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BRIEF REPORT

Coagulation factor inhibitors in COVID-19: From SARS-CoV-2 vaccination to infection

Jeremy W. Jacobs MD, MHS[1] | Brian D. Adkins MD[2] | Shannon C. Walker MD[3,4] | Garrett S. Booth MD, MS[3] | Allison P. Wheeler MD, MSCI[3]

[1]Department of Laboratory Medicine, Yale School of Medicine, New Haven, Connecticut, USA

[2]Department of Pathology, Division of Transfusion Medicine and Hemostasis, University of Texas Southwestern, Dallas, Texas, USA

[3]Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[4]Vanderbilt Vaccine Research Program, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Correspondence
Allison P. Wheeler, Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA.
Email: allison.p.wheeler@vumc.org

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Abstract

Background: Recent reports have highlighted patients with COVID-19 and vaccine recipients diagnosed with coagulation factor inhibitors. This is challenging. as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been identified as a prothrombotic risk factor, with heparin treatment decreasing mortality. However, both infection and vaccination have been associated with immune-mediated hematologic abnormalities, including thrombocytopenia, further rendering these groups at risk for both hemorrhagic and thrombotic events.

Objectives: We sought to characterize the incidence and clinical findings of coagulation factor inhibitors in patients with COVID-19 and vaccine recipients.

Methods: We queried the US Centers for Disease Control and Prevention's Vaccine Adverse Event Reporting System (VAERS), a publicly accessible database, for reports of potential bleeding episodes or coagulation disturbances associated with SARS-CoV-2 vaccination. We performed an additional comprehensive literature review to identify reports of SARS-CoV-2 infection or vaccination-associated coagulation factor inhibitors.

Results: VAERS data showed 58 cases of coagulation factor inhibitors, suggesting a rate of 1.2 cases per 10 million doses. A total of 775 articles were screened and 15 were suitable for inclusion, with six reports of inhibitors after vaccination and nine reports of inhibitors after infection. Inhibitor specificity for factor VIII was most common. Among reported cases, two patients expired due to hemorrhage, one following infection and one following vaccination.

Conclusion: The incidence of coagulation factor inhibitors in patients with SARS-CoV-2 vaccination and infection appears similar to the general population. Nonetheless, given the importance of heparin therapy in treating hospital patients, recognition of inhibitors is important.

KEYWORDS
blood coagulation factor, coagulation factor inhibitor, COVID-19, COVID-19 vaccine, SARS-CoV-2

Essentials

- Coagulation factor inhibitors are rare in the general population at 1.5 per million annually.
- We queried the Centers for Disease Control and Prevention's Vaccine Adverse Event (VAERS) database of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination through December 27, 2021.
- There were 58 factor inhibitor reports in VAERS and rare literature case reports with COVID-19.
- The rate of factor inhibitors in SARS-CoV-2 vaccination is 1.2 per 10 million doses.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of COVID-19, is capable of potentiating numerous hematologic derangements in those infected. Much research has focused on mechanisms by which this virus contributes to a prothrombotic state; however, there is mounting evidence that other hematologic anomalies, such as immune thrombocytopenia,[1] autoimmune hemolytic anemia,[2] and vaccine-induced thrombosis and thrombocytopenia[3] may also be associated with SARS-CoV-2 infection and/or vaccination. Hypotheses for development of these immune dyscrasias include immune hyperstimulation, molecular mimicry, and antibody cross reactivity with antigens on platelets and red blood cells.[4,5] Despite significant research and insight gained into the mechanisms of these presumptive autoimmune cytopenic phenomena, little is known about the potential for SARS-CoV-2 to elicit a severe bleeding phenotype secondary to autoreactivity.[6-9]

Several case reports have recently described acquired coagulation factor inhibitors in the setting of SARS-CoV-2 infection[7-9] or following SARS-CoV-2 vaccination.[10-13] While few cases have been reported, determining whether these hematologic abnormalities are related to SARS-CoV-2 infection or vaccination, or are simply temporal associations, is important as a recent randomized controlled trial demonstrated decreased mortality with therapeutic-dose heparin for patients admitted with COVID-19 and elevated D-dimers.[14] Therefore, to provide insight into this potential relationship between acquired immune-mediated mechanisms underlying bleeding phenotypes and COVID-19, we reviewed all documented cases of patients with autoantibodies specifically directed against blood coagulation factors in the setting of SARS-CoV-2 infection or vaccination. The epidemiology, coagulation parameters, and patient outcomes were documented. Furthermore, we assessed the US Centers for Disease Control's (CDC) Vaccine Adverse Event Reporting System (VAERS) to ascertain an estimate of potential cases not published in the medical literature and estimate the risk per vaccine dose.

2 | METHODS

2.1 | Case selection

The CDC's VAERS database was queried to assess for reports of potential bleeding episodes or coagulation laboratory abnormalities associated with receipt of a COVID-19 vaccine as of December 27, 2021. The VAERS database is a publicly available national database comanaged by the CDC and the US Food and Drug Administration (FDA), and serves as a passive surveillance system for detecting potential adverse events associated with vaccines authorized or licensed by the FDA. This database accepts and analyzes reports of adverse events submitted by any person, including the general public, health care professionals, and vaccine manufacturers.

Information regarding adverse events submitted to VAERS includes vaccine type, administration date, adverse event onset, current illnesses and medications, medical history, prior history of adverse events following vaccination, and demographics. Not all information was available for every report. Duplicate VAERS cases were excluded from analysis.

A comprehensive literature review was also performed to identify all reports of SARS-CoV-2 infection or vaccination associated with coagulation factor autoantibodies. Five biomedical databases (PubMed, EMBASE, Web of Science, Scopus, Google Scholar) were reviewed for relevant articles from December 1, 2019, through December 26, 2021, according to a standardized search protocol (Figure 1). Journal titles and abstracts were screened by two authors according to specific inclusion criteria, and all included publications were coded into relevant categories.

