Outcomes of SARS-CoV-2 Infection among Children and Young People with Pre-existing Rheumatic and Musculoskeletal Diseases.

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Competing interests: personal consultant fees from Boehringer Ingelheim Portugal, Lda, all unrelated to this manuscript. LPCDR received support for specific activities: grants from Abbvie, Novartis, Lilly Portugal, Amgen Biofarmacêutica, Grünenthal S.A., MSD, Medac, A. Menarini Portugal - Farmacêutica, S.A., Pfizer, UCB Pharma, ROCHE Farmacêutica Química, Lda; and non-financial support from Pfizer, and Grünenthal GmbH, all unrelated to this manuscript.

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Word count manuscript: 3144

Tables: 3

References: 20

Key messages:

- **What is already known about this subject?**
    - Some adults with rheumatic and musculoskeletal diseases (RMDs) are at increased risk of COVID-19-related death.
- **What does this study add?**
    - Hospitalisation for COVID-19 among children and young people with underlying RMDs were rare in this study with the majority having mild affects only.
    - Treatment with biologics, such as TNF inhibitors, did not appear to be associated with more severe COVID-19 in children and young people with RMDs.
- **How might this impact on clinical practice or future developments?**
    - Whilst protective measures, as indicated by local policy, are important to follow with respect to minimising risk of acquiring SARS-CoV-2 infection, parents and families can be reassured that these data do not support a high probability of severe COVID-19 in the majority of children and young people with underlying RMDs.

Abstract

Objectives: Some adults with rheumatic and musculoskeletal diseases (RMDs) are at increased risk of COVID-19-related death. Excluding post-COVID-19 multisystem inflammatory syndrome of children, children and young people (CYP) are overall less prone to severe COVID-19 and most experience a mild or asymptomatic course. However, it is unknown if CYP with RMDs are more likely to have more severe COVID-19. This analysis aims to describe outcomes among CYP with underlying RMDs with COVID-19.

Methods: Using the European Alliance of Associations for Rheumatology (EULAR) COVID-19 Registry, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, and the CARRA-sponsored COVID-19 Global Paediatric Rheumatology Database (COVID-19 GPRD), we obtained data on CYP with RMDs who reported SARS-CoV-2 infection (presumptive or confirmed). Patient characteristics and illness severity were described, and factors associated with COVID-19 hospitalisation were investigated.

Results: 607 CYP with RMDs <19 years-old from 25 different countries with SARS-CoV-2 infection were included, the majority with juvenile idiopathic arthritis (JIA; N=378; 62%). Forty-three (7%) patients were hospitalised; three of these patients died. Compared with JIA, diagnosis of systemic lupus erythematosus, mixed connective tissue disease, vasculitis, or other RMD (OR 4.3; 95%CI 1.7, 11) or auto-inflammatory syndrome (OR 3.0; 95%CI 1.1, 8.6) was associated with hospitalisation, as was obesity (OR 4.0; 95%CI 1.3, 12).

Conclusions: This is the most significant investigation to date of COVID-19 in CYP with RMDs. It is important to note that the majority of CYP were not hospitalised, although those with severe systemic RMDs and obesity were more likely to be hospitalised.

Background

Worldwide, as of 11th January 2022, there were over 308 million confirmed cases of COVID-19, including over 5.4 million deaths.[1] The collective experience is that children, especially younger children, seem less susceptible to symptomatic Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) illness and reports of death are rare.[2,3] However, less is known about the impact of comorbidity and especially immunosuppression on the risk of severe COVID-19 in the paediatric population.

