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BRIEF REPORT

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

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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
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, autoimmune hemolytic anemia, and vaccine-induced thrombosis and thrombocytopenia 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. 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.

Several case reports have recently described acquired coagulation factor inhibitors in the setting of SARS-CoV-2 infection or following SARS-CoV-2 vaccination. 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. 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 and Prevention’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
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
| Age, y | Sex  | Comorbidities                                                                 | Vaccine                          | Days to onset following vaccination | Laboratory studies                                                                 | Factor inhibitor | Death reported? |
|--------|------|-------------------------------------------------------------------------------|----------------------------------|------------------------------------|-----------------------------------------------------------------------------------|-----------------|-----------------|
| 69     | Male | Prostate cancer in remission, HTN, DM2                                        | BNT162b2 (Pfizer/BioNTech)       | 1                                  | 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              |
| Age, y | Sex | 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)
| Age, y | Sex | 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.

*aSex (binary) is the demographic variable reported by the CDC VAERS database.*
| Author(s)          | Age (years) | Patient sex/gender | Comorbidities                                                                 | Vaccine          | Dose | Days to onset following vaccination | Laboratory studies                                                                 | Factor inhibitor | Outcome               |
|-------------------|-------------|--------------------|------------------------------------------------------------------------------|------------------|------|------------------------------------|---------------------------------------------------------------------------------|-----------------|----------------------|
| Radwi and Farsi   | 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   | 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     | 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 0.3 IU/mL, FVIII inhibitor 39.9 BU/mL | Factor VIII     | Alive                |
| Farley et al      | 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  | 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    | 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; FVII, factor VIII; HTN, hypertension; PT, prothrombin time; PTT, partial thromboplastin time; SARS-CoV-2, severe acute respiratory disorder coronavirus 2; VWF, von Willebrand factor.

*Based on the specific demographic variable reported by the authors.
| Author(s)                     | Patient age, y | Patient sex/gender | Comorbidity                                                                 | Presentation                                                                 | Laboratory studies                                                                 | Factor inhibitor | Treatment                                                                 | Outcome            |
|------------------------------|----------------|--------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------|----------------------------------------------------------------------------|-------------------|
| Franchini et al7             | 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 al8                 | 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 (22-35 s); 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 al9                | 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             |
| Ghafoori et al17             | 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; FVII 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 al18                 | 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             |
| Author(s)          | Patient age, y | Patient sex/ gender | 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        | IVlg (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%; FXI 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; 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; IVlg, 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.

*aBased 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 titeres 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. General population data show a cumulative rate of 1.5 cases per million persons/year, and a cohort of 501 patients with FVIII inhibitors demonstrated that 11.8% and 11.6% were associated with malignancy and autoimmune diseases, respectively. 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, hepatitis C virus and HIV infections, and following influenza vaccination. 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 heterogeneous 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. 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. 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.

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