2.2 | Data analysis

All cases describing the development of a blood coagulation factor inhibitor following a SARS-CoV-2 vaccine dose reported to the CDC's VAERS database were included, regardless of time interval from vaccination to confirmation of coagulation abnormality. We also included all case reports, case series, letters and correspondence, and case-control and cohort studies with available and relevant clinical data in the published literature. For cases that met inclusion criteria, we abstracted demographic, laboratory, treatment, and outcomes data.

To analyze outcomes, a binary parameter of either alive or deceased at the time of the report was used. If the suspected cause of death was reported by the original authors, we included the data for those patients reported to be deceased. The outcome of cases reported in the CDC's VAERS database was either "deceased" or "not deceased" at the time of the submitted report.

All statistical analyses were conducted using PRISM version 9.2.0 (GraphPad Software, San Diego, CA, USA). Distribution was non-normal using a D'Agostino-Pearson test, and groups were compared

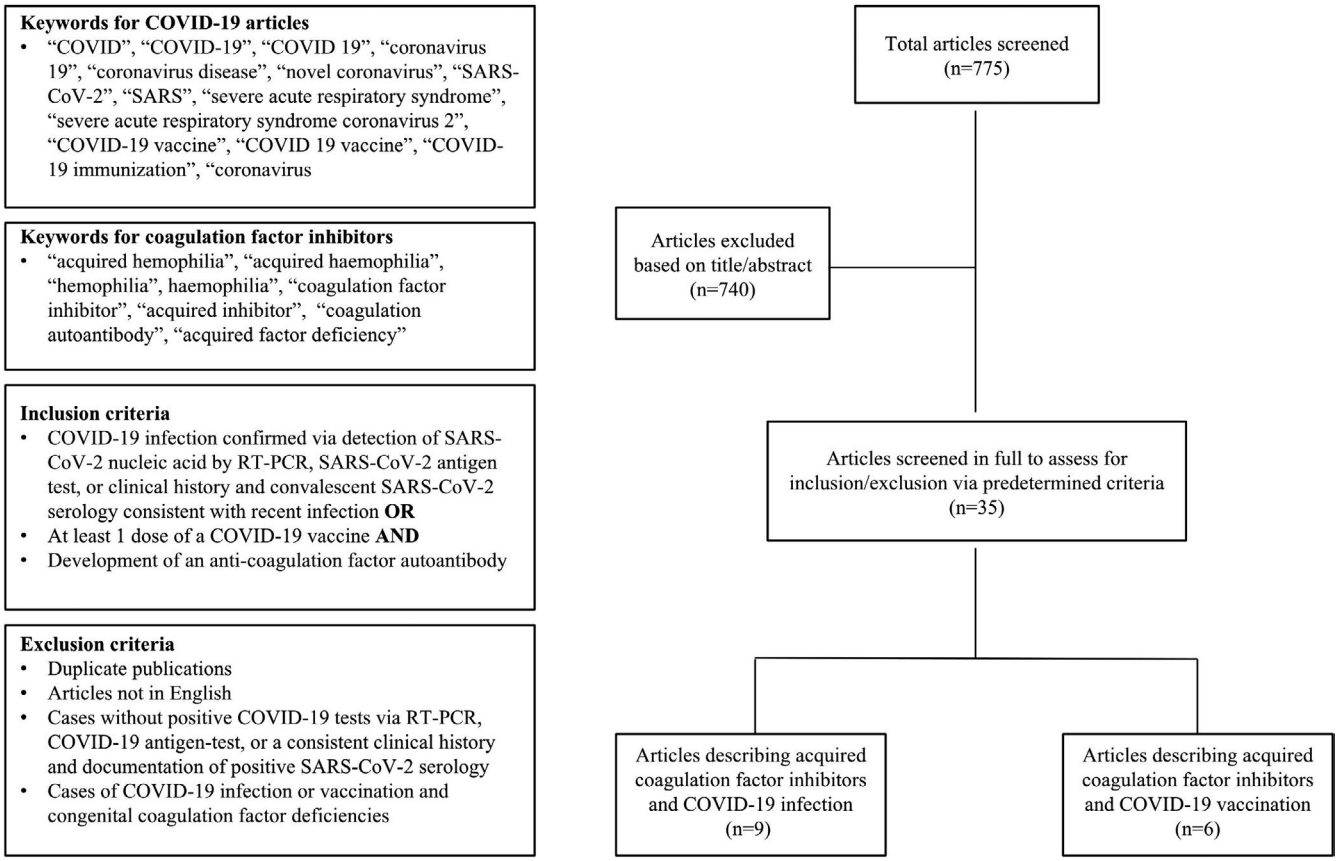

FIGURE 1 Case review search method and standardized protocol

using Mann-Whitney tests. Contingency tables were assessed using Fisher exact test. $P < .05$ was considered significant.

3 | RESULTS

3.1 | SARS-CoV-2 vaccination

3.1.1 | VAERS database findings

Review of the CDC's VAERS database as of December 27, 2021, identified 58 reports (29 men, 29 women) of acquired FVIII inhibitors potentially associated with a COVID-19 vaccine (Table 1). No other acquired coagulation factor inhibitors were identified. As of December 27, 2021, 503 480 667 vaccines had been administered, suggesting a rate of 1.2 cases per 10 million doses. Fourteen (24%) of these were reported in patients receiving the mRNA-1273 vaccine and 44 (76%) patients received the BNT162b2 vaccine. No reports following administration of the Janssen COVID-19 vaccine were identified. The mean age of these patients was 75.4 (standard deviation [SD], 13.4) years. There was no significant difference in age ($P = .15$), sex ($P > .99$), or days to onset ($P = .65$) between vaccine manufacturers. A greater proportion of mRNA-1273 vaccine recipients developed inhibitors after the first dose (70%; 7/10) compared to BNT162b2 recipients, who predominantly developed inhibitors after the second dose (65.6%; 25/38), though this difference was not significant ($P = .07$). For 39 patients with clinical history available, 18.0% (7/39) had a history of malignancy, 15.4% (6/39) had a history of autoimmune disease, and 2.6% (1/39) had a prior history of a factor VIII (FVIII) inhibitor. The timing to onset of symptoms was highly variable, with a mean of 24.2 (SD, 23.3) days, ranging from 2 to 101 days since the most recent dose. Three patients were reported to be deceased from hemorrhagic sequelae.

