HEMATOLOGY

Review

Combination of Evans syndrome and COVID-19: a systematic review of reported cases

Suwen Li[1], Ranran Li[2], Yuyao Li[1,3], Yuefen Hu[4], Yan Liu[1], Jing Qin[5], Zizhen Qin[7], Qi Feng[6], Zi Sheng[1], Chaoyang Li[1], Jun Peng[1,7,8]

[1]*Department of Hematology, Qilu Hospital of Shandong University, Jinan, China;*
[2]*Department of Radiology, Ningjin County People's Hospital, Dezhou, China;*
[3]*School of Clinical Medicine, Shandong First Medical University, Jinan, China;*
[4]*Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China;*
[5]*School of Clinical and Basic Medical Sciences, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, China;*
[6]*Shandong Provincial Key Laboratory of Immunohematology, Qilu Hospital of Shandong University, Jinan, China;*
[7]*Advanced Medical Research Institute, Cheeloo College of Medicine, Shandong University, Jinan, China;*
[8]*Shandong Key Laboratory of Hematological Diseases and Immune Microenvironment, Qilu Hospital of Shandong University, Jinan, China*

Background - Evans syndrome is a rare autoimmune disease characterized by simultaneous or sequential primary immune thrombocytopenia and autoimmune hemolytic anemia. Despite the low incidence of Evans syndrome after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, its progression may threaten public health. This review offers an up-to-date summary of the works on the association between coronavirus disease 2019 (COVID-19) and Evans syndrome to explore the pathogenic mechanisms, epidemiological characteristics, clinical presentations, diagnostic markers, and treatment strategies.

Material and methods - We searched PubMed and Web of Science to identify articles that explored the relationship between COVID-19 and Evans syndrome. We collected and organized all reported cases of Evans syndrome following COVID-19 or SARS-CoV-2 vaccination over the past 4 years and also expanded the search to examine other cases of post-infection Evans syndrome.

Results - Thirteen cases were included with an average age of 42 years of whom 12 survived and one died. Two cases were associated with pregnancy and four with vaccination, two involved epileptic seizures, and three had a history of autoimmune disease.

Discussion - Patients with Evans syndrome and exposure to SARS-CoV-2 have a potential risk of bleeding. This risk should prompt close monitoring of bleeding biomarker dynamics and early initiation of hemostatic treatments, including platelet transfusion, corticosteroids, thrombopoietin receptor agonists, intravenous immunoglobulin and rituximab.

Keywords: *Evans syndrome, coronavirus disease 2019, bleeding risk, hemostasis therapy, vaccine.*

INTRODUCTION

Evans syndrome was initially defined as the simultaneous or sequential occurrence of primary immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA)[1]. Nowadays, the definition of Evans syndrome has been expanded to include the concurrent or sequential occurrence of at least two autoimmune cytopenias, among which ITP and warm reactive antibody AIHA have a high concurrent frequency, but autoimmune neutropenia is also observed, albeit less frequently[2-4]. Recent research highlighted that this

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Correspondence: Chaoyang Li
e-mail: lichaoyang@sdu.edu.cn

disease presents with more severe clinical manifestations and is associated with profound immune dysregulation or thrombo-inflammation, compared to primary ITP and AIHA.

Evans syndrome is a severe systemic autoimmune disease, not merely a hematologic disorder, in which there is a breakdown of immune self-tolerance[1,2,5-7]. The syndrome can be categorized into pediatric and adult forms[3,8-14]. The underlying etiology and exact pathogenesis remain unclear, although immune regulation disorders may be involved[3,15-22]. The loss of autoimmune tolerance may be a multistep process and a cascade reaction. Severe immune cytopenia, such as Evans syndrome, AIHA, or ITP, can be an early, potentially dangerous, and difficult-to-treat manifestation of an underlying inborn error of immunity[23-32]. Evans syndrome in childhood is frequently associated with inborn errors of immunity, and clinical research has found that there is a high frequency of potentially pathogenic variants in immune genes in over half of patients, suggesting that early-onset, multilineage autoimmune cytopenia should prompt genetic testing[33-35]. However, sequential occurrence of Evans syndrome in adults accounts for 20-50% of all cases[7]. Michel *et al*.[2] showed that this disease is a secondary in 56% of adult patients (mostly associated with malignancies and autoimmune diseases); in contrast, primary immunodeficiencies were identified in only 9% of cases[2,8,36-38]. In conclusion, as a potentially life-threatening condition, Evans syndrome is not merely a coincidental combination of immune cytopenias but rather a chronic state of profound dysregulation of the immune system that may be linked to other lymphoproliferative disorders and primary immunodeficiencies.

Since the coronavirus disease 2019 (COVID-19) pandemic, an increasing amount of research has indicated that COVID-19 could disrupt the immune system[39]. This disruption manifests in various fields, including abnormal immune responses, production of aberrant cytokines or chemokines, accelerated immune reactivity, and sharp increases in inflammatory factors. COVID-19 emerged as a stimulating trigger for various secondary autoimmune diseases. Notably, it could induce the progression and recurrence of Evans syndrome, thereby amplifying the risks of morbidity and mortality, with prognostic implications[40-42]. Previous research demonstrated that COVID-19 could induce hematologic disorders, such as thrombocytopenia, and coagulation abnormalities, including bleeding and thrombosis[40,42]. A previous study reviewed earlier data of COVID-19 pandemic associated with Evans syndrome in December 2021[42]. Since then, more research has focused on the potential association between COVID-19 and Evans syndrome, raising new challenges for the management of individuals with Evans syndrome during the pandemic.

The purpose of this systematic review was to provide an up-to-date summary of data on the combination of Evans syndrome and COVID-19, considering the impact of the pandemic on immune system function and the manifestation of various secondary autoimmune diseases.

