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Musculoskeletal Manifestations of COVID-19: A Systematic Search and Review

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Coronavirus disease (COVID-19) started its journey around the world from Wuhan, China and gradually became a pandemic. COVID-19 often affects the respiratory system, but symptoms may include fatigue, myalgia, arthralgia, arthritis, and spine and bone pain as presenting complaints. In the present systematic search and review, we aim to highlight the musculoskeletal manifestations during COVID-19.

PubMed Central and Google Scholar search engines were searched for the key words “muscle pain”, “joint pain”, “body ache”, and “fatigue”, in Covid-19 patients.

After screening, a total of 76 articles dated between January 1 and July 1, 2020 met the inclusion criteria and were included in the study. All articles were published in English comprising 36,558 COVID-19 cases. In cross-sectional studies, fatigue was found in 55%, myalgia in 26%, and arthralgia in 20% of cases, respectively. In cohort studies, fatigue was found in 35%, myalgia in 15%, and arthralgia in 5%, respectively. Sporadic case reports also mention back pain, bone pain, myositis, and arthritis as presenting symptoms of COVID-19.

Fatigue was the most frequent musculoskeletal (MSK) manifestation of COVID-19 followed by myalgia and joint pain. The frequency of the different MSK manifestations in COVID-19 may vary widely among different geographic regions.

MSK like fatigue, myalgia and arthralgia are frequent symptoms in COVID-19 patients and may vary in different countries.

Keywords: Arthralgia, COVID-19, Fatigue, MSK symptoms, Myalgia, Systematic review

Introduction

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by SARS coronavirus 2 (SARS-CoV-2) began at Wuhan, China and was declared a threatening global pandemic by the World Health Organization on 11 March 2020 [1]. As of 10 April 2021, more than 134 million people have been affected by this SARS-CoV-2 infection, and more than 2.9 million people have died due to Covid-19 [2]. The mortality of this pandemic disease ranges between 0.4% and 7%, mostly from respiratory failure, sepsis, and coagulopathy [3]. However, the complete course of the disease is not yet understood [4]. According to Yang et al., SARS-CoV-2 is transmitted from human to human at an estimated rate of transmission of 3.77 [5]. The incubation period of COVID-19 generally ranges between 1 to 14 days (median 5.1 days) [6]. Individuals with COVID-19 may present with a wide range of symptoms such as fever, cough, nausea, vomiting, dyspnea, myalgia, fatigue, arthralgia, headache,

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diarrhea, and rarely arthritis [7]. Cohort studies in the United Kingdom [8] found clusters of symptoms on admission into hospital with COVID-19. The most common symptom cluster encompassed respiratory problems including cough, sputum, shortness of breath, and fever. Three other clusters have been observed, comprising (i) musculoskeletal cluster symptoms of myalgia, joint pain, headache, and fatigue; (ii) Enteric cluster symptoms of abdominal pain, vomiting, and diarrhea; and (iii) mucocutaneous cluster, which is less common [8]. Chen et al. investigated 99 patients with SARS-C0V-2 infection at Wuhan, China, and found 51% of patients had pre-existing chronic diseases such as (i) cardiovascular and cerebrovascular diseases, (ii) endocrine system disease, (iii) digestive system disease, (iv) airway diseases, (v) malignancies, and (vi) neurological diseases. In this epidemiological study, fever (83%) and cough (82%) were the most frequent presenting symptoms, followed by shortness of breath (31%), muscle ache (11%), fatigue (9%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%) [9]. Myalgia and body ache are also common symptoms in patients with viral infections such as dengue and influenza [10]. Myalgia reflects generalized inflammation and cytokine response and can be the main symptom at onset in 36% of patients with COVID-19 [10]. Myalgia and fatigue in patients with COVID-19 may persist for a longer period than in other viral infections and may be unresponsive to conventional painkillers [11]. According to Kucuk et al., muscle pain may be associated with virus load [11]. An acute flare of inflammatory joint diseases, such as rheumatoid arthritis, lupus, ankylosing spondylitis, Sjogren's syndrome, polymyalgia rheumatic, and juvenile idiopathic arthritis, has been observed among hospitalized COVID-19 patients [12]. The neurological system [13] and the heart [14] may also be involved in COVID-19.

Muscle injury was found in 4.8-19.3% of patients with COVID-19 having myalgia with increased serum creatinine kinase (CK) > 200 U/L [15]. To the best of our knowledge, the only review article on the musculoskeletal manifestation of COVID-19 was published by Cipollaro et al., who categorized musculoskeletal manifestations into fatigue and arthralgia/myalgia [16]. These symptoms were mainly attributed to inflammation and immune response and associated with inflammatory and infection-related parameters such as Interleukin-6, Pro-calcitonin, and C reactive protein [16]. Cipollaro et al. hypothesized that the endothelium or the peripheral nerves can be damaged directly by the virus [16].

The current study purposed to review the musculoskeletal (MSK) manifestations of COVID-19 in order to aid physicians in recognizing the condition.

Materials and Methods

In this systematic search and review, studies published in English between January 1 and July 1, 2020 documenting MSK features of COVID-19 were enrolled for retrospective analysis. Medline (PubMed) and Google Scholar search engines were used to acquire relevant articles using the following keywords: "COVID-19" or "coronavirus" or "SARSCov2" and "myalgia", "muscle pain", "joint pain", "body ache", and "fatigue", and were used for the *population (MSK problem in COVID-19), intervention, comparison (exposed to COVID-19), and outcome (PICO) model* (Table 1). Boolean Logic (AND, OR, and NOT) was employed to generate different combinations of search strings. Three researchers (KMR, RSA, and AMT) carefully studied every article and collected the information on a prefabricated data sheet. Insight regarding the treatment of these MSK features has not been provided. PRISMA [17] was used to show how articles were selected. This review is not registered with any international database. Microsoft Excel-16 was used for data screening and extraction. Articles other than English and review articles were excluded. A flowchart (Figure 1) summarizes the systematic search and review. A standard template was developed to capture relevant traits of the review objective, such as (i) author(s) information, (ii) publication year, (ii) study design, (iv) effect size (if any), (v) gender, (vi) MSK symptoms, and (vii) study locations. Study types such as cross-sectional, case-control, case report and case series describing MSK manifestations were included, but correspondence, letters to the editors, expert opinions, and editorials were excluded. It can be difficult to differentiate some musculoskeletal complaints from that of neurological symptoms, but only MSK features of COVID-19 were included in this study.

Quality assessment and data synthesis

Two reviewers (KMR and HM) independently assessed the quality of the studies using as standard guidelines "The Quality Assessment Tools for Quantitative Studies" developed by the Effective Public Health Practice Project [18] (EPHPP). Any disagreements between these two reviewers were resolved by discussion and with the involvement of another reviewer (HF). The Critical Appraisal Skills Program (CASP) checklist [19] was not used in the current review, because no randomized clinical trials were found. Moreover, systematic reviews were excluded in accordance with the inclusion criteria.

