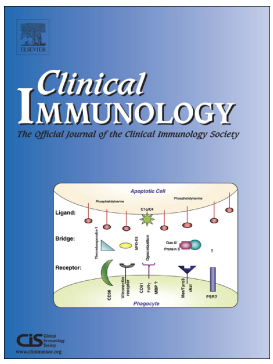

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Mohammed Ayyad, Walaa Abu Alya, Anas Mufeed Barabrah, Sara Mohammed Darawish, Yazan AlHabil, Majdeddin MohammedAli, Mustafa Zafer Nabilsi, Diya Asad, Laith A. Ayasa, Daniel Matassa

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Autoimmune Hemolytic Anemia in COVID-19 Patients: A Systematic Review of 105 cases on Clinical Characteristics and Outcomes

Mohammed Ayyad, MD[1,] Walaa Abu Alya, MD[2], Anas Mufeed Barabrah, MD[3], Sara Mohammed Darawish, MD[3], Yazan AlHabil, MD[5], Majdeddin MohammedAli, MD[4], Mustafa Zafer Nabilsi, MD[3], Diya Asad, MD[3], Laith A. Ayasa, MD[3], Daniel Matassa, MD[1]

[*]Contributed equally as a first co-author.

[1]Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA.

[2]Department of Medicine, Cleveland Clinic Fairview Hospital, Cleveland, Ohio

[3]Faculty of Medicine, Al-Quds University, Jerusalem, State of Palestine.

[4]Department of General Surgery, Brooklyn Hospital Center, Brooklyn, NY

[5]Department of Medicine, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, 00970, Palestine

Corresponding Author

Mohammed Ayyad, MD
Department of Medicine
Rutgers New Jersey Medical School
185 S Orange Ave, Newark, NJ 07103, USA
Phone: +972 59-521-5643
Email: dr.mohammad.ayyad@gmail.com
ORCID ID: 0000-0001-9772-2365

Abbreviations

AIHA - Autoimmune Hemolytic Anemia

ALI - Acute Lung Injury

ARDS - acute respiratory distress syndrome

CINAHL - Cumulative Index to Nursing and Allied Health Literature

COVID - Coronavirus Disease

Abstract

Background: COVID-19 has been linked to autoimmune hemolytic anemia (AIHA), a rare but serious condition causing red blood cell destruction. This systematic review examines the clinical characteristics, management, and outcomes of AIHA in COVID-19 patients.

Methods: A systematic search of PubMed, CINAHL, and Scopus identified 85 studies encompassing 105 patients. Data on demographics, clinical features, and treatment outcomes were extracted.

Results: Of 1,402 articles, 85 met inclusion criteria. Most patients were male (54.3%) with a mean age of 50.6 years, predominantly from Asia (83.5%). Cold agglutinin AIHA was most common (48.2%). Presenting symptoms included fatigue, dyspnea, and fever. Steroids were the most effective treatment, used in 95% of recovered cases. Mortality was 14.3%, with 26.7% of deaths directly related to AIHA.

Conclusions: COVID-19 is associated with AIHA, often presenting with non-specific symptoms. Early recognition and prompt steroid therapy are critical for improving outcomes. Further research is needed to guide management.

Keywords: COVID-19; Autoimmune hemolytic anemia; SARS-CoV-2; Immune-mediated hemolysis; AIHA COVID-induced hemolysis.

Introduction

COVID-19 (coronavirus disease 2019) is a viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China, in November 2019. According to the World Health Organization (WHO), it was classified as a global pandemic in March 2020 due to the significant morbidity and mortality caused by it.

The mechanism by which SARS-CoV-2 leads its way into host cells is by binding the viral spike protein to the angiotensin-converting enzyme 2 receptor (ACE2) expressed on the surface of host cells. SARS-CoV-2 infection can result in an acute host immunological response, inflammatory responses, and cytokine storm, leading to acute respiratory distress syndrome (ARDS), acute lung injury (ALI), and a wide spectrum of disease manifestations ranging from mild or asymptomatic diseases to severe diseases with multiorgan involvement [1–3]. Extra-pulmonary manifestations can result from the virus, such as acute cardiac injury, arrhythmias, acute kidney injury, acute brain injury, endocrine abnormalities, and multi-organ failure, all of which have fatal consequences [4].

Autoimmune Hemolytic Anemia (AIHA) is a rare immune-mediated disease caused by anti-RBC membrane autoantibodies, causing red blood cell (RBC) destruction and hematological dysregulation. According to its etiology, AIHA is classified as primary or idiopathic, occurring in approximately 50% of cases, or secondary, accompanying and complicating underlying diseases, such as autoimmune diseases, lymphoproliferative disorders, and, in rare cases, viral infections [1, 5]. Although AIHA is considered to have a relatively low incidence, recently there has been an increasing prevalence of reported hemolytic anemia cases, predominantly associated with the formation of autoantibodies/agglutinins in the context of COVID-19 [6, 7]. The exact

mechanism by which COVID-19 is attributed to AIHA is unknown, however, Putry et al. [8] suggested a possible underlying pathophysiology of COVID19-induced AIHA, where the viral spike protein of COVID-19 that attaches to the respiratory tract has structural similarities with RBC surface ankyrin-1 protein, a mechanism known as molecular mimicry, in which the virus has a structure resembling that of a normal host protein, causing cross-reactivity against self-antigens [1, 5, 9, 10].

Importantly, COVID-19 has been associated with the development of cold agglutinin disease (CAD) and warm antibody hemolytic anemia. Agglutinins, such as IgM and IgG autoantibodies, play a key role in diagnosing and managing AIHA by distinguishing between different types based on temperature reactivity. This differentiation is vital for tailoring treatment strategies, such as avoiding cold exposure in CAD and using targeted therapies including complement inhibitors [11].

Finally, since anemia in COVID-19 patients has been associated with a fourfold increase in the likelihood of in-hospital mortality—potentially linked to a higher frequency of ICU admissions and the need for ventilatory support, along with the severe consequences it entails [12, 13]—this review aims to highlight the relationship between AIHA and COVID-19 infection. We also aim to examine and describe the various clinical characteristics of this condition, along with the demographics and management strategies, to serve as an up-to-date comprehensive review on the topic.

