Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Pediatric patients with immune-mediated diseases on immunosuppressants have low risk of severe COVID-19 and no increase in flare rate after SARS CoV-2 exposure

In response to the publication by Zsigmond et al. we report the very low risk of severe COVID-19 in immunosuppressed children in Romania.[1]

Children are prone to asymptomatic or mild infection. In the first pandemic year, reported deaths for children and young adults from England attributed to SARS CoV-2 infection were two per million.[2] During the Delta and Omicron variants surge, the hospitalization rate in children increased especially for those aged <4 years without an increase in mortality rate,[3] but remained ten

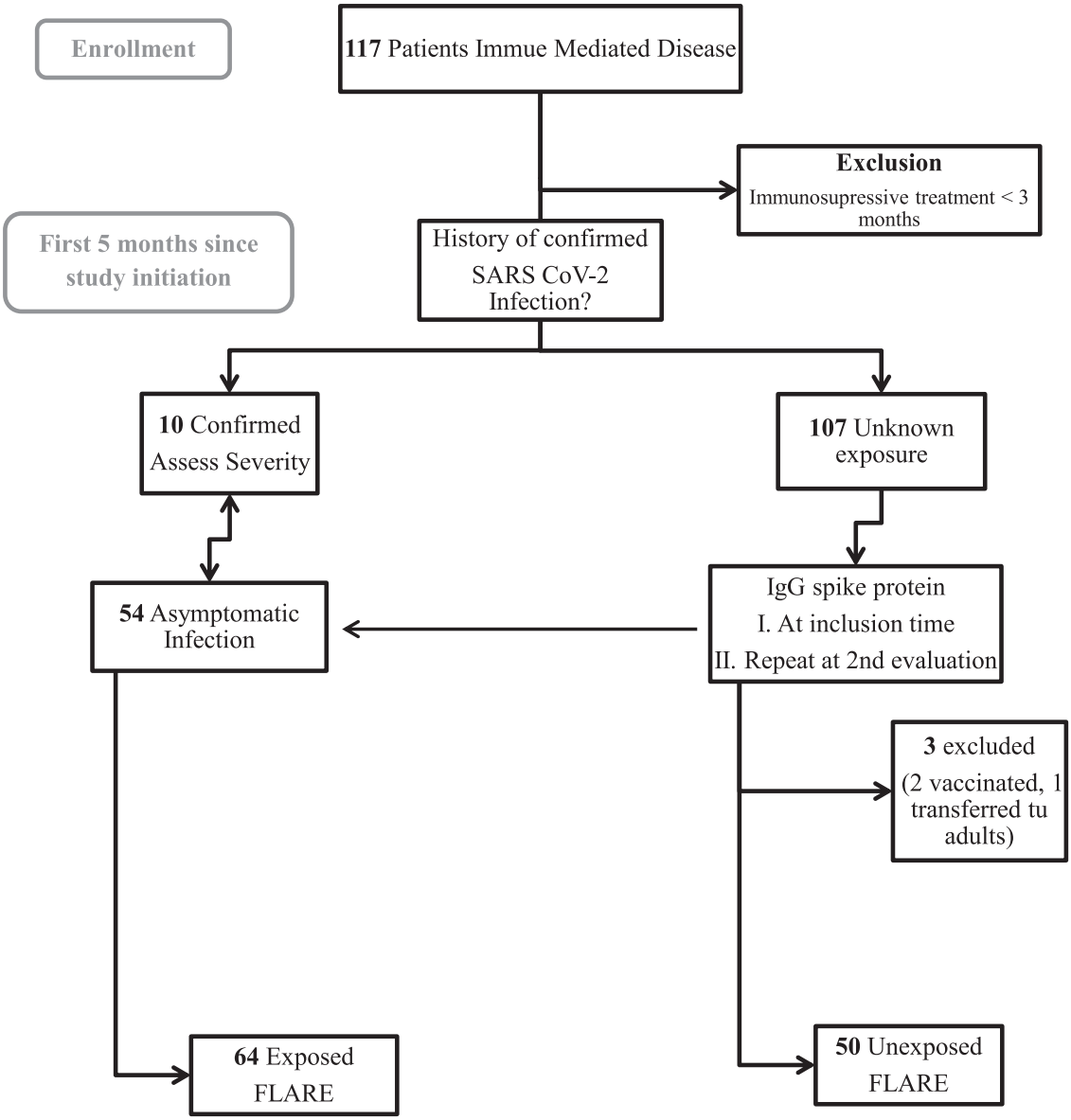

Fig. 1. Flow diagram of the study: enrollment, inclusion and exclusion criteria, follow-up. Exposed: subjects with previously confirmed infection by RT-PCR or rapid antigen on the nasal-pharyngeal swab material AND subjects with positive anti spike antibodies at first or second evaluation during the first five months of the study. Unexposed: subjects with negative anti spike antibodies after one or two consecutive tests performed in the first five months.

