrenal gland (9% of all bleeding events, 95% CI: 5–14); notably, adrenal gland hemorrhage or necrosis is often secondary to outflow obstruction due to venous thrombosis, and has been reported in up to 50% of patients with post-orthopaedic surgery spontaneous HIT.[4] The thrombotic involvement of multiple vascular beds is a known feature of VITT,[11,14,15] and we show that most thrombosis sites were associated with at least another thrombotic event in four out of five cases, with the notable exception of CVST and CNS arterial thrombosis, which were isolated in 49 and 39% of cases, respectively. Lastly, we found an overall mortality of 24% (95% CI: 19–29) in our patient population. The mortality of HIT, on the contrary, ranges from 6.3 to 15.9%.[17] Our results suggest that, in VITT, the excess mortality is likely driven by CVST. In fact, across all thrombosis sites, except for CVST, mortality was higher in patients with nonisolated thrombosis.

Our study has some limitations. This was a systematic review based on results from two scientific databases (PubMed and Embase) and restricted to papers in English. Due to the low quality of available studies on VITT (mainly case reports and case series with high heterogeneity and low frequencies of observed events), the process of meta-analysis produced data distortion and an unreliable assessment of heterogeneity through the I^2 statistics (not shown). Moreover, the results of our study might have been skewed by publication bias and under-representation of descriptions of VITT from developing countries, where adenoviral vector vaccines are still widely used and tests to detect anti-PF4 antibodies are not available. For instance, we have included in our analysis only one report of VITT from a country with limited resources, a case series of two VITT patients from India: only one of the two patients was eligible due to the difficulty in obtaining anti-PF4 antibody testing results in the other.[19] We included the presence of documented thrombosis in our definition of VITT diagnosis. We think that this choice accounts for a more accurate identification of cases, although it prevented us from describing the proportion of patients presenting with isolated bleeding. Finally, we described thrombotic and bleeding events as a proportion of all events, instead of the proportion of patients with any thrombotic or bleeding event. This approach prevents direct comparisons with previous systematic reviews or cohort studies on VITT and HIT, but better serves the purpose of showing the association of thrombotic events and of calculating the ratio of venous-to-arterial thrombosis in VITT.

Despite these limitations, this study, based on stringent inclusion criteria and including studies published up to July 31, 2022, not only provides confirmation to previous findings on VITT,[11,14,15] but also highlights its differential aspects compared with other platelet-consumptive disorders. VITT emerges as a highly prothrombotic disorder with a tropism for the CNS, demonstrated by the high frequency of CVST and CNS arterial thrombosis. Elucidating the reasons for the neurotropism of VITT is beyond the scope of this article, although it has been hypothesized that, in VITT, thrombosis mediated by the release of neutrophil extracellular traps could be favored in the CNS because of the reduced expression of DNAse I by the brain endothelium.[20] Moreover, VITT is characterized by the co-association of multiple thrombotic events, which is not a known feature of HIT but has been described in medical spontaneous HIT,[4] suggesting that clinicians should have a low level of clinical suspicion to run tests to document multifocal thrombosis. The commonest isolated thrombosis sites are CVST and CNS arterial thrombosis. It is unclear whether this reflects underdiagnosis of other thrombosis sites or distinct pathogenic mechanisms, as both CVST and stroke were found to be more prevalent in patients with PF4-independent VITT antibodies.[21] Finally, bleeding is more frequent in VITT than in other platelet-consumptive disorders, but this is likely a consequence of the high frequency of CVST, resulting in ICH from elevated venous pressure. A clinical syndrome

similar to VITT has been described in a patient vaccinated with Gardasil[22] and, in the near future, adenoviral vector vaccines could be employed for the prevention of communicable diseases other than COVID-19. Thus, a better understanding of the distinct clinical presentation of VITT could inform future surveillance, diagnosis, and treatment practices.

In conclusion, our study provides insights into the distinct thrombotic and bleeding patterns of VITT compared with other platelet disorders and adds to the body of knowledge of PF4-mediated disorders.

What is known about this topic?

- Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare adverse reaction to adenoviral vector vaccines against SARS-CoV-2 mediated by antibodies against platelet factor 4 (PF4).
- The anti-PF4 antibodies of VITT induce thrombocytopenia and thrombosis, similarly to heparin-induced thrombocytopenia (HIT), albeit without prior exposure to heparin.
- In VITT, cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis (SVT), and intracranial hemorrhage (ICH) are common occurrences. However, the distinct patterns of bleeding and thrombosis of VITT compared with HIT remain unknown.

What does this paper add?

- In this systematic review of 366 patients with VITT, we found a venous-to-arterial thrombosis ratio of 4.1 and that up to 36% (95% CI: 31–41) of patients experienced bleeding, with ICHs accounting for 68% (95% CI: 59–75) of all bleeding events.
- Venous thrombosis at unusual sites, particularly CVST, and central nervous system (CNS) arterial thrombosis were more common in VITT compared with HIT.
- Most thrombosis sites were associated with at least another thrombotic event in four out of five cases, with the notable exception of CVST and CNS arterial thrombosis, which were isolated in 49% (95% CI: 42–56) and 39% (95% CI: 25–55) of cases, respectively.
- The overall mortality in the study population was 24% (95% CI: 19–29), likely driven by the high frequency of CVST and ICH.
- VITT is a highly prothrombotic adverse reaction with a predominance of venous thrombosis—similarly to HIT—but with a higher frequency of venous thrombosis at unusual sites, of CNS and multi-vessel involvement, and of bleeding, which is however likely secondary to the specific location of thrombotic events.

Note

Please find the completed PRISMA 2020 statement available in the Supplementary Material (available in the online version).

Data Availability Statement

The raw data supporting the results of this study will be made available upon reasonable request.

Authors' Contribution

G.M.P. and S.B. conceptualized the study and coordinated the group. C.A. and B.P. performed study selection and, together with E.P. and B.C., performed data extraction. C.A. prepared the figure. E.P., C.P., and R.P. analyzed the data and prepared the tables. B.C. and E.P. wrote the first draft of the manuscript. G.M.P., M.S., and S.B. critically reviewed the content and edited the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

None declared.

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