The Development or Exacerbation of an Autoimmune Disorder Associated with SARS-CoV-2 infection: a Systematic Review of Case Reports

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Abstract

Background: Infections have long been studied as environmental triggers of autoimmunity. Previous associations between coronavirus and autoimmune disorders make severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus identified in December 2019, a potential candidate for autoimmune disorder development. Indeed, an increasing number of these cases have been reported prompting a characterization and summarization of existing evidence.

Objectives: This review aims to characterize and summarize case reports documenting the development or exacerbation of an autoimmune disorders associated with SARS-CoV-2 infection.

Methods: A bibliographic search of Embase was performed from inception to July 2020. Studies included reported the development or exacerbation of an autoimmune disorder associated with SARS-CoV-2 infection. Quality was judge using Joanna Briggs Institute Critical Appraisal Checklist for Case Reports and piloted forms were used for data collection. Data were summarized using descriptive statistics and narrative synthesis.

Results: From 304 entries, 85 different cases were included, 41%-99% with good appraisal across quality domains. Sixty-two (72.9%) patients had no previous autoimmune disorder and 70 (82.4%) developed it *De novo*, the most frequent being Guillain–Barré syndrome and multisystem inflammatory syndrome in children. Eighteen (21.2%) cases of autoimmune disorders, mostly in remission, exacerbated. Organ-specific disease was found in 57 (67.1%) and systemic in 28. Disease affection was categorized into groups, the most frequent being neurological (36; 42.4%), vasculitis (19; 22.4%), blood (15; 17.6%), and connectivitis/systemic lupus erythematosus/antiphospholipid syndrome (6; 7.1%). The median coronavirus disease-2019 to *De novo* autoimmune disorder latency was 11 days (IQR = 5.75-16).

Conclusions: Although, as a systematic review of case reports, this study cannot verify causality, it provides support for further studies on the relationship between SARS-CoV-2 and autoimmune disorders. Furthermore, it delivers a characterization and summarization of existing reports making it a resource for clinicians to be aware of possible autoimmune disorder complications while taking care of their SARS-CoV-2 infected patients.

Background

Autoimmunity is an immune response directed against a self-antigen and its presence is a defining characteristic of an autoimmune disorder (AD). In the US, the estimated prevalence of ADs is 7.6–9.4% [1]. Infections are one of the most well-studied environmental triggers for autoimmunity [2-4], possibly through “molecular mimicry”, epitope spreading, “bystander activation”, and cryptic antigens processing and presentation [2]. Infections have also been associated with AD exacerbations, possibly via the same mechanisms [5].

In December 2019, a cluster of pneumonia cases was identified in Wuhan, China [6, 7], subsequently found to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [8, 9]. The infection is addresses as coronavirus disease 2019 (COVID-19) [10] and has already spread worldwide, leading to a global pandemic. Although most coronavirus infections are mild, two strains, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), have led to outbreaks and are associated with severe disease [11]. Infection by SARS-CoV-2 ranges from asymptomatic to critical condition and has already claimed millions of lives.

As SARS-CoV-2 infection has taken global proportions affecting a myriad of diverse patients, and has also been known to provoke hyperstimulation of the immune system through cytokine storm [12] and prolonged viral shedding [13], it is a potential candidate for AD association. Indeed, reports of ADs following COVID-19 have already been described (e.g. Kawasaki disease-like multisystem inflammatory syndrome in children (MIS-C)) [14, 15]. Additionally, SARS-CoV-2 forms a sister clave with SARS-CoV [9] (based on phylogeny, taxonomy, and established practice) which has cross-reaction with lung epithelial cells as a potential mechanism of pathogenesis [16, 17]. Moreover, MERS-CoV has also been associated with ADs such as Guillain-Barré syndrome (GBS) [18] and possibly immune thrombocytopenia [19]. Because of these findings and the increasing number of case reports, a characterization and summarization of existing evidence on the association of ADs and SARS-CoV-2 infection is necessary.

Although case reports cannot verify causality between the infection and ADs, it can identify unrecognized associations, generate hypotheses for subsequent studies and warn clinicians of possible complications. For these purposes, a systematic review of case

reports was performed documenting the development of an AD, related complications and autoimmune comorbidity exacerbation associated with the SARS-CoV-2 infection.

Methods

This systematic review followed the recommendations of the PRISMA statement [20].

Eligibility criteria

Studies were eligible when they reported a case of SARS-CoV-2 infection and the development of an AD, related complication, or exacerbation of a preexisting autoimmune comorbidity with a temporal relation with COVID-19. Studies with no explicitly stated SARS-CoV-2 infection diagnosis or with autoimmune comorbidities without exacerbations were excluded. The study designs considered eligible were any case report/series where the patient's case information was provided separately. Studies where information about a case could not be distinguished from another were excluded.

Information sources and search

A bibliographic search was performed in Embase on 21/07/2020. The search strategy consisted of terms related to *COVID-19* or *SARS-CoV-2* AND *AD* (including autoimmunity-related terms and specific ADs) AND *Case report* or *Case series*. Each term was subsequently extended using synonyms and the subject headings functions of Embase (complete query in Additional file 1).

Study selection

Resulting entries were organized using EndNote X9.2. Duplicates were removed using the automated function. Title and abstract screening was carried out by two independent reviewers (NG and EM) and any entry which met eligibility criteria, where abstracts could not be obtained, or had insufficient information to access eligibility were considered for full-text review. Full text was then independently reviewed by the same two reviewers. A third researcher (CC) resolved disagreements. Publications not written in English or Portuguese were translated to English using Google Translate.

Data collection process and data items

A data extraction form was piloted with 15 random eligible entries. One reviewer (NG) extracted the data regarding studies' characteristics (author, publication date, methodology, country, number of cases), participants' characteristics (age, sex, comorbidities, AD comorbidities status and treatment), and case's characteristics (clinical features by area, COVID-19 confirmation test and treatment, laboratory, imaging, and other tests requested and findings, AD diagnosed and treatment, COVID-19 to AD latency, complications, hospitalization and intensive care unit (ICU) admission, patient outcome). Articles reporting on the same patient were counted as one case and combined to obtain more data.

Quality assessment

Quality was assessed independently by two reviewers (NG and EM) using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports [21]. Disagreements were resolved with a third researcher (CC). Each of the eight domains was given an answer of: yes (information present and clearly described), unclear (information present but not clearly described), no (information not present), and not applicable.

Data synthesis and analysis

A summary of the paper's publication, authorship, study design, patient's characteristics, and main findings was provided through detailed tables. The ADs retrieved for this review were diagnosis collected from the studies. When a diagnosis was not explicit, the

most probable cause was determined by reviewing the case's characteristics. A narrative synthesis was performed, and data were summarized using descriptive statistics: for categorical variables frequencies and percentages; for continuous variables means and standard deviations (SD), and medians and interquartile ranges (IQR) for skewed distributions (assessed with Shapiro–Wilk test).

Results

Study selection

The PRISMA flowchart details the selection process and the reasons for full-text exclusion (Figure 1). In summary, out of 304 entries 69 regarding 85 cases were considered eligible. Two articles reporting on the same patient were merged and therefore counted together.

Study characteristics

Main case characteristics are summarized in Table 1 and Additional file 2 and 3. Studies comprised 6 case series and 63 case reports published from January to June 2020, spanning 15 countries.

Quality appraisal

Good appraisal ranged from 41% to 99% across quality domains (Figure 2). Although most cases clearly reported the patient's demographic characteristics, current clinical condition, diagnostic tests and methods, and summarized takeaway lessons, they lacked key elements of good reporting: intervention or treatment protocols, post-intervention clinical condition, adverse or unanticipated events, and patient's history.

Demographical characteristics and clinical findings

General population and case characteristics are summarized in Table 2. The patients' age did not follow a normal distribution with a greater number of older patients (median: 53 (32-63 IQR) years) and ranged from 5 to 83 years old. Forty-five patients were male and 40 female (Table 2). Comorbidities were present in 45 (64,7%) cases, the most common: hypertension (24/45), diabetes mellitus (11/45), cerebrovascular disease (5/45), obesity (4/45), and psoriasis (4/45).

Clinical findings are detailed in Additional file 3. Most patients developed respiratory (72; 84.7%), mostly persistent cough, and non-specific symptoms (68; 80.0%), mainly fever. Additionally, nervous (48; 56.5%), gastrointestinal (27; 31.8%), and skin (21; 24.7%) clinical findings were also among the most common.

COVID-19-related characteristics

Nasopharyngeal and/or oropharyngeal swab real-time reverse transcription polymerase chain reaction (rRT-PCR) was used in 78 patients yielding 12 negative results (later confirmed through Immunoglobulin G (IgG) antibody serum testing). One patient was diagnosed only by IgG antibody serum testing and in six it was not clear which confirmation test was used. Additionally, one had positive rRT-PCR on cerebrospinal fluid (CSF) for SARS-CoV-2.

Seventy-nine (92.9%) cases requested general laboratory measurements, 66 (77.6%) inflammatory markers, 46 (54.1%) hemostasis system parameters and 43 (50.6%) immunological markers. Overall, the most requested laboratory tests were complete blood count (75.3%), c-reactive protein (63.5%), d-dimers (45.9%), ferritin (34.1%) and lactate dehydrogenase (LDH) (32.9%). The most common findings were high c-reactive protein, lymphocytopenia, high d-dimers, thrombocytopenia, leukocytosis, high ferritin, high LDH and anemia (Table 2).

Bilateral disease on chest computerized tomography (CT) and x-ray was found in 57 (67.1%) patients, while unilateral disease in six (7.1%), and nine (10.6%) had normal results. The most common findings were bilateral ground-glass opacities, bilateral pulmonary infiltrates, and diffused consolidations (Table 2).

