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Original article

Factors associated with COVID-19 severity in patients with spondyloarthritis: Results of the French RMD COVID-19 cohort

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ABSTRACT

Objectives: The objective of the current study was to evaluate the severity of COVID-19 and identify factors associated with severe disease outcomes in patients with spondyloarthritis (SpA), a chronic inflammatory rheumatic and musculoskeletal disease (RMD).
Methods: We utilized patient data from the French national multicenter RMD COVID-19 cohort (NCT04353609). The primary outcome was to describe COVID-19 characteristics in patients with SpA based on disease severity of COVID-19 (mild, moderate or severe) with serious infection including moderate and severe cases. The secondary outcome was to identify the factors associated with serious COVID-19 classification.
Results: Among the 626 patients with SpA (56% female, mean age 49 ± 14 years) from the French RMD cohort, COVID-19 severity was mild in 508 (81%), moderate in 93 (15%), and severe in 25 (4%) patients. Clinical signs and symptoms of COVID-19 were reported in 587 (94%) patients, with the most frequent presented symptom of fever (63%) and cough (62%), followed by flu-like symptoms (53%), agueusia (39%), anosmia (37%), dyspnea (32%) and diarrhea (19.9%). COVID-19 severity was associated with corticosteroid therapy (OR = 3.08 [95% CI: 1.44–6.58], $P = 0.004$) and age (OR = 1.06 [95% CI: 1.04–1.08], $P < 0.001$) while use of tumor necrosis factor inhibitor (TNFi, OR = 0.27 [95% CI: 0.09–0.78], $P = 0.01$) was associated with less severe disease. We did not identify an association between NSAID use and COVID-19 severity.
Conclusions: In this study, the majority of patients with SpA had a favorable COVID-19 outcome. We confirmed age and corticosteroids therapy had a negative impact on disease outcomes while TNFi use was protective.

1. Introduction

In November 2019, the emergence and rapid transmission of a new coronavirus, SARS-CoV-2, triggered an epidemic of severe febrile respiratory disease known as coronavirus disease 2019 (COVID-19). The high transmissibility of SARS-CoV-2 has resulted

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in a global pandemic. As such, this new infection has raised considerable concern regarding the management of patients with chronic diseases, comorbidities and/or immune-mediated disorders, such as spondyloarthritis (SpA). Studies in patients with COVID-19 and chronic inflammatory rheumatic and musculoskeletal disease (RMD), including SpA, suggest that the susceptibility to SARS-CoV-2 infection and severity of COVID-19 are similar to those in the general population [1,2]. The majority of data from large cohorts of patients with chronic inflammatory rheumatic diseases all reported that SpA, including SpA subtype psoriatic arthritis (PsA), was not associated with a higher risk of mortality, hospitalizations, or serious outcomes related to COVID-19 compared with other chronic inflammatory rheumatic diseases and immune-mediated inflammatory diseases (IMIDs) [3,4].

Conversely, analysis of health administrative data from a large cohort of COVID-19 cases in British Columbia, which included 378 patients with axial spondyloarthritis (AS), reported a significant increase in adjusted risk of hospitalization for COVID-19 (including hospitalization in intensive care unit [ICU]) for patients with AS compared with matched control cohort [5]. This trend was also observed in a meta-analysis of 2022 [6]. Moreover, data from a German cohort of 104 chronic inflammatory rheumatic diseases, identified 2 (33%) of the 6 patients with a COVID-19 fatal outcome had PsA [7]. The lack of an association between SpA and severe forms of COVID-19 may reflect a lack of power since SpA represented a small proportion of most inflammatory rheumatic diseases cohorts. In addition, the impact of more SpA-specific treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, or interleukin-17 inhibitors on the severity of COVID-19 is controversial and largely unknown [8,9]. The objective of the current study was to describe the clinical characteristics, disease severity, and course of COVID-19 in a large cohort of patients with SpA and to identify factors, including treatments, associated with serious outcomes.

2. Methods

2.1. Study design and patients

We used data from the French national multicenter RMD COVID-19 cohort, which has been described previously [10]. Briefly, the French RMD COVID-19 cohort included patients aged 18 years or older with confirmed chronic inflammatory rheumatic diseases and highly suspected or a confirmed diagnosis of COVID-19. The study was performed in compliance with MR-004 [11], received permission from Lille University Hospital and was declared to the Commission nationale de l'informatique et des libertés (reference DEC20-107). Eligible patients or their representatives were informed and the study was conducted in accordance with the principles of the Declaration of Helsinki. Patient consent was obtained for the use of medical data, which was carried out according to French law and good clinical practices. ClinicalTrials.gov Registry (NCT04353609).

