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REVIEW ARTICLE

The course of COVID-19 in paediatric patients – specific and non-specific clinical manifestations

Jacek Januszewski[1,B-D], Michał Tobiasz[2,B-D], Magdalena Tyczyńska[3,B-D], Alicja Forma[1,A,C-F], Karolina Kłodnicka[3,D], Julita Zembala[4,D], Agnieszka Turkosz[5,C,E], Jacek Baj[3,E-F]

[1] *Chair and Department of Forensic Medicine, Medical University, Lublin, Poland*
[2] *Department of Plastic, Reconstructive and Burn Surgery, Poland*
[3] *Department of Correct, Clinical and Imaging Anatomy, Chair of Fundamental Sciences, Medical University of Lublin, Lublin, Poland*
[4] *University Clinical Centre, Medical University, Warsaw, Poland*
[5] *Department of Gynecology and Obstetrics, Independent Public Health Care Centre, Puławy, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction and Objective. COVID-19 caused by SARS-CoV 2 is a still serious danger. The disease which triggered off the COVID-19 pandemic and one of the biggest health crises in many years, began in the city of Wuhan, China, in 2019. The aim of this review is to distinguish most of the specific and non-specific manifestations of the disease among children.
Review Methods. The literature review was based on different types of articles including reviews, meta-analyses, systemic reviews, and randomized controlled trials on PubMed, Web of Science, and Scopus databases. Key words featured COVID-19, MIS-C, SARS-CoV-2 manifestations, and specific, and non-specific manifestations of COVID-19. The literature search was performed until September 2023, and concerned only paediatric patients.
Brief description of the state of knowledge. Research based on already published studies prevents the forming of firm conclusions. There are different symptoms of COVID-19 infection, some of them are typical, mild, and do not concern medical care units. There are also some non-specific manifestations, often related to multisystem inflammatory syndrome in children (MIS-C), which are more severe and sometimes demand involving intensive care units.
Conclusions. A large group of infected children with asymptomatic or present mild symptoms of COVID-19. Non-specific manifestations, such as cardiovascular, gastrointestinal, psychiatric, neurological, ophthalmic, dermatological, or rheumatological symptoms, can potentially be misleading and require more attention.

Key words
infection, paediatrics, paediatric patients, COVID-19, pandemic, SARS-CoV-2, infectious

INTRODUCTION

COVID-19 caused by SARS-CoV-2 is a still serious topic in medical care. The disease which triggered the COVID-19 pandemic and one of the biggest health crises in many years, began in the city of Wuhan, China, in 2019. By January, the virus had spread all over China and in Februarythe first infections were observed in Europe [1]. SARS- CoV-2, discovered in the 20th century, is a single-stranded positive-sense RNA virus classified as betacoronaviridae, and belongs to the subfamily of Coronavirinae [2]. Initially, Coronavirus was mainly virulent for wild animals although there were some reports about human infections [3]. The main symptoms to which the media played a great deal of attention are coughing, fever, lack of taste and smell, or dyspnea [4]. However, some other COVID-19 manifestations might be considered atypical. Among the most common oral manifestations of COVID-19, herpetiform lesions, aphthous-like lesions, candidiasis, and oral lesions of Kawasaki-like disease can be distinguished [5]. Symptoms such as anorexia, diarrhea, nausea, or vomiting may be the most popular gastrointestinal manifestations of the disease; nonetheless, the appearance of more acute manifestations is possible, for example, bloody diarrhea [6]. There are also reports about some ocular manifestations of COVID-19. Conjunctival hyperaemia, conjunctival discharge, and epiphora are mentioned as the most prevalent ophthalmic symptoms of SARS-CoV-2 [7]. Even though the previously mentioned manifestations may not be considered an emergency, they might lead to multiple organ dysfunction.

As is well known, COVID-19 can be spread by many modes. Human-to-human transmission is possible by direct contact, droplet inhalation by sneezing or coughing, or even airborne [2, 8]. Every single contact with a fomite or belonging to an infected person may unfortunately lead to the sickness. [6] The virus is composed of 5 main structures: spike protein, membrane protein, E protein, nucleoprotein, and RNA [9]. Since the structure of SARS-CoV-2 includes spike proteins, it is possible to bind in the host cells via the receptor angiotensin-converting enzyme 2 (ACE2). ACE2 receptor is localized on the surfaces of many human organs, such as kidneys, blood vessels, heart, and lungs [10–12].

OBJECTIVE

The aim of this narrative review was an in-depth assessment of the specific as well as non-specific manifestations

Address for correspondence: Alicja Forma, Chair and Department of Forensic Medicine, Medical University, Jaczewskiego 8b, 20-090 Lublin, Poland
E-mail: aforma@onet.p

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of COVID-19 in paediatric patients. The review was performed using the PubMed database in September 2023, using the following key words: COVID-19, MIS-C, SARS-CoV-2 manifestations, and non-specific manifestations of COVID-19. Ultimately, the papers included reviews, meta-analyses, systemic reviews, as well as randomized controlled trials. There were no restrictions regarding the year of the publication. The authors also chose only articles written in English.

TRANSMISSION ROUTES OF SARS-COV-2

Droplets and bodily fluids. Throughout the pandemic, wild statements were made about the possibility of droplets or other body fluid transmissions, because enormous quantities of droplets are released by coughing or sneezing. An exposed person is therefore in danger of infection [13]. Recently, it has been proven that COVID-19 patients who have dry cough or sneeze produce droplets of sizes between 0.6 – 100 μm. While speaking and breathing, asymptomatic patients might also produce and exhale huge amounts of blobs in size up to 1 μm [14–16]. ACE2 receptors have expression in the intestine, testis, kidney, lung, liver, heart, brain, thyroid, bone marrow, blood vessels, urinary bladder, or adrenal glands. This is the point at which viruses invade organisms and may lead to life-threatening clinical symptoms [17, 18].

Airborne transmission. Turbulent airflow is caused, for example, by breathing, talking, sneezing or coughing. Humid and warm air prolong the lifetime of droplets from a fraction of a second to a fraction of a minute. A highly important issue is that the aerosol plumes are produced by coughing and sneezing at a speed fast enough to contaminate people nearby [14, 19, 20]. Numerous cases were reported with a high risk of COVID-19 infection on indoor surfaces such as homes or hospitals [21]. Extended exposure to polluted air as a result might cause potent COVID-19 forms [22].

Fomite transmission. An alternative source of contamination could be the gastrointestinal system. Medical studies presented a significant role of anal swabs in the COVID-19 diagnosis process. After 2 weeks of testing negative by the nasopharyngeal swab test, the anal swabs were inherent SARS-CoV-2 [23]. The danger of virus transmission increases during lavatory sharing. It was believed that the SARS-CoV-2 outbreak was brought on by inadequate lavatory airing, especially in apartments where toilet flushing transmits aerosols [24, 25]. Appropriate disinfection and scouring strategies have been suggested to cause the contamination to decrease. The transmission of microbes could occur while in contact with tainted surfaces which could cause the transfer of viable microbes to nasal, buccal, or ocular mucous membranes [26, 27].

Other routes of transmission. Another possible transfer form of COVID-19 is vertical transmission. Unfortunately, the virus can penetrate the placenta, cause vertical infection, and cause direct adverse effects on the foetus. However, such cases tend to be rare due to the low expression of ACE2 receptors on the placenta. As previously mentioned, ACE2 receptors are significantly important to SARS-CoV-2 transmission [28–31].

Sexual SARS-CoV-2 transmission is also confirmed in some cases. Multiple organs have ACE2 receptors which enable viral infection. Sexual contact is not the only method of transmission and there are many different ways of propagating SARS-CoV-2. Kissing, caressing, and hugging may lead to airborne transmission during sex [32–34].

Transmission routes most common amongst children. Studies show that despite the majority of paediatric cases being classified as family clusters, children are not the major vector of SARS-CoV-2 infection in the community. Parents were the most frequent source of infection, whereas siblings constituted only 5 % of all cases. A huge role in the transmission of COVID-19 among children is played by schools. The risk of infection acquired in school, however, is lower than that in households. According to reports, 13% of all transmissions took place in the school [35–37].

