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SHORT REPORT

COVID-19 infection among patients with autoinflammatory diseases: a study on 117 French patients compared with 1545 from the French RMD COVID-19 cohort: COVIMAI – the French cohort study of SARS-CoV-2 infection in patient with systemic autoinflammatory diseases

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ABSTRACT

Objective There is little known about SARS-CoV-2 infection in patients with systemic autoinflammatory disease (SAID). This study aimed to describe epidemiological features associated with severe disease form and death. Mortality between patients with and without SAID hospitalised for SARS-CoV-2 infection was compared.

Methods A national multicentric prospective cohort study was conducted from the French Rheumatic and Musculoskeletal Diseases (RMD) COVID-19 cohort. Patients with SAID were matched with patients with non-SAID on age±7 years, gender and number of comorbidities to consider important confounding factors. Impact of SAID on severity of SARS-CoV-2 infection was analysed using multinomial logistic regression for severity in three classes (mild, moderate and severe with mild status as reference). Fine-Gray regression model for length of hospital stay and binomial logistic regression model for risk of death at 30 days.

Results We identified 117 patients with SAID (sex ratio 0.84, 17 children) and compared them with 1545 patients with non-autoinflammatory immune-mediated inflammatory disorders (non-SAID). 67 patients had a monogenic SAID (64 with familial Mediterranean fever). Other SAIDs were Behçet' disease (n=21), undifferentiated SAID (n=16), adult-onset Still disease (n=9) and systemic-onset juvenile idiopathic arthritis (n=5). Ten adults developed severe form (8.6%). Six patients died. All children had a benign disease. After matching on age±7

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ As reported in the French RMD cohort, patients with inflammatory RMD are more likely to develop severe form when they have multiple comorbidities or they were under steroids over 10 mg/day.

WHAT DOES THIS STUDY ADD?

⇒ Children display more likely mild signs of COVID-19 with excellent prognosis.
⇒ When comparing patients with systemic autoinflammatory disease (SAID) and non-SAID after matching on age, sex and number of comorbidities, no significant difference in severity of COVID-19 between the two groups was found.
⇒ Associated comorbidities are more important than the underlying SAID, for developing a severe form or dying.
⇒ Colchicine or biotherapies against Interleukine IL-6 or IL-1 do not seem to be associated with high risk of severe form of COVID-19.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FUTURE DEVELOPMENTS?

⇒ In addition to common risk factors for severe COVID-19, patients with SAID on steroids should be considered of high risk for severe form.

years, sex and number of comorbidities, no significant difference between the two groups in length of stay and the severity of infection was noted.
Conclusion As identified in the whole French RMD COVID-19 cohort, patients with SAID on corticosteroids and with multiple comorbidities are prone to develop more severe COVID-19 forms.

INTRODUCTION

The pandemic related to SARS-CoV-2 infection has emerged since late 2019; Europe was affected in March 2020.[1] The virus caused many deaths in all countries. Patients with immune disorders were a concern of developing a severe form of COVID-19 especially those with systemic autoinflammatory diseases (SAIDs) in which, the innate immune system is improperly activated. The most frequent SAID worldwide is familial Mediterranean fever (FMF); three other monogenic diseases are also classified in the historical hereditary recurrent fevers: cryopyrin-associated periodic syndrome (CAPS), TNF receptor-associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD). Others are polygenic such as Behçet's disease and Still disease. It was initially difficult to predict if patients with SAID might develop an excessive inflammatory response when they contracted the virus.

To our knowledge, except few studies on FMF[2] and one on Behçet's disease,[3–7] little is known about both the risk factors and the diseases at risk of contracting a severe form of COVID-19.

