

EDITORIAL

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Musculoskeletal symptoms in SARS-CoV-2 (COVID-19) patients



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The novel SARS-CoV-2 (COVID-19) became a pandemic on 11 March 2020. The epidemiological picture is constantly evolving, and on 13 May, 4,170,424 cases and 287,399 confirmed deaths have been reported (WHO Report). People with COVID-19 infection may show several symptoms, including fever, cough, nausea, vomiting, dyspnea, myalgia, fatigue, arthralgia, headache, diarrhea, and rarely arthritis [1]. COVID-19 clinical features range from asymptomatic patients to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction [2, 3]. Influenza symptoms are associated with a cascade of inflammatory mediators. Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) levels in plasma and upper respiratory secretions directly correlate with the magnitude of viral replication, fever, and respiratory and systemic symptoms, including musculoskeletal clinical manifestations [4, 5]. Musculoskeletal symptoms such as fatigue, myalgia and arthralgia are common COVID-19 symptoms, but their prevalence has not yet been systematically investigated [6, 7]. We collected the published clinical data of the past 5 months to ascertain the prevalence of musculoskeletal symptoms and epidemiological characteristics published worldwide in COVID-19 patients.

Data were tabulated using Microsoft ExcelTM 2020 V.16.34. The value was showed as mean \pm SD. Student *t* test was used to reveal musculoskeletal symptoms between the total sample. To assess the incidence for each clinical variable, frequency analysis was performed. Regression analysis (R^2) was used to examine correlations between the total sample and musculoskeletal symptoms extracted. The level of significant was set at $p < 0.05$.

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The relevant reference and the data collected from the included articles are indicated in Tables 1 and 2.

Data on 12,046 patients (54% male and 46% females) were available. The number of patients in the selected studies ranged from 5 to 1590 patients (223 \pm 312 patients). The sex ratio (male to female) was 1:15, and the overall average of patients was 52.13 years. The majority of the studies arose from China, mainly from Wuhan; one was from Singapore [57], two from Europe [46, 59], one from the USA [36], and one from Bolivia [58]. Musculoskeletal symptoms were present from the earliest stage of the viral illness and were reported in patients necessitating intensive care in the end stage of the condition. The total prevalence of fatigue symptom was 25.6% ($R^2 = 0.56$; p value = 0.004), while the prevalence of arthralgia and/or myalgia was 15.5% ($R^2 = 0.66$; p value = 0.001; Fig. 1).

Eight studies reported a prevalence higher than 50% of patients with fatigue [8, 9, 24, 25, 28, 37, 46, 47], while three studies reported higher values for arthralgia/myalgia symptoms [50, 53, 59]. The prevalence of musculoskeletal symptoms in studies from Europe reached high values [46, 59]; Lechien et al., for example, reported on 417 COVID-19 patients from 12 European hospitals and found myalgia in 246 (59%) and arthralgia in 129 (31%) of these patients [59].

Clinical presentation of COVID-19 ranges from absence of symptoms to severe pneumonia. Fever, dry cough and fatigue are common symptoms, as indeed are myalgia and arthralgia [6, 53]. Most of the articles are retrospective single center studies: data were collected in a non-homogeneous way, especially regarding comorbidities, lifestyle habits, and severity of the illness. Based on our work, we cannot state, for example, whether children and younger patients less commonly present musculoskeletal symptoms at onset [63]. Most studies originate from China, which is not surprising, and it is not clear whether the prevalence of musculoskeletal