The mean FVIII inhibitor titer for 19 patients with reported results was 113 Bethesda units (BU)/mL (SD, 180 BU/mL), ranging from 1.84 BU/mL to >500 BU/mL.

3.1.2 | Literature review

Thirty-five articles fulfilled criteria for comprehensive screening to assess relevance for inclusion in the analysis (Figure 1). A total of 15 articles were included in the study, 6 of which described coagulation factor inhibitors associated with SARS-CoV-2 vaccination (Table 2).

Acquired coagulation factor inhibitors, including five FVIII inhibitors and one factor XIII (FXIII) inhibitor, were detected in six patients (mean age, 67.2 [SD, 12.6] years) following SARS-CoV-2 vaccination (three BNT162b2 vaccines, two mRNA-1273 vaccines, one vaccine manufacturer not reported). Half (3/6) of patients had risk factors

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TABLE 1 SARS-CoV-2 vaccine and coagulation factor inhibitors from CDC VAERS database

Age, y	Sex[a]	Comorbidities	Vaccine	Dose	Days to onset following vaccination	Laboratory studies	Factor inhibitor	Death reported?
69	Male	Prostate cancer in remission, HTN, DM2	BNT162b2 (Pfizer/BioNTech)	1	8	N/A	FVIII	No
77	Male	Cancer, possible urological mass vs hematoma	BNT162b2 (Pfizer/BioNTech)	1	30	FVIII level <1 iu/dL; FVIII inhibitor >500 BU/mL	FVIII	No
88	Female	N/A	BNT162b2 (Pfizer/BioNTech)	1	21	N/A	FVIII	No
63	Male	Dementia	BNT162b2 (Pfizer/BioNTech)	1	2	Mixing studies showed partial correction. FVIII levels <1	FVIII	No
89	Male	Polymyalgia rheumatica, paroxysmal atrial fibrillation, BPH	mRNA-1273 (Moderna)	1	2	PTT 71.5 s; FVIII <1%, with inhibitor titer 110.1 BU/mL	FVIII	No
86	Male	CKD, CAD	mRNA-1273 (Moderna)	1	29	N/A	FVIII	No
78	Male	HTN, ischemic heart disease, nephroangiosclerosis	BNT162b2 (Pfizer/BioNTech)	1	4	FVIII 3%	FVIII	No
84	Female	Acute coronary syndrome	BNT162b2 (Pfizer/BioNTech)	2	N/A	N/A	FVIII	No
81	Male	CHF, DM2, COPD, CKD	mRNA-1273 (Moderna)	N/A	1	FVIII inhibitor 84 BU/mL	FVIII	No
81	Male	N/A	mRNA-1273 (Moderna)	1	20	N/A	FVIII	No
67	Male	Sarcoidosis, HTN	BNT162b2 (Pfizer/BioNTech)	N/A	9	N/A	FVIII	No
85	Male	CKD, CAD	mRNA-1273 (Moderna)	1	29	N/A	FVIII	Yes - gallbladder hemorrhage
82	Female	HTN, hypothyroidism	BNT162b2 (Pfizer/BioNTech)	1	10	FVIII activity 3%, FVIII inhibitor 17.03 BU/mL	FVIII	No
N/A	Male	N/A	BNT162b2 (Pfizer/BioNTech)	2	30	FVIII 0.01 IU/mL with high-titer anti-FVIII inhibitors	FVIII	No
84	Female	N/A	BNT162b2 (Pfizer/BioNTech)	2	2	FVIII inhibitor 86 BU/mL	FVIII	No
84	Female	N/A	BNT162b2 (Pfizer/BioNTech)	2	56	FVIII 3%, FVIII inhibitor 532 BU/mL	FVIII	No
86	Female	HTN, Chronic leg ulcer	mRNA-1273 (Moderna)	2	20	N/A	FVIII	No
82	Female	HTN, dementia, anemia, CKD, thyrotoxicosis	BNT162b2 (Pfizer/BioNTech)	2	N/A	PTT >120, Factor VIII <0.01, FVIII inhibitor 38.8 BU/mL	FVIII	No
72	Male	Prostate carcinoma, HTN, DM2	BNT162b2 (Pfizer/BioNTech)	1	7	PTT 71, FVIII 0.01	FVIII	No
67	Male	Rheumatoid arthritis, Crohn disease, pulmonary legionellosis, obesity	BNT162b2 (Pfizer/BioNTech)	N/A	N/A	FVIII undetectable, FVIII inhibitor 15 BU/mL	FVIII	Yes - hemorrhagic shock
90	Female	Alzheimer disease, HTN, dyslipidemia, hiatal hernia, polymyalgia rheumatica	BNT162b2 (Pfizer/BioNTech)	2	16	FVIII inhibitor 2–3 BU/mL	FVIII	No
84	Female	N/A	BNT162b2 (Pfizer/BioNTech)	1	3	PTT ratio 2.19, FVIII 3%, FVIII inhibitor 15 BU/mL	FVIII	No
72	Female	N/A	mRNA-1273 (Moderna)	1	2	PTT 184 s	FVIII	No

TABLE 1 (Continued)

