# Systematic Review:

# Non-MIS-C postacute sequelae of COVID-19, is it autoimmune or autoinflammatory? A systematic review of the reported cases

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# Abstract:

## Introduction:

Coronavirus Disease 2019 (COVID-19) is by far the most world-altering pandemic to ever hit modern humanity. Three years after the very first case emerged in December 2019, the virus continues to bring upon global disarray in the acute phase of the infection as well as months afterwards, causing the virus’s morbidity and mortality to further skyrocket. This systematic literature review was conducted up till December 2022, comprising all the case reports that thoroughly discuss a myriad of non-Multisystem Inflammatory Syndrome In Children (non-MIS-C) post-acute sequalae of COVID-19 (PASC) in the paediatric population, also known as Long COVID Syndrome.  In this review, we aimed to highlight the prevalent time interval between COVID-19 infection and the development of various non-MISC post-infectious sequalae (PIS).

## Methods:

We conducted a holistic literature search on PubMed, Google Scholar, Google Search, and Scopus. Data bases were searched for studies that met our inclusion and exclusion criteria. The systematic review was performed on all case reports containing relevant outcome parameters such as age, sex, the interval between COVID-19 infection and subsequent PASC and, lastly, the need for hospitalization during the course of the disease.

## Results:

We collected a total of 78 case reports discussing the various post-infectious immune sequalae following COVID-19 infection in the paediatric population, consisting of a total of 109 patients. The final screening revealed an equal sex distribution, whereas the two commonest age intervals were school-aged children and adolescents, with 38% of the patients having been older than six years. Interestingly, hospital admission throughout the course of COVID-19 wasn’t a predictor of the subsequent PASC; forty-nine patients (44.9%) were hospitalized while sixty patients (55.1%) were not hospitalized. More importantly, the most predominant time interval between COVID-19 infection and the developing PASC was observed to be within 14 days since the start of COVID-19 infection, accounting for 61% of the cases.

## Conclusion:

These findings suggest a crucial link is slowly but surely unfolding between COVID-19 and an abundance of systemic post-infectious immune sequalae in the paediatric population, especially amongst children older than six years. Accordingly, meticulous follow-up and prompt management is largely encouraged for the paediatric population in case of unusual symptoms and signs following COVID-19 infection, regardless of COVID-19’s severity.

**Keywords:** COVID-19; postacute sequelae; autoinflammatory; autoimmune

# Background:

Acute infections are typically defined as self-limiting infections lasting usually less than six months and that usually lead to either complete resolution or death. While many studies cover the typical short-lived course and prognosis of acute infectious diseases, the link between acute infections and chronic disability remains understudied. Consequently, many patients suffering from the long-lasting sequelae of acute infections can easily be wrongly diagnosed or wrongly treated. Furthermore, there is insufficient data pertaining to PAIS since many cases- especially those which are sporadic- remain unrecognized. Post-acute sequelae (PAS) are symptoms that occur during the post-acute phase of an illness. While the exact definition of the post-acute phase is largely debatable and differs from one virus species to another, it is generally known as the phase after the virus becomes no longer detectable by PCR. 1–4

It is not unusual for acute infections to cause fleeting autoimmune symptoms due to disturbances in the innate and adaptive immune signaling pathways. Rarely, however, acute infections can progress to established autoimmune diseases. The main pathogenesis behind this progression is the molecular mimicry of pathogens, or the structural similarity between pathogenic proteins and self-proteins which causes auto-activation of self-reactive immune cells in some susceptible individuals. Furthermore, viral attacks lead to release of intracellular components, which, in turn, causes the activation of the innate immune system, the formation of autoantibodies, the stimulation of antigen-presenting cells, and the migration of immune cells to the site of damage.5–8

In general, PIS can be divided based on the time interval between the infection and the sequelae and based on the duration of the PIS into three broad subtypes. PIS can be rapidly- developing such as in the case of reactive arthritis which normally occurs 1-2 weeks after an infection in susceptible individuals. PIS can also take the form of chronic inflammation following nonpersistent viruses such as in the case of the reovirus, rotavirus A, causing celiac disease, an autoimmune disease triggered by gluten. However, the usual pattern is short-lived autoimmunity developing 4 weeks after the infection and that does not persist more than 6 months. Guillain-Barre Syndrome, ITP, and post-streptococcal immune complications are common examples of this pattern.9–11

Ever since the onset of the COVID-19 pandemic, the SARS-Cov-2 virus has quickly become an important focus of research. Due to the atypical cytokine release and immune system dysfunction following a COVID-19 infection, post-acute sequelae of COVID-19 (PASC) have appeared in several cases and such conditions have become known as 'long COVID'. Previous inflammatory conditions, advanced age, and obesity are all known risk factors. Just like its predecessors, SARS-CoV-1 and MERS-CoV, the COVID-19 virus can cause symptoms such as fatigue, dermatological and gastroenterological symptoms. In a recent study, 30% of COVID patients suffered from persistence of these symptoms even after the virus became undetectable by PCR. 12

The aim of this systematic review is to demonstrate all case reports of PIS of COVID-19 and to determine the prevalent time interval between acute infection and the development of PIS

# Methodology:

## A-Databases used:

A literature search has been performed in PubMed, Google Scholar, Google Search, Scopus.

## B-Search terms inclusion and exclusion criteria:

### 1-Inclusion Criteria:

**-Diagnoses:** The following terms and inclusion criteria were included in the search: “COVID-19” OR “SARS-CoV-2” (Severe Acute Respiratory syndrome Coronaviridae 2) AND “Autoimmune sclerosing cholangitis”, “Diabetes” OR “type 1 diabetes”, “Systemic Lupus Erythematosus” OR “Lupus Erythematosus Disseminatus” OR “Lupus Erythematosus, Systemic”, “Hemolytic uremic syndrome”, “Juvenile Idiopathic Arthritis”, "Familial Mediterranean Fever", “Autoimmune thyroid disease” OR “subacute thyroiditis”, “Autoimmune hepatitis”, “ANCA vasculitis”, "Tumour necrosis factor receptor-associated periodic syndrome", “ITP”, “HLH”, “Psoriasis”, “Guillain-Barre”, “Multiple Sclerosis” OR “ADEM” AND “Pediatrics” OR “Children”.

**-Age:** 0-18 years

### 2-Exclusion criteria:

-Any case with **multi-inflammatory syndrome of children (MISC) or Kawasaki** was excluded, any flare-up of pre-existing autoinflammatory condition was excluded.

-Any case **not addressing the outcome parameters** was excluded.

## C-Outcome parameters:

The main outcome parameters were the age, sex of the included cases, the interval between COVID-19 and the subsequent autoimmune sequelae, and the need for hospitalization during COVID-19 infection that preceded the resultant autoimmune sequelae.

# Statistical analyses

For statistical purposes, age was classified into 4 ranges: (0-2 years: infancy)/ (preschool children: 3-5 years)/ (school aged children 6-12 years)/ (adolescents 13-18 years).

Furthermore, the interval between COVID-19 and subsequent autoimmune sequelae was classified into three intervals: (immediate: 0-14 days)/ (classic: 15-28 days)/ delayed (>28 days).

Patients were categorized according to the aforementioned age ranges and time intervals as well as the need for hospital admission during COVID-19 and sex. The number and percentage of patients in each category of each outcome parameter was determined, and comparison between different categories of each outcome parameters was implemented using chi-square test and illustrated as a pie chart.

# Results:

We gathered a total of 78 reports of autoimmune sequelae following COVID-19, comprising a collective total of 109 patients. (References included in individual results)

Figure 1 is a PRISMA flow chart. Figure 2 is a detailed algorithm of the distribution and overlap of reports and number of patients per diagnosis.

## A-Overall Results:

The sex distribution in retrieved cases was equal between the two genders. Regarding the age, the commonest two age intervals involved were school-aged children and adolescents, with each accounting for 38% of the overall cases. Hospital admission during COVID-19 did not seem to be a good predictor of subsequent autoimmune sequelae as there was no statistically significant difference between the number of cases with hospital admission and those who were not admitted, 49 and 60 respectively. Finally, yet importantly, most of the observed postinfectious sequelae were observed within 14 days of the COVID-19 infection, accounting for 61% of the total cases. (Table 1-4) and Figure (3-6) illustrates the details of the overall results described in this paragraph).

## B-Individual Results (by alphabetical order of the respective autoimmune disorder)

### 1-Addison’s disease (Table 5)13

The relation between COVID-19 and Addison's disease has been reported in the literature. One case of a 14-year-old female was associated with primary adrenal insufficiency (Addison) as part of Autoimmune Polyglandular Syndrome Type 2, which required an ICU admission as mentioned by Floras et al.

## 2-ANCA vasculitis (Table 6)14–17

Acute ANCA associated vasculitis is a rare but documented condition following SARS-COV-2 infection in adults, but it is even rarer in the pediatric population. Here we present to you four case reports of pediatric ANCA associated vasculitis following an acute SARS-COV-2 infection. With the male to female ratio being 1:1. The mean age among the four patients was approximately 16 years old. 100% of the patients acquired said complication as an immediate sequela (within 0-4 weeks after COVID-19 infection) while none had delayed nor persistent sequelae. Two patients developed P-ANCA vasculitis as seen in Firenzen et al, and Weston et al, while the other two patients developed C-ANCA vasculitis. Two of the patients had pre-existing asthma as seen in Firenzen et al and Bryant et al. The general prognosis for post-COVID ANCA vasculitis in the previous patients was good with mild to moderate COVID-19 courses, however, the patient in Weston et al was admitted to the ICU due to worsening respiratory status. All patients recovered and were discharged after proper treatment.

### 3-Central demyelinating disorders (CDD) (Table 7)18–29

Concerning the data gathered about post-COVID patients suffering from demyelinating disorders other than GBS, we noticed almost an equal ratio of males and females (8 males to 11 females) in the reported cases. The youngest case reported was of a 3-year-old and the oldest being 16 years old. The average age was found to be 11 years.

The course of the preceding COVID infection was mostly mild. Five cases were asymptomatic, and the most reported symptom was fever. The time frame between infection and the neurological presentation ranged from a week to months with 3 cases presenting with neurological manifestation during the course of covid infection.

Of the 19 reported cases 7 cases were diagnosed as newly onset Acute Disseminated Encephalomyelitis (ADEM), 1 case was diagnosed as Anti-N-methyl-d-aspartate (anti-NMDA) receptor encephalitis and one case was that of unspecified encephalitis.

Two cases of optic neuritis were reported, as well as two cases of neuromyelitis Optica spectrum disorder. Three of the reported cases were of Multiple Sclerosis post Covid and one case exhibited Anti-myelin oligodendrocyte glycoprotein (anti-MOG) demyelinating disorder. One case developed Longitudinal extensive transverse myelitis (LETM).

Complete recovery was observed in 5 cases, meanwhile the rest of the cases suffered from mild remnants including, increased blind spot, persistent gait, residual diffuse weakness and unilateral papilledema. Furthermore, one patient experienced relapse post-treatment and was placed on rituximab.

### 4-Guillain Barre Syndrome (GBS) (Table 8)19,22,30–49

Although the number of adult COVID-19 infections diagnosed with Guillain-Barré Syndrome (GBS) is increasing, the occurrence of cases in paediatric population remains limited or perhaps underreported.

