Original article

Impact of COVID-19 on children with rheumatic diseases: a retrospective cohort analysis

Background: *Data concerning impact of COVID-19 on children with rheumatic disorders in developing countries are limited.*

Methods: *We conducted a retrospective analysis, examining the medical records of 49 children (15 males, 34 females) with rheumatologic disorders who got infected with SARS-CoV2. They were recruited, over a period of 17 months, from the Children's Hospitals of Ain Shams, Mansoura and Assiut Universities in Egypt. Data recorded were the type and duration of rheumatologic, antirheumatic treatment received, and COVID-19 presentation including severity, and outcome. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), lactate dehydrogenase enzyme (LDH), serum ferritin, and D-dimer levels were recorded.*

Results: *Our series included 25 SLE, 16 JIA, two polyarteritis nodosa, two dermatomyositis, two mixed connective tissue disease, one systemic sclerosis, and one HSP patients. They had median (IQR) age of 13 (10-14) years. Twenty-nine (59.2%) patients had active disease flare. Forty-one (83.7%) patients were on corticosteroids, and 35 (71.4%) were on add-on immunosuppressives. Twenty-nine patients were hospitalized with median (IQR) admission duration of 25 (14-38) days. They included 8 mild/asymptomatic, 4 moderate, 6 severe, and 11 critical COVID-19 cases. Seven cases with critical COVID-19 passed away with mortality rate of 14.3 %. The deceased cases had higher neutrophil/lymphocyte ratio (p=0.003), higher CRP levels (p= 0.041) and higher D-dimer (p=0.001) and ferritin levels (0.002) as compared to survivors.*

Conclusion: *Although reported to be milder in children, COVID-19 seems to have higher mortality among children with rheumatic disorders compared to rates reported in the general population. We could not find evidence for the impact of immunosuppressive treatment on COVID-19 related mortality, yet our findings need to be validated by wider scale prospective studies.*

Keywords: COVID-19; rheumatic diseases; mortality; children; pediatric; hospitalized, outcomes.

Rasha El-Owaidy[1], Elham Hossny[1], Dalia El-Ghoneimy[1], Zeinab A. El-Sayed[1], Shereen Reda[1], Ihab Elhakim[2], Hanan Ibrahim[3], Iman Ragab[4], Nesrine Radwan[1], Ghada Shousha[1], Amal Lotfy[1], Amr Elmekkawy[1], Ali Sobh[5], Naglaa Osman[6], Mariam Abdelnaby[1], Roba Al-Gaweesh[1], Rana Zakaria[1], Mostafa El-Amin[1], Yehia El-Gamal[1]

[1]Pediatric Allergy, Immunology and Rheumatology Unit; [2]Pediatric Nephrology Unit; [3]Pediatric Intensive Care Unit and [4]Pediatric Hematology/ Oncology Unit, Children's Hospital, Ain Shams University, Cairo, [5]Children's Hospital, Mansoura University, Mansoura; [6]Children's Hospital, Assiut University, Assiut; Egypt.

Correspondence:
Rasha El-Owaidy, MD, PhD, Associate professor of Pediatrics, Pediatric Allergy, Immunology and Rheumatology Unit Children's Hospital, Ain Shams University, Cairo 11566, Egypt.
Email: rasha2hasan@gmail.com

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[1] Children are as likely as adults to become infected with SARS-CoV-2 but they seem to have a milder disease course and better prognosis.[2,3] With spread of the virus, growing global data revealed rising numbers of affected children with different grades of COVID-19 severity including those presenting with the multisystem inflammatory syndrome in children (MIS-C).[4] It has been suggested that children with underlying conditions, such as congenital heart disease, bronchial pulmonary hypoplasia, chronic kidney disease, respiratory tract anomalies, severe malnutrition and immune deficiency may be more susceptible to increased COVID-19-related morbidity and mortality.[5] However, data on the impact of COVID-19 on children with rheumatic diseases are scant and this poses a great challenge to pediatric rheumatologists.