Quantitative variables were measures like frequency, and percentage. Confidence Interval (CI) values were also measured at 95%. The extracted data was analyzed, and the overall proportion was pooled for each MSK symptom.

Results

The reviewers' tried to address the objective of this review; however, no randomized clinical trial nor epidemiological study was found specifically reporting musculoskeletal manifestations of COVID-19 in detail within the study period.

A total of 1623 articles were found when searching with the keywords, but only 76 of these [3, 8, 9, 15, 20-91] met the inclusion criteria (Figure 1). The majority (59 out

of 76) of the included studies were cross-sectional type. There were also 5 cohort studies, 4 case series, and 8 case reports (Table 1). The reviewers rated all the included 76 studies [3, 8, 9, 15, 20-91] as 'weak' in quality assessment score (Table S1).

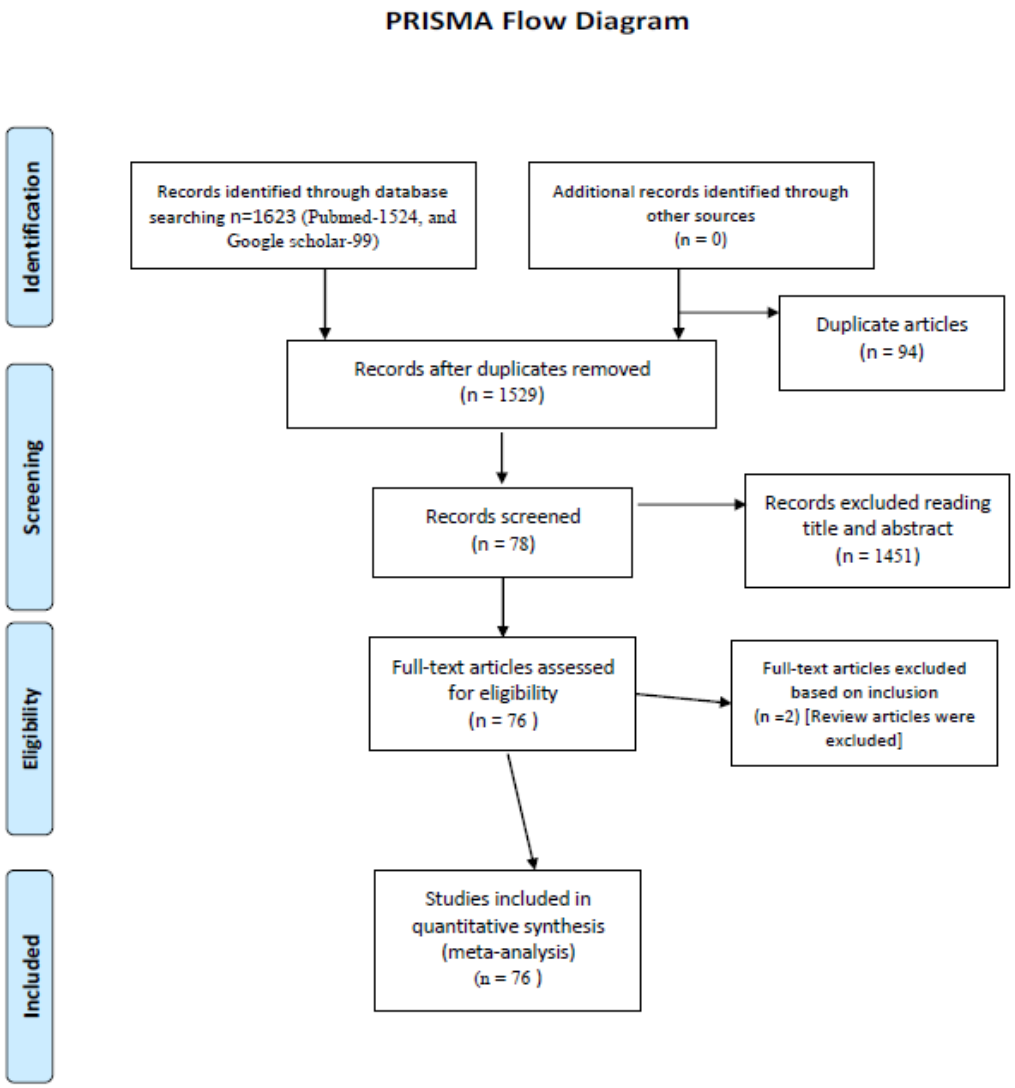

Figure 1. PRISMA flow diagram for the inclusion of articles in this review.

Table 1. Study design, year of publication, sample size, median age, and gender distribution reported in included articles

Articles	Country	Study design	Year	Sample total (N)	Median age	Male n (%)	Female n (%)
Docherty et al. [8]	UK	Prospective cohort study	2020	20,133	73	12,068 (60)	8065 (40)
Liang et al. [23]	China	Cross-sectional study	2020	1590	48.9	904 (56.8)	686 (43.2)
Lapostolle et al. [22]	France	Cross-sectional study	2020	1487	44	699 (47)	788 (53)
Guan et al. [36]	China	Cross-sectional study	2020	1099	47	640 (58.3)	459 (41.7)
Wang et al. [41]	China	Cross-sectional study	2020	1012	50	524 (51.8)	488 (48.2)
Lian et al. [44]	China	Cross-sectional study	2020	788	41	407 (51.6)	381 (48.4)
Zhang et al. [49]	China	Retrospective cohort	2020	663	55	321 (48.4)	342 (51.6)