We took the opportunity of the French national prospective registry collecting cases of COVID-19 in patients with immune diseases including SAIDs.[8] Our main question was to determine whether patients with SAIDs had an over-risk of severe form and death. Our secondary objectives were to assess whether the risk correlated to either the disease itself, the existence of comorbidities or the exposure to anti-inflammatory and immunosuppressive medications. In addition, we compared risk factors of patients with SAIDs with those with other inflammatory disorders included in the French RMD COVID-19 cohort.[8]

PATIENTS AND METHODS

Study design and patients

This multicentre, national cohort study (COVIMAI) analysed data from the French RMD COVID-19 cohort, which has been previously described.[8] Briefly, the French RMD COVID-19 cohort included paediatric and adult patients with confirmed inflammatory rheumatic and musculoskeletal diseases and highly suspected or a confirmed diagnosis of COVID-19. SAIDs were defined by the international criteria and included the four historical monogenic SAIDs (FMF, TRAPS, CAPS, MKD), undifferentiated SAIDs,[9] adult onset Still diseases (AOSDs) and Behçet's disease. We assessed and classified the severity of COVID-19 according to the level of care needed for each patient. Mild COVID-19 required ambulatory care; moderate COVID-19 required non-intensive hospital treatment and severe COVID-19 required admission to an intensive care unit or led to death. The study started on March 2020 and was done in compliance with the research methodology MR-004 (research not involving humans connected to studies and evaluations in the field of health), received legal approval from Lille University Hospital ULR 2694-METRICS (Lille, France) and was declared to the Commission Nationale de l'Informatique et des Libertés (reference DEC20-107).

Data collection

Cases of patients with inflammatory rheumatic and musculoskeletal diseases and highly suspected or confirmed COVID-19 were reported retrospectively. The individual data regarding diagnosis and specific ongoing treatments for inflammatory rheumatic and musculoskeletal diseases were captured from physicians via an electronic Case Report Form available online through a secured access. Data collected from patients' medical records have previously been described elsewhere.[8] All participants were followed until the worst COVID-19 outcome at the time of dataset lock. The present study was conducted on the database locked in 15 April 2021.

Outcomes

The primary outcome was to compare the severity of COVID-19 in patients with SAID with patients with non-SAID included in the French RMD COVID-19 cohort. The secondary outcomes were to compare frequency of deaths and duration of hospital stay in patients with or without SAID.

Statistical analysis

Quantitative variables were expressed as means (SD) in the case of normal distribution or medians (IQR) otherwise. Categorical variables were expressed as numbers (%). Normality of distributions was assessed using histograms and the Shapiro-Wilk test.

To consider important confounding factors, patients with SAIDs were matched with patients with non-SAID from the French RMD COVID-19 cohort on age±7 years, gender and number of comorbidities.

Impact of SAID on severity of SARS-CoV-2 infection was analysed, before and after matching, using multinomial logistic regression for severity in three classes (mild, moderate and severe with mild status as reference), Fine-Gray regression model for length of hospital stay (with death as competing event) and binomial logistic regression model (with link logit) for risk of death at 30 days.

All statistical tests were done at the two-tailed α level of 0·05. Data were analysed using SAS V.9.4 (SAS Institute).

This study is registered with ClinicalTrials.gov, NCT04353609.

RESULTS

We included 117 patients with SAID and compared them with 1545 patients with non-SAID. The disease