Methods

Protocol registration

We adhered to the guidelines set forth in the Cochrane Handbook for Systematic Reviews and Meta-Analyses and followed the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. Additionally, we implemented the guidelines for summarizing systematic reviews, focusing on the methodological development, conduct, and reporting of an umbrella review approach [15]. Our study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and holds the unique identifying number (UIN): ***CRD42024592054***.

Literature Search Strategy

We developed a comprehensive search strategy from inception until February 2025 to identify relevant studies. The following databases were systematically searched: CINAHL Nursing, PubMed, Google Scholar, Scopus CrossRef, and CINAHL Complete. The search terms were carefully selected to ensure the retrieval of pertinent articles. Various combinations of keywords were employed, including COVID-19, SARS-CoV-2, Autoimmune hemolytic anemia, AIHA, Hemolysis, Autoantibodies, Clinical characteristics, and Management strategies. The search was conducted using both free-text terms and controlled vocabulary (e.g., MeSH terms in PubMed). The Boolean operators "AND" and "OR" were used to refine the search and capture relevant articles.

Eligibility Criteria

We included all articles published in English that examined the relationship between COVID-19 and AIHA, specifically focusing on studies involving newly diagnosed AIHA following a COVID-19 infection, as well as those describing clinical features and management approaches for COVID-19-induced AIHA. We excluded studies unrelated to COVID-19 or AIHA, those that reported remission of pre-existing AIHA after COVID-19 infection. Articles focused solely on non-human subjects, review articles, and conference abstracts lacking original data were also excluded.

Identification and Selection of Studies

Two investigators (AB and SD) autonomously conducted a literature search utilizing the specified search terms. Subsequently, they cross-referenced their findings to mitigate any technical discrepancies. The identified articles were imported into Rayyan [16], where duplicates were detected and subsequently eliminated before the screening process commenced. Screening proceeded in two stages: initially, through title and abstract evaluation, followed by full-article examination. The screening phases were independently undertaken by two researchers (MM, AB), with conflicts resolved through consensus after review by two additional researchers (WA and DA) and a senior author (MAy).

Data Extraction from Included Studies

Two researchers (LA and MN) collected and recorded the data from the selected studies in an Excel spreadsheet using a data extraction form. The following information was extracted: study characteristics (e.g., authors, publication year, study design), participant characteristics (e.g., sample size, age, gender), study outcomes related to the association, clinical characteristics, and management strategies. The data were double-checked by a senior author (MAy), and any identified discrepancies were corrected. Finally, the data were evaluated using descriptive analysis methodologies.

Strategy for data synthesis

This was a comprehensive systematic review conducted with the purpose of extracting data to enable synthesis on the relationship between COVID-19 infection and the incidence of AIHA, as well as the most effective ways to manage the condition. Whenever possible, descriptive analysis of the retrieved data was used.

Assessment of risk of bias

Two reviewers independently assessed the risk of bias for case reports, case series, and cross-sectional studies using the Joanna Briggs Institute's critical appraisal tools [17, 18]. In any case of disagreement, consensus was reached with a third senior reviewer (MAy).

Results

Our search identified 1402 articles, out of which only 85 advanced to the data extraction phase based on the eligibility criteria, as illustrated in the PRISMA flowchart below (**Figure 1**).

Interestingly, all extracted articles consisted exclusively of 80 case reports, 4 case series, and 1 analytical cross-sectional study. Among the 85 studies included in this review, 23 were published in 2020, 27 in 2021, 13 in 2022, 12 in 2023, 9 in 2024, and 1 in 2025 [7, 9, 19–101]. Data were collected from a total of 105 individuals diagnosed with COVID-induced autoimmune hemolytic anemia. Out of these, 85 cases had their country reported, while 20 cases did not. Among the 85 reported cases, 71 (83.5%) were from Asia, 12 (14%) were from the USA, and 2 (2.35%) were from Europe. ***Figure 2*** illustrates the geographical distribution and year of publication of the studies included.

Demographic and clinical characteristics of patients with AIHA following COVID-19 infection

The analysis of the data from a cohort of 105 patients reveals several critical findings regarding the impact of COVID-19 on health outcomes. ***Table 1*** provides a summary of clinical characteristics extracted from the participants' data. The mean age of patients was 50.6 ±21.2 years, with a gender distribution comprising 57 males (54.3%) and 48 females (45.7%). Among the cohort, all 105 patients were confirmed positive for COVID-19. Immunological assessments indicated that of the 72 patients evaluated for agglutinins, 41 (48.2%) exhibited cold agglutinins, and 28 (32.9%) demonstrated warm agglutinins, 3 (3.5%) demonstrated mixed agglutinins, while 33 (15.4%) did not have documentation of their agglutinin status. Notably, the outcome analysis indicated that 82 patients (78%) achieved recovery, while 15 patients (14.29%) succumbed to the illness, resulting in an overall mortality rate of 16.4%, minding that we excluded 8 patients (7.61%) out of the 105 due to lack of data regarding the outcome, which may reflect gaps in reporting or follow-up in these specific studies.

In terms of laboratory findings, the average hemoglobin level among 90 subjects was 5.99 mg/dL, and the mean reticulocyte count for 45 participants was 8.54%. LDH levels in 70 subjects averaged 1105.37 U/L, while haptoglobin levels in 25 subjects showed an average of 30 mg/dL. ***Table 1*** and ***Figure 3*** illustrate the demographics, as well as disease and clinical characteristics of patients with AIHA following COVID-19 infection.

First Presenting Symptoms of Patients With COVID-19-Induced AIHA

Among the 98 cases reporting symptoms upon first presentation, the most reported symptoms were fever (40%), cough (39%), shortness of breath (41%), fatigue (42%), yellowish discoloration (12%), dark urine (10.98%), headache (10%), anosmia (8%), and pallor (5%). Notably, approximately 87.7% of patients exhibited at least one symptom of COVID-19, such as fever, cough, shortness of breath, anosmia, or weakness. In contrast, around 24.4% had at least one symptom related to hemolysis, including pallor, yellowish discoloration, or dark urine.

