Original Article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

New-onset hematologic disorders following COVID-19 vaccination: a systematic review

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Purpose: Coronavirus disease 2019 (COVID-19) vaccination reduced morbimortality rates due to severe acute respiratory syndrome coronavirus 2 infection worldwide. However, various complications have been reported, including hematologic disorders.
Materials and Methods: We conducted a systematic review to synthesize and analyze the current available evidence on the development of hematological disorders associated with COVID-19 vaccination.
Results: A total of 227 patients were reported in the papers that were selected to be included. There was a slight predominance of females (n=114, 50.22%) compared to males (n=113, 49.78%), and the calculated mean age was 54.86±18.94 years. The most frequently reported hematological disorders were Immune thrombocytopenic purpura (n=58, 25.55%), followed by thrombotic thrombocytopenic purpura (n=38, 16.74%). The less frequently recorded cases were acquired factor XIII/13 deficiency (n=2, 0.88%) and pernicious anemia (n=2, 0.88%). Messenger RNA (mRNA)-based COVID-19 vaccines, including Pfizer BioNTech 162b2 (n=106, 46.70%), Moderna mRNA 127-3 (n=42, 18.50%), and the Bivalent vaccine (n=1, 0.44%), were the most prevalent (n=150, 66.08%). Most cases developed after the first dose (n=120, 52.86%). In most cases, patient outcomes were favorable (n=175, 77.09%), but there were significant mortality cases (n=23, 10.13%)
Conclusion: Our findings suggest close monitoring of patients who receive the first dose with mRNA technology vaccines, regardless of sex, especially in adults, as they appear more vulnerable to developing hematologic disorders.

Trial Registration: PROSPERO Identifier: CRD42023452589

Keywords: Blood diseases; Hematologic diseases; COVID-19 vaccines; SARS-CoV-2 vaccines; Systematic review

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is continuously developing new variants that are spreading quickly across the globe [1]. Despite the World Health Organization (WHO) declaring the end of the pandemic on May 5, 2023, cases and deaths from

COVID-19 continue to be reported. As of April 14, 2024, there is an estimated prevalence of over 775 million confirmed cases and more than 7 million deaths from COVID-19 worldwide [2,3]. Although infection with SARS-CoV-2 is primarily known for causing substantial respiratory pathology, it can also lead to various extrapulmonary manifestations due to the presence of angiotensin-converting enzyme 2 (ACE2) receptors in other tissues [4]. Consequently, the infection has been observed to trigger hematological complications, mainly thromboembolic and prothrombotic events such as immune thrombocytopenic purpura (ITP) [5].

Therefore, the objective of developing an effective and safe vaccine has become crucial to combat COVID-19. According to the WHO, there 322 vaccine candidates in development, including Pfizer-BioNTech, Moderna, Gamaleya, Novavax, Oxford-AstraZeneca, Sinopharm, Bharat Biotech, Johnson & Johnson, and Sinovac [6]. The development of effective vaccines against SARS-CoV-2 has been crucial in reducing the impact of the disease on the population [7]. Multiple randomized clinical trials have demonstrated that these vaccines are both safe and effective [8,9]. Complete and booster vaccination against COVID-19 is effective against several variants including alpha, beta, gamma, delta, and omicron [10]. This is due to the production of neutralizing antibodies by B cells, which prevent the virus from entering the target cell. CD8+ T and CD4+ T helper cells also play a role in this process [11]. As of now, more than 13.5 billion vaccine doses have been administered globally [3].

It has been reported that there are various adverse effects related to vaccines such as fatigue, headache, myalgia, fever, pain, and redness at the injection site [12]. These symptoms are usually mild to moderate. However, there have been cases where vaccine-associated diseases have been reported. These include cardiovascular complications such as myocarditis, myopericarditis, pericarditis, takotsubo cardiomyopathy, and acute myocardial infarction [13-15]. Additionally, neurological conditions like Bell's palsy and Guillain Barré syndrome [16,17], endocrine diseases such as Graves' disease, subacute thyroiditis, and autoimmune diabetes mellitus [18-20], and ocular disorders like acute ocular neuroretinopathy have been associated with vaccination [21].

Numerous cases of hematological complications associated with COVID-19 vaccination have been reported in the literature. The objective of this study is to conduct a systematic review that includes case reports and case series documenting the development of hematologic disorders following COVID-19 vaccination. In this manuscript, we will describe the primary aims of this study.

The present study was conducted: 1) To provide a detailed description of the most relevant characteristics of studies that report the development of hematologic disorders associated with COVID-19 vaccination; 2) To perform a statistical analysis of the clinical and demographic characteristics; and 3) To compare the COVID-19 vaccine technologies that are most associated with the development of hematologic disorders.

MATERIAL AND METHODS

Protocol and registration

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [22]. The study protocol was reported in accordance with the PRISMA for protocols (PRISMA-P) 2015 [23]. Additionally, the review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023452589.

Objectives

The main goal of this study is to conduct a systematic review of studies that report the development of hematologic disorders associated with COVID-19 vaccination. The research question has been formulated following the key elements of the Population, Intervention, Comparator, and Outcomes (PICO) framework [24].

Population: persons ≥18 years who receive COVID-19 vaccine and develop hematologic disorders.

Intervention: all types of COVID-19 vaccines. Independent of dose (1st, 2nd and ≥3rd doses) and technology (inactivated vaccines, viral vector, nucleic acids, and subunits).

Comparator: Different vaccine technologies.

Outcomes: Development of hematologic disorders included: Aplastic anemia (AA), Autoimmune hemolytic anemia (AIHA), Acquired hemophilia, Thrombotic thrombocytopenic purpura (TTP), Vaccine-induced immune thrombotic thrombocytopenia (VITT), ITP, Leukemia, Lymphoma, Evans syndrome (ES), Hemolytic uremic syndrome (HUS), Hemophagocytic lymphohistiocytosis (HLH), Paroxysmal nocturnal hemoglobinuria (PNH), Acquired factor XIII/13 deficiency, and Pernicious anemia (PA).

Eligibility criteria

The eligibility criteria for the research question stated above were defined according to the PICO framework. The study included case reports and case series related to the

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development of hematologic disorders associated with COVID-19 vaccination. However, other study designs such as meta-analysis, systematic reviews, narrative reviews, letter to the editor, editorials, conference or conference abstracts, images, interviews, comments, correspondence, short reports, and press articles were excluded. Also, studies that reported other types of outcomes (not hematological disorders), studies with population under 18 years, and studies for which the authors did not have access to the full text were excluded.

