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Review

Clinical significance of hepatosplenic thrombosis in vaccine-induced immune thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination

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ABSTRACT

Background: Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare, serious complication after adenoviral COVID-19 vaccine administration that can involve various organ systems. We aimed to investigate the clinical significance of hepatosplenic thrombosis in patients with VITT.

Methods: We searched PubMed ePubs, Scopus, Embase, and Web of Science databases for studies published until April 28, 2021, involving patients with VITT after ChAdOx1 nCoV-19 vaccination. Demographic and clinical characteristics, including laboratory measurements, were collected and compared.

Results: Four case series and three case reports involving 48 cases of VITT were included. Hepatosplenic thrombosis was present in 8 cases (17%). Patients with hepatosplenic thrombosis had lower platelet counts (13,000 vs. 29,500/μL, p=0.016) and higher D-dimer levels (140.0 vs. 57.3 times upper limit of normal range, p=0.028). Multiple-site thrombosis was also associated with hepatosplenic thrombosis (88% vs. 15%, p<0.001).

Conclusions: This is the first study comparing clinical profiles of patients with VITT according to the presence of hepatosplenic thrombosis. Patients with hepatosplenic thrombosis had more severe presentations with lower platelet counts, higher D-dimer levels, and a higher rate of multiple-site thrombosis. Further studies with larger sample sizes are required to establish definitive evidence regarding the significance of hepatosplenic thrombosis in VITT.

VITT, vaccine-induced thrombotic thrombocytopenia; COVID-19, coronavirus disease 2019.

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Introduction

Since the first cases were discovered at the end of 2019, the ongoing COVID-19 pandemic has significantly altered the lives of people around the world. Vaccines to prevent infection from its causative organism, SARS-CoV-2, were developed by the end of 2020 and have now become humanity's hope of regaining normalcy by acquiring protective immunity against COVID-19. However, as vaccines against COVID-19 have been distributed globally at an unprecedented rate, cases of serious adverse events post-vaccination have been accumulating. Therefore, it is necessary to quickly assess, stratify, and evaluate serious adverse reactions of COVID-19 vaccines.

In particular, cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have been reported since February 2021, particularly after vaccination with the ChAdOx1 nCoV-19 vaccine, one of the adenovirus vector-based vaccines (Franchini et al., 2021; Greinacher et al., 2021; Mehta et al., 2021; Schultz et al., 2021; Scully et al., 2021; Thaler et al., 2021; Tiede et al., 2021). VITT is caused by immunoglobulin G molecules that recognize platelet factor 4 (PF4) bound to platelets, which eventually causes platelet activation and stimulation of the coagulation system; these antibodies are detectable through PF4 enzyme-linked immunosorbent assay (ELISA). Although not dependent on heparin or caused by heparin exposure, the disease process has been noted to be similar to heparin-induced thrombocytopenia (HIT) (Turnes et al., 2008). However, the mechanisms by which the components of this vaccine generate new antibodies or stimulate existing antibodies are largely unknown.

The clinical profile of VITT has not been completely elucidated, but it is reported to involve various organ systems, including the cerebral veins, pulmonary arteries, and the portal vein. Previously, we conducted a systematic review assessing the severity and clinical characteristics of people with VITT (Hwang et al., 2021a, 2021b). However, the role of hepatosplenic thrombosis in patients with VITT is little understood to date. Because the liver is responsible for nearly a quarter of the cardiac output, it is an important site of thrombosis with significant mortality and morbidity (Eipel et al., 2010; Sharma et al., 2016). We aimed to investigate the significance of hepatosplenic thrombosis in VITT after ChAdOx1 nCoV-19 vaccination.

Methods

Literature and search strategy

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Table S1). To systematically review all reported cases of VITT after ChAdOx1 nCoV-19 vaccination, we searched PubMed ePubs, Scopus, Embase, and Web of Science databases for articles published up to April 28, 2021. We used the following search algorithm: ("COVID-19" OR "SARS-CoV-2" OR coronavirus OR 2019-nCoV OR "wuhan coronavirus" OR "covid 2019") AND ("2019-ncov vaccine" OR "sars-cov-2 vaccine" OR "covid 19 vaccine" OR "covid-19 vaccine" OR "covid19 vaccine" OR "human coronavirus 2019 vaccine" OR "sars coronavirus 2 vaccine" OR "wuhan coronavirus vaccine") AND ("thrombosis" OR thrombosis OR "rethrombosis" OR "sclerothrombosis" OR "thrombo-obliterative disease" OR "thrombo occlusive" OR "thrombo obliterative" OR thrombotic). We did not impose restrictions on languages or publication date. Detailed search strategies are presented in Table S2.

Eligibility criteria and study selection

We included randomized controlled trials, cohort studies, observational studies, case series, and case reports involving cases with hemorrhagic or thrombotic events documented by clinical and radiologic findings that occurred after vaccination with the ChAdOx1 nCoV-19 vaccine. We included only the studies documenting clinical cases examined in a hospital setting, excluding reports of autopsies and postmortem examinations. We further excluded cases where vaccines other than the ChAdOx1 nCoV-19 vaccine were administered. Review articles, letters to the editors, abstracts, articles that did not contain sufficient information on the patients, including duplicate cases, were also excluded.

