COVID-19 and Immune-Mediated RBC Destruction
A Systematic Review

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ABSTRACT

Objectives: To summarize the epidemiologic, clinical, and laboratory characteristics of autoimmune hemolytic anemia (AIHA) secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or vaccination.

Methods: We conducted a systematic review using standardized keyword search to identify all reports of SARS-CoV-2 infection or vaccination and AIHA across PubMed, Web of Science, Scopus, and Google Scholar through September 24, 2021.

Results: Fifty patients (mean [SD] age, 50.8 [21.6] years) diagnosed with coronavirus disease 2019 (COVID-19) and AIHA were identified. AIHA subtypes and number of patients were as follows: cold AIHA (n = 18), warm AIHA (n = 14), mixed-type AIHA (n = 3), direct antiglobulin test (DAT)–negative AIHA (n = 1), DAT-negative Evans syndrome (n = 1), Evans syndrome (n = 3), and subtype not reported (n = 10). Mean (SD) hemoglobin at AIHA diagnosis was 6.5 [2.8] g/dL (95% confidence interval, 5.7-7.3 g/dL). Median time from COVID-19 symptom onset to AIHA diagnosis was 7 days. In total, 19% (8/42) of patients with COVID-19–associated AIHA with reported outcomes were deceased. Four patients (mean [SD] age, 73.5 [16.9] years) developed AIHA following SARS-CoV-2 vaccination: Pfizer-BioNTech BNT162b2 vaccine (n = 2); Moderna mRNA-1273 vaccine (n = 1); undisclosed mRNA vaccine (n = 1). AIHA occurred after 1 dose in 3 patients (median, 5 days).

Conclusions: SARS-CoV-2 infection and vaccination are associated with multiple AIHA subtypes, beginning approximately 7 days after infectious symptoms and 5 days after vaccination.

INTRODUCTION

The manifestations of symptomatic coronavirus disease 2019 (COVID-19) are heterogenous, with a broad spectrum of systemic complications described. Evidence is mounting that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral agent responsible for COVID-19, can induce a multitude of hematologic abnormalities, with an accumulation of case reports and small case series suggesting that autoimmune hemolytic anemia (AIHA) may be associated with COVID-19.1-10

AIHA is a rare disorder, with an estimated incidence of 1 to 3 per 100,000 people annually. Approximately half of all AIHA cases are idiopathic, while secondary cases are often associated with underlying autoimmune or lymphoproliferative diseases.11 Reports of AIHA occurring in the context of several infectious diseases have been described, but a few pathogens have a well-described association with AIHA, including human immunodeficiency virus (HIV), Mycoplasma pneumoniae, and Epstein-Barr virus (EBV).12,13

KEY POINTS

• The epidemiologic, clinical, and laboratory characteristics of patients with coronavirus disease 2019 (COVID-19) and autoimmune hemolytic anemia (AIHA) are unknown.

• COVID-19 is associated with warm and cold AIHA, with a mean hemoglobin of 6.5 g/dL at AIHA diagnosis, which occurs approximately 7 days after COVID-19 symptom onset.

• COVID-19 is a risk factor for the development of AIHA, and patients should be monitored for this rare but potentially fatal outcome.

KEY WORDS

COVID-19; SARS-CoV-2; SARS-CoV-2 vaccine; Autoimmune hemolytic anemia; Hemolysis; Cold agglutinin disease
Although, a definitive link between COVID-19 and AIHA has not been established, nor has an exact mechanism underlying this potential association been elucidated, several hypotheses have emerged, including immunologic hyperstimulation and molecular mimicry.\textsuperscript{1,14}

Most of the evidence proposing an association between COVID-19 and AIHA is based on single case report data, much of which are limited in scope, design, and analysis. Given this overall paucity of data, this systematic review aimed to analyze the epidemiology, laboratory and blood bank parameters, therapeutic interventions, outcome, and AIHA subtype in patients with SARS-CoV-2 infection or vaccination.

