Clinical Rheumatology (2022) 41:1779–1784
https://doi.org/10.1007/s10067-022-06186-z

BRIEF REPORT

Clinical course and seroprevalence of COVID-19 in children with rheumatic diseases—cross-sectional study from a reference centre in Spain

Clara Udaondo[1,2,3] · Claudia Millán-Longo[1] · Celia Permuy[4] · Laura Valladares[4] · Iker Falces-Romero[5] · Celia Muñoz-Gómez[1] · Mónica Morales-Higuera[1] · Rosa Alcobendas[1] · Agustín Remesal[1] · Sara Murias[1] · Cristina Calvo[2,3,4]

Received: 4 March 2022 / Revised: 7 April 2022 / Accepted: 17 April 2022 / Published online: 30 April 2022

Abstract

SARS-CoV-2 infections in children are frequently asymptomatic or mild and can go unnoticed. This study aimed to describe the seroprevalence and clinical course of SARS-CoV-2 in a cohort of children with rheumatic diseases in a real-life setting and assess possible risk factors. A cross-sectional study was performed in a paediatric rheumatology unit (September 2020 to February 2021). At inclusion, a specific questionnaire was completed and SARS-CoV-2 serology was performed. Demographics, treatment and disease activity of patients with and without laboratory-confirmed SARS-CoV-2 infection were compared. A total of 105 children were included. SARS-CoV-2 infection was demonstrated in 27 patients (25.7%). The mean age was 11.8 years, and most patients were females (72.4%). The most frequent underlying condition was juvenile idiopathic arthritis (70.3%; 19/27). Patients received immunosuppressive treatment in 78% of cases (21/27). Overall, 44.4% (12/27) of infected patients were asymptomatic. A total of 66.7% (18/27) of patients did not require medical assistance. Three patients required hospital admission because of COVID-19. Children with confirmed SARS-CoV-2 infection were less frequently in remission (52% vs 72%; p 0.014). Moderate disease activity and treatment with oral corticosteroids were associated with higher risk for SARS-CoV-2 (OR 5.05; CI 95%: 1.56–16.3 and OR 4.2; CI 95%: 1.26–13.9, respectively). In a cohort of Spanish paediatric patients with rheumatic diseases, clinical course of COVID-19 was mild, with more than one third of asymptomatic cases. Higher disease activity and oral corticosteroids appear to be risk factors for SARS-CoV-2 infection.

Key Points

- *We aimed to investigate the seroprevalence of SARS-CoV-2 infection in a cohort of Spanish paediatric patients with RD, testing both symptomatic and asymptomatic patients. We also compared treatment and disease activity of patients with and without laboratory-confirmed SARS-CoV-2 infection.*
- *In our cohort of 105 paediatric patients with rheumatic diseases, the clinical course of COVID-19 was mild and 44% of cases were asymptomatic. Three cases required hospital admission with no complications. Seroprevalence was 20%.*
- *No association was found between disease activity or treatment with corticosteroids and symptomatic or asymptomatic infection. Higher disease activity and treatment with oral corticosteroids appeared to be risk factors for laboratory-confirmed SARS-CoV-2 infection.*

Keywords COVID-19 · Child · Rheumatic diseases · Glucocorticoids

✉ Clara Udaondo
clara.udaondo@gmail.com

[1] Paediatric Rheumatology Unit, La Paz University Hospital, Paseo de la Castellana 261, 28046 Madrid, Spain

[2] La Paz Research Institute (IdiPaz), Madrid, Spain

[3] CIBERINFEC ISCIII, Madrid, Spain

[4] Paediatric Infectious Diseases Department, La Paz University Hospital, Madrid, Spain

[5] Microbiology and Parasitology Department, La Paz University Hospital, Madrid, Spain

Background

SARS-CoV-2 is responsible for the COVID-19 pandemic that has spread throughout the world in 2020. Disease in children represents at least 10% of identified cases and is relatively mild, with only a small proportion requiring hospitalisation [1]. However, a significant percentage of infections in children are asymptomatic and can go unnoticed.