Table 1 Demographics

| Study (year) | No. of patients | Sex | Age (mean SD or median IQR) | Study design | Country |
|-------------------|-----------------|----------------|--------------------------------|--|---------|
| Zheng et al. [8] | 99 | M 51 F 48 | 49.40 (SD 18.45) | Retrospective single center | China |
| Lei et al. [9] | 34 | M 14 F 20 | 55 (43–63) | Retrospective single center | China |
| Mo et al. [10] | 155 | M 86 F 69 | 54 (42–66) | Retrospective single center | China |
| Qian et al. [11] | 91 | M 37 F 54 | 50 (54–80) | Retrospective multi-center | China |
| Ma et al. [12] | 37 | M 20 F 17 | 62 (59–70) | Retrospective single center | China |
| Jin et al. [13] | 651 | M 331 F 246 | 46.0 (32–60) | Retrospective multi-center | China |
| Zheng et al. [14] | 161 | M 80 F 81 | 45.0 (33.5–57) | Retrospective single center | China |
| Wang et al. [15] | 80 | M 31 F 49 | 39.0 (32–48.5) | Retrospective multi-center (electronic database) | China |
| Chen et al. [16] | 203 | M 108 F 95 | 54.0 (20–91) | Retrospective single center | China |
| Zhou et al. [17] | 21 | M 13 F 8 | 66.1 (SD 13.94) | Retrospective single center | China |
| Lo et al. [18] | 10 | M 3 F 7 | 54 (27–64) | Retrospective single center | China |
| Huang et al. [19] | 41 | M 30 F 11 | 49.0 (41.0–58.0) | Prospective multi-center (electronic database) | China |
| Zhang et al. [20] | 645 | M 328 F 317 | 46.65 (SD 13.82) | Retrospective multi-center (electronic database) | China |
| Chen et al. [21] | 249 | M 126 F 123 | 51.0 (36–64) | Retrospective single center | China |
| Feng et al. [22] | 476 | M 271 F 205 | 53.0 (40–64) | Retrospective multi-center | China |
| Chen et al. [23] | 274 | M 171 F 103 | 62.0 (44–70) | Retrospective single center | China |
| Zhang et al. [24] | 140 | M 71 F 69 | 57.0 (25–87) | Retrospective multi-center | China |
| Lian et al. [25] | 788 | M 407 F 381 | 41.15 (SD 11.38) | Retrospective multi-center (electronic database) | China |
| Cai et al. [26] | 298 | M 145 F 153 | 47.5 (33–61) | Retrospective single center | China |
| Wan et al. [27] | 135 | M 72 F 63 | 47.0 (36–55) | Retrospective single center | China |
| Cao et al. [28] | 102 | M 53 F 49 | 54.0 (37–67) | Retrospective single center | China |
| Wang et al. [29] | 339 | M 166 F 173 | 69.0 (65–76) | Retrospective single center | China |
| Xu et al. [30] | 62 | M 36 F 27 | 41.0 (32–52) | Retrospective single center | China |
| Zhou et al. [31] | 191 | M 119 F 72 | 56.0 (46–67) | Retrospective multi-center cohort study | China |
| Wu et al. [32] | 201 | M 128 F 73 | 51.0 (43–60) | Retrospective single center cohort study | China |
| Du et al. [33] | 85 | M 62 F 23 | 65.8 | Retrospective multi-center | China |
| Wang et al. [34] | 69 | M 32 F 37 | 42.0 (35–62) | Retrospective single center | China |
| Guan et al. [35] | 1099 | M 640 | 47.0 (35–58) | Retrospective multi-center | China |

Table 1 Demographics (Continued)

