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Original article

Evaluation of the prevalence of new-onset musculoskeletal symptoms in patients hospitalized for severe SARS-CoV-2 infection during the first two COVID waves in France: A descriptive analysis of the clinical data warehouse of 39 hospitals in France



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ABSTRACT

Objective: To determine the prevalence of musculoskeletal (MSK) symptoms appearing after a SARS-CoV-2 infection.

Methods: This was an observational cohort based on data available at the Assistance publique-Hôpitaux de Paris (AP-HP) Clinical Data Warehouse (which includes data of more than 11 million patients treated in the 39 hospitals from AP-HP). The data collected included both ICD-10 codes in discharge summaries, and recurring wording expressions search on medical electronic documents. To be included in the analysis, patients had to have a positive RT-PCR for SARS-CoV-2 and be admitted in any department of AP-HP. Patients with previous history of any MSK condition were excluded. MSK conditions were considered if occurring up to 90 days after the positive RT-PCR. Demographics and disease characteristics including treatment were compared in both groups (MSK yes/no) by *t*-test or Chi² test, accordingly.

Results: In total, 17,771 patients had a positive SARS-CoV-2 RT-PCR at APHP and were admitted in any department of AP-HP. Among them, 15,601 had no previous history of MSK condition and among them, 1370 (8.8%) presented with MSK symptoms after the viral infection. The most prevalent MSK symptoms were back pain (32.9%), followed by arthralgia (29.9%), radicular pain (20.2%) and arthritis (22.8%). Patients with MSK symptoms (MSK+) were older (67 y vs. 64 y, $P < 0.01$), more frequently obese (29% vs. 25%, $P = 0.03$), hypertensive (34% vs. 30%, $P < 0.01$) and with diabetes (21% vs. 18%, $P < 0.01$). Treatment for SARS-CoV-2 was slightly different in both groups, with higher corticosteroids (40.7% vs. 29.0%, $P < 0.01$), antivirals (21.5% vs. 15.3%, $P < 0.01$) and immunosuppressors (8.5% vs. 4.5%, $P < 0.01$) prescription rates in the MSK+ group.

Conclusion: MSK symptoms occurred in almost 9% of patients admitted to the hospital after a SARS-CoV-2 infection, particularly in older and more comorbid patients. Further analysis evaluating whether these symptoms remain over time are needed.

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1. Introduction

The emergence of a new coronavirus, SARS-CoV-2, has shaken the world since December 2019. The main and most severe complication of this virus is the pneumonia, which complicates severe forms and appears to be the result of a cytokine storm. This lung manifestation was quickly described [1], and quite quickly after that other serious manifestations such as myocarditis [2] or encephalitis [3] appeared, making this viral infection a systemic

disease. Other manifestations were observed in these patients, either specific for SARS-CoV-2 (i.e. olfactory and gustatory dysfunction [3]) or at least more frequently than what would be expected in the general population or in a context of viral MERS-like infection (e.g. thromboembolisms [4] and dermatological manifestations such as pernio lesions and livedo [5]).

The musculoskeletal (MSK) system is a known target of viral infections: parvovirus, herpes, alphavirus and others can cause musculoskeletal inflammatory symptoms [6]. In this sense, MSK inflammatory manifestations have been reported following the resolution of the acute infection, but only based on sparse cases, with heterogeneous prevalence [7].

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All these remarks prompted us to conduct this analysis, aiming to determine the prevalence of MSK symptoms occurring after a SARS-CoV2 infection.

2. Methods

2.1. Study design

This was an analysis of the Assistance publique–Hôpitaux de Paris (AP–HP) Clinical Data Warehouse-COVID (CWD-COVID) observational database, which includes hospitalization-related data from the electronic medical records (EMR) of patients admitted in the 39 hospitals from AP–HP.

This study was approved by the institutional review board from the AP–HP CDW Scientific and Ethics Committee. All subjects included in this study were informed about the reuse of their data for research and subjects that objected to the reuse of their data were excluded in accordance with French legislation.

2.2. Patients

To be included in the analysis, patients had to have a positive RT-PCR for SARS-CoV-2 performed in any AP–HP hospital followed by a hospital admission between 1st March 2020 until 31st December 2020. Patients with a past history of any previous inflammatory MSK condition were excluded.

2.3. Data collected and definitions

MSK conditions considered were identified on the CWD-COVID either as ICD-10 codes (“M05 to M14” for *inflammatory polyarthropathies*; “M45” for *spondyloarthritis*) in discharge reports, or as recurring wording expressions search on the EMRs (‘arthralgia’, ‘arthritis’, ‘synovitis’, ‘tenosynovitis’, ‘enthesitis’, ‘back pain’, ‘radicular pain’), and were only considered if coded as discharge diagnosis or reported on an EMR up to 90 days after the positive RT-PCR. A previous inflammatory MSK condition was defined as the appearance of a code CIM-10 “M05-M14” or “M45” as the main or related diagnosis at the EMR discharge report of any previous admission at AP–HP.

