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REVIEW

Clinical Characteristics and Mechanisms of Musculoskeletal Pain in Long COVID

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Objective: Musculoskeletal (MSK) pain is being increasingly reported by patients as one of the most common persistent symptoms in post-COVID-19 syndrome or Long COVID. However, there is a lack of understanding of its prevalence, characteristics, and underlying pathophysiological mechanisms. The objective of this review is to identify and describe the features and characteristics of MSK pain in Long COVID patients.

Methods: The narrative review involved a literature search of the following online databases: MEDLINE (OVID), EMBASE (OVID), CINAHL, PsyclNFO, and Web of Science (December 2019 to February 2022). We included observational studies that investigated the prevalence, characteristics, risk factors and mechanisms of MSK pain in Long COVID. After screening and reviewing the initial literature search results, a total of 35 studies were included in this review.

Results: The overall reported prevalence of MSK pain in Long COVID ranged widely from 0.3% to 65.2%. The pain has been reported to be localized to a particular region or generalized and widespread. No consistent pattern of progression of MSK pain symptoms over time was identified. Female gender and higher BMI could be potential risk factors for Long COVID MSK pain, but no clear association has been found with age and ethnicity. Different pathophysiological mechanisms have been hypothesized to contribute to MSK pain in Long COVID including increased production of proinflammatory cytokines, immune cell hyperactivation, direct viral entry of neurological and MSK system cells, and psychological factors.

Conclusion: MSK pain is one of the most common symptoms in Long COVID. Most of the current literature on Long COVID focuses on reporting the prevalence of persistent MSK pain. Studies describing the pain characteristics are scarce. The precise mechanism of MSK pain in Long COVID is yet to be investigated. Future research must explore the characteristics, risk factors, natural progression, and underlying mechanisms of MSK pain in Long COVID.

Keywords: post-COVID-19 syndrome, post-acute COVID-19, chronic pain

Introduction

The lasting symptoms of COVID-19, now referred to as "Long COVID", are a public health concern. According to the National Institute for Health and Care Excellence (NICE) guidelines, "Long COVID" is defined as signs and symptoms that develop during or after an acute infection consistent with COVID-19 and persist longer than 4 weeks.[1] This comprises both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (beyond 12 weeks). The guidelines emphasize that the symptoms cannot be explained by an alternative diagnosis which is in keeping with the clinical case definition proposed by the WHO that also highlight the potential fluctuations and protracted nature of post-COVID-19 symptoms.[2]

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Long COVID presents as a clinically diverse condition, with published work reporting a plethora of symptoms, most commonly: fatigue, shortness of breath, pain, post-exertional malaise, persisting elevated temperature and cognitive dysfunction.[3–6] At the beginning of December 2021, estimated 1.3 million people in UK private households had Long COVID, 64% of whom reported an adverse impact of their symptoms/diagnosis on their ability to carry out activities of daily living (ADL).[3,7] Several theories have been posited to explain the etiology of Long COVID which include continued presence of the virus, re-infection with the same or possibly different strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), endothelial damage and hypercoagulation, dysautonomia, and dysfunctional immune response leading to chronic inflammation.[8–12]

It is becoming increasingly evident that musculoskeletal (MSK) pain, defined as pain arising from MSK structures, such as bones, muscles, joints, tendons and ligaments,[13] is common among Long COVID patients. A previous systematic review and meta-analysis reported a total prevalence of myalgia (muscle pain) and arthralgia (joint pain) ranging from 5.65% to 18.1% and 4.6% to 12.1%, respectively, in the 4 to 12 weeks following acute COVID-19 infection onset or hospitalisation.[14] The authors suggest that up to 10% of recovered COVID-19 patients will experience Long COVID pain of MSK origin.

MSK pain-related conditions are among the leading contributors to global disability, estimated to affect 1.71 billion people worldwide.[15] According to the latest Versus Arthritis report, approximately a third of the UK population is living with MSK conditions, which account for 21% of years lived with disability in the UK.[16] Research suggests MSK pain has higher prevalence rates in females and is more common in older people.[17–20] In addition to the negative impact on an individual's functional status and health-related quality of life,[21] the substantial costs of healthcare for MSK pain and associated loss of productivity pose a huge economic burden on societies.[22–24]

Given the increasing number of people with Long COVID and MSK pain, there is an urgent need for a holistic understanding of MSK pain in Long COVID to inform appropriate management and mitigate the growing burden of chronic pain. This narrative review will explore the latest reported literature on MSK pain in Long COVID. The aim of this review is to describe the prevalence, risk factors and the plausible mechanisms of MSK pain in Long COVID.

Methods

Identification of relevant studies was performed through literature search of the following online databases: MEDLINE (OVID), EMBASE (OVID), CINAHL, PsyclNFO and Web of Science. The search strategy included terms related to the condition (COVID-19; SARS-CoV-2; coronavirus; 2019-nCoV; Long COVID; Post-COVID; Long haul COVID), pain symptoms (pain; musculoskeletal pain; nociceptive pain; neuropathic pain; neuralgia; radiculopathy; widespread pain; arthralgia; myalgia; acute pain; chronic pain; pain mechanisms), and study methods (observational study; cross-sectional study; cohort study; case–control study; longitudinal study). The search was restricted to studies that were published in English between December 2019 and February 2022. Reviews, case studies, expert opinions, and editorial articles were excluded. The search terms were tailored to each database, as required (Table 1). Furthermore, the bibliographies of the relevant studies were scanned for additional relevant literature. A citation manager program (Endnote) was used to import all retrieved references and remove duplicates. Duplicates not identified by the program were manually excluded. After removal of duplicates and screening of the titles and abstracts of the literature search results, a total of 112 articles underwent full-text review. Following a full-text review, 35 articles were found suitable for inclusion in this review (Figure 1).