Twenty-six patients (30.6%) received no COVID-19 treatment. Among the remaining, hydroxychloroquine was the most common. Forty patients (47.1%) required supportive therapies: intubation (24; 28.2%), mechanical ventilator support (19; 22.4%) and high flow oxygen therapy (14; 16.5%). Antibiotics, mainly azithromycin, and antivirals, mostly lopinavir/ritonavir, favipiravir, and/or oseltamivir were also common. Some patients received other therapies, primarily comprising of anticoagulant and immunosuppressive therapies (mostly corticosteroids) (Table 2).

While 52 (61.2%) patients had no complication (other than AD), the remaining presented mostly cardiovascular complications (22/33) and secondary infection (10/33). Almost all cases (83; 97.6%) required hospitalization with 35 (41.2%) admitted to the ICU. Mean hospital stay was 16.76 (10.18 SD) days (information not available in 39 cases). Favorable outcome (recovery or hospital discharge) was reported in 55 cases (23 male; mean age: 46.61 years) and death in nine (8 male; mean age: 66.3 years) (Table 2).

AD-related characteristics

Sixty-two patients (72.9%) had no previous AD. Eighteen (21.2%), mostly in remission (13/18), experienced an exacerbation (the most frequent: psoriasis, myasthenia gravis, antiphospholipid syndrome (APS)/systemic lupus erythematosus (SLE), Crohn's disease, immune thrombocytopenic purpura (ITP), multiple sclerosis), while 70 (82.4%) developed *De novo* AD (three had *De novo* AD plus exacerbation) (Table 2). The most common were GBS, MIS-C, ITP, acute disseminated encephalomyelitis (ADEM), autoimmune meningoencephalitis, APS and autoimmune hemolytic anemia (AIHA). A total of 22 different ADs developed, while 12 distinct AD exacerbations were found.

ADs were categorized into organ-specific disease (57; 67.1%): neurological, blood, inflammatory bowel disease (IBD), skin, endocrinological, and ophthalmological; and systemic disease (28; 32.9%): vasculitis, connectivitis/SLE-APS, arthritis, endocrinological. Median COVID-19 to *De novo* AD latency was 12 (6-16 IQR) days (Table 2). Mean COVID-19 to AD exacerbation latency was 6.56 (8.14 SD) days.

Organ-specific disease

Neurologic-related AD

Median age was 54 (45.25-61.75 IQR), 16 were female and 30 had no previous AD. While four were exacerbations (two multiple sclerosis and two myasthenia gravis previously in remission), the majority were *De novo* ADs: GBS (14; 38.9%), ADEM (6; 16.7%), autoimmune meningoencephalitis (6; 16.7%), CNS vasculitis (2; 5.6%), anti-MOG associated encephalomyelitis (1; 2.8%), anti-NMDA receptor encephalitis (1; 2.8%), non-classified encephalitis (1; 2.8%), and oculomotor nerve palsy (1; 2.8%). Three subtypes of GBS were reported: four acute inflammatory demyelinating polyneuropathy, three acute motor and sensory axonal neuropathy, and three Miller-Fisher syndrome. Median COVID-19 to *De novo* AD latency was 12 (7-15 IQR) days (Table 2).

The most common laboratory finding was CSF high protein level: five cases with pleocytosis and five without. Five patients had high CSF IgG, one patient had positive anti-MOG antibody, another both anti-NMDA receptor and anti-cardiolipin antibodies, and another anti-ganglioside antibodies (Asialo GM1). Of 24 brain magnetic resonance imaging (MRI) requested, 12 were normal, with white matter lesions the most common feature found in the remainders. In 12, out of 14 cases with GBS, nerve conduction studies aided the diagnosis (Table 2).

Most patients received intravenous immunoglobulin (IVIG), corticosteroids, plasmapheresis, and plasma exchange, while 3 received no AD treatment. Four patients required supportive therapy (intubation and mechanical ventilator support) for GBS and myasthenia gravis exacerbation. Nevertheless, supportive therapy for COVID-19 was needed in 21. Mean hospitalization time was 19.2 (11.24 SD) days and death was reported in five (Table 2).

Blood-related AD

Median age was 53 (38-65 IQR), nine were female and 10 had no previous AD. Two had ITP exacerbations (previously in remission), and 13 experienced *De novo* ADs: ITP (8; 53.3%), AIHA (4; 26.7%) (one cold agglutinin disease and one warm agglutinin disease), and autoimmune thrombotic thrombocytopenic purpura (1; 6.7%). Median COVID-19 to *De novo* AD latency was 10 (6.25-15.75 IQR) days (Table 2).

The most common laboratory finding was thrombocytopenia and anemia. Other virus screens were negative (Epstein–Barr virus, hepatitis virus, Human Immunodeficiency Virus (HIV), Cytomegalovirus). Four patients had positive direct Coombs test, two with high cold agglutinin titers, one of these also with positive antinuclear antibodies (ANA). One case reported low ADAMTS-13 activity and positive ADAMTS-13 inhibitory antibodies, another antiplatelet antibodies, and another positive (albeit weak) anti-platelet factor 4/heparin antibodies. Two cases performed bone marrow aspirate, revealing normal cellularity with increased megakaryocyte count (Table 2). Chest and brain CT revealed two pulmonary embolism and two intracerebral hemorrhages.

All patients received AD treatment, the majority with corticosteroids, IVIG, platelet transfusions and red blood cell transfusions. For COVID-19, four required no treatment and only three required ICU admission. Mean hospitalization time was 19.85 (11.16 SD) days and one death was reported (Table 2).

Other organ-specific ADs

Three cases had an exacerbation of IBD: one ulcerative colitis (UC) and one Crohn's disease previously in remission, and one active Crohn's disease. The Crohn's disease patients also presented *De novo* IgA vasculitis and Kawasaki disease. Age ranged from 14 to 26 years old. The UC case was a pregnant woman with proctitis, Disease Activity Index score of 3, and active chronic inflammation on biopsies, treated with methylprednisolone and cyclosporine, and ultimately undergoing spontaneous abortion. Abdominal CT and MRI enterography found ileitis in both Crohn's disease cases. One (previously in remission) also had perianal abscess and fistula requiring drainage, antibiotics, and infliximab, while the other received the regular adalimumab treatment (Table 1).

Concerning skin-related ADs, two exacerbations of psoriasis (one in remission) and one *De novo livedo reticularis* were reported. The psoriasis cases occurred in a 73-year-old male 14 days after COVID-19 onset, and in a 71-year-old female 4 days after, neither receiving AD treatment. The *livedo reticularis* case occurred in a 57-year-old male with high d-dimers and positive ANAs, 8 days after COVID-19 onset, and treated with low-molecular-weight heparin (Table 1).

For endocrinological-related ADs, one diabetes mellitus type 1 exacerbation in the form of diabetic ketoacidosis, and one autoimmune hypothyroidism exacerbation was reported. The diabetic ketoacidosis case occurred in a 60-year-old male 5 days after COVID-19 onset, complicating with secondary bacterial infection and pulmonary embolism. He was treated with insulin and required ICU admission. The autoimmune hypothyroidism exacerbation received no treatment and occurred concurrent with *De novo* ITP in a 65-year-old female with elevated thyroid peroxidase antibodies, 11 days after COVID-19 onset (Table 1).

An ophthalmological-related AD befell an 11-year-old male with left retinal vasculitis on ocular *fundus* examination, negative autoimmune panel, and chilblains (Table 1).

Systemic disease

Vasculitis-related AD

Median age was 13 (9-36 IQR), eight were female, and 15 had no previous AD. One had an exacerbation of anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis in the form of glomerulonephritis and 18 experienced *De novo* ADs: MIS-C (11; 57.9%), cutaneous small-vessel vasculitis (2; 10.5%), multisystem inflammatory syndrome in adults (MIS-A) (1; 53%), Kawasaki disease (1; 53%), immunoglobulin A (IgA) vasculitis (1; 53%), non-classified vasculitis (1; 53%), and gallbladder vasculitis (1; 53%). Median COVID-19 to *De novo* AD latency was 5 (0-13 IQR) days (Table 2). When MIS-C and Kawasaki disease are not counted, median age was 59 (25-83 IQR), two out of seven were female, and median COVID-19 to *De novo* AD latency was 13 (7.5-37 IQR) days. As previously mentioned, two cases had, concurrent with *De novo* AD, an exacerbation of Crohn's disease. Gastrointestinal (15; 78.9%) (mostly abdominal pain) and skin (13; 68.4%) findings were common clinical findings. Nine (47.4%) patients had no complications while the remaining experienced mainly cardiogenic shock (8; 42.1%), and acute kidney injury (6; 31.6%).

Fourteen (73.7%) cases had hemostasis system-related findings: high d-dimers, fibrinogen, INR, and prothrombin time; 16 (84.2%) inflammatory markers: high c-reactive protein, procalcitonin, ferritin, lactate dehydrogenase, and erythrocyte sedimentation rate; 6 (31.6%) increased serum interleukin 6, interleukin 8, and/or tumor necrosis factor- α ; and 11 (57.9%) liver markers: high alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase, direct hyperbilirubinemia, and hypoalbuminemia. Seven (36.8%) cases reported high troponins and one (5.3%) elevated myoglobin. The IgA vasculitis case had high complement C4

and serum IgA, and one cutaneous small-vessel vasculitis case had anti-cardiolipin antibodies. The ANCA-associated vasculitis exacerbation case was cytoplasmic-ANCA positive, and the MIS-A case presented positive ANAs, anti-Ro/SSA and low complement C3 and C4. From 14 heart ultrasounds requested, seven reported depressed left ventricular systolic function, five coronary artery dilatation, and three pericardial effusion. Abdominal CT exams showed bowel inflammation (ileitis and/or colitis) in four cases. Three patients underwent skin lesion biopsy, all wielding leukocytoclastic vasculitis as the major finding (Table 2).