Articles	Country	Study design	Year	Sample total (N)	Median age	Male n (%)	Female n (%)
Li et al. [38]	China	Case series	2020	655	43	367 (56)	288 (44)
Jin et al. [50]	China	Cross-sectional study	2020	652	46	331 (50.7)	246 (49.3)
Zhang et al. [43]	China	Cross-sectional study	2020	645	46	328 (50.9)	317 (49.1)
Li et al. [51]	China	Cross-sectional study	2020	548	60	279 (51)	269 (49)
Feng et al. [52]	China	Cross-sectional study	2020	476	53	271 (56.9)	205 (43.1)
Lechien et al. [24]	Europe	Cross-sectional study	2020	417	36	154 (36.9)	263 (63.7)
Goyal et al. [21]	USA	Cross-sectional study	2020	393	62.2	238 (60.6)	155 (39.4)
Gayam et al. [20]	USA	Retrospective cohort	2020	350	57		
Wang et al. [28]	China	Cross-sectional study	2020	339	71	166 (49)	173 (51)
Graef et al. [37]	Spain	Case series	2020	306			
Cai et al. [53]	China	Cross-sectional study	2020	298	47	145 (48.6)	153 (51.3)
Chen et al. [54]	China	Cross-sectional study	2020	274	62	171 (62.4)	103 (37.6)
Tian et al. [55]	China	Cross-sectional study	2020	262	47	127 (49.5)	135 (51.5)
Chen et al. [56]	China	Cross-sectional study	2020	249	51	126 (50.6)	123 (49.4)
Xiong et al. [57]	China	Cross-sectional study	2020	244	42	120 (49.2)	124 (50.8)
Dai et al. [45]	China	Cross-sectional study	2020	234	44.6	136 (58.1)	98 (41.9)
Mao et al. [15]	China	Cross-sectional study	2020	214	58.7	87 (40.7)	127 (59.3)
Chen et al. [35]	China	Cross-sectional study	2020	203	54	108 (53.2)	95 (46.8)
Wu et al. [58]	China	Cross-sectional study	2020	201	51	128 (63.7)	73 (36.3)
Zhou et al. [3]	China	Retrospective cohort	2020	191	56	119 (62)	72 (38)
Zheng et al. [32]	China	Cross-sectional study	2020	161	45	80 (49.7)	81 (50.3)
Mo et al. [33]	China	Cross-sectional study	2020	155	54	86 (55.5)	69 (44.5)
Zhang et al. [42]	China	Cross-sectional study	2020	140	57	71 (50.7)	69 (49.3)
Liu et al. [59]	China	Cross-sectional study	2020	137	57	61 (44.5)	76 (55.5)
Wan et al. [60]	China	Cross-sectional study	2020	135	47	72 (53.3)	63 (46.6)
Lei et al. [31]	China	Cross-sectional study	2020	119	49	77 (64.7)	42 (35.3)
Chen et al. [46]	China	Cross-sectional study	2020	118	31	0	118 (100)
Cao et al. [61]	China	Cross-sectional study	2020	102	54	53 (52)	49 (48)
Lovell et al. [27]	UK	Case series	2020	101	82	64 (63.4)	37 (36.6)
Zhao et al. [62]	China	Cross-sectional study	2020	101	44	56 (55.5)	45 (44.5)
MaChen et al. [9]	China	Cross-sectional study	2020	99	55	67 (67.6)	32 (32.3)
Zheng et al. [63]	China	Cross-sectional study	2020	99	49	51 (51.5)	48 (48.5)

Articles	Country	Study design	Year	Sample total (N)	Median age	Male n (%)	Female n (%)
Qian et al. [64]	China	Cross-sectional study	2020	91	50	37 (40.7)	54 (59.3)
Xu et al. [65]	China	Cross-sectional study	2020	90	50	39 (43.3)	51 (56.7)
Xu et al. [66]	China	Cross-sectional study	2020	90	50	39 (43.3)	51 (56.7)
Du et al. [67]	China	Cross-sectional study	2020	85	65.8	62 (72.9)	23 (27.1)
Qi et al. [68]	China	Cross-sectional study	2020	70	39.8	39 (55.7)	31 (44.3)
Wang et al. [25]	China	Cross-sectional study	2020	69	39	32 (46.5)	37 (53.5)
Xu et al. [69]	China	Cross-sectional study	2020	62	39	35 (56)	27 (46)
Helms et al. [47]	France	Cross-sectional study	2020	58	63		
Chu et al. [70]	China	Cross-sectional study	2020	54	39	36 (66.7)	18 (33.3)
Yang et al. [91]	China	Cross-sectional study	2020	52	59.7	35 (67)	17 (33)
Xu et al. [71]	China	Cross-sectional study	2020	50	39	29 (58)	21 (42)
Huang et al. [72]	China	Cross-sectional study	2020	41	39	30 (73)	11 (27)
Joob and Wiwanitkit [39]	Thailand	Cross-sectional study	2020	40			
Ma et al. [73]	China	Cross-sectional study	2020	37	39	20 (54.1)	17 (45.9)
Huang et al. [74]	China	Cross-sectional study	2020	34	39	14 (41.2)	20 (58.8)
Lei et al. [34]	China	Retrospective cohort	2020	34	39	14 (41.2)	20 (58.8)
Zhang et al. [75]	China	Cross-sectional study	2020	28	39	17 (60.7)	11 (39.3)
Li et al. [76]	China	Cross-sectional study	2020	25	39	10 (40)	15 (60)
Huang et al. [40]	China	Cross-sectional study	2020	22	39	6 (27.3)	16 (72.7)
Zhou et al. [77]	China	Cross-sectional study	2020	21	39	13 (61.9)	8 (38.1)
Xia et al. [78]	China	Cross-sectional study	2020	20	39	13 (65)	7 (35)
Godaert et al. [79]	France	Cross-sectional study	2020	17	39	8 (47.1)	9 (52.9)
Pung et al. [80]	Singapore	Cross-sectional study	2020	17	39	7 (41.2)	10 (58.2)
Escalera-Antezana et al. [81]	Bolivia	Cross-sectional study	2020	12	39	6 (50)	6 (50)
Dong et al. [82]	China	Cross-sectional study	2020	11	39	5 (45.5)	6 (54.5)
Lo et al. [83]	China	Cross-sectional study	2020	10	39	3 (30)	7 (70)
Xia et al. [84]	China	Cross-sectional study	2020	10	56.5	6 (60)	4 (40)
Ye et al. [85]	China	Cross-sectional study	2020	5	39	2 (40)	3 (60)
Toscano et al. [48]	Italy	Case series	2020	5	61	4 (75)	1 (25)
Zhu et al. [86]	China	Case report	2020	1	39	1 (100)	0
Zhang et al. [26]	USA	Case report	2020	1	39	1 (100)	0
Song et al. [29]	South Korea	Case report	2020	1	39	0	1 (100)

Articles	Country	Study design	Year	Sample total (N)	Median age	Male n (%)	Female n (%)
Kenanidis et al. [87]	Greece	Case report	2020	1	39	0	1 (100)
Sinha et al. [88]	USA	Case report	2020	1	39	1 (100)	0 (0)
Taşkın et al. [89]	Turkey	Case report	2020	1	39	0 (0)	1 (100)
Moeinzadeh et al. [90]	Iran	Case report	2020	1	39	1 (100)	0 (0)
Beydon et al. [30]	France	Case report	2020	1	25	1 (100)	0
Total 76				**36,558**		**20,268 (55.4)**	**15,461 (42.3)**

A total of 36,558 COVID-19 patients were described in these 76 studies, of whom 55.4% were male; for 2.4% of the patients, no gender had been mentioned (Table 1).

The majority of the 76 included studies were from China (Table 1). By far, the largest single study of COVID-19 patients (n = 20,133) came from the UK cohort which reported fatigue, muscle aches, and joint pain at approximate frequencies of 35%, 15%, and 5%, respectively, as the presenting complaint (Docherty et al.) [8]. Seven additional articles from Europe [24, 30, 37, 47, 48, 79, 80, 87] and 3 from the USA [20, 21, 26] were also included. A study in Belgium with 417 (263 females) COVID-19 patients reported arthralgia in 32% and myalgia in 58% of the cases [24]. In one French study, MRI delineated myositis was described in an early COVID-19 patient [30]. COVID-19 MSK features had also been documented in Singapore [80], Thailand [39], Bolivia [81], South Korea [29], and Turkey [89], and these countries each contributed one article. Evidence shows that fatigue, myalgia/body ache, and arthralgia are the most prevalent musculoskeletal symptoms in COVID-19**.** Sporadic case reports also mentioned back pain, bone pain, myositis, and arthritis as the presenting complaints of COVID-19 (Table 7). One study from Iran reported myopathy, myalgia, and arthralgia in COVID-19 patients complicated by glomerulonephritis [90].