MATERIALS AND METHODS

Search strategy and selection of articles

We searched PubMed and Web of Science to identify representative articles that explored the relationship between COVID-19 and Evans syndrome. Epidemiology, diagnosis, and treatment were addressed. We collected and organized all reported cases of Evans syndrome following COVID-19 or vaccination against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiological cause of COVID-19, over the past 4 years. Meanwhile, we expanded the inclusion criteria to include other "post-infectious" cases of Evans syndrome, such as those associated with tuberculosis, human immunodeficiency virus (HIV)/*Talaromyces marneffei*, severe trauma with multiple infections, dengue diseases and malignant thymoma with parvovirus B19 infection. The first search, using the keywords "Evans syndrome" to retrieve case reports, was performed on April 27, 2023, followed by another search on May 13, 2023, a third on September 27, 2023, and the last one on November 25, 2024. We then meticulously screened these reports to identify COVID-19 cases. No restrictions were imposed on the language, age, or country of origin. A total of 66 and 73 relevant articles were identified in the PubMed and Web of Science databases, respectively. After removing duplicates and articles unrelated to COVID-19 and those not meeting the inclusion criteria, explained in the search strategy, we identified four reviews and 15 articles that explored the relationship between COVID-19 and Evans syndrome in 13 patients and were

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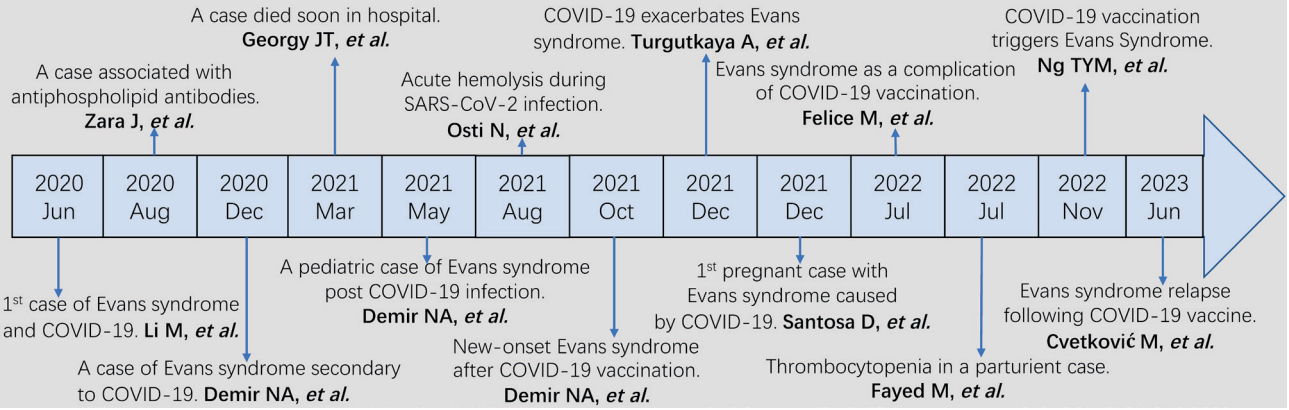

Figure 1 - Timeline and summary of the literature examined in this review
COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2.

included for further analysis. **Figure 1** presents an outline of all the cases included, shown on a timeline. In addition, seven other cases of infection-related Evans syndrome, such as those related to tuberculosis and HIV infection, were included in this study.

Data extraction

The following data were retrieved from each report (**Tables I-III**):

1. authors' name and year of publication of the case;
2. age and gender of the patients;
3. medical history;
4. clinical characteristics at presentation;
5. diagnosis of Evans syndrome and COVID-19;
6. comorbidities;
7. laboratory test results;
8. treatment received;
9. patients' outcomes.

RESULTS

The articles identified cover the discovery and development of Evans syndrome, from epidemiology and pathogenesis to clinical presentation and treatment, and outline the relationship with COVID-19. Previous studies have demonstrated that COVID-19 may induce or exacerbate Evans syndrome through various mechanisms, including molecular mimicry, red blood cell membrane abnormalities, and excessive inflammatory responses, thereby potentially increasing bleeding risk in infected patients.

Sixty-seven reports were considered in this study. Specifically, 37 were related to Evans syndrome and another 20 references report a relationship between COVID-19 and Evans syndrome, while 10 references were related to COVID-19. Overall, a total of 13 cases were presented in the articles eligible for full-text screening and analysis, comprising six males and seven females, with ages ranging from 6 to 85 years (average, 42 years), with a predominant occurrence in adults (**Table I**). Among these patients, 12 survived, and one died (**Table III**). Two cases were associated with pregnancy, two involved epileptic seizures, and four were associated with vaccination. Additionally, three patients had histories of autoimmune disease; one may have suffered a lupus-related condition. Elderly patients have a significantly worse prognosis than younger patients because they are often affected by underlying comorbidities, complicating their treatment. Notably, bleeding manifestations were very common among the patients and the only patient who died, reported by Georgy *et al.*[50], had intracerebral hemorrhage (**Table I**).