CLINICAL MANIFESTATIONS DEPENDING ON THE AGE OF CHILDREN

Although the rate of incidence among children is not particularly high, there are some reports about children contracting COVID-19. The severity of the disease may be asymptomatic, mild, moderate, severe, or critical leading to death, but most children present mild or moderate symptoms. Referring to symptoms, the most commonly observed are cough, rhinorrhea, nasal congestion, tachypnea, and vomiting [38, 39] (Tab. 1).

SEVERITY OF COVID-19 AMONG CHILDREN

Diagnosis of paediatric patients. According to the current state of knowledge, Real-Time Polymerase Chain Reaction (RT-PCR) is the gold standard in diagnosing COVID-19 infection. Test sensitivity is estimated to be about 62% on the day of first appearance of symptoms, and even up to 80.3% three days after development of symptoms. Biological discharges with the highest positive rates are bronchoalveolar lavage (93%) and sputum (72%). Pharyngeal and nasal swabs give positive rates between 32% – 63%. Faeces and saliva may also contain viral nucleic acids. Moreover, there are some serologic methods of SARS-CoV-2 virus detection. Tests using specific characters of antibodies IgA, IgM, and IgG which are targeted at SARS-CoV-2 spike protein (S) and nucleocapsid protein (N), can bind and detect them, thus giving a clear sign of infection. The potential high-level effectiveness in detecting multisystem inflammatory syndrome in children (MIS-C) has been reported. Children with MIS-C present considerably higher antibody rates compared with those with asymptomatic or mild COVID-19 infection. However, serologic tests may be negative in an early phase of illness because of the developing time of antibodies [45–48].

General symptoms. As previously mentioned, the course of COVID-19 infection among children may differ, with reports indicating asymptomatic, mild, moderate, severe, or critical forms of the disease. The general symptoms are often quite similar to those presented in adults; owever, it depends on the age of the patients. In the group of neonates and infants, manifestations such as feeding difficulties or

Table 1. Distribution of the frequency of an infection and manifestations among children in different age

Age	Distribution of COVID-19 infections among children (%)	Most common clinical manifestations of COVID-19 in a group of children	Ref.
0–4	20.6	Fever** Feeding difficulty* Intussusception* Bronchiolitis* Apnea* Cough Tachypnea Diarrhea Rhinorrhea Somnolence Rash	[40–44]
5–11	37.9	Fever Cough Myalgia Shortness of breath Headache Sore throat Diarrhea Nausea/Vomiting Loss of smell /taste	[40–44]
12–15	26.3	Fever Cough Shortness of breath Headache Myalgia Sore throat Diarrhea Nausea/Vomiting Loss of smell/ taste Runny nose Abdominal pain	[40–44]
16–17	1.,3	Fever Cough Shortness of breath Headache Myalgia Sore throat Diarrhea Nausea/Vomiting Loss of smell/taste Runny nose	[40–44]

** most commonly presented in infants and neonates; * most commonly presented in infants 9 (0–1)

apnea occur [40]. There are reports about pregnant women with COVID-19 infection who gave birth to sick children. Nonetheless, the complications mostly concerned the childbirth or preterm delivery rather than the course of the infection among children. The neonates usually presented symptoms similar to their mothers, such as fever, cough, or diarrhea [49]. Older children presented mild symptoms, or were even not invisible. The most common manifestations in children with the disease were fever, cough, rhinorrhea, sore throat, headache, vomiting, diarrhea, fatigue, myalgia, tachycardia, tachypnea and rash [39]. Loss of smell or taste was unusual in those under the age of 18 years; however, there were also reports about atypical manifestations of SARS-CoV-2 infection among children. Croup as a manifestation of the illness was observed among some paediatric patients [50]. Other cutaneous manifestations besides rush are possible, but rarer. The lesions may include erythema multiforme, urticaria, or vesicular exanthema [51].

Radiological findings. There are different methods for diagnosing COVID-19. Radiology might be helpful, and chest CT or x-ray (CXR) could show some changes corresponding with symptoms presented by patients. Research has shown that consolidations were the most frequently observed lung lesions. Moreover, CT presented a higher sensitivity in detection compared to the CXR [52, 53]. Infected people usually presented bilateral lesions and some chest CT scans showed unilateral lesions, ground-glass opacity, consolidations, or crazy paving patterns in the chest CT imaging. Pneumonia was reported to be predominantly bilateral in 75.5% and unilateral in 20.4%, with most cases localized in the lower lobes. Ground glass patterns seen in the chest CT scans occurred with halo, broncho-vascular bundle thickening, grid‑ form shadow, air bronchogram, and hydrothorax [54, 55]. The most commonly reported chest X-ray findings include ground-glass opacities and lung consolidations similar to chest CT. However, in some groups of patients, there were no visible radiological findings in CRX or CT although patients presented clinical symptoms [56–58].

Laboratory findings. According to diagnosing methods, there are also laboratory markers that may confirm COVID-19 infection. The population of white blood cells (WBC) usually stays at normal level or tends to decrease. There are reports about lymphopenia or thrombocytopenia and patients with a high leukocyte count (>10 × 109/L), lower lymphocyte count (<0.4 × 109/L), and higher neutrophil count (>7 × 109/L), who may present predispositions to a severe course of the SARS- CoV-2 infection [59,60]. Biomarkers, including procalcitonin, C‑ reactive protein (CRP), interleukin‑ 6 (IL‑ 6), lactate dehydrogenase (LDH), ferritin, erythrocyte sedimentation rate, or fibrinoge, are prone to be at higher level of risk. Patients presented higher alanine aminotransferase activity, higher aspartate aminotransferase activity, higher creatine kinase activity, higher creatinine level, and lower total protein level [53, 54, 61]. Cardiac markers which include N‑ terminal proB‑ type natriuretic peptide, troponin, and B‑ type natriuretic peptide were reported to be elevated. Of interest is that patients with SARS-CoV-2 infections had a significantly higher rate of D-dimer and fibrin degradation product (FDP) [53, 54, 57,62–64].

Multisystem inflammatory syndrome in children. Multisystem inflammatory syndrome in children (MIS-C) is a post-infectious hyperinflammatory disorder due to the SARS-CoV-2 infection observed among a small group of children. It is relatively a new pathology so the precise definition is still changing. According to the current state of knowledge WHO defined MIS-C as a syndrome that includes age between 0–19, clinical presentation, evidence of infection or contact with patients who have COVID-19, elevated inflammation markers, and exclusion of other microbial inflammation causes. Multisystem inflammatory syndrome may be associated with age or chronic illnesses. The exact association between MIS-C and COVID-19 infection is still investigated but the possible cause might be a cytokine storm. Dysregulated immune response and endothelial damage mainly caused by proinflammatory cytokines such as IL-18, IL-8, IL-6, tumor necrosis factor (TNF-α), and interferon γ (IFN-γ) could lead to multiple organ failure. Patients presented higher levels of C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH) thrombocytopenia, ferritin, D-dimer, and N-terminal pro-B type natriuretic peptide (NT-proBNP), [65–68]. Mild symptoms of MIS-C are mostly fever, cough, sore throat, abdominal pain, vomiting, diarrhea, conjunctivitis, and rash. Organ dysfunction symptoms may include tachycardia, hypotension, or breathing problems [68]. MIS-C could lead to heart blocks, pericarditis, valvulitis [69, 70]. The treatment of multisystem inflammatory syndrome in children may be various. In most cases, the therapy includes intravenous immunoglobulin (IVIG), intravenous corticosteroids, Infliximab, Anakinra, Tociluzimab, and Siltuximab (both IL6 inhibitors). Thromboprophylaxis and Thrombosis also play an important role in the treatment. In emergency membrane oxygenation cardiopulmonary bypass (ECMO) was necessary [68, 71–74].