Information sources

To conduct the current systematic review, we performed a selective bibliographic search using electronic databases such as PubMed, Scopus, Embase, and consulted the Web of Science platform. Our initial search was carried out on August 8, 2023, and then updated on November 23, 2023. Finally, the last search was conducted on April 16, 2024, to ensure the completeness of the study. Moreover, we manually reviewed the reference lists of included studies to ensure thoroughness.

Search strategy

Two authors designed a search strategy using terms obtained from the Medical Subject Headings of the National Library of Medicine: "Blood Diseases," "Hematological Diseases," "COVID-19 Vaccines," and "SARS-CoV-2 Vaccines." In addition, specific terms were used for the included diseases: "Aplastic Anemia," "Hemolytic Anemia," "Hemophilia," "Thrombotic Thrombocytopenic Purpura," "Immune Thrombocytopenic Purpura," "Leukemia," "Lymphoma," "Evans Syndrome," "Hemolytic Uremic Syndrome," "Hemophagocytic Syndrome," and "Paroxysmal Hemoglobinuria." These terms were linked using the Boolean terms AND or OR. The search strategy was developed for each database and is detailed in **Supplementary Data 1**. The search was limited to English language publications and was not restricted by publication date.

Study selection process

To remove any duplicate items, we downloaded all references to an EndNote document. Then, we exported all the references to the Rayyan QCRI website (https://www.rayyan.ai/). Two authors then screened the studies independently to check for eligibility. After that, they went through selected studies in full text to exclude manuscripts that did not meet the inclusion criteria. Additionally, they checked the reference lists of all the included studies to identify any potentially includable studies. If there was any disagreement, a third author was consulted to resolve the issue.

Data extraction process

The authors extracted the data of interest from studies and compiled it in a Microsoft Excel sheet. The data included important characteristics such as the first author's name, year of publication, country, sex, age, history of comorbidities, type of vaccine, dose, time until symptom onset, clinical manifestations, laboratory tests, additional tests, final diagnosis, complications, treatment, and outcome. For specific hematologic disorders, additional relevant data was also extracted. In case of any disagreement in the extracted data, the authors resolved it with each other.

Bias risk and quality assessment

The Joanna Briggs Institute (JBI) tool is used to evaluate the quality of studies such as case reports and case series [25,26]. The JBI provides four options for assessment: "Yes, No, Unclear, and Not applicable." Moreover, affirmative responses are summed up from 0 to 8. Articles with a score below 4 are considered of low quality while those with a score above 4 are considered of high quality. The JBI checklist for case reports comprises of 8 items which include patient demographics, medical history, current clinical condition, description of diagnostic tests, treatment, clinical condition after intervention, adverse events, and provision of take-away lessons. For case series, the checklist comprises of 10 items which include inclusion criteria, method of disease measurement, validity of diagnostic methods, consecutive inclusion of participants, completeness of participant inclusion, reporting of demographic characteristics, clinical information, outcomes, presentation of demographic information from the clinic, and adequacy of statistical analysis.

Synthesis and analysis of data

Descriptive data was synthesized and analyzed using SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA). Categorical data, including sex, type of vaccine, dose, clinical manifestations, antecedents, and treatment were presented as proportions (number with %). Numerical data such as age and time to onset of symptoms were expressed as mean ± standard deviation (SD).

RESULTS

Study selection

The search conducted across four databases retrieved a total of 2,501 records, published from inception to April 16, 2024. After removing duplicates, 1,915 records remained. In this initial screening, 1,450 records were removed based on the

selection of studies by title and abstract. Subsequently, 465 studies were reviewed in full text, eliminating 290 records due to reporting other types of studies, outcomes, or not meeting the inclusion criteria. Of the remaining 175 manuscripts, a total of 49 records were excluded for various reasons: reporting other types of results (relapses or exacerbations), lack of access to full text, and being written in languages other than English. From the 126 records that remained, reference lists were reviewed to identify potentially includable studies. This process retrieved a total of 48 studies. Finally, this review included a total of 174 studies, consisting of 143 case report studies and 31 case series studies. **Fig. 1** provides a detailed overview of the study selection process through a PRISMA 2020 flow diagram.

Characteristics of included studies

A total of 174 studies were included, consisting of 143 case report studies and 31 case series studies, with a total of 227 patients analyzed and distributed across different types of hematologic disorders. All the studies were published between 2021 and 2024, a period that spans from the beginning of vaccine administration to the present. Regarding epidemiological data, the frequency and proportion of information from different continents were calculated, revealing the following: Europe (n=90, 39.65%), where Italy (n=30/90, 33.33%) had the highest number of reported cases; Asia (n=70, 30.84%), where Japan (n=20/70, 28.57%) had the highest number of reported cases; North America (n=58, 25.55%), with the United States (n=56/58, 96.55%) reporting the most cases; Africa (n=4, 1.76%); Oceania (n=2, 0.88%); transcontinental (n=2, 0.88%); and South America (n=1, 0.44%). Regarding risk factors, comorbidities, and medical history, it was observed that 25.99% (n=59) had no medical history, 23.35% (n=53) had missing data, and 50.66% (n=115) had various medical histories, which are detailed in **Supplementary Data 2**. Clinical manifestations, laboratory tests, specific tests, anatomical pathology, and histology, as well as the management and treatment of each type of hematological disorder, are described in detail in **Supplementary Data 2**.

Clinical and demographic characteristics

The study included a total of 227 patients who developed newly diagnosed hematologic disorders after receiving the COVID-19 vaccine. The most common associated disorder was ITP (n=58, 25.55%), followed by TTP (n=38, 16.74%) and