Data from one analysis of adults with rheumatic and musculoskeletal diseases (RMDs) has shown that presence of rheumatoid arthritis, lupus or psoriasis (as a group) is associated with increased risk of COVID-19-related death compared with those without comorbid RMDs.[4] However, this analysis did not account for the effects of treatments or disease activity. In another analysis of almost 4,000 adults with RMDs, moderate to high RMD disease activity and certain types of therapies (e.g. B-cell depletion, alkylating agents) were associated with COVID-19-related death.[5] A recent systematic literature review suggested that the increased risk of severe COVID-19 cannot be generalised to all patients with RMDs and it is probably restricted to very specific subgroups of patients with RMDs.[6]

According to data from seven countries, as of January/February 2021, approximately 1.7 deaths per 1,000,000 population attributable to COVID-19 have occurred in individuals up to 19 years old, contributing 0.48% of estimated total all-cause mortality.[7] In a recent (pre-print) systematic review of children and young people with COVID-19, those with comorbid conditions were at increased risk of hospital admissions to critical care, although only eight patients in this review were considered to have an RMD.[8]

It remains unknown whether children and young people with RMDs who acquire COVID-19 have a more severe COVID-19 course and if there is additional risk attributable to either underlying disease or its therapy. It is important to understand the impact of COVID-19 on these individuals to inform national guidelines on protective measures (i.e. recommendations to stay home and avoid face-to-face contact), vaccination guidance, and address individual decisions regarding heightened social distancing measures for paediatric RMD patients and their families. Critically for this age group is the need to ensure they continue to have full and appropriate access to school and education, with in-person attendance if safe to do so.

Around the recognised outset of the COVID-19 pandemic, individual national and international efforts to collect, analyse, and disseminate data about COVID-19 in patients with paediatric RMDs were rapidly established. In collaboration with the COVID-19 Global Rheumatology Alliance,[9] there were three organised cooperative efforts for COVID-19 in paediatric RMDs internationally: (1) the European Alliance of Associations for Rheumatology (EULAR)/Paediatric Rheumatology European Society (PReS) sponsored COVID-19 Registry, consisting of >10,000 clinician-entered reports of individuals with RMDs with COVID-19[10] including children, collecting cases from across Europe; (2) inclusion of SARS-CoV-2 infection reporting for the United States Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry; (3) the CARRA-sponsored COVID-19 Global Paediatric Rheumatology Database (COVID-19 GPRD) for international reporting of subjects not covered by either of the other two efforts. Data collection was designed to align between efforts and this collaboration has yielded the largest collection of COVID-19-related data for patients with paediatric onset RMDs to date.

The aims of this global analysis are: (1) to describe characteristics of those children and young people with pre-existing RMDs with COVID-19, (2) to describe outcomes following COVID-19, and (3) to identify characteristics that are associated with more severe COVID-19 outcomes.

Methods

DATABASES

The data analysed comprise cases reported to the EULAR COVID-19 Registry, the CARRA Registry, and the COVID-19 GPRD. Data were entered by the treating rheumatologist or their designee directly into data entry websites. For some countries in Europe (France, Germany, Greece, Italy, Portugal and Sweden), under an existing agreement, cases were transferred from other national COVID-19 registries into the EULAR COVID-19 Registry. It was not possible for patients or families to report directly into any of the registries, but mild or asymptomatic cases of COVID-19 reported to a rheumatologist could be entered subsequently by a physician. The EULAR COVID-19 Registry data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at The University of Manchester, United Kingdom.[11] REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The COVID-19 GPRD study is operated by Boston Children's Hospital (USA) and utilizes REDCap Cloud (nPhase, Inc., USA) for data entry from the USA, Canada, and international sites not participating in the EULAR COVID-19 Registry. For patients with RMDs enrolled in the CARRA Registry (prospective observational cohort) and who also tested positive for SARS-CoV-2 infection, data are collected in Rave (Medidata Solutions Inc., USA). Data reported in the EULAR COVID-19 Registry and the COVID-19 GPRD are collected on an ad hoc basis. CARRA Registry investigators were instructed to report all SARS-CoV-2 infections in registry subjects as a safety event of special interest (ESI). Complete CARRA Registry ESI reports were validated, abstracted, and combined with data from the COVID-19 GPRD; these data elements were then mapped to and harmonized with the EULAR COVID-19 Registry dataset for combined data analyses.