Rheumatic disease (RD) could be considered as a risk factor for COVID-19, due to complications related to the viral disease, possible disease flare during and after SARS-CoV-2 infection, presence of comorbidities and immunosuppressive treatment [2, 3]. Poorly controlled active RD or certain pharmaceutical agents such as corticosteroids may increase the risk of infection and serious disease in adults. However, immune-mediated inflammatory disease and the use of TNF inhibitors are not associated with a worse clinical outcome [4–6].

Small case series show that evolution of COVID-19 in hospitalised children with RD is moderately favourable, although at least one fatality has been reported [7–9]. Data about the course of mild or asymptomatic infections in children are scarce, with little evidence in children with rheumatic diseases. We aimed to investigate the seroprevalence of SARS-CoV-2 infection and clinical course of COVID-19 in a cohort of paediatric patients with RD and to compare data of patients with laboratory-confirmed SARS-CoV-2 infection versus patients without laboratory-confirmed infection to assess possible risk factors.

Methods

A cross-sectional study was performed including all paediatric patients diagnosed with any rheumatic disease in a rheumatology unit of a reference hospital in Madrid, Spain, from September 2020 to February 2021. All patients were offered the possibility to participate, in a real-life setting. Exclusion criteria were absence of informed consent. The study was approved by the ethics committee of the participating hospital.

The BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine was recommended for adolescents aged 12 years and older by the European Medicines Agency (EMA) on May 28, 2021. This study was performed before this date, so none of the patients in our cohort was vaccinated against SARS-CoV-2.

At inclusion, a specific questionnaire was completed by parents. Demographics, disease activity and COVID-19-related symptoms were obtained. Serology of SARS-CoV-2 (chemiluminescence: ELISA COVID-19 Virclia IgG) was performed at the same time as their next routine laboratory tests. In case of fever or respiratory symptoms, PCR for SARS-CoV-2 was performed according to public health recommendations, and this information was retrieved in the questionnaire. Asymptomatic patients were defined as those who had evidence of SARS-CoV-2 infection (documented positive IgG) who did not report any known symptoms of infection. Also, current asymptomatic infection could be documented in case PCR was performed in asymptomatic patients who had a close contact with a positive case. Previous SARS-CoV-2 positive PCR at any time was considered as evidence of past infection.

Children were classified according to disease activity, measured at the time of the performed SARS-CoV-2 serology or during COVID-19 in case of symptomatic infection. Disease activity was assessed using JADAS27 in the case of JIA, and patients were classified according to this score into three groups: remission (JADAS27 score ≤ 1), mild disease activity (JADAS27 score between 1.1 and 2) and moderate/high disease activity (JADAS27 score above 2.1) [10]. Non-JIA patients were classified using the Physician's Global Assessment (PGA) in three groups: 0: remission, 1: mild disease activity and 2–3: moderate/high disease activity. Demographics, treatment and disease activity from laboratory-confirmed SARS-CoV-2 patients were compared to the data of patients without laboratory-confirmed SARS-CoV-2.

Values were expressed as percentages for discrete variables or as mean and standard deviation for continuous variables. Median and interquartile ranges were used for non-parametric variables. Continuous variables were compared using the Student *t*-test or non-parametric tests, where appropriate. Categorical variables were compared by the χ^2 test and Fisher exact test. A 2-sided value of $p < 0.05$ was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM. Version 21.0, IBM Corp, Armonk, NY).

Results

Overall, 105 children with rheumatic diseases were included, which account for approximately 20% of eligible patients seen in the unit in this period of time. Mean age was 11.8 years old (SD 4.5), and the majority of the patients were females (72.4%). Detailed description of the study cohort is shown in Table 1. Most of the children were diagnosed with juvenile idiopathic arthritis (JIA) (70.3; 19/27), as this is the most prevalent rheumatic disease, followed by PFAPA (11.1%; 3/27), systemic lupus erythematosus (SLE) (7.4%; 2/27), uveitis (3.7%; 1/27), vasculitis (3.7%; 1/27) and STAT3 gain of function (3.7%; 1/27). A total of 21/27 (78%) patients received immunosuppressive therapy, most of them biologic TNF inhibitors (16/27; 59%). Regarding disease activity, 14/27 (52%) were considered in clinical remission by their clinicians. Seroprevalence (positivity of SARS-CoV-2 IgG antibodies) was 20% (21/105). SARS-CoV-2 infection was confirmed in 27 patients (25.7%): 9 with both previous positive PCR and IgG antibodies, 5 with previous positive PCR but negative antibodies, one with previous positive PCR and indeterminate antibodies

and 12 with positive IgG antibodies without evidence of previous positive PCR. Twelve out of 27 (44%) patients were not aware of having recovered from COVID-19 before the participation in this study.