| Study (year) | No. of patients | Sex | Age (mean SD or median IQR) | Study design | Country |
|-------------------------------|-----------------|------------------------------|--------------------------------|-----------------------------|-----------|
| | | F 459 | | | |
| Goyal et al. [36] | 393 | M 238 F 155 | 62.2 (49–74) | Retrospective multi-center | USA |
| Zhang et al. [37] | 28 | M 17 F 11 | 65.0 (56–70) | Retrospective single center | China |
| Chen et al. [38] | 118 | M 0 F 118 | 31.0 (28–34) | Retrospective single center | China |
| Wang et al. [39] | 1012 | M 524 F 488 | 50.0 (39–58) | Retrospective multi-center | China |
| Xia et al. [40] | 10 | M 6 F 4 | 56.5 | Retrospective single center | China |
| Liang et al. [41] | 1590 | M 904 F 674 | 48.9 (SD 16.3) | Retrospective multi-center | China |
| Dai et al. [42] | 234 | M 136 F 98 | 44.6 | Retrospective single center | China |
| Li et al. [43] | 25 | M 12 F 13 | 45.6 | Retrospective single center | China |
| Chu et al. [44] | 54 | M 36 F 18 | 39 | Retrospective single center | China |
| Qi et al. [45] | 70 | M 39 F 31 | 39.5 | Retrospective multi-center | China |
| Godaert et al. [46] | 17 | M 8 F 9 | 86.5 | Retrospective single center | France |
| Ye et al. [47] | 5 | M 2 F 3 | 30.0 | Retrospective single center | China |
| Huang et al. [48] | 22 | M 6 F 16 | 22.0 (16.0–23.0) | Retrospective single center | China |
| Tian et al. [49] | 262 | M 127 F 135 | 47.5 | Retrospective single center | China |
| Huang et al. [50] | 34 | M 14 F 20 | 56.2 | Retrospective single center | China |
| Xia et al. [51] | 20 | M 13 F 7 | 1.5 | Retrospective single center | China |
| Zhao et al. [52] | 101 | M 56 F 45 | 44.44 | Retrospective multi-center | China |
| Xu et al. [53] | 51 | M 25 F 26 | 41.6 | Retrospective single center | China |
| Li et al. [54] | 548 | M 279 F 269 | 60.0 (48–69) | Retrospective single center | China |
| Xu et al. [55] | 90 | M 39 F 51 | 50.0 (18–86) | Retrospective single center | China |
| Lei et al. [56] | 119 | M 77 F 42 | 49.0 (SD 13.6) | Retrospective multi-center | China |
| Pung et al. [57] | 17 | M 7 F 10 | 40.0 | Retrospective single center | Singapore |
| Xu et al. [71] | 50 | M 29 F 21 | 42.3 | Retrospective single center | China |
| Escalera-Antezana et al. [58] | 12 | M 6 F 6 | 36.5 | Retrospective single center | Bolivia |
| Lechien et al. [59] | 417 | M 154 F 263 | 36.9 (SD 11.4) | Retrospective multi-center | Europe |
| Dong et al. [72] | 11 | M 5 F 6 | 40.3 | Retrospective single center | China |
| Total: 54 | 12,046 | M 6427 (54%) F 5597 (46%) | 52.13 | | |