Most patients received antibiotic prophylaxis, IVIG, corticosteroids, immunosuppressive therapy (tocilizumab, anakinra, or cyclophosphamide), and acetylsalicylic acid, while two received no AD treatment. Most patients required ICU admission with one Kawasaki disease, and seven MIS-C patients requiring rescue and supportive therapy for cardiogenic shock. Nevertheless, most required no COVID-19 treatment. Death was reported in two and mean hospitalization time was 14.92 (10.48 SD) days (Table 2).

Connectivitis/SLE-APS-related AD

Median age was 67 (50-69.25 IQR) and three were female. Four cases had no previous AD and developed *De novo* APS, and two had APS/SLE (previously in remission) and APS exacerbations. Median COVID-19 to *De novo* AD latency was 25.5 (12-45 IQR) days (Table 2).

The *De novo* APS cases had positive anti-beta-2-glycoprotein I and anti-cardiolipin antibodies, and high d-dimers, while three had high fibrinogen, prothrombin and partial thromboplastin time, and one high fibrin degradation products (Table 2). Patients had multiple cerebral (5; 83.3%) and bilateral cerebellar (3; 50.0%) infarctions on brain CT. On doppler ultrasound one patient had bilateral jugular venous thrombi. One *De novo* APS case complicated with index finger dry gangrene and another with two digits and lower limbs bilateral ischemia.

Three cases received AD treatment, one with acetylsalicylic acid, low-molecular-weight heparin and plasma exchange, and two with IVIG, one of which with eltrombopag, platelet transfusions and prednisone. Five required COVID-19 treatment, three with supportive therapy. Mean hospitalization time was 21.17 (18.76 SD) days with four ICU admissions and one reported death (APS exacerbation) (Table 2).

Other systemic AD

For Arthritis-related ADs, one ankylosing spondylitis exacerbation (previously in remission) and one *De novo* non-classified arthritis were reported. The ankylosing spondylitis case occurred in a 53-year-old female 22 days after COVID-19 onset with normal brain MRI and nerve conduction studies, and was treated with etanercept. The non-classified arthritis case occurred in a 57-year-old male 20 days after COVID-19 onset with negative ANAs, rheumatoid factor and anti-cyclic citrullinated peptide antibodies, and the synovial fluid was crystal-free on polarized microscopic examination (Table 1).

One endocrinological-related AD case, a 32-year-old female with autoimmune polyglandular syndrome type 1, presented with hypoparathyroidism exacerbation with low serum calcium, and was treated with calcitriol and calcium supplementation. She required ICU admission for COVID-19 (Table 1).

Discussion

This review describes 22 different *De novo* ADs and 12 distinct AD exacerbations associated with SARS-CoV-2 infection.

As AD cases in children (<18 years) have been reported following SARS-CoV-2 infection, most notably MIS-C [14, 15], one could argue the existence of more associations. In this regard, entry age was not restricted, and besides MIS-C and Kawasaki disease, AIHA and retinal vasculitis were also found. The reported higher prevalence of older patients, cardiovascular risk factor comorbidity, and cardiovascular disease could be explained by their added risk of severe COVID-19 and hospital admission [91, 92], in line with this review's inpatient cohort. Contrary to the literature on AD gender differences [93], there were more males than females found (9:8).

COVID-19 was predominantly diagnosed through rRT-PCR, the present recommendation. Laboratory and radiologic findings were similar to those found in the literature [7, 91, 94]. Treatment was heterogeneous, reflecting the immaturity of the disease knowledge. Most were treated with hydroxychloroquine and antibiotics (predominantly azithromycin), the recommendation at the time. Additionally, similar to another review [94], a reduced number of patients received no treatment for COVID-19, and intubation,

mechanical ventilator support, and mortality were higher than the general population, suggesting greater disease severity, which, again, may relate to the number of hospitalizations in this cohort. Furthermore, more patients than expected required ICU admission which may be explained by the association of AD complications.

Most cases had no previous AD and, ultimately, all developed one, which supports the causal relationship hypothesis. Furthermore, most patients with AD comorbidity exacerbations were previously in remission.

The majority presented with neurological affection. Neurological complications have been common in COVID-19 [95-98]. The dissemination to the nervous system through the cribriform plate, olfactory bulb [99] and virus damaged capillary endothelium [100] have been hypothesized for such association. When referring to a neurological AD, other mechanisms such as the hyperinflammatory state leading to blood-brain barrier disruption, extensive tissue damage, and epitome exposure, could instead contribute to its development, as only one case reported positive CSF rRT-PCR for SARS-CoV-2 and specific antibody driven subtypes of autoimmune encephalitis were found: anti-MOG associated encephalomyelitis and anti-NMDA receptor encephalitis. The most common neurological AD found was GBS, which is a typical post respiratory or gastrointestinal infection disorder [101, 102]. Among other pathogens [101], MERS-CoV was associated with GBS [18]. The median COVID-19 to *De novo* AD latency of 12 days and mean hospitalization time of 19.2 days resembles the 1–2 weeks latency and the 2–4 weeks peak clinical deficit reported in the literature [101, 102]. Although the preceding pathogen infection is usually connected with one clinical phenotype [101], three subtypes were found. Another neurological AD found, ADEM, is already associated with viral infections. Although more common in pediatric age, all cases found were adults [103]. Though few patients required supportive therapy for neurological AD, downplaying its severity, it should be noted that many required it for COVID-19.

The majority of vasculitis found were MIS-C, a disorder similar to Kawasaki disease that has been connected with the rise of SARS-CoV-2 cases [15]. As Kawasaki disease presumably develops in genetically susceptible hosts after exposure to a trigger, suspected to be an upper respiratory tract infection [104], a similar mechanism could be occurring here. Although predominantly having mild COVID-19, most cases required ICU admission and eight children (with MIS-C and Kawasaki disease) develop cardiogenic shock.

The most common blood-related AD was ITP. As secondary ITP has been associated with cross-reaction with HIV antigens, creating autoantibodies and immune complexes [105-107], the same might occur with SARS-CoV-2. However, although not always present [108], out of eight ITP cases, only two rendered positive antiplatelet antibodies, and COVID-19 has been associated with thrombocytopenia, the degree of which related to the severity of SARS-CoV-2 infection [109].

In the final major group, APS, four anti-beta-2-glycoprotein I and anti-cardiolipin antibody positive patients complicated with multiple thrombotic events. Though antiphospholipid antibodies can be present in acute infections, they usually present with low levels and are not associated with thrombotic events [110]. Infections are also suspected triggers as they preceded APS in many cases [111, 112].

Limitations

Even though good appraisal in several quality domains was seen across studies, key elements of good reporting were lacking, and 21 cases did not report an outcome. Likewise, other reviews shared the same findings [94]. A possible explanation might be the urgency to publish new information, as COVID-19 is a recently identified disease. This, however, may lead to a lack of important information that could further the knowledge of possible associations with ADs. Nevertheless, all cases were included as a way to find the most possible number of associations.

Although numerous associations between infections and ADs are described, the acute state of infection and hyperinflammatory state which occurs with COVID-19 could mimic the immunological findings of an AD. Since the reported autoimmune manifestations might encompass the immunological component of the infection, caution is warranted when interpreting the results. Nevertheless, a high suspicion rating is always necessary when considering an AD diagnosis.

Furthermore, milder AD cases might not be represented due to publication bias as more severe cases are more likely to be published and diagnosed.

Although a thorough search was done, using an expansive search query to be as inclusive as possible, methodological limitations are still present. First, only one database was used and, even though this review provides a look at the first image of the COVID-19 pandemic, it may have missed studies that were published since the search date. Additionally, despite using piloted forms and training to minimize inaccuracies, only one reviewer performed data extraction.

Conclusions

This systematic review provides a characterization and summarization of AD cases associated with SARS-CoV-2 infection. There are some findings that may suggest the existence of this relationship and although this study as a review of case reports cannot verify causality, it supports further studies and provides a resource for clinicians to be aware of possible AD complications of SARS-CoV-2 infected patients.

Declarations

Availability of Supporting Data

The data set supporting the results of this article is included within the article (and its additional files).

Competing interests

None of the authors have any financial or non-financial competing interests to disclose.

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None.

Author's contributions

NG performed the screening, study selection, data collection, analysis, and interpretation, conceptualized and drafted the manuscript. EM performed screening and study selection, analyzed data, and contributed to the writing of the manuscript. CC aided in data analysis and interpretation and performed critical revision of the article. PMT contributed to conception and design of the work. All authors have reviewed and approved the manuscript for submission.

Abbreviations

AD: Autoimmune disorder; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; MERS-CoV: Middle East respiratory syndrome coronavirus; MIS-C: Multisystem inflammatory syndrome in children; GBS: Guillain-Barré syndrome; ICU: Intensive care unit; JBI: Joanna Briggs Institute; SD: Standard deviations; rRT-PCR: Real-time reverse transcription polymerase chain reaction; IgG: Immunoglobulin G; CSF: Cerebrospinal fluid; LDH: Lactate dehydrogenase; CT: Computerized tomography; APS: Antiphospholipid syndrome; SLE: Systemic lupus erythematosus; ITP: Immune thrombocytopenic purpura; ADEM: Acute disseminated encephalomyelitis; AIHA: Autoimmune hemolytic anemia; IBD: Inflammatory bowel disease; MRI: Magnetic resonance imaging; IVIG: Intravenous immunoglobulin; HIV: Human Immunodeficiency Virus; ANA: Antinuclear antibodies; UC: Ulcerative colitis; ANCA: Anti-neutrophil cytoplasmic antibodies; MIS-A: Multisystem inflammatory syndrome in adults; IgA: Immunoglobulin A

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Tables

Table 1. Summary of general population and case characteristics.