Treatment Approaches and Outcomes in AIHA Following COVID-19 Infection

The management of the 105 subjects varied across the included articles. Notably, 16 subjects were not included in the management plan analysis due to the lack of documentation of clear management plans. The data analyzed and described was obtained from for 89 subjects with well-documented management plans.

Out of the 89 patients, 82 subjects recovered. Notably, 78 of the 82 recovered patients (95%) received steroid treatment. Further analysis of various therapeutic interventions revealed differing recovery rates (***Figure 4***). Blood transfusions were given in 49 out of 57 recipients, with a recovery rate in this specific subpopulation reaching up to 85.9%. Rituximab showed

efficacy in 15 out of 17 patients, achieving a recovery rate of 88.2%. For patients treated with intravenous immunoglobulins (IVIG), 12 out of 14 (85.7%) recovered, while plasmapheresis had a recovery rate of 83.4% (5 out of 6).

Upon more in-depth analysis (***Figure 5***), the most used steroid regimen included prednisone or methylprednisolone. Among the 18 patients treated exclusively with steroids, a notable recovery rate of 88.9% (n=16) was observed. In a subset of 12 patients who received both steroids and blood transfusions, the recovery rate increased slightly to 91.6% (n=11). The highest recovery rate was achieved with the combination of steroids, blood transfusions, and ventilation, where 14 patients demonstrated a recovery rate of 92.8% (n=13).

Additionally, 4 patients treated with a combination of steroids, blood transfusions, and IVIG achieved complete recovery. Similarly, another group of 4 patients receiving steroids, blood transfusions, and rituximab also achieved full recovery. Among the latter group, 3 patients who additionally received IVIG had a recovery rate of 66.7% (n=2). Notably, 4 patients who received steroids and rituximab only experienced complete recovery.

In contrast, among 6 patients receiving blood transfusions and ventilation only, the recovery rate was 50% (n=3). Similarly, 8 patients who received ventilation alone showed a recovery rate of 50%. However, among the 8 patients treated solely with blood transfusions, a higher recovery rate of 87.5% (n=7) was observed. For the remaining regimens used in recovered patients (n=8), although the sample sizes were not significant for detailed reporting, steroids were the common drug among these treatments. Notably, only 1 patient died among the various other regimens employed.

On the other hand, the average duration of treatment with these strategies was 23 days, while the average time to remission or stabilization among recovered patients across all treatment modalities was 18.9 ± 14.7 days, with a range from one day to a maximum of 88 days. Most studies defined recovery from AIHA as an increase in hemoglobin levels, resolution of hemolytic parameters—including LDH, bilirubin, and haptoglobin levels—and an improvement in clinical symptoms. These criteria indicate successful management and achievement of stable hematological status without ongoing hemolysis. However, some studies did not provide detailed information regarding the recovery of their patients.

Among the 15 patients who passed away, representing a mortality rate of 14.3%, which is higher than that of the general COVID-19 population. A thorough analysis of the causes of death revealed that four cases (26.7%) were directly attributed to severe hemolysis, either due to hyperhemolysis-induced multi-organ failure or cardiovascular collapse. While AIHA was identified as a significant risk factor for mortality in COVID-19 patients, many deaths (66.7%) were primarily due to COVID-19-related complications rather than AIHA alone. These included intracerebral stroke (one case, 6.7%), neurologic complications (two cases, 13.3%), respiratory failure (three cases, 20%), and septic shock with multi-organ failure (two cases, 13.3%). Additionally, one patient (6.7%) died from acute liver failure due to sub-massive hepatic necrosis, which was exacerbated by post-COVID immune dysregulation and AIHA. In one instance, the exact cause of death was not clearly documented, limiting its classification. ***Figure 6*** provides a summary of the causes of death among the 15 deceased patients

Lastly, a total of 15 patients were reported to have preexisting disorders (***Table 2***), with 10 of them diagnosed with specific types of cancer indicating a significant association between

preexisting cancer diagnoses and the overall health status of the patients. The most frequently observed was chronic lymphocytic leukemia and marginal zone lymphoma.

Quality assessment of included articles

Quality assessment was performed using the Joanna Briggs Institute's critical appraisal tools [17, 18]. For more details regarding quality assessment of the included articles, please refer to ***Supplementary Table 1***. We assessed the quality of all included articles as good. Most articles clearly presented patient demographics, clinical histories, diagnostic methods, and treatment interventions, often offering valuable insights into treatment effectiveness. Whenever there was a discrepancy between quality assessors, consensus was reached by consulting a senior author (MAy).

Discussion

Hemolytic anemia in COVID-19 patients results from a complex interplay of pathophysiological mechanisms. Importantly, AIHA is commonly triggered by viral infections including HIV, Hepatitis C, Mumps, Measles, Rubella and Parvovirus, however, COVID-19 induced AIHA is an emerging clinical entity that is becoming more recognized [102]. The interaction between SARS-CoV-2 and erythrocytes encompasses various proposed pathways. Oxidative stress induced during SARS-CoV-2 infection leads to methemoglobinemia, causing non-hemolytic anemia. On the other hand, specific viral proteins, particularly S and ORF3a, may bind to hemoglobin, resulting in denaturation and immunological agglutination. The virus's affinity for erythrocytes is linked to CD147, facilitating entry through endocytosis and potentially causing dysregulation and hemolysis. Intra-erythrocytic oxidative stress, driven by the viral load, heightens susceptibility to micro-angiopathic inflammations [1]. SARS-CoV-2 may impact the structural

proteins and lipid metabolism of RBCs, affecting their oxygen transport function. Factors such as reduced G6PD activity and altered levels of the bioactive lipid mediator S1P contribute to RBC deformability and susceptibility to hemolysis [103, 104]. Overall, the hemolytic anemia observed in COVID-19 patients results from both direct RBC injury and the indirect induction of autoantibodies against the RBC membrane, collectively shaped by the junction of these pathophysiological processes [1].