Children with rheumatologic disorders are believed to be immunocompromised by the diseases itself and/or the use of immunosuppressive treatment. In addition, their underlying immune dysregulation may increase the risk of developing a cytokine storm, multisystem organ inflammation and failure, and the so-called "macrophage activation syndrome".[6,7] The aim of our study was to describe epidemiological and clinical characteristics of patients with rheumatologic disorders presenting with COVID-19 in three tertiary referral hospitals in Egypt, and to explore the impact of COVID-19 on their outcome

METHODS

This retrospective analysis used the medical records of children (less than the age of 18 years) with rheumatologic disorders who were diagnosed with SARS-CoV2 infection. Patients were recruited from three Egyptian cities: Cairo, Mansoura and Assiut and the data were collected from 3 centers, namely: the Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Ain Shams University, the Pediatric Allergy, Immunology and Rheumatology Unit, Children's Hospital, Assiut University and the Children's Hospital, Mansoura University, during the period from March 1, 2020, to August 1, 2021. We followed the Centre for Disease Control and Prevention (CDC) case definition for COVID-19,[8] and the World Health Organization (WHO) classification for COVID-19 severity.[9]

Records of the patients were examined for their SARS-CoV-2 PCR/serology results, data concerning their rheumatologic diagnoses and duration, and outcome of hospital admission. We also collected data about COVID-19 clinical presentation as well as results of complete blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), lactate dehydrogenase enzyme (LDH), serum ferritin and D-dimer levels. Radiological abnormalities were recorded when present, in addition to the immunosuppressive treatment received and patients' adherence to treatment in the last 3 months before acquiring SARS-CoV-2 infection.

Statistical methods

Data were statistically described in terms of range, median and interquartile range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Mann Whitney U test for independent samples. For comparing categorical data, Chi-square (X^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Two- sided p values less than 0.05 was considered statistically significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows was used for all statistical analyses.

RESULTS

Over 17 months period, 49 children and adolescents with rheumatologic diseases (15 males, 34 females) received the diagnosis of COVID-19 being defined as 28 confirmed and 21 probable cases. Out of our series, 29 underwent hospital admission while the remaining 20 were managed as outpatients. The whole cohort included 25 patients (51%) with systemic lupus erythematosus (SLE), 16 (32.7%) with juvenile idiopathic arthritis (JIA), two (4.1%) with polyarteritis nodosa (PAN), two (4.1%) with dermatomyositis, two (4.1%) with Mixed connective tissue disease (MCTD), one (2.1%) with systemic sclerosis and one (2.1%) with Henoch Schoenlein purpura (HSP). Their age ranged from 6 to 16 with median (IQR) value of 13 (10-14) years. Twenty-nine (59.2%) patients had rheumatologic disease flare at the time of SARS-CoV-2 acquisition while symptoms of the remaining 20 (40.8%) were controlled. Forty-one (83.7%) patients were on corticosteroid therapy for their rheumatic illness, and 35 (71.4%) were on

add-on immunosuppressives. Fourteen patients were not adherent to their antirheumatic treatment, 6 of them stopped their treatment completely for periods ranging between 2 and 8 weeks before presentation for fear of being more susceptible to SARS-CoV-2 infection. The main clinicodemographic and laboratory features for the whole cohort are shown in tables 1 and 2. The 29 patients who were admitted to the COVID-19 isolation ward stayed for periods ranging from 9 to 65 days with a median (IQR) duration of 25 (14-38) days. These included 8 mild/asymptomatic, 4 moderate, 6 severe and 11 critical COVID-19 cases. The remaining 20 patients were managed as outpatients and had mild/asymptomatic COVID-19 infection. Table 3 and figures 1-3 show the main clinical features of the hospitalized patients (n=29).

All patients with critical, severe, and moderate COVID-19 illness received n-methyl prednisolone pulsed therapy, eight received intravenous immunoglobulins (1-2 gm/kg) and four received anti-IL-6 (tocilizumab at 8 mg per kg), in addition to antibiotic treatment. COVID-19 severity among the studied cases did not show significant variation with gender (p= 0.14), rheumatic diagnosis (p= 0.201), rheumatic disease activity status (p= 0.072) or adherence to the anti-rheumatic treatment (p= 0.159), but varied significantly with the type of immunosuppressive received, as 10 of the 11 critical COVID-19 cases were on cyclophosphamide, rituximab, or mycophenolate mofetil. All patients receiving methotrexate had mild/asymptomatic COVID-19 illness (X^2=43.769, p= 0.001) (figure 4).