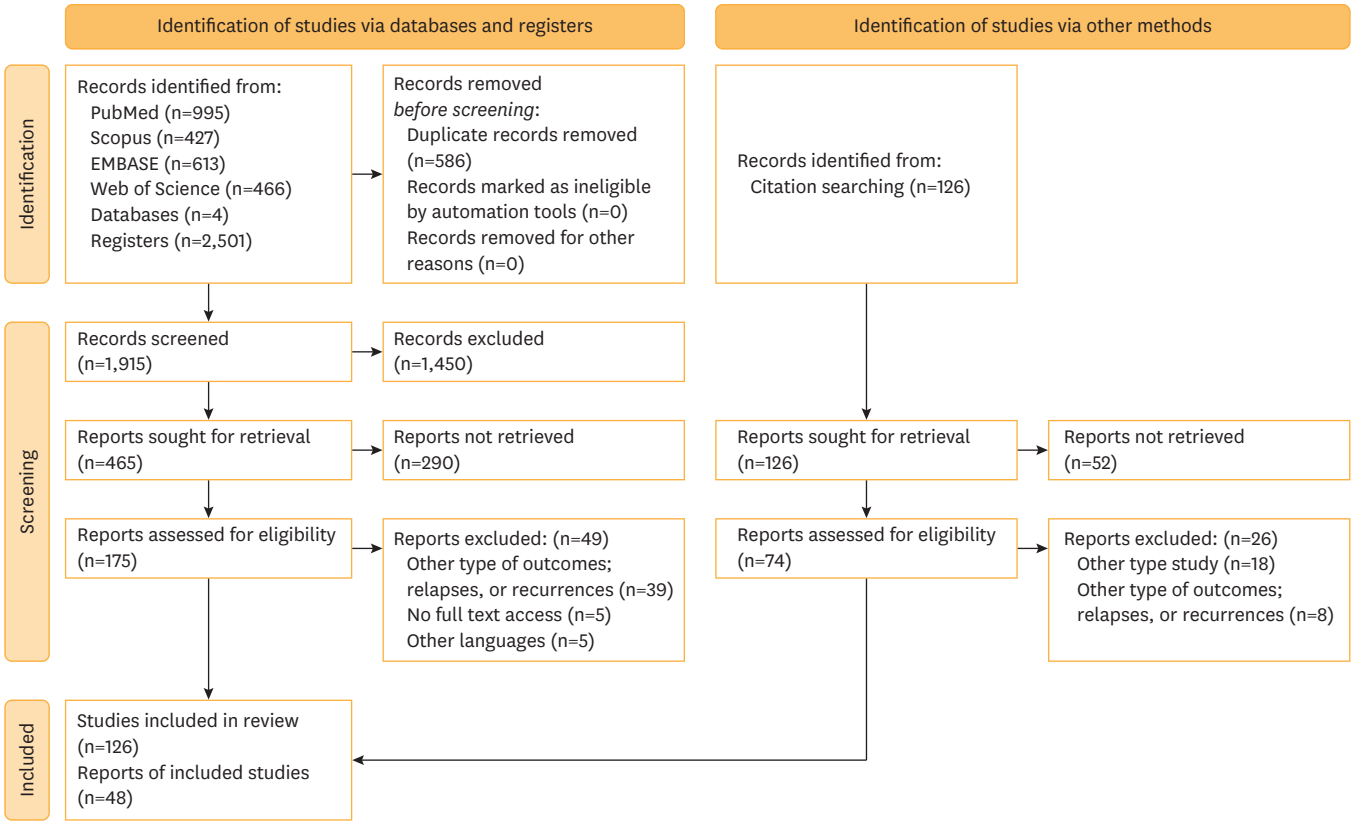

Fig. 1. Flow diagram PRISMA 2020.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; COVID-19, coronavirus disease 2019.

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VITT (n=21, 9.25%). It was observed that most cases were thrombotic phenomena. The less common and rare disorders were acquired factor XIII/13 deficiency (n=2, 0.88%) and PA (n=2, 0.88%). A nearly equal distribution was observed between both sexes, with females (n=114, 50.22%) compared to males (n=113, 49.78%), with an estimated ratio of approximately 1.008:1, respectively. The mean age calculated for the development of hematological disorders associated with COVID-19 vaccination was 54.86 years, with a standard deviation of 18.94 years. The minimum age observed was 18 years and the maximum age was 95 years.

Messenger RNA (mRNA) vaccines were the most prevalent (n=150, 66.08%), while cases associated with viral vector vaccines (n=64, 28.19%) and inactivated vaccines (n=10, 4.41%) were also reported. Most hematological disorders were associated with the first dose (n=120, 52.86%), followed by the second dose (n=85, 35.68%), with only a few cases associated with the third dose (n=19, 8.37%). The time from vaccine administration to the onset of clinical manifestations varied for each type of hematological disorder. Regarding outcomes, there were significant mortality cases (n=23, 10.13%), others did not respond well to treatment or had complications in their recovery and were categorized as unfavorable (n=15, 6.61%). However, most patients had a favorable outcome with a good response to treatment and, in many cases, complete hematological remission of the disease (n=175, 77.09%). **Table 1** provides detailed characteristics for each type of hematological disorder associated with COVID-19 vaccination.

mRNA technology vaccines, including Pfizer BioNTech 162b2 (n=106, 46.70%), Moderna mRNA 127-3 (n=42, 18.50%), and the bivalent vaccine (n=1, 0.44%) were the most prevalent (n=150, 66.08%). Additionally, other vaccines using viral vector technology (n=64, 28.19%) and inactivated vaccines (n=10, 4.41%) were observed. A subgroup analysis was carried out to evaluate the vaccines associated with the

Table 1. Summary data on the development of new-onset hematologic disorders following COVID-19 vaccination

Adverse effect (hematological disorders)	Number of cases	Sex (M/F)	Age (yr)	Vaccine technology				Dose vaccine				Time to onset of clinical signs (days)	Development		
			Mean ± SD	Inactivated	Viral vector	mRNA	NR	1st	2nd	≥3rd	NR	Mean ± SD	Favorable	Unfavorable	Death	NR
Immune thrombocytopenic purpura	58	25/33	53.63±20.86	1	19	38	0	40	17	1	0	10.16±8.06	53	1	0	4
Thrombotic thrombocytopenic purpura	38	18/20	50.34±17.84	2	10	26	0	21	16	1	0	16.63±12.5	32	2	4	0
Hemophagocytic lymphohistiocytosis	23	12/11	47.86±17.03	2	6	14	1	16	6	1	0	11.59±11.19	17	0	3	3
Acquired hemophilia A	22	15/7	73.36±10.61	1	1	20	0	10	12	0	0	19.45±19.78	18	1	3	0
Vaccine-induced immune thrombotic thrombocytopenia	21	12/9	43.80±15.94	2	15	4	0	10	1	3	7	13.14±6.08	11	1	9	0
Aplastic anemia	20	14/6	58.15±16.12	0	3	15	2	7	10	3	0	32.5±38.72	15	3	2	0
Lymphomas	14	8/6	60.42±15.39	0	3	11	0	4	7	3	0	24.9±52.02	7	5	0	2
Autoimmune hemolytic anemia	10	4/6	64±15.84	0	2	8	0	5	3	2	0	24.4±27.33	10	0	0	0
Hemolytic uremic syndrome	7	2/5	47.42±14.65	0	3	4	0	4	1	2	0	7.71±6.77	6	1	0	0
Leukemias	4	1/3	58±11.11	0	1	3	0	0	1	3	0	1.3±0.47	2	0	1	1
Paroxysmal nocturnal hemoglobinuria	3	0/3	46.33±12.68	0	0	3	0	1	2	0	0	4±3	0	0	0	3
Evans syndrome	3	1/2	64.66±14.42	0	1	2	0	2	1	0	0	10±5.65	3	0	0	0
Acquired factor XIII/13 deficiency	2	0/2	76.5±1.5	0	0	2	0	0	2	0	0	14	0	1	1	0
Pernicious anemia	2	1/1	48±3	2	0	0	0	0	2	0	0	14	1	0	0	1