The research entails that reported paediatric cases of SARS-CoV-2 infection associated with GBS had an average age of 16 years. In general, the age group varied drastically, with the youngest reported case being a 2-months-old male infant 15 days after the course of covid infection, and the oldest reported patient being a 17-year-old female with a short course of COVID infection 8 days  prior to the neurological complications. We assume that the severity of the infection is not directly linked to the Guillain Barre manifestations, since 7 of the reported cases were asymptomatic, and the rest of the cases demonstrated variable degrees of severity,16 cases showed a mild course, and 8 cases were severe and required PICU admission and mechanical ventilation.

All cases showed immediate post-COVID neurological complications ranging from 0 to 4 weeks after acquiring the infection. To elaborate, the time interval between the disease and the sequelae was around 1 week in 7 cases, 2 weeks in 10 cases, 3 weeks in 2 cases, and 1 month in 11 cases. The shortest interval reported was 2 days.

Full recovery was observed in most cases with the use of IVIG and physiotherapy. However, weakness in neck and limbs muscles persisted in 8 of the cases (out of 43) regardless of therapy.1 case showed complete recovery after IVIG except for general hyporeflexia, diminished fine touch sensation in limbs, and persistent lower limbs weakness, and required home ventilation. 4 cases even acquired new deficits and 2 patients died of respiratory muscle paralysis.

### 5-Hepatitis (Table 9)50,51

Hepatic involvement has been widely described as part of the acute setting of SARS-COV-2 infection, manifesting as a mild increase in liver enzymes without hepatic dysfunction, which eventually subsides as the clinical course of COVID-19 improves. Severe COVID-19 infection in the pediatric population can result in MIS-C and multiorgan failure, including hepatic failure. With that being said, here we present five case reports of isolated hepatitis with or without hepatic failure as the main presentation of COVID-19 infection in children. The female to male ratio was found to be 3:2 with 150% of females being more susceptible to acquire said complication. The mean age among patients was approximately 6 years old. 100% of the patients developed an immediate (within 0-4 months from start of COVID-19 infection) post-COVID19 sequelae and none suffered from delayed or persistent sequelae.

 The course of COVID-19 infection was mild in three patients and moderate to severe in two infant patients as seen in Antala et al at the ages of 6 months and 4 months. Three of the five patients acquired complications such as acute liver failure with resistant coagulopathy which is seen in Osborn et al and the two infants in Antala et al. The 4-month-old infant in Antala et al also acquired acute kidney injury as well as seizures. Two patients developed hepatic encephalopathy as seen in Osborn et al and the 16-year-old male patient in Antala et al. It should be noted that four out of the five patients were admitted to the PICU with an average length of stay of approximately 5 days.

Ultimately, all patients received all needed treatment and were discharged accordingly.

### 6-Hemo-lymphocytic histiocytosis (HLH) (Table 10)52–55

Four cases of de novo HLH were reported following COVID-19 infections. It was found that the age of the patients varied from neonates to school age in both diseases with a predominance of preschool age (mean age = 3). HLH showed equal affection in both males and females (1:1). Three cases presented with symptoms of HLH several weeks after COVID, but one had symptoms during the course of COVID. The severity of the preceding COVID infection ranged from unremarkable to severe with two of the cases having required ICU admission during their COVID infection.

It is worth noting that one case presented with concomitant post-COVID viral encephalitis with cerebral atrophy and another case was diagnosed as Chédiak‐Higashi syndrome.

### 7-Hemolytic uremic syndrome (HUS) (Table 11)56–60

Eight cases were documented with HUS following COVID-19 in the paediatric age group. The mean age of the patients was 7 years.  All HUS cases were males with only one case report of COVID related to HUS in a female. Only two cases required ICU admission during the course of the preceding COVID.

It is worth noting that all HUS cases were atypical HUS, except for one case of concomitant COVID-19 and Shiga toxin-associated HUS.

In all cases, treatment was given with zero mortality.

### 8-Immune thrombocytopenic purpura (ITP) (Table 12)61–69

The literature investigated 10 paediatric case reports discussing post-COVID-19 Idiopathic thrombocytopenic purpura (ITP).  It was found  that ITP in children can be triggered by various viruses including HIV, hepatitis B, hepatitis C, cytomegalovirus (CMV), varicella zoster virus (VZV), and recently SARS-COV-2. In spite of ITP being more common in males, the female to male ratio among the cases collected from literature is 3:2. The mean age was 8 years. Results found that only 3 patients developed ITP during the course of COVID, while the remaining seven developed symptoms after an average of 3.7 weeks of being infected with COVID-19. Seven out of ten cases had a mild course of COVID-19 infection prior to ITP, while only one case required ICU admission for 14 days after the infection progressed to ARDS.

All patients recovered successfully after receiving the proper steroid & IVIG treatment.

### 9-Psoriasis (Table 13)70,71

Most of the reported cases in literature reported exacerbations were of pre-existing psoriasis following an attack of COVID. However, two papers reported de-novo cases. The first reported 9 cases of de-novo appearance, consisting of 6 males and 3 females. The mean age was 10 years.

Eight of the nine cases had a mild course of the preceding covid infection and only one patient needed hospital admission. The patients developed various variants of psoriasis with guttate psoriasis being the most common. Six of the patients have previous family history of psoriasis. The second paper reported a 13-year-old male with a previously mild course of COVID-19 infection that developed psoriasis vulgaris that responded fully to topical steroids.

### 10-Sclerosing cholangitis (Table 14)72

Only one case of post-COVID development of autoimmune sclerosing cholangitis has been reported in the paediatric age group at the time of date collection.  It manifested as a delayed post-COVID autoimmune sequelae 2 months after the setting of a SARS-COV-2 infection in a 14-year-old male patient. The presence of advanced fibrosis observed in the patient’s liver biopsy suggests that the autoimmune process may have started before the COVID-19, and the infection itself accelerated the progression of the disease. However, the lack of other reported cases makes this theory hard to prove.

The patient had a mild course of the preceding COVID-19 infection. All symptoms of AISC subsided after receiving a two month course of Prednisone as well as Azathioprine.

### 11-Systemic Lupus Erythromatosus (Table 15)73,74

As for SLE triggered by COVID-19, two cases were reported at the time of this paper. Both cases were of female patients. The first case was a 13-year-old patient who was hospitalised after developing severe pneumonia during the course of COVID-19 infection. The interval between COVID-19 infection and development of SLE was 2 months. The patient required plasma exchange to show improvement.

The second patient was an 18-year-old female who had a simultaneous onset of SLE with COVID-19 infection. She was hospitalized and needed mechanical ventilation. She also developed severe attacks of DVT with positive antiphospholipid antibodies and lupus anticoagulant and, unfortunately, went into cardiac arrest after developing cardiac tamponade and could not be resuscitated.

### 12-Thyroiditis (Table 16)13,71,75–80

Much like other endocrine post-COVID19 sequelae, paediatric thyroid complications are not uncommon. Some would even hypothesise COVID-19 being an endocrine disorder given the amount of sites it affects besides the respiratory system. Many papers have attributed this to the fact that COVID-19 virus utilises an entry receptor, the ACE-2 receptor. The ACE-2 receptor is expressed in many endocrine tissues, one of which is the thyroid follicular cell, rendering it more susceptible to the relentless virus.

Table 16 contains the relevant papers to our search criteria, describing the most prominent paediatric thyroid complications among the PICS, age, sex, course of the COVID-19 infection and whether or not it was a de-novo complication. Accordingly, the female to male ratio was found to be 5:4, with the female sex being the most predominant and the mean age being approximately 14 years.

While four patients have acquired an immediate post-COVID-19 sequelae ranging between 2-4 weeks after COVID-19 infection and five other patients have acquired delayed post-COVID19 sequelae ranging between 4 weeks up to 6 months, no patients were reported with persistent paediatric post-COVID19 thyroid complications lasting more than 6 months.

Seven out of nine of the patients were previously healthy while two out of the nine had pre-existing hyperthyroid states at the time of COVID-19 infection. Seven out of nine of patients had a rather mild self-limiting course of COVID-19, while two required ICU admission as seen in Victoria et al. However, all patients recovered and were discharged eventually after adequate treatment.

Three of the nine patients were found to have acquired autoimmune hypothyroidism, one case of which was associated with primary adrenal insufficiency as part of Autoimmune Polyglandular Syndrome Type 2 in Flokas et al. (mentioned in Addison's Table).  Two patients developed a thyrotoxic storm on top of a pre-existing state of hyperthyroidism, while two others developed De-novo Grave’s disease, one of which was also associated with a thyrotoxic storm as seen in Qureshi et al and Rocket et al.

Unlike thyroid complications in adults, subacute thyroiditis was much less commonly reported, with one case in Brancatella et al. Lastly, a post-COVID19 thyroid abscess was reported in Maithani et al despite absence of any relevant congenital anomalies.

### 13-Tumour Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) (Table 17)81

Regarding TRAPS, only a single case report of post-COVID TRAPS was found in a 6-year-old female of delayed onset, 4 months after a COVID infection of unspecified severity.

The patient suffered from three attacks of MAS (Macrophage Activation Syndrome) as a presentation of TRAPS for which she was hospitalized and treated.

She recovered after being admitted to the PICU (Pediatric Intensive Care Unit) for 22 days and received methylprednisolone and anakinra.

### 14-Type 1 Diabetes Mellitus (T1DM) (Table 18)60,82–90

Similarly, SARS-COV-2 has proven to manifest itself through catalyzing a diabetic ketoacidosis (DKA) and unmasking Autoimmune type 1 diabetes mellitus particularly in children. The mechanism for that is hypothesized to be similar to that of thyroid-related sequelae: through ACE-2 receptors found in the endocrine part of the pancreas. Furthermore, a recent study by Govender et al reported that COVID-19 can precipitate insulin resistance in some patients causing chronic metabolic disorders that wouldn’t have existed otherwise. All in all, the exact relation between SARS-COV-2 and Type 1 diabetes milletus remains uncertain and requires further research.

According to the 10 case reports collected, we have concluded a male predominance with a male: female ratio of 7:3, where females are 43% less likely to acquire post-COVID19 Type 1 diabetes mellitus. The mean age for said complication is approximately 9 years old. Moreover, 100% of the patients developed a de-novo type 1 diabetes mellitus with none having a pre-existing disease.

In nine patients out of ten, post-COVID19 type 1 diabetes mellitus was immediate (manifesting anytime between the start of COVID-19 infection and 4 weeks after) with only 1 case being delayed, Naguib et al (manifesting 1-6 months after start of COVID-19 infection) and none reporting persistent (lasting more than 6 months) post-COVID19 complications. Only one patient exhibited mild COVID-19 symptoms seen in Lanca et al while the rest of the patients exhibited high severity.

Eight patients have been admitted to the PICU with a median length of stay of approximately 3 days. However, seven of them were eventually discharged after clinical improvement.

Out of the 10 patients, one death was reported in Brothers et al due to multisystem failure, metabolic acidosis and fungal urosepsis by Candida Galbrata resistance to Azoles despite DKA resolution.

# Discussion:

Throughout our conduction of this systematic review of all non-MISC postinfectious immune sequelae of COVID-19, the two key findings uncovered were the rapid development of those immune sequelae in less than 14 days from the onset of COVID-19 and the high prevalence of these complications in children older than 6 years old.

Different pathogeneses underlie different types of similar postinfectious disorders. For instance, despite the incomplete understanding of reactive arthritis, it is hypothesized that T lymphocytes are induced by bacterial fragments such as lipopolysaccharide and nucleic acids when invasive bacteria reach the systemic circulation. These activated cytotoxic T-cells then attack the synovium. It is still unclear whether reactive arthritis involves the production of autoantibodies or not, but the rapid development of this postinfectious complication within days of the initial infection suggests a T cell-mediated auto-inflammatory process rather than a classic autoimmune disorder. 91,92

Another extreme example of postinfectious sequelae is the celiac disease process which is rarely observed after Rota virus infection. This occurs because Rota viruses disrupt the intestinal immune homeostasis, eventually facilitating T cell-mediated immunity against dietary antigens. Type I IFN and interferon regulatory factor 1 signaling play a central role by blocking regulatory T cell conversion and promoting helper T cell immunity.