Synthesis of Results

Prevalence of Pain

Numerous studies have reported the prevalence of MSK pain and other persistent symptoms of COVID-19. The overall reported prevalence ranged widely from 0.3% to 65.2% (Table 2). The heterogeneity of participants (in relation to the severity of acute illness) and measurements at different timepoints after the acute infection may contribute to the wide range of prevalence reported in these studies. Myalgia and arthralgia appear to be the most common MSK pain symptoms that have been reported in 18 out of 35 studies. The lowest prevalence was reported by Mohiuddin Chowdhury et al, for both mild

Table 1 Search Strategy (OVID)

Long COVID		**Pain**		**Observational Studies**
COVID-19*	AND	Pain*	AND	"observational stud*"
SARS-CoV-2		"Musculoskeletal pain"		"cross-sectional stud*"
Coronavirus		"Chronic pain"		"Cohort stud*"
2019-nCov		"acute pain"		"case-control stud*"
"Long COVID*"		"Nociceptive pain"		"longitudinal stud*"
Post-COVID*		Neuropath* or Neuralgia		
Post-acute		Radiculopathy		
"long haul*"		"widespread pain"		
		"joint pain" or Arthralgia		
		"muscle pain" or Myalgia		
		Long-term		
		Prolong*		
		Persist*		
		Mechanisms*		
		Pathophysiolog*		
		Etiolog*		
		Aetiolog*		
Combined with OR		Combined with OR		Combined with OR
Limits: Human, Adult, English language (December 2019 to February 2022) Exclude: Reviews, case studies, expert opinion, editorial articles, and pre-prints				

Note: *Truncation command to search for the root of the free-text word with any alternative ending.

body ache and back pain (0.3%) persisting for 4 weeks following recovery.[25] The highest prevalence of 65.2% COVID-19 survivors reporting new-onset pain at 16 weeks after hospital discharge has been reported by Carvalho-Soares et al[26]

Characteristics of Pain

Only 8 studies described the characteristics of pain, 4 of which found pain localized to a particular region to be most common,[26–29] while others reported a higher prevalence of widespread and generalized pain.[30,31] Of the studies that reported localized pain symptoms, cervical spine and lower extremities were the most affected regions followed by lumbar spine and upper extremities.[26] One study showed that nociceptive-type pain was considerably more common than neuropathic-type pain.[29] Another study reported that the most common regional areas for arthralgia are knee joint, ankle joint and shoulder joint, while the most common areas for myalgia are lower leg, arm, and shoulder girdle.[30]

Most studies so far have focused on patients who were severely ill requiring hospitalization (24 studies). Only 6 studies evaluated patients recovering at home and did not require hospitalization. The remaining 5 studies included both hospitalized and non-hospitalized patients with only 2 comparing the difference in MSK pain prevalence rates between hospitalized and non-hospitalized patients. Goërtz et al compared hospitalized patients with three subgroups of non-hospitalized patients (confirmed, suspected and symptom-based COVID-19) and reported a higher prevalence of MSK pain in non-hospitalized patients than hospitalized patients (Table 2).[32] Similarly, Jacobson et al noted chest pain in 14.7% of non-hospitalized patients in comparison to only 9.1% in hospitalized patients.[33] In contrast, there was a higher prevalence of myalgia in hospitalized patients (22.7%) compared to non-hospitalized patients (16.8%). Another important factor to consider is the difference in MSK complications between severely ill hospitalized patients who require admission to the intensive care unit (ICU) and those who were admitted to the ward due to COVID-19 infection. This has been investigated by Leite et al, where patients admitted to the ICU reported a higher prevalence of persistent pain (33.9%) than those in the ward (27.1%).[34]