COVID-19, coronavirus disease 2019; M, male; F, female; SD, standard deviation; mRNA, messenger RNA; NR, not reported.

development of *de novo* hematological disorders. It was found that the Pfizer BioNTech 162b2 vaccine was the most frequently reported and was associated with nearly all types of hematologic disorders. A slight predominance of males (53.77%) over females (46.23%) was observed. The average age of the cases was 54.07±21.08 years, and most were related to the second (50.00%) and first doses (41.51%) of the vaccine. The average time for the appearance of the first clinical manifestations was calculated at 16.89±25.86 days. Detailed analysis for all types of vaccines is shown in **Table 2**.

Risk of bias and quality

The risk of bias and quality of the 174 included studies was assessed using the JBI tool. A total of 143 case report studies were evaluated with the 8-item case report checklist. The assessment results showed that 123 studies were rated as high quality, and 20 studies were rated as low quality. For case series studies, a total of 31 studies were evaluated using the JBI tool's 10-item case series checklist. We estimated a cutoff point of >5 as high quality and ≤5 as low quality. The assessment results were as follows: 17 studies were rated as high quality, and 14 studies were rated as low quality. The detailed evaluation with the corresponding questions for each item and checklist is shown in **Supplementary Data 3**.

DISCUSSION

Our study is the first to systematically synthesize and analyze the development of de novo hematologic disorders associated with COVID-19 vaccination. Other studies have examined hematologic disorders separately but included research that reported relapses or exacerbations in patients previously diagnosed with a hematological disorder. However, the pathophysiological mechanisms differ substantially between these groups. It was observed that the development of hematological disorders related to COVID-19 vaccination was more common in adults and older adults, with an almost equal distribution between men and women. Most reported cases occurred after the administration of mRNA technology vaccines, primarily following the first dose. The clinical manifestations and therapeutic management varied according to the type of hematological disorder. Most patients responded well to treatment, achieved complete hematological remission, made a full recovery, and were finally discharged. However, it is important to note that mortality rates were significant, particularly in cases of thrombotic events.

Table 2. Analysis of COVID-19 vaccines associated with the development of new-onset hematologic disorders

Vaccine technology		Inactivated (n=10)			Viral vector (n=64)			mRNA (n=150)			Unspecified vaccines (n=3)
		Sinopharm	CoronaVac	NR	Oxford-AstraZeneca	Johnson & Johnson	Pfizer BioNTech 162b2	Modern mRNA 127-3	Bivalent	NR	NR
Number of cases		6	3	1	56	8	106	42	1	1	3
Sex	n (%)	M: 4 (66.67%) F: 2 (33.33%)	M: 2 (66.67%) F: 1 (33.33%)	F: 1 (100.00%)	M: 30 (53.57%) F: 26 (46.43%)	M: 0 (0.00%) F: 8 (100.00%)	M: 57 (53.77%) F: 49 (46.23%)	M: 18 (42.86%) F: 24 (57.14%)	F: 1 (100.00%)	M: 1 (100.00%)	M: 1 (33.33%) F: 2 (66.67%)
Age (yr)	Mean ± SD	45.16±16.32	59±20.83	43	53.41±15.76	55.75±15.16	54.07±21.08	60.16±17.39	43	55	56±13.95
Adverse effect most associated (hematological disorders)		TTP, VITT, ITP, HLH, PA	AHA, TTP, ITP	HLH	AA, AIHA, AHA, TTP, VITT, ITP, Lymphoma, ES, HUS, HLH	TTP, ITP, Leukemia, Lymphoma, HLH	AA, AIHA, AHA, TTP, VITT, ITP, Lymphoma, ES, HUS, HLH, PNH, Autoimmune F13 deficiency	AA, AIHA, AHA, TTP, VITT, ITP, Leukemia, Lymphoma, HUS, HLH	Leukemia	Leukemia	AA, HLH
Dose vaccine	n (%)	1st: 2 (33.33%) 2nd: 3 (50.00%) NR: 1 (16.67%)	2nd: 3 (100.00%)	1st: 1 (100.00%)	1st: 45 (80.36%) 2nd: 5 (8.93%) NR: 6 (10.71%)	1st: 8 (100%)	1st: 44 (41.51%) 2nd: 53 (50.00%) ≥3rd: 9 (8.49%)	1st: 21 (50%) 2nd: 15 (35.71%) ≥3rd: 6 (14.29%)	≥3rd: 1 (100.00%)	1st: 1 (100.00%)	1st: 1 (33.33%) 2nd: 1 (33.33%) ≥3rd: 1 (33.33%)
Time to onset of clinical signs (days)	Mean ± SD	15.4±4.36	27±4.24	NR	12.57±9.32	18.33±12.72	16.89±25.86	14.24±18.75	1	2	44±16

COVID-19, coronavirus disease 2019; NR, not reported; mRNA, messenger RNA; M, male; F, female; SD, standard deviation; TTP, thrombotic thrombocytopenic purpura; VITT, vaccine-induced immune thrombotic thrombocytopenia; ITP, immune thrombocytopenic purpura; HLH, hemophagocytic lymphohistiocytosis; PA, pernicious anemia; AHA, acquired hemophilia A; AA, aplastic anemia; AIHA, autoimmune hemolytic anemia; ES, Evans syndrome; HUS, hemolytic uremic syndrome; PNH, paroxysmal nocturnal hemoglobinuria.