Table 1. Clinicodemographic parameters of the studied rheumatic children with COVID-19 (n=49)

Variable		**Number (%) or Range [median (IQR)]**
Age (years)		6-16 [13 (10-14)]
Rheumatic disease duration (years)		0-4 [2 (0.18-3)]
Gender	Male	15 (30.6%)
	Female	34 (69.4%)
Rheumatic illness	Previously diagnosed	40 (81.6%)
	New onset	9 (18.4%)
Rheumatic disease diagnosis	SLE	25 (51%)
	JIA	16 (32.7%)
	Polyarteritis nodosa	2 (4.1%)
	Dermatomyositis	2 (4.1%)
	MCTD	2 (4.1%)
	HSP	1 (2%)
	Systemic sclerosis	1 (2%)
Rheumatic disease activity	Flare	29 (59.2%)
	Quiescent	20 (40.8%)
Rheumatic disease treatment	Corticosteroids	41 (83.7%)
	Methotrexate	16 (32.7%)
	Cyclophosphamide	8 (16.3%)
	Mycophenolate mofetil	7 (14.3%)
	Cyclophosphamide and Rituximab	2 (4.1%)
	Cyclosporine	1 (2%)
	Etanercept	1 (2%)
Compliance on anti-rheumatic treatment	Non-compliant	14 (28.6%)
	Compliant	35 (71.4%)
COVID-19 severity	Asymptomatic/mild	28 (57.1%)
	Moderate	4 98.2%)
	Severe	6 (12.2%)
	Critical	11 (22.4%)
COVID-19 outcome	Survivors	42 (85.7%)
	Deceased (non-survivors)	7 (14.3%)

HSP: Henoch Schoenlein purpura; JIA: juvenile idiopathic arthritis; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus

A total of 9 cases were admitted to the pediatric intensive care unit (PICU) with critical COVID-19 illness, of whom 7 required mechanical ventilation and eventually passed away with an overall mortality rate of 14.3 %. The 7 deceased cases comprised one boy and 6 girls. Their original illness was SLE (5 cases), systemic JIA (one case) and PAN (one case). Six out of the seven patients had rheumatic disease activity at time of SARS CoV-2 infection acquisition, and three were not adherent to their antirheumatic medications. Three cases were on cyclophosphamide monthly infusion therapy, one was on combined therapy of cyclophosphamide with rituximab, one on mycophenolate mofetil and 2 were on corticosteroid therapy only. Survivors (n=42) of COVID-19 illness had comparable data with non survivors (n=7) in terms of age (p= 0.908), gender (p= 0.414), rheumatic diagnosis (p= 0.571), rheumatic disease activity status (p= 0.129), anti-rheumatic treatment (p= 0.197) and adherence to treatment (p= 0.366). However, the deceased cases had higher neutrophil/lymphocyte ratio (z= -2.959, p=0.003), higher CRP levels (z= -2.042, p= 0.041) and higher D-dimer and ferritin levels (z= -3.427, -3.068; p=0.001, 0.002, respectively).

Table 2. Laboratory parameters of the studied rheumatic children with COVID-19 (n=49)

Feature	Range	Median (IQR)
TLC /µl	2300-28280	11100 (3200-21400)
ANC /µl	756-26360	7800 (2560-18320)
ALC /µl	276-3360	1198 (700-2730)
N/L ratio	0.77-21.42	5.8 (3-8)
Hgb (gm/dl)	5.9-12.62	9 (8.0-10.5)
PLT /µl	120000-639400	349000 (193000-450000)
CRP (mg/L)	4.8-284	90 (9-133)
ESR (mm/hr)	15-124	95 (70-110)
LDH (IU/L)	164-658	420 (312-600)
D dimer (ug/mlFE)	420-8408	3110 (700-7490)
Ferritin (ng/ml)	106-4531	1200 (204-2000)

ALC: absolute lymphocyte count; ANC: absolute neutrophil count; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; Hgb: hemoglobin; LDH: lactate dehydrogenase; N/L ratio: neutrophil/lymphocyte ratio; PLT: platelets count; TLC: total leukocyte count.