Age, y	Sex[a]	Comorbidities	Vaccine	Dose	Days to onset following vaccination	Laboratory studies	Factor inhibitor	Death reported?
83	Male	HTN, CKD, prostate adenocarcinoma in remission	BNT162b2 (Pfizer/BioNTech)	2	32	FVIII 4%, FVIII inhibitor 4.8 BU/mL	FVIII	No
90	Female	HTN	BNT162b2 (Pfizer/BioNTech)	2	6	FVIII <1%	FVIII	No
75	Female	COVID-19 ≈6 months prior, HTN, mitral valve repair, tricuspid valve repair, COPD	BNT162b2 (Pfizer/BioNTech)	1	9	FVIII <1%, FVIII inhibitor 12.12 BU, FIX 113%, FXI 90%	FVIII	No
76	Female	Paraesophageal hiatal hernia and Nissen fundoplication	mRNA-1273 (Moderna)	1	N/A	PTT 122 s, FVIII <3%, FVIII inhibitor 11.2 BU/mL, VWF <3%	FVIII	No
88	Female	Dyslipidemia, HTN, gastric ulcer, breast cancer	mRNA-1273 (Moderna)	2	67	N/A	FVIII	No
84	Male	HTN, transient ischemic attack	BNT162b2 (Pfizer/BioNTech)	2	24	N/A	FVIII	No
62	Female	Diffuse large B-cell lymphoma, kidney tumor, rheumatoid arthritis	BNT162b2 (Pfizer/BioNTech)	2	1	FVIII level 0.10	FVIII	No
90	Male	Ischemic heart disease, total hip replacement	BNT162b2 (Pfizer/BioNTech)	2	34	N/A	FVIII	No
82	Male	Dyslipidemia, aortic valve repair, DM2, HTN, atrial fibrillation, prostate cancer	BNT162b2 (Pfizer/BioNTech)	2	22	partial thromboplastin time, 2.49 (normal, 0.80-1.20), FVIII 2%, FVIII inhibitor 1.84 BU/mL	FVIII	No
86	Female	N/A	BNT162b2 (Pfizer/BioNTech)	1	11	FVIII <1%, FVIII inhibitor 51.6 BU/mL	FVIII	No
69	Female	N/A	BNT162b2 (Pfizer/BioNTech)	2	16	N/A	FVIII	No
59	Male	Myelodysplastic syndrome, rheumatoid arthritis	BNT162b2 (Pfizer/BioNTech)	N/A	N/A	N/A	FVIII	No
66	Male	HTN, dyslipidemia	BNT162b2 (Pfizer/BioNTech)	1	10	PTT ratio 2.7, FVIII <10%	FVIII	No
84	Male	N/A	BNT162b2 (Pfizer/BioNTech)	2	9	FVIII 1.75%	FVIII	No
68	Female	Hypothyroidism, dyslipidemia, endometriosis, HTN, rheumatic fever	BNT162b2 (Pfizer/BioNTech)	2	57	PTT ratio 2.3, FVIII 2%,	FVIII	No
83	Male	N/A	BNT162b2 (Pfizer/BioNTech)	2	36	FVIII 0%	FVIII	No
72	Female	Asthma, dyslipidemia, HTN, osteoarthritis, acquired hemophilia A in remission	BNT162b2 (Pfizer/BioNTech)	2	56	FVIII 4%	FVIII	No
76	Female	N/A	BNT162b2 (Pfizer/BioNTech)	1	7	N/A	FVIII	No
90	Male	DM2, stroke, obstructive arteriosclerosis of lower extremities, CKD, COVID-19	BNT162b2 (Pfizer/BioNTech)	1	70	PTT >84 s, FVIII 3%,	FVIII	Yes - hemorrhage

(Continues)

TABLE 1 (Continued)

Age, y	Sex[a]	Comorbidities	Vaccine	Dose	Days to onset following vaccination	Laboratory studies	Factor inhibitor	Death reported?
25	Female	Obesity with loss of 45 kg since gastric sleeve surgery, cholecystectomy, appendectomy	BNT162b2 (Pfizer/BioNTech)	2	10	Factor IX 176.3%; Factor XI 128%; PTT 45 s; FVIII <1%; FVIII inhibitor 88.5 BU/mL	FVIII	No
45	Female	N/A	BNT162b2 (Pfizer/BioNTech)	2	N/A	PTT ratio 2.7, FVIII <1%	FVIII	No
59	Female	None	mRNA-1273 (Moderna)	N/A	18	N/A	FVIII	No
81	Male	Coronary heart disease	BNT162b2 (Pfizer/BioNTech)	N/A	10	N/A	FVIII	No
84	Female	Complete left bundle branch block, dyslipidemia, hypothyroidism, tuberculosis	BNT162b2 (Pfizer/BioNTech)	2	39	FVIII 10%	FVIII	No
55	Male	N/A	BNT162b2 (Pfizer/BioNTech)	2	10	N/A	FVIII	No
53	Female	Rheumatoid arthritis, OSA	mRNA-1273 (Moderna)	2	2	N/A	FVIII	No
43	Female	None	BNT162b2 (Pfizer/BioNTech)	2	21	PTT 86.1 s, FVIII <5%, FVIII inhibitor 78.4 BU/mL	FVIII	No
81	Male	Angiodysplasia of cecum, BPH, DM2, valvular heart disease	BNT162b2 (Pfizer/BioNTech)	2	101	PTT 103.4 s, FVIII 1%,	FVIII	No
79	Male	Laryngeal carcinoma, granulomatosis with polyangiitis, HTN	BNT162b2 (Pfizer/BioNTech)	2	48	N/A	FVIII	No
90	Male	Post-cortisone aseptic necrosis of the femoral head, first-degree atrioventricular block, carotid artery stenosis, chronic interstitial nephritis, dilated cardiomyopathy, CKD, DM2, systemic lupus erythematosus	mRNA-1273 (Moderna)	N/A	2	N/A	FVIII	No
89	Female	Arthrosis, osteoporosis, polymyalgia rheumatica, COPD, HTN	mRNA-1273 (Moderna)	N/A	82	N/A	FVIII	No
60	Female	N/A	BNT162b2 (Pfizer/BioNTech)	N/A	32	FVIII inhibitor >500 BU/mL	FVIII	No
73	Female	N/A	BNT162b2 (Pfizer/BioNTech)	2	30	PTT 68.9 s, FVIII 4.8%, FVIII inhibitor 4.8 BU/mL	FVIII	No
72	Male	N/A	BNT162b2 (Pfizer/BioNTech)	N/A	N/A	N/A	FVIII	No
76	Male	DVT, HTN	mRNA-1273 (Moderna)	1	63	N/A	FVIII	No

Abbreviations: BPH, benign prostatic hypertrophy; BU, Bethesda Units; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM2, diabetes mellitus type 2; DVT, deep venous thrombosis; FVII, factor VII; FVIII, factor VIII; HTN, hypertension; N/A, not available in the report; OSA, obstructive sleep apnea; PTT, partial thromboplastin time; VWF, von Willebrand factor.