Study	Patient's characteristics	COVID-19 confirmation test COVID-19 to AD latency	AD developed vs AD exacerbation	Main AD related laboratory findings	Treatment	Admission and outcomes
Sedaghat, Z. and N. Karimi [22] (2020) Iran Case report	Male 65 DM (Type 2)	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: <14 days	<i>De novo</i> : Guillain-Barré syndrome (Acute motor and sensory axonal neuropathy)	-	AD: Immunoglobulin COVID-19: Hydroxychloroquine; Lopinavir/Ritonavir; Azithromycin	Hospitalization: >14 days Outcome: Not reported
Chiu, J. S., et al. [23] (2020) USA Case report	Male 10 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	<i>De novo</i> : Kawasaki Disease	-	AD: Ibuprofen; Normal saline bolus; Dopamine	Hospitalization: unknown duration Outcome: Not reported
Allez, M., et al. [24] (2020) France Case report	Male 24 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	<i>De novo</i> : IgA vasculitis Exacerbation: Crohn's disease (Previously in remission with: Ileocecal surgical resection; Adalimumab)	-	AD: Low molecular weight heparin; Methylprednisolone	Hospitalization: 7 days Outcome: Favorable
Dolinger, M. T., et al. [25] (2020) USA Case report	Male 14 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	<i>De novo</i> : MIS-C Exacerbation: Crohn's disease (Previously active)	High serum IL-6; High serum IL-8; High serum TNF- α	AD: Enoxaparin; Intravenous fluid therapy; Infliximab; Piperacillin/tazobactam; Drainage of perianal abscess; Ciprofloxacin; Metronidazole COVID-19: Hydroxychloroquine; Azithromycin	Hospitalization: 13 days Outcome: Favorable
Ottaviani, D., et al. [26] (2020) Italy Case report	Female 66 Hypertension	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 7 days	<i>De novo</i> : Guillain-Barré syndrome	-	AD: Immunoglobulin COVID-19: Lopinavir/Ritonavir; Hydroxychloroquine; Intubation	Hospitalization: >10 days ICU admission: Yes Outcome: Not reported
Scheidl, E., et al. [27] (2020). Germany Case report	Female 54 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 21 days	<i>De novo</i> : Guillain-Barré syndrome (Acute inflammatory demyelinating polyneuropathy)	CSF high protein level	AD: Immunoglobulin	Hospitalization: >7 days Outcome: Favorable
Parsons, T., et al. [28] (2020)	Female 51	COVID-19 confirmation	<i>De novo</i> : Acute disseminated	CSF high protein level	AD: Methylprednisolone; Immunoglobulin	Hospitalization: $\geq$ 59 days

USA Case report	-	test: Positive rRT-PCR COVID-19 to AD latency: [0-18] days	encephalomyelitis		COVID-19: Intubation; Sedative drips	Outcome: Favorable
Zanin, L., et al. [29] (2020). Italy Case report	Female 54 Anterior communicating artery aneurysm	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: >1 day	<i>De novo</i> : Acute disseminated encephalomyelitis	-	AD: Acosamide; Levetiracetam; Phenytoin COVID-19: Antiretroviral; Hydroxychloroquine; Dexamethasone; Intubation; Tracheostomy	Hospitalization: ≥34 days ICU admission: Yes Outcome: Favorable
Hanafi, R., et al. [30] (2020) France Case report	Male 65 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 6 days	<i>De novo</i> : CNS Vasculitis	Thrombocytopenia	COVID-19: Oxygen therapy (high-concentration mask (15L/min)); Spiramycin; Amoxicillin and clavulanic acid	Hospitalization: >6 days ICU admission: Yes Outcome: Not reported
Patil, N. R., et al. [31] (2020) USA Case report	Female 51 Breast cancer; Venous thromboembolism	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	<i>De novo</i> : Autoimmune hemolytic anemia (Cold agglutinin disease)	Anemia	AD: Red blood cell transfusion; Folic acid; Recommended use of warm intravenous fluids and blood products; Unfractionated heparin COVID-19: Hydroxychloroquine; Oxygen therapy (6L/min); Methylprednisolone	Hospitalization: >4 days Outcome: Favorable
Moeinzadeh, F., et al. [32] (2020). Iran Case report	Male 25 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	Exacerbation: ANCA-associated vasculitis - Glomerulonephritis (Previously active with: Hydroxychloroquine)	Anemia; Positive C-ANCA	AD: Methylprednisolone; Plasmapheresis; Immunoglobulin; Cyclophosphamide COVID-19: Hydroxychloroquine; Levofloxacin	Hospitalization: 15 days Outcome: Favorable
Farzi, M. A., et al. [33] (2020). Iran Case report	Male 41 DM (Type 2)	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 10 days	<i>De novo</i> : Guillain-Barré syndrome (Acute inflammatory demyelinating polyneuropathy)	-	AD: Immunoglobulin COVID-19: Lopinavir/Ritonavir; Hydroxychloroquine	Hospitalization: >17 days Outcome: Favorable
Webb, S., et al. [34] (2020) UK Case report	Male 57 Hypertension	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 7 days	<i>De novo</i> : Guillain-Barré syndrome (Acute inflammatory demyelinating polyneuropathy) Exacerbation: Psoriasis (Status not specified)	CSF high protein level	AD: Immunoglobulin; Intubation; Tracheostomy COVID-19: Amoxicillin and clavulanic acid	Hospitalization: >7 days ICU admission: Yes Outcome: Not reported
Lantos, J. E., et	Male	COVID-19	<i>De novo</i> : Guillain-	-	AD: Immunoglobulin	Hospitalization:

al. [35] (2020). USA Case report	36 Strabismus	confirmation test: Positive rRT-PCR COVID-19 to AD latency: 2 days	Barré syndrome (Miller Fisher syndrome)		COVID-19: Hydroxychloroquine	4 days Outcome: Favorable
Manganotti, P., et al. [36] (2020) Italy Case report	Female 50 -	COVID-19 confirmation test: Unclear COVID-19 to AD latency: 16 days	<i>De novo</i> : Guillain- Barré syndrome (Miller Fisher syndrome)	CSF high protein level	AD: Immunoglobulin COVID-19: Lopinavir/Ritonavir; Hydroxychloroquine; Antibiotic therapy; Oxygen therapy (FiO2: 35%)	Hospitalization: 24 days Outcome: Favorable
Virani, A., et al. [37] (2020) USA Case report	Male 54 Hypertension; Dyslipidemia;	COVID-19 confirmation test: Positive rRT-PCR COVID-19	<i>De novo</i> : Guillain- Barré syndrome (Acute inflammatory demyelinating polyneuropathy)	-	AD: Mechanical ventilator support; Immunoglobulin COVID-19: Amoxicillin; Steroids; Hydroxychloroquine; Azithromycin	Hospitalization: 7 days ICU admission: Yes Outcome: Favorable
Rana, S., et al. [38] (2020) USA Case report	Restless leg syndrome; Chronic back pain	COVID-19 to AD latency: 12 days				
Artru, F., et al. [39] (2020) Switzerland Case report	Male 38 Obesity; Cirrhosis (alcoholic liver disease); Chronic thrombocytopenia	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 10 days	<i>De novo</i> : Immune thrombocytopenic purpura Exacerbation: IgA nephropathy (Status not specified)	-	AD: Platelet transfusions; Immunoglobulin; Dexamethasone COVID-19: Oxygen therapy (6L/min); Hydroxychloroquine; Amoxicillin and clavulanic acid	Hospitalization: 36 days Outcome: Favorable
Yang, Y., et al. [40] (2020) China Case report	Female 32 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 13 days	<i>De novo</i> : Immune thrombocytopenic purpura	Thrombocytopenia	AD: Methylprednisolone; Platelet injection COVID-19: Oseltamivir; Lianhua qingwen capsule (Chinese medicine)	Hospitalization: 27 days Outcome: Favorable
Bomhof, G., et al. [41] (2020) Netherlands Case series	Male 59 Neuroendocrine tumour of the small bowel	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 10 days	<i>De novo</i> : Immune thrombocytopenic purpura	High serum IL-6; Thrombocytopenia; Positive antiplatelet antibodies	AD: Platelet transfusion; Immunoglobulin; Dexamethasone	Hospitalization: ≥27 days Outcome: Favorable
	Female 66 Hypertension	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 7 days	<i>De novo</i> : Immune thrombocytopenic purpura	Thrombocytopenia	AD: Platelet transfusion; Dexamethasone; Immunoglobulin	Hospitalization: ≥22 days Outcome: Favorable

	Male 67	COVID-19 confirmation test: Hypertension; DM	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 17 days	<i>De novo</i> : Immune thrombocytopenic purpura	High serum IL-6; Thrombocytopenia	AD: Platelet transfusions COVID-19: Intubation; Unfractionated heparin	Hospitalization: 13 days ICU admission: Yes Outcome: Death
Lévesque, V., et al. [42] (2020) Canada Case report	Male 53	Hypertension; Dyslipidemia; DM (Type 2)	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 23 days	<i>De novo</i> : Immune thrombocytopenic purpura	Thrombocytopenia; Positive anti-PF4	AD: Immunoglobulin; Dexamethasone; Platelet transfusions; Red blood cell transfusions; Tranexamic acid; Endobronchial clot removal; Romiplostim; Vincristine; Methylprednisolone (pulse doses) COVID-19: Intubation; Mechanical ventilator support; Prone positioning; Propofol; Fentanyl; Cisatracurium; Ceftriaxone; Azithromycin; Unfractionated heparin; Tracheostomy	Hospitalization: ≥39 days ICU admission: Yes Outcome: Favorable
Hayden, A., et al. [43] (2020) USA Case report	Female 51	-	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: Unclear	Exacerbation: Systemic lupus erythematosus, Antiphospholipid syndrome (Previously in remission with: Hydroxychloroquine; Azathioprine; Belimumab; Warfarin)	Thrombocytopenia	AD: Platelet transfusions; Immunoglobulin; Prednisone; Eltrombopag	Hospitalization: 12 days Outcome: Favorable
Quintana-Castanedo, L., et al [44]. (2020) Spain Case report	Male 11	-	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: Unclear	<i>De novo</i> : Retinal vasculitis	-	-	Outcome: Not reported
Mayor-Ibarguren, A., et al [45]. (2020) Spain Case report	Female 83	Hypertension; Transient ischaemic attack; Atrial fibrillation; Chronic kidney disease	COVID-19 confirmation test: Negative rRT-PCR; Positive IgM and IgG COVID-19 to AD latency: 30 days	<i>De novo</i> : Cutaneous small vessel vasculitis	Positive anti- cardiolipin antibodies	AD: Prednisone	Hospitalization: 10 days Outcome: Favorable
Negrini, S., et al. [46] (2020) Italy Case report	Male 79	Hypertension; Myocardial infarction; COPD;	COVID-19 confirmation test: Positive rRT- PCR COVID-19	<i>De novo</i> : Cutaneous small vessel vasculitis	-	COVID-19: Hydroxychloroquine; Enoxaparin; ceftaroline; Methylprednisolone; Oxygen therapy (8 L/min; FiO2: 40%)	Hospitalization: >25 days ICU admission: Yes Outcome: Death