Three investigators (SHP, SBL, and JIS) identified the eligible studies by screening titles and abstracts independently. When the titles and abstracts of studies met the inclusion criteria, their full texts were reviewed for final selection. Any disagreement was resolved through consensus-based discussion among the authors.

Data extraction

Three investigators (SHP, SBL, and JIS) extracted data on demographic and clinical characteristics such as age, sex, ethnicity, pre-existing medical conditions, onset of symptoms, type of symptoms, presence of hepatosplenic thrombosis, laboratory data, including immunologic and platelet activation assays, the location and the number of sites where thrombosis and/or hemorrhage occurred, treatment modalities, and mortality. Hepatosplenic thrombosis was defined as thrombosis that occurred in the portal vein, splenic vein, or any of the intrahepatic vessels.

Analysis

Continuous variables were presented as medians with interquartile ranges (IQRs), whereas categorical variables were expressed as frequencies and percentages. Cases were classified into two groups according to the presence or absence of hepatosplenic thrombosis. The two groups were compared with each other using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Differences were deemed statistically significant when two-tailed $p<0.05$. Statistical analyses were performed with R version 4.0.4 (R Core Team, Vienna, Austria).

Results

A total of 673 articles were identified through database search after duplicates were removed. Among them, four case series and three case reports involving a total of 48 patients with VITT after ChAdOx1 nCoV-19 vaccination were identified (Figure 1 and Table 1) (Franchini et al., 2021; Greinacher et al., 2021; Mehta et al., 2021; Schultz et al., 2021; Scully et al., 2021; Thaler et al., 2021; Tiede et al., 2021).

Demographic and clinical characteristics of included cases are presented in Table 1 and Table 2. All included cases were reported from European countries, predominantly the United Kingdom and Germany. There were more female cases (65%) than male cases. Hepatosplenic thrombosis was present in 8 out of 48 patients (17%). Neurologic symptoms appeared in 60% of patients without hepatosplenic thrombosis and 20% of patients with hepatosplenic thrombosis. Patients with hepatosplenic thrombosis had lower median platelet counts (13,000 vs. 29,500/μL, p=0.016) and higher median D-dimer levels (140.0 vs. 57.3 times upper limit of

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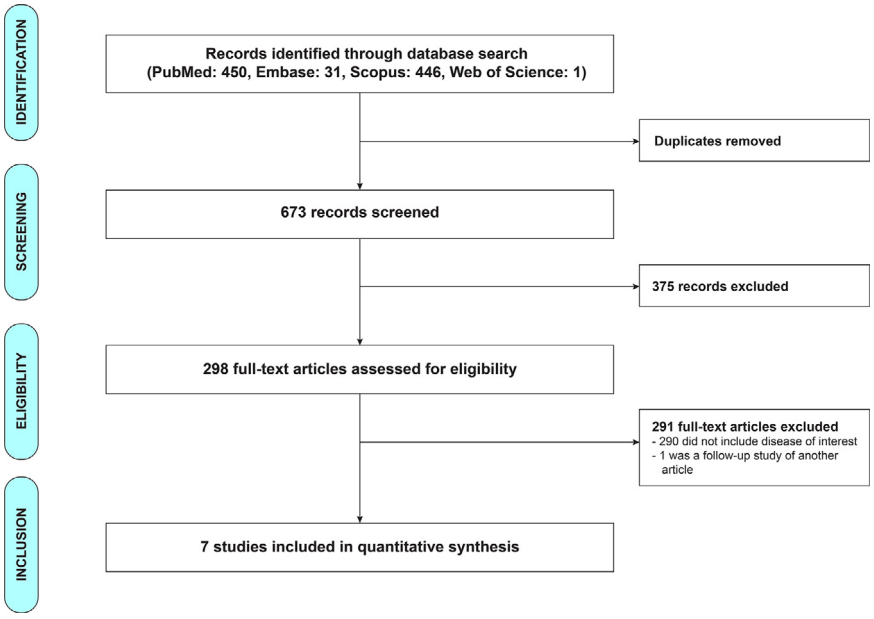

Figure 1. Study selection

Table 1
Characteristics of included studies.

Authors	No. of cases	Nation	Age	Gender or % female	Days between vaccination and symptom onset	First or second dose	Mortality	Location of thrombosis and/or hemorrhage
Franchini et al.	1	Italy	50	M	11	First	100% (1/1)	CVT, ICH
Greinacher et al.	11	Germany, Austria	22–49	81%	5–16	First	54.5% (6/11)	9 CVT, 3 SVT, 3 PE, 4 Other
Schultz et al.	5	Norway	32–54	80%	≤ 10	First	60% (3/5)	5 CVT, 1 SVT
Scully et al.	23	United Kingdom	46 (median)	61%	6–24	First	30% (7/23)	14 CVT, 4 PE, 1 DVT, 2 SVT
Mehta et al.	2	United Kingdom	32, 25	M	6–9	First	100% (2/2)	2 CVT
Thaler et al.	1	Austria	62	F	8	First	0% (0/1)	Isolated thrombocytopenia
Tiede et al.	5	Germany	41–67	F	5–11	First	0% (0/5)	1 CVT, 2 arterial infarction, 1 TIA, 1 SVT

CVT, cerebral venous thrombosis; ICH, intracerebral hemorrhage; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; TIA, transient ischemic attack.

normal range, p=0.028) than those without hepatosplenic thrombosis. There were no significant differences in age, sex, days between vaccination and admission, and laboratory values such as prothrombin time, activated partial thromboplastin time, fibrinogen, and anti-PF4 antibody levels (Table 2).