Our paper encompasses a thorough review of 85 papers published between 2020 and 2025, presenting a comprehensive analysis of COVID-19-induced AIHA. Notably, all of the 105 subjects had confirmed COVID-19 infections with new-onset AIHA developing after initial infection.

In our study of 105 participants, averaging 50.6 years of age, we observed a slightly higher prevalence of AIHA among males. This is contrary to a systematic review on COVID-19 and immune-mediated RBC destruction which showed no significant gender influence on AIHA onset in COVID-19 patients [105]. However, several studies have revealed that there could be gender disparities in autoimmune responses related to COVID-19 infections. Specifically, a study involving 987 patients hospitalized for SARS-CoV-2-induced pneumonia revealed that males had higher likelihood of severe disease and to have positive autoantibodies against type I interferons. These autoantibodies, which can neutralize IFN-I, were linked to an elevated risk of severe outcomes. Importantly, asymptomatic individuals or those with mild to moderate forms of the disease did not exhibit these autoantibodies [106].

When comparing outcomes to general COVID-19 patients, our review found that those with AIHA had a recovery rate of 78% and a mortality rate of 14.3%. In contrast, patients without AIHA experienced significantly better outcomes, with a study of 1,233 general COVID-19 cases reporting a mortality rate of only 5.8% and a recovery rate of 94.16%. [107]. Furthermore, data from 12 U.S. states collected between October 2023 and April 2024 revealed that among 1,320 adults hospitalized with COVID-19, the mortality rate during hospitalization was 6.9% [108]. These findings suggest that AIHA may considerably worsen the prognosis for COVID-19 patients compared to the general population.

On the other hand, our study revealed a mean duration of 13.1 days between COVID-19 detection and AIHA manifestation. Likewise, Lazarian et al. reported a range of 4 to 13 days between COVID-19 symptoms and AIHA onset with marked hemolysis [71]. However, one paper suggests a median duration of 7 days from COVID-19 symptom onset to AIHA diagnosis, with a diagnostic range from 0 to 20 days post-symptom development [105]. The insight on the duration between the infection and symptom onset may play a crucial part in raising awareness regarding this matter among health-care professionals, where they can closely monitor patients at risk for a set period, particularly in hospitalized patients.

In terms of symptomology and clinical presentation, approximately 87.7% of patients exhibited COVID-19-related symptoms such as fever, cough, and shortness of breath, while only about 24.4% displayed symptoms indicative of hemolysis, including pallor, jaundice, or dark urine. This pattern contrasts with primary AIHA, where hemolytic manifestations are more pronounced at onset of diagnosis. The delayed emergence of hemolytic symptoms, often during the cytokine storm phase of COVID-19, may be attributed to systemic inflammation masking early signs of

anemia and diagnostic overshadowing by dominant respiratory symptoms where physicians might prioritize COVID-19 management. These findings highlight the need for heightened clinical suspicion and screening for hemolysis in COVID-19 patients, particularly those with disproportionate anemia or elevated hemolysis markers, to ensure timely intervention and management of this potentially severe complication.

In our review, the average hemoglobin level among 90 subjects was 5.99 mg/dL, with clearely elevated LDH levels and reticulocyte count. Similarly, Jacob et al.'s assessed COVID-19 related RBC destruction and found that the mean hemoglobin was 6.5 g/dL, with a nadir reaching 5.7 g/dL [105]. LDH levels were measured at 1,124 U/L, and haptoglobin levels were documented at 27.3 mg/dL. All 14 tested individuals showed cold agglutinins, and 78% were considered clinically significant. Additionally, in their study, 19% of participants were reported as deceased. Of the deceased patients, 5 had cold AIHA, 1 had Evans syndrome, and the AIHA classification was not specified in 2 cases. Remarkably, 88% of their reported deceased patients presented multiple underlying medical comorbidities, including previous AIHA in remission, immune thrombocytopenic purpura in remission, thalassemia, and G6PD deficiency. These findings capitalize the importance of laboratory studies and their role in aiding in diagnosis within the context of COVID-19 and AIHA [105].

In terms of treatment, our study aligns with the growing body of evidence supporting the positive impact of steroids in managing COVID-19-induced AIHA [71, 109]. Specifically, our findings demonstrate a significant correlation between the administration of steroids and improved recovery in 78 out of 84 patients. Steroids have been recognized for effectively reducing mortality in severe COVID-19 cases by mitigating the inflammatory response and preventing cytokine storm. The immunosuppressive properties of steroids play a crucial role in regulating

the hyperactive immune response associated with severe cases, thereby preventing further organ damage and respiratory distress. Steroids are commonly used to treat AIHA by suppressing the immune response and alleviating the destruction of red blood cells [110]. In addition, our study observed improvement in 15 out of 17 patients who received rituximab and 49 out of 57 patients who underwent blood transfusions. These findings align with another review, which suggest steroids as the gold standard in management plans, with rituximab being an excellent add-on therapy in cases where steroids may not suffice [109].

In terms of clinical outcomes, AIHA in COVID-19 patients demonstrates a dual role in mortality, acting both as a direct contributor and a compounding factor that amplifies disease severity. While 26.7% of deaths were directly linked to AIHA-induced complications such as hyperhemolysis and multi-organ failure, the majority (66.7%) stemmed from COVID-19-driven systemic complications such as respiratory failure, septic shock, and neurologic events. This pattern aligns with broader trends observed in COVID-19 mortality, where immune dysregulation and hyperinflammation exacerbate preexisting conditions or trigger secondary organ damage. The interplay between AIHA and COVID-19 creates a vicious cycle of pathology. AIHA-induced hemolysis reduces oxygen-carrying capacity, worsening tissue hypoxia in patients already compromised by COVID-19-related lung injury [13]. Concurrently, systemic inflammation from SARS-CoV-2 infection—marked by cytokine storms and complement activation—intensifies hemolysis and precipitates complications such as disseminated intravascular coagulation [111, 112]. This bidirectional relationship highlights why AIHA patients face disproportionately higher mortality compared to the general COVID-19 population. Notably, the predominance of COVID-19-related fatalities in this cohort mirrors findings from studies on stroke outcomes in COVID-19 patients, where hypercoagulability and

endothelial dysfunction led to significantly worse prognoses than in non-COVID stroke cases [113].