Table 1

	Non-Autoinflammatory diseases(n=1545)	Autoinflammatory diseases (n=117)
Age (years)		
Mean±SD	54.7±17.5	38.7±20.5
<18	41/1545 (2.7)	17/117 (14.5)
18–54	700/1545 (45.3)	74/117 (63.2)
55–64	328/1545 (21.2)	8/117 (6.8)
65–74	260/1545 (16.8)	9/117 (7.7)
≥75	216/1545 (14.0)	9/117 (7.7)
Female gender	1038/1545 (67.2)	64/117 (54.7)
Comorbidities		
Respiratory disease	204/1543 (13.2)	6/117 (5.1)
Interstitial lung disease	60/1543 (3.9)	0/117 (0.0)
COPD	61/1543 (4.0)	2/117 (1.7)
Asthma	95/1543 (6.2)	4/117 (3.4)
Cardiovascular disease	177/1543 (11.5)	11/117 (9.4)
Coronary heart diseases	146/1543 (9.5)	9/117 (7.7)
Stroke	42/1543 (2.7)	5/117 (4.3)
Diabetes	156/1543 (10.1)	8/117 (6.8)
BMI (kg/m²)	26.0 (22.0 ; 29.0)	23.0 (21.0 ; 26.0)
<30	1054/1388 (75.9)	98/111 (88.3)
30–39.9	297/1388 (21.4)	10/111 (9.0)
≥40	37/1388 (2.7)	3/111 (2.7)
Hypertension	361/1543 (23.4)	12/117 (10.3)
Cancer	57/1543 (3.7)	3/117 (2.6)
Smoking	139/1543 (9.0)	8/117 (6.8)
Chronic renal failure	80/1543 (5.2)	5/117 (4.3)
Number comorbidities		
0	674/1543 (43.7)	76/117 (65.0)
1	466/1543 (30.2)	26/117 (22.2)
2	230/1543 (14.9)	8/117 (6.8)
3	103/1543 (6.7)	4/117 (3.4)
4	58/1543 (3.8)	3/117 (2.6)
>4	12/1543 (0.8)	0/117 (0.0)
Rheumatic or inflammatory Diseases treatments		
Corticosteroid	460/1542 (29.8)	20/117 (17.1)
Systemic corticosteroid doses≥10 mg/day	176/458 (38.4)	6/20 (30.0)
NSSAIDs	147/1542 (9.5)	2/117 (1.7)
Colchicine	10/1542 (0.6)	72/117 (61.5)
Hydroxychloroquine	146/1542 (9.5)	0/117 (0.0)
Methotrexate	553/1542 (35.9)	13/117 (11.1)
Leflunomide	66/1542 (4.3)	0/117 (0.0)
Salazopyrine	17/1542 (1.1)	0/117 (0.0)
Mycophenolate Mofetil /mycophenolic acid	41/1542 (2.7)	0/117 (0.0)
Azathioprine	18/1542 (1.2)	4/117 (3.4)
IgIV	10/1542 (0.6)	0/117 (0.0)
Targeted biologic or synthetic therapies		
anti-TNF	469/1542 (30.4)	18/117 (15.4)
anti-IL6R	56/1542 (3.6)	5/117 (4.3)
anti-IL17A	51/1542 (3.3)	0/117 (0.0)

Continued

Table 1 Continued

	Non-Autoinflammatory diseases(n=1545)	Autoinflammatory diseases (n=117)
anti-IL1	2/1542 (0.1)	12/117 (10.3)
abatacept	34/1542 (2.2)	1/117 (0.9)
JAK inhibitor	56/1542 (3.6)	1/117 (0.9)
Rituximab	83/1542 (5.4)	0/117 (0.0)
Other biologics	33/1542 (2.1)	1/117 (0.9)

Values are presented as no./total no. (%) unless otherwise indicated
COPD, Chronic obstructive pneumopathy disease; IgIV, Intravenous immunoglobulins.

distribution of the 117 patients with SAID was respectively: monogenic SAID (n=67; 57.3%) including FMF (n=64) and CAPS (n=3), Behçet's disease (n=21; 17.9%), undifferentiated SAID (n=15; 12.8%), AOSD (n=9; 7.7%) and Systemic Juvenile Idiopathic Arthritis (sJIA) (n=5; 4.3%) (online supplemental table 1). Seventeen children had COVID-19 at a median age of 12 years ranging from 3 to 16 years. Ten cases occurred during the first wave (March, April 2020) and seven cases from the second wave (September 2020 onwards). The diseases were FMF (n=7; 41%), PFAPA (n=2), CAPS (n=2), sJIA (n=3), unclassified SAID (n=2) and DADA2 (n=1). Symptoms of COVID-19 were benign in children; none had risk factors for severe COVID-19; seven patients were on colchicine; others were receiving biotherapies (anti-IL-1: n=4; anti-IL-6: n=1; anti TNF: n=2) (online supplemental table 2).

The mean age in each group was 38.7±20.5 for SAID versus 54.7±17.5 for non-SAID. Among the SAIDs, there was a clear predominance of adults (85.5%) with most patients aged between 18 and 54 years (63.2%). The proportion of women was 54.7% in the SAID cohort and 67.2% in the non-SAID cohort. The proportion of patients with SAID with at least one known comorbidity of severe SARS-CoV-2 infection was 35%. Most patients were on colchicine (61.5%) in line with the high proportion of FMF among patients with SAID (table 1). In the SAID group, at least one comorbidity was noted in 35% versus 57% in the non-SAID group. Colchicine and anti-IL-1 biotherapy were, respectively, 61.5% and 10.3% in the monogenic SAID group, whereas in the non-SAID group, systemic corticosteroids under 10 mg/day (38.4%), methotrexate (35, 9%), anti-TNF (30.4%) and anti-IL-6R (3, 6%) were taken (table 1).