Gastrointestinal and hepatic manifestations. Increasing evidence emphasizes the role of SARS-CoV-2-mediated extra-respiratory manifestations, including gastrointestinal and hepatic symptoms. Viruses can be detected in the digestive system (duodenum, colon, rectum, anal region, and stool). These areas present expression of candidate coreceptors and auxiliary proteins that not only facilitate entry of the virus, but also have profuse amounts of viral angiotensin-converting enzyme 2 receptor (ACE2). They exhibit the expression of host transmembrane serine protease 2 (TMPRSS2), essential for virus-cell fusion induction. Hence, viral replication occurring in the intestinal epithelial cells can be observed [75, 76]. SARS-CoV-2 creates dysbiosis and alternates the gut-lung axis. SARS-CoV-2 facilitates a clear T-cell response stimulating cytokine storm in the intestines and liver, which causes inflammatory bowel damage. Intestinal manifestations include the loss of appetite, abdominal pain, nausea and vomiting, and diarrhoea, which could act as a marker of the severity of the disease [77]. In children, diarrhoea constitutes the most frequently occurring symptom, often described as mild and self-limiting. In the liver, hypertransaminasaemia usually occurs in patients with a severe progression of the disease, with the incidence ranging from 40% – 60% [78]. As opposed to the respiratory secretions, SARS-CoV-2 remains longer in stools, which significantly impacts the spread of disease [79]. All this evidence leads to the recognition of the potential faecal-oral route of disease transmission. A retrospective case series study of paediatric patients with post-COVID-19 liver manifestations showed two distinct clinical patterns. One group of previously healthy infants, presented acute liver failure that hastily progressed to the necessity for liver transplantation. The liver explant revealed massive necrosis with lymphocytic infiltration and cholangial proliferation. Another group of children, aged 8 – 13 years, displayed cholestasis and hepatitis. A liver biopsy was performed in two children who showed parenchyma inflammation with lymphocytic portal, as well as the bile duct proliferations. All three children were provided with a steroid treatment, which resulted in liver enzyme improvement and overall successful therapy [80].

The case was reported of a 14-year-old non-obese boy with the multisystem inflammatory syndrome in children (MIS-C), who presented a diffusely painful abdomen, jaundiced skin, as well as hepatosplenomegaly. He presented a multiorgan failure with a compromised haemodynamic status and high levels of alanine aminotransferase, aspartate aminotransferase, as well as indications of cholestasis. Although fully recovered from MIS-C, during the follow-up appointment the patient was diagnosed with hepatic steatosis. Hence, it is suggested that hepatic steatosis might be associated with the MIS-C, SARS-CoV-2 infection, or infection treatment. The causative factors primarily entail a prolonged usage of corticosteroids and their impact on the inhibition of fatty acid oxidation occurring in the mitochondria [81].

Olfactory and gustatory dysfunctions. The tissue distribution of ACE2, a particle that enables clathrin-dependent viral endocytosis, shows its strong expression in vascular endothelial cells and the oral and nasal mucosa. These results suggest not only other viral transmission paths, but also explain various extrapulmonary manifestations [82]. Neurological symptoms associated with SARS-CoV-2 infection include hypogeusia and anosmia. In a Chinese series of 214 patients infected with the SARS-CoV-2, 36.4% of them presented with neurological symptoms, including 9% of patients with hypogeusia or hyposmia [83].

With regards to paediatric cases, SARS-CoV-2 infection usually causes less severe symptoms than those observed in adults. Unfortunately, both neurological involvement and symptoms, such as hypogeusia and anosmia in youth, have been poorly described [84]. Research performed on a group of 280 Spanish patients with a mean age of 10.4 years, concluded that even though the occurrence of either anosmia or hypogeusia in children infected with SARS-CoV-2 was lower than that observed in adult patients, it lasted longer. While no relationship was found between the occurrence of either anosmia or hypogeusia and the greater severity of the disease, these symptoms should be recognized to help identify patients with lesser clinical expression of said infection [85]. Another experimental group study involved 68 children over 6 years old, who recovered from COVID-19. Research methods included neurological examination, cognitive status verification, otolaryngologist examination, and assessment of smell and taste. The analysis was undertaken 6 – 8 weeks after COVID-19 recovery and, in some patients, after one year. Children who recovered from infection had a decrease in their smell capability compared to those who had never suffered from COVID-19. Both the olfactory thresholds and taste identification scores were identical after recovery, whether anosmia was reported during COVID-19 or not, and regardless of either hyperthermia level, occurrence of headache, or hyperhidrosis during COVID-19. Moreover, evidence suggested that in children and adolescents, there is a relationship between depressive symptoms and partial hyposmia, with the severity of symptoms varying from low to high, but not caused by the viral infection itself. After one year, a re-examination of 21 children showed that the sensitivity to odorants increased significantly. Furthermore, the thresholds of smell in children who were infected with SARS-CoV-2 and those who were not, revealed that olfactory sensitivity in children can be restored to normal values [86].

Neurological manifestations. Even though respiratory symptoms and multi-system inflammatory syndrome in children (MIS-C) are the main focus of scientific research, it has been observed that neurological phenomena are also highly associated with the COVID-19 infection. Two cell membrane proteins are the foremost necessities of viral invasion: ACE2 receptor, and TMPRSS2, both of which can be expressed within the central nervous system (CNS) [87]. A prospective multi-centred observation study using the International Severe Acute Respiratory and Emerging Infection Consortium cohort was conducted. It included a total of 2,972 children, patients hospitalized due to COVID-19, and assessed for neurological symptoms. The most frequently noted neurological manifestations at admission included fatigue (20.4%), altered consciousness (6.8%), myalgia (7.6%), dysgeusia (1.9%), anosmia (2.2%), and seizure (5.2%). Furthermore, it was shown that among the children, the only neurological complication occurring more frequently in the intensive care unit (ICU) compared to the non-ICU (7.1% vs. 2.3%, P <.001) was seizures. The prevalence of stroke increased with age, while central nervous system infection and seizure were steadily decreasing. Chronic neurological disease, high blood pressure, as well as the use of extracorporeal membrane oxygenation, were associated with a greater risk of stroke, and impaired consciousness was associated with CNS infection, stroke, and seizure [88]. Another study reported that 28% of paediatric patients in the USA who suffered from COVID-19 experienced headaches. Among children diagnosed with MIS-C in New York, 31 – 47% experienced neurological symptoms which involved impaired mental status, headache, or even encephalopathy. Likewise, a multi-centre study of children with MIS-C across the USA discovered that 5% suffered from severe neurological difficulties, such as coma, seizure, aseptic meningitis, encephalitis, or even demyelinating disorders. In the UK, among 27 children diagnosed with MIS-C, four presented new-onset neurological symptoms, such as dysphagia, dysarthria, cerebellar ataxia, encephalopathy, and peripheral. The MRI or CT changes involved the splenium of the corpus callosum, and all patients presented with shock, fever, and rash. Reversible lesions of the corpus callosum have been observed in Kawasaki disease, along with other viral and inflammatory encephalopathies [89].

The main differences between patients with a primary neurological disorder and those with paediatric inflammatory multi-system syndrome – temporally associated with SARS-CoV-2 (PIMS-TS) – have been identified. When compared with patients with a primary neurological disorder, more patients with PIMS-TS needed intensive care, but their treatment outcomes were overall similar [90]. Facial nerve palsy has been reported as another possible complication associated with COVID-19. Its prevalence significantly increased during the pandemic, both in adult and paediatric emergency departments. A case of a 15-month-old infant who presented only right peripheral facial nerve palsy without any other neurological manifestations has been described. Serological tests for common infections were negative, but showed the presence of SARS-CoV-2 IgG antibodies. MRI revealed enhancement of the intra-auricular tract of the right facial nerve. Surprisingly, the patient and her family experienced mild respiratory symptoms quite early on, namely, fever, anosmia, and ageusia, but all of them were reported to recover spontaneously. It has been suggested, that along with other well-known infections that cause facial nerve palsy, both SARS-CoV-2 swab and serology tests should be carried out. Facial palsy can represent an immune-mediated neurological complication of the SARS-CoV-2 infection [91]. Another example of neurologic complications of COVID-19 is a case of longitudinally extensive transverse myelitis (LETM) in a 3-year-old girl who did not present any earlier symptoms. The patient had a positive SARS-CoV-2 nasopharyngeal PCR and presented with the onset of weakness, just three weeks after her family presented respiratory symptoms. Such a picture of the disease might be an example of the post-infectious demyelinating syndrome [92].