Rheumatic fever is another classic example of a postinfectious sequelae. Rheumatic fever develops within a 2-4 weeks interval after the initial infection. Autoantibodies to myosin, tropomyosin, and collagens have been identified. 93

According to our study, in the case of post-COVID-19 infections, 61% of the postinfectious sequelae occurred within 14 days of the infections, with many occurring during the course of the disease. This rapid onset of postinfectious sequelae to SARS-CoV-2 suggests a rather similar auto-inflammatory process to the post-infectious diseases previously mentioned, with dysregulated immunity leading to wide-spread activation of T- cells and hypercytokinemia.

In COVID-19, next generation sequencing has revealed activated CD8+, Th1, Th17, NK and NKT cells together with other innate immune cells that secrete additional cytokines to target virus‐infected cells, and their overstimulation together with effector innate immune cells may lead to tissue damage. 94

Moreover, CD8+ T cells expressing high levels of PD‐1, CTLA‐4, TIGIT, granzyme B and perforin were increased in the severe group compared with the mild group. This data suggests that SARS‐CoV‐2 infection may lead to the functional impairment in CD4+ T cells and uphold excessive activation of CD8+ T cells. 95

Another interesting finding in our study was the high prevalence of postinfectious sequelae in children and adolescents older than six years. This is thought to be due to a distinct group of lymphocytes known as regulatory T cells (Tregs), which are key inflammatory response regulators and play a pivotal role in immune tolerance and homeostasis. Treg-mediated robust immunosuppression provides self-tolerance and protection against autoimmune diseases. However, once this system fails to operate or poorly operates, it leads to an extreme situation where immune system reacts against self-antigens and destroys host organs and, consequently, causes autoimmune and autoinflammatory diseases. There is established evidenced that Treg decline with age. However, no study to date quantified their abundance during different pediatric age intervals. 96

# Conclusion:

This is the largest systematic review to date of all non-MISC post-infectious immune sequelae (PIS) of COVID-19. Results suggest that PIS commonly occur immediately (within 14 days) after infection with Covid-19 , which prompts the conclusion of an auto-inflammatory process rather than a classic autoimmune pathology. On that account, more evidence is needed to focus on the underlying mechanisms, as this can contribute to enhancing the management of patients by giving a variety of immune modulators immediately after COVID-19 infection. In addition, equal care should be given to hospitalized  and non-hospitalized patients after infection because the severity of COVID-19 did not prove to be a predictor of occurrence of post-infectious immune sequelae. Close attention should be given to patients above 6 years of age as our data suggest a high predilection for complications in this age group.

Any risk of Bias has been illustrated in Figure 7 97

PRISMA chart has been designed using the updated guidelines for reporting for systematic reviews 98

# List of abbreviations:

|  |  |
| --- | --- |
| **Abbreviation** | **Definition** |
| A-ANCA | Acute  anti-neutrophil cytoplasmic antibody |
| ACE-2 | Angiotensin-converting enzyme 2 |
| ACTH | Adrenocorticotropic hormone |
| ADEM | Acute Disseminated Encephalomyelitis |
| AHA | Acute Hemolytic Anemia |
| AIH | Autoimmune hepatitis  |
| AIHA | Autoimmune hemolytic anemia |
| AKI | Acute kidney injury |
| ALL | Acute Lymphocytic Leukemia |
| ALT | Alanine Aminotransferase |
| ANA antibodies | Anti-nuclear antibodies, |
| ANCA | Anti-neutrophil cytoplasmic antibody |
| Anti-MOG | Anti- myelin oligodendrocyte glycoprotein |
| Anti-NMDA-R | Anti-N-methyl-d-aspartate (NMDA) receptor encephalitis |
| APS2 | Autoimmune polyglandular syndrome type 2 |
| ARDS | Acute Respiratory Distress Syndrome   |
| AST | Aspartate Aminotransferase |
| BAL | Broncho-alveolar lavage |
| BUN | Blood urea nitrogen |
| C-ANCA | Cytoplasmic anti-neutrophil cytoplasmic antibody |
| CD | Celiac Disease  |
| CD4+ | Cluster of differentiation 4 a co receptor for t helper receptor |
| CD8+ | Cluster of differentiation 8 |
| CDD | Central Demyelinating Disorders |
| CMV | Cytomegalovirus |
| COVID | Coronavirus disease |
| COVID 19: | Coronavirus disease of 2019  |
| Cr | Creatinine |
| CSF | Cerebro-spinal fluid |
| CT | computed tomography, |
| CTLA‐4 | Cytotoxic T-lymphocyte–associated antigen 4 |
| DAMPs | Damage-associated molecular patterns |
| DKA | Diabetic ketoacidosis  |
| DVT | Deep Venous Thrombosis |
| EEG | Electroencephalography,  |
| ER | Emergency room |
| FFB | Flexible fibro-optic bronchoscopy |
| FiO2 | Fraction of inspired oxygen |
| FT3 | Free triiodothyronine . |
| FT4 | Free thyroxine.  |
| GBS | Guillain Barre Syndrome |
| GCS | Glasgow coma scale |
| GGT | Gamma -glutamyl transferase  |
| Hb | Hemoglobin |
| Hct | Hematocrit |
| HFNC | High flow nasal cannula |
| HIV | Human Immunodeficiency Virus |
| HLH | Hemophagocytic lymphocytic histiocytosis   |
| HUS | Hemolytic uremic syndrome |
| ICU | Intensive Care unit |
| IFN | Interferons  |
| INR | International Normalized Ratio |
| ITP | Idiopathic thrombocytopenic purpura |
| ITP | Immune thrombocytopenic purpura |
| IV | Intravenous  |
| IVIG | Intravenous immune globulin |
| LETM | Longitudinal extensive transverse myelitis |
| MAS | Macrophage Activation Syndrome |
| MERS-CoV  | Middle East respiratory syndrome coronavirus |
| MIS-C | Multi-Inflammatory Syndrome of Children  |
| MPO antibodies | Myeloperoxidase antibodies |
| MRI | Magnetic resonance imaging |
| MS | Multiple Sclerosis |
| NK | Natural Killer Cell |
| NKT | Natural Killer T-Cell |
| NMSOD | Neuro Myelitis Optica Spectrum Disorder |
| PAIS | Post acute infections sequelae |
| P-ANCA | Perinuclear anti-neutrophil cytoplasmic antibody |
| PAS | Post-acute sequelae  |
| PASC | Post-acute sequelae of COVID19  |
| PCR | Polymerase chain reaction |
| PD‐1 | Programmed cell death protein 1 |
| PICS | Post-Intensive Care Syndrome |
| PICU | Pediatric Intensive Care unit |
| PIS | Post Infectious Sequelae |
| PR3 antibodies  | Anti-protease 3 antibodies |
| PSC | Primary Sclerosing Cholangitis |
| SARS-COV-2 | Severe acute respiratory syndrome coronavirus 2. |
| SARS-CoV-2 | Severe Acute Respiratory syndrome Coronavirus 2 |
| SLE | Systemic Lupus Erythromatosus |
| T1DM | Type 1 Diabetes Mellitus |
| Tg | Thyroglobulin |
| Th1 | T helper type 1 |
| Th17 | T helper type 17 |
| TIGIT | T cell immuno-receptor with Ig and ITIM domains |
| TPO | Thyroid peroxidase |
| TRAPS | Tumor Necrosis Factor Receptor Associated Periodic Syndrome |
| Tregs | regulatory T cells |
| TSH | Thyroid stimulating hormone. |
| TSI | Thyroid stimulating immunoglobulins. |
| UDCA | Ursodeoxycholic acid |
| URI  | Urinary tract infection. |
| VZV | Varicella Zoster Virus |
| Yrs | Years |

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**Figure 1:**

Title: Figure 1: PRISMA 2020 flow diagram for our systematic review to show study selection process

No abbreviations

**Figure 2:**

Title: Detailed number of case series and reports per diagnosis

Abbreviations:

CDD: Central demyelinating disorder, GBS: Guillain Barre syndrome, DM: Type 1 Diabetes Mellitus, HLH: Hemo-lymphocytic histiocytosis, HUS: hemolytic uremic syndrome, SLE: Systemic Lupus Erythematosus, TRAPS: Tumor Necrosis receptor associated periodic syndrome

**Figure 3:**

Title: Pie chart for illustration of Sex distribution in patients with autoimmune COVID-19 sequelae

Abbreviations: COVID-19: Coronavirus disease 2019

**Figure 4:**

Title: Pie chart for illustration of age distribution in patients with autoimmune COVID-19 sequelae

Abbreviations: COVID-19: Coronavirus disease 2019, Y: years

**Figure 5:**

Title: Pie chart for illustration of Hospital admission during COVID-19 in patients who developed autoimmune COVID-19 sequelae

Abbreviations: COVID-19: Coronavirus disease 2019

**Figure 6:**

Title: Pie chart for illustration for Interval between COVID-19 and respective autoimmune COVID-19 sequelae

Abbreviations: COVID-19: Coronavirus disease 2019. D: days

**Figure 7:**

Title: Risk of bias assessment

No abbreviations

|  |  |  |  |
| --- | --- | --- | --- |
|  | Female | Male | P value |
| N (%) | 54 (50) | 55(50) | 0.92 |

Table 1: Sex distribution in patients with autoimmune COVID-19 sequelae

Abbreviations: N: Number

Table 2: Age Distribution in patients with autoimmune COVID-19 sequelae

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Infancy (0-2y) | Preschool Children (3-5y) | School Children (6-12y) | Adolescents (13-18y) | P Value |
| N (%) | 11 (10) | 15 (14) | 42 (38) | 41 (38) | <0.001 |

Abbreviations:

N: Number

Table 3: Hospital admission during COVID-19 in patients who developed autoimmune COVID-19 sequelae

|  |  |  |  |
| --- | --- | --- | --- |
|  | Hospital Admission  | No Hospital admission | P value |
| N (%) | 49 (45) | 60 (55) | 0.29 |

Abbreviations:

N: Number

Table 4: Interval between COVID-19 and respective autoimmune COVID-19 sequelae

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Immediate (0-14 days) | Classic (15-28 days) | Delayed (>28 days) | P value |
| N (%) | 67 (61) | 15 (14) | 27 (25) | <0.001 |

Abbreviations:

N: Number

**Table 5: Addison as post-acute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age | Sex | Interval between COVID-19 infection and disorder | Course of preceding COVID-19 infection | Outcome | Notes |
| (Flokas, Bustamante, and Kanakatti Shankar 2022) | 14  | Female  | 21 days  | Congestion and fatigue for three weeks. | * She was restarted on hydrocortisone 50 mg/m2/day and weaned down to a maintenance physiologic dose.
* Aldosterone was <1 ng/dL and plasma

renin was 0.43 ng/mL/h (normal range 0.25–5.82), and she started on fludrocortisone 0.05 mg daily. | * Due to persistent hemodynamic instability and

catecholamine dependence, despite improvement in her inflammatory markers, a random cortisol was drawn and was <1 μg/dL.* Hydrocortisone stress dose at 50 mg/m2/day was initiated, and this led to improvement in her clinical condition and was able to wean off vasopressor support.
* Baseline ACTH level was elevated to>1,250 pg/mL (normal range 9–57 pg/mL), and both baseline and stimulated cortisol were <1 μg/dL, confirming a diagnosis of primary adrenal insufficiency.
* 21-hydroxylase anti-adrenal antibodies were positive.
* A diagnosis of primary adrenal insufficiency and autoimmune hypothyroidism in addition to MIS-C was made.
 |

**Abbreviations:**

ACTH: Adrenocorticotropic hormone

MIS-C: Multisystem inflammatory syndrome in children.