DATA COLLECTION

The data collected across the registries include patient demographic information (age, sex at birth, country of residence), primary RMD diagnosis, RMD disease activity (tick box: remission, low, moderate, high, or unknown), RMD treatments including glucocorticoid use and which disease modifying anti-rheumatic drug (DMARD) the patient was on at the time of COVID-19, and comorbidities (tick box: none, ocular inflammation, interstitial lung disease, asthma, diabetes, obesity, hypertension, cerebrovascular accident, renal disease, inflammatory bowel disease, heart disease). Information on COVID-19 include diagnosis date, whether the case was presumptive or confirmed (via PCR, antigen test, antibody test, or other laboratory assay), clinical symptoms (tick box), hospitalisation and/or death due to COVID-19, and whether the patient stopped rheumatic therapies.

ETHICS APPROVAL

The EULAR COVID-19 physician-reported Registry was determined "not human subjects' research" by the UK Health Research Authority and the University of Manchester and no informed consent was required for anonymous data to be uploaded to the registry. The CARRA Registry is approved by the Duke University IRB (Pro00054616), and informed consent was obtained for participation in the CARRA Registry. COVID-19 GPR Database is approved by the Boston Children's Hospital IRB (P00034912) on an expedited basis, with waiver of informed consent and authorisation.

INCLUSION CRITERIA

All children and young people <19 years of age at the time of detection of SARS-CoV-2 infection or the development of COVID-19 illness (presumptive or confirmed) were included in the primary analyses. Individuals with juvenile idiopathic arthritis (JIA) aged 19 and over were included for additional descriptive analyses. The CARRA Registry required documentation of positive SARS-CoV-2 testing (PCR, antigen, or antibody) in order to be validated as a COVID-19 ESI. These cases underwent validation by two independent reviewers.

Cases for this analysis were included from initial COVID-19 date (EULAR COVID-19 Registry: 27th March 2020; CARRA Registry: 1st March 2020; COVID-19 GPRD: 13th April 2020) until a cut-off date of 20th July 2021 for the EULAR COVID-19 Registry, 25th May 2021 for the CARRA Registry, and 23rd June 2021 for the COVID-19 GPRD.

STATISTICAL ANALYSIS

Demographic characteristics of all children and young people aged <19 years were described using relevant categorical and continuous variables and patients who died were further characterised. Rheumatology diagnosis was categorised into four groups: (i) JIA, (ii) systemic lupus erythematosus (SLE), mixed-connective tissue disease (MCTD), vasculitis or other RMD (including Behcet's disease, inflammatory myopathy, systemic sclerosis, localised scleroderma), (iii) auto-inflammatory syndromes (including tumour necrosis factor receptor-associated periodic syndrome (TRAPS), cryopyrin-associated auto-inflammatory syndromes (CAPS), and familial Mediterranean fever (FMF)), (iv) other (including chronic recurrent multifocal osteomyelitis, sarcoidosis, ocular inflammation, "other", or was left blank).

Logistic regression (complete case) was used to assess factors associated with COVID-19 hospitalisation, including: age, sex, rheumatology diagnosis (four categories as above), obesity (BMI ≥30; tick box [EULAR] or combination of BMI and tick box [CARRA Registry and CARRA GPRD]), glucocorticoid use, and disease modifying anti-rheumatic drug (DMARD) use (none, conventional-synthetic DMARD only, biologic or targeted-synthetic DMARD only, combination therapy). Odds ratios (OR) and 95% confidence intervals (CI) are presented for each variable individually (univariable logistic regression). For the multivariable logistic regression, all variables in the univariable analysis were included as it was believed that each was an important factor to be accounted for. Disease activity was also included in the multivariable analysis with unknown (i.e. missing) included as an indicator variable (categories: remission, low, moderate to high, or unknown). Finally, dataset (EULAR or CARRA [CARRA Registry and CARRA GPRD]) was included in the multivariable model to account for differences between data collection. One patient with unknown sex was dropped from this analysis.

Two sensitivity analyses of the logistic regression were conducted. The first without inclusion of two patients retrospectively diagnosed with SLE after presentation with COVID-19 (both of whom died), given uncertainties regarding the possibility of COVID-19-induced autoimmune disease and the small number of deaths and serious illness reported in the data. The second excluded disease activity from the model due to the large amount of missing data.

Patients with JIA over 19 years old were included in a further descriptive analysis regarding age, sex, rheumatology diagnosis, hospitalisations and deaths.