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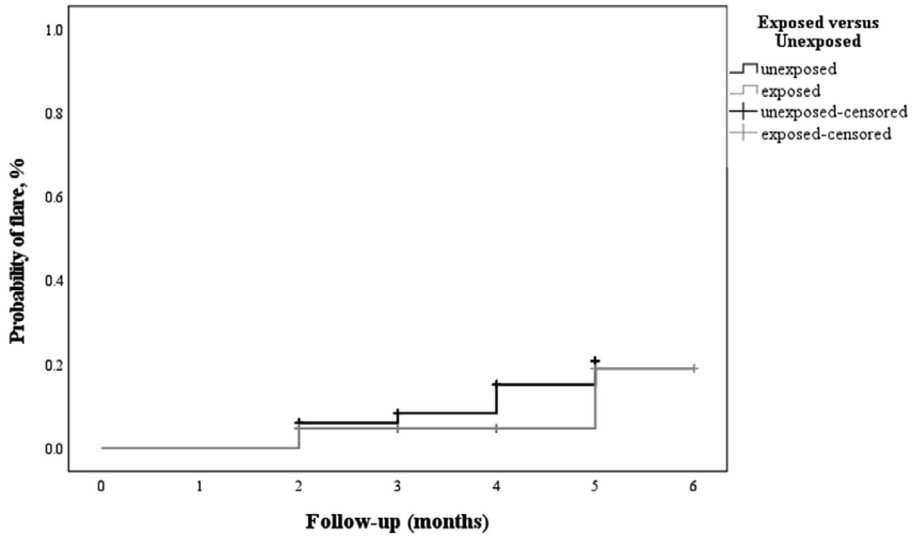

Fig. 2. The Kaplan Meier curves for flare-ups in the exposed and unexposed group. The 4-month risk of flare in the exposed and unexposed groups was 9% versus 14% ($p = 0.45$, Log Rank test). Flare-up evaluation started from the date of confirmed SARS CoV-2 infection (no more than six months) or from the first spike protein measure and lasted until study closure. Exposed: subjects with previously confirmed infection by RT-PCR or rapid antigen on the nasal-pharyngeal swab material AND subjects with positive anti spike antibodies at first or second evaluation during the first five months of the study. Unexposed: subjects with negative anti spike antibodies after one or two consecutive tests performed in the first five months. Flare-up: the need to modify previous treatment - initiate or increase dose of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (systemic or local, as intra-articular glucocorticoid injection) or escalation of therapy from synthetic to biologic disease-modifying-anti-rheumatic-drugs (DMARDs).

times lower compared to flu-associated-hospitalization from the 2017 to 2018 season.[4]

Severe SARS CoV-2 infection in children is rare but unveiling risk factors for worse outcomes can help identify high-risk groups and impose protective measures. According to CDC, use of corticosteroids and other immunosuppressive drugs includes these patients in high risk group for severe COVID-19.[5] However, there is controversy among risk-reporting studies in immunosuppressed children with conditions ranging from autoimmunity to malignancy.[6-9] Apart from infection severity, virus exposure increased concerns about medium term flare-ups in rheumatic-disease patients due to both treatment discontinuation and COVID-19-related distress.[10,11]

We investigated the rate of severe outcomes related to COVID-19 in a cohort of pediatric patients diagnosed with immune-mediated diseases and treated with immunosuppressive medication. Secondly, we estimated the rate of asymptomatic infection through a seroprevalence survey and determined the risk of disease flare-up after virus exposure.

We enrolled pediatric patients aged <19 years diagnosed with immune-mediated diseases in a tertiary care center, Department of Clinical Immunology, National Institute of Mother and Child, Bucharest, Romania. The study was conducted between July 1, 2021 and March 30, 2022.

We included patients with a defined diagnosis of immune-mediated disease and continuous treatment with immunosuppressive medication three months before enrollment. We collected data regarding demographics, disease activity, treatment, and clinical features of past confirmed SARS CoV-2 infection by real time PCR (RT-PCR) or rapid antigen test on the nasal-pharyngeal swab during regular face-to-face evaluations. Qualitative detection of antibodies against spike protein from serum sample of each subject was assayed by fluorescence immunoassay using the FREND™ COVID-9 IgG/IgM Duo. The flow diagram of the study is presented in Fig. 1.