Data source: US Department of Health and Human Services, Public Health Service, Centers for Disease Control (CDC)/Food and Drug Administration, Vaccine Adverse Event Reporting System (VAERS) 1990 - 12/17/2021, CDC WONDER online database. Accessed at http://wonder.cdc.gov/vaers.html on December 27, 2021.

[a]Sex (binary) is the demographic variable reported by the CDC VAERS database.

TABLE 2 SARS-CoV-2 vaccine and coagulation factor inhibitors from case reports

Author(s)	Age (years)	Patient sex/ gender[a]	Comorbidities	Vaccine	Dose	Days to onset following vaccination	Laboratory studies	Factor inhibitor	Outcome
Radwi and Farsi[10]	69	Man	Diabetes, HTN, prostate adenocarcinoma in remission; no personal or family history of bleeding disorders	Not reported	1	9	PT 10.8 s, PTT 115.2 s, abnormal mixing study, FVIII activity 1%; FVIII inhibitor 80 BU/mL	Factor VIII	Alive
Shimoyama et al[11]	78	Woman	Not reported	BNT162b2 (Pfizer/ BioNTech)	2	14	PT 10.9 s, PTT 25.9 s, FVIII activity >201%, FVIII inhibitor negative, FXIII antigen 59% (reference >70%), FXIII activity <3%	Factor XIII	Deceased due to cerebral hemorrhage
Lemoine et al[12]	70	Male	Polymyalgia rheumatica, hepatitis C virus with spontaneous clearance; no personal or family history of bleeding	mRNA-1273 (Moderna)	1	2	PT 13.5 s, PTT 57.5 s, abnormal PTT mixing study, FVIII activity.03 IU/mL, FVIII inhibitor 39.9 BU/mL	Factor VIII	Alive
Farley et al[13]	67	Male	HTN, pulmonary sarcoidosis not on therapy	BNT162b2 (Pfizer/ BioNTech)	2	19	PTT 72 s, abnormal PTT mixing study, FVIII activity <1%, FVIII inhibitor 110 BU/mL	Factor VIII	Alive
Portuguese et al[15]	76	Woman	Asthma, Raynaud phenomenon, multiple episodes of large, upper extremity ecchymoses 1 year prior with decreased VWF	mRNA-1273 (Moderna)	1	4	PTT 122 s, VWF antigen 5%, VWF activity <3%, FVIII activity <3%, FVIII inhibitor 11.2 BU/ mL	Factor VIII	Alive
Gonzalez et al.[16]	43	Female	None	BNT162b2 (Pfizer/ BioNTech)	2	21	PT 13.6 s, PTT 86.1 s, abnormal PTT mixing study, FVIII activity <5%, FVIII inhibitor 78.4 BU/ mL	Factor VIII	Not reported

Abbreviations: BU, Bethesda Units; FVIII, factor VIII; HTN, hypertension; PT, prothrombin time; PTT, partial thromboplastin time; SARS-CoV-2, severe acute respiratory disorder coronavirus 2; VWF, von Willebrand factor.

[a]Based on the specific demographic variable reported by the authors.

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TABLE 3 SARS-CoV-2 infection and coagulation factor inhibitors

Author(s)	Patient age, y	Patient sex/ gender[a]	Comorbidity	Presentation	Laboratory studies	Factor inhibitor	Treatment	Outcome
Franchini et al[7]	66	Man	History of FVIII inhibitor successfully treated 9 y prior with complete remission	Fever, cough, asthenia, difficulty breathing for 3 days; extensive trunk hematoma	SARS-CoV-2 RT-PCR positive; PTT ratio, 2.87 (normal, 0.82-1.18), FVIII activity <1%, FVIII inhibitor 19 BU/mL	Factor VIII	rFVIIa until bleeding ceased and oral prednisone and cyclophosphamide (1 mg/kg/d for 4 wks, then gradually tapered)	Alive
Olsen et al[8]	83	Woman	No personal or family history of bleeding	Spontaneous bruising 1 wk after SARS-CoV-2 infection and resolution without treatment; extensive ecchymoses, iliac muscle hematoma on CT	SARS-CoV-2 RT-PCR negative, SARS-CoV-2 IgM negative, SARS-CoV-2 IgG positive; PTT 78 s (22-32 s); PTT 1:1 mix 0 min 33 s (22-35s); PTT 1:1 mix 60 min 56 s (22-35 s); INR, 0.95 (0.9-1.09); FVIII activity 2.2%; Inhibitor, 25 BU/mL	Factor VIII	Rituximab and prednisone	Alive
Hafzah et al[9]	73	Male	CKD, BPH, dyslipidemia; on apixaban for pulmonary emboli in the setting of COVID-19	Spontaneous ecchymoses of left thigh and left arm 4 mo following onset of COVID-19	INR 1.0 s, PTT 105 s; normal factor IX and XI activity; normal von Willebrand factor antigen; abnormal PTT mixing study; factor VIII activity <1%, factor VIII inhibitor 70.4 BU/mL	Factor VIII	Prednisone and cyclophosphamide daily	Alive
Ghafouri et al[17]	89	Man	HTN, DM2, advanced prostate cancer in remission	Generalized weakness, asymptomatic COVID-19 which progressed to acute respiratory failure 1 wk following admission	SARS-CoV-2 RT PCR positive; PTT, 100-130 s; abnormal PTT mixing study; FVIII activity <1%; FVIII inhibitor 2222 BU/mL; chromogenic FVIII <1%; PTT-LA screening and hexagonal phase phospholipid test positive for LA	Factor VIII		Deceased due to cardiopulmonary failure
Wang et al[18]	65	Man	CHF, sick sinus syndrome with pacemaker, COPD, Hashimoto thyroiditis	Acute dyspnea, chest pain, 1-wk history of numerous atraumatic subcutaneous ecchymoses on right extremity	SARS-CoV-2 RT-PCR negative on admission; total SARS-CoV-2 antibody test, positive (titer 5.28); PTT, 63.6 s (27.5-35.5 s); 2-h mixing study 71.9 s; FVIII activity <1%; FVIII inhibitor 176 BU	Factor VIII	Methylprednisolone IV 1 mg/kg transitioned to oral prednisone taper; weekly rituximab for 4 wks; 5-d course of cyclophosphamide 300 mg daily followed by oral cyclophosphamide taper	Alive