Lastly, our study identified preexisting disorders, particularly oncological conditions, in 15 subjects, underscoring the importance of nuanced considerations of age-appropriate and hematological cancer screening in the diagnosis and management of COVID-19-associated AIHA. Of note, a meta-analysis involving 3377 patients with hematologic malignancies and COVID-19 demonstrated a significant mortality risk, particularly in hospitalized patients, with an overall mortality rate of 34% and a higher rate of 39% among those admitted [114]. This highlights the critical need for heightened attention and care for individuals with underlying oncological conditions when dealing with COVID-19.

Future Directions

Firstly, more extensive multicenter cohort studies are needed to delineate the precise epidemiological and clinical features of AIHA in the context of COVID-19. Future research should explore the underlying pathophysiological mechanisms in greater depth, particularly the role of oxidative stress, viral proteins, and immune response dysregulation. Given the significant association between steroid treatment and improved outcomes, randomized controlled trials should be conducted to validate the efficacy of steroids, COVID-19-specific treatments, and other immunosuppressive therapies, such as rituximab, in optimizing recovery for patients with severe conditions. Moreover, there is a critical need to investigate the impact of underlying conditions, such as oncological disorders, on the prognosis and treatment response of COVID-19-associated AIHA. Understanding the interplay between these preexisting conditions and AIHA can guide personalized treatment approaches. The potential benefits of adjunctive

therapies such as IVIG and plasmapheresis also warrant further exploration through controlled trials. Additionally, the role of newer therapeutic agents, including tocilizumab, needs to be evaluated to establish their effectiveness in AIHA cases unresponsive to conventional therapies. Finally, given the observed timelines for AIHA onset following COVID-19 infection, there is a need for heightened vigilance and early diagnostic strategies in at-risk populations, particularly those with history of COVID-19 related AIHA.

Strengths and Limitations

One of the key strengths of our review is its systematic methodology, which allowed for an extensive analysis of 85 articles published across diverse regions. Additionally, the detailed extraction and synthesis of demographic data, clinical characteristics, treatment modalities, and outcomes provide valuable insights into the epidemiology and management of AIHA in the context of COVID-19. The focus on both cold and warm AIHA, along with the detailed examination of treatment responses, adds significant depth to the existing literature, highlighting the effectiveness of steroids and the potential role of other immunosuppressive therapies.

However, our study has several limitations. The reliance on case reports and case series, which inherently carry a risk of publication bias and limited generalizability, constrains the ability to draw definitive conclusions about the broader population. Additionally, the variability in diagnostic criteria and treatment protocols across different regions and studies makes it challenging to standardize the findings. The lack of control groups in the reviewed studies further limits the ability to establish causal relationships between COVID-19 and AIHA or to compare the effectiveness of different treatments. Lastly, the incomplete reporting on AIHA

types in a few studies reduces the granularity of the analysis, potentially overlooking significant differences in the clinical course and management of cold versus warm AIHA.

Conclusions

Our systematic review examined the link between COVID-19 and AIHA, emphasizing the varied clinical presentations and the critical need for early recognition and treatment. The findings highlight the predominant use of steroids, which were associated with improved outcomes, and underscore the importance of timely intervention. Recovery rates were significantly higher in patients who received combined therapies such as steroids, blood transfusions, and other immunomodulatory treatments, although severe complications, including multi-organ failure and respiratory failure, contributed to a notably higher mortality rate. The diverse geographical origins of the cases and the broad age range of affected individuals point to the global and non-discriminatory nature of this complication. Physicians should maintain a high index of suspicion for AIHA in COVID-19 patients and consider comprehensive treatment strategies, particularly for those with preexisting conditions, to enhance patient care and outcomes.

Author contributions

MAy and WA contributed to the design of the study, data analysis, data interpretation, and drafting of the manuscript. AB, YA, LA, MN, SD, MM, and DA contributed to design of the study, data collection, data entry, and quality assessment. All authors have reviewed and given their approval for the final version of the manuscript. MA and DM contributed to the supervision of the work and final drafting. Each author has been actively involved in the work and is willing to take full responsibility for its content.

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Competing interests

The authors declare no competing interests.

Data Availability Statement

The dataset utilized during to conduct this study is available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no conflicts of interest to declare regarding this research study.