Demographics (age and sex), comorbidities (obesity, hypertension and diabetes), in-hospital COVID-related medications, ICU admissions and death (within the 30 days after positive PCR) were also retrieved.

2.4. Statistical analysis

The prevalence of each and any MSK manifestation was calculated as a percentage. Median time to occurrence for each and any of the MSK manifestation by Kaplan–Meier curves. Patients characteristics were compared between patients with and without MSK manifestations by *t*-test or Chi² test, accordingly. As a sensitivity analysis, the same comparisons were performed for the first COVID wave (from 1st March 2020 until 31st August 2020) and for the second COVID wave (from 1st September to 31st December 2020).

3. Results

Among the 17,771 patients with a positive RT-PCR for SARS-CoV-2 performed in AP–HP and admitted subsequently in any AP–HP hospitals, 2170 had a previous history of MSK condition and were therefore excluded from this analysis. Among the remaining 15601 patients, 1370 (8.8%) presented with at least one MSK symptom.

Table 1

Patients and disease characteristics (including treatment) of patients with and without post-COVID inflammatory musculoskeletal symptoms.

	Post-COVID MSK symptoms	
	Yes n = 1370	No n = 14,231
Demographics		
Age (years) ^a #	66.8 ± 18.0	63.6 ± 20.9
Male sex	782 (57.1%)	8083 (56.8%)
Comorbidities		
Obesity \$	273 (28.7%)	1758 (25.4%)
Hypertension#	467 (34.1%)	4293 (30.2%)
Diabetes#	286 (20.9%)	2551 (17.9%)
SARS-CoV-2 infection severity		
COVID-related ICU admission	420 (30.7%)	4180 (29.4%)
30-days mortality#	107 (7.8%)	2404 (16.9%)
SARS-CoV-2 Treatment		
Any treatment#	818 (59.7%)	6251 (43.9%)
Hydroxychloroquine	152 (11.1%)	1362 (9.6%)
Antiviral drugs#	294 (21.5%)	2175 (15.3%)
Corticosteroids#	557 (40.7%)	4133 (29.0%)
Betamethasone	10 (0.7%)	52 (0.4%)
Dexamethasone#	368 (26.9%)	3073 (21.6%)
Methylprednisolone#	72 (5.3%)	463 (3.3%)
Prednisolone#	89 (6.5%)	502 (3.5%)
Prednisone#	220 (16.1%)	1300 (9.1%)
Immunosuppressive drugs#	117 (8.5%)	637 (4.5%)
Anakinra#	36 (2.6%)	155 (1.1%)
Tocilizumab#	59 (4.3%)	422 (3.0%)
Sarilumab#	29 (2.1%)	91 (0.6%)
Baricitinib	0 (0.0%)	2 (0.0%)

Results in bold are significant as follow: \$ = *P* < 0.05; # = *P* < 0.

^a Results are presented as mean (± standard deviation) or number (percentage) as appropriate.

The most prevalent symptoms were low back pain (32.9%), followed by arthralgia (29.9%), radicular pain (20.2%) and synovitis/arthritis (22.8%) (Fig. 1).

Median delay from positive PCR to any MSK manifestation onset was 10 days, but ranged from 6 days for spondyloarthritis and 14 days for arthritis (Figure S1) [See the supplementary material associated with this article online].

Mean age was 63.9 years. Patients with MSK symptoms were older and were more frequently comorbid with obesity, hypertension and diabetes.

There were no differences on gender nor on the ICU admission rate between groups, while 30-days mortality was twice more frequent in the non-MSK group. When looking at the 9-days mortality: mortality was still significantly lower in the MSK group but the magnitude of the difference was reduced (11.4% vs. 16.1%, *P* < 0.01).

Treatment for SARS-CoV-2 was slightly different in both groups, with higher corticosteroids, antivirals and immunosuppressive drugs prescription rates in the MSK group (Table 1).

Interestingly no differences on the prevalence of MSK symptoms were observed between the two waves. However, treatment modalities were significantly different, with a decrease on the hydroxychloroquine and antiviral prescription, and a significant increase in the glucocorticoid's prescription, particularly dexamethasone (Table 2).

4. Discussion

In our study, almost 9% patients admitted to the hospital after a SARS-CoV-2 infection presented with MSK symptoms in the 3 months following their discharge.

The most prevalent symptom was back pain, present in one third of patients, followed by arthralgia and arthritis. Interestingly, radicular pain was present in near 20% of patients. Almost no enthesitis and tenosynovitis were identified, but this could be expected as they are quite specific terms that might easily be underreported.