The diagnosis of Evans syndrome typically relied on laboratory findings, such as routine blood examination, direct and indirect antiglobulin tests, peripheral blood smear and bone marrow biopsy, coupled with clinical presentations of hemorrhage or hemolysis. Each case's specific clinical manifestations and laboratory indicators, as well as peripheral blood smear and bone marrow findings of Evans syndrome are shown in **Table I** and **Table II**, respectively. The laboratory investigations of COVID-19 were primarily reverse transcriptase polymerase chain reaction (RT-PCR) analysis for SARS-CoV-2 in nasopharyngeal swab material and

Table I - *Patients' demographics, clinical manifestations and laboratory indicators of Evans syndrome*

Authors[Ref]	Age, sex	Clinical manifestations	Hb	PLT	RPI/ Ret	DAT/ IAT	Auto-Ab	TBIL	D-BIL	I-BIL	Hp	LDH	D-D
Fayed M, *et al.*[51]	23, F	PE, hematemesis, bruising	7.1	<10	6%	DAT+	NA	NA	NA	NA	<30	263	2.63
Demir NA, *et al.*[65]	22, M	Jaundice	3.9	100	352,000	DAT+ IAT+	NA	9	7.6	NA	<8	792	1,700
Turgutkaya A, *et al.*[42]	63, F	Petechiae on the legs	6.5	2	316,000	DAT+	NA	NA	NA	NA	NA	426	NA
Hidaka D, *et al.*[53]	53, F	Jaundice, anemia	6.9	39	365,400	DAT+ IAT+	ANA+, LA+	6.4	NA	6.1	3	771	NA
De Felice M, *et al.*[55]	85, M	Icteric sclerae, hematoma ecchymosis	10	8	10%	DAT+	NA	4	2.8	NA	20	400	NA
Osti N, *et al.*[43]	77, F	Jaundice, hemoglobinuria	5.7	286	257,900	DAT+ IAT+	CSA	7.21	0.97	NA	<0.08	604	NA
Santosa D, *et al.*[52]	29, F	DIC, hematemesis, melena, hematuria	10	2	1.90%	DAT+	NA	4.6	1.7	2.9	NA	NA	1,400
Georgy JT, *et al.*[50]	33, M	ICH, melena ecchymoses	7.5	6	6.87%	+	NA	1.23	0.46	NA	NA	1,953	NA
Manzo ML, *et al.*[47]	6, M	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ng TYM, *et al.*[54]	43, F	Gingivorrhagia, bruising	5.8	7	125,900	DAT+	Anti-dsDNA	NA	NA	NA	<30	2,226	NA
Li M, *et al.*[48]	39, M	Popliteal DVT, hemoptysis epistaxis	6.5	3	22%	+	NA	NA	NA	NA	<2	947	NA
Zarza J, *et al.*[64]	30, F	DVT, gingivorrhagia, epistaxis	8.9	2	7%	DAT+	ANA+, LA+	NA	NA	NA	NA	NA	370
Cvetković M, *et al.*[56]	47, M	Purpura, oral mucosal hemorrhage	4.5	8	120,000	DAT+ IAT+	NA	6.23	1.16	NA	<0.08	633	NA

F: female; M: male; PE: pulmonary emboli; DIC: disseminated intravascular coagulation; ICH: intracerebral hemorrhage; NA: not applicable; DVT: deep venous thrombosis; Hb (g/dL): hemoglobin; PLT ($\times 10^9$/L): platelets; RPI/Ret (/mL): reticulocyte production index or count; DAT: direct antiglobulin test; IAT: indirect antiglobulin test; Auto-Ab: auto-antibodies; ANA: anti-nuclear antibody; LA: lupus anticoagulant; CSA: cold sensitive autoantibodies; anti-dsDNA: anti-double-stranded deoxyribonucleic acid; APA: antiphospholipid antibody; TBIL (mg/dL): total bilirubin; D-BIL (mg/dL): direct bilirubin; I-BIL (mg/dL): indirect bilirubin; Hp (mg/dL): haptoglobin; LDH (U/L): lactate dehydrogenase; D-D (ng/mL): D-dimer.

Table II - *Peripheral blood smear and bone marrow biopsy for Evans syndrome*

Authors[Ref]	Peripheral blood smear	Bone marrow biopsy
Fayed M, *et al.*[51]	Microcytic hypochromic anemia, anisocytosis, polychromasia	NA
Demir NA, *et al.*[65]	No schistocytes, polychromasia	20% of erythroblasts exhibited dysplastic changes
Turgutkaya A, *et al.*[42]	No schistocytes, decreased platelets, polychromasia, erythrocytes, hemolysis	NA
Hidaka D, *et al.*[53]	No schistocytes	M/E ratio 0.2, Erythroid hyperplasia
De Felice M, *et al.*[55]	No schistocytes, highlighted reticulocytes and nucleated RBC	Erythroid hyperplasia, mild megakaryocyte increase
Osti N, *et al.*[43]	Anisopoikilocytosis, RBC with basophilic stippling and knizocytes	NA
Santosa D, *et al.*[52]	Spherocytes	NA
Georgy JT, *et al.*[50]	No schistocytes, highlighted nucleated RBC, poikilocytosis, polychromasia	NA
Li M, *et al.*[48]	Microspherocytes, highlighted nucleated RBC and reticulocytes	NA
Zarza J, *et al.*[64]	NA	Hyperplasia and dysplastic erythroid precursors, megakaryocyte increase

RBC: red blood cells; NA: not applicable; M/E: myelocyte/erythroblast.

Table III - *Clinical characteristics, imaging feature and laboratory indicators for COVID-19*