Table 3. Clinical and imaging features of the hospitally admitted children with rheumatologic disorders and COVID-19 (n=29)

Feature	Number (percentage)
Fever	29 (100 %)
Cutaneous manifestations	
Vasculitic rash	7 (24 %)
Malar rash	3 (10.3 %)
Bullous rash	1 (3.4 %)
Polyarthritis	6 (20.7 %)
Acute kidney injury	6 (20.7 %)
GIT	
Vomiting, diarrhea, abdominal pain	8 (27.6 %)
Acute pancreatitis	3 (10.3 %)
Respiratory	
Respiratory distress	16 (55.2 %)
Ground glass opacities	10 (34.5 %)
Consolidation patches	12 (41.4 %)
Pneumothorax	3 (10.3 %)
Cardiac	
Carditis	7 (24 %)
Pericardial effusion	10 (34.5 %)
Valvular lesions	8 (27.6 %)
Neurological	
Agitation, abnormal behavior	2 (6.9 %)
Convulsions	3 (10.3 %)
Tremors, choreoathetosis	1 (3.4 %)
Impaired consciousness	3 (10.3 %)
Hemiparesis	1 (3.4 %)
Vascular	
Pulmonary embolism	2 (6.9 %)
Retinal vascular insult	2 (6.9 %)
Shock (cardiogenic or septic)	9 (31 %)
Cytokine storm syndrome	11 (38 %)
COVID-19 severity	
Asymptomatic/ mild	8 (33.3 %)
Moderate	4 (13.8 %)
Severe	6 (20.7 %)
Critical	11 (37.9 %)
Mechanical ventilation and death	7 (24 %)

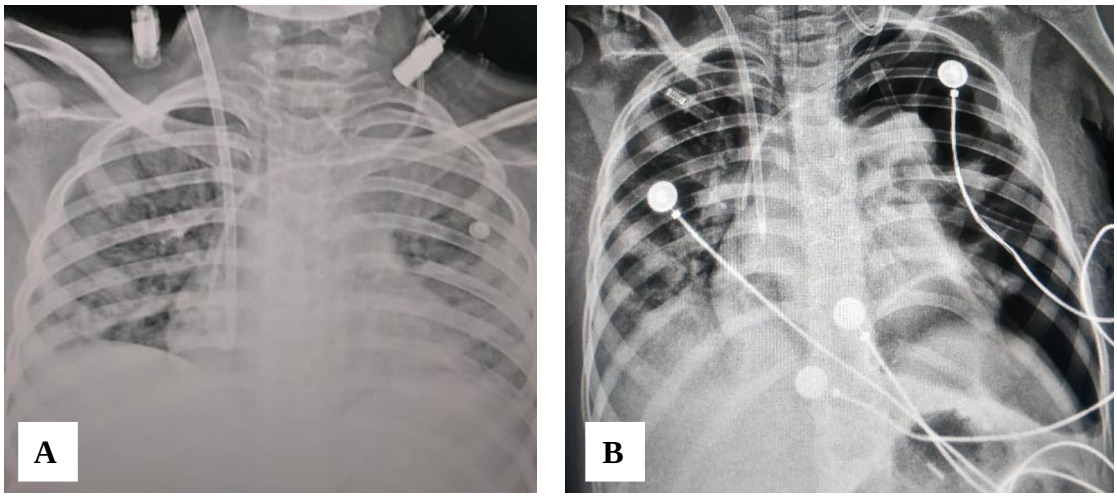

Figure 1. Chest X-ray of an SLE patient with COVID-19 showing bilateral consolidation (A). the patient developed spontaneous pneumothorax later on (B)