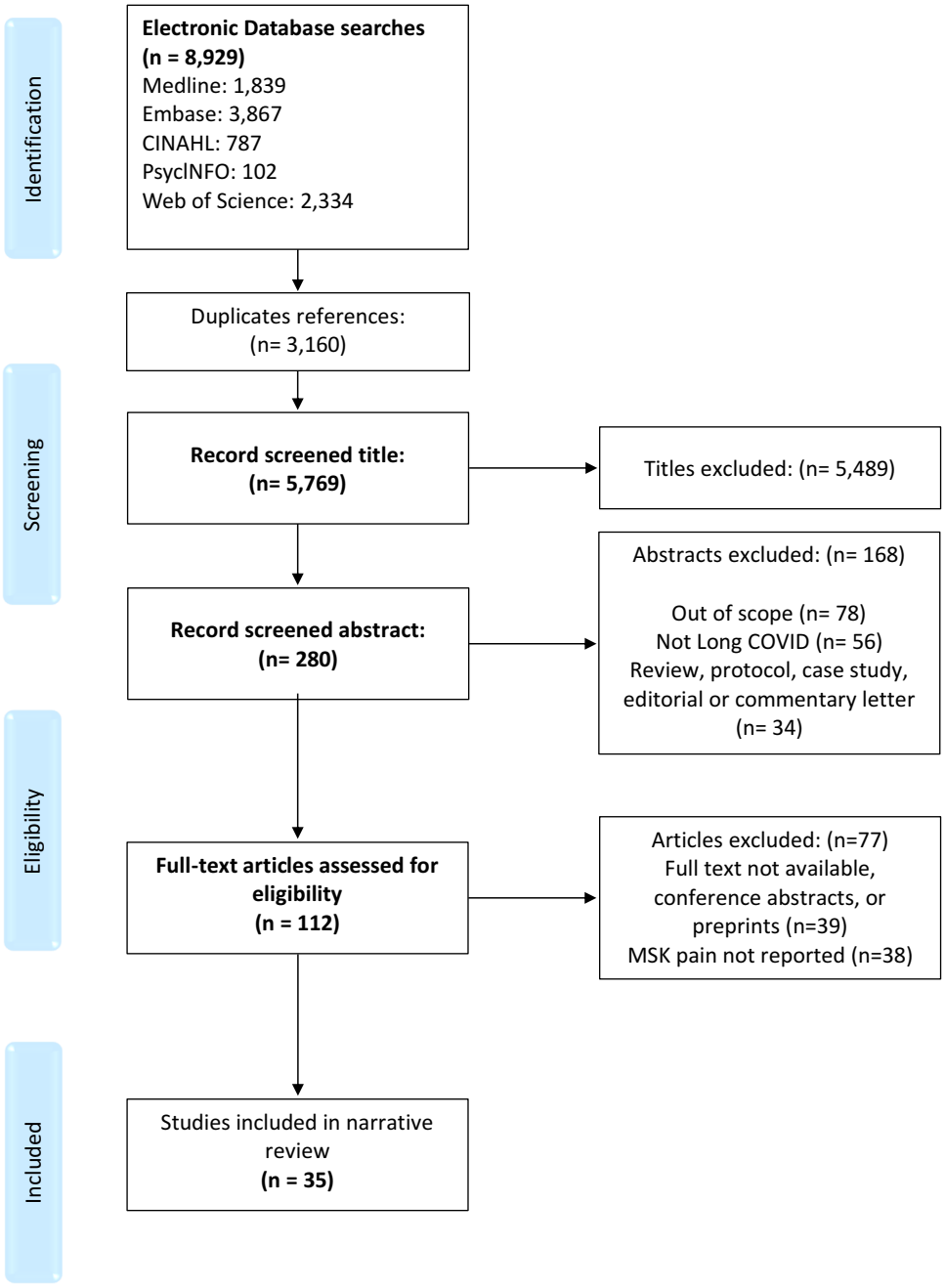

Figure 1 Flow Diagram of screening and selection process.

The data from 7 longitudinal studies following patients at multiple time points showed no consistent pattern of progression of MSK pain symptoms over time. Karaarslan et al followed-up patients at 3 months and 6 months post-discharge and reported a decline in the prevalence of myalgia, arthralgia, low back pain and neck pain (Table 2).[30] In contrast, Lu et al observed an increase in myalgia symptoms at 13 weeks post-discharge (25%) comparing to baseline (15%).[35] Similarly, Carvalho-Schneider et al's study revealed an increase from 9.8% to 16.3% in the prevalence of arthralgia from day 30 to day 60 post-onset.[36] Nevertheless, the same study observed a fluctuating pattern for chest pain with prevalence values of 14%, 18% and 13.1% at onset of COVID-19 infection, day 30 and day 60 after symptom onset, respectively.[36] A fluctuating pattern has also been reported by Leth et al, for myalgia and chest pain symptoms, with a decrease in the prevalence from the baseline to 6 weeks after onset, followed by an increase at 12 weeks (Table 2).[37]

Table 2 Characteristics of Relevant Studies

Author, Year Country	Sample Size (Male/ Female)	Hospitalization	Type of Study	Time Point(s)	MSK Pain Type and Prevalence at Follow-Up (s)	Pain Characterizations and Location	Risk Factors	Hypothesized Mechanisms
Adnan et al (2021)[27] Pakistan	55 (35–20)	No	Cross-sectional study	Not clear	Myalgia and Arthralgia (63.63%) in male (36.36%) in female	Back ache 45.45% Knee joint 18.18% Mixed 18.18% Hip joint 9.09% Ankle joint 5.45%	The prevalence of Myalgia and Arthralgia increase with aging and was higher in the lower socio-economic status.	Not available
Bai et al (2021)[28] Italy	377 (240–137)	Yes	Prospective cohort study	Median of 6 weeks from symptom onset	Musculoskeletal pain 21.2%	Joint pain or myalgia No, ever (57%) Ongoing (21.2%) Resolved (19.6%) Unknown (2.1%)	Female gender, older age and active smoking were associated with long COVID syndrome, but not severity of the acute disease.	Not available
Bellan et al (2021)[89] Italy	200 (122/78)	Yes	Prospective longitudinal study	Baseline, 17 weeks and 52 weeks.	Arthralgia/myalgia Baseline (19.3%) At week 17 (6.5%) At week 52 (21.9%)	Not available	Not available	Not available
Bileviciute-ljungar et al (2022)[31] Sweden	100 (18/82)	No (90%) Yes (10%)	Cross-sectional study	A mean of 47 weeks since the start of the infection.	Head/face 27% Throat/neck 5% Shoulder/arms 5% Chest 16% Legs 12% Pain sites varied 15%	The mean value of pain intensity during the last week was 4.4/10 75% reported generalized pain.	Comorbidities Wealthy middle-aged women	Not available
Carfì et al (2020)[90] Italy	143 (90/53)	Yes	Case series	Mean of 7 weeks after onset of the first COVID-19 symptoms	Arthralgia 27.3%	Not available	Not available	Not available

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Table 2 (Continued).