**MATERIALS AND METHODS**

**Case Selection**

We performed a comprehensive literature review to identify all reports of SARS-CoV-2 infection or vaccination. We analyzed these studies to determine by keyword search any description of immune-mediated RBC destruction. The comprehensive list of keywords was as follows:

- COVID-19: “COVID,” “COVID-19,” “COVID 19,” “coronavirus 19,” “coronavirus disease,” “novel coronavirus,” “SARS-CoV-2,” “SARS,” “severe acute respiratory syndrome,” “severe acute respiratory syndrome coronavirus 2,” “COVID-19 vaccine,” “COVID 19 vaccine,” “COVID-19 immunization,” “coronavirus vaccine,” “COVID vaccine”
- AIHA: “autoimmune hemolytic anemia,” “hemolytic anemia,” “hemolysis,” “Coombs-positive anemia,” “Coombs hemolysis,” “AIHA,” “immune hemolysis,” “cold agglutinin,” “cold agglutinin disease,” “warm autoimmune anemia,” “mixed autoimmune hemolytic anemia,” “Evans Syndrome”

Searches were conducted across 4 scientific databases (PubMed, Web of Science, Scopus, Google Scholar) according to a standardized search protocol through September 24, 2021. Abstracts and titles were screened according to specific inclusion criteria. The search method is depicted in Figure 1. All included publications were coded into relevant categories based on a standardized protocol.

In addition to the multidatabase search, we queried the US Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS) to look for reports of potential adverse events (AEs) associated with receipt of a SARS-CoV-2 vaccine.\textsuperscript{15}

**Inclusion Criteria**

Inclusion criteria for this analysis were as follows: (1) COVID-19 confirmed by detection of SARS-CoV-2 nucleic acid by reverse transcription–polymerase chain reaction (RT-PCR) or receipt of 1 or more dose of a SARS-CoV-2 vaccine and (2) case reports, case series, and cohort studies describing 1 or more patients with a diagnosis of AIHA.

**Exclusion Criteria**

Exclusion criteria for this analysis were (1) duplicate publications, (2) articles not in English, (3) reviews or in vitro or in vivo experiments, (4) cases with concerns regarding temporality or unobserved associations between COVID-19 and AIHA, (5) cases without positive COVID-19 tests by RT-PCR, and (6) cases of COVID-19 and concurrent hemolysis secondary to nonimmune etiologies.

**Data Analysis**

We selected 92 articles for screening to assess their relevance for inclusion in the analysis. In total, 88 reports described COVID-19 infection, and 4 referenced SARS-CoV-2 vaccination. We included 43 reports in the study, 39 of which describe AIHA associated with COVID-19 and 4 of which describe AIHA associated with SARS-CoV-2 vaccination. The following is a comprehensive record of data categories extracted from the articles:

- Bibliographic information: titles, authors, number of patients
- Patient data: age, sex, comorbidities, symptoms of COVID-19 at presentation, time from COVID-19 symptom onset or SARS-CoV-2 vaccination to AIHA diagnosis, therapeutic interventions for AIHA, immunization status
- Laboratory data: hemoglobin at presentation, hemoglobin nadir, lactate dehydrogenase (LDH) at AIHA diagnosis, haptoglobin at AIHA diagnosis, SARS-CoV-2 RT-PCR test result
- Blood bank data: direct antiglobulin test (DAT) results, cold agglutinin evaluation, cold agglutinin titers, thermal amplitude test, other blood bank serologic results
- Outcome: patient alive or deceased at the time of the report

The classification of AIHA subtype was determined by review of the authors’ reported diagnosis. In cases where the original authors did
not explicitly classify the subtype of AIHA, we reported the diagnosis simply as “AIHA” in TABLE 1 and TABLE 2. For these unclassified cases in which the clinical, laboratory, and blood bank evaluation were sufficient to clearly indicate a definitive AIHA classification, we included our AIHA classification in addition to the original unclassified diagnosis (see “Results”). To analyze outcomes, we used a binary parameter of either alive or deceased at the time of the report. If the original authors reported the suspected cause of death, we included the data for those patients reported to be deceased. All statistical analyses were conducted using Microsoft Excel, version 16.53 (Microsoft).

RESULTS

COVID-19 and AIHA
A total of 50 patients with AIHA associated with SARS-CoV-2 infection (TABLE 1) and 4 patients with AIHA associated with SARS-CoV-2 vaccination (TABLE 4) were included in the analysis. The mean (SD) age of patients with SARS-CoV-2 infection and AIHA was 50.8 (21.6) years. In total, 83% (33/40) of patients with reported medical history had at least 1 comorbidity. Eighteen patients were diagnosed with cold AIHA, 14 with warm AIHA, 3 with mixed AIHA, 1 with DAT-negative AIHA, 1 with DAT-negative Evans syndrome, and 3 with Evans syndrome; in 10 cases, the original authors did not report the AIHA subtype. Following review of the 10 cases of AIHA that were not classified in the original reports, we subsequently classified 3 as probable cold AIHA and 4 as probable warm AIHA; 3 could not be classified because of insufficient data.