	Acute heart failure	to AD latency: 10 days				
Del Giudice, P., et al. [47] (2020) France Case report	Male 83 Obesity; DM (Type 2); Hypertension; Mesenteric ischemia; Distal arteriopathy; Myocardial infarction	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 13 days	<i>De novo</i> : Vasculitis Exacerbation: Polymyalgia rheumatica (Status not specified; treated with: Prednisolone)	Thrombocytopenia	-	Hospitalization: >1 days Outcome: Death
Nasiri, S., et al. [48] (2020) Iran Case report	Male 73 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 14 days	Exacerbation: Psoriasis (Status not specified; treated with: Cyclosporine; Methotrexate)	-	COVID-19: Hydroxychloroquine; Lopinavir/Ritonavir; Acetaminophen	Hospitalization: 7 days Outcome: Favorable
Novi, G., et al. [49] (2020) Italy Case report	Female 64 Hypertension; MGUS	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: 25 days	<i>De novo</i> : Acute disseminated encephalomyelitis Exacerbation: Vitiligo (Status not specified)	CSF high protein level	AD: Methylprednisolone; Immunglobulin; Prednisone	Hospitalization: 17 days Outcome: Favorable
Pfefferkorn, T., et al. [50] (2020). Germany Case report	Male 51 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 12 days	<i>De novo</i> : Guillain-Barré syndrome	CSF high protein level; Pleocytosis	AD: Immunglobulin; Plasma exchange COVID-19: Intubation; Mechanical ventilator support; Tracheostomy	Hospitalization: 31 days Outcome: Favorable
Panariello, A., et al. [51] (2020). Italy Case report	Male 23 Substance Use Disorder (THC; cocaine and phencyclidine)	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	<i>De novo</i> : Anti-NMDA receptor encephalitis	CSF high protein level; Pleocytosis; High serum IL-6; Positive anti-cardiolipin antibodies	AD: Haloperidol; Promazine; Midazolam; Aripiprazole; Quetiapine; Antibiotic prophylactic therapy; Valproate; Dexamethasone; Immunglobulin COVID-19: Oxygen therapy; Hydroxychloroquine; Darunavir/cobicistat	Hospitalization: >21 days Outcome: Not reported
Vega Hernández, P., et al. [52] (2020) Spain Case report	Female 13 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	<i>De novo</i> : Autoimmune hemolytic anemia Exacerbation: Psoriasis (Status not specified)	Anemia; Positive direct Coombs test	AD: Methylprednisolone (pulse doses); Prednisone	Hospitalization: 14 days Outcome: Favorable
Yokogawa, N., et al. [53] (2020)	Male 57	COVID-19 confirmation	<i>De novo</i> : Acute arthritis	-	-	Hospitalization: 27 days

Japan Case report	Hypertension; Hyperlipidemia	test: Positive rRT-PCR COVID-19 to AD latency: 20 days				Outcome: Favorable
Pinto, A. A., et al. [54] (2020) UK Case report	Female 44 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 5 days	<i>De novo</i> : Anti-MOG associated encephalomyelitis	CSF high protein level; Pleocytosis; Positive anti-MOG antibody	AD: Methylprednisolone; Prednisolone; Plasma exchange COVID-19: Supportive care	Hospitalization: 18 days Outcome: Favorable
Singh, S. and R. Govindarajan [55] (2020). USA Case report	Female 36 Thymic hyperplasia	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	Exacerbation: Myasthenia Gravis (seronegative generalized) (Previously in remission with: Prednisone; Mycophenolate Mofetil; Pyridostigmine; Immunoglobulin)	-	AD: Plasmapheresis; Stress dose IV steroids; Intubation COVID-19: Supportive care	Hospitalization: 24 days Outcome: Favorable
Capes, A., et al. [56] (2020). Belgium Case report	Male 62 Hypertension; Oropharyngeal squamous cell carcinoma	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 16 days	<i>De novo</i> : Autoimmune hemolytic anemia	Thrombocytopenia; Anemia; Positive ANA; Positive direct Coombs test	AD: Red blood cell transfusion COVID-19: Intubation	Hospitalization: >19 days ICU admission: Yes Outcome: Not reported
Barzegar, M., et al. [57] (2020) Iran Case report	Female 42 Major depression disorder; Hypothyroidism; Pulmonary embolism	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	Exacerbation: Multiple sclerosis (relapsing-remitting), Myasthenia gravis, (Previously in remission with: Fingolimod)	-	AD: Methylprednisolone; Glatiramer acetate COVID-19: Azithromycin; Ceftriaxone; Oxygen therapy; Hydroxychloroquine; Oseltamivir; Piperacillin/tazobactam	Hospitalization: 13 days Outcome: Favorable
Murt, A., et al. [58] (2020) Turkey Case report	Male 41 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 15 days	<i>De novo</i> : Immune thrombocytopenic purpura	Thrombocytopenia	AD: Dexamethasone; Immunoglobulin COVID-19: Favipiravir	Hospitalization: ≥9 days Outcome: Favorable
Zhao, H., et al. [59] (2020). China Case report	Female 61 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: ≤3 days	<i>De novo</i> : Guillain-Barré syndrome	CSF high protein level	AD: Immunoglobulin COVID-19: Supportive care; Umifenovir; Lopinavir/Ritonavir	Hospitalization: 30 days Outcome: Favorable

Padroni, M., et al. [60] (2020) Italy Case report	Female 70 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 23 days	<i>De novo</i> : Guillain-Barré syndrome (Acute motor and sensory axonal neuropathy)	CSF high protein level	AD: Immunoglobulin; Intubation; Mechanical ventilator support	Hospitalization: >8 days Outcome: Not reported
Alberti, P., et al. [61] (2020) Italy Case report	Male 71 Hypertension; Abdominal aortic aneurysm; Lung cancer	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 4 days	<i>De novo</i> : Guillain-Barré syndrome (Acute motor and sensory axonal neuropathy)	CSF high protein level; Pleocytosis	AD: Immunoglobulin COVID-19: Oxygen therapy (FiO2: 60-80%); Lopinavir/Ritonavir; Hydroxychloroquine; Mechanical ventilator support (CPAP); Prone positioning	Hospitalization: 1 day Outcome: Death
Zulfiqar, A. A., et al. [62] (2020) France Case report	Female 65 Hypertension	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 8 days	<i>De novo</i> : Immune thrombocytopenic purpura Exacerbation: Autoimmune hypothyroidism (Status not specified)	Thrombocytopenia	AD: Immunoglobulin; Platelet transfusions; Prednisolone; Eltrombopag COVID-19: Amoxicillin and clavulanic acid; Low molecular weight heparin; Oxygen therapy	Hospitalization: 14 days Outcome: Favorable
Nesr, G., et al. [63] (2020) UK Case report	Female 34 Pregnant (second trimester)	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	Exacerbation: Immune thrombocytopenic purpura (Previously in remission)	Thrombocytopenia	AD: Immunoglobulin; Prednisolone	Hospitalization: 2 days Outcome: Favorable
Arnaud, S., et al. [64] (2020) France Case report	Male 64 DM (Type 2)	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 23 days	<i>De novo</i> : Guillain-Barré syndrome	CSF high protein level	AD: Immunoglobulin COVID-19: Cefotaxime; Azithromycin; Hydroxychloroquine	Hospitalization: ≥27 days Outcome: Favorable
Ma, J., et al. [65] (2020). China Case report	Male 69 -	COVID-19 confirmation test: Positive IgM and IgG COVID-19 to AD latency: 49 days	<i>De novo</i> : Antiphospholipid syndrome	High serum IL-6; Thrombocytopenia; Positive anti-beta-2-glycoprotein I; Positive anti-cardiolipin antibodies	AD: Low molecular weight heparin; Aspirin; Plasma exchange COVID-19: Antibiotic therapy; Ribavirin; Intubation; Mechanical ventilator support (pressure control (PC) mode; FiO2: 40%; PEEP: 8 cmH2O); Immunoglobulin; Supportive care	Hospitalization: >61 days ICU admission: Yes Outcome: Not reported
Hu, Z., et al. [66] (2020) China Case report	Female 72 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency:	Exacerbation: Immune thrombocytopenic purpura (Previously in remission with: Prednisone;	Thrombocytopenia	AD: Immunoglobulin; Platelet transfusions; Methylprednisolone COVID-19: Umifenovir; Darunavir/cobicistat	Hospitalization: 29 days Outcome: Favorable