Results

CHILDREN AND YOUNG PEOPLE

There were a total of 607 children and young people under the age of 19 years old included from 25 different countries; 464 from the EULAR COVID-19 Registry and 143 from the CARRA datasets (CARRA Registry and CARRA GPRD) (table 1). Of these, 499 (82%) were confirmed SARS-CoV-2 cases (majority with PCR; N=425), 399 (66%) were female, and median age was 14 years old (interquartile range [IQR] 9 to 16). The majority of children and young people had JIA (N=378; 62%); 140 with polyarticular (37% of JIA), 112 with oligoarticular (30% of JIA), 44 with enthesitis-related JIA (12% of JIA), 34 with systemic JIA (9% of JIA), 16 psoriatic (4% of JIA), and 33 other or unknown (9% of JIA). There were also 78 (13%) patients with auto-inflammatory syndromes, 47 (8%) with SLE or MCTD, 16 (3%) with vasculitis and 15 (2%) with inflammatory myopathy.

Table 1: Patient characteristics, rheumatic disease information, and main COVID-19 outcomes of 607 children and young people under the age of 19 years with COVID-19.

		All Patients	Not Hospitalised	Hospitalised
N		607	564 (93%$^\$$)	43 (7%$^\$$)
Dataset	EULAR COVID-19 Registry	464 (76%)	437 (77%)	27 (63%)
	CARRA Datasets (CARRA Registry and CARRA COVID-19 GPRD)	143 (24%)	127 (23%)	16 (37%)
Sex	Female	399 (66%)	369 (65%)	30 (70%)
	Male	207 (34%)	194 (34%)	13 (30%)
	Unknown	1 (<1%)	1 (<1%)	0
Age, years	Median (IQR)	14 (9, 16)	14 (10, 16)	14 (8, 17)
	Range	1 to 18.9	1 to 18.9	2 to 18
Primary rheumatology diagnoses	Juvenile Idiopathic Arthritis (JIA)	378 (62%)	360 (64%)	18 (42%)
	Polyarticular	*139 (23%)*	*137 (24%)*	*2 (5%)*
	Oligoarticular	*112 (18%)*	*108 (19%)*	*4 (9%)*
	Systemic	*34 (6%)*	*29 (5%)*	*5 (12%)*
	Psoriatic	*16 (3%)*	*16 (3%)*	*0*

	Enthesitis-related	44 (7%)	39 (7%)	5 (12%)
	Other / Unknown	33 (5%)	31 (6%)	2 (5%)
	Systemic Lupus Erythematosus / MCTD / Vasculitis / Other RMD#	87 (14%)	73 (13%)	14 (33%)
	Auto-inflammatory syndromes (e.g. TRAPS, CAPS, FMF)	78 (13%)	71 (13%)	7 (16%)
	Other##	64 (11%)	60 (11%)	4 (9%)
Comorbidities	None stated	505 (83%)	472 (84%)	33 (77%)
	Ocular inflammation	38 (6%)	36 (6%)	2 (5%)
	Obesity (BMI ≥30)	34 (6%)	28 (5%)	6 (14%)
	Asthma	7 (1%)	7 (1%)	0
Disease activity	Remission	194 (32%)	178 (32%)	16 (37%)
	Low	159 (26%)	152 (27%)	7 (16%)
	Moderate	40 (7%)	36 (6%)	4 (9%)
	High	6 (1%)	3 (<1%)	3 (7%)
	Unknown###	208 (34%)	195 (35%)	13 (30%)
Confirmed or Suspected	Confirmed	499 (82%)	465 (82%)	34 (79%)
	Suspected	108 (18%)	99 (18%)	9 (21%)
Most frequently reported symptoms	Asymptomatic	140 (23%)	137 (24%)	3 (7%)
	Fever	236 (39%)	203 (36%)	33 (77%)
	Cough	181 (30%)	163 (29%)	18 (42%)
	Rhinorrhoea	111 (18%)	105 (19%)	6 (14%)
	Headache	107 (18%)	96 (17%)	11 (26%)
	Anosmia	105 (17%)	104 (18%)	1 (2%)
Treatment at onset of COVID-19 infection	Any DMARD	423 (70%)	395 (70%)	28 (65%)
	csDMARD monotherapy	143 (24%)	132 (23%)	11 (26%)
	b/tsDMARD monotherapy	156 (26%)	144 (26%)	12 (28%)
	Combination therapy (cs and bDMARD)	124 (20%)	119 (21%)	5 (12%)
	Any csDMARD	267 (44%)	251 (45%)	16 (37%)
	Methotrexate	198 (33%)	189 (34%)	9 (21%)
	Antimalarials	48 (8%)	40 (7%)	8 (19%)
	Mycophenolate	28 (5%)	24 (4%)	4 (9%)
	Cyclophosphamide	0	0	0
	Any b/tsDMARD	280 (46%)	263 (47%)	17 (40%)
	Anti-TNF inhibitor	200 (33%)	193 (34%)	7 (16%)
	IL-6 inhibitor	30 (5%)	27 (5%)	3 (7%)
	IL-1 inhibitor	19 (3%)	15 (3%)	4 (9%)
	Rituximab	11 (2%)	9 (2%)	2 (5%)
	JAK inhibitor	6 (1%)	6 (1%)	0
	Glucocorticoids	66 (11%)	56 (10%)	10 (24%)
	In combination with cs/btsDMARD	56 (9%)	49 (9%)	7 (16%)
Required Hospitalisation	Yes	43 (7%)	0	43 (100%)