Author, Year Country	Sample Size (Male/ Female)	Hospitalization	Type of Study	Time Point(s)	MSK Pain Type and Prevalence at Follow-Up (s)	Pain Characterizations and Location	Risk Factors	Hypothesized Mechanisms
Carvalho-Soares et al (2021)[26] Brazil	46 (21/25)	Yes	Controlled cross-sectional study	Mean 16 week after hospital discharge	De novo pain 65.2% De novo chronic pain 19.6% Location of de novo pain: Head and neck 66.7% Upper limbs 16.7% Thorax and/or abdomen 16.7% Dorsal and/or low back 46.7% Lower limbs 36.7% Widespread pain 23.3%	COVID-19 pain was more frequently located in the head/neck and lower limbs Frequency of de novo pain: <15 days/month 13.3% ≥ 15 days/month 50% Trend of de novo pain after discharge: Improved 17.2% Unchanged 44.8% Worsened 0% Not informed 37.9%	Not available	Not available
Carvalho-Schneider et al (2021)[36] France	150 (66/84)	Yes	Prospective cohort study	1 week, 4 weeks and 8.5 Weeks	Chest pain Onset (14%) Day 30 (18%) Day 60 (13.1%) Arthralgia Onset (-) Day 30 (9.8%) Day 60 (16.3%)	Not available	Not available	Not available
Ferna´ndez-de-las-Pen-as et al (2021)[38] Spain	738 Patients reporting myalgia at admission (n=369) (176/193) Control: Patients without myalgia at admission (n=369) (176/193)	Yes	Case-control study	A mean of 31 weeks after hospital discharge	Overall prevalence of MSK post-covid pain of 38%, 31 weeks post-discharge -With myalgia group (42.5%) -without myalgia group (34.5%)	Musculoskeletal pain Locations (Cervical spine, Thorax-chest, Lumbar spine, Widespread pain, Upper extremity, Shoulder area, Wrist-elbow, Lower extremity, Hip region, Knee)	Presence of myalgia at the onset of SARS-cov-2 and hospital admission	Prolonged inflammatory response associated with Covid-19 (cytokine mediated), viral neurotropic properties, Lead to hyperexcitability of peripheral and central nervous systems (nociplastic pain), Emotional and social factors (psychosocial mechanisms)

Galal et al (2021)[91] Egypt	430 (156/274)	Yes	Cross-sectional study	Follow-up mean 5 weeks	Myalgia 60% Arthralgia 57.2%	Not available	Not available	Not available
Goërtz et al (2020)[32] Netherlands	2113 (310/1803)	112 hospitalized 2001 non-hospitalized	Cross-sectional study	Mean 11 weeks	Myalgia (36%) Pain between shoulder blades (33%) Arthralgia (22%)	Not available	Not available	Not available
Graham et al (2021)[44] USA	100 (30/70) (n=50 lab. +ve PCR Control n=50 -ve PCR)	No	Prospective study	Baseline and an average of 20 weeks after symptom onset	Myalgia Overall 55% +ve 60% -ve 50% Pain other than chest Overall 43% +ve 40% -ve 46%	Not available	Not available	Not available
Havervall et al (2021)[92] Sweden	323 (55/268)	No	Cross-sectional study	At the 34-week follow-up Participants reported symptoms ≥8, ≥17 and ≥34 weeks	Myalgia/Arthralgia ≥8 weeks (2.2%) ≥17 weeks (1.9%) ≥34 weeks (0.6%)	Not available	Not available	Not available
Horwitz et al (2021)[93] USA	126 (75/51)	Yes	Prospective observational study	4 weeks and 26 weeks post-hospital discharge	Muscle/body ache (38%) Arthralgia (33%) Chest pain (21%)	Not available	Not available	Not available
Huang et al (2021)[61] China	1276 (681/595)	Yes	Ambi-directional cohort study	26 weeks and 52 weeks after symptoms onset.	Myalgia 26 weeks (3%) 52 weeks (4%) Arthralgia 26 weeks (11%) 52 weeks (12%) Chest pain 26 weeks (5%) 52 weeks (7%)	Not available	Not available	Not available

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Table 2 (Continued).

Author, Year Country	Sample Size (Male/ Female)	Hospitalization	Type of Study	Time Point(s)	MSK Pain Type and Prevalence at Follow-Up (s)	Pain Characterizations and Location	Risk Factors	Hypothesized Mechanisms
Iqbal et al (2021)[41] Pakistan	158 (71/87)	No	Cross-sectional study	Mean of 5 weeks since recovery (from acute phase)	Arthralgia (47.5%) Chest pain (35.4%)	Not available	Not available	Not available
Jacobs et al (2020)[94] Italy	183 (112/71)	Yes	Prospective cohort study	Baseline and 5 weeks post-hospitalization	Myalgia 51% Arthralgia 54.7%	Not available	Not available	Not available
Jacobson et al (2021)[33] USA	118 (63/55)	Hospitalized n=22 Non-hospitalized n=96	Cross-sectional study	Median of 17 weeks	Myalgia Total 17.9% Hospitalized 22.7% Non-hospitalized 16.8% Chest pain Total 13.7% Hospitalized 9.1% Non-hospitalized 14.7%	Not available	Not available	Not available
Kamal et al (2020)[95] Egypt	287 (103/184)	Yes	Cross-sectional study	Median of 8.5 weeks	Arthralgia (31.4%) Chest pain (28.9%)	Not available	Not available	Not available