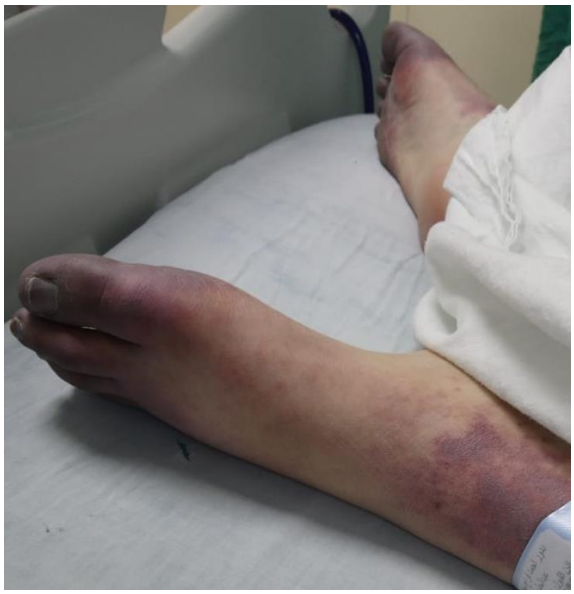

Figure 2. Vasculitic rash in an SLE patient with COVID-19

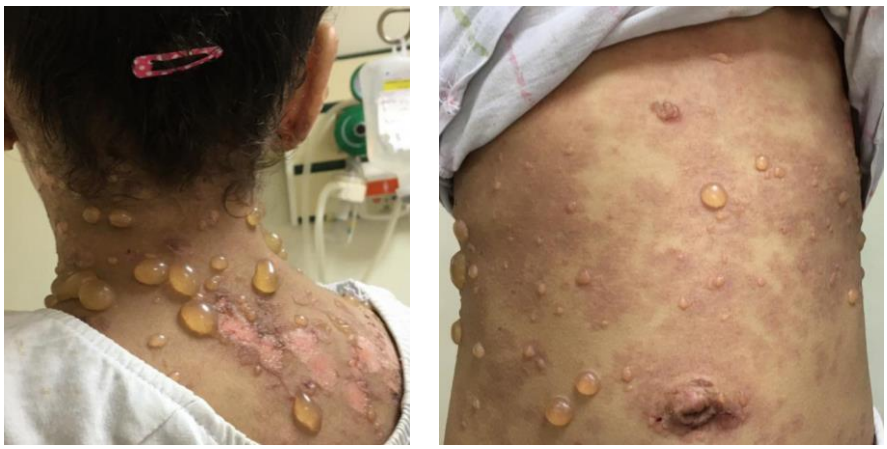

Figure 3. Bullous eruption in a newly diagnosed SLE patient with confirmed COVID-19

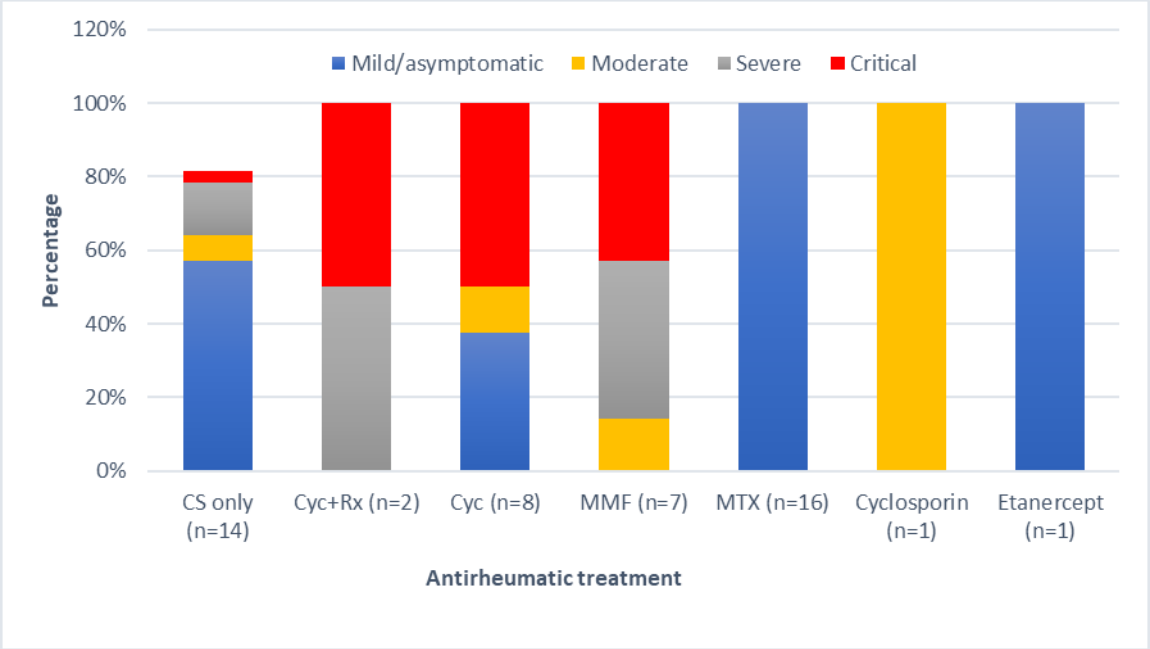

Figure 4. COVID-19 degree of severity with different antirheumatic treatment modalities among studied children (n=49)

CS: corticosteroids; Cyc: cyclophosphamide; MTX: methotrexate; MMF: mycophenolate mofetil; Rx: rituximab