Up to 5/15 patients with positive PCR did not have IgG antibodies and one more had indeterminate antibodies. Seroconversion rate (proportion of PCR-positive patients who developed positive IgG antibodies) was 60% (9/15) in our cohort. The diagnosis of the non-seroconverters was 3 JIA, 1 PFAPA, 1 uveitis and 1 lupus. In two cases, a possible explanation could be that the serology was performed more than 6 months after the positive PCR. There were no significant differences in terms of diagnosis or treatment with seroconverters.

The most frequent clinical manifestation for COVID-19 was fever or low-grade fever (11/27, 41%). Other frequent findings were headache (18.5%; 5/27), odynophagia (18.5%; 5/27), gastrointestinal symptoms (11%; 3/27) and anosmia/ageusia (11%; 3/27). A total of 44% (12/27) of infections were asymptomatic. Three patients required hospital admission; none of them needed oxygen supplementation or intensive care unit admission. One patient with PFAPA was admitted because of multisystemic inflammatory syndrome (MIS-C) suspicion which was not confirmed. The second admitted patient was diagnosed with SLE onset and antiphospholipid syndrome with deep venous thrombosis. The third patient was a girl with vasculitis and renal impairment with mild symptoms who was admitted for observation because of her underlying disease. The patient with PFAPA received a single dose of prednisolone at 2 mg/kg. The other two admitted patients were under treatment with corticosteroids at a low dose (less than 0.3 mg/kg in both cases). Overall, 67% (18/27) of cases did not require any treatment or medical assistance for COVID-19. Among the patients in the study, 59% (16/27) had close contact with an individual with confirmed COVID-19.

We compared the baseline characteristics of patients with and without laboratory-confirmed SARS-CoV-2 (positive PCR or positive IgG antibodies) and found a significantly lower percentage of patients in clinical remission (52% vs 72%, p 0.014) and a higher percentage of patients with moderate-high disease activity (30% vs 8%, p 0.007).

Table 1 Baseline characteristics of children with rheumatic diseases who tested positive or negative for SARS-CoV-2

	SARS-CoV-2 positive	SARS-CoV-2 negative	*p*
n	27	78	105
Age	11.7 (±4.7 SD)	11.8 (±4.5 SD)	
Ethnicity: Caucasic	25/27 (92%)	74/78 (95%)	
Gender: female	19/27 (70%)	57/78 (73%)	0.80
Diagnosis			0.82
	JIA 19/27 (70%)	JIA 55/78 (70%)	
	Periodic fever 3/27 (11%)	Periodic fever 4/78 (5%)	
	SLE 2/27 (7%)	SLE 8/78 (10%)	
	Uveitis 1/27 (4%)	Uveitis 5/78 (6%)	
	Other 2/27 (7%)	Other 6/78 (8%)	
	Vasculitis 1/27 (4%)	MCTD 2/78 (2.5%)	
	STAT3 GOF mutation 1/27 (4%)	CNBO 2/78 (2.5%)	
		JDM 1/78 (1.2%)	
		Behçet 1/78 (1.2%)	
Immunosuppressive therapy*			
None		10/78 (12.8%)	
Biologic	18/27 (67%)	49/78 (63%)	0.15
TNFi	16/27 (59%)	42/78 (54%)	
Other	3/27 (11%)	21/78 (27%)	
Oral corticosteroids	7/27 (26%)	6/78 (8%)	**0.036**
Disease activity*			
Remission	14/27 (52%)	56/78 (72%)	**0.014**
Mild activity	5/27 (18%)	16/78 (20%)	
Moderate/high	8/27 (30%)	6/78 (8%)	