Overall findings

All articles together comprised in total 36,561 COVID-19 cases. Fatigue was found in 55%, myalgia in 26%, and arthralgia in 20% of cases (Tables 2, 5, and 6) in cross-sectional studies. In cohort studies, fatigue was found in 35%, myalgia in 15%, and arthralgia in 5% of cases (Table 3).

Table 2. Fatigue as a manifestation in COVID-19 in cross-sectional studies

Author(s)	Year	Sample total	Frequency	Proportion	95% CI	
					Upper limit	Lower limit
Liang et al. [23]	2020	1590	681	0.43	0.4	0.45
Lapostolle et al. [22]	2020	1487	886	0.6	0.57	0.62
Guan et al. [36]	2020	1099	419	0.38	0.35	0.41
Wang et al. [41]	2020	1012	419	0.41	0.38	0.45
Lian et al. [44]	2020	788	139	0.18	0.15	0.2
Jin et al. [50]	2020	652	23	0.04	0.02	0.05
Zhang et al. [43]	2020	645	118	0.18	0.15	0.21
Li et al. [51]	2020	548	258	0.47	0.43	0.51
Lechien et al. [24]	2020	417	129	0.31	0.27	0.36
Wang et al. [28]	2020	339	135	0.4	0.35	0.45
Cai et al. [53]	2020	298	13	0.04	0.02	0.07
Chen et al. [54]	2020	274	137	0.5	0.44	0.56
Tian et al. [55]	2020	262	69	0.26	0.21	0.32

Author(s)	Year	Sample total	Frequency	Proportion	95% CI	
					Upper limit	Lower limit
Chen et al. [56]	2020	249	39	0.16	0.10	0.24
Dai et al. [45]	2020	234	31	0.13	0.09	0.18
Chen et al. [35]	2020	203	16	0.08	0.05	0.12
Wu et al. [58]	2020	201	65	0.32	0.26	0.39
Zheng et al. [32]	2020	161	64	0.4	0.32	0.48
Mo et al. [33]	2020	155	113	0.73	0.65	0.8
Zhang et al. [42]	2020	140	105	0.75	0.67	0.82
Liu et al. [59]	2020	137	44	0.32	0.24	0.41
Chen et al. [46]	2020	118	19	0.16	0.11	0.21
Cao et al. [61]	2020	102	56	0.55	0.45	0.65
Zheng et al. [63]	2020	99	72	0.73	0.63	0.81
Qian et al. [64]	2020	91	40	0.44	0.34	0.55
Xu et al. [65]	2020	90	2	0.02	0.00	0.08
Xu et al. [66]	2020	90	19	0.21	0.13	0.31
Du et al. [67]	2020	85	50	0.59	0.48	0.69
Wang et al. [25]	2020	69	29	0.42	0.3	0.55
Chu et al. [69]	2020	54	9	0.17	0.08	0.29
Xu et al. [71]	2020	50	8	0.16	0.07	0.29
Huang et al. [72]	2020	41	18	0.44	0.28	0.6
Ma et al. [73]	2020	37	4	0.11	0.03	0.25
Huang et al. [74]	2020	34	22	0.65	0.46	0.8
Zhang et al. [75]	2020	28	18	0.64	0.44	0.81
Li et al. [76]	2020	25	17	0.68	0.46	0.85
Huang et al. [40]	2020	22	5	0.23	0.08	0.45
Zhou et al. [77]	2020	21	5	0.24	0.08	0.47
Xia et al. [78]	2020	20	1	0.05	0.00	0.25
Godaert et al. [79]	2020	17	10	0.59	0.33	0.82
Dong et al. [82]	2020	11	2	0.18	0.02	0.52
Xia et al. [84]	2020	10	3	0.3	0.07	0.65
Ye et al. [85]	2020	5	5	1.00	0.48	1.00
Total 43		**Overall Positivity**		**0.55**	**0.29**	**0.67**

Table 3. Fatigue, myalgia, and arthralgia as symptoms in COVID-19 in cohort studies

Author(s)	Year	Sample total	Frequency	Proportion	95% CI	
					Lower limit	Upper limit
Fatigue						
Docherty et al. [8]	2020	20,133	7052	0.35	0.34	0.36
Zhang et al. [49]	2020	663	208	0.31	0.28	0.35
Gayam et al. [20]	2020	350	292	0.83	0.79	0.87
Zhou et al. [3]	2020	191	44	0.23	0.17	0.3
Lei et al. [34]	2020	34	25	0.74	0.56	0.87
Total 5		**Overall Positivity**		**0.36**	**0.21**	**0.49**
Myalgia						
Docherty et al. [8]	2020	20133	3020	0.15	0.15	0.16
Zhang et al. [49]	2020	663	63	0.1	0.07	0.12
Gayam et al. [20]	2020	393	94	0.24	0.22	0.32
Lei et al. [34]	2020	34	22	0.65	0.46	0.8
Total 4		**Overall positivity**		**0.15**	**0.11**	**0.53**
Arthralgia						
Docherty et al. [8]	2020	20,133	1007	0.05	0.05	0.05
Total 1		**Overall Positivity**		**0.05**	**0.05**	**0.05**

Fatigue and Weakness

The overall prevalence of fatigue in cross-sectional studies was 55% [95% CI, 0.29-0.67] [Table 2]. The overall positivity for fatigue in cohorts was 36% [95% CI, 0.21-0.49] (Table 3). However, the overall positivity for fatigue in case series was 25% [95% CI, 0.22-.28] (Table 4). The frequency of fatigue varied widely between 4% and 68%, and between 23% and 83% in cross-sectional and cohort studies, respectively (Tables 2, 3).