Dermatological manifestations. Chilblains are one of the most prevalent cutaneous expressions of COVID-19 in children. Other frequently described symptoms are maculopapular rash, urticaria, erythema multiforme, and papulovesicular eruptions [93]. Compiled incidence involved: chilblain-like lesions (n = 173; 88.3%), maculopapular rash (n = 16; 8.2%), erythema multi-form-like lesions (n = 12; 6.1%), varicella-like exanthema (n = 1; 0.5%), and urticaria (n = 1; 0.5%) [94]. Acral ischaemic lesions, which are similar to chilblains and more common in adolescents, were reported worldwide during the COVID- 19 outbreak. They mainly affect toes and feet while being less frequent on the fingers and hands. The lesions, may appear as either dark purpuric macules, iolaceous or erythematous swellings, or vesiculobullous lesions with prominent vascular damage. Most patients have either mild general symptoms or none at all, as well as negative nasopharyngeal PCR and serological tests [95]. Urticaria, in which rates might be underrated in children, occurs in about 10% – 20% of patients with skin lesions suffering from the SARS-CoV-2 infection. Other forms of exanthems, which relation to the illness, remains unknown, and were reported during the SARS-CoV-2 outbreak and included purpuric rashes, pityriasis rosea-like eruptions, maculopapular exanthems, and oral findings [96, 97]. A small percentage of paediatric patients develop severe multi-system involvement termed MIS-C, which can vary in its mucocutaneous manifestations [98]. MIS-C is characterized by laboratory markers of inflammation fever, multi-system involvement, and generally severe illness that usually requires urgent hospitalization. Skin findings, initially compared with Kawasaki disease, likely represent distinct phenomena and remain poorly characterized. 'Rash' is often the sole descriptor of skin lesions in many patients. Case reports provide us with more details, showing a broad range of various lesion morphologies (polymorphic, morbilliform, maculopapular, urticarial, erythrodermic, purpuric reticular, petechial,), as well as their variable anatomical distribution [99].

Psychiatric manifestations. Clinical data reveals that impairments in the function of one or more organs can persist for a long time, being characterized as a post-COVID or long-COVID syndrome. Fatigue and cognitive dysfunctions, such as concentration problems, a specific decline in attention, short-term memory deficits, general memory loss, language and praxis abilities, encoding, and verbal fluency, impairment of executive functions and psychomotor coordination, are among the most common neuropsychiatric symptoms of the above-mentioned syndrome. Studies reporting the occurrence of neuropsychiatric symptoms were integrated into meta-analyses which included 147 studies, to estimate pooled prevalence. The symptoms with the highest incidence were depression (23.0% (95% CI 11.8% – 40.2%, n=43 128, 10 studies), anxiety (15.9% (5.6% to 37.7%, n=42 566, 9 studies), as well as impaired mental status (8.2% (95% CI 4.4% – 14.8%, n=49 326, 19 studies) [100]. Several patients were also suffering from depression, anxiety, sleep deprivation, or even post-traumatic stress disorder (PTSD). It was shown that patients with long COVID-19 might present changes in brain functioning, such as brain hypometabolism and hypoperfusion of the cerebral cortex, as well as changes in the brain structure, and further functional connectivity.

Children and adolescents constitute rather a minority of COVID-19 cases; therefore, data on their long-term sequelae after SARS-CoV-2 infections are limited [101]. Many cross-sectional studies have analyzed the impact of COVID-19 and lockdown on children and youths. The findings show that the nature and extent of this influence depend on various factors, including developmental age, education level, pre-existing mental health problems, economic status, and quarantine, which occurred due to infection or fear of the said infection. Studies report that young children present disturbed sleep patterns, experience nightmares, and clinginess, have a poor appetite, and also present inattentiveness and significant separation problems. Extended school and activity centre closures exposed the children and youths to severely hindered educational and psychological development, as they experience loneliness, anxiety and insecurity.

Exacerbation in symptoms and behavioural problems in children with mental health conditions can be observed because of their lack of adaptation to various environmental changes. The children who attend therapy are at high risk of being derailed from treatment and special education, and economically underprivileged children are prone to exploitation and abuse. Quarantined children are at great risk for developing mental health-related issues [102–105].

Ophthalmic manifestations. Ophthalmic manifestations of COVID-19 contagions are quite common. Various symptoms that may be correlated with SARS-CoV-2 were observed, with the most common ocular symptom in COVID-19-infected patients being conjunctivitis. Cases of benign COVID-19 infection with conjunctivitis accounted for 8.66% of patients. All symptomatic patients reported having had previous redness in either one or both eyes. There has been a rise in the spread of a condition similar to Kawasaki's illness, with a strong correlation to COVID-19. Iridocyclitis, vitreous opacities, papilloedoema, subconjunctival haemorrhage, and conjunctival injection are all symptoms of Kawasaki illness, a self-limiting vasculitis. The most frequent eye symptom detected in currently accessible material has been conjunctivitis. COVID-19 can cause ocular inflammation in multi-system inflammatory syndrome patients. Bilateral non-granulomatous acute anterior epitheliopathy and corneal punctate epitheliopathy in children with the MIS-C brought on by COVID-19 have both been documented [108,109]. Studies demonstrated a fair amount of conjunctival hyperaemia or conjunctival discharge as part of the present symptoms during COVID-19 infection among the paediatric population. No less severe ocular symptoms included rubbing the eyes, ocular pain, tearing, or eyelid swelling [107,110–112]. Paediatric individuals who were infected by SARS-CoV-2 seldom reported orbital inflammatory diseases; however, there were some confirmed cases of sinusitis, cerebral abnormalities, and unilateral ocular cellulitis. Furthermore, the pathological changes in the retina caused by inflammatory processes linked to SARS-CoV-2 infection, such as cotton-wool spots, microhemorrhages, and vein dilatation, have been emphasized in the past few years [110].

Cardiovascular manifestations. Cardiac manifestations during COVID-19 infection are a general consequence. Multi-system inflammatory syndromes in children (MIS-C), cardiovascular manifestations are more often related than SARS-CoV-2 infection with benign symptoms. Cardiac involvement is developed in children with MIS-C who constitute up to 67 – 80%, and it is more widespread than Kawasaki disease in children with MIS-C. Ventricular dysfunction, coronary artery aneurysms, aberrant conduction, and arrhythmias are some of the cardiac symptoms. In distinguishing coronary artery abnormalities, coronary artery dilation should be mentioned. Coronary artery dilatation – origin unknown – may cause vasculitis or systemic hyper-inflammation. Another significant manifestation of COVID-19 infections is the incidence of arrhythmias. ECG results show that arrhythmias occur in up to 70% of MIS-C patients. Low QRS amplitude and T-wave abnormalities are the most typical findings. There have also been reports of first-, second-, and third-degree heart blocks, ventricular or atrial tachycardia, or bradyarrhythmia occurring. In certain children, myocarditis is also present. Two possible etiologies for the cardiac damage caused by COVID-19 include direct viral injury to the heart and myocardial damage incurred by the hyperinflammatory process.

Children with COVID-19 myocarditis had higher CRP levels, used inotropes for a shorter length of time, and returned to normal left ventricular systolic function more quickly than those without the condition. It is reported that 50% of all children with MIS-C may have ventricular dysfunction. As mentioned above, one of the numerous possible causes could be myocarditis. A significant influence in the development of ventricular dysfunction might also be played by immunological abnormalities incurred by inflammatory processes. When MIS-C is suspected, it is suggested to perform an urgent electrocardiogram (ECG), transthoracic echocardiogram, troponin, and assessment of the level of brain natriuretic peptide (BNP) [113–115, 117–119, 121, 122].

