American Journal of Medical Case Reports, 2022, Vol. 10, No. 2, 29-34
Available online at http://pubs.sciepub.com/ajmcr/10/2/3
Published by Science and Education Publishing
DOI:10.12691/ajmcr-10-2-3

COVID 19: A Case Series of Diverse Clinical Presentations at a Tertiary Hospital in Nigeria

Adegoke Oluwakemi T[1,*], Bamigboye-Taiwo Olukemi T[1], Afeniforo Olufunke G[1], Okeniyi John A[1], Omotoye Babatunde S[2], Olorunmoteni Oluwatosin E[1], Adegoke Adedokun I[3]

[1]Department of Paediatrics, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria
[2]Department of Surgery, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria
[3]Department of Obstetrics and Gynaecology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria
*Corresponding author: aktpillar@yahoo.com

Received December 09, 2021; Revised January 14, 2022; Accepted January 23, 2022

Abstract COVID-19 is a disease which originated in China in 2019 and has rapidly spread to become a pandemic. COVID-19 is less common in children and young adults and cases among this group of individuals are usually not as severe as in the elderly, the immunocompromised or those with co-morbidities. Research of COVID-19 in children is not as robust as in adults probably due to the aforementioned reason. We report four cases of COVID-19 in children who had mild to severe disease course. These children had other co-morbid illnesses such as malaria, bacterial sepsis and rheumatic heart disease. Two of these children had rarer severe complications of the disease hardly reported in children, these were; pleural effusion and cholestatic liver disease. It may be important to screen every child that requires hospital admission for COVID-19 in order to make early diagnosis of the disease and to commence appropriate therapy where necessary. This may forestall development of complications including death in such children.

Keywords: *COVID-19, sepsis, cholestatic jaundice, malaria, pleural effusion, rheumatic heart disease*

Cite This Article: Adegoke Oluwakemi T, Bamigboye-Taiwo Olukemi T, Afeniforo Olufunke G, Okeniyi John A, Omotoye Babatunde S, Olorunmoteni Oluwatosin E, and Adegoke Adedokun I, "COVID 19: A Case Series of Diverse Clinical Presentations at a Tertiary Hospital in Nigeria." *American Journal of Medical Case Reports*, vol. 10, no. 2 (2022): 29-34. doi: 10.12691/ajmcr-10-2-3.

1. Introduction

An epidemic of acute respiratory syndrome-like illness broke out in 2019 in Wuhan, China. The disease was later named COVID-19 and was found to be caused by a corona virus subsequently labelled SARS-CoV-2. [1] The disease further spread to other parts of the world and the outbreak was declared a public health emergency of international concern on 30th January 2020, and a pandemic on 11th March 2020 by the World Health Organization. [2]

SARS-CoV-2 is spread from person to person usually by droplet nuclei or contact. Upon entry into the respiratory tract, the virus enters epithelial cells by interacting with its receptor, angiotensin-converting enzyme 2 (ACE-2), and another co-receptor which may be transmembrane protease serine 2 (TMPRSS2) or a disintegrin metallopeptidase domain 17 (ADAM17). [3] Free and phagocytosed virions can pass from the lungs to other organs via the circulation. Angiotensin-converting enzyme 2 is expressed in many organs including the type II alveolar cell of the lung, proximal convoluted tubular cells of the kidneys, myocardial cells and enterocytes of the small intestine. Therefore, the virus can enter many cell-types in the body resulting in multi-organ involvement. [3] The ongoing active cell multiplication incite a cytokine storm which causes acute respiratory distress syndrome and respiratory failure. While this progression occurs mostly in the elderly or people with co-morbidities, children and younger adults present frequently with a mild pneumonia. Some infected persons may be asymptomatic while others develop non-pneumonia manifestations. [1]

Children tend to have less severe course of disease due to various factors. Some of these include absence of age-related epithelial damage, lower density and distribution of ACE-2 and TMPRSS2, fewer comorbidities, more frequent recurrent or concurrent infections, and non-specific off-target effects of live vaccines. [4] Despite these protective influences, children can still develop severe disease that may sometimes be fatal.