The median (interquartile range [IQR]) time frame from COVID-19 symptom onset to AIHA diagnosis was 7 (6.5) days, ranging from 0 to 20 days following development of COVID-19 symptoms. The mean (SD) hemoglobin value at AIHA diagnosis was 6.5 (2.8) g/dL (95% confidence interval [CI], 5.7-7.3 g/dL), the mean (SD) hemoglobin nadir was 5.7 (2.3) g/dL (95% CI, 4.6-6.8 g/dL), the mean (SD) LDH level was 1,124 (828) U/L (95% CI, 833-1,415 U/L), and the mean (SD) haptoglobin level was 27.3 (50.9) mg/dL (95% CI, 8.8-45.8 mg/dL). DAT was positive in 96% (48/50) of patients, a large proportion of whom were positive for C3 (30/38 [79%]), both with (16/38 [42%]) and without (14/38 [37%]) concurrent immunoglobulin G (IgG) (TABLE 2). Cold agglutinins were identified in all 14 patients tested, 64% (9/14) of whom had titers performed. In total, 78% (7/9) of cold agglutinin titers were considered clinically significant based on the titer (≥64), ranging from 8 to 16,384. Thermal amplitude testing was performed in 5 patients, and all 5 had clinically significant cold agglutinins because all reacted at 30°C (n = 2) or 37°C (n = 3).

In total, 44% (22/50) of patients with COVID-19 and AIHA were female. There was no statistically significant difference in the mean