Authors[Ref]	Clinical presentation	Imaging feature	WBC	Lymph	COVID-19 test	Main medical history	Vaccine for COVID-19	Outcome
Fayed M, *et al.*[51]	Pleuritic chest pain, dyspnea	Pulmonary embolism	9.9	NA	+	IDA, asthma, postpartum		Alive
Demir NA, *et al.*[65]	Weakness, dyspnea, fever	COVID-19 pneumonia	11.6	1.3	+	No		Alive
Turgutkaya A, *et al.*[42]	Cough, fever	Bilateral lung pneumonia	13.12	1,140	+	NA		Alive
Hidaka D, *et al.*[53]	Dyspnea, inspiratory wheezing	NA	5.33	34%	NA	Asthma, VKH	BNT162b2 vaccine	Alive
De Felice M, *et al.*[55]	NA	Bilateral interstitial pneumonia	4.95	790	NA	AF, hypertension	BNT162b2 vaccine	Alive
Osti N, *et al.*[43]	Asthenia	NA	15.8	NA	+	Hypertension, AML prolapse, LLVI		Alive
Santosa D, *et al.*[52]	Dry cough, fever, dyspnea, nausea, anosmia, fatigue	NA	5.8	696	NA	Gravida 2 Para 1 Abortus 0, Pregnant		Alive
Georgy JT, *et al.*[50]	Headache, GTCS	NA	12	NA	+	NA		Died
Manzo ML, *et al.*[47]	GTCS	NA	NA	NA	+	Evans syndrome		Alive
Ng TYM, *et al.*[54]	Lethargy, headache, exertional dyspnea, syncope	NA	NA	NA	NA	SLE, ITP	BNT162b2 vaccine	Alive
Li M, *et al.*[48]	Sore throat, productive cough, fever, chills, dyspnea	NA	11	1,700	+	NA		Alive
Zarza J, *et al.*[64]	Nasal congestion, sore throat, cough, loss taste, anosmia	NA	1.9	1,635	+	DVT of right lower limb		Alive
Cvetković M, *et al.*[56]	Weakness	NA	NA	NA	NA	Splenectomy	BNT162b2 vaccine	Alive

NA: not applicable; GTCS: generalized tonic-clonic seizures; WBC (×10^9/L): Lymph (/μL): lymphocytes; COVID-19: coronavirus disease 2019; WBC (×10^9/L): white blood cells; IDA: iron-deficiency anemia; VKH: Vogt–Koyanagi–Harada disease; AF: atrial fibrillation; AML: anterior mitral leaflet, LLVI: lower limb venous insufficiency; SLE: systemic lupus erythrocytosis; ITP: idiopathic thrombocytopenic purpura; DVT: deep vein thrombosis.

a rapid antibody test (**Table III**). In the early stage of the COVID-19 pandemic, chest computed tomography was also vital for the diagnosis.

Mainstaytreatmentspredominantlyincludecorticosteroids (dexamethasone, methylprednisolone, prednisone, prednisolone) and intravenous immunoglobulin (IVIG), with platelets and red blood cells transfusions frequently being used in emergency scenarios. Antiviral agents, hydroxychloroquine, as well as essential nutritional and oxygen support, constitute supportive therapies, although there were no specific antiviral drugs for the management of SARS-CoV-2 in the early stage of the pandemic. Prophylactic heparin treatment should be considered in most cases. When the aforementioned approaches yield suboptimal outcomes, the utilization of rituximab and thrombopoietin receptor agonists (eltrombopag, avatrombopag, romiplostim) could be contemplated. Major treatments and recommended managements are summarized in **Figure 2**. The specific details of each case and treatment outcome varied, and it is important to refer to the individual case reports and studies to obtain more comprehensive information. Among the included patients, nine had an obvious bleeding risk with initial platelet counts <10×10^9/L and hemorrhagic manifestations (**Table I**), so close monitoring and preventive measures throughout treatment were important to lower their risk of bleeding. Notably, antiviral treatments for the included cases were mainly hydroxychloroquine, favipiravir and remdesivir, but not bioavailable SARS-CoV-2 3C-like protease inhibitors. Paxlovid (Pfizer, New York, NY, USA) or simnotrelvir (Simcere Pharmaceutical, Nanchino, China) might have been more effective in these patients.

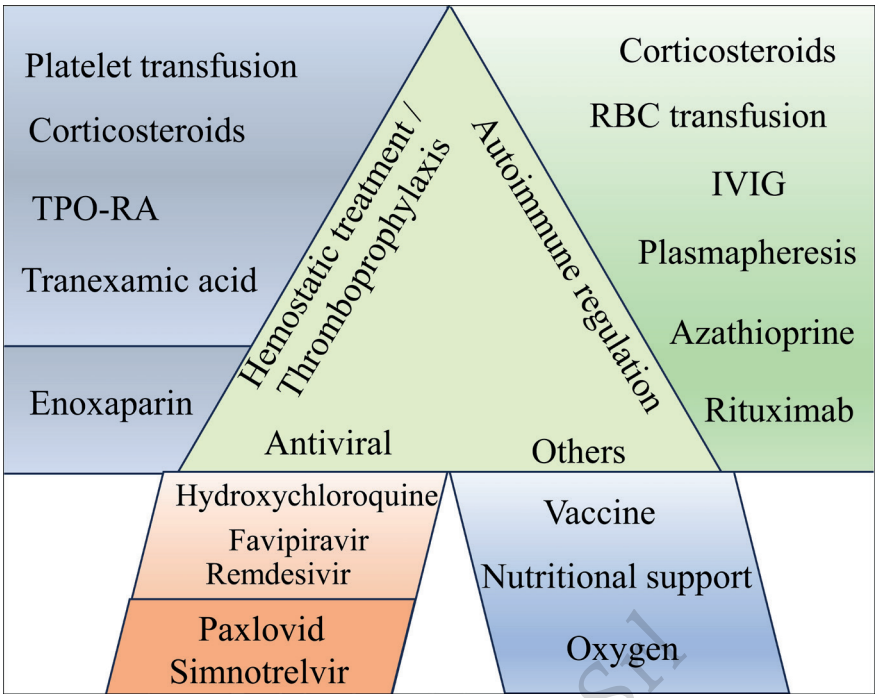

Figure 2 - Major treatments and recommended managements for Evans syndrome and COVID-19
TPO-RA: thrombopoietin receptor agonists: RBC: red blood cell; IVIG: intravenous immunoglobulin.

DISCUSSION

In this section, we delve into the core findings highlighting the key points and significant aspects of Evans syndrome and COVID-19. Furthermore, we consider the distinct characteristics of pregnancy-related and vaccine-related autoimmune diseases, along with cases involving epileptic seizures. By thoroughly examining these specific subgroups, we aim to gain valuable insights into the unique complexities and potential implications of these special scenarios.