Table 2 Musculoskeletal symptoms

| Study (year) | No. of patients | Fatigue (nr/%) | Arthralgia/Myalgia (nr/%) |
|--------------------|-----------------|----------------|---------------------------|
| Zheng et al. [37] | 99 | 72 (73%) | 12 (12%) |
| Lei et al. [36] | 34 | 25 (73.5%) | 11 (32.4%) |
| Mo et al. [60] | 155 | 60 (73.2) | 50 (61.0%) |
| Qian et al. [61] | 91 | 40 (43.96%) | 5 (5.49%) |
| Ma et al. [62] | 37 | 4 (10.8%) | 4 (10.8%) |
| Jin et al. [10] | 651 | 119 (18.2%) | / |
| Zheng et al. [11] | 161 | 64 (39.8%) | 18 (11.2%) |
| Wang et al. [12] | 80 | 28 (35%) | 19 (23.75%) |
| Chen et al. [13] | 203 | 16 (7.9%) | 54 (26.6) |
| Zhou et al. [14] | 21 | 5 (23.8%) | 2 (9.5%) |
| Lo et al. [15] | 10 | / | 3 (30%) |
| Huang et al. [16] | 41 | 18 (44%) | / |
| Zhang et al. [17] | 645 | 118 (18.3%) | 71 (11%) |
| Chen et al. [18] | 249 | 39 (15.7%) | / |
| Feng et al. [19] | 476 | / | 59 (12.4%) |
| Chen et al. [20] | 274 | 137 (50%) | 60 (22%) |
| Zhang et al. [58] | 140 | 105 (75%) | / |
| Lian et al. [47] | 788 | 139 (17.6%) | 91 (11.5%) |
| Cai et al. [21] | 298 | 13 (4.3%) | / |
| Wan et al. [22] | 135 | / | 44 (32.5%) |
| Cao et al. [9] | 102 | 56 (54.9%) | 35 (34.3) |
| Wang et al. [32] | 339 | 135 (39.9%) | 16 (4.7%) |
| Xu et al. [26] | 62 | / | 32 (52%) |
| Zhou et al. [27] | 191 | 44 (23%) | 29 (15%) |
| Wu et al. [29] | 201 | 65 (32.3%) | / |
| Du et al. [33] | 85 | 50 (58.8%) | 14 (16.5%) |
| Wang et al. [35] | 69 | 29 (42%) | 21 (30%) |
| Guan et al. [33] | 1099 | 419 (38%) | 164 (15%) |
| Goyal et al. [46] | 393 | / | 94 (24%) |
| Zhang et al. [24] | 28 | 18 (64%) | 4 (14%) |
| Chen et al. [34] | 118 | 19 (16%) | / |
| Wang et al. [41] | 1012 | / | 170 (17%) |
| Xia et al. [38] | 10 | 3 (30%) | / |
| Liang et al. [39] | 1590 | 680 (43%) | 278 (17%) |
| Dai et al. [40] | 234 | 31 (13%) | 21 (9%) |
| Li et al. [41] | 25 | 17 (68%) | / |
| Chu et al. [42] | 54 | 9 (17%) | 3 (6%) |
| Qi et al. [43] | 70 | / | 12 (17%) |
| Godaert et al. [7] | 17 | 10 (59%) | / |
| Ye et al. [28] | 5 | 5 (100%) | / |
| Huang et al. [44] | 22 | 5 (23%) | 4 (18%) |
| Tian et al. [45] | 262 | 69 (26%) | / |
| Huang et al. [8] | 34 | / | 22 (65%) |
| Xia et al. [48] | 20 | 1 (5%) | / |

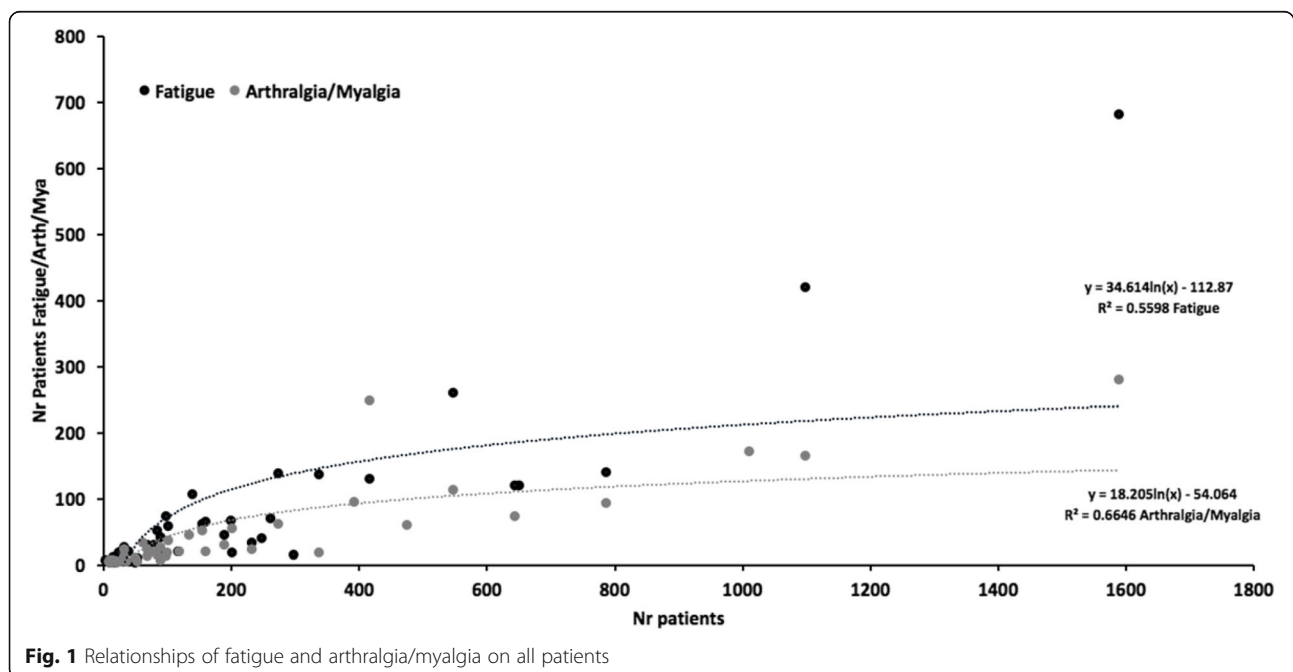
Table 2 Musculoskeletal symptoms (Continued)