Karaarslan et al (2022)[30] Turkey	285 (172/173)	Yes	Prospective cohort study	13 weeks and 26 weeks following the hospitalization.	Myalgia 13 weeks (40.55%) 26 weeks (15.09%) Arthralgia 13 weeks (39.18%) 26 weeks (18.59%) Low back pain 13 weeks (24.74%) 26 weeks (11.23%) Back pain 13 weeks (31.62%) 26 weeks (14.39%) Neck pain 13 weeks (20.62%) 26 weeks (9.47%)	Severity, type, and locations of rheumatic and musculoskeletal symptoms Arthralgia and myalgia were mostly widespread (64.2% and 69.8%, respectively); if regional, arthralgia was mostly in the knee, foot-ankle, and shoulder, and myalgia was mostly in the lower leg, arm, and shoulder girdle.	Female patients were more likely to have myalgia and joint pain at 26 weeks.	Immune response and pro-inflammatory cytokines generated after infection/direct invasion/injury of musculoskeletal cells by SARS-cov-2 through the angiotensin-converting enzyme 2 (ACE2) receptor Cellular invasion by SARS-COV -2, inflammatory and the immune response, and sequelae of post-critical illness, transforming growth factor beta (TGF-β) overexpression causing a prolonged state of immunosuppression and fibrosis
Leite et al (2021)[34] Brazil	1696 (745/951)	Yes	Cross-sectional study	4 weeks after hospital discharge	Pain Total (28.5) 26.4%-30.8% ICU (33.9) 29.0%-39.1% Ward (27.1) 24.7%-29.6%	Not available	Not available	Not available
Leth et al (2021)[37] Denmark	49 (21/28)	Yes	Prospective longitudinal study	Baseline, 6 weeks, and 12 weeks	Myalgia Baseline (47%) 6 weeks (16%) 12 weeks (35%) Chest pain Baseline (17%) 6 weeks (10%) 12 weeks (20%)	Not available	Not available	Not available
Lu et al (2020)[35] China	60 (34/26)	Yes	Prospective study	Baseline and 13 weeks after hospital discharge	Myalgia At acute stage (15%) At follow-up (25%)	Not available	Not available	Not available

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Table 2 (Continued).

Author, Year Country	Sample Size (Male/ Female)	Hospitalization	Type of Study	Time Point(s)	MSK Pain Type and Prevalence at Follow-Up (s)	Pain Characterizations and Location	Risk Factors	Hypothesized Mechanisms
Magdy et al (2021)[39] Egypt	90 45 patients with post-COVID pain (15/30) 45 recovered from COVID-19 without pain (16/29)	Yes	Case-control study	Recovery duration 8.5 weeks	VAS [median] 8 (6–9) Frequency (days per week) 7 (3–7) Site of pain: Hands and feet (20%) Arms and legs (66.7%) Radicular (13.3%)	Pain character (n=45) Burning (33.3%) Painful cold (13.3%) Electric shock (37.8%) Burning and electric shock (11.1%) Burning and painful cold (4.4%) Associated symptoms: Tingling (15.6%) Numbness (42.2%) Itching (8.9%) Pins and needles (13.3%) Numbness and itching (4.4%) Numbness and pins and needles (8.9%) Pins, needles and tingling (2.2%) Pins, needles, numbness and tingling (4.4%) Hypothesia to touch (68.9%) Hypothesia to prick (31.1%) Allodynia: Yes (37.8%) No (62.2%)	Depression, Azithromycin use, moderate and severe COVID-19 are independent predictors of persistent post-COVID-19 pain. Serum NFL may serve as a potential biomarker for persistent neuropathic pain after COVID-19.	Direct neuro- invasive potential of SARS-cov-2. And massive release of pro- inflammatory mediators (cytokine storm) The higher the chance of exposure to the injurious effect of the virus, either through a longer duration of the COVID-19 infection or the severity of the infection, the greater the likelihood of pain. Both depression and neuropathic pain may arise from a common underlying inflammatory process induced by the cytokine storm.
Mahmud et al (2021)[96] Bangladesh	355 (207/148) N=162 with post-covid syndrome (symptomatic) N=193 no post-covid symptoms	Yes	Prospective cohort study	4 weeks after clinical improvement	Myalgia Total (0.6%) Symptomatic (1.2%) Arthralgia Total (1.4%) Symptomatic (4.8%) Chest pain Total (0.8%) Symptomatic (1.8%)	Not available	Not available	Not available

Mohiuddin Chowdhury et al (2021)[25] Bangladesh	313 (251/62)	Yes (n=62) No (n=251)	Prospective multicenter cross-sectional study	4 weeks following recovery.	Arthralgia (0.6%) Mild body ache (0.3%) Back pain (0.3%)	Not available	Not available	Not available
Moradian et al (2020)[97] Iran	200 (160/40)	Yes	Cross-sectional study	6 weeks after discharge	Myalgia 8%	Not available	Not available	Not available
Moreno-Perez et al (2021)[98] Spain	277 (146/131)	Severe (hospitalized) Mild (hospital follow-up)	Prospective covid study	8–12 weeks	Myalgias-arthralgias 19.6%	Not available	Not available	Not available
Ong et al (2021)[66] Singapore	288 (243/45)	Yes	Prospective longitudinal multicenter cohort study	4 weeks, 12 weeks, and 25 weeks post-symptom onset	Myalgia at 12 weeks or 25 weeks (22.7%)	Not available	Not available	Not available
Stavem et al (2021)[99] Norway	451 (198/253)	No	Cross-sectional study	6–26 weeks after symptom onset	Arthralgia (9%) Myalgia (8.5%)	Not available	Not available	Not available
Sykes et al (2021)[42] UK	134 (88/46) Ward-based n=107 ICU n=27	Yes	Cross-sectional study	Median of 16 weeks	Myalgia Total 51.5% Ward-based 49.5% ICU 59.3%	Not available	Not available	Not available
Taquet et al (2021)[40] USA	273,618 (121,461/ 152,157)	No	Retrospective cohort study	From 1 day to 26 weeks post-diagnosis From 13 weeks to 26 weeks post-diagnosis	Myalgia From 1 day to 26 weeks (3.24%) From 13 weeks to 26 weeks (1.54%) Pain From 1 day to 26 weeks (11.60%) From 13 weeks to 26 weeks (7.19%)	Not available	Females were significantly more likely to have myalgia $^{**}p < 0.01$/Patients with more severe illnesses (as proxied by hospitalization, ITU admission, or leukocytosis) were less likely to have myalgia/myalgia was more common in women and in younger patients, and notably so in those who had been less acutely ill	Not available

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Table 2 (Continued).