| TABLE 1 | Cases of Confirmed Coronavirus Disease 2019 Infection Associated With Autoimmune Hemolytic Anemia |
|----------|---------------------------------------------------------------------------------------------------|
| Author   | Patient Age, y | Patient Sex | Comorbidity | DAT | Reported Diagnosis | AIHA Treatment | RBC Transfusion (No. of Units) | Outcome |
| Capes et al | 62 | M | HTN, oropharyngeal SCC | IgG (−) C3d (−) | AHA | Not reported | Yes (8) | Alive |
| Jacobs et al | 33 | F | Hypothyroidism | IgG (+) C3d (−) | Mixed AIHA | Corticosteroids, rituximab | Yes (1) | Alive |
| Maslov et al | 48 | M | HTN, IDDM, obesity, ESRD | Positive | Cold AIHA | Not reported | Yes (not reported) | Deceased (intracerebral insult) |
| Lazarian et al | 61 | M | HTN, CKD, CLL | IgG (+) C3d (+) | Warm AIHA | Corticosteroids | No | Alive |
| Lazarian et al | 89 | F | HTN, CKD, atrial fibrillation, MGUS | IgG (+) C3d (+) | Warm AIHA | Corticosteroids | No | Alive |
| Lazarian et al | 62 | F | HTN, hepatic cirrhosis, MZL | IgG (−) C3d (+) | Cold AIHA | Corticosteroids, rituximab | No | Alive |
| Lazarian et al | 69 | F | Obesity, MZL | IgG (+) C3d (+) | Cold AIHA | Corticosteroids | No | Alive |
| Lazarian et al | 61 | M | HTN, CKD, diabetes, hypercholesterolemia, prostate carcinoma | IgG (−) C3d (−) | Cold AIHA | None | Yes (not reported) | Alive |
| Lazarian et al | 61 | M | Diabetes | IgG (+) C3d (+) | Warm AIHA | Corticosteroids, rituximab | No | Alive |
| Lazarian et al | 75 | M | Diabetes, hypercholesterolemia, obesity, COPD, CLL | IgG (+) | Warm AIHA | None | Yes (not reported) | Alive |
| Hindlerten et al | 56 | M | HTN | IgG (+) C3d (+) | Warm AIHA | IVIG, corticosteroids | No | Alive |
| Author | Patient Age, y | Patient Sex | Comorbidity | DAT | Reported Diagnosis | AIHA Treatment | RBC Transfusion (No. of Units) | Outcome |
|--------|---------------|-------------|-------------|-----|-------------------|----------------|--------------------------------|---------|
| Wahlster et al27 | 17 | M | Chronic immune thrombocytopenia | IgG (+) C3 (+) | Warm AIHA | Corticosteroids | Not reported | Alive |
| Zagorski et al25 | 46 | F | ITP, asthma | IgG (+) C3 (+) | Cold AIHA | None | Yes (not reported) | Deceased (cardiac arrest) |
| Lopez et al26 | 46 | F | Congenital thrombocytopenia | IgG (+) C3 (+) | Warm AIHA | IVIG, corticosteroids | Yes (3) | Alive |
| Singhavi et al27 | 20 | M | None | Not reported | AIHA | Corticosteroids | Yes (not reported) | Alive |
| Patil et al29 | 51 | F | Breast carcinoma | IgG (−) C3 (+) | Cold AIHA | Corticosteroids | Yes (not reported) | Alive |
| Jawed et al30 | Early 50s | M | HTN | IgG (−) C3d (+) | AHA | None | No | Alive |
| Wodzie et al22 | 24 | M | AHA in remission | IgG (+) C3 (+) | AHA | Corticosteroids, cyclophosphamide | Not reported | Deceased (fulminant Cryptococcus infection) |
| Bae et al31 | 51 | M | None | IgG (−) C3 (+) | AHA with DAT negative for IgG and C3 | IVIG for 3 d | Yes (1) | Alive |
| Vega Hernández et al27 | 13 | F | Psoriasis | IgG (+) C3d (+) | AHA | Corticosteroids | No | Alive |
| Huda et al29 | 54 | M | Diabetes | IgG (+) | AHA | Corticosteroids | Not reported | Not reported |
| Heis et al27 | 84 | M | Hypercholesterolemia | IgG (+) | Warm AIHA | Corticosteroids | Yes (5) | Alive |
| Raghuwanshi27 | 45 | M | Not reported | Positiveb | Cold AIHA | Not reported | Yes (2) | Not reported |
| Liput et al28 | 33 | F | None | IgG (−) C3 (+) | Warm AIHA | Corticosteroids | Yes (1) | Alive |
| Nesr et al26 | 80 | F | CLL | IgG (−) C3d (+) | Cold AIHA | Not reported | No | Alive |
| Huscenot et al27 | 43 | F | Obesity, multiple sclerosis | Positiveb | Cold AIHA | Not reported | Yes (not reported) | Not reported |
| Huscenot et al27 | 63 | M | HTN | IgG (+) C3d (+) | Cold AIHA | Not reported | Not reported | Not reported |
| Gupta et al27 | 77 | M | COPD, G6PD deficiency | C3d (+) | Cold AIHA | Corticosteroids | Yes (3) | Deceased (cardiovascular failure) |
| Renganathan et al27 | 42 | F | Not reported | Positiveb | Mixed AIHA | Corticosteroids | No | Not reported |
| Rosenzweig et al27 | 14 | F | Not reported | IgG (+) C3d (+) | Mixed AIHA | Corticosteroids, rituximab for 4 wk | Yes (not reported) | Alive |
| Ramos-Ruperto et al27 | 54 | M | None | IgG (−) C3d (+) | Cold AIHA | Corticosteroids, plasma exchange for 5 sessions | Not reported | Alive |
| Ramos-Ruperto et al27 | 72 | F | None | IgG (+) C3d (+) | Warm AIHA | Corticosteroids | Yes (not reported) | Alive |
| Ramos-Ruperto et al27 | 76 | F | HTN, hypothyroidism, CLL | IgG (+) C3d (+) | Warm AIHA | Corticosteroids | Yes (not reported) | Alive |
| Alagüé et al27 | 69 | F | CLL | C3 (+) | Cold AIHA | Corticosteroids, IVIG for 2 d, rituximab for 4 wk | Not reported | Alive |
| McGregor et al27 | 75 | M | HTN, CKD, obesity | Positiveb | AHA | Corticosteroids | Not reported | Deceased (multorgan failure) |
| Pandey et al27 | 31 | M | Not reported | IgG (+) C3 (+) | AHA | Corticosteroids | Yes (2) | Alive |
| Sujana et al27 | 59 | F | Not reported | Positiveb | AHA | Corticosteroids | Yes (9) | Alive |
TABLE 1 (cont)