2.2. Data collection

All cases of patients with SpA and highly suspected or confirmed COVID-19 were reported retrospectively. Positive diagnosis of COVID-19 included biological confirmation (PCR/serology), presence of evocative signs in CT scan, or anosmia or sudden ageusia, or typical symptoms of COVID-19 (in a patient with recent close contact with a known COVID-19 positive patient).

SpA were classified as axial SpA (axSpA), including ankylosing spondylitis, PsA, or other SpA, which included reactive arthritis. Disease activity was assessed by the physician according to four levels: remission, mild, moderate, or high activity. The individual data were captured from physicians by one national data entry portal. Data collected from patients medical records have previously been described in detail [10]. Before dataset lock in April 2021, the final database was monitored and missing data was collected, the evolution of COVID-19 was validated, duplicate or erroneous reports were removed, and checked for data consistency. All participants were followed until the worst COVID-19 outcome at the time of dataset lock.

2.3. Outcomes

The primary outcome was to describe the severity of COVID-19 infection in patients with SpA. The severity of COVID-19 was assessed and classified according to the 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 (ICU) or led to death. We defined serious COVID-19 to include moderate and severe COVID-19 cases. The secondary outcome was to identify the factors associated with serious COVID-19.

2.4. Statistical analysis

Categorical variables were expressed as numbers (percentage) and quantitative variables as mean (SD). Treatments were classified as corticosteroids, NSAIDs, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) including methotrexate, leflunomide, hydroxychloroquine and sulfasalazine, biological DMARDs including tumor necrosis factor inhibitor (TNFi), interleukin-17 inhibitor (il-17i), interleukin-23 inhibitors (p40 and p19), and Janus Kinase inhibitors (JAKi). Multiple logistic regression models were used to identify factors associated with serious COVID-19. In the univariate analysis, the following parameters were tested: sex, age, disease activity, subtype of spondyloarthritis, personal history of respiratory disease, cardiovascular disease, diabetes, asthma, cancer, hypertension or smoking, obesity (BMI > 30 kg/m^2) and all treatments mentioned above.

All variables with $P < 0.20$ in univariate analysis were proposed in the multivariate model. Treatment variables were included in the models, even if $P \geq 0.20$.

3. Results

3.1. Patient's characteristics

Records of 626 patients with SpA were collected between March 2020 and April 2021. The cohort included 403 axSpA (64%), 187 PsA (30%) and 36 other SpA, with 349 women (56%), mean age 49.3 ± 14.1 years, mean body mass index (BMI) 27.1 ± 5.4 and RMD disease duration 11.3 ± 9.8 years; 352 (56%) had at least one comorbidity, with obesity (19%), arterial hypertension (16%), and smoking (10%) being the most frequent. At the time of infection, RMD disease activity was low in 107 patients (32%), moderate in 55 (16%) and high in 21 (6%) patients. Clinical characteristics and RMD drug treatments stratified by COVID-19 severity are provided in Tables 1–3. Among them, 104 were treated with NSAIDs (17%), 186 with csDMARDs including 156 with methotrexate, and 460 (74%) with bDMARDs (379 anti-TNF, 57 anti-IL17, 15 anti-IL12/23, 9 others). Among the 45 patients treated with corticosteroids, the average dosage was 9.39 mg per day and 9 patients received more than 10 mg/d.

Table 1
Patient characteristics based on severity of COVID-19.

	Overall (n = 626)	Mild COVID-19 (n = 508)	Serious COVID-19	
			Moderate COVID-19 (n = 93)	Severe COVID-19 (n = 25)
Age, years	49.3 ± 14.1	46.8 ± 12.9	58.8 ± 14.9	63.8 ± 11.2
≥ 55	226 (36)	152 (29.9)	55 (59)	19 (76)
≥ 75	29 (5)	8 (2)	17 (18.2)	4 (16)
Gender, female	349 (55.7)	292 (57.4)	47 (50.5)	10 (40)
SpA				
Axial SpA[a]	403 (64)	342 (67)	50 (54)	11 (44)
Psoriatic arthritis	187 (30)	138 (27)	37 (40)	12 (48)
Other SpA	36 (6)	28 (6)	6 (7)	2 (8)

Data are mean (±SD) or n (%). SpA: spondyloarthritis.
[a] Includes axial spondyloarthritis.

Table 2
Patient comorbidities based on severity of COVID-19.