TABLE 3 (Continued)

Author(s)	Patient age, y	Patient sex/ gender[a]	Comorbidity	Presentation	Laboratory studies	Factor inhibitor	Treatment	Outcome
Bennett et al[19]	87	Female	CKD, DM2, HTN, hypothyroidism, Alzheimer disease	Cough, dyspnea, and diarrhea 2 wks after testing positive SARS-CoV-2 via RT-PCR; acute precipitous hemoglobin drop with left psoas muscle hematoma and left retroperitoneal cavity hematoma	INR, 5.7; PTT, 170.7 s; abnormal 1-h PTT mixing study; FV inhibitor 31.6 BU/mL	Factor V	IVIg (1 g/kg/d for 2 d), oral prednisone (1 mg/kg/d) 1 unit of platelets, TPE for 3 consecutive days with 100% FFP	Alive
Chiurazzi et al[20]	62	Woman	DM2, HTN	Recurrent hematuria and bleeding from sites of venous sampling 2 wk after treatment for COVID-19	PT, 45.5 s; INR, 4.09; PTT, 165 s; FII, FX, FVIII activities normal; FV activity 0.1%; FV inhibitor 4.0 BU/mL	Factor V	Dexamethasone 7.5 mg daily	Alive
Murray et al[21]	23	Man	No personal or family history of thrombosis or coagulopathy	Fever, productive cough, dyspnea	SARS-CoV-2 RT-PCR positive; PTT 76 s; abnormal 2-h PTT mixing study; normal FVIII, FIX, FXI, and von Willebrand factor; FXII activity 36%; FXII inhibitor <5 IU; negative testing for antiphospholipid antibodies	Factor XII	Supportive therapy with oxygen; prophylaxis for venous thrombosis with enoxaparin	Alive
Andreani et al[22]	80	Woman	Crohn disease, HTN, no personal history of bleeding	Fever, dyspnea, and need for oxygen therapy; two large axillary hematomas	SARS-CoV-2 RT-PCR positive; PTT ratio 1.49 (normal 0.80–1.18); abnormal PTT mixing study, FXI activity 37%, normal FVIII, FIX, FXII activity, negative antiphospholipid antibodies	Factor XI	Not reported	Alive

Abbreviations: BPH, benign prostatic hypertrophy; BU, Bethesda unit; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM2, diabetes mellitus type 2; FFP, fresh frozen plasma; FIX, factor IX; FVIII, coagulation factor VIII; FXI, factor XI; FXII, factor XII; HTN, hypertension; INR, international normalized ratio; IVIg, intravenous immunoglobulin; LA, lupus anticoagulant; PTT, partial thromboplastin time; rFVIIa, recombinant activated factor VII; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory disorder coronavirus 2; TPE, therapeutic plasma exchange.

[a]Based on the specific demographic variable reported by the authors.

for autoantibody formation: two patients with autoimmune disease and one patient with malignancy. No patients had a prior history of an inhibitor. The reported onset of bleeding symptoms following vaccine administration ranged from 48 hours after the first dose to 19 days after the second dose. One patient was deceased secondary to cerebral hemorrhage.

The average coagulation inhibitor titer for the five patients for which titers were reported was 64 BU/mL (SD, 39 BU/mL), ranging from 11.2 BU/mL to 110 BU/mL.

3.2 | SARS-CoV-2 infection

3.2.1 | Literature review

Nine of the 15 included articles described coagulation factor inhibitors associated with SARS-CoV-2 infection (Table 3). Five FVIII inhibitors, two factor V (FV) inhibitors, one factor XI (FXI) inhibitor, and one factor XII (FXII) inhibitor were identified among the nine patients (mean age, 69.8 [SD, 20.1] years). As expected, all patients except one with an acquired FXII inhibitor developed significant bleeding symptoms, predominantly large, expansive subcutaneous bleeding. For the eight patients with data available, the onset of bleeding ranged from 3 days to 4 months following COVID-19 symptom onset. Development of coagulation factor inhibitors did not correlate with the severity of infection, ranging from asymptomatic infection to severe cardiopulmonary failure. Forty-four percent (4/9) of patients had underlying risk factors for autoantibody formation, including two patients with autoimmune disease, one patient with malignancy, and one patient with a historical FVIII inhibitor treated 9 years prior that had been in remission since that time. One patient expired secondary to cardiopulmonary failure in the setting of recurrent hemorrhage.

The mean coagulation factor inhibitor for the seven patients with titers reported was 364 (SD, 821) BU/mL, ranging from 4 BU/mL (FV inhibitor) to 2222 BU/mL (FVIII inhibitor).

Therapeutic interventions to ameliorate bleeding symptoms included recombinant activated factor VII (rFVIIa) and anti-inhibitor coagulant complex. Immunosuppressive therapy regimens to eradicate the inhibitors were variable and included: rituximab, corticosteroids, and cyclophosphamide. Notably, one patient with a FV inhibitor did not respond to intravenous immunoglobulin and corticosteroid therapy; thus, three therapeutic plasma exchange procedures over consecutive days using one total body volume of 100% fresh frozen plasma during each procedure was performed with subsequent resolution of bleeding symptoms.