| Author            | Patient Age, y | Patient Sex | Comorbidity     | DAT | Reported Diagnosis | AIHA Treatment | RBC Transfusion (No. of Units) | Outcome          |
|-------------------|----------------|-------------|-----------------|-----|--------------------|----------------|-------------------------------|------------------|
| Nair et al<sup>34</sup> | 23             | M           | Asthma          | IgG (+) | Warm AIHA         | Corticosteroids for 3 mo | Yes (2) | Alive                        |
| Sari et al<sup>35</sup> | 94             | F           | CKD, HPeF       | IgG (−) C3 (+) | Cold AIHA        | Not reported | Yes (6) | Deceased (cardiopulmonary failure) |
| Ahmadnejad et al<sup>36</sup> | 49             | F           | Thalassemia     | IgG (−) C3 (+) | Cold AIHA        | Not reported | Yes (not reported) | Deceased (not reported) |
| Hassanein et al<sup>17</sup> | 48             | M           | Not reported    | IgG (−) C3d (+) | Cold AIHA        | Not reported | Yes (not reported) | Alive            |
| Campos-Cabrera et al<sup>18</sup> | 35             | F           | Not reported    | IgG (+) C3d (+) | Warm AIHA        | Corticosteroids, IVIG | Not reported | Alive            |
| Campos-Cabrera et al<sup>16</sup> | 58             | F           | Not reported    | IgG (+) C3d (+) | Warm AIHA        | Corticosteroids, IVIG | Not reported | Alive            |
| Li et al<sup>37</sup> | 39             | M           | Not reported    | Positive<sup>4</sup> | Evans syndrome | IVIG | Not reported | Alive            |
| Gruden et al<sup>15</sup> | 83             | F           | HTN             | IgG (−) C3 (−) | Evans syndrome, with DAT negative for IgG and C3d | Corticosteroids, IVIG for 5 d | Yes (1) | Alive            |
| Georgy et al<sup>1</sup> | 33             | M           | Not reported    | Positive<sup>4</sup> | Evans syndrome | Corticosteroids | Not reported | Deceased (intracerebral hemorrhage) |
| Zama et al<sup>26</sup> | 15             | M           | None            | IgG (+) C3 (+) | Evans syndrome | Corticosteroids for 32 d, IVIG for 3 d | Yes (6) | Alive            |
| Zama et al<sup>26</sup> | 2              | M           | 6 mo after HSCT for β-thalassemia major | IgG (+) C3 (+) IgM (+) | Cold AIHA | Corticosteroids for 42 d | Yes (not reported) | Alive            |
| Kumarhamy et al<sup>11</sup> | 50             | M           | None            | IgG(−) C3d (+) | Cold AIHA        | Corticosteroids | Yes (5) | Alive            |
| Hasan et al<sup>28</sup> | 45             | M           | Hypothyroidism  | Positive<sup>6</sup> | AHA | Corticosteroids for 12 wk | Not reported | Alive            |

AIHA, autoimmune hemolytic anemia; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DAT, direct antiglobulin test; ESKD, end-stage renal disease; HPeF, heart failure with preserved ejection fraction; HSCT, hematopoietic stem cell transplantation; HTN, hypertension; IDDM, insulin-dependent diabetes mellitus; Ig, immunoglobulin; ITP, immune thrombocytopenia purpura; IVIG, intravenous immunoglobulin G; MGUS, monoclonal gammopathy of undetermined significance; MZL, marginal zone lymphoma; RT-PCR, reverse-transcription polymerase chain reaction; SCC, squamous cell carcinoma.

<sup>a</sup>Cold AIHA compared with warm AIHA (6.2 g/dL vs 7.1 g/dL; P = .72) for those diagnosed with warm AIHA compared with cold AIHA (6.2 g/dL vs 7.1 g/dL; P = .38).

TABLE 2 Cases of Autoimmune Hemolytic Anemia Associated With Receipt of at Least 1 Dose of SARS-CoV-2 Vaccine

| Author      | Patient Age, y | Patient Sex | DAT | Timing of Symptoms | AIHA Treatment | RBC Transfusion (No. of Units) | Vaccine Received | Diagnosis     |
|-------------|----------------|-------------|-----|--------------------|----------------|-------------------------------|-----------------|--------------|
| Murdych<sup>16</sup> | 84             | M           | IgG (+) C3 (−) | 19 d after first dose | Corticosteroids | Yes (2) | BNT162z2b (Pfizer-BioNTech) | AHA            |
| Brito et al<sup>36</sup> | 88             | F           | IgG (+) C3 (+) | 2 d after second dose (23 d after first dose) | Corticosteroids | Yes (1) | mRNA vaccine | AHA            |
| Gaignard et al<sup>16</sup> | 77             | M           | IgG (+) C3 (+) | 5 d after first dose | Corticosteroids | Not reported | mRNA-1273 (Moderna) | Warm AIHA    |
| Aoun et al<sup>45</sup> | 45             | F           | IgG (−) C3 (−) | 3 d after first dose | RituXimab weekly for 4 wk | Yes (not reported) | BNT162z2b (Pfizer-BioNTech) | Cold AIHA |