Molecular mimicry

Immune tolerance may be disrupted by various mechanisms, including molecular mimicry, bystander activation, epitope spreading, neoantigen formation, and autoreactive effector cell immortalization[40,42,43]. Angileri *et al*.[44] recently proposed molecular mimicry as a mechanism linking COVID-19 and AIHA that involves the immunogenic epitope ankyrin-1 (ANK-1), a red blood cell membrane protein that shares peptide sequences with the SARS-CoV-2 spike protein[44,45]. ANK-1 shares a putative immunogenic-antigenic epitope (amino acids LLLQY) with 100% similarity to the SARS-CoV-2 surface glycoprotein spike protein, a molecular mimicry that may trigger the production of autoantibodies that bind to the red blood cell membrane, promoting the clearance of red blood cells and potentially inducing immune-mediated hemolytic anemia[42-45].

A meta-analysis of 7,613 patients found a significant decrease in platelet counts among patients with severe COVID-19[46]. The suggested mechanisms of such thrombocytopenia include SARS-CoV-2 entering hematopoietic cells via CD13 receptors, causing aberrant hematopoiesis, immune destruction due to molecular mimicry between platelet membrane components (especially glycoproteins) and virus antigens, and increased consumption due to endothelial injury and microangiopathy[47]. The best described mechanism is immune-mediated platelet destruction[47].

Recent studies indicated that reduced deformability, increased membrane protein oxidation, and abnormal membrane lipid composition may facilitate exposure to phosphatidylserine and complement deposition on the red blood cell membrane of COVID-19 patients[44,46]. Phosphatidylserine exposure may also affect platelet clearance and complement activation[44]. The presence of SARS-CoV-2 antigens may facilitate complement

deposition on red blood cells. Additionally, sustained inflammatory responses associated with infection, and oxidative stress against erythrocytes and platelet membranes, promote phosphatidylserine exposure, making red blood cells more vulnerable to attack and leading to hematological cell consumption. Furthermore, complement deposition may interfere with the results of direct antiglobulin tests[41,42]. As patients with Evans syndrome already have underlying immune dysregulation, immune system dysregulation induced by COVID-19 infection may further create favorable conditions for developing Evans syndrome[48]. The prevalence of cold complement-activating autoantibodies during SARS-CoV-2 infection in patients with Evans syndrome is much higher than that in patients with primary Evans syndrome, suggesting a more profound immune dysregulation encompassing the aforementioned molecular mimicry[43]. Moreover, virus-induced, excessive inflammatory responses may cross-activate certain parts of the immune system as "innocent bystanders", thus leading to attack on self-antigens[41].

Epidemiology

Epidemiological findings indicate that although Evans syndrome is more common in infancy, COVID-19 primarily affects adults, which may explains the higher incidence of COVID-19-induced Evans syndrome in adults and elderly patients[41,49].

Complications

Several relapses and complications, particularly infections and thrombosis, may occur during Evans syndrome, significantly affecting the survival of patients. COVID-19 infection and vaccination may increase the rate of exacerbations of Evans syndrome requiring immunosuppressive therapy, thereby increasing the burden of immune impairment and medication in these patients[41]. After treatment of bleeding with IVIG, three patients developed the risk of thromboembolic complications. Significantly, Georgy *et al*.[50] reported one Evans syndrome patient with COVID-19 who suffered from a 3-week history of gum bleeding, black tarry stools, and reddish spots on the skin who died on the third day after admission to hospital[50]. To the best of our knowledge, this case is the only documented fatal case of Evans syndrome and COVID-19 reported in the literature.

Diagnosis

The diagnosis of Evans syndrome is based on the exclusion of other possible conditions. Once other causes of thrombocytopenia have been ruled out, and a positive direct antiglobulin test is present, Evans syndrome can be diagnosed[51]. The majority of the cases included in this review, apart from a few in which specific diagnostic methods were not explicitly mentioned in the original text, involved the diagnostic strategy of exclusion.

Clinical signs related to Evans syndrome, including jaundice, anemia, cutaneous and mucosal petechiae, and ecchymoses, were also commonly observed (**Table I**). Regarding laboratory investigations (**Table I**), although the information provided in the case reports varied, most patients demonstrated decreased levels of hemoglobin and platelets, increased reticulocytes, a positive direct antiglobulin test, and significantly elevated lactate dehydrogenase levels. Anemia with anisocytosis and polychromasia, hemolysis with polychromasia and elevated reticulocyte and nucleated red blood cell counts were found in peripheral blood smears in most cases (**Table II**). Erythrocyte dysplasia and abnormal counts, as well as abnormalities of megakaryocyte development and count could be found in bone marrow biopsies in most cases (**Table II**). These findings can serve as laboratory evidence supporting the diagnosis of Evans syndrome.

The majority of patients included exhibited the typical symptoms of COVID-19, such as fever, shortness of breath and cough (**Table III**). Among the laboratory indicators of COVID-19, positive results from RT-PCR or serological antibody tests were the key factors, with additional pointers including radiographic evidence such as pulmonary ground-glass opacities, along with an assessment of the individual's vaccination history (**Table III**). It is worth noting that not all patients exhibited all criteria simultaneously. However, considering the backdrop of the COVID-19 pandemic and each patient's individual circumstances, the initiating diagnostic factors indicated in **Tables I-III** for suspicious cases within this context could also imply that the patient could be diagnosed with Evans syndrome and be infected with COVID-19. Further details are provided in the subsections below.