4 | DISCUSSION

Factor inhibitors are rare and tend to associate with advanced age, pregnancy, autoimmune conditions, or malignancy, though a large proportion have no identifiable cause.[23] General population data show a cumulative rate of 1.5 cases per million persons/year,[23] and a cohort of 501 patients with FVIII inhibitors demonstrated that 11.8% and 11.6% were associated with malignancy and autoimmune diseases, respectively.[24] However, the rate in SARS-CoV-2–vaccinated individuals appeared lower in this study, and accurate estimation of the incidence in patients with SARS-COV-2 infection has not been determined at this time. It remains unclear what, if any, etiologic role SARS-CoV-2 vaccination or infection plays in the pathogenesis of these inhibitors. Similarly, the association between acquired coagulation factor inhibitors and other infectious diseases and vaccinations is unknown, as only isolated case reports have described patients with influenza infection,[25] hepatitis C virus and HIV infections,[26] and following influenza vaccination.[27,28] Nevertheless, this comprehensive analysis of coagulation factor inhibitors in patients with COVID-19 and SARS-CoV-2–vaccinated individuals highlights both the challenge and necessity of making this diagnosis accurately and promptly given the potential hemorrhagic sequelae.

Coagulation factor inhibitors represent a heterogenous group of autoantibodies capable of disrupting any step in the clotting cascade either by direct inhibition or increased clearance of clotting factors, rendering standardization of therapy in this population challenging.[29] Most factor inhibitors increase the risk of a bleeding diathesis, with the notable exception of FXII inhibitors, as demonstrated by the patient in this study without bleeding. The hemorrhagic predisposition associated with coagulation factor inhibitors is especially concerning in patients admitted with COVID-19, as many receive therapeutic anticoagulation to prevent thromboembolic events. Current literature suggests that anticoagulation with heparin is preferred, as it has shown a reduction in inpatient mortality, while direct oral anticoagulants are being considered for use as anticoagulation after discharge.[14,29-31] While the incidence of acquired autoantibodies appears to be rare in patients following SARS-CoV-2 infection and SARS-CoV-2 vaccination, systemic anticoagulation in this group should be performed with great caution given the risk for catastrophic bleeding in these patients, highlighting the need for an individualized approach to management, and demonstrating the importance of laboratory assessment before systemic anticoagulation.

Limitations to this study include the retrospective nature of the methods and reliance on published literature for case details, as well as underreporting and incomplete data availability in the VAERS database. Given the high rates of publication in patients with COVID-19, potential causes for inhibitors may have been falsely attributed to the disease or vaccination, as approximately half of reported SARS-CoV-2–associated inhibitors include patients with comorbid conditions that could potentially contribute to autoantibody development. VAERS data are useful given their national scope, though the passive nature and variability of reported data are limitations. Furthermore, VAERS database information includes all reported side effects occurring in association with US-licensed vaccines, regardless of the geographic location of vaccination, while CDC data on vaccine dose administration are available only for doses provided within the United States, limiting case estimation accuracy. Nonetheless, this work provides a comprehensive review

of available data from currently published medical literature and the VAERS database system, and is the first study assessing acquired coagulation factor inhibitors in patients with SARS-CoV-2 infection and in SARS-CoV-2–vaccinated individuals.

Monitoring hemostasis in patients with COVID-19 remains complex, with the standard-of-care continually evolving. The incidence of coagulation factor inhibitors in patients with SARS-CoV-2 infection appears to be similar to the cumulative incidence in the general population. Nonetheless, given the thromboembolic risk and importance of heparin therapy, careful assessment and monitoring of coagulation status is a necessity in this high-risk population. Though the development of these inhibitors is rare in individuals with SARS-CoV-2 infection and following SARS-CoV-2 vaccination, clinicians and laboratories should be aware of this potential adverse event and be familiar with testing and management of patients with these inhibitors.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

JWJ designed the manuscript, analyzed the data, drafted the manuscript, and approved the final version. BDA drafted the manuscript, performed statistical analysis, interpreted the data, and approved the final version. SCW interpreted the data, revised the manuscript, and approved the final version. GSB analyzed the data, revised the manuscript, supervised the project, and approved the final version. APW supervised the project, revised the manuscript, and approved the final version.

ORCID

Jeremy W. Jacobs https://orcid.org/0000-0002-5719-9685
Brian D. Adkins https://orcid.org/0000-0002-9480-2762
Shannon C. Walker https://orcid.org/0000-0003-4390-3931
Garrett S. Booth https://orcid.org/0000-0002-8422-9480
Allison P. Wheeler https://orcid.org/0000-0003-3967-4873

TWITTER

Jeremy W. Jacobs @jwjacobs12
Brian D. Adkins @path_brian
Garrett S. Booth @DrGSBooth1
Allison P. Wheeler @allisonp1979