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A concise and detailed description of the hematologic disorders included in this review is follows:

Acquired or idiopathic AA is a rare disease, defined as part of the bone marrow failure syndrome, characterized by marked pancytopenia [27]. The etiologies vary, and the relationship between AA and vaccines is very rare and infrequent. However, there have been previous reports in the literature about the development of pancytopenia after vaccination against hepatitis B [28,29]. An immune predisposition in the HLA-DR3 gene is proposed, which could indirectly induce the vaccine to trigger a response of cytotoxic T cells and the subsequent production of interferon (IFN)-γ [28]. Additionally, severe AA has been reported following immunization against varicella and the H1N1 influenza virus [30,31]. The development of AA has also been reported as a possible association with infection by the SARS-CoV-2 [32]. However, there are few described cases, and it is suggested that SARS-CoV-2 may mediate an immunological response causing direct bone marrow toxicity [33]. Our study identified a total of 20 patients who developed newly onset AA associated with COVID-19 vaccination. A predominance in the male sex was observed (n=14/20, 70.00%) compared to the female gender (n=6/20, 30.00%). The calculated mean age was 58.15±16.12 years. mRNA-based vaccines were the most associated (n=15/20, 75.00%). Most cases were associated with the second dose (n=10/20, 50.00%). The time from vaccine administration to the onset of initial clinical manifestations was calculated at 32.5±38.72 days. The most reported clinical manifestations were epistaxis, bruising, bleeding, and petechiae. Most patients did not present risk factors or previous medical history, with only a few cases reporting Hashimoto's thyroiditis, thalassemia, and dyslipidemias. Most patients had a favorable outcome, with only 2 reported cases of death. The pathophysiological mechanisms of AA point to an alteration of acquired immunity, inducing a bone marrow disorder caused by an autoimmune attack mediated by cytotoxic T cells against hematopoietic stem cells [34]. Cytotoxic T cells produce pro-inflammatory cytokines such as IFN-γ and tumor necrosis factor-α, thereby inhibiting the hematopoietic system and leading to cell apoptosis through the Fas/Fas ligand pathway [35]. Although the pathophysiological mechanisms linking the development of AA with COVID-19 vaccines are not entirely clarified, there is a hypothesis of increased activation of CD8+ T cells and an immune-mediated response by mRNA-based vaccines, promoting an increase in IFN-γ levels [36].

AIHA is an acquired, uncompensated hemolysis caused by the host's immune system attacking its own antigens present in red blood cells [37]. Hemolysis can be either intravascular or extravascular; immunoglobulin (Ig) G mediates warm-induced hemolysis and IgM mediates cold-induced hemolysis [38]. The association of AIHA with vaccination is rare and infrequent. However, various case reports have documented the development of AIHA following vaccination against polio, measles, mumps, and rubella [39], diphtheria, pertussis, and tetanus [40,41], and influenza [42,43]. The mechanism by which this association occurs is unknown; however, it is proposed that molecular mimicry of viral antigens induces cross-reactivity between T cells and B cells. Additionally, vaccine adjuvants may contribute [42,43]. On the other hand, some studies have noted an association with SARS-CoV-2 [44,45]. The mechanism by which SARS-CoV-2 induces the development of AIHA may involve direct damage to red blood cells or indirect damage through the induction of autoantibodies against the erythrocyte membrane [46]. Our study identified a total of 10 patients who developed new-onset AIHA associated with COVID-19 vaccination. There was a female predominance (n=6/10, 60.00%) compared to male (n=4/10, 40.00%). The calculated mean age was 64±15.84 years. mRNA technology vaccines were most associated (n=8/10, 80.00%). Most cases were associated with the first dose (n=5/10, 50.00%). The time from vaccine administration to the onset of the first clinical manifestations was calculated to be 24.4±27.33 days. The most reported clinical manifestations were fatigue, respiratory difficulty, jaundice, weakness, and the appearance of dark urine. Most patients had risk factors or prior medical history such as hypertension, diabetes mellitus, chronic kidney disease, psoriatic arthritis, thrombocytopenia, thrombosis, among others. All patients had a favorable outcome. Vaccines may contribute to the development of autoimmune disorders through various mechanisms such as molecular mimicry, polyclonal lymphocyte activation, epitope spreading, bystander activation, and the presentation of cryptic antigen determinants [47]. AIHA development may be related to some of these processes; however, the underlying pathophysiological mechanisms of this condition are not yet known.

Acquired hemophilia A (AHA) is a rare X-linked recessive hereditary bleeding disorder characterized by a deficiency of coagulation factor VIII, caused by the formation of antibodies against factor VIII [48,49]. The association between AHA and vaccines is very rare. However, there have been two case reports of AHA associated with vaccination against the H1N1 influenza virus [50,51]. The development of AHA has also been reported as a possible association with SARS-CoV-2 infection [52,53]. It is suggested that antibodies directed against the SARS-CoV-2 spike protein may be responsible for the development of autoimmunity, as well

as cross-reactivity with tissue antigens [54]. Our study identified a total of 22 patients who developed new-onset AHA associated with COVID-19 vaccination. A predominance of male sex (n=15/22, 68.18%) was observed compared to female sex (n=7/22, 31.82%). The calculated mean age was 73.36±10.61 years. mRNA-based vaccines were the most associated (n=20/22, 90.91%). Most cases were associated with the second dose (n=12/22, 54.54%). The time from vaccine administration to the onset of the first clinical manifestations was calculated at 19.45±19.78 days. The most reported clinical manifestations were the appearance of bruising, ecchymosis, bleeding, and petechiae. Most patients had risk factors or a previous medical history, such as hypertension, diabetes mellitus, and, in some cases, primarily in the older adult population, benign prostatic hyperplasia and cancer. Cases of rheumatoid arthritis, polymyalgia rheumatica, and Sjogren's syndrome were also observed. Most patients had a favorable outcome, with only three reported deaths. The mechanisms related to the development of AIHA and COVID-19 vaccines are not well understood. Two possible mechanisms have been proposed: molecular mimicry of antigens and stimulation of latent T or B cells. Molecular mimicry could promote the induction of anti-spike IgG antibodies that act as inhibitors of factor VIII. On the other hand, the stimulation of latent T or B cells, through the presentation facilitated by the major histocompatibility complex class II of SARS-CoV-2 spike protein peptides to preexisting factor VIII-specific T cell clones, may lead to their activation and result in the production of autoantibodies [55].