Evans syndrome and COVID-19 in pregnant patients

Two cases were pregnancy-related. Fayed *et al*.[51] reported a 23-year-old parturient who received epidural analgesia

and was subsequently diagnosed with Evans syndrome[51]. The patient experienced post-delivery pleuritic chest pain and pulmonary embolism and chest computed tomography showed bilateral ground-glass lung opacities. This prompted testing for SARS-CoV-2, which confirmed the infection. Neuraxial anesthesia is contraindicated in pregnant patients with severe thrombocytopenia because of the increased risk of spinal epidural hematoma. Santosa *et al*.[52] reported the case of a 29-year-old full-term pregnant Indonesian woman who was diagnosed with Evans syndrome and presented with typical symptoms after confirmation of COVID-19. As her condition deteriorated, signs of fetal distress appeared, and a high-risk emergency delivery via Cesarean section was performed[52].

Vaccination-related and autoimmune disease-related cases

Among the four vaccination-related cases, two had autoimmune disease, which indicates that mRNA SARS-CoV-2 vaccination may trigger autoimmune disorders[53,54]. De Felice *et al*.[55] found one individual who received SARS-CoV-2 vaccine and subsequently developed Evans syndrome[55]. Although the relationship between vaccination against COVID-19 and Evans syndrome is unclear, it highlights the importance for physicians of assessing the benefits and risks of SARS-CoV-2 vaccines carefully for each patient[56]. Physicians should be aware of these potential side effects and closely monitor hematological conditions following vaccination.

Cvetković *et al*.[56] reported a 47-year-old man with pre-existing Evans syndrome who, through previous treatment with glucocorticoids, IVIG, azathioprine, vinblastine, and splenectomy, had achieved complete remission. After the second dose of BNT162b2 vaccine, he developed mucocutaneous bleeding and thrombocytopenia. Initial treatment with prednisone and azathioprine produced no improvement. On day 28, there was a relapse of Evans syndrome[56]. This report indicates that a comprehensive assessment of the patient's status, including the state of autoimmune disease (stable or active), dosage and duration of immunosuppressant use, and age, is important before vaccination.

Seizure-related cases

The two cases of epileptic seizures included in this review were characterized by rapid onset and progression[47,50]. The divergent outcomes of the two cases underline the importance of early intervention and the patient's overall state of health for a favorable prognosis.

Manzo *et al*.[47] reported the case of a 6-year-old patient with Evans syndrome who had his first brief epileptic seizure 10 days before testing positive for SARS-CoV-2[47]. Compared to previous cases, this patient had a shorter duration of illness, received timely treatment, exhibited mild initial symptoms, and was younger, all of which may have contributed to the more favorable prognosis.

The other case presented with sudden-onset headache and subsequently experienced a generalized tonic-clonic seizure shortly after admission. Unfortunately, the patient died on the third day of hospitalization[50]. Brain computed tomography revealed an intracerebral hemorrhage in the right capsulo-ganglionic region with edema and a midline shift. As this patient was the only one who died among the 13 included in this review, we highlight the importance of an early assessment of bleeding risk and prompt hemostatic therapy.

Tuberculosis-related cases

Tuberculosis is a contagious bacterial infectious disease caused by *Mycobacterium tuberculosis* which can damage multiple organs and systems. Although respiratory tract infection is its main manifestation, it can also be extrapulmonary. In tuberculosis patients, the hematological system mainly shows anemia and leukocytosis, which also exist in other diseases. Immunocompromised patients are at a higher risk of tuberculosis infection. Additionally, tuberculosis can affect the immune system and is associated with autoimmune disorders. Evans syndrome concurrently with tuberculosis is extremely rare[57].

We found one case with no medical history of disease but who was diagnosed as having concurrent severe pulmonary tuberculosis and Evans syndrome[57]. The 69-year-old female had fever and shortness of breath. Chest computed tomography showed extensive miliary nodules, and she quickly developed respiratory failure needing intubation and ventilation. A sputum smear was 3+ for acid-fast *bacilli*. Blood tests later showed hemolytic anemia, a positive direct Coombs test, and platelet antibody IgG. She was diagnosed with disseminated pulmonary tuberculosis and Evans syndrome and recovered after treatment with antituberculosis drugs and glucocorticoids.

Blood Transfus. 2025; 23(4): 365-378 doi: 10.2450/BloodTransfus.860

We also found an exceedingly rare case of Evans syndrome associated with tubercular pleural effusion[58]. The patient was first regarded as having AIHA, but the occurrence of thrombocytopenia later led to the diagnosis of Evans syndrome. The concomitant presence of tuberculosis and Evans syndrome made treatment with immunosuppressive drugs more challenging.

It is hypothesized that in patients with tuberculosis, Evans syndrome may occur because lymphocytes produce antibodies against blood cells in response to the tubercular pathogen. Molecular mimicry between unknown antigens of tubercular *bacilli* and platelet surface antigens might cause thrombocytopenia in Evans syndrome patients with tuberculosis.

Kim *et al*.[10] reported a case of tuberculosis *cutis orificialis* in a patient with pre-existing Evans syndrome and discussed the possibility that impaired cellular immunity and long-term use of immunosuppressive medications in Evans syndrome could be predisposing factors for tuberculosis, so Evans syndrome and tuberculosis could predispose to each other. In the case described, the patient had concurrent symptoms of tuberculosis and Evans syndrome, and a possible but undetermined pathophysiological factor could account for their coexistence[57,58].

Secondary Evans syndrome in AIDS patients with Talaromyces marneffei infection

Hematological complications are common in HIV patients and can be attributed to the virus itself or may be secondary to opportunistic infections and antiretroviral therapy or even to nutritional deficiency[59]. Autoimmune cytopenias may be the initial presentation in patients with HIV infection or can develop while on treatment with antiretroviral therapy. However, these cytopenias usually resolve after initiation of antiretroviral therapy[59].