We report the diversity of COVID-19 manifestations in this series of four children who had mild to severe infection. This is especially important because epidemiological reports show that Nigerians and many other African countries have had fewer cases of the disease compared to developed countries, with severe disease rarely reported in children. The range of clinical presentations described in these few patients also indicate the need for heightened index of suspicion in making a diagnosis of COVID-19 in the clinical setting.

2. Case Reports

2.1. Case 1

We admitted a 7-year old boy with complaints of progressively worsening dyspnea on exertion and recurrent fever of two months. He had chest pain, palpitations and weight loss but no cough, orthopnea nor paroxysmal nocturnal dyspnea. There was no contact with anyone having similar complaints. He developed painful deformity of the left arm and inability to bear weight on his right leg about three weeks before presentation. There was no trauma prior to the development of the deformities. He had been on admission for 15 days at the referring center where he was transfused with blood twice. His hemoglobin genotype was AS. His development had been normal. He was referred to our hospital following echocardiographic diagnosis of an acquired heart disease.

At presentation, he was conscious, dyspneic, pale, febrile with peripheral temperature of 38.6^0C, and had no digital clubbing. There was evidence of wasting with zygomatic and clavicular prominence and his weight was 18kg which was on the 2nd centile. He was tachycardic with a heart rate of 170 beats/minute, had normal blood pressure, apex beat was displaced to the 6th left intercostal space anterior axillary line, he had first and second heart sounds with a grade 3/6 pansystolic murmur loudest at the apex. Oxygen saturation was 95% in room air. He was tachypneic with a respiratory rate of 50 cycles/minute. He had soft, tender hepatomegaly. There was tender deformity of the proximal left arm and right mid-thigh with inability to move both limbs.

Diagnoses of acquired heart disease probably rheumatic heart disease with congestive heart failure and pathological fractures of the left humerus and right femur were made. A diagnosis of COVID-19 was suspected due to the increasing number of cases in the country at that time and the series of travels the patient had made across many states within the country. Echocardiography report showed rheumatic valvular heart disease. X-rays of the left arm and right thigh both showed fractures with cortical thinness. Complete blood count showed anemia with hematocrit of 21%, normal white blood cell count with relative neutrophilia, and normal platelet count. Peripheral blood film showed hypochromia and microcytosis. There was left shift with immature to mature neutrophil ratio greater than 0.2 and toxic granulation. He had mild hypoalbuminemia with normal calcium and phosphate levels while serum vitamin D level was deficient at 14.8ng/ml (30-70ng/ml). Polymerase chain reaction (PCR) test was positive for SARS-CoV-2.

Patient was given intravenous ceftriaxone. He had no specific treatment for COVID-19 apart from oral zinc and vitamin C which were added to his medications when the PCR test was noted to be positive. He was transfused with whole blood and his post-transfusion hematocrit was 26%. Congestive heart failure was treated with intravenous frusemide, and then oral spironolactone and hydrochlorothiazide. Patient's clinical condition improved and a repeat PCR test done nine days after admission returned negative. He was discharged on the fifteenth day of admission. The patient is being followed up at another hospital closer to their home.

2.2. Case 2

A three-year-old girl was admitted with fever, vomiting, dark urine and pallor. The illness started three days before admission. She had difficulty in breathing which was noticed at presentation. She had a similar illness three months before admission for which she was transfused, otherwise, there was no other history to suggest sickle cell disease. Some of her male cousins had passed dark urine in the past.

At presentation, she was conscious but lethargic, severely pale, anicteric and in respiratory distress. Her weight was 12kg, between the 2nd and 9th centile. She was tachypneic and tachycardic with oxygen saturation of 90% in room air. The breath sounds were vesicular. There was soft and tender hepatomegaly.

A diagnosis of severe malaria with anemic heart failure was made. Differential diagnoses were glucose-6-phosphate dehydrogenase (G6PD) deficiency and sickle cell anemia. She was severely anemic with hematocrit of 10%. Total white cell count and differentials were normal while she had low platelet count of 64000cell/mm3. Her peripheral blood film showed macrocytosis, microcytosis, hypochromia and demonstration of trophozoites of Plasmodium falciparum. Hemoglobin genotype was AA while a qualitative G6PD assay was normal. She had positive IgM and negative IgG antibody test for the SARS-CoV-2, necessitating confirmatory PCR test which turned out positive.