AIHA, autoimmune hemolytic anemia; DAT, direct antiglobulin test; Ig, immunoglobulin; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

For patients with RBC transfusion therapy data reported, 74% (28/38) received at least 1 unit of RBCs. The number of transfused RBCs was documented for 25 patients, with a mean (SD) of 2.6 (3.2) units and a median (IQR) of 1 (0–5) unit transfused to these patients.
patients. Corticosteroids (n = 35), the most common of which was prednisone 1 mg/kg per day, were the most frequently used therapy for AIHA, while intravenous IgG (IVIG) 1 mg/kg per day (n = 9), rituximab 375 mg/m² weekly (n = 5), and cyclophosphamide (n = 1) were employed in select patients. One patient with cold AIHA received 5 sessions of plasma exchange in addition to corticosteroids, but the replacement fluid type was not reported.

In total, 19% (8/42) of patients with reported outcomes were deceased. The mean (SD) age of the deceased patients was 55.8 (22.4) years (95% CI, 40.3-71.3 years). Of the deceased patients, 5 had cold AIHA and 1 had Evans syndrome; in 2 patients, the original authors did not classify the AIHA. In total, 88% (7/8) of deceased patients had multiple underlying medical comorbidities, including hemolytic risk factors such as a history of AIHA in remission, immune thrombocytopenic purpura in remission, thalassemia, and G6PD deficiency.

SARS-CoV-2 Vaccination and AIHA

New-onset AIHA was reported in 4 patients following receipt of a SARS-CoV-2 vaccine. Two of these patients received the BNT162b2 (Pfizer-BioNTech) vaccine; 1 received the mRNA-1273 (Moderna) vaccine; and 1 received an mRNA vaccine, but the specific vaccine and manufacturer were not reported. Lot numbers were unavailable in all cases. In total, 75% (3/4) of patients developed AIHA after an initial dose of vaccine, while the fourth patient developed AIHA 2 days after the second dose. This patient had received the first dose of the same vaccine 21 days prior without complication. Warm AIHA occurred in 1 patient, and 1 patient developed cold AIHA. For the other 2 patients, the original authors did not report the AIHA subtype, but following review, both represent cases of probable warm AIHA.

The mean (SD) age of these patients was 73.5 (16.9) years (95% CI, 56.9-90.1 years), and only 2 of the 4 patients reported underlying medical conditions. Two patients underwent SARS-CoV-2 RT-PCR testing, and both tested negative. All 4 patients denied recent signs or symptoms of infection, and none endorsed historical SARS-CoV-2 infection. The median (IQR) time from vaccine administration to AIHA symptoms after 1 dose was 5 (3-19) days.

Corticosteroid therapy was instituted for 3 patients, and rituximab was used in 1 patient. Blood product transfusion data were available for 3 patients, all of whom were transfused with at least 1 unit of RBCs. One patient received 2 units, 1 patient received 1 unit, and the number of units was not reported for the third patient.

As of September 24, 2021, 219 reports had been submitted to the CDC VAERS describing AIHA, cold agglutinins, hemolysis, and warm AIHA as AEs associated with a SARS-CoV-2 vaccination. Details regarding the specific vaccine and symptom onset were not available.

**DISCUSSION**

To date, 50 cases of AIHA associated with RT-PCR–confirmed COVID-19 have been reported. This number is miniscule compared with the more than 220 million reported cases of COVID-19 worldwide, but the significant case fatality rate (CFR) (19%) among patients with COVID-19–associated AIHA indicates a high risk of mortality in those who do develop this sequela. Although the small number of patients and the high rate of comorbidities in these patients may certainly influence the CFR, the overall mean age (50.8 years) of patients with COVID-19 and associated AIHA as well as the mean age (55.8 years) of deceased patients with AIHA is important. This finding highlights the severity of AIHA associated with COVID-19 and underscores the need for heightened awareness and further investigation into this potentially fatal association.