TTP is a thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and organ ischemia related to disseminated microvascular thrombi rich in platelets. TTP is primarily caused by autoantibodies against the protease ADAMTS13, which functions to cleave von Willebrand factor (vWF) [56]. ADAMTS13 protease is associated with biallelic mutations in the ADAMTS13 gene or an immune-mediated deficiency (anti-ADAMTS13 antibodies). TTP is related to an ADAMTS13 deficiency, which leads to an accumulation of hyperadhesive platelet vWF multimers in the blood. This induces the spontaneous formation of microthrombi rich in platelets in small arterioles or capillaries, causing generalized microvascular ischemia [57]. The association of TTP with vaccination is infrequent. Cases related to vaccination against H1N1 influenza [58,59], pneumococcal vaccine [60], and rabies vaccine [61,62] have been reported in the literature. However, the mechanisms underlying this association are unknown. The development of TTP has also been reported as a possible association with SARS-CoV-2 infection. A systematic review study by Taherifard et al. [63] evaluated autoimmune hematologic disorders during SARS-CoV-2 infection and found TTP in three patients. Another study by Chaudhary et al. [64] evaluated 11 patients diagnosed with COVID-19-associated TTP. It is proposed that a possible mechanism is that SARS-CoV-2 induces hypercoagulability caused by direct damage to endothelial cells and an imbalance due to reduced ADAMTS13 protease levels secondary to the inflammatory process of COVID-19 [64,65]. Our study identified a total of 38 patients who developed new-onset TTP associated with COVID-19 vaccination. A slight female predominance was observed (n=20/38, 52.63%) compared to male patients (n=18/38, 47.37%). The average age of the patients was 50.34±17.84 years. Vaccines based on mRNA technology were the most associated (n=26/38, 68.42%); however, cases related to viral vector vaccines (n=10/38, 26.32%) and inactivated vaccines (n=2/38, 5.26%) were also observed. Most cases were associated with the first dose of the vaccine (n=21/38, 55.26%), followed by the second dose (n=16/38, 42.11%). The time from vaccine administration to the onset of the first clinical manifestations was 16.63±12.5 days. The most reported symptoms included bruising, petechiae, bleeding, and ecchymosis, as well as nervous system manifestations such as vertigo, seizures, dysarthria, hemiparesis, confusion, and aphasias, among others. Most patients had no significant medical history, although important histories were noted, such as polycythemia, hypothyroidism, thalassemia, lymphomas, systemic lupus erythematosus, and Sjogren's syndrome, among others. Most patients had a favorable outcome; only four cases of mortality were reported. There is a suggestion of a possible abnormal response to vaccines that could trigger the formation of autoantibodies by B cells against ADAMTS13 through mechanisms of molecular mimicry [66].

VITT or thrombosis with thrombocytopenia syndrome is a recent definition that emerged from early descriptions of a safety signal involving COVID-19 vaccines based on AstraZeneca's adenovirus platform and later the Johnson & Johnson vaccine [67]. Our study identified a total of 21 patients who developed new-onset VITT associated with COVID-19 vaccination. There was a slight male predominance (n=12/21, 57.14%) compared to female (n=9/21, 42.86%). The average age of the patients was 43.80±15.94 years. Vaccines based on viral vector technology were most associated (n=15/21, 71.43%); however, there were also cases related to mRNA technology vaccines (n=4/21, 19.05%) and inactivated vaccines (n=2/21, 9.52%). It is important to note that the initial cases and the definition of VITT were primarily linked to vaccines based on viral vector technology. Most cases were associated with the first dose of the vaccine (n=10/21, 47.62%). The time from vaccine administration to

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the onset of the first clinical manifestations was 13.14±6.08 days. The most reported symptoms were headache, followed by nonspecific manifestations such as vomiting, nausea, and weakness, among others. Most patients did not have significant medical history, although some cases had diabetes mellitus or hypertension. Most patients had a favorable outcome (n=11/21, 52.38%), although significant mortality cases were reported (n=9/21, 42.86%), which highlights the importance of close monitoring in these patients who develop this disorder. VITT is an antibody-mediated disorder against anti-PF4 antibodies that is developed after vaccine administration. Following vaccination, PF4 meets vaccine components, activating B cells that express high-affinity receptors for PF4. As a result, anti-PF4 antibodies are released and form immune complexes containing PF4 and anti-PF4 Ig. These immune complexes induce the generation of procoagulant platelets, promote platelet/neutrophil aggregates, and stimulate neutrophil NETosis. The release of DNA during the NETosis process amplifies immune injury and activates complement, which is deposited on the endothelium, causing further damage [68].

ITP is an autoimmune blood disorder characterized by a significant decrease in platelet count. In this condition, platelets and their precursors become targets of a dysfunctional immune system [69]. Recently, cases of moderate to severe ITP associated with SARS-CoV-2 infection have also been identified, with various potential mechanisms involved, including molecular mimicry, cryptic antigen expression, and epitope spreading [70]. Rare cases of ITP related to measles, mumps, and rubella vaccines have been previously documented [71]. Other reports suggest possible associations of ITP with vaccines against rabies [72], polio [73], and human papillomavirus [74], among other vaccines, although the underlying mechanisms remain unknown. Our study showed that ITP was the most frequent hematological disorder, which may be due to previous research suggesting that people may develop ITP as an immune reaction to vaccination combined with a genetic predisposition since vaccines are designed to mimic actual infections and trigger immune responses [71]. We identified 58 patients who developed new-onset ITP associated with COVID-19 vaccination. A sex female predominance was observed (n=33/58, 56.90%) compared to male (n=25/58, 43.10%). The average age of the patients was 53.63±20.86 years. mRNA technology vaccines were most associated with the cases (n=38/58, 65.52%), although there were also significant cases related to viral vector technology vaccines (n=19/58, 32.76%) and inactivated vaccines (n=1/58, 1.72%). Most cases were associated with the first dose of the vaccine (n=40/58, 68.97%). The time from vaccine administration to the onset of the first clinical manifestations was 10.16±8.06 days. The most common reported symptoms included bleeding, petechiae, bruising, nosebleeds, and other hemorrhages, all related to the marked thrombocytopenia the patients had. Data on medical history or risk factors for many patients were not obtained, though there were mentions of histories of lymphomas, autoimmune thyroiditis, hypothyroidism, rheumatoid arthritis, diabetes mellitus, and hypertension, among others. Most patients had a favorable outcome; no mortality cases were reported. The mechanisms of the association between ITP development and COVID-19 vaccines are not entirely clear. However, hypotheses have been proposed regarding molecular mimicry and cross-reactions between vaccine antigens and host molecules, promoting the activation of autoreactive B or T lymphocytes, the emergence of antiplatelet antibodies, epitope spreading, a polyclonal immune response, and the final expression of ITP [75].

Leukemia is a type of blood cancer that starts in blood-forming tissues such as the bone marrow and leads to the production of large quantities of immature blood cells that enter the bloodstream. We classify leukemias as acute and chronic. Acute leukemias include B-cell and T-cell acute lymphoblastic leukemia [76]. Meanwhile, chronic leukemias include chronic myelomonocytic leukemia and T-cell large granular lymphocytic leukemia [77,78].

Our study identified only 2 cases of acute leukemias after COVID-19 vaccination: B-cell acute lymphoblastic leukemia and T-cell acute lymphoblastic leukemia. The cases involved a 43-year-old woman and a 55-year-old man. Both cases were associated with mRNA technology vaccines, the woman after receiving a booster dose and the man after receiving the first dose. The time between vaccine administration and the onset of initial clinical manifestations was one day for the woman and two days for the man. The most reported clinical symptoms were dizziness, difficulty breathing, general discomfort, and a lymph node swelling. The patients had no risk factors nor prior medical history. Only one case reported a favorable outcome. The mechanisms that explain this association are still unknown.