She was transfused with blood, and given intranasal oxygen, intravenous artesunate and subsequently artemisinin-based combination therapy. She made significant improvement on these medications and the oxygen saturation became normal without any additional treatment. She was discharged on oral vitamin C, E and zinc supplements on the 5th day of admission and was to return for follow up PCR test. The patient improved significantly after discharge with no sequelae obvious to the caregivers. She had another febrile illness few months after, which she unfortunately succumbed to.

2.3. Case 3

We admitted a 13-year old boy with right knee pain of three weeks. He fell on his right knee while playing football in school and immediately developed pain at the site. He noticed gradual swelling of the knee few days after the fall. Right knee pain was severe enough to prevent him from ambulating. Two weeks before presentation, he developed high grade, intermittent fever. He had chest pain and respiratory distress which were present for three days before he was admitted. He also developed jaundice 3 days before presentation with passage of dark urine. His past medical history was not significant.

At presentation, he was conscious, not pale, icteric with a greenish hue, and in respiratory distress. His weight was 44kg, between the 50th and 75th centile. He was tachypneic with a respiratory rate of 38 cycles per minute. There were reduced breath sounds and coarse crepitations in the middle and lower lung zones bilaterally. He had high-normal pulse rate of 100beats/minute, blood pressure and heart sounds were normal. He had mild hepatosplenomegaly. The right knee was diffusely swollen,

warm to touch, tender and there was reduced mobility. Diagnoses of sepsis with pneumonia and septic arthritis of the right knee were made. A differential diagnosis of sickle cell disease was considered.

Chest X-ray showed patchy and reticulonodular opacities in both lung fields, the right worse than the left (Figure 1). X-ray of the right knee and leg showed no obvious bony abnormality and joint space appeared normal (Figure 2). Blood culture and knee aspirate microscopy, culture and sensitivity both yielded growth of Staphylococcus aureus with similar sensitivity pattern. Hemoglobin electrophoresis revealed genotype of AA and G6PD assay was normal. Complete blood count showed low normal hematocrit of 30%, leukocytosis of 27,500cells/mm3, with neutrophilia of 90% while platelet count was normal. Urinalysis showed significant bilirubinuria and trace urobilinogen. Screening for hepatitis B and C were negative. Antibody test for HIV was negative.

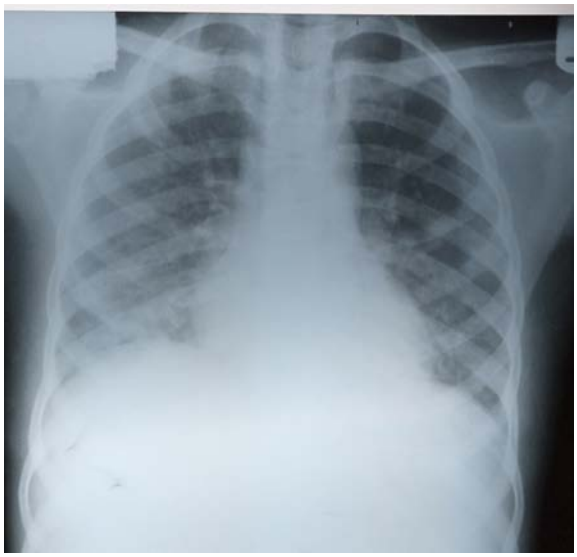

Figure 1. Chest X-ray showing bilateral patchy and reticulonodular opacities

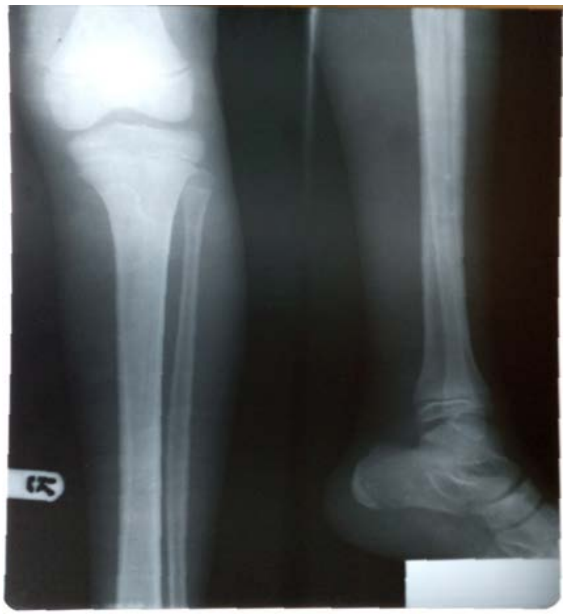

Figure 2. X-ray of the right leg with no obvious abnormality except for mild soft tissue swelling