JIA, juvenile idiopathic arthritis; *SLE*, systemic lupus erythematosus; *MCTD*, mixed connective tissue disease; *JDM*, juvenile dermatomyositis; *CNBO*, chronic non-bacterial osteitis; *TNFi*, TNF inhibitors

*At the time of COVID-19 diagnosis or at the time of the SARS-CoV-2 serology in absence of a COVID-19 diagnosis

Bold emphasis used in entries with statistical differences

Oral corticosteroids were higher in patients diagnosed with SARS-CoV-2 infection (26% vs 8%, *p* 0.036), and the three admitted patients received treatment with corticosteroids. Having symptomatic COVID-19 (15/27) did not correlate with disease activity (0.052) in our cohort. Patients with moderate/high disease activity were five times more likely to test positive for SARS-CoV-2 (odds ratio (OR) 5.05, CI 95%: 1.56–16.3). The OR for testing positive for SARS-CoV-2 in patients treated with oral corticosteroids was 4.2 (CI 95%: 1.26–13.9).

Discussion

To the best of our knowledge, this is the first study of seroprevalence in this patient population, testing both children with and without suspected COVID-19. Most infections were mild; more than 1/3 were asymptomatic and 2/3 did not require any medical assistance. The severity of our cases was similar to that described in the literature [7, 8, 11]. Clemente et al. described the outcomes of COVID-19 in 77 paediatric patients with rheumatic diseases in a multicentre observational prospective study from Spain. Most cases were mild, with one third of asymptomatic cases. In line with our findings, their results suggest that associated comorbidities and treatment with glucocorticoids increase the risk of hospital admission [12]. Results from the national paediatric rheumatology database in Germany show similar results, with 76 cases of COVID-19 in children with rheumatic diseases, with mild outcome and good recovery in the majority of cases, and no relevant impact on disease activity [13].

Ihara et al. retrospectively described 14 COVID-19 confirmed cases in paediatric patients with RD, reporting mild to moderate symptoms and no complications. Seroprevalence in their cohort was 2.2%, although testing was performed only in symptomatic cases, so asymptomatic infections may have been left undetected [14].

Seropositivity for SARS-CoV-2 was 20% in our cohort. According to a national registry, seroprevalence for SARS-CoV-2 infection in Spain during the same study period (December 2020) was 12.5% in adults and 7.7% in children [15]. Even though the results of the study presented here cannot be compared with data on the seroprevalence of SARS-CoV-2 IgG in children in Spain, whose participants were selected by randomisation and stratification (province, city size), and not a selected population with rheumatic diseases in a single centre at one period of time, the higher seroprevalence in our cohort could be partially explained by the high percentage of asymptomatic infections. Preliminary evidence suggests that children are just as likely to become infected with SARS-CoV-2 as are adults, but are less likely to be symptomatic or develop severe symptoms [10]. Another possible explanation is a potential selection bias as families who believe they have been infected with SARS-CoV-2 are more likely to participate in the study. Also, there could be a negative selection bias in other seroprevalence studies, since healthy children are less likely to voluntarily undergo invasive tests such as blood tests as required for serology.

In this study, 21/26 patients received treatment for their RD, the most common being TNF inhibitors. These do not appear to be a risk factor for COVID-19 in adult patients [4, 6, 11]. In our work, the mild clinical course and the high percentage (44%) of asymptomatic infections support the same hypothesis. Children with active disease and corticosteroid treatment had a higher risk of SARS-CoV-2 infection, similarly to that described in adults with RD [4, 5, 8]. High disease activity is a risk factor for an increased rate of infections both in children and adult patients with RD [16, 17]. Here, children with moderate to high disease activity were five times more likely to test positive for SARS-CoV-2. Likewise, those treated with oral corticosteroids were four times more likely than those children who were not receiving oral corticosteroids. Surprisingly, having symptomatic COVID-19 did not correlate with disease activity, but the limited number of cases in our cohort may have affected the result.