**Reference: (in text 13)**

Flokas, Myrto Eleni, Victoria H. Bustamante, and Roopa Kanakatti Shankar. 2022. “New-Onset Primary Adrenal Insufficiency and Autoimmune Hypothyroidism in a Pediatric Patient Presenting with MIS-C.” *Hormone Research in Paediatrics* 95(4): 397–401. https://www.karger.com/Article/FullText/525227.

**Table 6: ANCA Vasculitis as post-acute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Age (years)** | **Sex** | **Interval between COVID-19 infection & autoimmune disorder** | **Course of preceding  COVID-19** | **Outcome** | **Notes** |
| (Reiff et al. 2021) | 17 | Male | 7 days | Presented with fever, drenching night sweats, cough, nasal congestion, hemoptysis and chest tightness. | Recovered | * Chest X-ray revealed a 5 cm left upper lobe mass and a 3 cm right paratracheal mass & CT showed multiple bilateral cavitary lung lesions, largest within the left upper lobe measuring 6.5 cm in diameter.
* Positive c-ANCA and PR3 antibodies.
 |
| (Bryant, Spencer, and Yalcindag 2022) | 16 | Female | 7 days  | Mild upper respiratory symptoms with anosmia | Recovered | * Presented with worsening persistent cough (at first non productive then productive with green sputum), wheezing, difficulty in breathing resistant to bronchodilators, myalgia.
* Had history of bronchial asthma.
* Chest X-ray revealed perihilar and bilateral upper lobe consolidations.
* CT revealed extensive multifocal pulmonary nodules and regions of consolidation with multiple areas of cavitation and central bronchiectasis with diffuse bronchial wall thickening as well as reactive mediastinal and hilar adenopathy.
* Positive C-ANCA,  PR3 & ANA antibodies.
 |
| (Fireizen et al. 2021) | 17 | Male | 60 days  | * Pneumonia and respiratory insufficiency, requiring high flow nasal cannula (HFNC) up to 30 LPM, FiO2 50%.
* Chest X‐ray showed moderate bilateral infiltrates
 | Recovered after treatment  and resolution of AKI and diffuse alveolar hemorrhage (DAH). | * Presented with elevated blood pressure, worsening knee & lower back pain as well as generalized body aches, hematuria, and proteinuria, and diagnosed with acute kidney injury (AKI) with a BUN/Cr of 16/1.30.
* One month later, presented again with worsening cough, fatigue, exertional dyspnea, and amber‐colored urine.
* He developed acute respiratory insufficiency requiring respiratory support with HFNC (40 LPM, FiO2 60%), AKI (BUN/Cr 30/1.52), and was revealed to have significant anemia (Hb/Hct 5.5/16.8).
* CT, FFB, Bal revealed diffuse alveolar hemorrhage.
* Positive ANA, P-ANCA, MPO antibodies.
* History of bronchial asthma
 |
| (Powell et al. 2021) | 12 | Female | 14 to 28 days  | Asymptomatic  | * patient was admitted ICU due to worsening respiratory status
* improved on methylprednisolone, rituximab,and cyclophosphamide
 | * PCR testing during hospitalization was negative.
* tested positive for COVID-19 IgG antibodies
* diagnosis of anti-MPO ANCA vasculitis with pulmonary and renal involvement
 |

**Abbreviations**

SARS-COV-2: Severe acute respiratory syndrome type 2,
ANCA antibodies: Anti-neutrophil cytoplasmic antibody,
C-ANCA antibodies: Cytoplasmic anti-neutrophil cytoplasmic antibody,
P-ANCA antibodies: Perinuclear anti-neutrophil cytoplasmic antibody,
PR3 antibodies: Anti-protease 3 antibodies,
ANA antibodies: Anti-nuclear antibodies,
MPO antibodies: Myeloperoxidase antibodies,
CT: computed tomography,
HFNC: High flow nasal cannula,
FiO2: Fraction of inspired oxygen,
AKI: Acute kidney injury,
BUN/Cr: Blood urea nitrogen/ Creatinine,
HB/Hct: Hemoglobin/Hematocrit,
FFB: Flexible fibro-optic bronchoscopy,
BAL: Bronchoalveolar lavage.

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Table 7: Central demyelinating disorders as postacute sequelae of COVID-19

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age (yrs) | Sex | Interval between infection and autoimmune disorder | Course of preceding COVID | Outcome | Notes |
| (Khair et al. 2022) | 8 | Male  | One month  | Mild respiratory symptoms | Complete recovery  | * Presented with Diplopia, imbalance, gait ataxia
* Diagnosed as Anti-MOG antibody demyelinating disorder
 |
| 13  | Female | 2 months | Fatigue and loss of sense of smell and taste | moderate improvement with residual diffuse weakness | * Presented with symptoms prior to covid infection with flare up after infection
* Presented by Headache, nausea, vomiting, dizziness, numbness, tingling, walking difficulty.
* Diagnosed as Relapsing neuromyelitis Optica spectrum disorder (NMOSD) ( tested positive for  anti-Aquaporin-4 antibodies )
 |
| 14 | Female  | 5 to 6 weeks | Asymptomatic  | Unreported  | * Presented with right leg weakness and left eye pain
* Diagnosed as new onset MS
 |
| (Das et al. 2022) | 16 | Female  | 4 months | Unreported  | Patient was placed on Rituximab. Follow up information unreported  | * Presented by sudden blindness in the right eye and radicular pain in both lower limbs
* Positive family history of autoimmune disease
* Diagnosed as newly onset NMOSD
 |
| (Sandoval et al. 2021) | 14 | Male |  | Positive PCR  | Complete strength recovery, persistent hyperreflexia in the left lower limb, right eye papilledema, and increased blind spot.  | * Presented by headache, blurry vision, papilledema, right VI cranial nerve palsy, asymmetric mild paraparesis. Bilateral ankle clonus, left Babinski sign
* Diagnosis of MS could not be confirmed despite Brain and spine MRI: multifocal demyelinating lesions with signs of activity
* Diagnosed as a Multifocal demyelinating event.
 |
| (Saini et al. 2022) | 14 | Female  | 8 weeks  | No respiratory involvement | No complications | * Presented with blurring of vision
* Diagnosed as newly onset MS
 |
| 4 | Male  | 8 weeks | No respiratory involvement | No complications | * Presented with Fever for 15 days and Irritability
* Diagnosed as newly onset ADEM
 |
| 3 | Male  | 6 weeks  | No respiratory involvement | No complications | * Diagnosed as newly onset LETM
 |
| (Carta et al. 2022) | 16 | Male  | At time of presentation  | Asymptomatic  | Full recovery  | * Presented with Complete bilateral horizontal gaze palsy
* MRI showed typical MS findings
 |
| (Akçay et al. 2021) | 9  | Male  | 3 days | Fever, headache, Vomiting | Discharged tracheotomized after 60 months o hospital stay with incomplete recovery  | * Presented with Status epilepticus
* Needed PICU admission
* Diagnosed as newly onset ADEM
 |
| 9  | female | 5 days | Fever, vomiting diarrhea | Complete recovery  | * Presented with afebrile seizures
* Needed PICU admission
* Diagnosed as newly onset ADEM
 |
| (Poyrazoğlu et al. 2022) | 10  | Male  | During disease course  | fever, headache and myalgia | Incomplete recovery  | * Presented with inability to walk
* Diagnosed as Transverse myelitis and and ADEM by MRI
 |
| (Cay-Martínez et al. 2021) | 7 | Female  | 1 week  | Asymptomatic  | Incomplete recovery with resolution of sensory deficits but little improvement in lower limb strength | * Presented with acute lower extremity flaccid paralysis and numbness
* Diagnosed as newly onset ADEM
 |
| (de Miranda Henriques-Souza et al. 2021) | 12 | Female  | 5 days | skin rash, headache, and fever. | Incomplete recovery  | * Presented with acute, progressive, bilateral, and symmetrical motor weakness
* Diagnosed as a newly onset ADEM.
 |
| (Manzo et al. 2021) | 6 | Male | 10 days  | Asymptomatic  | Full recovery  | * Presented with generalized tonic-clonic seizure with spontaneous resolution
* History of Fisher-Evans syndrome
* Diagnosed as ADEM
 |
| (Urso et al. 2022) | 5 | Female | 2 days | Mild; cough and fever.  | Patient received IVIG, showed clinical improvement and was discharged after two weeks of hospitalization. | * Patient presented with a painful swelling in the latero-cervical aspect of her neck with a large erythematous patch of the overlying skin.
* The condition was followed in the following days by altered mental status, increased irritability, sleepiness, lack of energy, and lethargy
* Diagnosed as encephalitis
 |
| (Sánchez-Morales et al. 2021) | 15 | Female | During the course of the disease  | Fever,headache, vomiting | Needed hospitalization Visual acuity fully recovered after treatment  | * Patient presented with diplopia, bilateral ocular pain, and diminished visual acuity, left VI cranial nerve paresis.
* MRI revealed optic nerve hyperintensities
* Diagnosed as Bilateral optic neuritis, left VI cranial nerve paresis
 |
| 14 | Female | During the course of the disease  | Headache, myalgia, arthralgia | Needed hospitalization Visual acuity fully recovered after treatment  | * Presented with headache, left ocular pain, diminished visual acuity of left eye.
* MRI: left optic nerve hyperintensity
* Diagnosed as left optic neuritis
 |
| 14 | Male  | During the course of the disease  | Asymptomatic | Rankin Score: 0Absolute control of epilepsyPresence of psychiatric symptoms post discharge | * Presented with altered behavior and mental status, seizures, insomnia, orolingual dyskinesias
* Positive anti-NMDA-R antibodies in CSF
* Diagnosed as Anti NMDA encephalitis
 |

**Abbreviations:**

* Anti-MOG: Anti- myelin oligodendrocyte glycoprotein
* MS: Multiple Sclerosis
* LETM: Longitudinal extensive transverse myelitis
* NMSOD: NeuroMyelitis Optica Spectrum Disorder
* ADEM: Acute Disseminated Encephalomyelitis
* PICU: Pediatric Intensive Care Unit
* IVIG: Intravenous immune globulin
* MRI: Magnetic resonance imaging
* Anti-NMDA-R: **Anti**-N-methyl-d-aspartate (**NMDA**) **receptor** encephalitis
* CSF: Cerebro-spinal fluid