REFERENCES

1. Bhattacharjee S, Banerjee M. Immune thrombocytopenia secondary to COVID-19: a systematic review. *SN Compr Clin Med*. 2020;2(11):2048-2058. doi:10.1007/s42399-020-00521-8
2. Jacobs JW, Booth GS. COVID-19 and immune-mediated RBC. *Am J Clin Pathol*. 2021;aqab210. doi:10.1093/ajcp/aqab210 [Online ahead of print]
3. Pishko AM, Bussel JB, Cines DB. COVID-19 vaccination and immune thrombocytopenia. *Nat Med*. 2021;27:1145-1146. doi:10.1038/s41591-021-01419-1
4. Mahévas M, Moulis G, Andres E, et al. Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: a French multicentre series. *Br J Haematol*. 2020;190:e224-e229. doi:10.1111/bjh.17024
5. Dotan A, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y. The SARS-CoV-2 as an instrumental trigger of autoimmunity. *Autoimmun Rev*. 2021;20:102792. doi:10.1016/j.autrev.2021.102792
6. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136:489-500. doi:10.1182/blood.2020006520
7. Franchini M, Glingani C, De Donno G, et al. The first case of acquired hemophilia A associated with SARS-CoV-2 infection. *Am J Hematol*. 2020;95:E197-E198. doi:10.1002/ajh.25865
8. Olsen GM, Rinder HM, Tormey CA. De novo acquired hemophilia as an immune dysregulation phenomenon following SARS-CoV-2 infection. *Transfusion*. 2021;61:989-991. doi:10.1111/trf.16254
9. Hafzah H, McGuire C, Hamad A. A case of acquired hemophilia A following SARS-CoV-2 infection. *Cureus*. 2021;13:e16579. doi:10.7759/cureus.16579
10. Radwi M, Farsi S. A case report of acquired hemophilia following COVID-19 vaccine. *J Thromb Haemost*. 2021;19:1515-1518. doi:10.1111/jth.15291
11. Shimoyama S, Kanisawa Y, Ono K, Souri M, Ichinose A. First and fatal case of autoimmune acquired factor XIII/13 deficiency after COVID-19/SARS-CoV-2 vaccination. *Am J Hematol*. 2022;97(2):243–245. doi:10.1002/ajh.26426
12. Lemoine C, Giacobbe AG, Bonifacino E, Karapetyan L, Seaman C. A case of acquired haemophilia A in a 70-year-old post COVID-19 vaccine. *Haemophilia*. 2022;28(1):e15–e17. doi10.1111/hae.14442
13. Farley S, Ousley R, Van Wagoner N, Bril F. Autoimmunity after coronavirus disease 2019 (COVID-19)vaccine: a case of acquired hemophilia A. *Thromb Haemost*. 2021;121(12):1674-1676. doi:10.1055/a-1579-5396
14. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial [published correction appears in JAMA Intern Med. 2021 Dec 28]. *JAMA Intern Med*. 2021;181:1612-1620. doi:10.1001/jamainternmed.2021.6203
15. Portuguese AJ, Sunga C, Kruse-Jarres R, Gernsheimer T, Abkowitz J. Autoimmune- and complement-mediated hematologic condition recrudescence following SARS-CoV-2 vaccination. *Blood Adv*. 2021;5:2794-2798. doi:10.1182/bloodadvances.2021004957
16. Gonzalez R, Gutierrez-Nunez J, Fonseca Ferrer V, Torres G, Alvarez CN. "Dark skin"-acquired hemophilia A after Pfizer-BIONTECH COVID-19 vaccine. *Chest*. 2021;160:A1384. doi:10.1016/j.chest.2021.07.1265
17. Ghafouri S, Rettig M, Kahlon KS. An 89-year-old man with COVID-19-associated coagulopathy presenting with a prolonged partial thromboplastin time, lupus anticoagulant, and a high titer of factor VIII Inhibitor. *Am J Case Rep*. 2020;21:e926728. doi:10.12659/AJCR.926728
18. Wang KY, Shah P, Roarke DT, Shakil SA. Severe acquired haemophilia associated with asymptomatic SARS-CoV-2 infection. *BMJ Case Rep*. 2021;14:e242884. doi:10.1136/bcr-2021-242884
19. Bennett J, Cunningham MT, Howard C, Hoffmann M, Plapp FV. Acquired factor V inhibitor in the setting of coronavirus disease 2019 infection. *Blood Coagul Fibrinolysis*. 2021;32:294-297. doi:10.1097/MBC.0000000000001009
20. Chiurazzi F, Tufano A, Esposito M, et al. Acquired factor V inhibitor after coronavirus disease 2019 (COVID-19). *Semin Thromb Hemost*. 2022;48(01):124-126. doi:10.1055/s-0041-1735452
21. Murray NP, Guzman E, Del Prado M. Transient acquired factor XII deficiency associated with moderately severe Covid-19 pneumonia. *Hematol Transfus Cell Ther*. 2021;43:515-517. doi:10.1016/j.htct.2021.06.017

22. Andreani G, Uscello L, Montaruli B, et al. Acquired factor XI deficiency during SARS-CoV-2 infection: not only thrombosis. *TH Open*. 2020;4:e233-e235. doi:10.1055/s-0040-1714696
23. Franchini M, Castaman G, Coppola A, et al. Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management. *Blood Transfus*. 2015;13:498-513. doi:10.2450/2015.0141-15
24. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost*. 2012;10:622-631. doi:10.1111/j.1538-7836.2012.04654.x
25. Peña-Muñoz F, Parras E, Compan O, et al. Acquired haemophilia A in association with influenza A and urinary tract infection. *Eur J Case Rep Intern Med*. 2020;7:001678. doi:10.12890/2020_001678
26. Zeichner SB, Harris A, Turner G, Francavilla M, Lutzky J. An acquired factor VIII inhibitor in a patient with HIV and HCV: a case presentation and literature review. *Case Rep Hematol*. 2013;2013:628513. doi:10.1155/2013/628513
27. Moulis G, Pugnet G, Bagheri H, et al. Acquired factor VIII haemophilia following influenza vaccination. *Eur J Clin Pharmacol*. 2010;66:1069-1070. doi:10.1007/s00228-010-0852-z
28. Pirrotta MT, Bernardeschi P, Fiorentini G. A case of acquired haemophilia following H1N1 vaccination. *Haemophilia*. 2011;17:815. doi:10.1111/j.1365-2516.2011.02493.x
29. Hadid T, Kafri Z, Al-Katib A. Coagulation and anticoagulation in COVID-19. *Blood Rev*. 2021;47:100761. doi:10.1016/j.blre.2020.100761
30. Lopes RD, de Barros E, Silva PGM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397:2253-2263. doi:10.1016/S0140-6736(21)01203-4
31. Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2022;399(10319):50-59. doi:10.1016/S0140-6736(21)02392-8

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