The most common site of thrombosis in patients without hepatosplenic thrombosis was the brain (80%). The brain was also the most common extra-hepatosplenic site of thrombosis in patients with hepatosplenic thrombosis (50%). Two or more sites of thrombosis were observed at a higher rate in patients with hepatosplenic thrombosis than in those without hepatosplenic thrombosis (88% vs. 15%, p<0.001). Cardiovascular or intracardiac thromboses were observed more frequently in patients with hepatosplenic thrombosis than in patients without hepatosplenic thrombosis (25% vs. 0%, p=0.025). Thromboses in medium to large-sized vessels were also observed more frequently in patients with hepatosplenic thrombosis than in those without hepatosplenic thrombosis (38% vs. 8%, p=0.049) (Table 3).

Applied treatment methods were described in 25 of 48 cases. There was no significant difference in treatment methods between the two groups. Heparin was administered to 60% of patients with hepatosplenic thrombosis and to 45% of patients without hepatosplenic thrombosis. Corticosteroids were administered in all cases except 1. Intravenous immunoglobulin (IVIG) was administered to 40% of cases with hepatosplenic thrombosis and 35% of cases without hepatosplenic thrombosis (Table 4). Although not statistically significant, the case fatality rate was higher in patients with hepatosplenic thrombosis (50% vs. 39%, p=0.697).

Discussion

VITT clinically presents as arterial or venous thrombosis with moderate or severe thrombocytopenia. Its presentation has been described to be similar to those seen in severe HIT except for the absence of previous heparin use (Klok et al., 2021; Turnes et al., 2008). HIT is caused by PF4-binding antibodies which form an immune complex with the PF4-heparin complex and in turn activates FcγRIIA receptors on the platelet surface. This stimulation induces downstream activation of Bruton tyrosine kinase as a critical signaling pathway for subsequent steps in platelet activation. VITT differs from HIT in that viral proteins and free DNA in the vaccine bind to PF4. This complex acts as a neoantigen to induce the

Table 2
Demographic and clinical characteristics of patients with and without hepatosplenic thrombosis after ChAdOx1 nCoV-19 vaccination.

Characteristics	Total (n=48) Number of patients (%) / Median [IQR]	No hepatosplenic thrombosis (n=40) Number of patients (%) / Median [IQR]	Hepatosplenic thrombosis (n=8) Number of patients (%) / Median [IQR]	P-value
Demographic information				
Age	46.0 [32.0–55.0]	44.0 [33.0–57.5]	54.0 [32.0–55.0]	0.894
Age > 60 years	9/37 (24.3%)	8/32 (25.0%)	1/5 (20.0%)	1.000
Age > 40 years	21/37 (56.8%)	18/32 (56.2%)	3/5 (60.0%)	1.000
Female	24/37 (64.9%)	21/32 (65.6%)	3/5 (60.0%)	1.000
Days between vaccination and admission[ǂ]	10.0 [8.0–13.5]	10.0 [8.0–14.0]	9.5 [6.5–12.0]	0.311
Clinical presentations				
Systemic	6/25 (24%)	5/20 (25.0%)	1/5 (20.0%)	1.000
Neurologic	13/25 (52%)	12/20 (60.0%)	1/5 (20.0%)	0.160
Bleeding	3/25 (12%)	3/20 (15.0%)	0/5 (0.0%)	1.000
Gastrointestinal	2/25 (8%)	2/20 (10.0%)	0/5 (0.0%)	1.000
Musculoskeletal	3/25 (12%)	3/20 (15.0%)	0/5 (0.0%)	1.000
Laboratory findings				
Platelet				
Platelet count	27,000.0 [16,000.0–62,000.0]	29,500.0 [17,000.0–64,000.0]	12,500.0 [10,500.0–25,000.0]	**0.02**
Platelet count < $25 \times 10^3/\mu L$	21/46 (45.7%)	15/38 (39.5%)	6/8 (75.0%)	0.117
PT[†]				
PT INR	1.2 [1.1–1.4]	1.2 [1.1–1.4]	1.2 [1.1–1.3]	0.667
Prolonged PT[†]	26/36 (72.2%)	22/30 (73.3%)	4/6 (66.7%)	1.000
aPTT[††]				
aPTT sec	31.0 [25.9–37.4]	29.0 [25.0–36.0]	34.5 [32.7–41.6]	0.233
Prolonged aPTT[††]	14/35 (40.0%)	12/29 (41.4%)	2/6 (33.3%)	1.000
Fibrinogen				
Fibrinogen (mg/dL)	130.0 [100.0–230.0]	130.0 [105.0–240.0]	120.0 [95.0–201.5]	0.597
Fibrinogen < 150 mg/dL	22/38 (57.9%)	18/31 (58.1%)	4/7 (57.1%)	1.000
Fibrinogen < 200 mg/dL	24/38 (63.2%)	19/31 (61.3%)	5/7 (71.4%)	1.000
D-dimer				
D-dimer (ratio to upper limit of normal range)	74.0 [26.7–140.0]	57.3 [20.3–128.3]	140.0 [96.7–150.4]	**0.028**
Elevated D-dimer level (>500 mg/L, FEU)	40/40 (100.0%)	33/33 (100.0%)	7/7 (100.0%)	-
HIT ELISA (n=42) [ψ]				
HIT ELISA (OD)	2.3 [1.4–3.0]	2.5 [1.6–3.0]	1.3 [1.0–2.8]	0.356
HIT ELISA positive	40/42 (95.2%)	33/35 (94.3%)	7/7 (100.0%)	1.000
Positive for functional platelet activation assay	18/20 (90.0%)	13/15 (86.7%)	5/5 (100.0%)	1.000
Mortality	19/47 (40.4%)	15/39 (38.5%)	4/8 (50.0%)	0.697

aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; IQR, interquartile range; PT, Prothrombin time.
[ǂ] If days between vaccination and admission were not given, days between vaccination and the onset of symptoms were presented.
[†] PT normal range, 10.0–12.0 sec; PT INR normal range, 0.9–1.1
[††] aPTT normal range, 25.0–35.0 sec; aPTT ratio normal range, 0.8–1.2.

development of antibodies against PF4 and a mechanism similar to that in HIT proceeds (Ahmed et al., 2007).

Although VITT is a systemic condition, its clinical manifestation and severity appear to be related to the location of the thrombus. Clinical sequelae resulting from the obstruction of blood flow depend on the importance of the organs involved and the amount of blood flow involved. We recently investigated the severity and clinical characteristics of VITT induced by adenoviral COVID-19 vaccines (Hwang et al., 2021a, 2021b) and found that the presence of intracerebral hemorrhage and cerebral venous thrombosis (CVT) was associated with mortality in patients with adenoviral COVID-19 vaccine-associated VITT. Likewise, since the liver is directly connected to the splanchnic vessels, hepatosplenic thrombosis can result in a major obstruction in the systemic circulation. Furthermore, obstruction in the portal vein could deplete the liver of two-thirds of its blood supply (Simonetto et al., 2020). Therefore, the clinical forms of hepatosplenic thrombosis depend on the specific location of the thrombus in the hepatosplenic circulation, the degree of portal vein obstruction, and its extension into the superior mesenteric or splenic vein. Intestinal ischemia, necrosis, or perforation resulting from a disruption in splanchnic blood flow can lead to fatal conditions such as systemic infection in association with intestinal microbes (Kumar et al., 2001).

To our knowledge, this is the first study to compare the clinical profiles of patients with and without hepatosplenic thrombosis among VITT cases. Patients with hepatosplenic thrombosis showed more severe clinical findings than patients without hepatosplenic thrombosis, such as lower platelet counts, higher D-dimer levels, and more thrombotic sites. Although it was difficult to evaluate the statistical significance because of the small number of cases, we observed a higher case fatality rate in patients with hepatosplenic

Table 3
Thrombosis and hemorrhage of patients with and without hepatosplenic thrombosis after ChAdOx1 nCoV-19 vaccination.

Thrombosis/Hemorrhage	Total (n=48) Number of patients (%)	No hepatosplenic thrombosis (n=40) Number of patients (%)	Hepatosplenic thrombosis (n=8) Number of patients (%)	P-value
Thrombosis				
Presence of thrombosis	46 (95.8%)	38 (95.0%)	8 (100.0%)	1.000
Two or more sites of thrombosis	13 (27.1%)	6 (15.0%)	7 (87.5%)	**< 0.001**
Location of thrombosis				
Brain	36 (75.0%)	32 (80.0%)	4 (50.0%)	0.094
Cerebral venous thrombosis	31 (64.6%)	27 (67.5%)	4 (50.0%)	0.428
Middle cerebral artery thrombosis	2 (4.2%)	2 (5.0%)	0 (0.0%)	1.000
Arterial cerebral ischemic attack	3 (6.2%)	3 (7.5%)	0 (0.0%)	1.000
Heart	2 (4.2%)	0 (0.0%)	2 (25.0%)	**0.025**
Myocardial infarction	1 (2.1%)	0 (0.0%)	1 (12.5%)	0.167
Intraventricular thrombus	1 (2.1%)	0 (0.0%)	1 (12.5%)	0.167
Pulmonary system	9 (18.8%)	6 (15.0%)	3 (37.5%)	0.159
Pulmonary embolism	8 (16.7%)	5 (12.5%)	3 (37.5%)	0.116
Not specified	1 (2.1%)	1 (2.5%)	0 (0.0%)	1.000
Gastrointestinal system	2 (4.2%)	1 (2.5%)	1 (12.5%)	0.309
Medium to large-sized vessels	6 (12.5%)	3 (7.5%)	3 (37.5%)	**0.049**
Deep vein thrombosis	3 (6.2%)	2 (5.0%)	1 (12.5%)	0.429
Acute aortic thrombosis	1 (2.1%)	0 (0.0%)	1 (12.5%)	0.167
Aortoiliac thrombosis	1 (2.1%)	0 (0.0%)	1 (12.5%)	0.167
Internal jugular vein thrombosis	1 (2.1%)	1 (2.5%)	0 (0.0%)	1.000
Inferior vena cava thrombosis	1 (2.1%)	0 (0.0%)	1 (12.5%)	0.167
Others	1 (2.1%)	1 (2.5%)	0 (0.0%)	1.000
Hemorrhage				
Presence of hemorrhage	12 (25.0%)	11 (27.5%)	1 (12.5%)	0.659
Location of hemorrhage				
Intracerebral hemorrhage	7 (14.6%)	6 (15.0%)	1 (12.5%)	1.000
Subarachnoid hemorrhage	3 (6.2%)	3 (7.5%)	0 (0.0%)	1.000
Adrenal hemorrhage	1 (2.1%)	1 (2.5%)	0 (0.0%)	1.000
Not specified	1 (2.1%)	1 (2.5%)	0 (0.0%)	1.000