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**Table 8: GBS as post-acute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age (years) | Sex | Interval between COVID-19 infection and Autoimmune Disorder | Course of COVID-19 infection | Outcome | Notes |
| (El Mezzeoui et al. 2021) | 3 | Female | 2 weeks | Not specified | Patient was treated by 5 cycles of IVIG 0.5 ml/kg/day then discharged after spending 1 month in the paediatric unit. | She presented with progressive and ascending Paraesthesia evolvingtwo weeks after respiratory infection. |
| (Héber Samuel Colares Costa et al. 2022) | 3 | Female | 1 week | Mild (Flu-like) | Patient improved after the second dose of IVIG. | Patient presented with lameness, ataxia, bilateral facial paralysis, ophthalmoplegia, and diplopia. |
| (Curtis et al. 2021) | 8 | Male  | During the course of COVID-19 infection.  | Asymptomatic.  | PICU admission, mechanical ventilation for 5 days. Patient improved after IVIG.* After 6 weeks, regained bilateral dorsiflexion and plantarflexion, the ability to sit independently and was working on ambulation.
 | Patient presented with bilateral lower extremity weakness that progressed to paralysis and the inability to walk which progressed to upper limbs and dyspnea later.  |
| (Mehra et al. 2020) | 13 | Female | 1 month | Fever | PICU admission and two weeks of ventilation.  complete neurological recovery and discharge after 6 weeks of hospitalisation, IVIG and plasmapheresis.  | Patient presented with high grade fever, cough , vomiting, progressive body rash complicating with shock.  After 7 days, no response to painful stimuli or spontaneous eye opening, quadriparetic with facial weakness, weak diaphragmatic excursion and seizures.  |
| (Khera et al. 2021) | 11 | Female | Not specified  | Fever | PICU admission and mechanical ventilation.  After 6 weeks of hospitalisation ( IVIG, plasmapheresis), the patient walks independently and has good bowel and urinary control.  | Patients presented with acute onset of flaccid paralysis and respiratory failure, bowel and bladder incontinence and lack of sensation.  |
| (Das et al. 2021) | 7 | Male | Not specified. | Asymptomatic  | PICU admission and mechanical ventilation. Extubated after 3 days.Clinical improvement.  | Patient presented with bilateral, symmetrical, lower-limb weakness and paresthesia for 8 d, with no antecedent viral illness.  He had areflexia, poor gag reflex, and a single breath count of 8, requiring mechanical ventilation. |
| (Frank et al. 2021) | 15  | Male | During the course of COVID-19 infection. | Mild (no respiratory symptoms) | Patient received IVIG , however, improvement was mild and he was on physiotherapy.  | Patient presented with presenting frontal headaches with retro-orbital painaccompanied by fever evolving to weakness and pain of the lower limbs, which ascended to upperlimbs. |
| (Paybast, Gorji, and Mavandadi 2020) | 14 | Female  | 3 weeks | Upper respiratory tract infection 3 weeks earlier. | Complete recovery after IVIG except for general hyporeflexia and decreased light touch sensation in the distal limbs.  | Patient presented with bilateral progressive limb weakness and quadri paresthesia, headaches, dizziness, absent deep tendon reflexes.  His father had the same symptoms.  |
| (Al Haboob 2021) | 11 | Male | 3 weeks | Vomiting, diarrhoea, abdominal pain and headache for 3 weeks.  | PICU admission and intubation.  Discharged after IVIG administration with normal conscious level, normal muscle tone, cranial nerve palsy, normal muscle tone , grade 4 muscle power, normal gag and cough reflexes. | Patient was lethargic, tachypnic, fatigued, no fever, bilateral sixth nerve palsy and double vision of lateral gaze.  The diagnosis of Miller Fischer syndrome (MFS) with posterior reversible encephalopathy syndrome in association with COVID-19 infection was made. |
| (Sánchez-Morales et al. 2021)   | 9 | Male | Not specified. | Asymptomatic  | Patient recovered the ability to walk and run independently.  | Patient presented with pain in lower limbs, ascending weakness, hypotonia, diminished muscle strength in lower limbs. |
| 14 | Male | Not specified. | Fever and rhinorrhea.  | Patient recovered the ability to walk and run independently. | Paresthesia in feet, ascending weakness, hypotonia, diminished tendon reflexes in the lower limbs. |
| 12 | Female | Not specified  | Not specified | Patient recovered the ability to walk and run independently. | Dysphonia, hypotonia, ascending weakness, diminished tendon reflexes in upper limbs and absent reflexes in lower limbs. |
| (Krueger et al. 2021)    | 16 | Female | During the course of COVID-19 infection. | Mild | Patient received acyclovir, IVIG and methylprednisolone. After 15 days of hospitalisation, the patient was discharged after clinical improvement.  | Patient presented with diarrhoea and 5 days later withParaesthesia and progressive difficulty to walk. |
| 15  | Male | 15 days | Mild (no respiratory involvement) | Patient received IVIG after which there was significant clinical improvement.  | Patient presented with pain, paraesthesia, and weakness in the lower limbs followed by the upper limb’s involvement, without respiratory impairment. |
| 5  | Female | During the course of the disease. | Mild (No respiratory involvement) | Symptoms decreased after CSF withdrawal and Acetazolamide.  | Patient presented with intense headache, fever, vomiting, and horizontal diplopia.High CSF pressure (70 cmH2O) and normal analysis.  |
| 0.2 | Male | 15 days | Dry cough, fever, and diarrhoea.15 days later, symptoms developed into dyspnoea and hypoxemia requiring mechanical ventilation. | He was treated with intravenous phenobarbital with an improvement of the epileptic events and was discharged after 25 days of hospitalisation · without any apparent neurologic deficits. | Three days after being mechanically ventilated, patient presented with the deviation of the eyes and automaticmasticatory movements. |
| (Krishnakumar et al. 2021) | Adolescent (age is not specified) | Male | 2 weeks | Mild; Fever. | Not specified. | Patient presented with progressive proximal weakness of the bilateral lower limbs without bladder or bowel involvement. |
| (Michael, Madaan, and Shekhar 2021) | 4 | Female | 2 weeks | Mild; Fever. | · Muscle weakness involved respiratory muscles requiring mechanical ventilation.· Patient received IVIG, showed clinical improvement and was discharged at day 10 of hospitalisation. | Patient presented with a two-day history of pain in the neck, neck floppiness, change in voice, drooling, and bilateral arm weakness. |
| (Mussinatto et al. 2022) | 9 | Female | Not specified | Not specified | · She received IVIG with mild improvement and was discharged after 15 days of hospitalisation.· She’s on strict neurological follow and physiotherapy.  | Patient presented with progressive weakness and gait instability over the last month. |
| (Terencio, Patiño, and Jamora 2021) | 16 | Female | During the course of COVID-19 infection. | Asymptomatic | Patient received IVIG 1gm/kg/day and showed significant improvement. She was discharged after 5 days with a steppage gait but able to walk independently. | · She presented a seven-day history of progressive symmetric ascending quadriparesis and paraesthesia.· The patient developed urinary incontinence and constipation on the 9th day of illness.  |
| (Kanou et al. 2022) | 9 | Male | During the course of COVID-19 infection. | Asymptomatic | · Patient received analgesics only for his back pain, however, he didn’t receive IVIG.· Patient showed gradual but promising improvement after a few months of conservative treatment.  | Presented with unbalanced gait, backpain and lower limb we0000akness. |
| (Akçay et al. 2021) | 6 | Male | 1 week | Two days of fever followed by severe respiratory muscle weakness requiring mechanical ventilation. | Patient received plasma exchange sessions with 5% albumin, Methylprednisolone, IVIG.He was discharged at day 60 of hospitalisation with absent reflexes, weakness in upper and lower limbs and on home ventilation. | She presented with symmetric ascending paralysis. |
| (Manji et al. 2020) | 12 | Male | 1 week | Mild and treated symptomatically at home. | Patient was admitted to PICU, however, he extubated accidentally on day five in PICU and died despite resuscitation attempts. | Patient presented with acute progressive symmetric ascending quadriparesiswith bilateral facial paresis. |
| (Khalifa et al. 2020) | 11 | Male | 20 days | · An acute upper respiratory tract infection with low-grade fever treated at home with acetaminophen and azithromycin.· Chest CT showed patchysubsegmental faint opacifications with an atelectasis in the lingula | Patient received IVIG and clinically improved. | Patient presented with acute onset of un-steady gait and the inability to walk or climb stairs associated with tingling sensation felt in both the legs and feet of 1-day duration. |
| (Qamar et al. 2022) | 6 | Female | 1 month | Asymptomatic | Patient received IVIG over the course of two days and was discharged after clinical improvement. | Patient presented with acute, progressive weakness of lower limbs with no history of recent infection. |
| (Araújo et al. 2021) | 17 | Female | 8 days | Fever, nausea, severe vomiting and diarrhoea.  | Clinical improvement after IVIG administration.  | Patient presented with severe low back pain that had anteriorized to the groin area, followed by weakness of extremities with loss of ambulation. Acute flacci tetraparesis worse in the lower limbs with areflexia in patella and tendon achilles, hyporeflexia in upper limbs.  |
| (Sandoval et al. 2021) | 8 | Male  | During the course of Covid | Asymptomatic | Discharged after 18 d; moderate improvement in facial diparesis, ophthalmoparesis, and strength; walking with aids | * On admission the patient presented with ophthalmoparesis, facial diparesis, acute progressive ascending flaccid tetraparesis, areflexia, headache.
* EMG/NCS: moderate acute motor axonal neuropathy (AMAN) with incipient signs of reinnervation
* Guillain-Barr´e syndrome AMAN variant with multiple cranial nerve impairment
 |

**Abbreviations:**

GBS: Guillain-Barré Syndrome

PICU: Paediatric Intensive Care Unit

IVIG: Intravenous immune globulin

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Table 9: Hepatitis as post-acute sequelae of COVID-19

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age (yrs) | Sex | Interval between COVID-19 infection & autoimmune disorder | Course | Outcome | Notes |
| (Osborn, Szabo, and Peters 2022) | 3 | Female | 21 days | * She had a mild fever and cough.
* She received no medications, did not require hospitalization, and symptoms resolved in 5 days.
 | Recovered and discharged after 18 days of hospitalization on Azathioprine as steroid-sparing maintenance therapy. | * Presented to the ER with jaundice, fatigue, and oliguria.
* She showed worsening coagulopathy (INR 2.7), cholestasis (conjugated bilirubin of 3.8mg/dL), and hyperammonemia to 317 µmol/L along with altered mental status consistent with hepatic encephalopathy grade I–II.
* A liver biopsy showed acute submassive hepatic necrosis, lobular collapse, and an intense mixed inflammatory infiltrate, consisting primarily of CD3+ T lymphocytes.
* Elevated anti liver-kidney-microsomal antibody

(anti-LKM) titer of 1:1280, suggestive of type II autoimmune hepatitis. |
| (Antala et al. 2022) | 0.5 | Female | During the course of COVID-19 infection.  | * Presented to ER with new onset irritability, poor feeding, recurrent emesis and progressive lethargy over a span of 24 hours.
* GCS of 8, unresponsive & shallow breathing.
 | * Hospitalized for 13 days, admitted to PICU for 5 days where she became more responsive.
* Recovered and discharged eventually.
 | * Presented to ER with shallow breathing, GCS of 8, hypothermia (95.58C), epistaxis and decreased pupillary light response.
* Coagulopathy resistant for vitamin K suggesting acute liver failure.
 |
| 0.33 | Male  | During the course of COVID-19 infection.  | Presented to ER with feeding difficulties, vomiting, hypotonia, diaphoresis, and progressive lethargy over 12 hours. | * Hospitalized for 15 days, admitted to PICU for 10 days where he was intubated, resuscitated with isotonic saline and dextrose, and started on epinephrine infusion.
* Recovered and discharged eventually.
 | * He was febrile (38.78C), tachycardic, tachypneic, hypotensive, and unresponsive.
* Worsening coagulopathy resistant to vitamin K suggesting acute liver failure.
* Associated kidney injury (Creatinine= 0.7, n=0.1-0.4) and seizure activity on video EEG.
 |
| 16 | Female | 3 days | Presented with cough, congestion, and fever. | * Hospitalized for 2 days, admitted to the ICU for 3 days where she received 80 mg IV methylprednisolone for empiric treatment of COVID-19.
* Recovered and discharged eventually.
 | * Presented to the ER with emesis and abdominal pain.
* Stage 1 encephalopathy which is resolved by time of discharge.
 |
| 11 | Male | 2 days | Afebrile without other symptoms. | * Admitted to ICU for 1 day where he received intravenous fluids for dehydration.
* Recovered and discharged eventually.
 | Presented with non-bloody, non-bilious emesis and abdominal pain. |

**Abbreviations:**

Yrs: Years
ER: Emergency room,
INR: International normalized ratio,
GCS: Glasgow coma scale,
PICU: Pediatric intensive care unit,
EEG: Electroencephalography,
ICU: Intensive care unit,
IV: Intravenous ,
CD3: Cluster of differentiation 3

**References: (in text 50, 51)**

Antala, Swati et al. 2022. “Severe Hepatitis in Pediatric Coronavirus Disease 2019.” *Journal of pediatric gastroenterology and nutrition* 74(5): 631–35.