This study has some limitations. While this is one of the larger studies about SARS-CoV-2 infection in children with RD, sample size is still small. Even if eligible patients were any children with rheumatic diseases, SARS-CoV-2 antibodies were more likely tested in patients who were already getting other laboratory studies drawn, and these patients are more likely to be on immunosuppressive therapy. Also, the ratio of participants was small, so selection bias cannot be discarded. The association with steroid medication and disease activity has been described in adult patients with rheumatic diseases, but glucocorticoid treatment is certainly a consequence of higher disease activity. Rheumatic diseases are highly heterogeneous, and thus information on current levels of disease activity, specific disease-related comorbidities and the use of glucocorticoids and/or DMARDs, all of which are themselves risk factors for serious infection, is needed to further understand what is driving this increased risk of COVID-19 severe course. In order to clarify whether medication or disease activity represent an independent risk factor, a multivariate analysis is required, for which the number of cases of SARS-CoV-2 infected patients in the study presented here is too small, and further studies are needed to answer this question. Despite these study limitations, this study brings a reassuring message to RD patients and healthcare practitioners, as COVID-19 infection is generally mild with a

high percentage of asymptomatic infections. Larger studies with bigger sample size and multivariate analysis are required to assess the relationship between disease activity, corticosteroids and symptoms of COVID-19 infection. In the meantime, our results support the idea that maintaining inactive disease is very important in prevention of COVID-19 infection, as it is in other infections.

Conclusions

In a cohort of paediatric patients with rheumatic diseases, SARS-CoV-2 infection was demonstrated in 25.7% of cases. Seroprevalence was 20% in this study. The clinical course was mild, with one third of asymptomatic cases. Severe infections were not observed among the patients. Higher disease activity and the use of oral corticosteroids appeared to be risk factors for laboratory-confirmed SARS-CoV-2 infection. Children with rheumatic disease in clinical remission may not be considered as a risk population for severe COVID-19.

Abbreviations JIA: Juvenile idiopathic arthritis; PFAPA: Periodic fever, adenopathy, pharyngitis and aphthous stomatitis; SLE: Systemic lupus erythematosus; RD: Rheumatic disease; PCR: Polymerase chain reaction; MIS-C: Multisystemic inflammatory syndrome; MCTD: Mixed connective tissue disease; JDM: Juvenile dermatomyositis; CNBO: Chronic non-bacterial osteitis

Acknowledgements Authors would like to thank Dr. Kinga Sandor Bajusz for helping with the translation and English correction of the manuscript. We would also like to thank all study participants and their families for their involvement in the study.

Author contribution CU and CC contributed to the study conception and design. MMH, CML and CMG helped with patient recruitment. CP and LV helped with data collection. Material preparation and analysis were performed by CU, RA, SM and AR. Serologies were performed by IFR. The first draft of the manuscript was written by CU and all authors commented on previous versions of the manuscript. CC performed the final data analyses and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study was approved by the ethics committee of Hospital La Paz (code PI-4457). The authors confirm that their study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained by parents and mature minors.

Consent for publication Not applicable.

Disclosures None.