Myalgia, myositis

The frequency of myalgia varied widely among the studies, e.g., between 5% and 63%, and 10% and 65% in cross-sectional and cohort studies, respectively (Tables 5, 6). The overall positivity for myalgia in cross-sectional, cohort, and case series studies with COVID-19 was 26% [95% CI, 0.17-0.61] [Table 5], 15% [95% CI, 0.11- 0.53] (Table 3), and 40% [95% CI, 0.03-.83] (Table 4), respectively. In a cross-sectional study among US citizens with COVID-19, Goyal et al. [21] enumerated myalgia in about 63% of cases. In another multicenter retrospective study with 1,487 COVID-19, Lapostolle et al. documented myalgia in 57% of the patients [22]. Lechien et al. found 13% among 417 patients presenting with myalgia [24]. Wang et al. [28] found that about 5% of cases presented with myalgia in their cross-sectional studies among an elderly Chinese population; Dai et al. [45] reported a similar frequency of myalgia in their study among a general Chinese population. Docherty et al. (2020) mentioned that approximately 15% of patients manifested myalgia in their prospective cohort study which included 20,133 SARS-CoV-2 cases [8]. Gayam et al. reported that about 1 in every 4 (~24%) COVID-19 patients reported myalgia among New York City dwellers [20]. Moreover, Lei et al. reported a frequency of myalgia in 65% cases of their cohort in China [34]. Zhang et al. [49], however, reported myalgia in only 10% of their cohort. Lovelli et al. reported myalgia in 35% in their case series [27]. Song et al. [29] reported raised muscle enzyme (creatinine kinase [CK] 42,670 U/L) in a patient with COVID-19 with coexisting rheumatoid arthritis. Zhang et al. reported muscle injury, evident by raised muscle enzyme CK at 42,670 unit per liter [26], and Beydon et al. described increased serum creatinine kinase concentration in a COVID-19 patient [30]. Myalgia was not reported by Guan et al. in their cross-sectional study, but 13.7% of the respondents had an elevated CK level at an average of 90 U/L [36]. Lei et al. [31] and Zheng et al. [32] also reported mild to moderately raised muscle enzymes in their retrospective studies.

In a 61-year-old woman, COVID-19 was described with myalgia, fever, fatigue, subcutaneous nodules, aphthous ulceration, and arthralgia. Histopathology of a skin biopsy unveiled diffuse neutrophilic infiltration in the upper dermis and vascular proliferation with swollen endothelial cells and extravasated erythrocytes; in the lower dermis and at the periphery of the lobules of subcutaneous fat tissue, small granulomas were found

composed of epithelioid histiocytes, multinuclear giant cells infiltrated with histocytes, lymphocytes, and sparse neutrophils, all favoring erythema nodosum-like Sweet's syndrome [89]. Zhang et al. documented muscle pain in 14.3% of cancer cases infected with COVID-19 [75]. MRI-documented myositis (external obturator muscle and quadricipital) has also been documented in COVID-19 patients [30]. One patient initially reported diffuse myalgia and proximal lower limb muscle weakness (on MRC bilateral hip flexors, strength was 3/5) with a history of frequent falls, before developing fever and respiratory symptoms and signs (ground-glass opacity on CT chest). He had elevated serum creatinine kinase, C reactive protein, and lymphocytopenia [30]. Sporadic rhabdomyolysis had also been reported; for example, Guan et al. reported two cases of rhabdomyolysis in COVID-19 patients [36]. One study showed a statistical association between elevated CK levels and mortality [3]. As in autoimmune myositis, COVID-19 myositis may be linked with myocarditis and may lead to mortality. Studies have reported elevations in N-terminal pro-brain natriuretic peptide and troponin in myocarditis [92]. Lovell et al. described bone pain as a manifesting symptom in about 23% of COVID-19 cases in the UK [27].

Table 4. Fatigue, myalgia, and arthralgia as symptoms in case series studies in COVID-19

Author(s)	Year	Sample total	Frequency	Proportion	At 95% CI	
					Lower limit	Upper limit
Fatigue						
Li et al. [38]	**2020**	655	184	0.28	0.25	0.32
Lovell et al. [27]	**2020**	101	9	0.09	0.04	0.16
Total 2	**Overall positivity**			0.25	0.22	0.28
Myalgia						
Graef et al. [37]	2020	306	233	0.76	0.71	0.81
Li et al. [38]	2020	655	78	0.12	0.1	0.15
Lovell et al. [27]	2020	101	35	0.35	0.25	0.45
Total 3	**Overall positivity**			**0.4**	**0.03**	**0.85**
Arthralgia						
Graef et al. [37]	**2020**	306	4	0.01	0.0	0.03
Li et al. [38]	**2020**	655	78	0.12	0.1	0.15
Total 2	**Overall positivity**			**0.07**	**0.06**	**0.09**

Table 5. Myalgia as a manifestation in COVID-19 in cross-sectional studies

Author(s)	Year	Sample Total	Frequency	Proportion	95% CI	
					Lower limit	Upper limit
Lapostolle et al. [22]	2020	1487	845	0.57	0.54	0.59
Wang et al. [41]	2020	1012	170	0.17	0.09	0.28
Lian et al. [44]	2020	788	91	0.12	0.09	0.14
Zhang et al. [43]	2020	645	71	0.11	0.09	0.14
Li et al. [51]	2020	548	66	0.12	0.09	0.15
Feng et al. [52]	2020	476	111	0.23	0.2	0.27
Lechien et al. [24]	2020	417	55	0.13	0.1	0.17

Author(s)	Year	Sample Total	Frequency	Proportion	95% CI	
					Lower limit	Upper limit
Goyal et al. [21]	2020	393	246	0.63	0.58	0.67
Wang et al. [28]	2020	339	16	0.05	0.03	0.08
Cai et al. [53]	2020	298	81	0.27	0.22	0.33
Tian et al. [55]	2020	262	60	0.23	0.18	0.28
Dai et al. [45]	2020	234	11	0.05	0.02	0.08
Mao et al. [15]	2020	214	23	0.11	0.07	0.16
Chen et al. [35]	2020	203	21	0.1	0.07	0.15
Wu et al. [58]	2020	201	54	0.27	0.21	0.34
Zheng et al. [32]	2020	161	29	0.18	0.12	0.25
Mo et al. [33]	2020	155	95	0.61	0.53	0.69
Wan et al. [60]	2020	135	44	0.33	0.25	0.41
Lei et al. [31]	2020	119	44	0.37	0.28	0.46
Chen et al. [46]	2020	118	18	0.15	0.09	0.23
MaChen et al. [9]	2020	99	17	0.17	0.1	0.26
Zheng et al. [63]	2020	99	11	0.11	0.06	0.19
Qian et al. [64]	2020	91	12	0.13	0.07	0.22
Xu et al. [65]	2020	90	5	0.06	0.02	0.12
Xu et al. [66]	2020	90	8	0.09	0.04	0.17
Du et al. [67]	2020	85	25	0.29	0.2	0.4
Qi et al. [68]	2020	70	19	0.27	0.17	0.39
Wang et al. [25]	2020	69	12	0.17	0.15	0.19
Xu et al. [69]	2020	62	21	0.34	0.22	0.47
Chu et al. [70]	2020	54	32	0.59	0.45	0.72
Yang et al. [91]	2020	52	3	0.06	0.01	0.16
Xu et al. [71]	2020	50	6	0.12	0.05	0.24
Huang et al. [72]	2020	41	8	0.2	0.00	0.35
Joob and Wiwanitkit [39]	2020	40	18	0.45	0.29	0.62
Huang et al. [74]	2020	34	4	0.12	0.03	0.27