In the SAID group, 90 patients (76.9%) displayed mild form, 17 patients (14.5%) with moderate form and 10 patients (8.6%) with severe form. When comparing the severity between the two groups, the difference was closed to the significant level (with mild form as reference p=0.064), patients with SAID displayed a significantly lower proportion of moderate forms (14.5% vs 22.5%, OR 0.56, 95% CI 0.33 to 0.95). Severe forms were not different between the two groups (8.6% vs 11.2%, OR 0.66, 95% CI 0.34 to 1.29). The days of hospitalisation were similar between the two groups (HR 0.83, 95% CI 0.51 to 1.36) and there were no differences on the death rate (OR 1.00 (95% CI 0.43 to 2.35)). After matching on age±7 years, sex and number of comorbidities, we could not find any significant difference between the two groups (table 2).

Concerning the patients who died in the SAID group: two had severe FMF on colchicine and anakinra, one of them had AA amyloidosis; two had Behçet's disease, including a 35-year-old patient; one elderly patient had Still's disease and one had unclassified SAID. Half were on corticosteroids >10 mg/day. All had numerous comorbidities and 2/3 were over 65 years old (tables 3 and 4).

Table 2

	Before matching				After matching			
	Autoinflammatory diseases (n=117)	non-Autoinflammatory diseases (n=1545)	Effect size (95% CI)	P-value	Autoinflammatory diseases (n=116)	non-Autoinflammatory diseases (n=116)	Effect size (95% CI)	P-value
Severity of COVID-19 Infection								
Mild	90 (76.9)	1025 (66.3)	1.00 (ref)	0.064	89 (76.7)	92 (79.3)	1.00 (ref)	0.86
Moderate	17 (14.5)	347 (22.5)	0.56 (0.33 to 0.95)		17 (14.7)	16 (13.8)	1.10 (0.52 to 2.31)	
Severe	10 (8.6)	173 (11.2)	0.66 (0.34 to 1.29)		10 (8.6)	8 (6.9)	1.29 (0.49 to 3.42)	
Length of hospital stay (days),								
median (IQR)	8 (4 to NA)	10 (5 to 22)	0.83 (0.51 to 1.36)	0.45	8 (4 to NA)	11 (4 to NA)	0.99 (0.52 to 1.88)	0.96
Death	6 (5.1)	79 (5.1)	1.00 (0.43 to 2.35)	0.99	6 (5.2)	5 (4.3)	1.21 (0.36 to 4.08)	0.76

Values are presented as no./total no. (percentage) unless otherwise indicated.
Matching on age+/- 7 years, sex and number of comorbidities. A 5-year-old male patient with asthma in autoinflammatory disease could not be matched with a control