Our study found only 2 cases of chronic leukemias after COVID-19 vaccination: T-cell large granular lymphocytic leukemia and chronic myelomonocytic leukemia. The female patients, aged 60 and 74, had received mRNA (Moderna) and viral vector (Johnson & Johnson) vaccines, respectively, after the first dose. The time until the appearance of the initial clinical symptoms was 1 day for 1 patient and immediate for the other. The most common symptoms were fatigue, discomfort, fever, cough, vomiting, and generalized weakness. The 60-year-old patient had no relevant medical history, while the 74-year-old patient had a history

of asthma, high blood pressure, and dyslipidemia. The first patient had a favorable outcome, while the second had a fatal outcome. The mechanisms linking this association are still unknown.

Lymphoma is a group of malignant lymphocyte neoplasms with over 90 subtypes that are classically classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) [79]. NHL is the most common hematological malignant neoplasm worldwide [80]. The occurrence of a lymphoma subtype following vaccination is very rare, but cases have been reported in the literature. For instance, there has been a report of the development of marginal zone B-cell lymphoma and cutaneous lymphoid hyperplasia following influenza vaccination [81]. Another case reported the development of marginal zone lymphoma 1 month after receiving the H1N1 influenza vaccine [82]. Peripheral T-cell lymphoma was also reported to occur after influenza vaccination [83]. The mechanisms for this association are unknown. Reviews have also examined B-cell lymphoma and diffuse large B-cell lymphoma in relation to SARS-CoV-2 as a process of co-infection [84,85]. However, more studies are needed to better evaluate this co-infection and possible association. Not all studies suggest the development of lymphomas; there has been 1 reported case showing possible remission of HL induced by SARS-CoV-2. The authors of this report proposed mechanisms of cross-reaction of pathogen-specific T cells with tumor antigens and subsequent activation of natural killer cells through inflammatory cytokines secreted in response to the SARS-CoV-2 infectious process [86]. Our study identified 14 patients who developed new-onset lymphomas associated with COVID-19 vaccination. There was one case in a male patient and three cases in female patients. The mean age was calculated as 58±11.11 years. There was a slight male predominance (n=8/14, 57.14%) compared to females (n=6/14, 42.86%). mRNA vaccines were most frequently associated (n=11/14, 78.57%). Most cases were associated with the second dose (n=7/14, 50%). The time from vaccine administration to the onset of initial clinical symptoms was calculated to be 24.9±52.02 days. The most reported clinical manifestations were respiratory distress, followed by some nonspecific symptoms such as general malaise, fatigue, dizziness, vomiting, and generalized weakness. Most patients did not present risk factors nor prior medical history, except for one case with a history of asthma, high blood pressure, and dyslipidemia. Most patients had a favorable outcome, with only 1 reported death. The mechanisms explaining this association remain unknown.

ES is defined as the concurrent association of AIHA with ITP, and less frequently with autoimmune neutropenia [87]. The pathophysiological mechanisms that lead to ES are not fully understood. Possible mechanisms include: CTLA4 receptor deficiency causing deregulation of T cell homeostasis; TTP2 molecule deficiency leading to immunosenescence and autoimmunity; and deficiencies in helper T cells and increases in cytotoxic T cells causing elevated concentrations of IFN-γ and subsequent activation of B cells against erythrocytes and platelets [88]. ES as a side effect following vaccination is very rare. One case has been reported in the literature after influenza vaccination [89]. The development of ES due to SARS-CoV-2 infection has also been reported [90,91]. Proposed mechanisms for this possible association include molecular mimicry, the spread of hidden epitopes, and the formation of neoantigens [90]. Additionally, the intersection of autoimmunity and predisposing immune dysregulation could be involved [91]. In our study, we identified only three patients who developed new-onset ES associated with COVID-19 vaccination. Among them, there was 1 male patient and 2 female patients. These cases were associated with mRNA and viral vector vaccines, after receiving either the first or second dose. The period from vaccine administration to the onset of initial clinical symptoms was 10±5.65 days. The most common clinical symptoms included bruising, ecchymosis, bleeding, and respiratory distress, among others. Noteworthy medical histories reported included Vogt-Koyanagi-Harada disease, Hashimoto's disease, and atrial fibrillation. All patients had a favorable outcome. The mechanisms explaining this association remain unknown.

HUS is a rare variant of thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure caused by abnormalities in the alternative complement pathway [92]. The mechanisms that give rise to this condition are due to various genetic defects in complement pathway factors or acquired autoantibodies against complement regulators [93]. HUS has been associated with vaccination against measles, mumps, and rubella [94,95]. Additionally, there are reports linking it to the hepatitis B vaccine [96]. However, this association is very rare and uncommon, and the pathophysiological mechanisms are entirely unknown. Various infectious causes have been associated with HUS, including infection with SARS-CoV-2, which has been reported as an infectious trigger for the development of HUS. It is suggested that COVID-19 has direct effects on the activation of the alternative complement pathway [97,98]. In our study, we identified only 7 patients who developed new-onset HUS associated with COVID-19 vaccination. There was a predominance of female patients (n=5/7, 71.43%) compared to male patients (n=2/7, 28.57%). The average age calculated was

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47.42±14.65 years. Most cases were associated with mRNA-based vaccines (n=4/7, 57.14%), followed by viral vector vaccines (n=3/7, 42.86%), and the majority was associated with the first dose (n=4/7, 57.14%). The time from vaccine administration to the onset of first clinical manifestations was 7.71±6.77 days. Clinical symptoms were nonspecific, such as general malaise, nausea, and vomiting, among others. Regarding outcomes, most patients had a favorable evolution; there were no cases of mortality. The mechanisms by which this association occurs are completely unknown.