		≤5 days	Cyclosporine; Interferon alfa)			
Lopez, C., et al. [67] (2020). USA Case report	Female 46 Congenital thrombocytopenia	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 4 days	<i>De novo</i> : Autoimmune hemolytic anemia (Warm agglutinin disease)	Thrombocytopenia; Anemia; Positive direct Coombs test	AD: Immunoglobulin; Red blood cell transfusions; Prednisone COVID-19: Azithromycin; Hydroxychloroquine	Hospitalization: 9 days Outcome: Favorable
Abdi, S., et al. [68] (2020) Iran Case report	Male 58 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	<i>De novo</i> : Acute disseminated encephalomyelitis	-	AD: Dexamethasone	Hospitalization: 13 days ICU admission: Yes Outcome: Death
Oriot, P. and M. P. Hermans [69] (2020) Belgium Case report	Male 60 Hypothyroidism; Obstructive sleep apnea syndrome	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 5 days	Exacerbation: Type 1 diabetes mellitus (Treated with: Glargine; Glulisine; Empagliflozin)	-	AD: Intravenous fluid therapy; Insulin COVID-19: Mechanical ventilator support	Hospitalization: >43 days ICU admission: Yes Outcome: Favorable
Reyes-Bueno, J. A., et al. [70] (2020) Spain Case report	Female 51 -	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: 15 days	<i>De novo</i> : Guillain-Barré syndrome (Miller Fisher syndrome)	CSF high protein level	AD: Immunoglobulin; Gabapentin	Hospitalization: ≥19 days Outcome: Favorable
Waltuch, T., et al. [71] (2020) USA Case series	Male 13 Hypothyroidism	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: Unclear	<i>De novo</i> : MIS-C	High serum IL-6; High serum IL-8; High serum TNF-α	AD: Intravenous fluid therapy; Meropenem; Linezolid; Immunoglobulin; Tocilizumab; Anakinra COVID-19: Intubation; Enoxaparin	Hospitalization: >2 days ICU admission: Yes Outcome: Not reported
	Male 10 Asthma	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 12 days	<i>De novo</i> : MIS-C	High serum IL-6; High serum IL-8; High serum TNF-α	AD: Intravenous fluid therapy; Cefepime; Clindamycin; Dopamine; Immunoglobulin; Tocilizumab; Linezolid	Hospitalization: unknown duration ICU admission: Yes Outcome: Not reported
	Male 5 -	COVID-19 confirmation test: Negative	<i>De novo</i> : MIS-C	High serum IL-6; High serum IL-8; High serum TNF-α	AD: Intravenous fluid therapy; Ceftriaxone; Clindamycin; Enoxaparin; Dopamine; Immunoglobulin; Tocilizumab	Hospitalization: >3 days ICU admission: Yes

		rRT-PCR; Positive IgG COVID-19 to AD latency: Unclear				Outcome: Not reported
	Female 12 -	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: Unclear	<i>De novo</i> : MIS-C	High serum IL-6; High serum IL-8; High serum TNF- α	AD: Intravenous fluid therapy; Cefepime; Vancomycin; Metronidazole	Hospitalization: unknown duration ICU admission: Yes Outcome: Not reported
Sokolovsky, S., et al. [72] (2020) USA Case report	Female 36 -	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 5 days	<i>De novo</i> : MIS-A	Positive ANA; Positive anti- Ro/SSA; Low complement C3 and C4	AD: Intravenous fluid therapy; Aspirin; Immunoglobulin; Methylprednisolone; Prednisone	Hospitalization: 6 days Outcome: Favorable
Albiol, N., et al. [73] (2020) Spain Case report	Female 57 Hypertension; Breast cancer	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: 6 days	<i>De novo</i> : Autoimmune thrombotic thrombocytopenic purpura	Thrombocytopenia; Anemia; Positive ADAMTS-13 inhibitor	AD: Methylprednisolone; Immunoglobulin; Plasma infusion; Plasma exchange COVID-19: Lopinavir/Ritonavir; Hydroxychloroquine; Azithromycin	Hospitalization: 17 days Outcome: Favorable
Chiotos, K., et al. [74] (2020). USA Case series	Female 14 -	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: Unclear	<i>De novo</i> : MIS-C	-	AD: Epinephrine; Norepinephrine; Vancomycin; Cefepime; Clindamycin; Doxycycline; Immunoglobulin; Methylprednisolone; Aspirin COVID-19: Intubation; Mechanical ventilator support	Hospitalization: 17 days ICU admission: Yes Outcome: Favorable
	Male 12 -	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: Unclear	<i>De novo</i> : MIS-C	-	AD: Milrinone; Epinephrine; Vasopressin; Methylprednisolone (pulse dose); Immunoglobulin; Vancomycin; Cefepime; Clindamycin COVID-19: Mechanical ventilator support	Hospitalization: 12 days ICU admission: Yes Outcome: Favorable
	Female 9 -	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency:	<i>De novo</i> : MIS-C	-	AD: Intravenous fluid therapy; Immunoglobulin; Methylprednisolone; Aspirin; Mechanical ventilator support; Furosemide; Piperacillin/tazobactam; Ciprofloxacin; Vancomycin	Hospitalization: 8 days ICU admission: Yes Outcome: Favorable

0 days						
	Female 5	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	<i>De novo</i> : MIS-C	Pleocytosis	AD: Epinephrine; Milrinone; Immunoglobulin; Methylprednisolone; Anakinra; Methylprednisolone (pulse dose); Vancomycin; Cefepime; Ceftriaxone COVID-19: Intubation; Mechanical ventilator support	Hospitalization: 11 days ICU admission: Yes Outcome: Favorable
	Female 5	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: Unclear	<i>De novo</i> : MIS-C	-	AD: Dopamine; Epinephrine; Immunoglobulin; Methylprednisolone; Aspirin; Vancomycin; Cefepime	Hospitalization: 11 days ICU admission: Yes Outcome: Favorable
	Female 6	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	<i>De novo</i> : MIS-C	-	AD: Norepinephrine; Dopamine; Epinephrine; Milrinone; Immunoglobulin; Methylprednisolone; Methylprednisolone (pulse dose); Vancomycin; Ceftriaxone; Metronidazole COVID-19: Intubation; Mechanical ventilator support	Hospitalization: >7 days ICU admission: Yes Outcome: Not reported
	Kutlu, Ö. and A. Metin [75] (2020) Turkey Case report	Female 71 - COVID-19 to AD latency: 4 days	Exacerbation: Psoriasis (Previously in remission)	-	COVID-19: Oseltamivir; Hydroxychloroquine	Hospitalization: >4 days Outcome: Not reported
	Female 32	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	Exacerbation: Autoimmune polyglandular syndrome type 1 (hypoparathyroidism) (Previously in remission with: rhPTH (1-84); Glucocorticoid)	-	AD: Calcitriol; Calcium supplementation COVID-19: Oxygen therapy; Intubation; Mechanical ventilator support; Lopinavir/Ritonavir; Ribavirin; Hydroxychloroquine; Azithromycin; Piperacillin/tazobactam; Trimethoprim/sulfamethoxazole; Norepinephrine; Dobutamine; Hydrocortisone	Hospitalization: 37 days ICU admission: Yes Outcome: Favorable
	Beccuti, G., et al. [76] (2020) Italy Case report	Female 32 - COVID-19 to AD latency: Unclear	Exacerbation: Autoimmune polyglandular syndrome type 1 (hypoparathyroidism) (Previously in remission with: rhPTH (1-84); Glucocorticoid)	-	AD: Calcitriol; Calcium supplementation COVID-19: Oxygen therapy; Intubation; Mechanical ventilator support; Lopinavir/Ritonavir; Ribavirin; Hydroxychloroquine; Azithromycin; Piperacillin/tazobactam; Trimethoprim/sulfamethoxazole; Norepinephrine; Dobutamine; Hydrocortisone	Hospitalization: 37 days ICU admission: Yes Outcome: Favorable
	Male 69	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 18 days	<i>De novo</i> : Antiphospholipid syndrome	Thrombocytopenia; Anemia; Positive anti-beta-2- glycoprotein I; Positive anti- cardiolipin antibodies	AD: Immunoglobulin COVID-19: Mechanical ventilator support; Oseltamivir	Hospitalization: >24 days ICU admission: Yes Outcome: Not reported
	Female 65	COVID-19 confirmation test: Unclear	<i>De novo</i> : Antiphospholipid syndrome	Thrombocytopenia; Anemia; Positive anti-beta-2- glycoprotein I;	COVID-19: Antibiotic therapy	Hospitalization: >33 days ICU admission: Yes
	Hypertension; DM; Stroke	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 18 days	<i>De novo</i> : Antiphospholipid syndrome	Thrombocytopenia; Anemia; Positive anti-beta-2- glycoprotein I;	COVID-19: Antibiotic therapy	Hospitalization: >33 days ICU admission: Yes
	Zhang, Y., et al. [77] (2020) China Case series	Hypertension; DM; Stroke - COVID-19 to AD latency: 18 days	<i>De novo</i> : Antiphospholipid syndrome	Thrombocytopenia; Anemia; Positive anti-beta-2- glycoprotein I;	COVID-19: Antibiotic therapy	Hospitalization: >33 days ICU admission: Yes