	Required oxygen / ventilation	*8 (1%)*	-		*8 (19%)*
	None needed	*35 (6%)*	-		*35 (81%)*
Deaths due to COVID-19####		3 (<1%)	0		3 (7%)

$Row percentage.

#Other RMD includes: Behcet's disease, inflammatory myopathy, systemic sclerosis, localised scleroderma.

##Other includes: chronic recurrent multifocal osteomyelitis, sarcoidosis, ocular, "other", or was left blank.

###94% of which are from the CARRA dataset and the EULAR French data subset.

####Two deaths occurred in subjects who were diagnosed with SLE around the same time as COVID-19: one with SLE manifestations recognised at the time of COVID-19 presentation, one with SLE manifestations in the preceding 2 months.

Body mass index (BMI); biologic or targeted-synthetic (b/ts); Childhood Arthritis and Rheumatology Research Alliance (CARRA); CARRA-sponsored COVID-19 Global Paediatric Rheumatology database (COVID-19 GPRD); conventional-synthetic (cs); Cryopyrin-Associated Auto-inflammatory Syndromes (CAPS); disease modifying anti-rheumatic drug (DMARD); European Alliance of Associations for Rheumatology (EULAR); Familial Mediterranean Fever (FMF); interleukin (IL); interquartile range (IQR); janus-kinase (JAK); mixed-connective tissue disease (MCTD); rheumatic and musculoskeletal disease (RMD); tumour necrosis factor (TNF); tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

The majority of patients did not report any comorbidities (83%), although 38 (6%) had ocular inflammation (largely uveitis in association with JIA), and 34 (6%) were reported to be obese. Less than 1% reported comorbid inflammatory bowel disease, diabetes mellitus, or renal disease. Twelve (2%) patients reported more than one comorbidity.

Of these 607 children and young people, 43 (7%) were admitted to hospital. A higher proportion were reported as hospitalised in CARRA data versus the EULAR registry (11% vs 6%), as well as those with SLE/MCTD (16%) and systemic JIA (15%) compared with other JIA patients (4%). One hundred and forty (23%) patients had asymptomatic COVID-19. The most common symptoms overall were fever (N=236; 39% of all patients) and cough (N=181; 30% of all patients), with hospitalised patients reporting fever more frequently (77% vs 36%).