HLH is a rare clinical condition characterized by sustained and ineffective activation of the immune system, leading to severe systemic hyperinflammation [99]. Cases of HLH associated with SARS-CoV-2 infection have been reported, possibly due to a dysregulated inflammatory response [100,101]. Previous cases of PNH following influenza vaccination have also been observed, possibly associated with a temporary elevation of proinflammatory cytokines induced by the vaccines [102]. Our study identified a total of 23 patients who developed new-onset HLH associated with COVID-19 vaccination. There was an almost even distribution between sex, with 12 male (52.17%) and 11 female (47.83%). The average age was 47.86±17.03 years. mRNA-based vaccines were more commonly associated with the cases (n=14/23, 60.87%). Most cases were related to the first dose of the vaccine (n=16/23, 69.57%). The average time from vaccine administration to the onset of first clinical manifestations was 11.59±11.19 days. The most reported clinical symptoms included primarily fever, followed by myalgias, respiratory distress, fatigue, sweating, and hepatosplenomegaly, among others. Some patients had a medical history of conditions such as myelodysplastic syndrome, lymphomas, cancer, among others, while others had no significant history. Most patients had a favorable outcome; however, three deaths were reported. The development of HLH is possibly associated with the excessive and disordered immune response that COVID-19 vaccines produce, playing a significant role in the pathogenesis of cytokine storms, particularly involving interleukin (IL)-1β and IL-2R [103].

PNH is a rare, complement-mediated clonal hemolytic anemia that results from the clonal expansion of stem cells with a somatic mutation in the PIGA gene [104]. These mutations can be triggered by various factors, including viral infections, exposure to chemicals, or radiation, but in most cases, they are idiopathic. Recently, there has been a link between the development of PNH and SARS-CoV-2 infection [105,106]. Previous cases of PNH have been observed following influenza vaccination, possibly associated with the immune response due to the adjuvants they contain [107]. In our study, we identified only 3 patients who developed new-onset PNH associated with COVID-19 vaccination. All cases were in women with an average age of 46.33±12.68 years. All cases were related to mRNA technology vaccines, and most were associated with the second dose. The time from vaccine administration to the onset of the first clinical manifestations was 4±3 days. The most common clinical symptoms were fatigue, headache, and difficulty breathing. One patient had a history of prior SARS-CoV-2 infection, although no direct relationship with the infection was established. As for the prognosis, data was not obtained. The mechanisms by which this association occurs are completely unknown.

Coagulation factor XIII (13) is a pro-transglutaminase that plays an important role during the final stage of clot formation. Its acquired deficiency is usually transient, and one proposed cause is related to the consumption of coagulation factors during and after surgical procedures due to the activation of coagulation and expected perioperative bleeding [108]. The primary clinical manifestation of FXIII deficiency is bleeding, which can be spontaneous or secondary to hemostatic challenges [108]. No cases in the literature have associated the development of acquired factor XIII deficiency with SARS-CoV-2 infection or other vaccines. Our study identified only 2 case reports of acquired factor XIII deficiency following COVID-19 vaccination. Both patients were women aged 75 and 78 years, and the cases were related to the mRNA technology vaccine (Pfizer BioNTech) after receiving the second dose. The time until the onset of the first clinical symptoms was two weeks. The most common symptoms were purpura, bruising, and ecchymosis. The patients had no risk factors or prior medical history, except one who had a history of oncological surgery. The 78-year-old patient had a fatal outcome due to complications by cerebral and subarachnoid hemorrhage. The mechanisms causing this association are unknown, but they could be like those of acquired hemophilia A.

PA is an autoimmune disease related to autoimmune gastritis (AG), but they differ significantly since PA can occur after AG when there is a deficiency of the gastric intrinsic factor, which in turn leads to a vitamin B12 deficiency [109]. There are no documented cases in the literature that associate the development of PA with SARS-CoV-2 infection or other vaccines. Our study identified only one case series reporting the onset of PA in 2 patients after COVID-19 vaccination. One was a 51-year-old man and the other a 45-year-old woman, both linked to inactivated technology vaccine (Sinopharm) after receiving the second dose. The time from the administration of the vaccine to the onset of the first clinical symptoms was reported for only one patient,

which was 2 weeks. The most common clinical symptoms reported were weakness, lethargy, abdominal pain, nausea, and vomiting. The described patients had no risk factors or prior medical history. Only one case reported a favorable outcome. The mechanisms by which this association occurs are completely unknown.

Our study had several limitations. First, the present systematic review includes case report and case series studies due to limited original studies regarding the various hematologic complications. Thus, there is a potential risk given that case report and case series studies are not indicative. Therefore, the results should be interpreted with caution.

Secondly, although the search was exhaustive in the various databases, including manual review of the reference lists of the included studies, we did not rule out that there may have been related studies that we did not include.

Third, our eligibility criteria included studies published in English. Therefore, we may have overlooked several studies published in other languages.

Fourth, our study included only patients ≥18 years, which limited the number of cases found since there are studies that report on hematologic disorders associated with COVID-19 vaccines in pediatric population. Finally, although the sample size obtained in this review is relatively small and presents lower generalizability, this could be attributed to the novel nature of the course of these vaccine-associated complications.

In addition, we would like to point out the following: although the inclusion criteria specify the consideration of case report studies and case series, we also included some studies presented in letters to the editor and other similar formats. This is because certain scientific journals publish studies reporting cases in these formats, rather than in the conventional manner. These studies provided valuable and necessary information, so we consider them as case report and/or case series studies.

Future large-scale, multifunctional observational studies are recommended to evaluate the development of these disorders and to clarify the pathophysiological mechanisms underlying the hematological disorders associated with COVID-19 vaccination. The present study was based on collected data from case report studies and case series, due to the paucity of original studies. It is also suggested that future systematic reviews including original studies, such as randomized clinical trials and observational studies, should be conducted. These studies could address and evaluate the incidence and prevalence rates on the development of hematological disorders associated with COVID-19 vaccination.

In conclusion, our study is the first study to systematically synthesize and analyze the development of hematologic disorders associated with COVID-19 vaccination. Our findings suggest maintaining close surveillance is recommended in patients receiving the first dose of mRNA technology vaccines, regardless of sex, especially in the adult population, as they are more prone to develop hematological disorders according to the collected data. The development of these disorders is uncommon even in cases of thrombotic phenomena, considering the large number of immunized patients worldwide. Therefore, it is important to note that neither the risk nor the causal relationship on the development of hematological disorders associated with COVID-19 vaccination has been demonstrated. However, it is essential to report and analyze all possible adverse events and complications to monitor vaccine safety. Clinicians should be aware of these unusual vaccine-related disorders. In addition, large-scale, multifunctional observational studies are recommended to evaluate the development of these disorders and to clarify the underlying pathophysiological mechanisms related to COVID-19 vaccination. Further studies are also recommended to establish a more comprehensive characterization of the risk factors associated with fatal outcomes.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1
Databases: PubMed, Scopus, Embase, and Web of Science platform.

Supplementary Data 2
Characteristics of the included studies on the hematologic disorders following COVID-19 vaccination (Tables S1-S14).

Supplementary Data 3
Risk of bias and quality assessment using the JBI tool (Tables S15 and S16).

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