DISCUSSION

Our study describes the presentation and outcome of a cohort of SARS-CoV-2 infected pediatric patients with various rheumatic diseases. Out of 49 cases, 4 had moderate, 6 had severe and 11 had critical COVID-19 illness while mortality rate reached up to 14.3%. COVID-19 related mortality is reported to be rare in the pediatric age group in general. In another multicenter study in Egypt,[10] that included 40 SARS-CoV-2 infected children with no underlying chronic illness, there was no severe/critically ill cases, and no deaths were reported. A relevant study reported hospital admission in 10/55 pediatric rheumatology patients due to COVID-19 with one case deceased.[11] Using the European Alliance of Associations for Rheumatology COVID-19 Registry, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, and the CARRA-sponsored COVID-19 Global Paediatric Rheumatology Database, Kearsley-Fleet et al, analyzed the data f 607 pediatric patients with rheumatic disease who acquired SARS-CoV2 infection from 25 different countries. They observed a hospital admission rate of 7 % and mortality rate of 0.4 %.[12] Another group of investigators compared 152 pediatric patients with rheumatic disorders and COVID-19 to 506 non-rheumatic COVID-19 children. They noted that the presence of rheumatic disease increased the risk of both hospitalization and symptomatic infection but did not increase the mortality risk.[13] Data from Sudan, however, showed a mortality rate of 5.4% among children with rheumatic illness in general.[14]

The presence of underlying disease, a heightened inflammatory response, disease and/or drug related organ damage and the possible effect of immunosuppression, in addition to the socioeconomic conditions and incautious health behaviors are all possible factors that might explain the more severe/fatal presentation of COVID-19 among our rheumatic patients. Worth to note that our study relied mostly on their presentation rather than active screening, and thus some milder or asymptomatic cases might have gone unreported or untested, which might have led to overestimation of the morbidity and mortality rates among our series. Comparison of our patients to non-rheumatic COVID-19 affected children and adolescents could have provided more conclusive results.

In our retrospective cohort, COVID-19 severity varied significantly with the anti-rheumatic treatment used, where 10/11 critical COVID-19 were on cyclophosphamide, rituximab, or mycophenolate mofetil, while all those on methotrexate had asymptomatic/mild COVID-19 illness. This might reflect the effect of rheumatic disease severity that necessitated more aggressive therapy rather than the effect of the medications themselves. Our observation is weakened by the small sample size and the consecutive non-stratified

random sampling employed that did not allow for the even distribution of the studied sample according to the antirheumatic treatment modalities. Thus, the safety of the antirheumatic drugs whether conventional or biological cannot be confirmed from our analysis. Rheumatic-disease factors that were reported to be associated with the risk of death included disease activity in addition to glucocorticoid, rituximab and/or sulfasalazine use.[15] According to the American College of Rheumatology Guidance, the task force unanimously agreed that primary control of underlying rheumatic disease with judicious use of immunosuppressive treatment is of utmost importance, to minimize diseases flares and immune dysregulation.[16] In a cohort of children with rheumatic diseases, biological treatments did not have a negative impact on COVID-19 outcome and the authors recommended that caution should be taken during the infection period because interruption of treatment might exacerbate the rheumatic disease activity. The decision should be taken on individual basis considering the current biological agent, primary disease status, COVID-19 severity, and the available guidelines.[17] Also, patients with rheumatic disorders are encouraged to strictly adhere to their treatment to avoid disease relapse and the need for hospital admission that may expose them to SARS-CoV-2 infection.

Pulmonary embolism was rarely reported in pediatric COVID-19 patients.[18,] It was detected in two of our patients with confirmed COVID-19 without evidence of other deep venous thrombosis and both patients eventually died. The first was a known patient with SLE and crescentic class IV lupus nephritis who was on regular hemodialysis. She had lupus anticoagulant antibody and elevated D-dimer level (9020 ug/mlFE); yet could not be maintained on anticoagulation due to thrombocytopenia, repeated mucosal bleeding and eventually hemothorax. The second patient had PAN with history of previous bilateral foot gangrene. She has been on low molecular weight heparin before developing pulmonary embolism. It has been demonstrated that the hyperinflammatory response to SARS-CoV-2 can lead to massive endothelial damage, and generalized viral induced coagulopathy, resulting in pulmonary embolism, venous, arterial, and microvascular thrombosis, lung endothelial injury and acute respiratory distress syndrome.[19]

Ferritin, D-dimer and neutrophil/lymphocyte ratio results in our series showed significantly higher levels among deceased patients versus survivors, reinforcing the potential predictive value of these markers for COVID-19 related mortality. COVID-19 coagulopathy on top of dysregulated immune responses orchestrated by inflammatory cytokines, lymphocyte cell death, hypoxia, and endothelial damage has been previously addressed.[20,21]