On the second and third days of admission, patient was noticed to be having worsening jaundice, and worsening respiratory distress with hypoxemia requiring oxygen supplementation. He had an episode of epistaxis with minimal bleeding. A diagnosis of COVID-19 with hepatitis was considered. Liver function test showed evidence of cholestatic jaundice with conjugated hyperbilirubinemia of total bilirubin level at 182 µmol/l (reference range less than 20 µmol/l) and conjugated fraction at 153 µmol/l (less than 5 µmol/l), alkaline phosphatase (ALP) of 943 IU/l (80-304 IU/l), gamma glutamyl transferase (GGT) of 240 IU/l (10-45 IU/l). Aspartate aminotransferase (AST) was 46 IU/l (5-46 IU/l) while alanine aminotransferase (ALT) was 17 IU/l (5-49 IU/l) and there was severe hypoalbuminemia with serum albumin measuring 19 g/l (35-50 g/l). Clotting profile showed normal prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR). Abdominal ultrasound showed an enlarged liver with regular outline, homogenous parenchymal echogenicity with preserved intra and extrahepatic biliary tree/vascular channels. COVID antibody test was positive for IgG and IgM, and PCR test for SARS-CoV-2 was also positive. Electrolytes and urea levels were normal.

He had intravenous cefuroxime and oral azithromycin. He had supportive therapy with vitamin K and zinc tablets. He was transfused with plasma on four occasions on account of the sepsis and severe hypoalbuminemia. He had incision and drainage of about 25mls of seropurulent aspirate from the right knee and subsequent application of a back slab. Right knee swelling and pain initially subsided but recurred on the 6th day of admission. There was no aspirate on re-attempt at drainage, however the joint was copiously irrigated with normal saline. He had blood transfusion once due to falling hematocrit. He had continuous fever for the first week of admission, with peak as high as 39.1°C, and then swinging pyrexia in the 2nd week with eventual resolution by the 15th day. Jaundice cleared gradually and repeat liver function test done on the 14th day of admission showed total and conjugated bilirubin of 36 µmol/l and 34 µmol/l respectively, ALP, AST and ALT of 360, 13 and 6 IU/l respectively. Repeat PCR test for SARS-CoV-2 was negative by the 13th day on admission. He was discharged on the 18th day of admission with remnant swelling of the right knee. He took antibiotics for a total of 44 days. He was able to commence ambulation with crutches assisted by physiotherapy and has been seen regularly on follow up visits. Patient is alive and well, ambulating properly without crutches.

2.4. Case 4

A five-year old girl was admitted on account of fever of three weeks, chest pain and progressively worsening difficulty in breathing with eventual orthopnea of two weeks. There was weight loss; but no cough, drenching night sweat nor contact with anybody suspected to have tuberculosis or similar symptoms. She had the Bacillus Calmette Guerin vaccine against tuberculosis at birth. She was given over the counter medications before presenting at the hospital.

Physical examination at presentation revealed a conscious, acutely ill-looking girl with severe respiratory

distress. She had normal temperature initially but had fever while on admission. Her weight was 16kg which was on the 25th centile. Chest wall was bulging on the left hemithorax with reduced movement. Percussion notes were dull on same side and breath sounds were absent. She had tachycardia. There was soft and tender hepatomegaly which was palpated 10cm below the right costal margin, and she also had splenomegaly.