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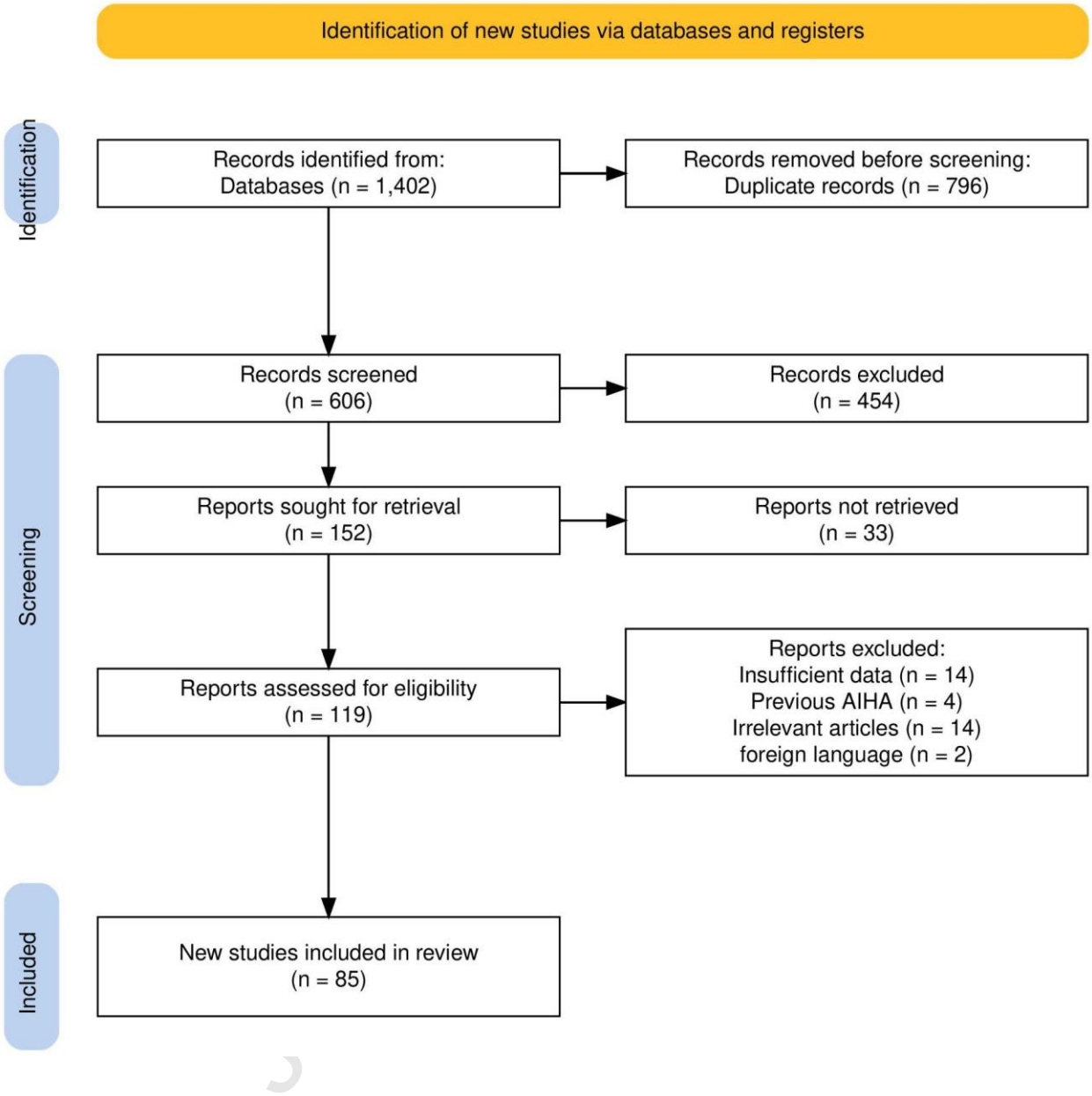

Figure 1: PRISMA flow diagram of literature screening for patients with AIHA post-COVID-19 infection.

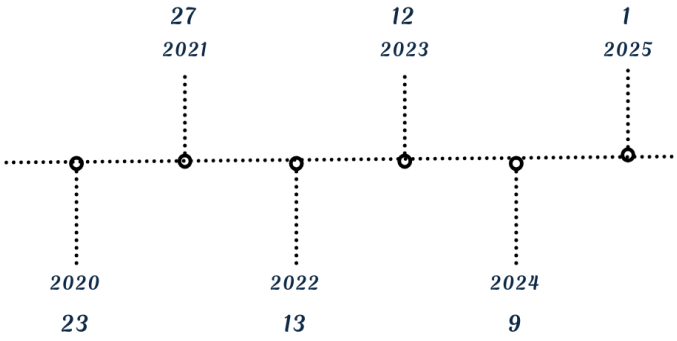

Figure 2: Geographic distribution and year of publication of the 85 included studies in our review.

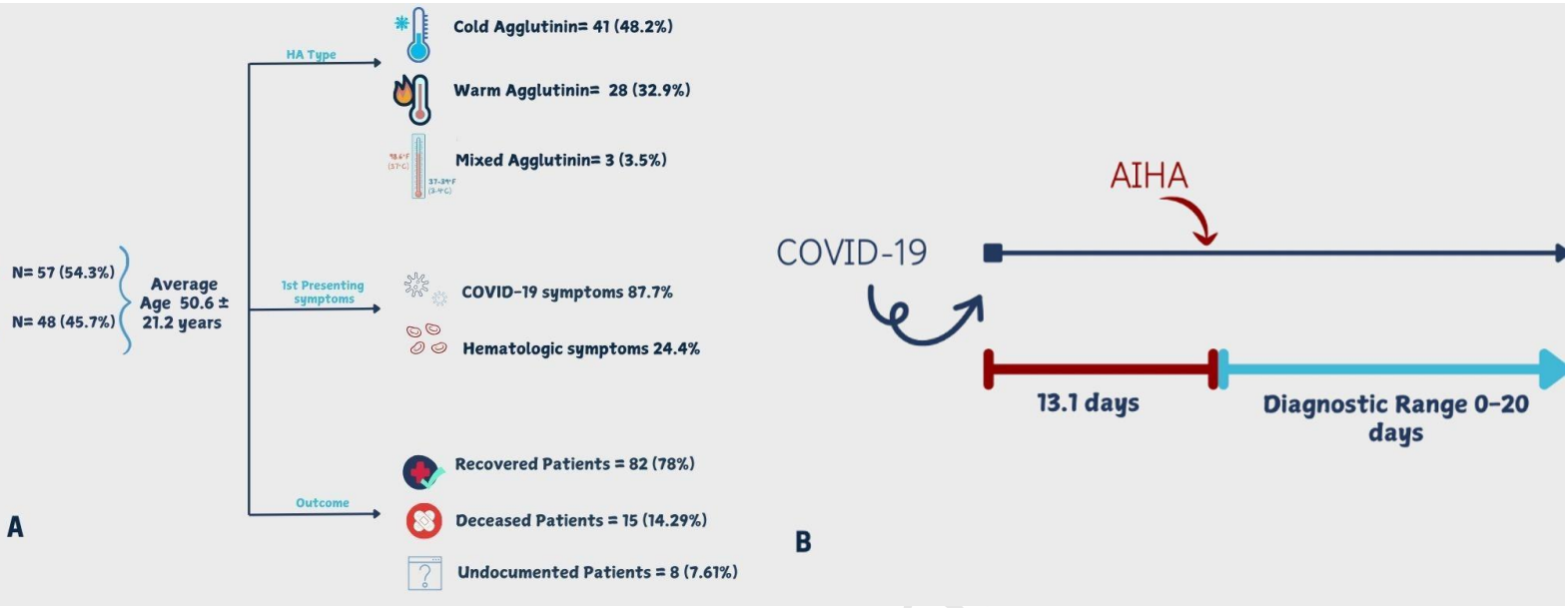

Figure 3: A) Demographic and clinical characteristics of patients with COVID-19-induced AIHA infection. B) The mean duration between COVID-19 infection and onset of AIHA.