Clinical and laboratory differentiation between COVID-19 and flare of the rheumatic disease especially SLE can be challenging in clinical practice. Both can present with similar constitutional symptoms and when severe can lead to multisystem organ failure and features that mimic septic shock. Carditis, hepatitis, vasculitic skin rash and renal disease which are usual rheumatologic manifestations are reported as well in COVID-19.[22-25] Peripheral, bilateral, ground glass opacities (GGO) and multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines (crazy-paving) are not specific for COVID-19 pneumonia and can be seen in several rheumatic diseases.[26,27] There could be elevation of acute phase reactants such as the ESR, serum ferritin and CRP as well as hypoalbuminemia in both conditions. Lymphopenia which is a constant feature of a large sector of COVID-19 patients is also a sign of SLE activity and a side effect of glucocorticoid therapy.[28] COVID-19 was reported to present with a wide spectrum of neurological defects that might be present in neuro-lupus as well; radiological and CSF picture offer limited value in the differentiation.[29,30] Also, MIS-c clinical and laboratory features overlap with those of sJIA activity, but fortunately, treatment is the same. [31,32] Meticulous clinical observation and laboratory/radiological data interpretation together with the judicious introduction/tapering of anti-rheumatic treatment on case-by-case basis are all essential during management of SARS-CoV-2 infected rheumatic patients.

REFERENCES

1. World Health Organization Coronavirus disease 2019 (COVID-19) Situation Report – 51, March 11, 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed in June 2021.
2. **Ludvigsson JF.** Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088-95 .
3. **Hossny E, El-Owaidy R.** COVID-19 in children: current data and future perspectives. Egypt J Pediatr Allergy Immunol. 2020; 18(1):3-9 .