	Overall (n = 626)	Mild COVID-19 (n = 508)	Serious COVID-19	
			Moderate COVID-19 (n = 93)	Severe COVID-19 (n = 25)
Comorbidities				
Cardiovascular disease	29 (5)	14 (3)	11 (12)	4 (16)
Diabetes	44 (7)	28 (6)	10 (11)	6 (24)
Asthma	47 (8)	38 (8)	7 (8)	2 (8)
Smoking	65 (10)	58 (11)	5 (5)	2 (8)
Hypertension	97 (16)	60 (12)	29 (31)	8 (32)
Body mass index, > 25 kg/m^2	180 (28)	136 (27)	30 (32.2)	14 (56)
Body mass index, > 30 kg/m^2	148 (23)	113 (22)	28 (30)	7 (28)
Respiratory disease	60 (9.5)	43 (8.4)	12 (13)	5 (20)
Coronary heart disease	29 (5)	14 (3)	11 (12)	4 (16)
Patient with at least one comorbidity	352 (56)	264 (52)	67 (72)	21 (84)

Data are mean (±SD) or n (%).

Table 3
Patient treatments based on the severity of the infection COVID.

	Overall (n = 626)	Mild COVID-19 (n = 508)	Serious COVID-19	
			Moderate COVID-19 (n = 93)	Severe COVID-19 (n = 25)
Treatments				
NSAIDs	104 (17)	90 (18)	9 (10)	5 (20)
Corticosteroids	45 (7)	24 (5)	15 (16)	6 (24)
csDMARD	166 (26)	120 (23)	40 (43)	6 (24)
Methotrexate	156 (24)	115 (23)	35 (37.6)	6 (24)
Sulfasalazine	14 (2)	10 (2)	4 (4)	0 (0)
bDMARD	460 (73)	390 (77)	56 (60)	14 (56)
TNFi	379 (61)	327 (64)	42 (45)	10 (40)
IL-17i	57 (9)	47 (9)	7 (8)	3 (12)
IL-23i (p19 or p40)	15 (2)	10 (2)	4 (4)	1 (4)
tsDMARD				
JAKi	11(2)	9 (2)	0 (0)	2 (8)

Data are mean (±SD) or n (%). DMARD: disease-modifying anti-rheumatic drugs; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; tsDMARD: targeted synthetic DMARD; NSAIDs: non-steroidal anti-inflammatory drugs; TNFitumor: necrosis factor inhibitors; IL-17i: interleukin-17 inhibitor; IL-23i: interleukin-23 inhibitor; JAK: Janus kinase.

3.2. COVID-19

The COVID severity was mild in 508 (81%), moderate in 93 (15%), and severe in 25 (4%) patients, which includes 6 deaths. COVID-19 was confirmed 423 (67%) of the cases by PCR, while 99 (16%) patients had a thoracic CT scan with a compatible image with COVID-19 (ground glass image, crazy paving) [12], 76 (12%) had positive serology, and 20 (3%) had a positive antigen test. Clinical signs and symptoms of COVID-19 were reported in 587 (93.7%) patients, including anosmia and agueusia in 220 and 234 patients, respectively. The most frequent presented symptoms were fever (63%) and cough (62%), followed by flu-like symptoms (53%), agueusia (39%), anosmia (37%), dyspnea (32%) and diarrhea (20%). Only 23 respiratory distress were recorded (4%). The less frequent symptoms of COVID-19 were conjunctivitis (n = 11), meningitis (n = 6) and skin frostbites (n = 6). At the end of the follow-up period, 17% of patients still had persistent symptoms such asthenia, dysgeusia, anosmia, cough, and dyspnea.

Throughout the study period, 3 female patients were infected twice with COVID-19, 2 with axSpA and 1 with PsA, with mean age was 56 years. All were overweight (2 with BMI > 30 and 1 with BMI > 25), one without treatment and 2 were treated with infliximab. In all cases, COVID-19 was confirmed by PCR and their severity was mild to moderate.

3.3. Multivariate analysis

Factors independently associated with serious COVID-19 severity were corticosteroid therapy (OR = 3.08 [95%CI: 1.44–6.58] P = 0.004) and age (OR = 1.06 [95% CI: 1.04–1.08], P < 0.001) whereas

Table 4
Association between patient characteristics, treatments and severity of COVID 19.