Most patients (N=423; 70%) were on DMARD therapy at the time of COVID-19. There were 267 (44%) patients on a conventional-synthetic DMARD (predominantly methotrexate, N=198), 143 of those as monotherapy and 124 in combination with biologic DMARDs. No patients were on combination therapies of conventional-synthetic DMARDs with targeted-synthetic DMARDs. There were 280 (46%) patients on biologic or targeted-synthetic DMARDs (predominantly anti-TNF therapy, N=200), 156 of those as monotherapy. There were a similar proportion of hospitalised and non-hospitalised patients discontinuing either their conventional-synthetic, or biologic or targeted-synthetic DMARD therapy at the time of COVID-19 diagnosis (approximately one third). Eleven percent (N=66) of patients were receiving glucocorticoid treatment at the time of COVID-19; of these, 36 patients reported dosage with median dose 6.5 mg/kg (IQR 3.8 to 12.3).

Among those for whom disease activity at the time of COVID-19 had been recorded, the majority were in remission (N=194; 49% of those with data) or had low disease activity (N=159; 40% of those with data). Disease activity at the time of COVID-19 was unavailable for 208 (34%) patients, primarily from the CARRA datasets and the EULAR French data subset (non-recorded at all in the French data subset). Hospitalised patients more often had moderate (9% vs 6%) or high (7% vs <1%) disease activity than non-hospitalised patients.

Three patients died with PCR confirmed SARS-CoV-2 (table 2). One death in a female <5 years old with a pre-existing auto-inflammatory syndrome (unknown disease activity status), on low dose glucocorticoids and methotrexate (described in further detail elsewhere[12]). Two deaths occurred in subjects from lower-resource areas who were diagnosed with SLE around the same time as they developed COVID-19 (one with SLE manifestations recognised at the time of COVID-19 presentation, another with preceding SLE manifestations but not yet diagnosed).

Table 2: Description of the three fatalities in children and young people with COVID-19.

Patient	Age	Sex	Rheumatology Diagnosis	Comorbidities	Glucocorticoids	Rheumatology Treatment	Disease Activity	Time from COVID onset to death
1	<15 years	Female	Systemic Lupus Erythematosus	None	None	Antimalarials Intravenous Immunoglobulin	High	8 days
2	<10 years	Female	Systemic Lupus Erythematosus	None	Yes (dose unknown)	None	High	9 days
3	<5 years	Female	Auto-inflammatory syndrome	None	Yes (low dose)	Methotrexate	Unknown	7 days

Factors associated with hospitalisation in children and young people with COVID-19 (Table 3) included diagnosis of SLE/MCTD, vasculitis or other RMD (OR 4.3; 95% CI 1.7, 11) or auto-inflammatory syndromes (OR 3.0; 95% CI 1.1, 8.6) compared with JIA, and obesity (OR 4.0; 95% CI 1.3, 12). When the analysis was repeated, (i) excluding the two patients who died who were retrospectively diagnosed with SLE after presentation with COVID-19 (supplementary table 1), and (ii) excluding disease activity as a confounder (supplementary table 2), the estimates did not change substantially.

Table 3: Factors associated with hospitalisation in children and young people with COVID-19 (N=606).

	Univariable Odds Ratio (95% Confidence Intervals)	Multivariable Odds Ratio[#] (95% Confidence Intervals)
Female (vs Male)	1.2 (0.6, 3.8)	1.1 (0.6, 2.4)
Age (years)	1.0 (0.9, 1.1)	1.0 (0.9, 1.0)
Rheumatic Disease		
JIA	[comparator]	[comparator]
SLE/MCTD, Vasculitis	3.8 (1.8, 8.1)*	4.3 (1.7, 11)*
Auto-inflammatory syndromes	2.0 (0.8, 4.9)	3.0 (1.1, 8.6)*
Other	1.3 (0.4, 4.1)	1.7 (0.5, 5.5)
Obesity	3.1 (1.2, 8.0)*	4.0 (1.3, 12)*
Glucocorticoid use	2.7 (1.3, 5.9)*	2.1 (0.8, 5.6)
DMARD use		
None stated	[comparator]	[comparator]
csDMARD only	0.9 (0.4, 2.1)	0.6 (0.2, 1.7)
b/tsDMARD only	0.9 (0.4, 2.1)	1.5 (0.6, 3.6)
Combination therapy	0.5 (0.2, 1.3)	0.4 (0.1, 1.5)