Osborn, Julie, Sara Szabo, and Anna L. Peters. 2022. “Pediatric Acute Liver Failure Due to Type 2 Autoimmune Hepatitis Associated With SARS-CoV-2 Infection: A Case Report.” *JPGN Reports* 3(2): e204.

**Table 10: HLH as postacute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age  | Sex | Interval between infection and autoimmune disorder | Course of preceding COVID | Outcome | Notes |
| (Greenmyer et al. 2022) | 5 years | Female | 4.5 weeks  | Presented with fever and papular rash for three days  | 8th month in remission  | Condition caused:* Steroid induced myopathy, hyperglycemia, thrush, Cushingoid features
* Hematopoietic cell transplant causing engraftment syndrome,
* respiratory failure;
* secondary adrenal insufficiency;
* veno-occlusive disease
* transplant-associated thrombotic microangiopathy

Patient needed ICU admission |
| (Rjoop, Barukba, and Rusan 2021) | 7 years | Male | 2 weeks | Mild attack | Recovery after 3 days of steroid therapy |  |
| (Kalita et al. 2021) | 2 years | Male | 2 weeks | Disease course showed feeding intolerance, fever (39.6̊C), diarrhoea, and vomiting for two days | Monitored in PICU at time of publishing | Associated with post-covid viral encephalitis with cerebral atrophy |
| (Lange et al. 2021) | 6 weeks | female | During the course | fever of up to 40°C and poor feeding | Recovery | Patient has been diagnosed with Chédiak‐Higashi syndrome.Needed hematopoietic stem cell transplantation |

**Abbreviations:**

Yrs: Years

HUS: Hemolytic Uremic Syndrome

HLH: Hemophagocytic lymphohistiocytosis

TRAP: TNF receptor-associated periodic syndrome

**References: (in text 52-55)**

Greenmyer, Jacob R. et al. 2022. “COVID‐19‐associated Secondary Hemophagocytic Lymphohistiocytosis Requiring Hematopoietic Cell Transplant.” *eJHaem* 3(3): 1025–28. https://onlinelibrary.wiley.com/doi/10.1002/jha2.456.

Kalita, Pranjal et al. 2021. “Secondary Hemophagocytic Lymphohistiocytosis in Post-COVID-19 Patients: A Report of Two Cases.” *Cureus*. https://www.cureus.com/articles/67827-secondary-hemophagocytic-lymphohistiocytosis-in-post-covid-19-patients-a-report-of-two-cases.

Lange, Matthias et al. 2021. “Primary Haemophagocytic Lymphohistiocytosis (Chédiak‐Higashi Syndrome) Triggered by Acute SARS‐CoV‐2 Infection in a Six‐week‐old Infant.” *British Journal of Haematology* 195(2): 198–200. https://onlinelibrary.wiley.com/doi/10.1111/bjh.17669.

Rjoop, A., M. Barukba, and O. Al Rusan. 2021. “A Rare Case of Post COVID-19 Hemophagocytic Lymphohistiocytosis in a Pediatric Patient.” *AJCP*.

**Table 11: HUS as postacute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age | Sex | Interval between infection and HUS | Course of preceding COVID | Outcome | Notes |
| (Van Quekelberghe et al. 2022) | 4 months  | Male  | 4 weeks | Fever and mild respiratory symptoms. | * Admitted to PICU on day 8 of hospitalisation.
* Received Ecolizumab , antibiotic (pipercillin- Tazobactam) & peritoneal dialysis
* Received lisinopril, amlodipine, and clonidine due to severe hypertension.
* Five months after discharge, the patient still suffered from hypertension and persistent proteinuria.
 | * Patient had a history of prematurity (26 weeks of gestation) and known neurological abnormalities since birth (microcephaly, joint contractures, axial hypotonia)
 |
| 4.5 months | Male  | During the course of COVID-19 infection.  | Presented with pyrexia, diarrhoea, and reduced drinking | * Treated empirically with eculizumab, triple therapy for hypertension and peritoneal dialysis for acute kidney injury and anuria.
* 5 months after discharge, the patient still had hypertension and mild persistent proteinuria.
 |  |
| (Alizadeh et al. 2021) | 16 months | Male  | During the course of COVID-19 infection.  | Fever, emesis and respiratory distress.  | * Patient was discharged after being treated with Eculizumab and advised to receive it every 3 weeks for aHUS.
 | * Patient presented with fever, emesis, and respiratory distress.
* Diagnosed as DKA on top of diabetes milletus type 1 and atypical haemolytic uremic syndrome.
* Admitted to PICU for DKA management.
* Patient had a history of prematurity at 34 weeks’ gestation, intrauterine growth restriction, severe failure to thrive, microcephaly, pachygyria, agenesis of the corpus callosum, postnatal embolic stroke with residual cranial nerve IV palsy, retinopathy of prematurity, and multiple dysmorphisms without a unifying genetic disorder
 |
| (Azukaitis et al. 2022) | 3 years  | Male  | During the course of COVID-19 infection.  | Patient presented with fever, coryza, cough, decreased urine output lasting for 3 days, and a history of non-bloody diarrhoea 1 week prior to admission. | * Peritoneal dialysis was performed due to anuria and acute kidney injury.
* Patient was discharged on day 22 of hospitalisation after proper treatment with mild anaemia, and normal platelet count, persistent proteinuria and haematuria.
 |  |
| (Khandelwal et al. 2022)3 patients excluded as they are flare-up of pre-existing conditions |  10 years |  Female | 10 | Fever without respiratory manifestations | * Persistent CKD
 |  |
| 4 years |  Male | 21 | * Fully recovered no residual CKD
 |  |
| (Richardson, Su, and Iragorri 2022) | 6 years | Male | During the course of the disease |  | * Both patients developed CKD
 |  |
| 10 years | Male | During the course of the disease | Bloody diarrhoeaOliguria Thrombocytopenia |  |

**Abbreviations:**

Yrs: Years

HUS: Hemolytic Uremic Syndrome

**References: (in text 56-60)**

Alizadeh, Faraz et al. 2021. “Toddler With New Onset Diabetes and Atypical Hemolytic-Uremic Syndrome in the Setting of COVID-19.” *Pediatrics* 147(2). https://publications.aap.org/pediatrics/article/147/2/e2020016774/36266/Toddler-With-New-Onset-Diabetes-and-Atypical.

Azukaitis, Karolis et al. 2022. “Possible Microangiopathic Overlap between COVID‐19 and Shiga Toxin‐associated Hemolytic Uremic Syndrome.” *Pediatric Blood & Cancer* 69(12). https://onlinelibrary.wiley.com/doi/10.1002/pbc.29798.

Khandelwal, Priyanka et al. 2022. “Anti-Factor H Antibody Associated Hemolytic Uremic Syndrome Following SARS-CoV-2 Infection.” *Pediatric Nephrology* 37(9): 2151–56. https://link.springer.com/10.1007/s00467-021-05390-4.

Van Quekelberghe, Chantal et al. 2022. “Atypical Hemolytic Uremic Syndrome Induced by SARS-CoV2 Infection in Infants with EXOSC3 Mutation.” *Pediatric Nephrology* 37(11): 2781–84. https://link.springer.com/10.1007/s00467-022-05566-6.

Richardson, Gina M., Sharon W. Su, and Sandra Iragorri. 2022. “Case Report: Diarrhea-Associated Hemolytic Uremic Syndrome in the Era of COVID-19.” *Frontiers in Pediatrics* 10. https://www.frontiersin.org/articles/10.3389/fped.2022.979850/full.

**Table 12: ITP as postacute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age (yrs) | Sex | Interval between infection and autoimmune disorder | Hospital admission during the course of Covid | Outcome | Notes |
| (Ringoringo and Hartoyo 2021) | 0.75  | Male | During the course of COVID-19 infection. | Yes | Recovery after Megadose methylprednisolone. |  |
| (Marinescu et al. 2022) | 8  | Female | During the course of COVID-19 infection.  | Yes | Recovery after IV methylprednisolone, platelet concentrate and 2 doses of IVIG.  | Presented to the emergency department with generalised petechiae and ecchymoses & fever. |
| (Dongre et al. 2021) | 5.5  | Female | 22 days | Yes | Hospitalised for 4 weeks.Recovery after prednisolone (tapering dose) and eltrombopag. | Presented with reddish-purple spots on neck, shoulder, arms and legs.History of concomitant ALL |
| (Ceglie et al. 2022) | 11  | Male | 4 weeks | Yes | Recovery after 2 doses of IVIG. | Presented with diffuse petechiae and ecchymoses. |
| (Behlivani et al. 2021) | 15 | Male | 5 weeks |  No  | Recovered after IVIG | Presented with epistaxis, petechiae, bruises for 7 days. |
| 3  | Female | 3 weeks | No  | Recovered after IVIG | Presented with low-grade fever for 24 h, epistaxis, and melaena (due to nasal bleeding) |
| (Rosenzweig, McThenia, and Kaicker 2020)(One patient excluded only AIHA) | 16  | Male | 3-4 weeks | No | Recovery after corticosteroid therapy.  | Presented with rash and mouth sores. |
| (Vadakkekara, Mathew, and Khera 2022) | 1.5 | Female | 5 weeks | No | Recovery after a single dose of IVIG. | Presented with fever and ecchymoses over limbs for two weeks. |
| (Tsao, Chason, and Fearon 2020) | 10 | Female | 3 weeks | No | Clinical improvement after acetaminophen, diphenhydramine and IVIG. | Presented with generalised petechiae & bruises.  |
| (Patel et al. 2020) | 12  | Female | During the course of COVID-19 infection. | Yes | Recovery after IVIG and corticosteroids/ ARDS improved with tocilizumab and remdesivir. | Presented with 5 days of fever, non-productive cough, 2 days of non-bloody emesis, worsening shortness of breath, and haematuria. |

**Abbreviations:**

Yrs: years

ITP: Immune thrombocytopenic purpura

COVID: coronavirus disease

COVID 19: coronavirus disease of 2019

IV: intravenous

IVIG: intravenous immunoglobulin

ALL: acute lymphocytic leukaemia

AIHA: acute haemolytic anaemia

ARDS: acute respiratory distress syndrome

ICU: intensive care unit

**References: (in text 61-69)**

Behlivani, Evangelia, Athanasios Tragiannidis, Emmanuel Hatzipantelis, and Paraskevi Panagopoulou. 2021. “Immune Thrombocytopenia Secondary to COVID‐19 Infection: Report of Two Cases.” *Pediatric Blood & Cancer* 68(10). https://onlinelibrary.wiley.com/doi/10.1002/pbc.29175.