Rheumatological manifestations. The musculoskeletal system may be also afflicted by SARS-CoV-2, and some malformations related to COVID-19 infection have been reported. Myalgia, which is defined as muscle aches and pains, has frequently been noted in even 50% of COVID-19 patients. Numerous case reports have mentioned myositis and rhabdomyolysis in COVID-19 patients, both as a presenting symptom and as a late consequence. A few cases of SARS-CoV-2 causing necrotizing autoimmune myositis have also been documented. Unknown processes underlie the involvement of the muscles in COVID-19. Skeletal muscles are directly invaded by SARS-CoV-2 because they contain an ACE2 receptor, through which the virus is transmitted.

The participation of immune-mediated pathways in SARS-CoV-2 muscle involvement is a different and better-known idea. Arthralgia is present in 2.5% of patients in whom a COVID-19 symptom has been detected. Only a few cases of acute clinical arthritis due to COVID-19 have been documented to date. Among other chronic rheumatologic conditions, Graves' disease, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, psoriatic spondyloarthritis, and reactive arthritis have been reported. Regarding a connection between the child population and COVID-19 rheumatological manifestations, the reports are not entirely clear. More study has to be carried in this therapeutic area [123–129].

CONCLUSIONS

According to all the research and collected data, there are numerous specific and non-specific clinical manifestations of COVID-19 infection among children. A large group of infected children is asymptomatic or present mild symptoms of illness, depending on the age of the patients. Symptoms such as fever, feeding difficulty, intussusception, bronchiolitis, apnea, cough, tachypnea, diarrhea, and rhinorrhea are the most common in the group of 0 – 4-year-old children. In a group of older children aged 5 – 17, the most common and typical symptoms are fever, cough, sore throat, headache, myalgia, or diarrhea. Non-specific COVID-19 might present as gastrointestinal and hepatic abnormalities, olfactory and gustatory dysfunctions, such as hypogeusia or anosmia, neurological and ophthalmic manifestations, such as fatigue, altered consciousness, myalgia, dysgeusia, anosmia, seizure, conjunctivitis, bilateral non-granulomatous acute anterior epitheliopathy, and corneal punctate epitheliopathy.

Cardiovascular manifestations, which included ventricular dysfunction, coronary artery aneurysms, aberrant conduction and arrhythmias, were some of the most worrying non-specific symptoms of SARS-CoV-2. It is also alarming there have been reports about some psychiatric abnormalities related to COVID-19, such as short-term memory deficits, concentration problems, general memory loss, a specific decline in attention, language and praxis abilities, impaired encoding and verbal fluency, as well as impairment of executive functions and psychomotor coordination. Dermatological and rheumatological symptoms, although quite rare findings, are also a part of non-specific manifestations of COVID-19 infection.

REFERENCES

1. Mohamadian M, Chiti H, Shoghli A, et al. COVID-19: Virology, biology and novel laboratory diagnosis. J Gene Med. 2021 Feb;23(2):e3303. doi: 10.1002/jgm.3303
2. Umakanthan S, Sahu P, Ranade AV, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). Postgrad Med J. 2020 Dec;96(1142):753–758. doi:10.1136/postgradmedj-2020-138234
3. Hu B, Guo H, Zhou P, et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021 Mar; 19(3):141–154. doi:10.1038/s41579-020-00459-7
4. Atzrodt CL, Maknojia I, McCarthy RDP, et al. A Guide to COVID-19: a global pandemic caused by the novel coronavirus SARS-CoV-2. FEBS J. 2020 Sep; 287(17):3633–3650. doi:10.1111/febs.15375
5. Iranmanesh B, Khalili M, Amiri R, et al. Oral manifestations of COVID-19 disease: A review article. Dermatol Ther. 2021 Jan; 34(1):e14578. doi:10.1111/dth.14578
6. Kariyawasam JC, Jayarajah U, Riza R, et al. Gastrointestinal manifestations in COVID-19. Trans R Soc Trop Med Hyg. 2021 Dec 2;115(12):1362–1388. doi:10.1093/trstmh/trab042
7. Zhong Y, Wang K, Zhu Y, et al. Ocular manifestations in COVID-19 patients: A systematic review and meta-analysis. Travel Med Infect Dis. 2021 Nov-Dec;44:102191. doi:10.1016/j.tmaid.2021.102191
8. Juchnowicz D, Baj J, Forma A, et al. The Outbreak of SARS-CoV-2 Pandemic and the Well-Being of Polish Students: The Risk Factors of the Emotional Distress during COVID-19 Lockdown. J Clin Med. 2021 Mar 1;10(5):944. doi:10.3390/jcm10050944
9. Baj J, Forma A, Teresińska B, et al. How Does SARS-CoV-2 Affect Our Eyes-What Have We Learnt So Far about the Ophthalmic Manifestations of COVID-19? J Clin Med. 2022 Jun; 13;11(12): 3379. doi: 10.3390/jcm11123379
10. Khan M, Adil SF, Alkhathlan HZ, et al. COVID-19: A Global Challenge with Old History, Epidemiology and Progress So Far. Molecules. 2020 Dec 23;26(1):39. doi:10.3390/molecules26010039
11. Yesudhas D, Srivastava A, Gromiha MM. COVID-19 outbreak: history, mechanism, transmission, structural studies and therapeutics. Infection. 2021 Apr;49(2):199–213. doi:10.1007/s15010-020-01516-2
12. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis. 2021 May; 40(5):905–919. doi:10.1007/s10096-020-04138-6
13. Ge ZY, Yang LM, Xia JJ, et al. Possible aerosol transmission of COVID-19 and special precautions in dentistry. J Zhejiang Univ Sci B. 2020 May;21(5): 361–368. doi:10.1631/jzus.B2010010
14. Salian VS, Wright JA, Vedell PT, et al. COVID-19 Transmission, Current Treatment, and Future Therapeutic Strategies. Mol Pharm. 2021 Mar 1;18(3):754–771. doi:10.1021/acs.molpharmaceut.0c00608
15. Jayaweera M, Perera H, Gunawardana B, et al. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res. 2020 Sep; 188:109819. doi:10.1016/j.envres.2020.109819
16. Geng Y, Wang Y. Stability and transmissibility of SARS-CoV-2 in the environment. J Med Virol. 2023 Jan; 95(1):e28103. doi:10.1002/jmv.28103
17. Rahman S, Montero MTV, Rowe K, et al. Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence. Expert Rev Clin Pharmacol. 2021 May; 14(5): 601–621. doi: 10.1080/17512433.2021.1902303.
18. Li MY, Li L, Zhang Y, et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020 Apr 28; 9(1): 45. doi: 10.1186/s40249-020-00662-x
19. Tabatabaeizadeh SA. Airborne transmission of COVID-19 and the role of face mask to prevent it: a systematic review and meta-analysis. Eur J Med Res. 2021 Jan 2; 26(1): 1. doi:10.1186/s40001-020-00475-6
20. Borak J. Airborne Transmission of COVID-19. Occup Med (Lond). 2020 Jul 17; 70(5): 297–299. doi:10.1093/occmed/kqaa080.
21. Zhao X, Liu S, Yin Y, et al. Airborne transmission of COVID-19 virus in enclosed spaces: An overview of research methods. Indoor Air. 2022 Jun; 32(6): e13056. doi: 10.1111/ina.13056.
22. Domingo JL, Marquès M, Rovira J. Influence of airborne transmission of SARS-CoV-2 on COVID-19 pandemic. A review. Environ Res. 2020 Sep; 188: 109861. doi: 10.1016/j.envres.2020.109861.
23. Karia R, Gupta I, Khandait H, et al. COVID-19 and its Modes of Transmission. SN Compr Clin Med. 2020; 2(10): 1798–1801. doi: 10.1007/s42399-020-00498-4
24. Abney SE, Bright KR, McKinney J, et al. Toilet hygiene-review and research needs. J Appl Microbiol. 2021 Dec; 131(6): 2705–2714. doi: 10.1111/jam.15121.
25. Onakpoya IJ, Heneghan CJ, Spencer EA, et al. SARS-CoV-2 and the role of fomite transmission: a systematic review. F1000Res. 2021 Mar 24; 10: 233. doi: 10.12688/f1000research.51590.3.
26. Arienzo A, Gallo V, Tomassetti F, et al. A narrative review of alternative transmission routes of COVID 19: what we know so far. Pathog Glob Health. 2023 Jun; 23: 1–15. doi: 10.1080/20477724.2023.2228048.
27. Mourmouris P, Tzelves L, Roidi C, et al. COVID-19 transmission: a rapid systematic review of current knowledge. Osong Public Health Res Perspect. 2021 Apr; 12(2): 54–63. doi: 10.24171/j.phrp.2021.12.2.02.
28. Jamieson DJ, Rasmussen SA. An update on COVID-19 and pregnancy. Am J Obstet Gynecol. 2022 Feb; 226(2): 177–186. doi: 10.1016/j.ajog.2021.08.054.
29. Rasmussen SA, Jamieson DJ. COVID-19 and Pregnancy. Infect Dis Clin North Am. 2022 Jun; 36(2): 423–433. doi: 10.1016/j.idc.2022.01.002.
30. Moore KM, Suthar MS. Comprehensive analysis of COVID-19 during pregnancy. Biochem Biophys Res Commun. 2021 Jan 29; 538: 180–186. doi: 10.1016/j.bbrc.2020.12.064.
31. Facciolà A, Micali C, Visalli G, et al. COVID-19 and pregnancy: clinical outcomes and scientific evidence about vaccination. Eur Rev Med Pharmacol Sci. 2022 Apr; 26(7): 2610–2626. doi: 10.26355/eurrev_202204_28499.
32. Abdollahpour S, Badiee Aval S, Khadivzadeh T. Do Not Neglect the Covid-19 Transmission Through Sexual Intercourse. J Sex Marital Ther. 2021; 47(7): 731–737. doi: 10.1080/0092623X.2021.1938765.
33. Cipriano M, Giacalone A, Ruberti E. Sexual Behaviors During COVID-19: The Potential Risk of Transmission. Arch Sex Behav. 2020 Jul; 49(5): 1431–1432. doi: 10.1007/s10508-020-01757-0