Author, Year Country	Sample Size (Male/ Female)	Hospitalization	Type of Study	Time Point(s)	MSK Pain Type and Prevalence at Follow-Up (s)	Pain Characterizations and Location	Risk Factors	Hypothesized Mechanisms
Venturelli et al (2021)[100] Italy	767 (515/252)	Yes	Cross-sectional study	Median of 11.5 weeks after discharge	Myalgia Female (3.6%) Male (3.9%) Chest pain Female (3.6%) Male (2.9%)	Not available	Not available	Not available
Wahlgren et al (2022)[29] Sweden	158 (97/61)	Yes	Descriptive ambidirectional cohort study	21 weeks	Pain (34.8%) Neuropathic type pain (5.1%) Nociceptive type pain (31.0%) Headache (17.7%) Pain in extremities (10.1%) Generalized pain (3.8%) Trunk (2.5%)	34.8% reported new or aggravated pain. Nociceptive-type pain was considerably more common than neuropathic-type pain For nociceptive pain, headache was the most common pain localization.	Not available	Not available
Xiong et al (2021)[101] China	538 (245/293)	Yes	Retrospective cohort study	12 weeks	Arthralgia 7.6% Myalgia 4.5% Chest pain 12.3%	Not available	Not available	Not available
Zhou et al (2021)[102] China	89 (46/43)	Yes	Longitudinal study	3 weeks after discharge	Myalgia and arthralgia (2.2%)	Not available	Not available	Not available

Risk Factors

Only 6 of the 35 studies reported risk factors associated with the prevalence of MSK symptoms in Long COVID patients.[27,30,31,38–40] Sex differences were found in 3 studies, with females being significantly more likely to report myalgia ($p = 0.022$ in Iqbal et al);[41] $p < 0.01$ in Taquet et al,[40] and arthralgia ($p < 0.05$ in Sykes et al)[42] than males. Two studies reported opposite trends for the association between age and prevalence of MSK pain of different origin, with increasing age associated with increased prevalence of arthralgia ($p < 0.001$ in Iqbal et al),[41] and decreased prevalence of myalgia ($p < 0.05$ in Taquet et al).[40]

Karaarslan et al found no associations with age, sex or length of hospital stay after controlling for other variables.[30] Nevertheless, the study found a statistically significant association between higher body mass index (BMI) and increased risk of presenting persistent arthralgia ($p = 0.012$) and myalgia ($p = 0.015$),[30] consistent with the findings by Sykes et al ($p = 0.012$ for myalgia).[42]

The 2 studies investigating the severity of acute COVID-19 illness (as indicated by admission to ICU) showed contradicting findings: Leite et al found that admission to ICU related to higher prevalence of pain at 1 month after hospitalization,[34] whereas Taquet et al found a lower prevalence of myalgia at 6 months.[40] The presence of myalgia at hospital admission or acute COVID-19 infection onset was identified as a risk factor for MSK pain in Long COVID patients by Fernández-de-las-Peñas et al, with 42.5% of those with myalgia during acute phase reporting Long COVID MSK pain compared to 34.5% of those without myalgia (OR 1.41 95% CI 1.04–1.904, $p = 0.02$).[38] No studies investigated the impact of ethnicity and/or pre-existing conditions on the development of MSK pain after acute COVID-19 infection.

Proposed Pathophysiological Mechanisms

No dedicated mechanistic studies on MSK pain were found in relation to Long COVID. Nevertheless, 2 of the 35 studies proposed underlying mechanisms in reference to research on previous coronavirus outbreaks or inferred knowledge from the basic molecular and cellular mechanisms of SARS-CoV-2 infection.[30,43] Both studies suggested the involvement of virus-induced prolonged inflammatory response, associated pro-inflammatory cytokines and immune cell hyperactivation. Another hypothetical mechanism proposed by the authors was the direct viral entry of cells of the MSK and nervous systems mediated by angiotensin-converting enzyme 2 (ACE2) receptor.[30,43] Fernández-de-las-Peñas et al also proposed the potential role of inflammation- and neurotropic virus-induced neuronal hyperexcitability of peripheral and central nervous systems in promoting MSK nociplastic pain.[38] The authors also mentioned the potential contribution of psychosocial factors.[38] A few studies noted similarities between Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), including common symptoms of fatigue and myalgia, which may be suggestive of common pathological mechanisms.[42,44]

Discussion

This review summarizes current research on the prevalence and characteristics of MSK pain in Long COVID patients, potential risk factors and mechanisms underlying the development of persistent post-COVID MSK symptoms. Evidence supports that MSK pain is common among Long COVID patients, with studies reporting an overall prevalence of from 0.3% to 65.2%. Only a few studies described the characteristic features of MSK pain in Long COVID. To our knowledge, there has been no study so far that has performed a true longitudinal follow-up to understand the progression of MSK pain symptoms. In addition, as far as we are aware, no study is yet to investigate the underlying pathophysiological mechanisms other than proposing plausible hypotheses of direct viral entry, systemic inflammation, central and peripheral sensitization, and psychosocial factors. Female sex, increasing age, higher BMI and severity of acute COVID-19 illness were identified as potential risk factors in some studies. The current literature mostly used a cross-sectional approach to investigate the sequelae of COVID-19. Future studies need to focus on longitudinal assessment of MSK pain in Long COVID patients at multiple time points after the acute phase of infection. The repeated-measures design of longitudinal studies will facilitate monitoring and evaluation of the natural progression of MSK pain in Long COVID highlighting whether pain symptoms improve, worsen, or remain the same over time. It is important to also capture the fluctuations in the symptoms as Long COVID is recognized as a relapsing and remitting condition with a protracted course.[12]