We identified the case of a 32-year-old HIV-positive female with a 5-day history of breathlessness with pallor, icterus, and splenomegaly[59]. Tests indicated that she had severe anemia and thrombocytopenia. She was treated as having Evans syndrome with steroids and transfusions. Readmitted later, she received rituximab and, after splenic infarcts were found, she underwent splenectomy. Four months after the splenectomy she was doing well, with improved blood counts.

Talaromyces marneffei is a common, opportunistic fungus in individuals with HIV infection. Patients with acquired immunodeficiency syndrome (AIDS)/*T. marneffei* with secondary Evans syndrome are extremely rare but we need to be alert to the possible occurrence of secondary Evans syndrome in AIDS/*T. marneffei* patients. They present with a severe systemic condition including severe inflammatory reaction, worsening liver and coagulation function, and worsening immune status. Clinicians should start effective antifungal treatments promptly in AIDS patients with suspected *T. marneffei* infection[60].

The development of Evans syndrome in HIV-infected patients may be associated with an underlying deficiency in humoral or cell-mediated immunity. All the AIDS/*T. marneffei* patients with secondary Evans syndrome had really low $CD4^+$ T-cell counts, and some also had low $CD8^+$ T-cell and $CD19^+$ B-cell counts. Three patients had simultaneous hemophagocytic lymphohistiocytosis, with key factors including immunomodulation imbalance, immunocompetent cell accumulation, and inflammatory cytokine production. The pathogenesis of *T. marneffei* infection associated with Evans syndrome may involve a severe inflammatory response syndrome caused by congenital or post-infection immune deficiency or severe infection[60].

Evans syndrome driven by other infections

Evans syndrome in association with multiple infections following severe trauma is very rare and we found just one case. In this case, the patient developed Evans syndrome after multiple traumas, related surgical interventions, and complications including bacterial cholangitis, fungal lower respiratory tract infection, and sinusitis[61]. Since autoimmune diseases were not confirmed, trauma, invasive surgery, transfusions, and/or infections might have induced Evans syndrome. No prior reports have described Evans syndrome caused by trauma or fungal infection. These factors could trigger cytokine release, leading to a cytokine storm and excessive immune dysregulation, causing Evans syndrome[61]. As the complications can be fatal and unnoticed without recognizing Evans syndrome, more similar cases are needed to clarify the clinical course.

We also collected the first case reporting an association between dengue disease and Evans syndrome in a child[62]. The hemorrhagic appearances of severe dengue are due to plasma leakage as a result of increased vascular permeability, severe thrombocytopenia, and

hemoconcentration[62]. A 6-year-old male with no significant medical history presented with various symptoms for 5 days, was hospitalized with probable dengue and warning signs, had a torpid course with multiple manifestations, was diagnosed with severe dengue and taken to the pediatric Intensive Care Unit. Hematological abnormalities included bilineage cytopenia, which was later determined to be due to Evans syndrome rather than dengue-related hematological manifestations, requiring platelet transfusions. In the context of an endemic tropical disease in many regions with a broad spectrum of clinical and paraclinical manifestations and a wide range of severe complications, we think it is important to identify unusual clinical patterns that require timely interventions to avoid definitive, secondary injuries or a fatal outcome[62]. Finally, there is a case report of a 39-year-old Hispanic man with a recently treated malignant thymoma who developed syncope and dyspnea and was found to be anemic and thrombocytopenic with laboratory findings consistent with AIHA (but low reticulocyte count). He also had acute parvovirus B19 infection. He was diagnosed with Evans syndrome, supported by bone marrow biopsy findings, and was treated with steroids and red blood cell transfusion and improved. This is the first reported case of Evans syndrome likely triggered by both thymoma treatment and parvovirus B19 infection[63].

Treatment

The widely used therapeutic approaches for patients with Evans syndrome and COVID-19 are corticosteroids and IVIG. However, it is crucial to consider the potential bleeding risk at the same time. If outpatients or hospitalized patients have a potential risk of bleeding, treatments such as platelet transfusions, corticosteroids, IVIG, thrombopoietin receptor agonists and tranexamic acid should be recommended early, especially in those with Evans syndrome who need earlier attention to prevention of bleeding[41,42,64,65]. As thrombopoietin receptor agonists require about 5 days to produce a platelet response, and rituximab usually takes 3-5 weeks, early administration of platelet transfusions, IVIG and corticosteroids should be considered with a high priority, especially for patients with a serious bleeding risk or bleeding manifestations.

SARS-CoV-2 mRNA vaccines have been observed to exacerbate autoimmune hematological disorders, autoimmune rheumatic diseases and systemic lupus erythematosus[54,66-70]. Patients with Evans syndrome may have inadequate responses to vaccines and an increased risk of exacerbation of autoimmune cytopenia during immunosuppression. Therefore, it is recommended that there is an interval between vaccination and receiving rituximab treatment, and that this should be as long as possible[41]. Four patients with Evans syndrome were included in this study based on their having received SARS-CoV-2 mRNA vaccines. Vaccination should be administered at the lowest possible corticosteroid dose during treatment and patients should be monitored closely for reactivation of autoimmune cytopenia, as this is manageable if recognized promptly[41,71].

Given the prevalence of autoimmune cytopenia in patients with COVID-19, sudden and significant decreases in peripheral blood cell counts should be closely monitored. Prompt evaluation of markers of hemolysis and consideration of the possibility of Evans syndrome are crucial to ensure timely and appropriate treatment. The risk of COVID-19-related thrombosis, caused by thrombo-inflammation, endothelial activation, and antiphospholipid antibodies, is amplified by the ongoing hemolysis and increased fractions of young platelets in Evans syndrome[40,42]. This underscores the importance of early prevention of complications such as thrombosis[40,42].