	DM; Coronary artery disease	COVID-19 to AD latency: 33 days		Positive anti-cardiolipin antibodies		Outcome: Not reported
	Male 70 Hypertension; Emphysema; Nasopharyngeal carcinoma; Stroke	COVID-19 confirmation test: Unclear COVID-19 to AD latency: 10 days	<i>De novo:</i> Antiphospholipid syndrome	Anemia; Positive anti-beta-2-glycoprotein I; Positive anti-cardiolipin antibodies	COVID-19: Antibiotic therapy; Ribavirin	Hospitalization: >24 days ICU admission: Yes Outcome: Not reported
Brun, G., et al. [78] (2020) France Case report	Female 54 Hypertension	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 10 days	<i>De novo:</i> CNS vasculitis	-	AD: Steroid COVID-19: Intubation; Mechanical ventilator support; Prone positioning; Hydroxychloroquine; Azithromycin; Amoxicillin and clavulanic acid	Hospitalization: >12 days Outcome: Not reported
Bruni, A., et al. [79] (2020) Italy Case report	Male 59 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 44 days	<i>De novo:</i> Gallbladder vasculitis	High serum IL-6; Thrombocytopenia	AD: Meropenem; Tigecycline; Laparotomic cholecystectomy COVID-19: Tocilizumab; Oxygen therapy; Prone positioning; Intubation; Mechanical ventilator support; Rocuronium; Intravenous fluid therapy; Norepinephrine; Azithromycin; Hydroxychloroquine; Enoxaparin	Hospitalization: >44 days ICU admission: Yes Outcome: Favorable
Reichard, R. R., et al. [80] (2020) USA Case report	Male 71 Myocardial infarction	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	<i>De novo:</i> Acute disseminated encephalomyelitis	High serum IL-6	COVID-19: Oxygen therapy; Intubation; Prone positioning; Sedation/paralysis; Vasopressor support; Stress dose IV steroids	Hospitalization: >13 days Outcome: Death
Verheyden, M., et al. [81] (2020) Belgium Case report	Male 57 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 8 days	<i>De novo:</i> Livedo reticularis	Positive ANA	AD: Low molecular weight heparin COVID-19: Oxygen therapy; Paracetamol; Hydroxychloroquine	Hospitalization: 8 days Outcome: Favorable
Pilotto, A., et al. [82] (2020) Italy Case report	Male 60 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	<i>De novo:</i> Encephalitis	CSF high protein level; High CSF IL-6; High CSF IL-8; High CSF TNF- α ; High CSF β 2-microglobulin	AD: Ampicillin; Acyclovir; Methylprednisolone; Prednisone COVID-19: Lopinavir/Ritonavir; Hydroxychloroquine	Hospitalization: 11 days Outcome: Favorable
Wei, H., et al. [83] (2020) China Case report	Male 62 DM (Type 2);	COVID-19 confirmation test: Positive rRT-	<i>De novo:</i> Oculomotor nerve palsy	-	AD: Methylprednisolone; Immunoglobulin COVID-19: Oxygen therapy; Moxifloxacin; Oseltamivir;	Hospitalization: 12 days Outcome: Death

	Hypertension; Lacunar infarction	PCR COVID-19 to AD latency: Unclear			Ribavirin; Lopinavir; Paracetamol; Ibuprofen	
Rosen, M. H., et al. [84] (2020) USA Case report	Female 26 -	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: Unclear	Exacerbation: Ulcerative colitis (pancolitis) (Previously in remission)	-	AD: Methylprednisolone; Prednisone; Cyclosporine COVID-19: Azithromycin; Hydroxychloroquine	Hospitalization: 16 days Outcome: Favorable
Cerasti, D., et al. [85] (2020) Italy Case report	Female 47 Obesity	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 14 days	Exacerbation: Antiphospholipid syndrome (Status not specified)	-	COVID-19: Ganciclovir; Oseltamivir; Darunavir; Cobicistat; Meropenem; Linezolid; Supportive care; Intubation	Hospitalization: 9 days Outcome: Death
Lee, J. M. and S. J. Lee [86] (2020) South Korea Case report	Female 53 -	COVID-19 confirmation test: Unclear COVID-19 to AD latency: 22 days	Exacerbation: Ankylosing spondylitis exacerbation (Previously in remission with: Etanercept; Methotrexate)	-	AD: Etanercept	No admission Outcome: Favorable
Arca, K. N. and A. J. Starling [87] (2020) USA Case report	Female 58 Chronic migraine; Stroke; Restless leg syndrome	COVID-19 confirmation test: Unclear COVID-19 to AD latency: Unclear	Exacerbation: Multiple sclerosis (Previously in remission with: Fingolimod)	-	COVID-19: Hydroxychloroquine; Azithromycin; Intubation	Hospitalization: unknown duration ICU admission: Yes Outcome: Favorable
Zoghi, A., et al. [88] (2020) Iran Case report	Male 21 -	COVID-19 confirmation test: Negative rRT-PCR; Positive IgG COVID-19 to AD latency: 10 days	<i>De novo</i> : Acute disseminated encephalomyelitis	CSF high protein level; Pleocytosis	AD: Plasma exchange; Vancomycin; Meropenem; Acyclovir	Hospitalization: 14 days ICU admission: Yes Outcome: Favorable
Anand, P., et al. [89] (2020) USA Case series	Female 42 Hepatitis B	COVID-19 confirmation test: Positive rRT-PCR COVID-19 to AD latency: 0 days	Exacerbation: Myasthenia Gravis (MuSK+) (Previously in remission with: Prednisone)	-	AD: Prednisone; Immunoglobulin	Hospitalization: 5 days Outcome: Favorable
Dogan, L., et al. [90] (2020) Turkey Case series	Male 49 -	COVID-19 confirmation test: Positive rRT-	<i>De novo</i> : Autoimmune meningoencephalitis	High serum IL-6	AD: Plasmapheresis COVID-19: Intubation; Mechanical ventilator support; Prone positioning;	Hospitalization: 34 days ICU admission: Yes

	PCR COVID-19 to AD latency: 13 days			Lopinavir/Ritonavir; Azithromycin; Ceftriaxone; Hydroxychloroquine; Favipiravir	Outcome: Favorable
Male 59 Hypertension	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 15 days	<i>De novo</i> : Autoimmune meningoencephalitis	CSF high protein level	AD: Plasmapheresis COVID-19: Intubation; Mechanical ventilator support; Prone positioning; Azithromycin; Hydroxychloroquine; Favipiravir	Hospitalization: 39 days ICU admission: Yes Outcome: Favorable
Male 59 Hypertension; DM; Obesity	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 15 days	<i>De novo</i> : Autoimmune meningoencephalitis	CSF high protein level	AD: Plasmapheresis COVID-19: Intubation; Mechanical ventilator support; Prone positioning; Azithromycin; Hydroxychloroquine; Favipiravir	Hospitalization: 23 days ICU admission: Yes Outcome: Death
Female 51 Hypertension; DM	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 12 days	<i>De novo</i> : Autoimmune meningoencephalitis	CSF high protein level	AD: Plasmapheresis COVID-19: Intubation; Mechanical ventilator support; Azithromycin; Hydroxychloroquine; Favipiravir	Hospitalization: 33 days ICU admission: Yes Outcome: Favorable
Male 55 Hypertension	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 15 days	<i>De novo</i> : Autoimmune meningoencephalitis	CSF high protein level; High serum IL-6	AD: Plasmapheresis COVID-19: Intubation; Mechanical ventilator support; Prone positioning; Azithromycin; Hydroxychloroquine; Favipiravir	Hospitalization: >39 days ICU admission: Yes Outcome: Not reported
Male 22 Autism	COVID-19 confirmation test: Positive rRT- PCR COVID-19 to AD latency: 14 days	<i>De novo</i> : Autoimmune meningoencephalitis	CSF high protein level; High serum IL-6	AD: Plasmapheresis COVID-19: Intubation; Mechanical ventilator support; Prone positioning; Azithromycin; Hydroxychloroquine; Favipiravir	Hospitalization: 31 days ICU admission: Yes Outcome: Favorable

Abbreviations: A Disintegrin And Metalloproteinase with a Thrombospondin Type 1 Motif, Member 13 (ADAMTS-13); Anti-Neutrophil Cytoplasmic Antibodies (ANCA); Antinuclear antibody (ANA); Antiphospholipid Syndrome (APS); Autoimmune Disease (AD); Brain natriuretic peptide (BNP); Central Nervous System (CNS); Cerebrospinal fluid (CSF); Chronic Obstructive Pulmonary Disease (COPD); Coronavirus Disease 2019 (COVID-19); Diabetes Mellitus (DM); Fraction of Inspired Oxygen (FiO2); Immunoglobulin A (IgA); Immunoglobulin G (IgG); Immunoglobulin M (IgM); Intensive Care Unit (ICU); Interleukin 6 (IL-6); Interleukin 8 (IL-8); Monoclonal Gammopathy Of Undetermined Significance (MGUS); Multisystem Inflammatory Syndrome in Adults (MIS-A); Multisystem Inflammatory Syndrome in Children (MIS-C); Myelin Oligodendrocyte Glycoprotein (MOG); N-methyl-D-aspartate (NMDA); Platelet Factor 4 (PF4); Positive End-Expiratory Pressure (PEEP); Real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR); Recombinant Human Parathyroid Hormone (rhPTH); Systemic Lupus Erythematosus (SLE); Tumor necrosis factor α (TNF- α)

Table 2. Total and by group summary of findings. General population and case characteristics, laboratory findings divided by areas, COVID-19 related radiologic findings and treatment, and AD-related treatment summarized with frequencies and descriptive statistics for the total and all major groups.

			Total	Neurologic AD	Blood AD	Vasculitis AD	Connectivitis/ SLE/APS AD
General (N (%))	N*		85 (100%)	36 (42.4%)	15 (17.6%)	19 (22.4%)	6 (7.1%)
		Age (Median)	53 (32-63 IQR)	54 (45.25-61.75 IQR)	53 (38-65 IQR)	13 (9-36 IQR)	67 (50-69.25 IQR)
		Sex (N (% Female))	40 (47.1%)	16 (44.4%)	9 (60.0%)	8 (42.1%)	3 (50.0%)
		AD comorbidity	23 (27.1%)	6 (16.7%)	5 (33.3%)	4 (21.1%)	2 (33.3%)
		De novo AD	70 (82.4%)	32 (88.9%)	13 (86.7%)	18 (94.7%)	4 (66.7%)
		Exacerbation of AD	18 (21.2%)	4 (11.1%)	2 (13.3%)	1 (5.3%)	2 (33.3%)
		COVID-19 to <i>De novo</i> AD latency in days (Median)	12 (6-16 IQR)	12 (7-15 IQR)	10 (6.25-15.75 IQR)	5 (0-13 IQR)	25.5 (12-45 IQR)
		ICU admission	35 (41.2%)	14 (38.9%)	3 (20.0%)	12 (63.2%)	4 (66.7%)
		Outcome					
		Favorable	55 (64.7%)	23 (63.9%)	13 (86.7%)	11 (57.9%)	1 (16.7%)
		Death	9 (10.6%)	5 (13.9%)	1 (6.7%)	2 (10.5%)	1 (16.7%)
Laboratory findings (N (%))	CSF	CSF high protein level	20 (23.5%)	20 (55.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		CSF pleocytosis	6 (7.1%)	5 (13.9%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
		CSF albumin-cytological dissociation	5 (5.9%)	5 (13.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		CSF high IgG	5 (5.9%)	5 (13.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Immune markers	Anti-MOG antibodies	1 (1.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Anti-NMDA receptor antibodies	1 (1.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Anti-ganglioside antibodies (Asialo GM1)	1 (1.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Anti-cardiolipin antibodies	6 (7.1%)	1 (2.8%)	0 (0.0%)	1 (5.3%)	4 (66.7%)
		Anti-beta-2-glycoprotein I antibodies	4 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (66.7%)
		Direct Coombs Test	4 (4.7%)	0 (0.0%)	4 (26.7%)	0 (0.0%)	0 (0.0%)
		High cold agglutinin titers	2 (2.4%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)
		Anti-ADAMTS-13 inhibitory antibodies	1 (1.2%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
		Anti-platelet antibodies	1 (1.2%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
		Anti-platelet factor 4/heparin antibodies	1 (1.2%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
		ANA	3 (3.5%)	0 (0.0%)	1 (6.7%)	1 (5.3%)	0 (0.0%)
		High Complement	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
		Low complement	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
		High IgA serum levels	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
		ANCA	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
		Anti-Ro/SSA	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
	Hemostasis system markers	High d-dimers	32 (37.6%)	10 (27.8%)	5 (33.3%)	13 (68.4%)	4 (66.7%)