4. **Ebina-Shibuya R, Namkoong H, Shibuya Y, Horita N.** Multisystem Inflammatory Syndrome in Children (MIS-C) with COVID-19: Insights from simultaneous familial Kawasaki Disease cases. Int J Infect Dis. 2020;97:371-3 .
5. **Shen KL, Yang YH, Jiang RM, Wang TY, Zhao DC, Jiang Y, et al.;** China National Clinical Research Center for Respiratory Diseases; National Center for Children's Health, Beijing, China; Group of Respirology, Chinese Pediatric Society, Chinese Medical Association; Chinese Medical Doctor Association Committee on Respirology Pediatrics; China Medicine Education Association Committee on Pediatrics; Chinese Research Hospital Association Committee on Pediatrics; China Non-government Medical Institutions Association Committee on Pediatrics; China Association of Traditional Chinese Medicine, Committee on Children's Health and Medicine Research; China News of Drug Information Association, Committee on Children's Safety Medication; Global Pediatric Pulmonology Alliances. Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition). World J Pediatr 2020;16(3):232-9.
6. **Behrens EM, Koretzky GA.** Cytokine storm syndrome: looking toward the precision medicine era. Arthritis Rheumatol. 2017;69(6):1135-43.
7. **Askanase AD, Khalili L, Buyon JP.** Thoughts on COVID-19 and autoimmune diseases. Lupus Sci Med. 2020;7(1):e000396 .
8. Centre for Disease Control and Prevention-Coronavirus Disease 2019 (COVID-19) 2020 Interim Case Definition. Last updated April 20, 2020. Available from: https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/. Accessed on: December 1, 2021.
9. WHO. World Health Organization. Clinical management of COVID-19: Interim guidance. Last updated: May 27, 2020. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19. Accessed on: January 25, 2022.
10. **Abdel Baki A, Zaky S, Hosny H, Elassal G, Abdelbary A, Said A, et al.** COVID-19 in Egyptian Children: A Multicenter Study. J Pediatr Infect Dis 2021; 16(02): 57-61
11. **Villacis-Nunez DS, Rostad CA, Rouster-Stevens K, Khosroshahi A, Chandrakasan S, Prahalad S.** Outcomes of COVID-19 in a cohort of pediatric patients with rheumatic diseases. Pediatr Rheumatol Online J. 2021;19(1):94.
12. **Kearsley-Fleet L, Chang ML, Lawson-Tovey S, Costello R, Fingerhutová Š, Švestková N, et al;** CARRA Registry Investigators; COVID-19 Global Pediatric Rheumatology Database Investigators, Natter M, Hyrich KL. Outcomes of SARS-CoV-2 infection among children and young people with pre-existing rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2022;81(7):998-1005.
13. **Haslak F, Varol SE, Gunalp A, Kaynar O, Yildiz M, Adrovic A, et al.** Comparisons of Clinical Features and Outcomes of COVID-19 between Patients with Pediatric Onset Inflammatory Rheumatic Diseases and Healthy Children. J Clin Med. 2022;11(8):2102 .
14. **Dahman HAB.** Challenges in the diagnosis and management of Pediatric Rheumatology in the developing world: Lessons from a newly established clinic in Yemen. Sudan J Paediatr. 2017;17(2):21-29 .
15. **Grainger R, Kim AHJ, Conway R, Yazdany J, Robinson PC.** COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. Nat Rev Rheumatol. 2022;18(4):191-204 .
16. **Wahezi DM, Lo MS, Rubinstein TB, Ringold S, Ardoin SP, Downes KJ, et al.** American College of Rheumatology Guidance for the Management of Pediatric Rheumatic Disease During the COVID-19 Pandemic: Version 2. Arthritis Rheumatol. 2021;73(8):e46-e59.
17. **Demir F, Ulu K, Çağlayan Ş, Coşkuner T, Sözeri B.** Clinical course of COVID-19 in children with rheumatic disease under biologic therapy. Clin Exp Rheumatol. 2021;39 Suppl 128(1):36-37.
18. **Kipshidze N, Dangas G, White CJ, Kipshidze N, Siddiqui F, Lattimer CR, et al.** Viral coagulopathy in patients with COVID-19: treatment and care. Clin Appl Thromb Hemost. 2020;26:1076029620936776 .
19. **Chima M, Williams D, Thomas NJ, Krawiec C.** COVID-19-Associated Pulmonary Embolism in Pediatric Patients. Hosp Pediatr. 2021;11(6):e90-e94.
20. **Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, Luo M, Chen L, Zhao Y.** Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020 Jul;81(1):e6-e12.
21. **Iba T, Levy JH, Levi M, Thachil J.** Coagulopathy in COVID-19. J Thromb Haemost. 2020;18(9):2103-9.
22. **Gutiérrez-González LA.** Rheumatologic emergencies. Clin Rheumatol. 2015;34(12):2011-9 .
23. **Robson J, Mistry A, Bhamra K, Kluzek S, Luqmani R.** The systemically ill patient. In: Watts RA, Conaghan PG, Denton C, Foster H, Isaacs J, Muller-Ladner u, editors. Oxford Textbook of Rheumatology, 4th ed. Oxford University Press; 2013:112-7 .

24. **de Souza TH, Nadal JA, Nogueira RJN, Pereira RM, Brandão MB.** Clinical manifestations of children with COVID-19: A systematic review. Pediatr Pulmonol. 2020;55(8):1892-9.
25. **Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS.** Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-32 .
26. **Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al.** Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - Secondary Publication. J Thorac Imaging. 2020;35(4):219-27 .
27. **Rossi SE, Erasmus JJ, Volpacchio M, Franquet T, Castiglioni T, McAdams HP.** "Crazy-paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics. 2003;23(6):1509-19 .
28. **Lippi G, Plebani M.** Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020;25;58(7):1131-4 .
29. **de Amorim JC, Torricelli AK, Frittoli RB, Lapa AT, Dertkigil SSJ, Reis F, et al.** Mimickers of neuropsychiatric manifestations in systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2018;32(5):623-39 .
30. **Niazkar HR, Zibaee B, Nasimi A, Bahri N.** The neurological manifestations of COVID-19: a review article. Neurol Sci. 2020;41(7):1667-71 .
31. **Domínguez-Rojas J, Atamari-Anahui N, Chonlon-Murillo K, Tello M, Coronado-Muñoz Á.** Systemic lupus erythematosus complicated with macrophage activation syndrome mimicking COVID-19 multisystemic inflammatory syndrome in children. Bol Med Hosp Infant Mex. 2021;78(6):642-6 .
32. **Aydin F, Çelikel E, Ekici Tekin Z, Coşkun S, Sezer M, Karagöl C, et al.** Comparison of baseline laboratory findings of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis and multisystem inflammatory syndrome in children. Int J Rheum Dis. 2021;24(4):542-7.