A diagnosis of pneumonia with left pleural effusion was made. Pulmonary tuberculosis and COVID-19 were considered as differential diagnoses. A chest X-ray showed homogenous opacity of the left lung field with mediastinal shift towards the right, suggesting massive left pleural effusion (Figure 3). Complete blood count showed normal hematocrit of 38%, leukocytosis with white blood cell count of 12,700cells/mm3. There was relative neutrophilia of 62%, platelet count was normal. Her hemoglobin genotype was AA. Human immunodeficiency viral (HIV) antibody test was negative. Pleural aspirate for Gene-Xpert to detect Mycobacterium tuberculosis was negative. Pleural aspirate for microscopy and culture done on two different occasions did not grow any organism. Pleural fluid aspirate cytology showed chronic inflammatory cells comprising lymphocytes and plasma cells, without any epithelial cell in a hemorrhagic background. COVID-19 PCR test was positive and patient was subsequently managed in an isolation ward.

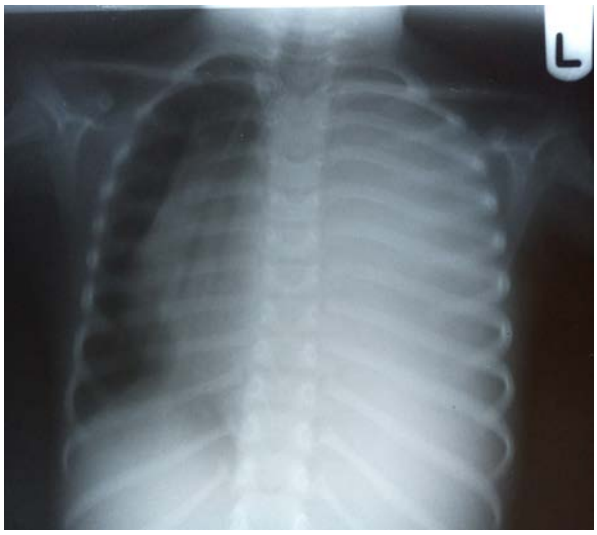

Figure 3. Chest X-ray showing homogenous opacity of the entire left lung field with mediastinal shift to the right

A chest tube was passed which initially drained 2.5L of serosanguinous fluid, and then 1490mls of fluid drained over the following seven days. The chest tube was removed after the drain remained inactive for 72 hours, on the 11th day on admission. She was given intravenous cefuroxime, oral azithromycin and supplements including vitamin C, vitamin E and zinc tablets. Patient's clinical condition gradually improved and respiratory distress resolved. A repeat PCR test for SARS-CoV-2 done 8 days after admission was negative. Patient was discharged 12 days after admission.

She represented 13 days after discharge with left chest pain. Repeat chest X-ray showed homogenous opacification of the left side of the chest. A chest ultrasound showed a left lung which was isoechoic to the liver suggesting consolidation due to grey hepatization, and minimal effusion measuring 48mls in its widest dimension. The right lung appeared normal. She was given analgesics in addition to her medications and was to be seen in clinic. However, she did not come for follow-up visit. She deteriorated at home and died few weeks after she was last seen at the hospital.

3. Discussion

COVID-19 is a multi-systemic disease that can affect virtually all organ-systems in the body. [5] Rheumatic heart disease (RHD) has been listed by the World Health Organization (WHO) as a risk factor for COVID-19 infection. [6] The risks posed by RHD to the development of a more severe COVID-19 progression may be associated with occurrence of complications such as heart failure. [6] Additionally, low socioeconomic class which is a risk factor for the development of RHD may prevent the patient from seeking care early enough if infected with the SARS-CoV-2. [6] Our index patient with RHD was from a low socioeconomic class and also had heart failure. It can be challenging to make a clinical diagnosis of COVID-19 in a patient with RHD because the two conditions have similar symptoms. However, the presence of fever in a patient with RHD should prompt physicians to look for alternative diagnosis such as COVID-19, apart from a repeat episode of acute rheumatic fever, as was the case with this patient. Another observed association in this patient was hypovitaminosis D. Studies have shown that patients with severe COVID-19 also have low levels of vitamin D,[(7)] however available evidence suggests that low vitamin D level may not be a risk factor for developing COVID-19, rather both conditions may occur concurrently because they have similar predisposing factors. [7,8]