34. Tatu AL, Nadasdy T, Nwabudike LC. Observations about sexual and other routes of SARS-CoV-2 (COVID-19) transmission and its prevention. Clin Exp Dermatol. 2020 Aug; 45(6): 761–762. doi: 10.1111/ced.14274.
35. Talic S, Shah S, Wild H, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. BMJ. 2021 Nov 17; 375: e068302. doi: 10.1136/bmj-2021–068302.
36. Chen F, Tian Y, Zhang L, et al. The role of children in household transmission of COVID-19: a systematic review and meta-analysis. Int J Infect Dis. 2022 Sep; 122: 266–275. doi: 10.1016/j.ijid.2022.05.016.
37. Williams PCM, Howard-Jones AR, Hsu P, et al. SARS-CoV-2 in children: spectrum of disease, transmission and immunopathological underpinnings. Pathology. 2020 Dec; 52(7): 801–808. doi: 10.1016/j.pathol.2020.08.001.
38. Cui X, Zhao Z, Zhang T, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol. 2021 Feb; 93(2): 1057–1069. doi: 10.1002/jmv.26398.
39. Nikolopoulou GB, Maltezou HC. COVID-19 in Children: Where do we Stand? Arch Med Res. 2022 Jan; 53(1): 1–8. doi: 10.1016/j.arcmed.2021.07.002.
40. Deville JD, Song E, Ouellette CP, et al. COVID-19: Clinical manifestations and diagnosis in children https://www.uptodate.com/contents/covid-19-clinical-manifestations-and-diagnosis-in-children (accessed on September 2023)
41. Toba N, Gupta S, Ali AY, et al. COVID-19 under 19: A meta-analysis. Pediatr Pulmonol. 2021 Jun; 56(6): 1332–1341. doi: 10.1002/ppul.25312.
42. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021 Jul; 180(7): 2019–2034. doi: 10.1007/s00431–021–03993–5.
43. Yasuhara J, Kuno T, Takagi H, et al. Clinical characteristics of COVID-19 in children: A systematic review. Pediatr Pulmonol. 2020 Oct; 55(10): 2565–2575. doi: 10.1002/ppul.24991.
44. Meena J, Yadav J, Saini L, et al. Clinical Features and Outcome of SARS-CoV-2 Infection in Children: A Systematic Review and Meta-analysis. Indian Pediatr. 2020 Sep 15; 57(9): 820–826. doi: 10.1007/s13312–020–1961–0.
45. Carlotti APCP, de Carvalho WB, Johnston C, et al. Update on the diagnosis and management of COVID-19 in pediatric patients. Clinics (Sao Paulo). 2020 Nov 30; 75: e2353. doi: 10.6061/clinics/2020/e2353.
46. Rai P, Kumar BK, Deekshit VK, et al. Detection technologies and recent developments in the diagnosis of COVID-19 infection. Appl Microbiol Biotechnol. 2021 Jan; 105(2): 441–455. doi: 10.1007/s00253–020–11061–5.
47. Chaimayo C, Kaewnaphan B, Tanlieng N, et al. Rapid SARS-CoV-2 antigen detection assay in comparison with real-time RT-PCR assay for laboratory diagnosis of COVID-19 in Thailand. Virol J. 2020 Nov 13; 17(1): 177. doi: 10.1186/s12985–020–01452–5.
48. Rostad CA, Chahroudi A, Mantus G, et al. Quantitative SARS-CoV-2 Serology in Children With Multisystem Inflammatory Syndrome (MIS-C). Pediatrics. 2020 Dec; 146(6): e2020018242. doi: 10.1542/peds.2020–018242.
49. Mirbeyk M, Saghazadeh A, Rezaei N. A systematic review of pregnant women with COVID-19 and their neonates. Arch Gynecol Obstet. 2021 Jul; 304(1): 5–38. doi: 10.1007/s00404–021–06049-z.
50. Venn AMR, Schmidt JM, Mullan PC. Pediatric croup with COVID-19. Am J Emerg Med. 2021 May; 43: 287.e1–287.e3. doi: 10.1016/j.ajem.2020.09.034.
51. Zhu F, Ang JY. COVID-19 Infection in Children: Diagnosis and Management. Curr Infect Dis Rep. 2022; 24(4): 51–62. doi: 10.1007/s11908–022–00779–0.
52. Qi K, Zeng W, Ye M, et al. Clinical, laboratory, and imaging features of pediatric COVID-19: A systematic review and meta-analysis. Medicine (Baltimore). 2021 Apr 16; 100(15): e25230. doi: 10.1097/MD.0000000000025230.
53. Chams N, Chams S, Badran R, et al. COVID-19: A Multidisciplinary Review. Front Public Health. 2020 Jul 29; 8: 383. doi: 10.3389/fpubh.2020.00383.
54. Cao Y, Liu X, Xiong L, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. J Med Virol. 2020 Sep; 92(9): 1449–1459. doi: 10.1002/jmv.25822.
55. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging. 2020 May; 47(5): 1275–1280. doi: 10.1007/s00259–020–04735–9.
56. Simsek Uzunoglu S, Akca H. Systematic Review: Clinical Symptoms and Laboratory and Radiology Findings in Children with COVID-19. Niger J Clin Pract. 2021 Sep; 24(9): 1259–1267. doi: 10.4103/njcp.njcp_577_20.
57. Yasuhara J, Watanabe K, Takagi H, et al. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol. 2021 May; 56(5): 837–848. doi: 10.1002/ppul.25245.
58. Khatami F, Saatchi M, Zadeh SST, et al. A meta-analysis of accuracy and sensitivity of chest CT and RT-PCR in COVID-19 diagnosis. Sci Rep. 2020 Dec 28; 10(1): 22402. doi: 10.1038/s41598–020–80061–2.
59. Vakili S, Savardashtaki A, Jamalnia S, et al. Laboratory Findings of COVID-19 Infection are Conflicting in Different Age Groups and Pregnant Women: A Literature Review. Arch Med Res. 2020 Oct; 51(7): 603–607. doi: 10.1016/j.arcmed.2020.06.007.
60. Baj J, Karakuła-Juchnowicz H, Teresiński G, et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. J Clin Med. 2020 Jun 5; 9(6): 1753. doi: 10.3390/jcm9061753.
61. Zhang G, Zhang J, Wang B, et al. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. Respir Res. 2020 Mar 26; 21(1): 74. doi: 10.1186/s12931–020–01338–8.
62. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020 Jun; 109(6): 1088–1095. doi: 10.1111/apa.15270.
63. Graff K, Smith C, Silveira L, et al. Risk Factors for Severe COVID-19 in Children. Pediatr Infect Dis J. 2021 Apr 1; 40(4): e137-e145. doi: 10.1097/INF.0000000000003043.
64. Cao J, Devaraj S. COVID-19 in Pediatrics: A Laboratory Perspective. J Appl Lab Med. 2020 Jul 1; 5(4): 824–828. doi: 10.1093/jalm/jfaa065.
65. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020 Nov; 20(11): e276-e288. doi: 10.1016/S1473–3099(20)30651–4.
66. Patel JM. Multisystem Inflammatory Syndrome in Children (MIS-C). Curr Allergy Asthma Rep. 2022 May; 22(5): 53–60. doi: 10.1007/s11882–022–01031–4.
67. Sperotto F, Friedman KG, Son MBF, et al. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021 Feb; 180(2): 307–322. doi: 10.1007/s00431–020–03766–6.
68. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020 Sep; 26: 100527. doi: 10.1016/j.eclinm.2020.100527.
69. Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev. 2021 Jun; 38: 51–57. doi: 10.1016/j.prrv.2020.08.001.
70. Waseem M, Shariff MA, Tay ET, et al. Multisystem Inflammatory Syndrome in Children. J Emerg Med. 2022 Jan; 62(1): 28–37. doi: 10.1016/j.jemermed.2021.07.070.
71. Liu K, Yu J, Song G. Global Myocardial Strain in Multisystem Inflammatory Syndrome in Children, Kawasaki Disease, and Healthy Children: A Network Meta-Analysis. Front Pediatr. 2022 Jun 27; 10: 848306. doi: 10.3389/fped.2022.848306.
72. Santos MO, Gonçalves LC, Silva PAN, Met al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J). 2022 Jul-Aug; 98(4): 338–349. doi: 10.1016/j.jped.2021.08.006.
73. Mahmoud S, El-Kalliny M, Kotby A, et al. Treatment of MIS-C in Children and Adolescents. Curr Pediatr Rep. 2022; 10(1): 1–10. doi: 10.1007/s40124–021–00259–4.
74. Wang Z, Zhao S, Tang Y, et al. Potentially effective drugs for the treatment of COVID-19 or MIS-C in children: a systematic review. Eur J Pediatr. 2022 May; 181(5): 2135–2146. doi: 10.1007/s00431–022–04388-w.
75. Levy E, Stintzi A, Cohen A, et al. Critical appraisal of the mechanisms of gastrointestinal and hepatobiliary infection by COVID-19. Am J Physiol Gastrointest Liver Physiol. 2021 Aug 1; 321(2): G99-G112. doi: 10.1152/ajpgi.00106.2021.
76. Pegoraro F, Trapani S, Indolfi G. Gastrointestinal, hepatic and pancreatic manifestations of COVID-19 in children. Clin Res Hepatol Gastroenterol. 2022 Apr; 46(4): 101818. doi: 10.1016/j.clinre.2021.101818.
77. Fathema K, Hassan MN, Mazumder MW, et al. COVID 19 in Children: Gastrointestinal, Hepatobiliary and Pancreatic Manifestation. Mymensingh Med J. 2021 Apr; 30(2): 570–579.
78. Villanueva Ch M, Faundez H R, Godoy M. Manifestaciones gastrointestinales y hepáticas de COVID-19 en niños [Gastrointestinal and hepatic manifestations of COVID-19 in children]. Rev Chil Pediatr. 2020 Aug; 91(4): 623–630. doi: 10.32641/rchped.vi91i4.2484.