Author(s)	Year	Sample Total	Frequency	Proportion	95% CI	
					Lower limit	Upper limit
Zhang et al. [75]	2020	28	11	0.39	0.22	0.59
Zhou et al. [77]	2020	21	4	0.19	0.05	0.42
Xia et al. [78]	2020	20	2	0.1	0.01	0.32
Godaert et al. [79]	2020	17	1	0.06	0	0.29
Escalera-Antezana et al. [81]	2020	12	5	0.42	0.15	0.72
Dong et al. [82]	2020	11	5	0.45	0.17	0.77
Lo et al. [83]	2020	10	1	0.1	0	0.45
Xia et al. [84]	2020	10	3	0.3	0.07	0.65
Total 43	**Overall positivity**			**0.26**	**0.17**	**0.61**

Table 6. Arthralgia as a manifestation in Covid-19 in cross-sectional studies

Author(s)	Year	Sample total	Frequency	Proportion	95% CI	
					Lower limit	**Upper limit**
Guan et al. [36]	2020	1099	164	0.15	0.13	0.17
Chen et al. [35]	2020	203	54	0.27	0.21	0.33
Mo et al. [33]	2020	155	95	0.61	0.53	0.69
Yang et al. [91]	2020	52	1	0.02	0.00	0.1
Joob and Wiwanitkit [39]	2020	40	1	0.03	0.00	0.13
Total 5	**Overall positivity**			**0.20**	**0.09**	**0.35**

Table 7. Predominant presentation among case reports

Author/s	Year	Predominant clinical features	Age	Gender
Zhu et al. [86]	2020	Arthralgia	39	Male
Zhang et al. [26]	2020	Myalgia and fatigue	39	Male
Song et al. [29]	2020	Myalgia, myositis, and arthralgia	39	Female
Kenanidis et al. [87]	2020	Myalgia, arthralgia, and fatigue	39	Female
Sinha et al. [88]	2020	Back pain and myalgia	39	Male
Taşkın et al. [89]	2020	Bone pain, arthralgia, and back pain	39	Female
Moeinzadeh et al. [90]	2020	Myalgia, arthralgia, and fatigue	39	Male
Beydon et al. [30]	2020	Myalgia, myositis, and fatigue	25	Male

Arthralgia

Arthralgia is less frequently seen in COVID-19 than myalgia [93]. The overall positivity for arthralgia is 20% [95% CI, 0.09-0.35] in cross-sectional studies (Table 6) and 5% [95% CI, 0.05-0.05] in cohort studies (Table 3). However, the overall positivity for arthralgia in case series is 7% [95% CI, 0.06- 0.09] (Table 4). Mo et al. reported 61% of their cases (n = 155) in China manifested with arthralgia [33]. Chen et al. also reported arthralgia in about 27% of their study participants (n = 203) in China [35]. Furthermore, Guan et al. reported that about 15% (164 out of 1099) participants in China developed arthralgia [36]. However, Docherty et al. reported that approximately 5% of cases manifested with joint pain among 20,133 COVID-19 patients in a UK cohort [8]. Graef et al. reported arthralgia in about one percent of COVID-19 patients (4 out of 306) in Spain in their case series [37]. Li et al. reported 78 out of 655 (~12%) respondents in their case series in China developed arthralgia [38].

Arthritis

About 3% of Thai patients manifested with arthritis [39]. Overt arthritis was otherwise not mentioned in the reviewed articles.

Low back pain (LBP)

Based on the emergency and out-patient data from 4 hospitals in Milan, the number of cases of acute LBP during the period from March 8, 2020 to April 8, 2020 was reduced to one-sixth of that during the same period in 2019. This may be ascribed to a reduction in traumatic cases owing to the lockdown and the reduced movement of people [94]. Huang et al. reported back pain as a presenting manifestation in 4.5% (1 out of 22) of their COVID-19 cases [40]. Sporadic case reports (Table 7) have mentioned LBP as the presenting symptom in COVID-19 [88, 89]; however, they could not classify whether the symptoms were due to involvement of the spine and/or due to the paraspinal soft tissues. Patients with LBP during COVID-19 underwent an MR of the lumbar spine, which revealed intramuscular edema (multifidua and erector spinae) in association with raised CRP, ESP, creatinine kinase, and D-dimer levels [95]. MRI-evidenced paraspinal myositis features were absent at the cervical and dorsal spine levels. Here, alongside muscular viral load, an immune-mediated parainfectious inflammatory response or adverse effects of drug- or critical illness-associated myopathy could be the explanation [95].

Mortality of COVID-19 cases with musc-loskeletal manifestations

The rate of mortality of COVID-19 patients with musculoskeletal presentations has not been documented; however, patients with myositis associated with COVID-19 may have a prolonged hospital stay, increased disease severity, and mortality [30, 95]. There is yet more to learn about mortality in cases of COVID-19 with musculoskeletal manifestations.

Discussion

Fatigue and weakness are the most frequently seen nonspecific non-respiratory manifestations of COVID-19. The overall prevalence of fatigue in cross-sectional studies was 55% [95% CI, 0.29-0.67] [Table 2]. The overall positivity for fatigue in cohorts was 35% [95% CI, 0.21- 0.49] (Table 3). However, the overall positivity for fatigue in case series is 25% [95% CI, 0.22-0.28] (Table 4).

The prevalence of fatigue differs between countries. In the USA, fatigue was seen in 83.3% of COVID-19 patients [20], and in the UK, more than 35% of patients presented with fatigue and weakness [8]. In China, about 40% of respondents manifested with fatigue and weakness [23, 36, 41], while in France, 60% of COVID-19 patients presented with fatigue and weakness [22]. A multi-center European study found more than 30% of COVID-19 patients complained of fatigue [24]. Mo et al. and Zhang et al. reported fatigue in about three in every four (73.2% and 75%, respectively) patients [33, 42] in their series. However, less than 20% of patients reported fatigue in some other Chinese studies [43-46]. Cytokine storm with increased serum concentrations of both proinflammatory cytokines and anti-inflammatory cytokines including IL-2R, IL-6, TNF –α and IL-10 may be responsible for the fatigue [96,97]. Moreover, psychological morbidity and anxiety may also be responsible for fatigue in patients with COVID-19 [98, 99]. This virus is not merely an episode of illness for the infected individual, but a life-changing disastrous experience which not only impairs physical wellbeing, but also mental health [99]. A systematic review and meta-analysis done by Ciaffi et al. reported fatigue as an initial manifestation in 31.7% of cases, and the estimated prevalence of fatigue was 35.6% (95% CI 0.297–0.420) [100], which is comparable with the overall frequency of fatigue reported in the current review.

Bone and m*uscle manifestations*

Myalgia is the second most frequent non-respiratory presentation inCOVID-19. It may be due to increased lactate dehydrogenase (LDH) in muscle injury and tissue damage [11]. Increased LDH in association with anaerobic glycolysis leads to increased lactate levels in both the damaged muscle and the serum. Muscle pain may increase further due to increased lactate levels with cytosolic low pH and oxygen levels. Hence, improvement of hypoxia by reducing virus load and increasing erythrocytes oxygenation can also improve LDH levels and pain, and painkillers may not be effective in such case [11]. In the current review, 26% and 15% of cases had myalgia in cross-sectional and cohort studies, respectively. These findings are consistent with the findings of a systematic review and meta-analysis conducted by Abdullahi et al. [101], who found myalgia in 19% (95% CI 16–23; I^2 95%) of their cases [101].