Figure 4: Clinical outcomes for patients with COVID-19-induced AIHA and the recovery rate for each therapy.

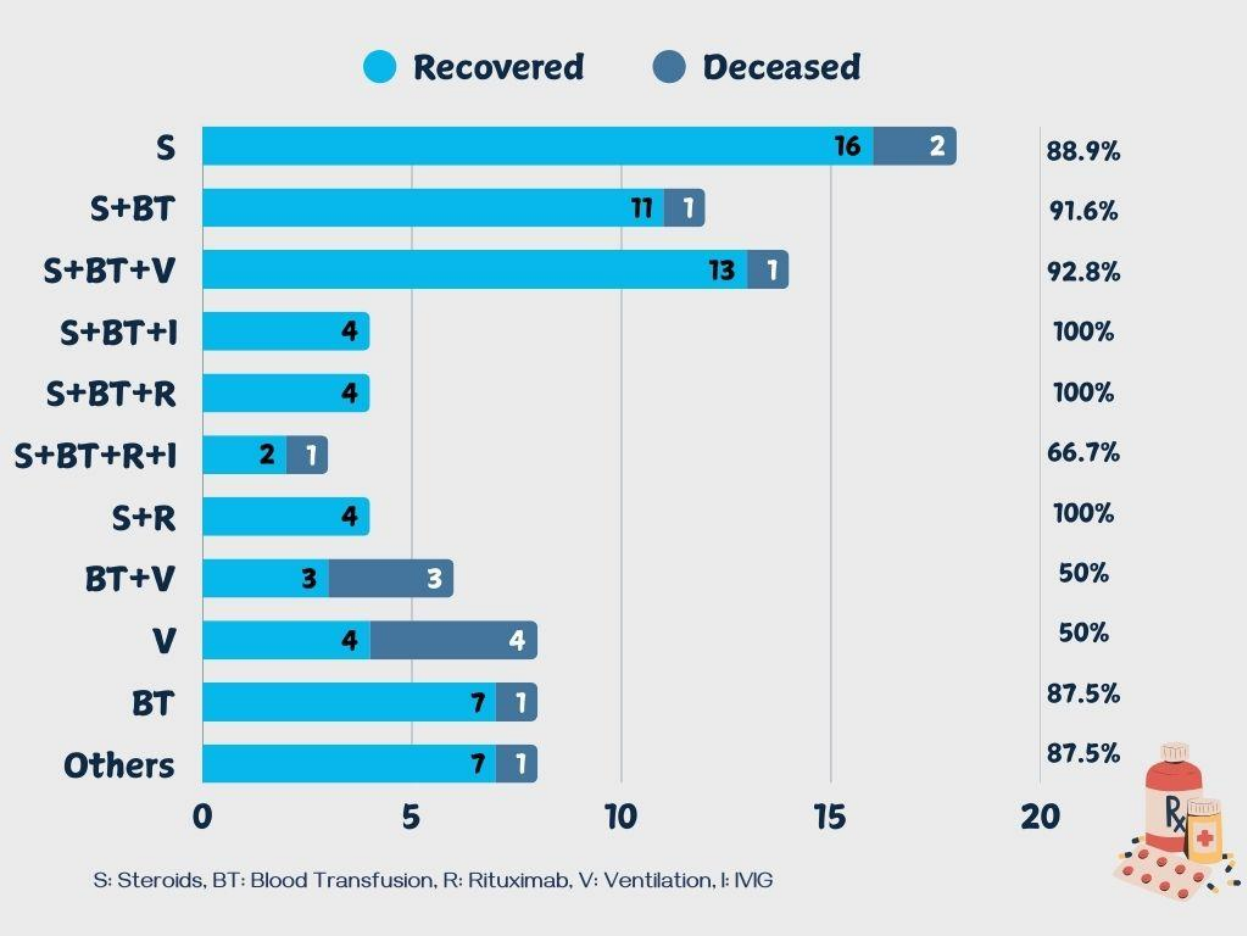

Figure 5: Clinical outcomes for the various drug regimens along with their corresponding recovery rates.