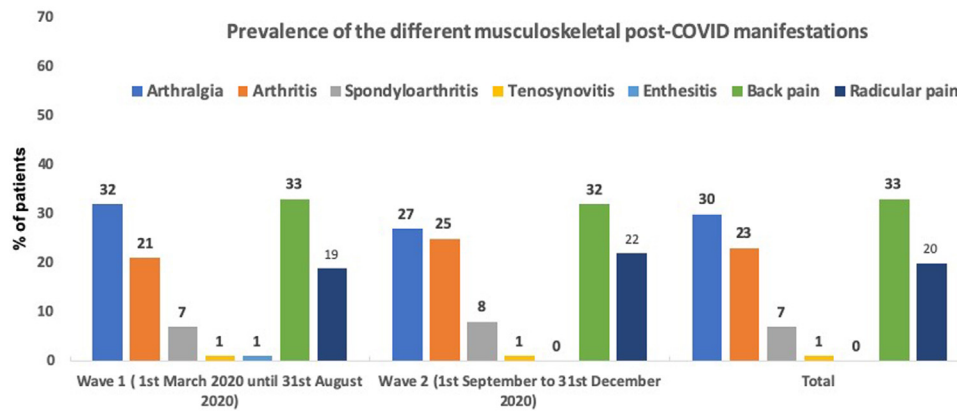


Fig. 1. Prevalence of the different types of musculoskeletal symptoms.

Table 2

Patients and disease characteristics (including treatment) of patients with and without post-COVID inflammatory musculoskeletal symptoms during the first (1st March to 31st August 2020) and second (1st September and 31st December 2020) COVID waves in France.

	Post-COVID inflammatory MSK symptoms (Wave 1)		Post-COVID inflammatory MSK symptoms (Wave 2)	
	Yes n = 780	No n = 8478	Yes n = 590	No n = 5753
Demographics				
Age	66.6 ± 18.0	64.2 ± 20.2#	67.2 ± 18.0	62.8 ± 21.8#
Male sex	456 (58.5%)	4919 (58.0%)	326 (55.3%)	3164 (55.0%)
Comorbidities				
Obesity	163 (29.8%)	1033 (25.6%)\$	110 (27.2%)	725 (25.1%)
Hypertension	270 (34.6%)	2601 (30.7%)\$	197 (33.4%)	1692 (29.4%)
Diabetes	160 (20.5%)	1502 (17.7%)	126 (21.4%)	1049 (18.2%)
SARS-CoV-2 infection severity				
COVID-related ICU admission	249 (31.9%)	2482 (29.3%)	171 (29.0%)	1698 (29.5%)
30-days mortality	62 (7.9%)	1563 (18.4%)#	45 (7.6%)	841 (14.6%)#
SARS-CoV-2 Treatment				
Any treatment	438 (56.2%)	3245 (38.3%)#	380 (64.4%)	3006 (52.3%)#
Hydroxychloroquine	143 (18.3%)	1319 (15.6%)	9 (1.5%)	43 (0.7%)
Antiviral drugs	216 (27.7%)	1687 (19.9%)#	78 (13.2%)	488 (8.5%)#
Corticosteroids	196 (25.1%)	1260 (14.9%)#	361 (61.2%)	2873 (49.9%)#
Betamethasone	7 (0.9%)	28 (0.3%)\$	3 (0.5%)	24 (0.4%)
Dexamethasone	63 (8.1%)	533 (6.3%)	305 (51.7%)	2540 (44.2%)#
Methylprednisolone	42 (5.4%)	291 (3.4%)#	30 (5.1%)	172 (3.0%)#
Prednisolone	48 (6.2%)	229 (2.7%)#	41 (6.9%)	273 (4.7%)\$
Prednisone	97 (12.4%)	565 (6.7%)#	123 (20.8%)	735 (12.8%)#
Cortisone	2 (0.3%)	19 (0.2%)	7 (1.2%)	17 (0.3%)#
Immunosuppressive drugs	95 (12.2%)	455 (5.4%)#	22 (3.7%)	182 (3.2%)
Anakinra	34 (4.4%)	154 (1.8%)#	2 (0.3%)	1 (0.0%)\$
Tocilizumab	39 (5.0%)	242 (2.9%)#	20 (3.4%)	180 (3.1%)
Sarilumab	29 (3.7%)	91 (1.1%)#	0 (0.0%)	0 (0.0%)
Baricitinib	0 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.0%)

Results are presented as mean (± standard deviation) or number (percentage) as appropriate. Results in bold are significant as follow: \$ = P < 0.05; # = P < 0.01.