Ceglie, Giulia et al. 2022. “Immune Thrombocytopenia in a Child with COVID‐19: Is It the Calm after the (Cytokine) Storm?” *Pediatric Blood & Cancer* 69(1). https://onlinelibrary.wiley.com/doi/10.1002/pbc.29326.

Dongre, Amol, Patel Zeeshan Jameel, Mahesh Deshmukh, and Shweta Bhandarkar. 2021. “Immune Thrombocytopenic Purpura Secondary to SARS-CoV-2 Infection in a Child with Acute Lymphoblastic Leukaemia: A Case Report and Review of Literature.” *BMJ Case Reports* 14(11): 1–5.

Marinescu, Adelina Raluca et al. 2022. “Severe Thrombocytopenic Purpura Associated with COVID-19 in a Pediatric Patient.” *Infection and Drug Resistance* 15(June): 3405–15.

Patel, Pratik A. et al. 2020. “Severe Pediatric COVID-19 Presenting With Respiratory Failure and Severe Thrombocytopenia.” *Pediatrics* 146(1). https://publications.aap.org/pediatrics/article/146/1/e20201437/37032/Severe-Pediatric-COVID-19-Presenting-With.

Ringoringo, Harapan Parlindungan, and Edi Hartoyo. 2021. “Megadose Methylprednisolone for Immune Thrombocytopenia in an Infant Positive for SARS-CoV-2: A Case Report.” *American Journal of Case Reports* 22. https://www.amjcaserep.com/abstract/index/idArt/931517.

Rosenzweig, Jaclyn D., Sheila S. McThenia, and Shipra Kaicker. 2020. “SARS‐CoV‐2 Infection in Two Pediatric Patients with Immune Cytopenias: A Single Institution Experience during the Pandemic.” *Pediatric Blood & Cancer* 67(9). https://onlinelibrary.wiley.com/doi/10.1002/pbc.28503.

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Vadakkekara, Jayakrishnan, Rini Mathew, and Sanjeev Khera. 2022. “COVID-19–Associated Immune Thrombocytopenia in a Toddler.” *Indian Journal of Pediatrics* 89(6): 623. https://doi.org/10.1007/s12098-022-04109-z.

**Table 13: Psoriasis as postacute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Age** | **Sex** | **Interval between infection and autoimmune disorder** | **Hospital admission during the course of Covid** | **Outcome** | **Notes** |
|  (Zitouni et al. 2022) | 2.5 yrs | Male  | Mean interval of 28 days  | Only one of the 9 patients needed hospital admission  | Unreported  | 6 patients had positive Family history of psoriasisDifferent type of psoriasis:3 patients had Guttate Psoriasis2 patients had Palmoplantar 2 patients had Plaque 1 had Scalp Psoriasis |
| 15 yrs | Male |
| 9 yrs | Male |
| 9yrs | Female |
| 7yrs  | Male |
| 16yrs | Female |
| 8yrs | Male |
| 10yrs | Male |
| 16yrs  | Female  |
| (Qureshi and Bansal 2021) | 13yrs | Male | 8 weeks  | No | Full recovery after receiving topical steroids  | Presented with groin rash refractory to different antifungal treatments Diagnosed as Psoriasis vulgaris  |

 **Abbreviations:**

Yrs: years

**References: (in text 70,71)**

Qureshi, Nadia K., and Sanjay K. Bansal. 2021. “Autoimmune Thyroid Disease and Psoriasis Vulgaris after COVID-19 in a Male Teenager” ed. Ozgur Kasapcopur. *Case Reports in Pediatrics* 2021: 1–3. https://www.hindawi.com/journals/cripe/2021/7584729/.

Zitouni, J. et al. 2022. “Children with Psoriasis and COVID‐19: Factors Associated with an Unfavourable COVID‐19 Course, and the Impact of Infection on Disease Progression (Chi‐PsoCov Registry).” *Journal of the European Academy of Dermatology and Venereology* 36(11): 2076–86. https://onlinelibrary.wiley.com/doi/10.1111/jdv.18361.

**Table 14:** Autoimmune sclerosing cholangitis as post-acute sequelae of COVID-19

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age | Sex | Interval between infection and autoimmune disorder | Hospital admission during the course of Covid | Outcome | Notes |
| (Zdanowicz et al. 2022) | 14yrs | Male | 8 weeks  | Yes  | Treatment was given for 2 months, it included UDCA and prednisone at first, then prednisone was tapered and azathioprine introduced.Patient was asymptomatic (with significant decrease in ALT, GGT) following  treatment. | Patient admitted for investigation of raised ALT and  AST 2 months after setting of COVID-19 infection.The needle liver biopsy showed a morphological picture of autoimmune liver disease with advanced fibrosis (Batts and Ludwig score 3) corresponding to the AIH/PSC overlap syndrome. |

**Abbreviations:**

ALT: Alanine Aminotransferase

AST:Aspartate Aminotransferase

GGT: Gamma -glutamyl transferase

UDCA: Ursodeoxycholic acid

AIH/PSC: Autoimmune hepatitis / Primary Sclerosing Cholangitis

**References: (in text 72)**

Zdanowicz, Katarzyna et al. 2022. “Autoimmune Sclerosing Cholangitis Might Be Triggered by SARS-CoV-2 Infection in a Child – a Case Report.” *Central European Journal of Immunology* 47(2): 183–87.

**Table 15: SLE as postacute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age  | Sex | Interval between infection and autoimmune disorder  | Hospital admission during the course of Covid | Outcome  | Notes |
| (Asseri et al. 2022) | 13yrs | Female | 2 months | Yes  | Improvement only after receiving 6 sessions of plasma exchange | Presented with diffuse alveolar haemorrhage and proteinuria  |
| (Mantovani Cardoso et al. 2020) | 18yrs  | Female | During Covid | Yes | Death | Presented with cardiac tamponade and renal affection the hypercoagulable state with DVT  |

**Abbreviations:**

yrs: years

 DVT: Deep Venous Thrombosis

**References: (in text 73,74)**

Asseri, Ali Alsuheel et al. 2022. “A Case Report of Pediatric Systemic Lupus Erythematosus with Diffuse Alveolar Hemorrhage Following COVID-19 Infection: Causation, Association, or Chance?” *Medicine* 101(33): e30071. https://journals.lww.com/10.1097/MD.0000000000030071.

Mantovani Cardoso, Eduardo, Jasmin Hundal, Dominique Feterman, and John Magaldi. 2020. “Concomitant New Diagnosis of Systemic Lupus Erythematosus and COVID-19 with Possible Antiphospholipid Syndrome. Just a Coincidence? A Case Report and Review of Intertwining Pathophysiology.” *Clinical Rheumatology* 39(9): 2811–15. https://link.springer.com/10.1007/s10067-020-05310-1.

**Table 16: Thyroid as postacute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age | Sex | Interval between COVID-19 infection and disorder | Course of preceding COVID-19 infection | Outcome | Notes |
| (Qureshi and Bansal 2021) | 13  | Male | 56 days | Mild course with low-grade fever, congestion, cough, and body aches that resolved in a few days. | * He started on methimazole 10 mg once daily and propranolol 10 mg twice a day for symptomatic relief.
* He showed clinical and biochemical improvement after treatment.
* He was determined to have psoriasis vulgaris and was treated with topical steroids resulting in complete resolution.
 | * Presented with dizziness, easy fatigability , difficulty sleeping, and a presyncopal episode, heat intolerance, weight loss (8 lbs during 2 months) despite increased appetite.
* Physical examination showed tachycardia at 102 beats per minute with mild exophthalmos and palpable thyroid. He had an erythematous lesion in intertriginous left groin.
* Elevated free T4 at 2.5 ng/dL (normal range: 0.7–1.5 NG/DL), undetectable TSH at <0.01 uIU/mL (normal range 0.50–4.80 uIU/mL).
* Elevated anti-thyroid peroxidase (TPO) antibodies at 946.2 IU/ml (normal <9.0 IU/ML) and elevated thyroid-stimulating immunoglobulins (TSIs) at 28.2 IU/L (normal<0.10 IU/L).
* With the presence of antibodies for both Graves and Hashimoto’s (with TSI predominance), he was diagnosed with hyperthyroidism from autoimmune thyroid disease.
 |
| (Rockett et al. 2021) | 16 | Male | 56 days | Presented with a diminished sense of smell, cough, chills, nausea, and fatigue. | Patients improved after methimazole and propranolol.  | * Presented to the emergency room with shortness of breath, chest pain, and worsening anxiety 19 days after onset of symptoms.
* His thyroid was enlarged and he had tremors in both hands.
* Laboratory analysis revealed a thyroid stimulating hormone (TSH) level of <0.005 mcunit/ml (normal=0.27- 4.20) and free thyroxine level of >7.77 ng/dl (normal=0.93-1.70) which was consistent with hyperthyroidism.
* Thyroid ultrasound demonstrated diffuse enlargement with heterogeneous echogenicity of bilateral thyroid lobes and isthmus with multiple small hypoechoic nodules.
* A diagnosis of thyrotoxicosis secondary to Graves’ disease was made.
 |
| (Das et al. 2022) | 16 | Female | 3 days | * She was afebrile, tachycardic and hypertensive.
* Chest X-ray showed cardiomegaly with pulmonary oedema.
 | * She received methimazole 20 mg a day in addition to oral heart failure drugs like Lasix, Lisinopril and Aldactone.
* Patient improved clinically but presented 3 months later with showed severely decreased left ventricular systolic function (ejection fraction 25%), severe dilation with the left-ventricular end-diastolic volume of 167 ml/m2, and mildly depressed right ventricular systolic function (ejection fraction 47%).
 | * Presented to the emergency room with difficulty of breathing, tachycardia, hypertension, exophthalmos, thyromegaly and a gallop on physical exam.
* room. Her echocardiogram showed severely decreased left ventricular systolic function (ejection fraction 14%), moderate to severe left ventricular dilation, mildly decreased right ventricular systolic function without any evidence of coronary artery dilation or pericardial effusion.
* Her thyroid-stimulating hormone level was extremely low (0.01 mICU/mL) with markedly elevated triiodothyronine (1070 pg/dL) and free thyroxine levels (3760 ng/dL).
* Diagnosed with decompensated heart failure and thyroid storm on top of Grave’s disease.
 |
| (Victoria Brocksmith Nicksic, Shardha Srinivasan, Elizabath Mann, and Rehm 2021) | 16 | Male | During the course of the disease.  | * Diaphoresis, and shortness of breath
 | * Patient was admitted to a paediatric ICU and started on methimazole 20 mg every 8 hours, potassium iodide