COVID-19 can occur as co-infection with other microorganisms such as viruses, bacteria and fungi. Malaria which is caused by the parasite, Plasmodium species, is a common cause of mortality in developing countries. Till date, there is very little report on concurrent malaria infestation in patients with COVID-19. The two diseases may however occur simultaneously in the same patient and it may be difficult to tell whether one predisposes to the other and what the consequences of one may be on the other. A case report of such co-infection has been documented in a 20-year-old man. [9] The patient had a protracted illness course spanning over three weeks unlike what was reported in our patient. Our patient had features of severe malaria but seemingly had a mild presentation of COVID-19. This is evidenced by the fact that the patient got significantly better within a few days after being treated for malaria and its complication of severe anemia. The patient did not receive any specific treatment for COVID-19. This may suggest that children with severe malaria are not necessarily predisposed to a more severe COVID-19 course where the two diseases occur at the same time.

On the other hand, bacterial co-infection with COVID-19 has been reported in a lot of studies. A systematic review of 24 studies showed the incidence of concurrent bacterial infection and COVID-19 to be 6.9%. [10] While some of these patients had bacterial infection prior to admission

into the hospital, others acquired it as a super-imposed infection. Some of the studies reviewed did not distinguish between these two categories. [10] Another review, [11] clearly demonstrated the rarity of bacterial co-infection with COVID-19 as at the time of admission, the incidence of which was reported to be 1.2-4.2%. The leading etiology among those who had community-acquired bacterial co-infection in the study [11] was Staphylococcus aureus as we also saw in one of the patients we reported. The presence of a specific focus of infection such as septic arthritis reported in the index patient, should prompt clinicians to not only suspect bacterial co-infection in COVID-19 patients, but also to entertain the possibility of a hematologic spread of such organisms. Other pointers to bacterial septicemic illness seen in our patient were continuous high-grade fever with temperatures greater than 39°C, and falling hematocrit. High-grade fever was reported to be more significantly common among patients who had COVID-19 with bacterial co-infection than those without it. [12]

COVID-19 induced hepatic injury has been described in a number of studies. The prevalence of hepatic injury in patients with COVID-19 can be as high as 22% as reported by a meta-analysis of eleven heterogenous studies. [13] The types of liver diseases have been classified into hepatocytic, where serum ALT and AST are three times the upper limit of normal, cholestatic, where serum ALP and GGT are more than two times normal, and mixed. [14] One of our patients had cholestatic liver injury with ALP and GGT measuring greater than three and five times the upper limit of normal respectively. Serum ALT and AST were however within normal limit. The exact cause of hepatic disease in patients with COVID-19 is unknown and it is not clear whether the virus acts directly on the hepatocytes or not. Cholestasis may arise from the binding of the virus to the angiotensin-converting enzyme present on cholangiocytes. [15] This may result in inflammatory reactions with subsequent clogging of the biliary pathway, leading to conjugated hyperbilirubinemia and elevation of the enzymes, ALP and GGT. Other possible explanation for the etiology of the cholestasis include: ischemia, cytokine storm, exacerbation of pre-existing liver disease, drug-induced toxicity, and sepsis-induced cholestasis. [15] Direct injury to the hepatocytes appeared to have been absent in our patient as ALT and AST were within normal limit, the liver was structurally normal on ultrasonography. Similarly, normal ALT and AST have been previously documented in COVID-19-associated cholestasis, [15] but this distinct entity is usually associated with higher mortality, [15,16] unlike our patient who had a relatively rapid recovery. Our patient also had hypoproteinemia, which has been found to be associated with higher mortality rate.

Pleural effusion can occur as a complication of COVID-19, with pooled incidence from meta-analyses ranging from 7.3%-9.5%. [17,18] Pleural effusion usually develops after 11 days of symptoms in infected patients, [17] similar to the observation in our patient. Despite the resolution of the pleural effusion, our patient did not fully recover as the affected lung appeared destroyed evidenced by X-ray and ultrasound features of consolidation detected two weeks after discharge, recurrence of symptoms, with deterioration in her health status subsequently leading to her death. It is worth noting that the patient did not have microbial evidence of tuberculosis or other bacterial infection and screening for HIV was negative. It is therefore possible that the SARS-Co-V-2 was mainly responsible for the pathological processes that led to the severe course of illness in the patient.