Patients with MSK symptoms were significantly older. This might be one of the reasons for the higher prevalence of back and radicular pain, seeming difficult to disentangle whether back and radicular pain were reactive to the viral infection or were purely related to a hospital stay in an elderly population. As for the presence of arthralgia, a large prevalence of this symptom post-COVID infection has already been reported [7], but the presence of arthritis in near 25% of cases might be a specific post-viral symptom. To date, only a few post-COVID arthritis cases have been reported [8,9], but in previous viral outbreaks such as influenza, Zika, and Ebola, immune-mediated symptoms have been reported, including arthritis [10].

It is worth mentioning that treatments used for COVID may have influenced also the prevalence of MSK: during the first wave, hydroxychloroquine was widely prescribed in France, and more

frequently in the MSK group; during the second wave (when the amount of evidence against the efficacy of hydroxychloroquine to treat COVID increased) treatment by corticosteroids for severe forms of COVID was generalized; these COVID-treatment trends may have reduced the likelihood for COVID patients overall to present with severe MSK symptoms but rather only mild symptoms; this would translate in lower probabilities for such symptoms to be reported as a diagnosis in the EMRs, potentially leading to MSK symptoms prevalence underestimation.

Interestingly, mortality was significantly lower in the MSK group. One plausible explanation could be that patients critically ill would have MSK were underreported in their EMR.

Another hypothesis behind this difference could be a selection bias: i.e. only patients who lived after COVID would have time to develop MSK symptoms. However, when evaluating the 9-days

mortality, the magnitude of the difference between both groups was reduced but remained statistically significant, with lower mortality in the MSK group.

Finally, one of the reasons behind this difference might be the larger use of corticosteroids in the MSK group, even during the first wave, e.g. before its use was consensual for the treatment of severe COVID forms; furthermore, even during the second wave, when corticosteroids were more frequently prescribed, the proportion of patients with such treatment was significantly more important in the MSK group. Also, the use of immunosuppressant drugs (e.g. tocilizumab) was significantly more frequent in the MSK group, even during the first wave, which might have had an influence on mortality.

This study has some limitations worth mentioning. The main limitation remains the identification of the MSK manifestations, as they were partly captured on the EMR by recurrent wording search, which might have hampered the accuracy of the diagnosis. In this sense, it is also not impossible that patients identified as 'not having a history of MSK symptoms' did actually have previous MSK symptoms that were simply never identified on previous EMR. Nevertheless, these limitations are frequently encountered in EMR-based data and claims databases analysis, and are usually counterbalanced by the large sample of patients analyzed.

Whether the patients with 'early' (within 90-days) MSK symptoms are more likely to develop 'Long-COVID' is unknown, and further studies aiming to determine how many of those patients will need a specific rheumatology treatment are needed.

Disclosure of interest

The authors declare that they have no competing interest.

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Data used in preparation of this article were obtained from the AP-HP COVID CDW Initiative database. A complete listing of the members can be found at: <https://eds.aphp.fr/covid-19>.

Appendix A. Supplementary data

Supplementary data (Figure S1) associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jbspin.2022.105450>.

References

- [1] Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20 [NEJMoa2002032].
- [2] Long B, Brady WJ, Koyfman A, et al. Cardiovascular complications in COVID-19. *Am J Emerg Med* 2020;38:1504–7.
- [3] Vitalakumar D, Sharma A, Kumar A, et al. Neurological manifestations in COVID-19 patients: a meta-analysis. *ACS Chem Neurosci* 2021;12:2776, <http://dx.doi.org/10.1021/acscchemneuro.1c00353>.
- [4] Mansory EM, Srigunapalan S, Lazo-Langner A. Venous thromboembolism in hospitalized critical and noncritical COVID-19 patients: a systematic review and meta-analysis. *TH Open* 2021;5:e286–94.
- [5] Schwartzberg LN, Advani S, Clancy DC, et al. A systematic review of dermatologic manifestations among adult patients with COVID-19 diagnosis. *Skin Health Dis* 2021;1:e20.
- [6] Marks M, Marks JL. Viral arthritis. *Clin Med (Lond)* 2016;16:129–34.
- [7] Zacharias H, Dubey S, Koduri G, et al. Rheumatological complications of COVID-19. *Autoimmun Rev* 2021;20:102883.
- [8] Parisi S, Borrelli R, Bianchi S, et al. Viral arthritis and COVID-19. *Lancet Rheumatol* 2020;2:e655–7.
- [9] Kocyigit BF, Akyol A. Reactive arthritis after COVID-19: a case-based review. *Rheumatol Int* 2021;41:2031–9.
- [10] Shah S, Danda D, Kavadihandha C, et al. Autoimmune and rheumatic musculoskeletal diseases as a consequence of SARS-CoV-2 infection and its treatment. *Rheumatol Int* 2020;40:1539–54.