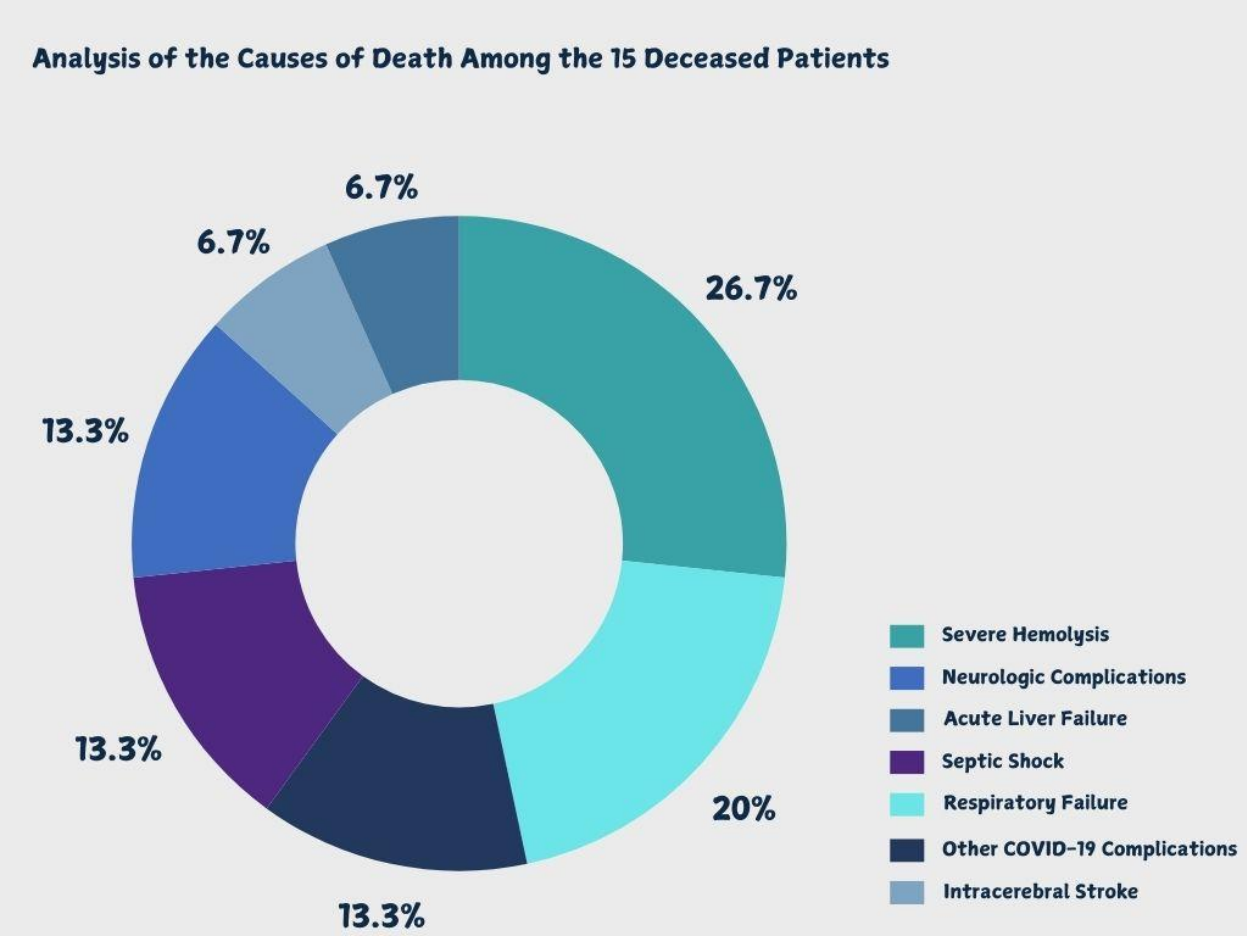

Figure 6: Causes of death among the 15 deceased patients included in the meta-analysis.

Table 1: Demographic and clinical characteristics of patients with COVID-19-induced AIHA

Characteristic	Data Extracted	Details
Mean Age	105 subjects out of 105	50.6 years
Gender	105 subjects out of 105	57males (54.3), 48 females (45.7%)
Confirmation of COVID-19 Infection	105 subjects out of 105	All cases are confirmed
Mean Days Between COVID-19 Detection and AIHA Manifestation	61 subjects out of 105	13.1 days
Cold/Warm Agglutinins	72 subjects out of 105	41 Cold (48.2%) 28 Warm (32.9.4%) 3 Mixed (3.5%)
Mean Hemoglobin Level	90 subjects out of 105	5.99 mg/dL
Mean Reticulocyte Count	45 subjects out of 105	8.54%
Mean Lactate Dehydrogenase	70 subjects out of 105	1105.37 U/L
Mean Haptoglobin Level	25 subjects out of 105	30 mg/dL
Outcome	97 subjects out of 105	82 recovered (78%) 15 deceased (14.29%) 8 no documented outcome (7.61%)

Table 2: Related pathology of patients with COVID-19-induced AIHA.

Related Pathology	Number of Subjects
Chronic Lymphocytic Leukemia	5
Marginal Zone Lymphoma	2
Breast Ductal Carcinoma	1
Oropharyngeal Squamous Cell Carcinoma	1
Prostate Cancer	1
IgM Monoclonal Gammopathy of Undetermined Significance	2
Mixed Connective Tissue Disease	1
Gallbladder Lithiasis	1
Fatty Liver and Acalculous Cholecystitis	1

Autoimmune Hemolytic Anemia in COVID-19 Patients: A Systematic Review of Clinical Characteristics and Outcomes

Mohammed Ayyad, MD[1,] Walaa Abu Alya, MD[2], Anas Mufeed Barabrah, MD[3], Sara Mohammed Darawish, MD[3], Yazan AlHabil, MD[5], Majdeddin MohammedAli, MD[4], Mustafa Zafer Nabilsi, MD[3], Diya Asad, MD[3], Laith A. Ayasa, MD[3], Daniel Matassa, MD[1]

[*]Contributed equally as a first co-author.

[1]Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA.

[2]Department of Medicine, Cleveland Clinic Fairview Hospital, Cleveland, Ohio

[3]Faculty of Medicine, Al-Quds University, Jerusalem, State of Palestine.

[4]Department of General Surgery, Brooklyn Hospital Center, Brooklyn, NY

[5]Department of Medicine, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, 00970, Palestine

Corresponding Author
Mohammed Ayyad, MD
Department of Medicine
Rutgers New Jersey Medical School
185 S Orange Ave, Newark, NJ 07103, USA
Phone: +972 59-521-5643
Email: dr.mohammad.ayyad@gmail.com
ORCID ID: 0000-0001-9772-2365

Highlights:

1. COVID-19 infection is implicated in the occurrence of autoimmune hemolytic anemia.
2. Patients with preexisting conditions, particularly hematologic disorders, show a higher risk for developing AIHA in the context of COVID-19.
3. Recovery rates were significant among patients treated with steroids, making it a potentially effective therapeutic regimen for this condition.
4. Early recognition and timely intervention are crucial for managing AIHA in COVID-19 patients to enhance recovery outcomes.
5. Better outcomes can be achieved by optimizing various treatment regimens for patients with COVID-induced AIHA.