79. Cooper S, Tobar A, Konen O, et al. Long COVID-19 Liver Manifestation in Children. J Pediatr Gastroenterol Nutr. 2022 Sep 1; 75(3): 244–251. doi: 10.1097/MPG.0000000000003521.
80. Sica R, Pennoni S, Penta L, et al. Gastrointestinal and hepatic involvement during COVID-19 pandemic: A focus on pediatric population and possible future implications. World J Gastroenterol. 2021 Oct 28; 27(40): 7000–7004. doi: 10.3748/wjg.v27.i40.7000.
81. Sica R, Pennoni S, Penta L, et al. New Onset of Hepatic Steatosis Post-Severe Multisystem Inflammatory Syndrome in Children (MIS-C): A Case Report. Int J Environ Res Public Health. 2021
82. Pousa PA, Mendonça TSC, Oliveira EA, et al. Extrapulmonary manifestations of COVID-19 in children: a comprehensive review and pathophysiological considerations. J Pediatr (Rio J). 2021 Mar-Apr; 97(2): 116–139. doi: 10.1016/j.jped.2020.08.007.
83. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China. JAMA Neurol. 2020; 77: 683–690.
84. LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021; 78: 536–547.
85. Púa Torrejón RC, Ordoño Saiz MV, González Alguacil E, et al. Smell and Taste Dysfunction in Pediatric Patients With SARS-CoV-2 Infection. Pediatr Neurol. 2022 Nov; 136: 28–33. doi: 10.1016/j.pediatrneurol.2022.07.006.
86. Namazova-Baranova L, Karkashadze G, Zelenkova I, et al. A non-randomized comparative study of olfactory and gustatory functions in children who recovered from COVID-19 (1-year follow-up). Front Pediatr. 2022 Sep 9; 10: 919061. doi: 10.3389/fped.2022.919061.
87. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181: 271–280. e278.
88. Cho SM, White N, Premraj L, et al; ISARIC Clinical Characterisation Group. Neurological manifestations of COVID-19 in adults and children. Brain. 2022 Sep; 10:awac332. doi: 10.1093/brain/awac332.
89. Lin JE, Asfour A, Sewell TB, et al. Neurological issues in children with COVID-19. Neurosci Lett. 2021 Jan 19; 743: 135567. doi: 10.1016/j.neulet.2020.135567.
90. Ray STJ, Abdel-Mannan O, Sa M, et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc Health. 2021 Sep; 5(9): 631–641. doi: 10.1016/S2352–4642(21)00193–0.
91. Decio A, Mazza A, Quadri V, et al. Neurological Manifestations of COVID-19 in Children: A Case of Facial Nerve Palsy. Pediatr Neurol. 2021 Mar; 116: 59. doi: 10.1016/j.pediatrneurol.2020.12.006.
92. Kaur H, Mason JA, Bajracharya M, et al. Transverse Myelitis in a Child With COVID-19. Pediatr Neurol. 2020 Nov; 112: 5–6. doi: 10.1016/j.pediatrneurol.2020.07.017.
93. Lavery MJ, Bouvier CA, Thompson B. Cutaneous manifestations of COVID-19 in children (and adults): A virus that does not discriminate. Clin Dermatol. 2021 Mar-Apr; 39(2): 323–328. doi: 10.1016/j.clindermatol.2020.10.020.
94. Ciechanowicz P, Dopytalska K, Szczerba M, et al. Dermatological manifestations of the Coronavirus disease 2019 in children: a systemic review. Postepy Dermatol Alergol. 2022 Jun; 39(3): 491–508. doi: 10.5114/ada.2020.99294.
95. Andina D, Belloni-Fortina A, Bodemer C, Bet al. Skin manifestations of COVID-19 in children: Part 1. Clin Exp Dermatol. 2021 Apr; 46(3): 444–450. doi: 10.1111/ced.14481.
96. Andina D, Belloni-Fortina A, Bodemer C, et al. Skin manifestations of COVID-19 in children: Part 2. Clin Exp Dermatol. 2021 Apr; 46(3): 451–461. doi: 10.1111/ced.14482.
97. Andina D, Belloni-Fortina A, Bodemer C, et al. Skin manifestations of COVID-19 in children: Part 3. Clin Exp Dermatol. 2021 Apr; 46(3): 462–472. doi: 10.1111/ced.14483.
98. Panda M, Agarwal A, Hassanandani T. Dermatological Manifestations of COVID-19 in Children. Indian Pediatr. 2022 May 15; 59(5): 393–399. doi: 10.1007/s13312–022–2521–6.
99. Brumfiel CM, DiLorenzo AM, Petronic-Rosic VM. Dermatologic manifestations of COVID-19-associated multisystem inflammatory syndrome in children. Clin Dermatol. 2021 Mar-Apr; 39(2): 329–333. doi: 10.1016/j.clindermatol.2020.10.021.
100. Rogers JP, Watson CJ, Badenoch J, et al. Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives. J Neurol Neurosurg Psychiatry. 2021 Sep; 92(9): 932–941. doi: 10.1136/jnnp-2021–326405.
101. Zawilska JB, Kuczyńska K. Psychiatric and neurological complications of long COVID. J Psychiatr Res. 2022 Dec; 156: 349–360. doi: 10.1016/j.jpsychires.2022.10.045.
102. Singh S, Roy D, Sinha K, et al. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. Psychiatry Res. 2020 Nov; 293: 113429. doi: 10.1016/j.psychres.2020.113429.
103. Markiewicz-Gospodarek A, Górska A, Markiewicz R, et al. The Relationship between Mental Disorders and the COVID-19 Pandemic—Course, Risk Factors, and Potential Consequences. Int. J. Environ. Res. Public Health 2022; 19: 9573. https://doi.org/10.3390/ijerph19159573
104. Sitarz R, Forma A, Karakuła K, et al. How Do Polish Students Manage Emotional Distress during the COVID-19 Lockdown? A Web-Based Cross-Sectional Study. J. Clin. Med. 2021; 10: 4964. https://doi.org/10.3390/jcm10214964
105. Karakuła KH, Nowacka O, Ryczkowski A, et al. "COVID-19-induced psychosis: two case reports and narrative literature review" Curr. Prob. of Psych. 2022; vol.23, no.3, 3922: pp.151–158. https://doi.org/10.2478/cpp-2022–0015
106. Sen M, Honavar SG, Sharma N, et al. COVID-19 and Eye: A Review of Ophthalmic Manifestations of COVID-19. Indian J Ophthalmol. 2021 Mar; 69(3): 488–509. doi: 10.4103/ijo.IJO_297_21.
107. Danthuluri V, Grant MB. Update and Recommendations for Ocular Manifestations of COVID-19 in Adults and Children: A Narrative Review. Ophthalmol Ther. 2020 Dec; 9(4): 853–875. doi: 10.1007/s40123–020–00310–5.
108. Al-Namaeh M. Ocular manifestations of COVID-19. Ther Adv Ophthalmol. 2022 Apr 12; 14: 25158414221083374. doi: 10.1177/25158414221083374.
109. Öztürk C, Yüce Sezen A, Savaş Şen Z, et al. Bilateral Acute Anterior Uveitis and Corneal Punctate Epitheliopathy in Children Diagnosed with Multisystem Inflammatory Syndrome Secondary to COVID-19. Ocul Immunol Inflamm. 2021 May 19; 29(4): 700–704. doi: 10.1080/09273948.2021.1909070.
110. Ichhpujani P, Singh RB, Dhillon HK et al. Ocular manifestations of COVID-19 in pediatric patients. Ther Adv Ophthalmol. 2023 Mar 14; 15: 25158414221149916. doi: 10.1177/25158414221149916.
111. Ma N, Li P, Wang X, et al. Ocular Manifestations and Clinical Characteristics of Children With Laboratory-Confirmed COVID-19 in Wuhan, China. JAMA Ophthalmol. 2020 Oct 1; 138(10): 1079–1086. doi: 10.1001/jamaophthalmol.2020.3690.
112. Valente P, Iarossi G, Federici M, et al. Ocular manifestations and viral shedding in tears of pediatric patients with coronavirus disease 2019: a preliminary report. J AAPOS. 2020 Aug; 24(4): 212–215. doi: 10.1016/j.jaapos.2020.05.002.
113. Wu EY, Campbell MJ. Cardiac Manifestations of Multisystem Inflammatory Syndrome in Children (MIS-C) Following COVID-19. Curr Cardiol Rep. 2021 Oct 1; 23(11): 168. doi: 10.1007/s11886–021–01602–3.
114. Oragui CC. Cardiovascular Manifestations of Multisystem Inflammatory Syndrome in Children (MIS-C) Associated With COVID-19. Cureus. 2023 Jul 16; 15(7): e41950. doi: 10.7759/cureus.41950.
115. Campanello C, Mercuri C, Derchi M, et al. Cardiovascular Manifestations in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19 According to Age. Children (Basel). 2022 Apr 20; 9(5): 583. doi: 10.3390/children9050583.
116. Jone PN, John A, Oster ME, et al. SARS-CoV-2 Infection and Associated Cardiovascular Manifestations and Complications in Children and Young Adults: A Scientific Statement From the American Heart Association. Circulation. 2022 May 10; 145(19): e1037-e1052. doi: 10.1161/CIR.0000000000001064.
117. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe. Circulation. 2021 Jan 5; 143(1): 21–32. doi: 10.1161/CIRCULATIONAHA.120.050065.
118. Kabeerdoss J, Pilania RK, Karkhele R, et al. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int. 2021 Jan; 41(1): 19–32. doi: 10.1007/s00296–020–04749–4.
119. Gawaz M, Scharf RE. COVID-19: Cardio-pulmonary and Vascular Manifestations. Hamostaseologie. 2021 Oct; 41(5): 347–348. doi: 10.1055/a-1370–0231.
120. Song MK, Kwon B. Arrhythmia and COVID-19 in children. Clin Exp Pediatr. 2023 May; 66(5): 190–200. doi: 10.3345/cep.2023.00024.