Table 4
Treatment modalities in patients with and without hepatosplenic thrombosis after ChAdOx1 nCoV-19 vaccination.

Treatment	Total (n=48) Number of patients (%)	No hepatosplenic thrombosis (n=40) Number of patients (%)	Hepatosplenic thrombosis (n=8) Number of patients (%)	P-value
Heparin	12/25 (48.0%)	9/20 (45.0%)	3/5 (60.0%)	0.645
Unfractionated heparin	7/25 (28.0%)	5/20 (25.0%)	2/5 (40.0%)	0.597
Low-molecular-weight heparin	5/25 (20.0%)	4/20 (20.0%)	1/5 (20.0%)	1.000
Corticosteroids	24/25 (96.0%)	19/20 (95.0%)	5/5 (100.0%)	1.000
Prednisolone	3/25 (12.0%)	2/20 (10.0%)	1/5 (20.0%)	0.504
Methylprednisolone	2/25 (8.0%)	2/20 (10.0%)	0/5 (0.0%)	1.000
Dexamethasone	1/25 (4.0%)	1/20 (5.0%)	0/5 (0.0%)	1.000
Transfusion				
Platelet	6/25 (24.0%)	5/20 (25.0%)	1/5 (20.0%)	1.000
Red blood cell	1/25 (4.0%)	1/20 (5.0%)	0/5 (0.0%)	1.000
Fibrinogen concentrate	1/25 (4.0%)	1/20 (5.0%)	0/5 (0.0%)	1.000
Surgery				
Craniectomy or hemicraniectomy	4/25 (16.0%)	4/20 (20.0%)	0/5 (0.0%)	0.549
Thrombectomy	1/25 (4.0%)	1/20 (5.0%)	0/5 (0.0%)	1.000
Intravenous immunoglobulin	9/25 (36.0%)	7/20 (35.0%)	2/5 (40.0%)	1.000
Tissue plasminogen activator	1/25 (4.0%)	0/20 (0.0%)	1/5 (20.0%)	0.200
Direct thrombin inhibitor (Argatroban)	4/25 (16.0%)	3/20 (15.0%)	1/5 (20.0%)	1.000
Eculizumab	2/25 (8.0%)	1/20 (5.0%)	1/5 (20.0%)	0.367

thrombosis. Additional studies with higher statistical power may better assess the differences in fatality.

Diffuse intravascular coagulation (DIC) and inflammatory cytokines induced by vaccination with the ChAdOx1 nCoV-19 vaccine could contribute to the development of PVT (Cui et al., 2018; Ewer et al., 2021), which may explain the association of hepatosplenic thrombosis with more severe VITT profiles and more thrombotic lesions in this study. According to a post-mortem examination of two typical cases of VITT, large vessel involvement was much more extensive than was detected by imaging. In this examination, microscopic findings revealed vascular thrombotic occlusion in the microcirculation of multiple organs and increased inflammatory infiltrates. In addition, immunohistochemical analysis showed the expression of vascular or perivascular adhesion molecules such as VICAM1 and CD66b+, CD163+, and CD61+ activated inflammatory cells expressing C1r, which suggested that multi-organ microvascular damage in VITT is induced through inflammatory processes involving an activation of the innate immune system and the complement pathway (Pomara et al., 2021a).

Portal vein thrombosis (PVT) is a rare entity known to be associated with a variety of underlying conditions such as liver cirrhosis, malignancies, and autoimmune diseases (Ogren et al., 2006). Acute PVT can progress into intestinal congestion or ischemia with abdominal pain, diarrhea, rectal bleeding, abdominal distension, vomiting, fever, or sepsis. Extensive splanchnic venous thrombosis can further cause ascites and variceal bleeding because of increased hydrostatic pressure. Persistent obstruction can lead to intestinal perforation, peritonitis, shock, and death from multiorgan failure (Kumar et al., 2015). Although the prognosis of PVT depends on the underlying disease, it is known that early intervention can

be effective. If acute PVT is detected and treated before progression to intestinal infarction, the prognosis can be relatively good. On the other hand, in the case of intestinal ischemia and multiorgan failure, the in-hospital mortality rate is about 20% to 50% (Kumar et al., 2001; Ponziani et al., 2010). Therefore, early diagnosis and intervention may contribute to improving the prognosis of hepatosplenic thrombosis in VITT.