It will be useful to determine whether Long COVID MSK pain symptoms evolve into a chronic pain syndrome, a condition characterized by sustained or recurring pain persisting beyond 3 months as defined by the World Health Organization (2018).[45] An increasing number of studies have reported similarities between the clinical presentation of Long COVID and that of known chronic pain syndromes.[42,44] For instance, a significant proportion of Long COVID patients have been found to meet the diagnostic criteria for fibromyalgia.[46] Although fibromyalgia remains a poorly understood condition that lacks effective treatment, these similarities may point to common pathophysiological mechanisms and inform potential therapeutic strategies for MSK pain in Long COVID. Commonly recommended strategies for fibromyalgia combine pharmacological, physical and psychological therapies in a multidisciplinary approach. Advances in the scientific understanding of Long COVID MSK pain may have applicability to those suffering from fibromyalgia and other syndromes that share similarities with Long COVID, such as ME/CFS.

Determining the mechanisms involved in the etiology of MSK pain in Long COVID is a key step in identifying potential biomarkers for targeted therapeutic interventions. There is evidence to support the hypotheses raised by the authors of some studies included in this review. Cells of the MSK and nervous systems, such as skeletal muscle cells and sensory neurons, are known to express ACE2,[47] thus suggesting they are prone to direct SARS-CoV-2-induced damage. Muus et al showed that the expression of mRNA ACE2 in skeletal muscle tissue is higher in females than in males due to differences in fat percentage, which may contribute to the sex differences observed in MSK pain prevalence.[48] Nevertheless, evidence of direct skeletal muscle viral entry is rare and still controversial with few postmortem studies reporting low levels[49,50] or absence[51,52] of viral SARS-CoV-2 RNA in skeletal muscle autopsy tissue. Hooper et al suggested that muscle injury in COVID-19 is more likely to be a secondary outcome of damage to skeletal muscle microvasculature rather than direct invasion into myocytes.[53]

Serum levels of creatinine kinase, a marker of muscle damage, are increased in COVID-19, particularly in patients that present with myalgia symptoms suggestive of elements of muscle injury contributing to muscle pain.[54–56] Indirect laboratory findings of muscle damage have been confirmed by histological and histochemical examination of skeletal muscle tissue obtained from autopsy of COVID-19-infected patients. The studies detected pathological features consistent with myopathies, as well as indications of peripheral neuropathic changes in some cases.[51,52,57] These findings were further corroborated by electromyography and nerve conduction studies.[58,59] For instance, a recent study evaluating 17 patients with Long COVID for peripheral neuropathy confirmed small-fiber neuropathy diagnosis in most of the patients in this group.[60] Myopathy and peripheral neuropathy could also contribute to myalgia and neuropathic pain in Long COVID.

SARS-CoV-2 is known to elicit an extensive inflammatory response marked by a so-called cytokine storm.[61–65] Ong et al reported that the abnormally elevated levels of proinflammatory cytokines (including interleukin-1β) persisted at 6 months after symptom onset, even in patients that remained asymptomatic during the acute phase of the disease.[66] Prolonged exposure to proinflammatory mediators, most notably tumor necrosis factor-α, interleukin-6, interleukin-1β and chemokines, is known to promote "peripheral sensitization" and hyperexcitability of nociceptors via interactions with membrane receptors.[67–72] It may also contribute to heightened responsiveness in the spinal cord and higher brain centers involved in pain processing, also referred to as "central sensitisation".[73–75] A self-report study by Goudman et al identified the presence of symptoms indicative of central sensitization in over 70% of recovered COVID-19 patients using the Central Sensitization Inventory (CSI) questionnaire.[76]

Another possible explanation for the development of MSK manifestations of Long COVID not mentioned in the included studies is a process of muscular deconditioning that occurs following long periods of immobility such as bedrest, hospitalization and prolonged periods of inactivity,[7,77–79] although this theory has been challenged as it does not explain long-term MSK symptoms in milder cases of COVID-19 infection.[80]

The presence of emotional stressors in the context of COVID-19 may lead to worsening of pre-existing MSK pain conditions or put individuals at increased risk of developing new-onset MSK pain after acute infection. For example, high levels of anxiety, depression, social isolation, fear and post-traumatic stress symptoms are well documented in pain literature to exacerbate the experience of pain and predispose individuals to pain chronification.[81–83] The contribution of risk factors, such as age, sex, ethnicity, mental health status, comorbidities and others, must be further evaluated in such

a way that they may be predictive of the development of MSK pain or predispose to exacerbation of pre-existing pain following COVID-19 infection. Figure 2 summarizes the hypothesized mechanisms and risk factors of MSK pain in Long COVID.

Although there is evidence to suggest the multifactorial nature of MSK pain in Long COVID, mechanistic studies are needed to confirm the causal relationship between central, peripheral, and psychological factors and MSK pain outcomes in Long COVID. Quantitative sensory testing (QST) protocols can be used to detect sensory alterations that reflect both peripheral and central sensitizations in Long COVID patients.[84] Structural and functional neuroimaging studies (for instance, magnetic resonance imaging, electroencephalography and transcranial magnetic stimulation) can help understand central mechanisms involved in the etiology of Long COVID MSK pain. Mechanistic studies will not only provide novel insights into the pathological processes underlying the development of MSK pain but also allow the identification of targetable biological markers of MSK pain in Long COVID. Early detection of biomarkers may help identify "at risk" patients who are likely to develop MSK pain following COVID-19 infection. This may help inform potential therapeutic interventions to relieve painful symptoms and prevent the development of chronic MSK pain in Long COVID.