Furthermore, Ciaffi et al. reported a 15.6% (95% CI 0.116–0.206) pooled estimation for prevalence of myalgia in their systematic review and meta-analysis [100].

Bone

New onset osteonecrosis, osteosclerosis, and osteoporosis were reported in patients with COVID-19 [102]. Ramani et al. reported that the development of osteonecrosis with osteosclerosis and osteoporosis may result from SARS-CoV-2-induced coagulopathy and steroid therapy [102].

Joint and spine manifestations

Joint pain was the third most frequent musculoskeletal manifestation of COVID-19 as revealed in the current review. Joint pain manifestations were more frequent among Chinese patients than in those in the UK and Spain [8, 33, 35, 38, 37, 49]. Ciaffi et al. reported joint pain as a manifestation of COVID-19 in their systematic review; however, they did not estimate the pooled frequency of joint pain [100].

Low Back Pain

The pooled prevalence of back pain in COVID-19 was 10% (95% CI 0.01–0.23) as reported by Abdullahi et al. in their systematic review and meta-analysis [101]. This percentage is higher than the findings in the current review, although the difference may be explained by the fact that Abdullahi et al. included chronic back pain, while the current study did not. It is important to take complaints of LBP seriously, as it may be due to intramuscular edema (multifidua and erector spinae) in association with raised CRP, ESP, creatinine kinase, and D-dimer levels [97]. An immune-mediated parainfectious inflammatory response may also be the explanation as well as adverse effects of drug- or critical illness-associated myopathy [97].

Arthralgia

As summarized in the current study, up to 15% of COVID-19 cases may have arthralgia.

Arthritis: Overt arthritis is very rare in COVID-19 as opposed to other viral infections where joint inflammation may be seen more frequently. In general, viral infections such as hepatitis C, Chikungunya, Ross River, Barmah Forest, Sindbis, O'nyong-nyong and Mayaro viruses, parvovirus B19, rubella or hepatitis B virus can cause self-limiting and/or persistent arthritis; as of today, however, that has not been proven for coronaviruses. It is suggested that treatment with glucocorticoids in SARS infection may suppress musculoskeletal manifestations. A large Korean study revealed a link between endemic human coronavirus, parainfluenza virus, and metapneumovirus and an increased prevalence of RA. However, this has not been proven with SARS-CoV-2 [93].

Non-specific MSK manifestations

Non-specific MSK complaints (for example, asthenia, and especially in the elderly) and limb weakness may cause diagnostic confusion with myopathy or neuropathy; hence before labeling these as COVID-19 complications, other explanations should be excluded [48, 79]. One case report stated that COVID-19 had been misdiagnosed as peri-prosthetic joint infection [87].

Neurological symptoms were excluded from the current study, but sometimes there is an overlap of pain due to affection of the (central) nervous system. Fatigue due to neurological symptoms cannot always be excluded as demonstrated in a young boy with Guillain Barré syndrome due to COVID-19 [103].

A limitation of the current study is that it cannot be estimated how long MSK symptoms may persist.

A strength of the current study is that to the best of our knowledge, it is the first systematic review of MSK symptoms in patients with COVID-19 and gives a complete review of MSK symptoms in all patients described in the first half year of the pandemic. It describes findings of studies from all over the world.

Conclusion

MSK, like fatigue, myalgia, and arthralgia, are frequent symptoms in COVID-19 patients and may vary in different countries. Unlike with other viral infections, in COVID-19 patients, episodic or persistent arthritis has not been reported. Sporadic case reports have described that myositis-associated symptoms may be linked with COVID-19 severity and with mortality. Further prospective studies are needed to further clarify this point.

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Declarations

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iii. Ethics approval: Not obtained.

iv. Consent to participate: Not applicable.

v. Consent for publication: All authors voluntarily consent to publication of this review.

vi. Availability of data and material (data transparency): All extracted data is kept by the principal author.

vii. Code availability (software application or custom code): Excel 2016 was used to record and analyze extracted data.

viii. Authors' contributions: Research idea and protocol were developed by MRK, TM, JJR, ABS, FH, MH, and SSI. Literature search was conducted by TM, ABS, MH, JJR, FH, SSI, and MRK. The quality of the selected studies was assessed by KMR and HM and supplemented by HF, when required. Data extraction was done by MRK, TM, ABS, JJR; analysis was done by MH, FH, and SSI. The manuscript was drafted, edited, and finalized by JJR, MRK, ABS, TM, SSI, FH, and MH.

Conflict of interest

None.

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Appendix 1

Table S1. Effective Public Health Practice Project (EPHPP) - Quality assessment tool for quantitative studies

	Particulars of the Studies				EPHPP Components						
Sl. No.	**Author**	**Year**	**Journal**	**Study design**	**Selection bias**	**Study design**	**Confounders**	**Blinding**	**Data collection method**	**Withdrawals And dropouts**	**Global rating**
1.	Docherty et al. [8]	2020	BMJ	Prospective cohort study	M	M	NA	NA	W	NA	Weak
2.	Liang et al. [23]	2020	European Respiratory Journal	Cross-sectional study	W	W	NA	NA	W	NA	Weak
3.	Lapostolle et al. [22]	2020	Internal and Emergency Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
4.	Guan et al. [36]	2020	New England Journal of Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
5.	Wang et al. [41]	2020	Clinical Microbiology and Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
6.	Lian et al. [44]	2020	Clinical Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
7.	Zhang et al. [49]	2020	Clinical Microbiology and Infection	Retrospective cohort	W	M	NA	NA	M	S	Weak
8.	Li et al. [38]	2020	Journal of Medical Internet Research	Case series	W	W	NA	NA	W	NA	Weak
9.	Jin et al. [50]	2020	Gut	Cross-sectional study	W	W	NA	NA	W	NA	Weak
10.	Zhang et al. [43]	2020	International Journal of Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
11.	Li et al. [51]	2020	Journal of Allergy and Clinical Immunology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
12.	Feng et al. [52]	2020	American Journal of Respiratory and Critical Care Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
13.	Lechien et al. [24]	2020	European Archives of Oto-Rhino-Laryngology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
14.	Goyal et al. [21]	2020	New England Journal of Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
15.	Gayam et al. [20]	2020	Journal of Medical Virology	Retrospective cohort	W	M	NA	NA	W	S	Weak
16.	Wang et al. [28]	2020	Journal of Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
17.	Graef et al. [37]	2020	Annals of the Rheumatic Diseases	Case series	W	W	NA	NA	W	NA	Weak
18.	Cai et al. [53]	2020	Allergy	Cross-sectional study	W	W	NA	NA	W	NA	Weak
19.	Chen et al. [54]	2020	BMJ	Cross-sectional study	W	W	NA	NA	W	NA	Weak
20.	Tian et al. [55]	2020	Journal of Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
21.	Chen et al. [56]	2020	Journal of Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
22.	Xiong et al. [57]	2020	The Journal of Pediatrics	Cross-sectional study	W	W	NA	NA	W	NA	Weak