To detect hepatosplenic thrombosis, early imaging is required for patients with abdominal symptoms and thrombocytopenia within 5 to 30 days after COVID-19 vaccination. Considering that most of the cases of hepatosplenic thrombosis included in this study did not present with abdominal pain and that multiple-site thrombosis was more common than in patients without hepatosplenic thrombosis, abdominal imaging may be helpful for patients with VITT who show severe thrombocytopenia or high D-dimer levels with or without abdominal pain. It is also notable that 44% of VITT cases with hepatosplenic thrombosis in this study did not present with CVT, a more well-known manifestation of VITT. Understanding the full scope of manifestations of VITT, including hepatosplenic involvement, is important in guiding timely recognition and proper management. Contrast-enhanced computed tomography of the abdomen and/or pelvis is the preferred modality of investigation, which is widely available and highly accurate for diagnosing vascular thrombosis and end-organ complications.

According to this study, there was no significant difference in treatment methods between patients with and without hepatosplenic thrombosis, although treatment data were available only in 25 out of 48 patients. Based on what is known to date, the British Society for Haematology has recommended the urgent use of IVIG to treat VITT, starting at a dose of 1 g/kg, under close clinical monitoring, regardless of the severity of thrombocytopenia (The British society for haematology, 2021). IVIG is known to inhibit platelet activation by blocking the FcγRIIA receptor. Depending on the risk of bleeding, additional doses of IVIG may be required. Corticosteroid therapy can be considered in conjunction with IVIG or independently when IVIG cannot be administered. In addition, non-heparin–based anticoagulation therapy such as direct oral anticoagulants, fondaparinux, danaparoid, or argatroban can be initiated when the platelet count is 30,000/μL or higher. For a very severe or resistant disease, plasmapheresis is a possible treatment option (Patriquin et al., 2021). Platelet transfusion is generally not recommended, as guidelines for platelet transfusion in severe thrombocytopenia with bleeding have not been established (Rizk et al., 2021). Emergent catheter-guided thrombolysis or thrombectomy may be required to prevent mortality.

An important point to note is the causality association between vaccination and the reported thrombotic and/or hemorrhagic events. We assessed the causality between vaccination and VITT through the WHO adverse events following immunization (AEFI) guidelines, which recommend a four-step determination of (1) order of incidence, (2) temporal proximity, (3) exclusion of other causes, and (4) published evidence of causal association followed by an autopsy to determine the causality between vaccine administration and AEFI (Pomara et al., 2021b). In all cases included in our study, the first two steps of (1) order of incidence and (2) temporal proximity are established because all thrombotic and/or hemorrhagic events occurred after ChAdOx1 nCoV-19 vaccine administration, and the interval between vaccination and symptom onset ranged from 5 to 24 days, within the scope of 3 weeks proposed by the guidelines. We were able to presume the third criterion, (3) the exclusion of other causes, by the absence of other causes in the individual clinical reports, but we could not verify the third step because the comprehensive medical and vaccination records of each patient were not accessible. Lastly, the fourth step of (4) published evidence of causal association is met by multiple reports in the literature supporting a causal relationship (Butler et al., 2021; MacIntyre, 2021). However, we were unable to access autopsy determination of causality through our systematic review. Under consideration of all these factors, we could conclude that the clinical scenarios in our panel of patients suggest a causality between vaccination and VITT, especially with the temporal association and supporting literature; however, without autopsy confirmation, our evidence does not meet the revised WHO AEFI guidelines.

In addition, according to the data from vaccine adverse event reporting systems, the frequency and outcome of VITT following ChAdOx1 nCoV-19 vaccination differ depending on the country. By 24 November, 2021, 380 and 47 cases of major thromboembolic events with thrombocytopenia following the first- and second-dose ChAdOx1 nCoV-19 vaccination, respectively, were reported in the United Kingdom, of which 74 (17%) had a fatal outcome (European Medicines Agency, 2021). In other words, this adverse event occurs in about 1.5 per 100,000 people after the first dose and 0.2 per 100,000 people after the second dose. In Australia, VITT occurs in about 2 per 100,000 people after the first dose and 0.3 per 100,000 people after the second dose, with an overall case fatality rate of as low as 3% (MacIntyre et al., 2021). In our study, when comparing the United Kingdom (n = 25) and Germany/Austria (n=17), case fatality rates in all VITT were similar at 36% and 35%, respectively. Hepatosplenic thrombosis was observed in 4 out of 25 cases in the United Kingdom (16%) and 3 out of 17 cases (18%) in Germany/Austria, with case fatality rates of 67% and 50%, respectively. Possible reasons for differences in the incidence and outcome may include differences in demographic characteristics, access to health care, the efficiency and capacity of health care systems, and early detection and administration of effective treatments such as IVIG; however, these differences may have simply come from differences in reporting rates between countries. Further accumulation of evidence from national surveillance data could shed some light on country-level differences and trends.