4. Conclusion

The description of these cases with differing clinical presentations show that children may also present with severe COVID-19 and evidence for the disease should be sought in children presenting with respiratory symptoms. It is worthy of note that three out of four of these children who had severe symptoms and or co-morbidity had evidence of viral clearance within two weeks of admission. However, effects of the virus on organ-systems may linger despite the absence of the virus in the body. Most of the researches referred to in this case series were conducted in adults. More researches are needed in children in order to know the burden of the disease, especially in developing countries.

Statement of Competing Interests

There is no conflict of interests to be declared. The authors did not receive any funding for this research.

List of Abbreviations

Angiotensin-Converting enzyme 2 (ACE-2)
Transmembrane protease serine 2 (TMPRSS2)
Glucose-6-phosphate dehydrogenase (G6PD)
Alkaline phosphatase (ALP)
Gamma glutamyl transferase (GGT)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Prothrombin time (PT)
Partial thromboplastin time (PTT)

References

[1] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID 19. *Nat Rev Microbiol*, 19: 141-154, 2021.

[2] World Health Organization. Rolling updates on coronavirus disease (COVID-19). Updated 31 July 2020. Available from https: www.who.int/emergencies/diseases/novel-coroa-2019/events-as-they-happen. [Accessed June 2, 2021].

[3] Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care*, 24:422 2020.

[4] Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child*, 106:429-439, 2021.

[5] Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*, e276-e288, Nov. 2020. [Accessed June 4, 2021].

[6] Beaton A, Zühlke L, Mwangi J, Taubert KA. Rheumatic heart disease and COVID-19. *Eur Heart J*, 41(42): 4085-4086, Nov 2020.

[7] Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf M-I, Benstoem C, et al. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews 2021*, Issue 5. Art. No.:CD015043. [Accessed August 10 2021].

[8] Butler-Laporte G, Nakanishi T, Mooser V, Morrison DR, Abdallah T, Adeyeye O, et al. Vitamin D and COVID-19 susceptibility and severity in the COVID-19 Host Genetics Initiative: A Mendelian randomization study. *PLoS Med* 18(6): e1003605. [Accessed Aug. 12, 2021].

[9] Eid MM. Co-infection with COVID-19 and malaria in a young man. *Dubai Med J*, 4:164-166, 2021.

[10] Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, Soucy JR, Daneman N. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect*, 26(12): 1622-1629, Dec 2020.

[11] Westblade LF, Simon MS, Satlin MJ. Bacterial coinfections in coronavirus disease 2019. *Trends Microbiol*, 29(10): 930-941, Oct 2021.

[12] He S, Liu W, Jiang M, Huang P, Xiang Z, Deng D, et al. Clinical characteristics of COVID-19 patients with clinically diagnosed bacterial co-infection: A multi-center study. *PLoS ONE*, 16(4): e0249668, April 2021. [Accessed Aug. 20, 2021].

[13] Merola E, Pravadelli C, de Pretis G. Prevalence of liver injury in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Acta Gastroenterol Belg*, 83(3):454-460, July-Sept 2020.

[14] Yu D, Du Q, Yan S, Guo X, He Y, Zhu G, et al. Liver injury in COVID-19: clinical features and treatment management. *Virol J*, 18: 121, 2021.

[15] Da BL, Suchman K, Roth N, Rizvi A, Vincent M, Trindade AJ, et al. Cholestatic liver injury in COVID-19 is a rare and distinct entity and is associated with increased mortality. *J Int Med*, 290(2): 470-472, Aug, 2021.

[16] Fu L, Fei J, Xu S, Xiang H, Xiang Y, Hu B, et al. Liver dysfunction and its association with the risk of death in COVID-19 patients: a prospective cohort study. *J Clin Transl Hepatol*, 8(3): 246-254, Sep. 2020.

[17] Chong WH, Saha BK, Conuel E, Chopra A. The incidence of pleural effusion in COVID-19 pneumonia: State-of- the-art review. *Heart & Lung*, 50(4):481-490, 2021.

[18] Rathore SS, Hussain N, Manju AH, Wen Q, Tousif S, Avendano-Capriles CA, et al. Prevalence and clinical outcomes of pleural effusion in COVID-19 patients: A systemic review and meta-analysis. *J Med Virol*, 1-11, 2021.