References

1. Sisk B, Cull W, Harris JM, Rothenburger A, Olson L 2020 National trends of cases of COVID-19 in children based on US State Health Department data. [cited 2021 Apr 27]; Available fromhttps://doi.org/10.1542/peds.2020-027425
2. Hasseli R, Mueller-Ladner U, Schmeiser T, Hoyer BF, Krause A, Lorenz HM, et al. 2020 National registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (ReCoVery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. RMD Open [Internet]. [cited 2021 May 5];6(2). Available from: https://pubmed.ncbi.nlm.nih.gov/32878994/
3. Xu C, Yi Z, Cai R, Chen R, Thong BYH, Mu R 2021 Clinical outcomes of COVID-19 in patients with rheumatic diseases: a systematic review and meta-analysis of global data [Internet]. Autoimmunity Reviews. Elsevier B.V. [cited 2021 Apr 27]. Available from https://doi.org/10.1016/j.autrev.2021.102778
4. Gianfrancesco M, Hyrich KL, Hyrich KL, Al-Adely S, Al-Adely S, Carmona L, et al. 2020 Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis [Internet] [cited 2021 Apr 24];79(7):859–66. Available from: /pmc/articles/PMC7299648/
5. Nuño L, Novella Navarro M, Bonilla G, Franco-Gómez K, Aguado P, Peiteado D, et al. 2020 Clinical course, severity and mortality in a cohort of patients with COVID-19 with rheumatic diseases [Internet]. Vol. 79, Annals of the rheumatic diseases. BMJ Publishing Group; [cited 2021 May 3]. p. 1659–61. Available from: /pmc/articles/PMC7677491/
6. Michelena X, Borrell H, López-Corbeto M, López-Lasanta M, Moreno E, Pascual-Pastor M, et al. 2020 Incidence of COVID-19 in a cohort of adult and paediatric patients with rheumatic diseases treated with targeted biologic and synthetic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum [Internet]. [cited 2021 Mar 11];50(4):564–70. Available from: /pmc/articles/PMC7229730/
7. Yildiz M, Haslak F, Adrovic A, Sahin S, Barut K, Kasapcopur O 2020 The frequency and clinical course of COVID-19 infection in children with juvenile idiopathic arthritis. Vol. 38, Clinical and experimental rheumatology. NLM (Medline); p. 1271–2.
8. Calvo C, Udaondo C 2021 COVID-19 in children with rheumatic diseases in the Spanish national cohort EPICO-AEP. J Rheumatol [Internet]. [cited 2021 Apr 27];jrheum.201548. Available from: www.jrheum.org
9. Quintana-Ortega C, Remesal A, Ruiz de Valbuena M, de la Serna O, Laplaza-González M, Álvarez-Rojas E, et al. 2021 Fatal outcome of anti-MDA5 juvenile dermatomyositis in a paediatric COVID-19 patient: a case report. Mod Rheumatol Case Reports [Internet]. [cited 2021 May 5];5(1):101–7. Available from: https://pubmed.ncbi.nlm.nih.gov/33019894/
10. Zimmermann P, Curtis N 2020 Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children [Internet]. Vol. 39, Pediatric Infectious Disease Journal. Lippincott Williams and Wilkins; [cited 2021 Apr 27]. p. 355–68. Available from: /pmc/articles/PMC7158880/
11. Demir F, Ulu K, Çağlayan Ş, Coşkuner T, Sözeri B 2021 Clinical course of COVID-19 in children with rheumatic disease under biologic therapy. Vol. 39, Clinical and experimental rheumatology. NLM (Medline); p. 36–7.
12. Clemente D, Udaondo C, de Inocencio J, Nieto JC, Del Río PG, Fernández AG, Palomo JA, Bachiller-Corral J, Lopez Robledillo JC, Millán Longo C, Leon L, Abasolo L, Boteanu A (2021) Clinical characteristics and COVID-19 outcomes in a regional cohort

of pediatric patients with rheumatic diseases. Pediatr Rheumatol Online J 19(1):162. https://doi.org/10.1186/s12969-021-00648-5 (PMID:34838054;PMCID:PMC8626725)

13. Sengler C, Eulert S, Minden K, Niewerth M, Horneff G, Kuemmerle-Deschner J, Siemer C, Berendes R, Girschick H, Hühn R, Borte M, Hospach A, Emminger W, Armann J, Klein A, Kallinich T (2021) Clinical manifestations and outcome of SARS-CoV-2 infections in children and adolescents with rheumatic musculoskeletal diseases: data from the National Paediatric Rheumatology Database in Germany. RMD Open 7(2):e001687. https://doi.org/10.1136/rmdopen-2021-001687 (PMID:34312307;PMCID:PMC8316693)
14. Ihara BP, Strabelli CAA, Simon JR, Viana VSL, Sallum AME, Kozu KT, et al. 2021 Laboratory-confirmed pediatric COVID-19 in patients with rheumatic diseases: a case series in a tertiary hospital [Internet]. Vol. 30, Lupus. SAGE Publications Ltd; [cited 2021 Apr 27]. p. 856–60. Available from: http://journals.sagepub.com/doi/https://doi.org/10.1177/0961203321998427
15. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M et al (2020) Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet 396(10250):535–544
16. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al. 2011 High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. [cited 2021 May 6];70(5):785–91. Available from: https://ard.bmj.com/content/70/5/785
17. Consolaro A, Giancane G, Schapapietra B, Davi S, Calandra S, Lanni S et al (2016) Clinical outcome measures in juvenile idiopathic arthritis. PediatrRheumatol Online J 14(1):23