	Mild COVID-19 (n = 508)	Serious COVID-19 (n = 118)	Adjusted effect size (95% CI)
Female sex	292 (57.4)	57 (48.3)	0.63 (0.38–1.04)
Age	46.8 ± 12.9	59.8 ± 14.4	1.06 (1.04–1.08)[a]
BMI > 30 kg/m^2	113 (22.4)	35 (29.6)	1.12 (0.64–1.94)
Axial SPA	342 (68)	61 (51.6)	0.77 (0.45–1.33)
NSAIDs	90 (17.7)	14 (11.8)	1.01 (0.49–2.05)
Corticosteroids	24 (4.7)	21 (17.7)	3.08 (1.44–6.58)[b]
Methotrexate	115 (22.6)	41 (34.7)	0.96 (0.53–1.71)
Sulfasalazine	10 (2)	4 (3.4)	7.6 (0.58–99.5)
bDMARD	390 (76.7)	70 (59.3)	2.92 (0.94–9.1)
TNFi	327 (64.3)	52 (44)	0.27 (0.09–0.78)[c]
IL-17i	47 (9.2)	10 (8.4)	0.37 (0.1–1.31)

Data are mean (±SD) or n (%). BMI: body mass index; NSAIDs: non-steroidal anti-inflammatory drugs; bDMARD: biologic disease-modifying anti-rheumatic drugs; TNFi: tumor necrosis factor inhibitors; IL-17i: interleukin-17 inhibitors; COPD: chronic obstructive pulmonary disease.

[a] P < 0.001.

[b] P < 0.005.

[c] P = 0.01.

TNFi (OR = 0.27 [95% CI: 0.09–0.78], P = 0.01) was associated with less serious COVID-19 severity. Treatments with NSAIDs (OR = 1.01 [95% CI: 0.49–2.05]) sulfasalazine (OR = 7.6 [95% CI: 0.58–99.5]), or IL17i (OR = 0.37 [95% CI: 0.10–1.31]) were not associated with the severity of the infection (Table 4).

Despite their association with severity in the univariate analysis, cardiovascular diseases, diabetes, hypertension, BMI > 30 kg/m^2, and active smoking did not emerge as risk factors in the multivariate analysis.

4. Discussion

In a large national sample of patients with RMD, we confirm favorable evolution for the majority of patients with SpA who contracted COVID-19 and identify a protective effect of anti-TNF. Our results are robust, based on a large national sample of patients, of which more than 56% had at least one comorbidity known to be associated with an increased risk of serious COVID-19. The methodology of the French RMD COVID-19 cohort allows the confirmation of the infection, by systematically recalling the practitioner, and thus allows the proper severity assessment of each infection. While we did not find any association between the severity of COVID-19 and the different subtypes of SpA, patients with PsA more often had comorbidities related to the severity of COVID-19 which is similar to prior reports in patients with psoriatic disease [13–15].

Regarding corticosteroid therapy, it is now well known that corticosteroids are associated with the severity of COVID-19 infection in patients with rheumatoid arthritis (RA). Since most IMID cohorts included both RA and SpA patients, our results confirm the harmful effect of steroids in both populations, even when analyzed independently [16,17].

The protective character of HLA (Human Leukocyte Antigen)-B27 has been suggested to explain the lower severity of COVID-19 in SpA [18]. Our results also suggest a protective role of anti-TNF, as previously shown [19,20]. This may be related to the cytokine storm and elevated levels of inflammatory mediators (such as TNF) occurring in the COVID-19 infection. However, the impact of anti-TNF on COVID outcomes in axSpA has not been confirmed in a large national study and remains largely unknown [18].

The current study has several limitations. In the absence of a formal sample size calculation, we cannot exclude a lack of adequate statistical power to detect significant differences, especially for treatment strategies that were not widely used, such as targeted DMARDs other than anti-TNF or NSAIDs. Although we analyzed a large population of patients with SpA from a single country, the impact of selection bias cannot be ruled out with reporting mainly of the most severe cases and an overestimation of the prevalence of serious COVID-19. Despite this, we had few severe cases of COVID-19 which precluded us from conducting an analyses in this particular subclass of patients.

In addition, we should also suggest a potential variation in the severity criteria used in our study: criteria for hospitalization and/or for admission ICU were maybe not the same during all the pandemic due to a better understanding of the infection and a fluctuation in severity of the COVID-19 waves due to less lethal variants.

In conclusion, the present study reports that the large majority of patients with SpA who contracted COVID-19 have favorable outcomes, regardless of SpA subtype. The follow-up of COVID-19 evolution confirmed the negative impact of corticosteroid therapy on the severity of COVID-19 and suggests use of TNF inhibitors is protective of severe COVID-19.

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Disclosure of Interest

The authors declare that they have no competing interest.

Contributors

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