ADULTS

There were 99 adults with JIA, 82 from the EULAR COVID-19 Registry and 17 from the CARRA dataset, with a median age of 26 years (IQR 20 to 34, range 19 to 72 years old). Of these adults, 76 (77%) were confirmed cases (majority with PCR; N=66), nine were hospitalised, and two died. The two deaths were in females with oligoarticular JIA with PCR confirmed SARS-CoV-2. One was 31-40 years old with moderate disease activity receiving glucocorticoid (dose 10mg) and combination conventional-synthetic DMARD with anti-TNF therapy at the time of COVID-19 diagnosis, with concomitant inflammatory bowel disease. The other was 61-70 years old in remission receiving no glucocorticoid or DMARD therapy, with asthma, diabetes, and hypertension.

Discussion

This is the most significant global investigation to date of short-term COVID-19 outcomes in children and young people with RMDs. Of the 607 cases reported, 7% were hospitalised, although less than one-in-five of these needed oxygen or ventilation, and three patients died. There were no associations between DMARD treatment (conventional-synthetic, biologic/targeted-synthetic, or combination therapy, compared with no DMARD treatment), or glucocorticoid use, with hospitalisation. However, children and young people with SLE/MCTD, vasculitis, other RMDs or auto-inflammatory syndromes were more likely to be hospitalised compared with those with JIA. As in multiple other reports in non-disease-specific populations, obesity represented a risk factor for more severe COVID-19 outcome.

These initial results are reassuring against the occurrence of severe COVID-19 illness (excluding multisystem inflammatory syndrome in children [MIS-C]) in the majority of individuals with paediatric RMDs, with only one-in-fifteen children and young people with RMDs with COVID-19 reporting hospitalisation. Using the same database structure, almost half of the cases reported in adults with RMDs were fatal cases, likely representing a significant bias in reporting.[5] If this same bias is present in the paediatric reports, it is possible that outcomes are even more favourable in this younger population, with many children and young people with RMDs experiencing milder COVID-19 not reporting the case to their physician, who in turn cannot report to the registries. The ad-hoc nature of voluntary reporting to these data sources prevents a population-based analysis.

Nonetheless, although uncommon in all children and young people, those with RMDs other than JIA (predominantly SLE/MCTD, vasculitis, or auto-inflammatory syndromes) were more likely to have serious outcomes, which is not surprising given the typically greater systemic involvement and need for more aggressive immunosuppressive therapy than the majority of individuals with JIA. In addition, patients with more severe JIA are often treated with anti-TNF DMARD therapies, which have been associated with less severe COVID-19 disease in some adult reports compared with other

therapies.[13–15] In adults with RMDs, those with SLE were at increased risk of COVID-19-related hospitalisation, and those with comorbidities such as hypertension, cardiovascular disease, chronic lung disease, chronic kidney disease, and diabetes, have been identified as being at increased risk of COVID-19-related hospitalisation and death.[5,13] Regarding obesity as a risk factor for more severe COVID-19, our data is in agreement with other studies evidencing poorer COVID-19 outcomes with obesity in the adult general population.[4,16] That obesity is also associated with severe COVID-19 in children is a new finding.

This analysis is the largest investigation of COVID-19 in children and young people with RMDs globally. However, it was not without limitations. SARS-CoV-2 infection reported to the combined registries included both presumptively diagnosed and confirmed cases, introducing possible misclassification bias. The authors believe this is not likely to have substantially confounded our results as the majority of severe COVID-19 cases would have been reported. In the treatment of COVID-19 deaths, we noted no significant difference in results of serious COVID-19 illness when excluding the two subjects without RMD diagnoses established prior to their presentation with COVID-19. Several limitations in data collection so far precluded drawing conclusions regarding other factors that have been shown to be associated with poor outcomes: (1) approximately one-third of the combined dataset had missing RMD disease activity, preventing meaningful exploration of this factor on short-term outcomes; (2) substantial differences in reporting of race and ethnicity between data sources prevented cross-mapping between efforts and we were unable to analyse whether Black, Asian and minority ethnic (BAME) groups with paediatric RMDs are at higher risk of COVID-19-related death compared with those of white ethnicity, as has been reported for the general population[4,17] and (3) we did not have access to data on SARS-CoV-2 variant types although all the data were collected prior to the emergence of the Omicron variant.[18] Our registries did not capture vaccination status at the time of data collection (although most cases occurred prior to approval of vaccination for the relevant age groups) and we do not capture long-term or late outcomes such as "long COVID"[19,20] or MIS-C. Finally, our data sources received very limited reporting from low-resource healthcare areas internationally.