Subjects were divided into two groups based on their exposure to the SARS CoV-2 virus:

(i) Exposed: previously confirmed infection by RT-PCR or rapid antigen on the nasal-pharyngeal swab material or positive anti spike antibodies at first or second evaluation during the first five months of the study.
(ii) Unexposed: negative anti spike antibodies after one or two consecutive tests performed in the first five months of the study.

Our primary outcomes were: need of hospitalization, intensive care unit (ICU) admission and mortality rate in immunosuppressed children with COVID-19. Our secondary outcomes were: seroprevalence survey and incidence of flare-ups in exposed versus unexposed subjects.

A total of 117 patients were enrolled, female to male ratio of 1.6, median age at inclusion time 11.1 years (range 1-18). Three patients were excluded from the study: two received Comirnaty COVID-19 vaccine and one patient was transferred to adult care facility. 68% of included patients had juvenile idiopathic arthritis (JIA). The most frequent immunosuppressive drug was methotrexate prescribed in 96 patients (84%), either as monotherapy or in association with other synthetic or biologic disease-modifying-anti-rheumatic-drugs (DMARDs).

A total of 20 patients (17.5%) had a confirmed SARS CoV-2 infection and four amongst them tested positive after two previous negative anti spike protein measures. Only one patient required hospitalization in the 14th day after confirmation date for bacterial pneumonia. The mortality rate was null in our cohort and none of our patients required ICU admission or oxygen supplementation. Immunosuppressive treatment in confirmed subjects included monotherapy with synthetic DMADRs, double or triple therapy with synthetic and biologic DMARDs and corticosteroids, with duration of therapy detailed in Supplementary Table 1. All 20 patients experienced minor symptoms (low-grade fever, rhinorrhea, cough or gastrointestinal symptoms) for up to seven days. According to confirmation date, four patients got infected during the pre-Delta variant period, when Alpha/Beta variants were predomi-

nant. Seven patients got infected during the Delta wave, classified as variant of concern (VOC) by CDC due to increased transmissibility and disease severity. Finally, nine patients got infected after January 2022, when the predominant variant was Omicron. None of the patients disrupted their chronic medication during acute infection.

As of month five of our study, 54 included subjects tested positive for Ig G antibodies to spike protein: 48 with positive serology at first measurement and 6 at second evaluation, three to four months distance. Nine (18%) subjects had a documented direct contact with a positive case, but no history of symptomatic infection. 50 subjects had negative Ig G antibodies to spike protein: 27 with two sequential negative serology tests three months apart and 23 with one negative serology test.

64 patients were included in the exposed group: ten with confirmed infection up to December 2021 and 54 with at least one positive serology test. 50 patients were included in the unexposed group: negative serology up to December 2021. The differences between groups in terms of age, gender, immune-related disease, type and duration of immunosuppressive therapy were not statistically significant (Supplementary Table 2).

We assessed flare-ups retrospectively for COVID-19 confirmed cases (follow-up for maximum six months starting confirmation date) and prospectively for subjects without history of a positive SARS CoV-2 test. During the median follow-up of four months (range two to six months), a total of 13 (11%) subjects flared. The risk of flare in the exposed and unexposed group was 9% and 14%, respectively ($p = 0.45$, Log Rank test, Fig. 2). Those who flared were more likely to be female, receive higher doses of corticosteroids and have monotherapy with synthetic DMARDs, $p < 0.05$ (Supplementary Table 2). Multivariate analysis using Cox model showed that only female gender was associated with an increased risk of flare-up (Supplementary Table 3).

The final seroprevalence survey results from March 2022 showed that 63% (62/99 patients) of immunosuppressed children in our cohort had previous asymptomatic infection (Supplementary Table 4).

This is the first report of clinical outcomes, seroprevalence survey and risk of flare related to SARS CoV-2 infection in a cohort of pediatric patients with rheumatic diseases from Romania. All subjects with confirmed infection had mild COVID-19 and none required medication interruption. Previous exposure to SARS CoV-2 virus did not seem to increase flare-ups on a medium term. Seroprevalence survey identified high asymptomatic infection, reinforcing previous clinical observations that risk of severe COVID-19 in immunosuppressed pediatric patients with rheumatic diseases is minimal.

Ethics approval

This cohort study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committee of our center approved the study protocol (approval date 16/06/2021).

Authorship contributions

All authors have contributed sufficiently to the scientific work and, therefore, share collective responsibility and accountability for the results. All authors have read and approved the final manuscript. AVC and AI contributed to the study conception and design, revised the manuscript for important intellectual content, performed data analysis and data interpretation, and drafted the manuscript; OMF gathered medical data and revised the manuscript.

Declaration of Competing Interest

The authors have no financial interests that impact this study. We also certify that there are no actual or potential conflicts of interest in relation to this article.

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Data for reference

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.06.012.

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