Table 3

	Monogenic recurrent fever	
	Non monogenic SAID (n=50)	**Monogenic SAID (n=67)**
Patient's characterisics		
Age (years)		
Median (IQR)	44.0 (34.0 ; 59.0)	29.0 (19.0 ; 43.0)
<18	4/50 (8.0)	13/67 (19.4)
18–64	37/50 (74.0)	45/67 (67.2)
≥65	9/50 (18.0)	9/67 (13.4)
Female gender	29/50 (45.3)	35/67 (54.7)
Comorbidities		
Respiratory disease	3/50 (6.0)	3/67 (4.5)
Interstitial lung disease	0	0
COPD	1/50 (2.0)	1/67 (1.5)
Asthma	2/50 (4.0)	2/67 (3.0)
Cardiovascular disease	6/50 (12.0)	5/67 (7.5)
Coronary heart diseases	4/50 (8.0)	5/67 (7.5)
Stroke	4/50 (8.0)	1/67 (1.5)
Diabetes	5/50 (10.0)	3/67 (4.5)
BMI (kg/m²)	25.0 (21.0 ; 28.0)	22.0 (20.0 ; 25.5)
<30	38/47 (80.9)	60/64 (93.8)
30–39.9	6/47 (12.8)	4/64 (6.3)
≥40	3/47 (6.4)	0/64 (0.0)
Hypertension	6/50 (12.0)	6/67 (9.0)
Cancer	2/50 (4.0)	1/67 (1.5)
Smoking	6/50 (12.0)	2/67 (3.0)
Chronic renal failure	2/50 (4.0)	3/67 (4.5)
Number comorbidities, median (IQR)		
0	25/50 (50.0)	51/67 (76.1)
1	16/50 (32.0)	10/67 (14.9)
2	5/50 (10.0)	3/67 (4.5)
3	3/50 (6.0)	1/67 (1.5)
4	1/50 (2.0)	2/67 (3.0)
>4	0	0
Rheumatic or inflammatory Diseases treatments		
Corticosteroid	19/50 (38.0)	1/67 (1.5)
Systemic corticosteroid doses≥10 mg	6/19 (31.6)	0/1 (0.0)
NSSAIDs	1/50 (2.0)	1/67 (1.5)
Colchicine	15/50 (30.0)	57/67 (85.1)
Hydroxychloroquine	0	0
Methotrexate	13/50 (26.0)	0/67 (0.0)
Leflunomide	0	0
Salazopyrine	0	0
Mycophenolate Mofetil / mycophenolic acid	0	0
Azathioprine	4/50 (8.0)	0/67 (0.0)
IgIV	0	0
Targeted biologic or synthetic therapies		
anti-TNF	14/50 (28.0)	4/67 (6.0)
anti-IL6	5/50 (10.0)	0/67 (0.0)
anti-IL17A	0	0
anti-IL1	4/50 (8.0)	8/67 (11.9)
abatacept	1/50 (2.0)	0/67 (0.0)
JAK inhibitor	1/50 (2.0)	0/67 (0.0)
Other biologics	1/50 (2.0)	0/67 (0.0)
Severity of COVID-19 Infection		
Mild	35/50 (70.0)	55/67 (82.1)
Moderate	9/50 (18.0)	8/67 (11.9)
Severe	6/50 (12.0)	4/67 (6.0)
Length of hospital stay (days), median (IQR)	12 (6 to NA)	5 (2 to NA)
Death	4/50 (8.0)	2/67 (3.0)

DISCUSSION

Patients of all ages with SAID can contract COVID-19 and without surprise, more frequently those with FMF, because it is the most frequent monogenic SAID worldwide and those with Behçet's disease, the most frequent polygenic SAID. Interestingly, neither patients with TRAPS nor MKD developed COVID-19 in this series, but some cases might be unreported.

Patients with SAID were younger compared with patients with non-SAID, and all children with SAID displayed a benign form of COVID-19 with excellent prognosis. Therefore, after matching with sex and age, there is no difference in the infection outcome: severe forms and deaths, between the two groups. Thus, the weight of comorbidities appeared more important than the underlying disease; indeed 41/117 (35%) patients with COVID-19+SAID displayed one or more comorbidities.

Colchicine, taken as a daily treatment by 72/117 patients with SAID (61.5%), was not associated with the severity of infection. Even though the number of patients is relatively low, there was no signal on a higher sensitivity to COVID-19 of patients receiving biotherapies targeting either TNF (n=4) or IL-1 (n=8). Interestingly, three patients receiving daily steroids >10 mg/day died including two patients with Behçet's disease. Chronic oral steroid intake has previously been reported to be associated with more severe COVID-19[7].

Table 4

	Age at time of the survey	Sex	Body mass index (kg/m^2)	Comorbidities* number type	Autoinflammatory disease	AA amyloidosis	Treatment	Biologics
1	75	W	20	2 COPD	Behçet disease	No	Steroids >10mg	No
2	34	H	43	3 Obesity Diabetes HT	Unclassified autoinflammatory disease	No	Colchicine	No
3	84	M	20	4 CVD CKD AVC	Still disease	No	Steroids> 10 mg	No
4	74	W	27	3 Diabetes HT	Behçet disease	No	Steroids>10 mg	No
5	58	M	21.8	2 HT CKD**	FMF	Yes	Colchicine	IL1-inhibitor (Anakinra)
6	81	M	22.9	5 CVD CKD** COPD HT	FMF	No	Colchicine	IL1-inhibitor (Anakinra)

CONCLUSION

In conclusion, COVID-19 affected more likely patients with FMF in our cohort. Severe forms occurred more frequently among patients with multiple comorbidities, and chronic intake of oral steroids.

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