There are currently no prospective or controlled randomized studies concerning the treatment of patients with both Evans syndrome and COVID-19. Early identification and treatment could potentially improve outcomes[50]. Although antiviral treatment for the cases included in this review consisted of hydroxychloroquine, favipiravir (Toyama Kagaku Kōgyō, Toyama, Japan) and remdesivir (Gilead Sciences, Foster City, CA, USA), we recommend the use of paxlovid or simnotrelvir which achieve better clinical outcomes as orally bioavailable SARS-CoV-2 3C-like protease inhibitors[72-74] (**Figure 2**). Most of the immunosuppressant drugs (e.g., corticosteroids) used for autoimmune cytopenia also have immunomodulatory activity that can alleviate inflammation and improve prognosis in COVID-19 cases[42]. Available evidence suggests that the use of immunomodulatory/immunosuppressant drugs for autoimmune cytopenia is not detrimental to the course of COVID-19[40]. High-dose IVIG is a safe and reasonable approach for patients with COVID-19-induced Evans syndrome, especially those

with a high risk of bleeding[40,71]. Alternative options are recombinant erythropoietin, which may be safer for patients with inadequate reticulocytosis, and rituximab[42]. Recent evidence from patients with inflammatory rheumatic diseases indicates that rituximab therapy is associated with a more severe clinical presentation of SARS-CoV-2 infection[43]. We, therefore, suggest a cautious approach when considering rituximab as a therapeutic strategy. Plasma exchange may be a resource in the acute setting, although it is not always feasible for elderly patients, particularly those with congestive heart failure[71]. Thrombosis is a potential negative complication in COVID-19-induced Evans syndrome, and particular attention should be given to thromboprophylaxis for as long as the platelet count allows[71].

The treatment of Evans syndrome patients with COVID-19 infection is difficult and may be best individualized according to the patient's characteristics because of the heterogeneity of hematological disorders. Collaboration among multidisciplinary experts is crucial for tailored treatment strategies. Early hemostatic therapy is particularly advisable for patients with a bleeding risk.

Regarding relapse of Evans syndrome upon COVID-19 infection or vaccination in patients with a history of the syndrome, we found limited data although this is a crucial aspect that needs further investigation. In the cases we analyzed, there was one report of a patient with pre-existing Evans syndrome who relapsed after the second dose of BNT162b2 vaccine. This indicates that vaccination may potentially trigger a relapse in some patients, but more studies are required to understand the underlying mechanisms and risk factors. Clinicians should closely monitor patients with a history of Evans syndrome after vaccination or during COVID-19 infection for any signs of relapse.

When comparing post-COVID-19 or post-vaccine Evans syndrome with primary Evans syndrome, it is difficult to state definitively that one is more severe than the other. However, in the cases we reviewed, post-COVID-19 Evans syndrome patients often presented with complex clinical situations, including concurrent COVID-19 symptoms and a higher frequency of bleeding manifestations. This may have been due, in part, to the fact that these patients were more closely monitored during the pandemic. Regarding whether infection or vaccine is more harmful, both seem to have the potential to trigger Evans syndrome, and the degree of harm may vary depending on an individual patient's factors such as underlying health condition and immune status. For example, in the pregnancy-related cases, COVID-19 infection led to significant complications, while in some vaccination-related cases, the development of Evans syndrome was observed after vaccination. More research is needed to quantify the relative harm.

Regarding the frequency of direct antiglobulin test-negative AIHA and IgM-driven AIHA, our data did not show a significantly higher frequency in post-infection Evans syndrome than in primary Evans syndrome. However, the sample size may have been too small to draw a definite conclusion. Future studies with larger number of patients are required to assess such differences accurately.

As far as concerns bleeding or thrombosis frequency, we observed a relatively high frequency of bleeding manifestations in post-COVID-19 Evans syndrome patients. This could be due to the combination of COVID-19-induced immune dysregulation and the underlying immune abnormalities in such patients. However, it is also possible that clinicians' higher awareness of these risks during the pandemic led to more frequent detection. Cases of thrombosis were less common in our series, but the risk of this complication does exist, especially considering the potential for thrombo-inflammation in Evans syndrome. The relationship between bleeding/thrombosis and different types of Evans syndrome (primary *vs* post-infection) requires further exploration.

Regarding the treatment response, there were no clear differences in the initial response to corticosteroids and IVIG between primary and post-infection cases of Evans syndrome. However, in some cases of post-COVID-19 Evans syndrome, the use of thrombopoietin receptor agonists and rituximab was considered earlier due to the severity of the condition. Nevertheless, additional studies are needed to establish a definite difference in treatment response. In terms of outcome, the mortality rate in our included cases was relatively low, and it was not possible to clearly distinguish a significant difference in outcome between primary and post-infection Evans syndrome. However, the long-term outcome and the potential for relapse in

post-infection Evans syndrome patients remain areas of concern and require further follow-up and research.

CONCLUSIONS

The information gained from conducting an up-to-date summary of the relevant research on COVID-19 and Evans syndrome, including the cases published in the literature, has highlighted the importance of close monitoring of bleeding biomarker dynamics and early initiation of hemostatic therapy. The obvious limitation of this study is that only a few publications were available on Evans syndrome and COVID-19, describing small cohort studies or single cases. More research should focus on determining the optimal management of SARS-CoV-2 infection, vaccination and Evans syndrome, further unravelling the mechanisms involved, optimal use of vaccines and SARS-CoV-2 3C-like protease inhibitors in the future. More epidemiological studies are essential to understand the connection between COVID-19 and Evans syndrome across diverse populations and regions. Additionally, post-pandemic monitoring of the long-term effects of COVID-19 vaccination in patients with Evans syndrome is crucial in order to optimize strategies to mitigate adverse reactions.

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AUTHORSHIP CONTRIBUTIONS

SL, CL and JP designed the study and wrote the manuscript. RL, YH, YL, JQ and ZQ revised the manuscript along with QF and ZS. All Authors read and approved the final manuscript.

The Authors declare no conflicts of interest.

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