| Study (year) | No. of patients | Fatigue (nr/%) | Arthralgia/Myalgia (nr/%) |
|-------------------------------|-----------------|----------------|---------------------------|
| Zhao et al. [49] | 101 | / | 17 (17%) |
| Xu et al. [25] | 51 | 2 (4%) | 8 (16%) |
| Li et al. [51] | 548 | 258 (47%) | 111 (20%) |
| Xu et al. [52] | 90 | 19 (21%) | 25 (28%) |
| Lei et al. [54] | 119 | / | 18 (15%) |
| Pung et al. [6] | 17 | / | 5 (29%) |
| Xu et al. [55] | 50 | 8 (16%) | 8 (16%) |
| Escalera-Antezana et al. [59] | 12 | / | 5 (42%) |
| Lechien et al. [57] | 417 | 129 (31%) | 246 (59%) |
| Dong et al. [56] | 11 | 2 (18%) | 1 (9%) |
| Total: 54 | Tot: 12,046 | 3085 (25.6%) | 1866 (15.5%) |

symptoms at onset is influenced by socio-geographical factors [64]. The most common symptoms in patients with mild to moderate clinical presentation of the condition are fever, fatigue, and dry cough, followed by other symptoms including headache, nasal congestion, sore throat, myalgia, and arthralgia [65, 66].

The evidence on the central role of inflammation during COVID-19 infection underlines the need to block this inflammatory cascade [30, 60–62, 67–70]. The presence of musculoskeletal symptoms is worrying: there is a high rate of use, especially in the middle age and elderly population, of NSAIDs. The fact that patients therefore report musculoskeletal symptoms is even more worrying because it may imply that the inflammatory reactions overcome the anti-inflammatory effect of such drugs.

Clinical features have to be analyzed deeply, especially considering the new evidences on COVID-19. Musculoskeletal symptoms should be married with laboratory findings, such as inflammatory and infection-related parameters (Interleukin-6, Procalcitonin, C-reactive protein). Understandably, the involvement of the musculoskeletal system has not been deeply investigated during this pandemic, but synovial and muscle biopsy, and joint fluid analysis, for example, should clarify how extensive the attack of the virus on the whole of the human body is. Until now, no report has been published on the presence of COVID-19 in the skeletal muscles, joint, or bones. The musculoskeletal symptoms are only anecdotally attributed to indirect effects, mainly arising from inflammatory and/or immune response, but other mechanisms can



be hypothesized, such as direct damage by the virus on the endothelium or peripheral nerves. These findings could help to plan specific rehabilitation protocols in COVID-19 patients.

As a new infectious disease, it is particularly important to underline the clinical features of COVID-19, especially in the early stage of the illness, to help clinicians to individuate and isolate patients earlier, and then minimize its diffusion. From the onset of the symptoms and to the most severe stages of COVID-19 disease, musculoskeletal symptoms, including myalgia, arthralgia, and fatigue, are a nearly constant presence. It is still unclear how the effects of COVID-19 on the musculoskeletal system are mediated.

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