Although our study focuses on the serious adverse effects of the COVID-19 vaccine, it is well known that the effectiveness of the vaccines against COVID-19 outweighs the risk. In the United States, vaccine campaigns were estimated to be associated with a reduction of approximately 140,000 COVID-19 deaths by May 2021 (Gupta et al., 2021). In Israel, where the vaccines against COVID-19 were rapidly disseminated, the effectiveness of the vaccines was estimated to be 91.5% for asymptomatic COVID-19, 97.2% for COVID-19 hospitalization, and 96.7% for COVID-19 mortality for the first 4 months of the vaccine campaign (Haas et al., 2021). In a study from Poland, more than 98% of patients with COVID-19 who were admitted to hospitals by May 2021 after the introduction of the vaccine were not previously vaccinated, and most of those previously vaccinated had received only the first dose less than 14 days before the onset of COVID-19 symptoms (Rzymski et al., 2021). In a study from Qatar, the estimated effectiveness for the first and second doses of mRNA-1273 against infection with the Delta (B.1.617.2) variant was 74% and 73%, respectively. The estimated vaccine effectiveness against severe, critical, or fatal COVID-19 from the Delta variant infection was 93% for BNT162b2 or 96% for mRNA-1273 after the second dose (Tang et al., 2021). In addition, it is estimated that 127,500 COVID-19 deaths and 24,144,000 SARS-CoV-2 infections have been prevented by September 2021 as a result of the COVID-19 vaccine program in the United Kingdom (UK Health Security Agency, 2021). Therefore, it is important to document and respond appropriately to COVID-19 vaccine-related adverse events, but it is equally important to ensure transparent and timely communication to encourage vaccine uptake in communities.

Our study has some limitations. First, because the data for this study were drawn from a pooled analysis of published articles, original medical records were unavailable and some clinical in-

formation could not be extracted. For example, although a significant number of cases did not report significant previous medical history, we could not assert an absence of pre-existing conditions through a review of electronic medical records. Second, the sample size of this study was relatively small because of the recent emergence of VITT and its rare nature. Furthermore, as we only included published cases with documented VITT with stringent exclusion criteria, this study may have been subject to publication bias. Third, the treatment methods applied to cases in this study were not highly consistent with the currently recommended treatment: heparin was administered in about half of the included cases, and the administration rate of IVIG was as low as 36%. This is likely due to the early occurrences of these case reports, when the clinical consensus regarding the VITT was not yet established. Further research is warranted to provide more definitive evidence regarding the significance of hepatosplenic involvement in VITT. Controlled studies regarding treatment options for VITT could also shed light on the relevance of the current guidelines.

In conclusion, to our knowledge, this is the first study to compare the clinical profiles among patients with VITT according to the presence or absence of hepatosplenic thrombosis. Among patients with VITT, lower platelet counts, higher D-dimer levels, and more thrombosis sites were found in cases with hepatosplenic thrombosis than in those without hepatosplenic thrombosis, suggesting a relatively higher severity of hepatosplenic thrombosis. To improve the prognosis of hepatosplenic thrombosis in VITT through timely intervention, follow-up studies with larger sample sizes and more comprehensive clinical data are warranted.

Author contributions

JH interpreted the data, wrote the first draft of the manuscript, and contributed to the writing of the final version of the manuscript. YJH interpreted the data, wrote the first draft of the manuscript, and contributed to the writing of the final version of the manuscript. DKY, SWL, and BKK interpreted the data and contributed to the writing of the final version of the manuscript. SBL identified the eligible studies and extracted data. SHP identified the eligible studies and extracted data. MHL, AK, LJ, KT, and LS contributed to the writing of the final version of the manuscript. SUK conceived and designed the study. JIS conceived and designed the study, contributed to the establishment of the methodological detail, identified the eligible studies, extracted data, and contributed to the writing of the final version of the manuscript. All authors critically revised the manuscript and agreed with the results and conclusions of this article.

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical Approval statement

Ethical approval was not required because this work was a pooled analysis of published articles.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.12.352.

References

Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. Postgrad Med J 2007;83:575–82. doi:10.1136/pgmj.2007.059188.

Butler M, Tamborska A, Wood GK, Ellul M, Thomas RH, Galea I, et al. Considerations for causality assessment of neurological and neuropsychiatric complications of SARS-CoV-2 vaccines: from cerebral venous sinus thrombosis to functional neurological disorder. J Neurol Neurosurg Psychiatry 2021;92:1144–51. doi:10.1136/jnnp-2021-326924.

Cui S, Fu Z, Feng Y, Xie X, Ma X, Liu T, et al. The disseminated intravascular coagulation score is a novel predictor for portal vein thrombosis in cirrhotic patients with hepatitis B. Thromb Res 2018;161:7–11. doi:10.1016/j.thromres.2017.11.010.

Eipel C, Abshagen K, Vollmar B. Regulation of hepatic blood flow: The hepatic arterial buffer response revisited. World J Gastroenterol 2010;16:6046–57. doi:10.3748/wjg.v16.i48.6046.

European Medicines Agency. COVID-19 vaccine safety update-Vaxzevria 2021.

Ewer KJ, Barrett JR, Belij-Rammerstorfer S, Sharpe H, Makinson R, Morter R, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. Nat Med 2021;27:270–8. doi:10.1038/s41591-020-01194-5.

Franchini M, Testa S, Pezzo M, Glingani C, Caruso B, Terenziani I, et al. Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination. Thromb Res 2021;202:182–3. doi:10.1016/j.thromres.2021.04.001.

Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med 2021;384:2092–101. doi:10.1056/NEJMoa2104840.

Gupta S, Cantor J, Simon KI, Bento AI, Wing C, Whaley CM. Vaccinations Against COVID-19 May Have Averted Up To 140,000 Deaths In The United States. Health Aff (Millwood) 2021;40:1465–72. doi:10.1377/hlthaff.2021.00619.

Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021;397:1819–29. doi:10.1016/S0140-6736(21)00947-8.

Hwang J, Lee SB, Lee SW, Lee MH, Koyanagi A, Jacob L, et al. Comparison of vaccine-induced thrombotic events between ChAdOx1 nCoV-19 and Ad26.COV.2.S vaccines. J Autoimmun 2021a;122. doi:10.1016/j.jaut.2021.102681.

Hwang J, Park SH, Lee SW, Lee SB, Lee MH, Jeong GH, et al. Predictors of mortality in thrombotic thrombocytopenia after adenoviral COVID-19 vaccination: the FAPIC score. Eur Heart J 2021b;42:4053–63. doi:10.1093/eurheartj/ehab592.

Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. Lancet Haematol 2021 S2352-3026(21)00306-9. doi:10.1016/S2352-3026(21)00306-9.

Kumar A, Sharma P, Arora A. Review article: portal vein obstruction–epidemiology, pathogenesis, natural history, prognosis and treatment. Aliment Pharmacol Ther 2015;41:276–92. doi:10.1111/apt.13019.

Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med 2001;345:1683–8. doi:10.1056/NEJMra010076.

MacIntyre CR. Using the Bradford-Hill criteria to assess causality in the association between CHADOX1 NCOV-19 vaccine and thrombotic immune thrombocytopenia. Global Biosecurity 2021;3. doi:10.31646/gbio.109.

MacIntyre CR, Veness B, Berger D, Hamad N, Bari N. Thrombosis with Thrombocytopenia Syndrome (TTS) following AstraZeneca ChAdOx1 nCoV-19 (AZD1222) COVID-19 vaccination - A risk-benefit analysis for people < 60 years in Australia. Vaccine 2021;39:4784–7. doi:10.1016/j.vaccine.2021.07.013.

Mehta PR, Apap Mangion S, Benger M, Stanton BR, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - A report of two UK cases. Brain Behav Immun 2021. doi:10.1016/j.bbi.2021.04.006.

Ogren M, Bergqvist D, Björck M, Acosta S, Eriksson H, Sternby NH. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol 2006;12:2115–19. doi:10.3748/wjg.v12.i13.2115.

Patriquin CJ, Laroche V, Selby R, Pendergrast J, Barth D, Côté B, et al. Therapeutic Plasma Exchange in Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med 2021;385:857–9. doi:10.1056/NEJMc2109465.

Pomara C, Sessa F, Ciaccio M, Dieli F, Esposito M, Garozzo SF, et al. Post-mortem findings in vaccine-induced thrombotic thombocytopenia. Haematologica 2021a;106:2291–3. doi:10.3324/haematol.2021.279075.

Pomara C, Sessa F, Ciaccio M, Dieli F, Esposito M, Giammanco GM, et al. COVID-19 Vaccine and Death: Causality Algorithm According to the WHO Eligibility Diagnosis. Diagnostics (Basel) 2021b;11:955. doi:10.3390/diagnostics11060955.

Ponziani FR, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol 2010;16:143–55. doi:10.3748/wjg.v16.i2.143.

Rizk JG, Gupta A, Sardar P, Henry BM, Lewin JC, Lippi G, et al. Clinical Characteristics and Pharmacological Management of COVID-19 Vaccine-Induced Immune Thrombotic Thrombocytopenia With Cerebral Venous Sinus Thrombosis: A Review. JAMA Cardiol 2021. doi:10.1001/jamacardio.2021.3444.

Rzymski P, Pazgan-Simon M, Simon K, Łapiński T, Zarębska-Michaluk D, Szczepańska B, et al. Clinical Characteristics of Hospitalized COVID-19 Patients Who Received at Least One Dose of COVID-19 Vaccine. Vaccines (Basel) 2021;9:781. doi:10.3390/vaccines9070781.

Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021. doi:10.1056/NEJMoa2104882.

Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021;384:2202–11. doi:10.1056/NEJMoa2105385.

Sharma AM, Zhu D, Henry Z. Portal vein thrombosis: When to treat and how? Vasc Med 2016;21:61–9. doi:10.1177/1358863X15611224.

Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol 2020;115:18–40. doi:10.14309/ajg.0000000000000486.

Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med 2021. doi:10.1038/s41591-021-01583-4.

Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Grafeneder J, et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). J Thromb Haemost 2021;19:1819–22. doi:10.1111/jth.15346.

The British society for haematology. Guidance from the expert haematology panel on Covid-19 vaccine-induced immune thrombocytopenia and thrombosis; 2021.

Tiede A, Sachs UJ, Czwalinna A, Werwitzke S, Bikker R, Krauss JK, et al. Prothrombotic immune thrombocytopenia after COVID-19 vaccination. Blood 2021;138:350–3. doi:10.1182/blood.2021011958.

Turnes J, Garcia-Pagan JC, Gonzalez M, Aracil C, Calleja JL, Ripoll C, et al. Portal hypertension-related complications after acute portal vein thrombosis: impact of early anticoagulation. Clin Gastroenterol Hepatol 2008;6:1412–17. doi:10.1016/j.cgh.2008.07.031.

UK Health Security Agency. COVID-19 vaccine surveillance report Week 42; 2021.