250 mg every 8 hours, propranolol 40 mg every 8 hours,and hydrocortisone 50 mg every 8 hours.* Patient recovered and was discharged on day 9 of hospitalisation.
 | * Patients with recently diagnosed hyperthyroidism presented with URI symptoms, tremor, palpitations, and weight loss, fever, hypertension.
* TSH <0.02 mIU/L and FT4 6.86 ng/dL on day 0.
* Diagnosed with thyroid storm on top of hyperthyroidism.
 |
| (Flokas, Bustamante, and Kanakatti Shankar 2022) | 14 | Female | 21 days  | * Congestion and fatigue for three weeks.
 | * Patient recovered.
 | * Presented in shock following one week of fever, lethargy, diarrhoea, and vomiting, worsening anaemia (Hb 6.9 g/dL).
* She was resuscitated with normal saline first then blood transfusion, epinephrine drip & admitted to ICU.
* Family reported she had a history of fatigue, constipation, dry skin, oligomenorrhea, and cold intolerance, and a family history of autoimmune hypothyroidism in her grandmothers.
* Diagnosed with autoimmune thyroiditis and primary adrenal insufficiency as part of APS2.
 |
| (Kumar et al. 2022) | 14  | Female and male twins  | 56 days  | * Mild course with anosmia, mild fever and myalgia
 | * Both of them started treatment of levothyroxine sodium 25 μg every day.
* They both recovered biochemically and clinically after the last follow up.
 | * Presented with easy fatigability, decreased appetite, and hair loss.
* The thyroid function test results showed a hypothyroid state with Thyroid Stimulating Hormone (TSH) levels of 16 mIU/mL (up to 4.7 mIU/mL);free T4 of 0.5 ng/dL (0.7-1.8 ng/dL).
* The Thyroid Antibody profile was positive for anti-thyroglobulin antibodies (Tg) of 252 IU/mL (less than 50 IU/mL) and anti-thyroid peroxidase antibodies (TPO) of 71.2 IU/mL (less than 50 IU/mL).
* A thyroid ultrasound scan showed the presence

Of heterogeneous and diffusely hypoechoic tissue.* Both were diagnosed with autoimmune thyroiditis and primary hypothyroidism.
 |
| (Brancatella et al. 2020) | 18 | Female | 14 days  | * Mild; Rhinorrhoea and cough.
 | * Recovered after 2 weeks of treatment with Prednisone.
 | * Patient presented with sudden fever (37.5 °C), fatigue, palpitations, and anterior neck pain radiating to the jaw.
* Thyroid ultrasound showed multiple, diffuse hypoechoic areas.
* At laboratory exams, free thyroxine (FT4) and free triiodothyronine (FT3) were both mildly elevated, thyrotropin (TSH) undetectable, thyroglobulin (Tg) detectable at low level with positive Tg Ab. TPO Ab and antibodies to the TSH receptor were negative.
* A diagnosis of subacute thyroiditis.
 |
| (Maithani et al. 2022) | 3 | Female  | 42 days  | * Mild managed by home isolation.
 | * Patient underwent incision and drainage under general anaesthesia and 6 cc of thick pus was drained from the thyroid gland and sent for microbiological analysis.
* Secondary suturing was done after 5 days.
* Patient completely recovered.
 | * Presented with sudden onset painful swelling in the neck region accompanied with intermittent high-grade fever for five days.
* The swelling was tender and firm with central fluctuations and fingers could be insinuated below the swelling.
* Thyroid function tests revealed a euthyroid status.
* Fine needle aspiration cytology findings were suggestive of acute suppurative thyroiditis.
* A diagnosis of post COVID-19 thyroid abscess was established based on clinical evaluation and investigations.
 |

**Abbreviations:**

Hb: Haemoglobin

APS2: Autoimmune polyglandular syndrome type 2

TSH: Thyroid stimulating hormone.

TPO: Thyroid peroxidase.

TSI: Thyroid stimulating immunoglobulins.

Tg: Thyroglobulin.

FT3: Free triiodothyronine.

FT4: Free thyroxine.

URI: Urinary tract infection.

ICU: Intensive care unit .

**References: (in text** 13,71,75–80)

Brancatella, Alessandro et al. 2020. “Subacute Thyroiditis After Sars-COV-2 Infection.” *The Journal of Clinical Endocrinology & Metabolism* 105(7): 2367–70. https://academic.oup.com/jcem/article/105/7/2367/5838793.

Das, Bibhuti B. et al. 2022. “SARS-CoV-2 Infection Induced Thyroid Storm and Heart Failure in an Adolescent Girl.” *Cardiology in the Young* 32(6): 988–92. https://www.cambridge.org/core/product/identifier/S1047951121004352/type/journal\_article.

Flokas, Myrto Eleni, Victoria H. Bustamante, and Roopa Kanakatti Shankar. 2022. “New-Onset Primary Adrenal Insufficiency and Autoimmune Hypothyroidism in a Pediatric Patient Presenting with MIS-C.” *Hormone Research in Paediatrics* 95(4): 397–401. https://www.karger.com/Article/FullText/525227.

Kumar, V. Sakaleshpur, S. R. Dhananjaya, H. S. Sathish, and S. Gowda. 2022. “Auto-Immune Thyroiditis in SARS-CoV-2 Exposed Twins.” *European Review for Medical and Pharmacological Sciences* 26(13): 4881–83.

Maithani, Tripti, Mudit Gupta, Rishabh Dogra, and Sharad Hernot. 2022. “Pediatric Thyroid Abscess: An Unusual Late Complication of COVID-19 Infection.” *International Journal of Otorhinolaryngology and Head and Neck Surgery* 8(4): 406. https://www.ijorl.com/index.php/ijorl/article/view/3438.

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Rockett, John, Colbert Nelson, Robert Pierce, and Amie Van Morlan. 2021. “A Case Report of Graves’ Disease Following SARS-CoV-2 Infection.” *International Journal of Contemporary Pediatrics* 8(7): 1260.

Victoria Brocksmith Nicksic, Santhi Logel, Shardha Srinivasan, Elizabath Mann, and Jennifer Leigh Rehm. 2021. “Thyroid Storm With Concurrent Covid-19 Infection in a Pediatric Patient.” *J Endocrine Soc,*.

**Table 17: Tumour necrosis factor receptor associated periodic syndrome (TRAPS) as postacute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Reference | Age (yrs) | Sex | Interval between infection and autoimmune disorder | Course of preceding COVID | Outcome | Notes |
| (Çağlayan et al. 2022) | 6 | Female | 4 months | Asymptomatic  | Admitted to PICU and moved to in-patient ward 22 days later. Patient improved on methylprednisolone and anakinra. | Presented by fever and pancytopenia. Diagnosed as MAS, for which she was given pulse dexamethasone and anakinra. Two more MAS attacks followed. Patient was diagnosed as TRAPS by genetic studies. |

**Abbreviations:**

Yrs: Years

TRAP: Tumour necrosis factor receptor-associated periodic syndrome

**References:**

Çağlayan, Şengül, Kadir Ulu, Mustafa Çakan, and Betül Sözeri. 2022. “A Rare Onset in Tumour Necrosis Factor Receptor–Associated Periodic Syndrome: Recurrent Macrophage Activation Syndrome Triggered by COVID-19 Infection.” *Rheumatology* 61(12): e366–67. https://academic.oup.com/rheumatology/article/61/12/e366/6613127.

**Table 18: Type 1 Diabetes Mellitus as post-acute sequelae of COVID-19**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Age (years)** | **Sex** | **Interval between infection and autoimmune disorder** | **Course of preceding COVID** | **Outcome** | **Notes** |
| Ordooei et al. 2021 | 10 | Male | 0 | Presented with respiratory distress & drowsiness.  | Hospitalised for 10 days (7 days in ICU & 3 days in ward)Discharged after recovery.  | 10 day history of polyuria & polydipsia and a 3 day history of vomiting. |
|  (Lança et al. 2022) | 13  | Male | During course of COVID | Afebrile, tachycardic, tachypnoeic.  | After 17 days of hospitalisation, a negative PCR for SARS-CoV-2, he was discharged, on a multiple daily injection insulin regimen. | 2-month history of progressive non-intentional weight loss with polyphagia and polyuria. Later, he developed abdominal pain, sporadic non-bilious vomits, diarrhoea and progressive weakness with nasal congestion, anosmia and odynophagia. He was afebrile, tachycardic and tachypneic. |
| 8 | Male | During the course of COVID-19 infection.  | Afebrile & mildly dehydrated.  | Discharged after stabilisation.  | Presented with polyphagia, polyuria with nocturia and a non-quantified weight loss since the last 2 weeks. |
| (Brothers et al. 2021) | 12 | Female | 4 days | Presented with rhinorrhoea progressing to dry cough, post-tussive non bilious emesis, shortness of breath, mottled skin and altered mental status.  | Death due to fungal sepsis on top of DM type 1 (C Galbrata resistance to Azoles) | After 24 hours in ICU, DKA resolved but progressive multi-organ failure, anion gap metabolic acidosis and fungal urosepsis developed. |
| (Nielsen-Saines et al. 2021) | 7  | Male | During the course of COVID—19 infections.  | Asymptomatic | Admitted to PICU for 4 days until stabilised. He was discharged later with recommendation to quarantine.  | Presented with progressive anorexia and a 10-pound weight loss over 3 weeks.3-day history of polydipsia, abdominal pain, nausea, and headache. |
| (Benyakhlef et al. 2021) | 3  | Male | During the course of COVID-19 infection  | Hospitalised for 10 days. Chest CT showed bilateral ground-glass opacities. Admitted to ICU for 2 days until clinical improvement.Respiratory distress required non-invasive ventilation. | Discharged after stabilisation with quarantine recommendation.  | Presented with acute dyspnoea accompanied with asthenia,vomiting, , respiratory distress was evident with swollen throat and conjunctival hyperaemia.2-week history of polyuria, polydipsia, 2 kg weight loss over the previous month.  |
| (Rabizadeh et al. 2020) | 16 | Male | During the course of COVID-19 infection | Mild dyspnoea and productive cough.  | 2-day ICU admission for hydration and insulin treatment. Patient was discharged with a basal- bolus insulin regimen after clinical improvement.  | Presented with a seven-day history of fatigue, weakness, nausea, polyuria, polydipsia, abdominal pain and a 2 kg weight loss over the previous 2 weeks. |
| (Soliman et al. 2020) | 0.7 | Male | During the course of COVID-19 infection  | Tachycardia, tachypnea, fever.  | PICU admission for 1 day until stabilisation. Discharged after clinical improvement.  | Presented with a two day history of fever, vomiting, 10% dehydration and rapid breathing. |
| (Naguib, Raymond, and Vidmar 2021) | 8 | Female | 8 weeks | Cough, rhinorrhoea, anorexia, and weight loss. | PICU admission for 5 days due to neurological and respiratory deterioration. Discharged at hospital day 10 after resuscitation, infliximab and IVIG. | presented with four days of polyuria, nocturia, polydipsia, anorexia, fever, diarrhoea, vomiting, lethargy, rash, and conjunctivitis. |
| (Daniel et al. 2020) | 15  | Female | During the course of COVID-19 infection. | Fever, abdominal pain, and vomiting.  | ICU admission for 5 days, 14-day hospitalisation. Discharged after stabilisation.  | Presented with acute onset of abdominal pain and vomiting |
| (Alizadeh et al. 2021) | 16 months | Male  | During the course of COVID-19 infection.  | Fever, emesis and respiratory distress.  | Patient was discharged after being treated with Eculizumab and advised to receive it every 3 weeks for aHUS. | * Patient presented with fever, emesis, and respiratory distress.
* Diagnosed as DKA on top of diabetes mellitus type 1 and atypical haemolytic uremic syndrome.
* Admitted to PICU for DKA management.
* Patient had a history of prematurity at 34 weeks’ gestation, intrauterine growth restriction, severe failure to thrive, microcephaly, pachygyria, agenesis of the corpus callosum, postnatal embolic stroke with residual cranial nerve IV palsy, retinopathy of prematurity, and multiple dysmorphisms without a unifying genetic disorder
 |

**Abbreviations:**

SARS-COV-2: severe acute respiratory syndrome coronavirus 2.

DKA: Diabetic Ketoacidosis

ACE-2: severe acute respiratory syndrome coronavirus 2.

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