The infectious agents known to be associated with AIHA predominate in either warm or cold AIHA, with only rare instances of a different AIHA subtype. In contrast, our findings demonstrate that COVID-19 is associated with both warm AIHA (28% of patients) and cold AIHA (38% of patients) for reasons that remain unclear.

Although the exact mechanism by which infectious pathogens induce AIHA has yet to be fully characterized, currently the most accepted hypothesis involves molecular mimicry between microbial epitopes and epitopes on RBCs. This mechanism has also been proposed as the predominant cause of AIHA associated with COVID-19 because studies have shown that epitopes on the SARS-CoV-2 spike protein share significant homology with ankyrin-1, an integral protein in the erythrocyte membrane. Because of the similarity between viral and erythrocyte proteins, antibodies targeting the spike protein on the SARS-CoV-2
virus may cross-react with erythrocytes, resulting in destruction of the RBC and subsequent anemia. Although this review and its associated epidemiologic findings are not designed to test this hypothesis, we demonstrate that the median time frame from COVID-19 symptom onset to AIHA diagnosis is approximately 7 days, indicating that AIHA typically presents during early active SARS-CoV-2 infection. This time frame corresponds to the period of immunoglobulin formation and supports the premise that these developing antibodies may cross-react with erythrocytes, leading to hemolytic anemia. Furthermore, the large proportion of patients with complement deposition on their RBCs may partially explain the severe hemolysis seen in these patients, as erythrocyte-bound complement in the setting of a hyperinflammatory immune response may predispose patients to a more severe form of intravascular hemolysis.

In addition to the 50 cases of AIHA associated with COVID-19, we identified 4 reported cases of AIHA in individuals recently vaccinated against SARS-CoV-2. Two of these 4 patients underwent testing for COVID-19 by RT-PCR following admission to the hospital for symptoms secondary to underlying hemolytic anemia. Both patients tested negative, while the other 2 had no respiratory symptoms but were not tested. None of the patients endorsed a history of COVID-19, and all denied symptoms before the development of AIHA. Notably, no cases of vaccine-associated AIHA were reported in the SARS-CoV-2 vaccine clinical trials, nor are there data on the package inserts for the Pfizer-BioNTech,65 Moderna,63 or Janssen67 vaccines. Despite this absence of data in clinical trials, there are rare cases of AIHA associated with other vaccines, including diphtheria-tetanus-pertussis68 and influenza69 vaccines, illustrating that vaccines have previously been associated with the development of AIHA. Thus, increased awareness of the potential for SARS-CoV-2 vaccination–induced AIHA is warranted.

This analysis is the first systematic review of AIHA associated with SARS-CoV-2 infection and vaccination, providing evidence that SARS-CoV-2 is associated with a subtype of warm or cold AIHA. We acknowledge several limitations to this study. Most importantly, most published cases lack comprehensive descriptions of the pertinent blood bank and serologic methods and results. Few authors described their techniques, reagents, and other essential details describing indirect and direct antiglobulin testing, elution studies, cold agglutinin titers, thermal amplitude testing, and the strength of positive reactions, all of which are crucial in the diagnosis and classification of immune-mediated hemolytic anemias. These scant data highlight the need for journals to implement standardized approaches requiring authors of manuscripts describing potential cases of hemolytic anemia to include their methods for evaluating and classifying AIHA as well as detailed test results. Despite these limitations, we found that complement is frequently deposited on erythrocytes in patients with COVID-19–associated AIHA irrespective of the AIHA subtype. This finding, in association with a mean hemoglobin under 7 g/dL at the time of diagnosis, indicates that COVID-19 may be associated with acute hemolysis, most commonly occurring within 10 days of symptom onset or vaccination. Increased awareness of this potential complication is warranted to mitigate morbidity and mortality in these patients.

**CONCLUSIONS**

It is accepted that COVID-19 is associated with significant disruptions to the normal hematologic physiology in a subset of patients. The association between COVID-19 and the development of potentially devastating AIHA, however, has not been systematically reviewed to date. We have characterized all documented cases of AIHA associated with either SARS-CoV-2 infection or vaccination, illustrating that SARS-CoV-2 should be considered an infectious agent capable of causing AIHA. Patients with COVID-19 should be monitored for this potential AE to mitigate morbidity and potential mortality.

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