	Particulars of the Studies				EPHPP Components						
Sl. No.	Author	Year	Journal	Study design	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals And dropouts	Global rating
23.	Dai et al. [45]	2020	International Journal of Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
24.	Mao et al. [15]	2020	JAMA Neurol	Cross-sectional study	W	W	NA	NA	W	NA	Weak
25.	Chen et al. [35]	2020	The Journals of Gerontology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
26.	Wu et al. [58]	2020	JAMA Internal Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
27.	Zhou et al. [3]	2020	The Lancet	Retrospective cohort	W	M	NA	NA	W	S	Weak
28.	Zheng et al. [32]	2020	Eur Rev Med Pharmacol Sci	Cross-sectional study	W	W	NA	NA	W	NA	Weak
29.	Mo et al. [33]	2020	Clinical Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
30.	Zhang et al. [42]	2020	Allergy	Cross-sectional study	W	W	NA	NA	W	NA	Weak
31.	Liu et al. [59]	2020	Chinese Medical Journal	Cross-sectional study	W	W	NA	NA	W	NA	Weak
32.	Wan et al. [60]	2020	Journal of Medical Virology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
33.	Lei et al. [31]	2020	Travel Medicine and Infectious Disease	Cross-sectional study	W	W	NA	NA	W	NA	Weak
34.	Chen et al. [46]	2020	New England Journal of Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
35.	Cao et al. [61]	2020	Clinical Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
36.	Lovell et al. [27]	2020	Journal of Pain and Symptom Management	Case series	W	W	NA	NA	W	NA	Weak
37.	Zhao et al. [62]	2020	American Journal of Roentgenology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
38.	MaChen et al. [9]	2020	The Lancet	Cross-sectional study	W	W	NA	NA	W	NA	Weak
39.	Zheng et al. [63]	2020	Journal of Clinical Virology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
40.	Qian et al. [64]	2020	QJM: An International Journal of Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
41.	Xu et al. [65]	2020	International Journal of Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
42.	Xu et al. [66]	2020	European Journal of Nuclear Medicine and Molecular Imaging	Cross-sectional study	W	W	NA	NA	W	NA	Weak
43.	Du et al. [67]	2020	American Journal of Respiratory and Critical Care Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
44.	Qi et al. [68]	2020	Journal of Hepatology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
45.	Wang et al. [25]	2020	Clinical Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
46.	Xu et al. [69]	2020	BMJ	Cross-sectional study	W	W	NA	NA	W	NA	Weak

Particulars of the Studies					EPHPP Components						
Sl. No.	**Author**	**Year**	**Journal**	**Study design**	**Selection bias**	**Study design**	**Confounders**	**Blinding**	**Data collection method**	**Withdrawals And dropouts**	**Global rating**
47.	Helms et al. [47]	2020	New England Journal of Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
48.	Chu et al. [70]	2020	Journal of Medical Virology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
49.	Yang et al. [91]	2020	The Lancet Respiratory Medicine	Cross-sectional study	W	W	NA	NA	W	NA	Weak
50.	Xu et al. [71]	2020	Journal of Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
51.	Huang et al. [72]	2020	The Lancet	Cross-sectional study	W	W	NA	NA	W	NA	Weak
52.	Joob and Wiwanitkit [39]	2020	Rheumatology International	Cross-sectional study	W	W	NA	NA	W	NA	Weak
53.	Ma et al. [73]	2020	Journal of Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
54.	Huang et al. [74]	2020	Travel Medicine and Infectious Disease	Cross-sectional study	W	W	NA	NA	W	NA	Weak
55.	Lei et al. [34]	2020	E Clinical Medicine	Retrospective cohort	W	M	NA	NA	W	S	Weak
56.	Zhang et al. [75]	2020	Annals of Oncology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
57.	Li et al. [76]	2020	International Journal of Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
58.	Huang et al. [40]	2020	Journal of Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
59.	Zhou et al. [77]	2020	Clinical and Translational Science	Cross-sectional study	W	W	NA	NA	W	NA	Weak
60.	Xia et al. [78]	2020	Pediatric Pulmonology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
61.	Godaert et al. [79]	2020	Journal of Infection	Cross-sectional study	W	W	NA	NA	W	NA	Weak
62.	Pung et al. [80]	2020	The Lancet	Cross-sectional study	W	W	NA	NA	W	NA	Weak
63.	Escalera-Antezana et al. [81]	2020	Travel Medicine and Infectious Disease	Cross-sectional study	W	W	NA	NA	W	NA	Weak
64.	Dong et al. [82]	2020	Allergy	Cross-sectional study	W	W	NA	NA	W	NA	Weak
65.	Lo et al. [83]	2020	International Journal of Biological Sciences	Cross-sectional study	W	W	NA	NA	W	NA	Weak
66.	Xia et al. [84]	2020	Journal of Clinical Virology	Cross-sectional study	W	W	NA	NA	W	NA	Weak
67.	Ye et al. [85]	2020	International Journal of Infectious Diseases	Cross-sectional study	W	W	NA	NA	W	NA	Weak
68.	Toscano et al. [48]	2020	New England Journal of Medicine	Case series	W	W	NA	NA	W	NA	Weak
69.	Zhu et al. [86]	2020	Infectious Diseases of Poverty	Case report	W	W	NA	NA	W	NA	Weak
70.	Zhang et al. [26]	2020	Cureus	Case report	W	W	NA	NA	W	NA	Weak

Sl. No.	Author	Particulars of the Studies		Study design	EPHPP Components						
		Year	Journal		Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals And dropouts	Global rating
71.	Song, et al. [29]	2020	Rheumatology International	Case report	W	W	NA	NA	W	NA	Weak
72.	Kenanidis et al. [87]	2020	Cureus	Case report	W	W	NA	NA	W	NA	Weak
73.	Sinha et al. [88]	2020	Clinical Nuclear Medicine	Case report	W	W	NA	NA	W	NA	Weak
74.	Taşkın et al. [89]	2020	Journal of the European Academy of Dermatology and Venereology	Case report	W	W	NA	NA	W	NA	Weak
75.	Moeinzadeh et al. [90]	2020	Iranian Journal of Kidney Diseases	Case report	W	W	NA	NA	W	NA	Weak
76. S	Beydon et al. [30]	2020	Annals of the Rheumatic Diseases	Case report	W	W	NA	NA	W	NA	Weak

S=STRONG, M=MODERATE, W=WEAK, and NA=NOT APPLICABLE

GLOBAL RATING: STRONG (no WEAK ratings), MODERATE (one WEAK rating), WEAK (two or more WEAK ratings)