121. Yasuhara J, Watanabe K, Takagi H, et al. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol. 2021 May; 56(5): 837–848. doi: 10.1002/ppul.25245.
122. Saed Aldien A, Ganesan GS, Wahbeh F, et al. Systemic Inflammation May Induce Cardiac Injury in COVID-19 Patients Including Children and Adolescents Without Underlying Cardiovascular Diseases: A Systematic Review. Cardiovasc Revasc Med. 2022 Feb; 35: 169–178. doi: 10.1016/j.carrev.2021.04.007.
123. Ramani SL, Samet J, Franz CK, et al. Musculoskeletal involvement of COVID-19: review of imaging. Skeletal Radiol. 2021 Sep; 50(9): 1763–1773. doi: 10.1007/s00256–021–03734–7.
124. Ahmed S, Zimba O, Gasparyan AY. COVID-19 and the clinical course of rheumatic manifestations. Clin Rheumatol. 2021 Jul; 40(7): 2611–2619. doi: 10.1007/s10067–021–05691-x.
125. Ciaffi J, Meliconi R, Ruscitti P, et al. Rheumatic manifestations of COVID-19: a systematic review and meta-analysis. BMC Rheumatol. 2020 Oct 28; 4: 65. doi: 10.1186/s41927–020–00165–0.
126. Migliorini F, Bell A, Vaishya R, et al. Reactive arthritis following COVID-19 current evidence, diagnosis, and management strategies. J Orthop Surg Res. 2023 Mar 15; 18(1): 205. doi: 10.1186/s13018–023–03651–6.
127. Ciaffi J, Vanni E, Mancarella L, et al. Post-Acute COVID-19 Joint Pain and New Onset of Rheumatic Musculoskeletal Diseases: A Systematic Review. Diagnostics (Basel). 2023 May 25; 13(11): 1850. doi: 10.3390/diagnostics13111850.
128. Shah S, Danda D, Kavadichanda C, et al. Autoimmune and rheumatic musculoskeletal diseases as a consequence of SARS-CoV-2 infection and its treatment. Rheumatol Int. 2020 Oct; 40(10): 1539–1554. doi: 10.1007/s00296–020–04639–9.
129. Pal A, Roongta R, Mondal S, et al. Does post-COVID reactive arthritis exist? Experience of a tertiary care centre with a review of the literature. Reumatol Clin (Engl Ed). 2023 Feb; 19(2): 67–73. doi: 10.1016/j.reumae.2022.03.005.