	High fibrinogen	13 (15.3%)	2 (5.6%)	3 (20.0%)	5 (26.3%)	3 (50.0%)
	INR	7 (8.2%)	0 (0.0%)	0 (0.0%)	7 (36.8%)	0 (0.0%)
	High prothrombin time	6 (7.1%)	0 (0.0%)	0 (0.0%)	3 (15.8%)	3 (50.0%)
	High partial thromboplastin time (aPTT)	3 (3.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (50.0%)
Inflammatory markers	High c-reactive protein	49 (57.6%)	18 (50.0%)	5 (33.3%)	17 (89.5%)	4 (66.7%)
	High procalcitonin	12 (14.1%)	0 (0.0%)	0 (0.0%)	12 (63.2%)	0 (0.0%)
	High ferritin	25 (29.4%)	10 (27.8%)	3 (20.0%)	10 (52.6%)	1 (16.7%)
	High lactate dehydrogenase	23 (27.1%)	7 (19.4%)	5 (33.3%)	9 (47.4%)	2 (33.3%)
	High erythrocyte sedimentation rate	14 (16.5%)	5 (13.9%)	0 (0.0%)	8 (42.1%)	0 (0.0%)
	High serum IL-6	14 (16.5%)	5 (13.9%)	2 (13.3%)	6 (31.6%)	1 (16.7%)
	High serum IL-8	5 (5.9%)	0 (0.0%)	0 (0.0%)	5 (26.3%)	0 (0.0%)
	High serum TNF- α	5 (5.9%)	0 (0.0%)	0 (0.0%)	5 (26.3%)	0 (0.0%)
	High troponins levels	9 (10.6%)	0 (0.0%)	0 (0.0%)	7 (36.8%)	2 (33.3%)
	High myoglobin level	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Other general laboratory measurements	Anemia	22 (25.9%)	3 (8.3%)	8 (53.3%)	8 (42.1%)	3 (50.0%)
	Reticulocytosis	4 (4.7%)	0 (0.0%)	4 (26.7%)	0 (0.0%)	0 (0.0%)
	Leukocytosis	29 (34.1%)	11 (30.6%)	4 (26.7%)	11 (57.9%)	3 (50.0%)
	Leukopenia	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)
	Lymphocytopenia	36 (42.4%)	7 (19.4%)	9 (60.0%)	14 (73.7%)	4 (66.7%)
	Thrombocytopenia	31 (36.5%)	6 (16.7%)	12 (80.0%)	9 (47.4%)	4 (66.7%)
	Thrombocytosis	3 (3.5%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Hyponatremia	8 (9.4%)	1 (2.8%)	0 (0.0%)	7 (36.8%)	0 (0.0%)
	High alanine aminotransferase (ALT)	17 (20.0%)	5 (13.9%)	1 (6.7%)	10 (52.6%)	0 (0.0%)
	High aspartate aminotransferase (AST)	13 (15.3%)	6 (16.7%)	1 (6.7%)	5 (26.3%)	0 (0.0%)
	High gamma-glutamyl transferase	2 (2.4%)	1 (2.8%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
	Direct hyperbilirubinemia	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (10.5%)	0 (0.0%)
	Indirect hyperbilirubinemia	3 (3.5%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	0 (0.0%)
	Hypoalbuminemia	12 (14.1%)	1 (2.8%)	0 (0.0%)	8 (42.1%)	3 (50.0%)
COVID-19 related radiologic findings (N (%))	Normal	9 (10.6%)	2 (5.6%)	2 (13.3%)	3 (15.8%)	0 (0.0%)
	Bilateral ground-glass opacities	34 (40.0%)	17 (47.2%)	4 (26.7%)	3 (15.8%)	4 (66.7%)
	Bilateral pulmonary infiltrates	12 (14.1%)	3 (8.3%)	3 (20.0%)	2 (10.5%)	3 (50.0%)
	Diffused consolidations	11 (12.4%)	8 (22.2%)	2 (13.3%)	0 (0.0%)	1 (16.7%)

Other tests (N)	Nerve conduction studies - GBS	12 (14.1%)	12 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Skin biopsy - leukocytoclastic vasculitis	3 (3.5%)	0 (0.0%)	0 (0.0%)	3 (15.8%)	0 (0.0%)
	Bone marrow aspirate - normal cellularity with an increased megakaryocyte count	2 (2.4%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)
AD treatment (N (%))	None	13 (15.3%)	3 (8.3%)	0 (0.0%)	2 (10.5%)	3 (50.0%)
	Immunoglobulin	42 (49.4%)	19 (52.8%)	10 (66.7%)	11 (57.9%)	2 (33.3%)
	Corticosteroids	35 (41.2%)	11 (30.6%)	12 (80.0%)	10 (52.6%)	1 (16.7%)
	Antibiotic prophylaxis	16 (18.8%)	3 (8.3%)	0 (0.0%)	13 (68.4%)	0 (0.0%)
	Plasma exchange therapies	13 (15.3%)	10 (27.8%)	1 (6.7%)	1 (5.3%)	1 (16.7%)
	Supportive therapy	12 (14.1%)	4 (11.1%)	0 (0.0%)	7 (36.8%)	0 (0.0%)
	Transfusion	12 (14.1%)	0 (0.0%)	11 (73.3%)	0 (0.0%)	1 (16.7%)
	Immunomodulator	9 (10.6%)	1 (2.8%)	1 (6.7%)	5 (26.3%)	0 (0.0%)
	Shock therapy	8 (9.4%)	0 (0.0%)	0 (0.0%)	8 (42.1%)	0 (0.0%)
	Anticoagulant	6 (7.1%)	0 (0.0%)	1 (6.7%)	3 (15.8%)	1 (16.7%)
	Other	5 (5.9%)	1 (2.8%)	1 (6.7%)	1 (5.3%)	0 (0.0%)
	Acetylsalicylic acid	5 (5.9%)	0 (0.0%)	0 (0.0%)	4 (21.1%)	1 (16.7%)
	Anticonvulsant	3 (3.5%)	3 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Thrombopoietin pathway therapy	3 (3.5%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	1 (16.7%)
	Cirurgy	3 (3.5%)	0 (0.0%)	1 (6.7%)	2 (10.5%)	0 (0.0%)
	Antiviric prophylaxis	2 (2.4%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Antipsychotic	1 (1.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Antifibrinolytic	1 (1.2%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
	NSAID	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
COVID-19 treatment (N (%))	None	26 (30.6%)	8 (22.2%)	4 (26.7%)	10 (52.6%)	1 (16.7%)
	Supportive therapy	40 (47.1%)	21 (58.3%)	6 (40.0%)	7 (36.8%)	3 (50.0%)
	Hydroxychloroquine	33 (38.8%)	20 (55.6%)	4 (26.7%)	4 (21.1%)	0 (0.0%)
	Antiviric therapy	28 (32.9%)	17 (47.2%)	4 (26.7%)	0 (0.0%)	4 (66.7%)
	Antibiotic therapy	31 (36.5%)	16 (44.4%)	5 (33.3%)	4 (21.1%)	4 (66.7%)
	Other	16 (18.8%)	4 (11.1%)	5 (33.3%)	3 (15.8%)	1 (16.7%)

Abbreviations: A Disintegrin And Metalloproteinase with a Thrombospondin Type 1 Motif, Member 13 (ADAMTS-13); Anti-Neutrophil Cytoplasmic Antibodies (ANCA); Antinuclear antibody (ANA); Antiphospholipid Syndrome (APS); Autoimmune Disease (AD); Cerebrospinal fluid (CSF); Coronavirus Disease 2019 (COVID-19); Immunoglobulin A (IgA); Immunoglobulin G (IgG); Immunoglobulin M (IgM); Intensive Care Unit (ICU); Interleukin 6 (IL-6); Interleukin 8 (IL-8); Interquartile range (IQR); Myelin Oligodendrocyte Glycoprotein (MOG); N-methyl-D-aspartate (NMDA); Nonsteroidal anti-inflammatory drug (NSAID); Systemic Lupus Erythematosus (SLE); Tumor necrosis factor α (TNF- α)

*In this case percentages refer to the 85 total population.

Figures

Figure 1

PRISMA flowchart. Search results and study selection process by stage according to the PRISMA statement guidelines.

JBI Critical Appraisal Checklist

Figure 2

JBI Critical Appraisal Checklist. Summary of results for each of the JBI Critical Appraisal Checklist for Case Reports quality domains.

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