Assessing the clinical significance of persistent MSK pain symptoms in Long COVID is crucial to estimate the burden on individuals and evaluate their rehabilitation needs. Studies should explore the severity of MSK symptoms and their impact on quality of life, functional status, and psychological wellbeing. Clinical and research studies must use condition-specific outcome measures that capture all aspects of this novel condition using the WHO International

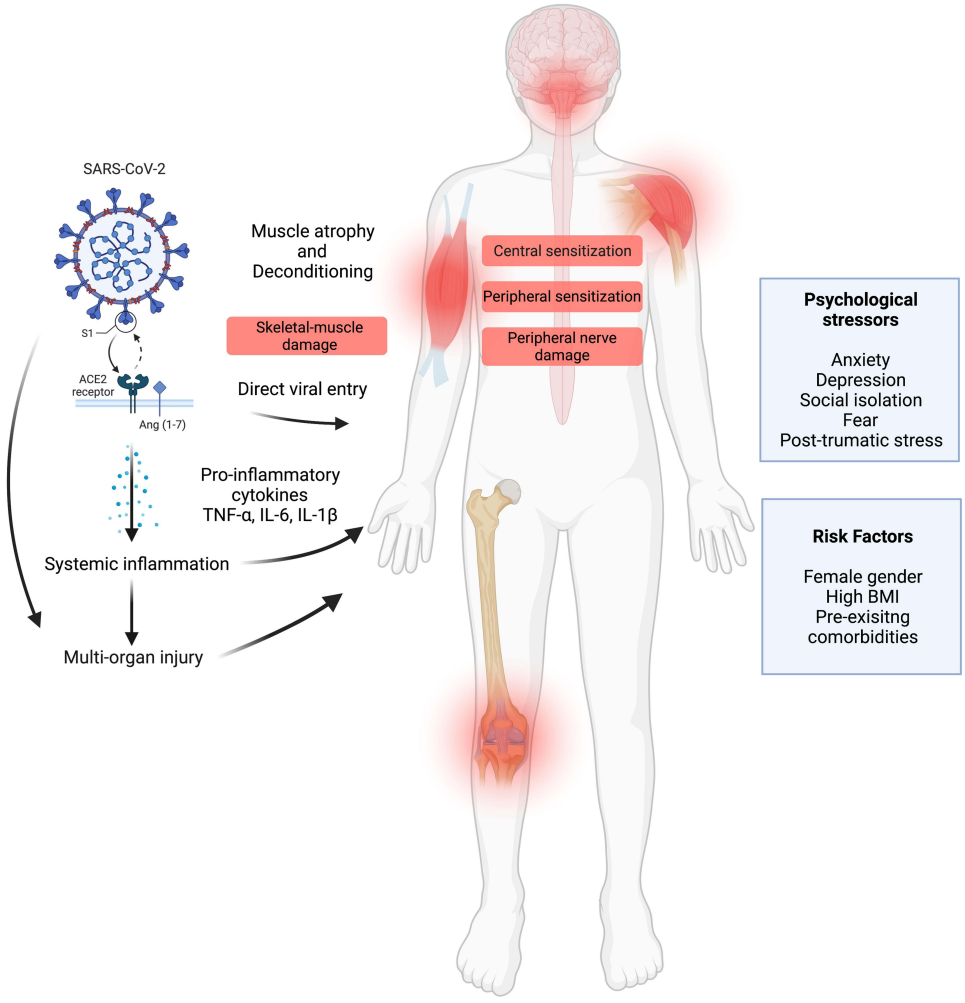

Figure 2 Hypothesized mechanisms and risk factors of MSK pain in Long COVID (Created with BioRender.com).

Classification of Functioning, Disability and Health (ICF) framework as a guide for the selection of measures.[85–88] This will inform clinical decision-making on allocation of resources to provide appropriate care and estimate the cost-effectiveness of the care.

Several limitations to this narrative review need to be acknowledged. The heterogeneity in the methodology of the studies reporting the prevalence of MSK pain in Long COVID made assimilation of findings from the studies challenging. Studies utilized different study designs; some used a prospective cohort method to follow-up patients over time, some used a cross-sectional method, and others used a retrospective design. Moreover, the studies used inconsistent definitions for Long COVID and reported the prevalence of symptoms at different time periods. In addition, most studies required evidence of a positive antigen or polymerase chain reaction (PCR) test resulting in their inclusion criteria. Therefore, the experience of patients who were not tested in the early stages of the pandemic due to the unavailability of the testing programs were not captured in these studies. However, this issue has been overcome in some recent studies that included cases of self-reported Long COVID without confirmatory evidence of COVID-19 infection.

Conclusion

The literature supports that MSK pain is common among Long COVID patients. The currently available literature suggests that MSK pain symptoms in Long COVID may present as localized pain in a particular region or generalized and widespread. Female gender and higher BMI could be potential risk factors for Long COVID MSK pain, with no clear association between age and ethnicity. The literature proposes different plausible pathophysiological mechanisms that contribute to the development of MSK pain in Long COVID including direct viral entry, systemic inflammation, central and peripheral sensitization, and psychosocial factors, although mechanistic studies are still lacking. Much of the current literature on Long COVID pays particular attention to reporting the prevalence alone of persistent MSK pain symptoms. Studies describing the pain features and characteristics are scarce. The longitudinal progression and understanding of the precise mechanisms of MSK pain in Long COVID remains to be properly researched. Further studies are required to fully characterize MSK pain in Long COVID, identify risk factors, study the natural evolution, and investigate the underlying mechanisms to identify targetable biomarkers of MSK pain in Long COVID. Researchers and clinicians should aim to mitigate the long-term burden of chronic MSK pain that seems likely to emerge from Long COVID.

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Disclosure

The authors report no conflicts of interest in this work.

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