In conclusion, understanding the impact of COVID-19 infection on children and young people with RMDs is important to inform national protection, education (such as school attendance), and vaccination guidance. We report the most significant investigation to date of short-term outcomes of COVID-19 in over 600 children and young people with RMDs. The majority of children and young people with RMDs appear to do well and experience mild COVID-19 disease. However, where hospitalisations did occur, they were more likely among those with SLE/MCTD, vasculitis, auto-inflammatory syndromes, and other paediatric RMDs compared with their peers with JIA. The data also showed for the first time that obesity is a relevant comorbidity also in children with RMDs, supporting that protection measures in those children should be strictly followed. While mortality has been reported, it appears to occur rarely in high-resource healthcare areas.

Acknowledgments

Data availability statement

Data are available upon reasonable request. Applications to access the data should be made to the EULAR COVID-19 Registry and CARRA Data and Sample Sharing Committees.

Competing Interests statement

RC reports personal AstraZeneca shares, unrelated to this manuscript. IKP reports personal fees by Novartis, SOBI, Chugai, Pfizer, AbbVie, BMS, all unrelated to this manuscript. FOR reports consulting/speaker's fees from Abbvie, Novartis, Pfizer and Sobi, all unrelated to this manuscript. NMW reports personal consultant fees from UCB, BMS, all unrelated to this manuscript. AS reports personal fees from lectures for AbbVie, Celltrion, MSD, Janssen, Lilly, Roche, BMS, and Pfizer, all unrelated to this manuscript. EM reports personal consultant fees from Boehringer Ingelheim Portugal, Lda, all unrelated to this manuscript. LPCDR received support for specific activities: grants from Abbvie, Novartis, Lilly Portugal, Amgen Biofarmacêutica, Grünenthal S.A., MSD, Medac, A. Menarini Portugal - Farmacêutica, S.A., Pfizer, UCB Pharma, Roche Farmacêutica Química, Lda; and non-financial support from Pfizer, and Grünenthal GmbH, all unrelated to this manuscript. PMM has received consulting/speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche and UCB, all unrelated to this manuscript, and is supported by the National Institute for Health Research (NIHR), University College London Hospitals (UCLH), Biomedical Research Centre (BRC). MN reports funding from Childhood Arthritis & Rheumatology Research Alliance, Inc (CARRA) to his informatics research and operations group at Boston Children's Hospital in its capacity as the CARRA Data Warehouse and associated work for CARRA and the CARRA Registry and has sponsored the COVID-19 Global Pediatric Rheumatology Database study, of which he is the Principal Investigator. MN also serves as Director of Informatics for CARRA, for which he receives no direct compensation but do receive research sponsorship for CARRA-related research, development, and operations (see above). He is also a co-investigator of the CARRA Registry and site Principal Investigator at Massachusetts General Hospital. KLH reports non-personal speaker's fees from Abbvie and grant income from BMS, UCB, and Pfizer, all unrelated to this manuscript, and is supported by the NIHR Manchester Biomedical Research Centre.

All other authors report no disclosures.

Ethics statements
Patient consent for publication not required.

Patient and Public Involvement statement
PPIE not included in this manuscript.

Disclaimer
The views expressed here are those of the authors and do not necessarily represent the views of the European Alliance of Associations for Rheumatology (EULAR), the (UK) National Health Service (NHS), the National Institute for Health Research (NIHR), the (UK) Department of Health, the (US) National Institutes of Health, the Childhood Arthritis and Rheumatology Research Alliance (CARRA), or any other organisation.

Presented at
This manuscript was presented in part at the 2021 Annual European Congress of Rheumatology (virtual) June 2-5th, and the 2021 Paediatric Rheumatology European Society (PReS) e-congress and PReS (virtual) young investigators meeting September 18-20th.

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