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Musculoskeletal Pain and Neuropathic Pain Features Among Individuals with Long COVID and a History of Pain: Characteristics and Impact on Health-Related Quality of Life

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Abstract

Background: Post-COVID-19 syndrome or Long COVID (LC) is a multi-system condition characterised by persistent symptoms beyond three months following SARS-CoV-2 infection. Pain, particularly musculoskeletal and neuropathic pain, is commonly reported and may substantially affect functioning and health-related quality of life (HRQoL). However, there is limited detailed characterisation of pain phenotypes and their differential impact on outcomes in LC. This study aimed to (i) characterise pain associated with LC, (ii) identify factors associated with pain type and severity, and (iii) examine its impact on HRQoL, physical activity, and work. **Methods:** A cross-sectional survey was conducted among adults with clinician-diagnosed or self-reported LC who reported current or previous joint, muscle, or nerve pain. Participants completed validated patient-reported outcome measures including the C19-YRS, Nordic Musculoskeletal Questionnaire, Pain Detect Questionnaire (PD-Q), Musculoskeletal Health Questionnaire, and EQ-5D-5L. Participants were classified into neuropathic, nociceptive, or ambiguous pain groups based on PD-Q scores. Descriptive analyses, group comparisons, and backward stepwise ordinary least squares regression were used to examine factors associated with overall pain (PD-Q Total). **Results:** Among 198 participants (73% female; mean age 52 ± 12.7 years; mean LC duration 2.4 years), 96% reported new or worsened pain following COVID-19 infection, with muscle pain (87%), joint pain (84%), and nerve pain (66%) most frequently reported. PD-Q scores suggestive of neuropathic pain were identified in 28% of participants and were associated with significantly greater pain intensity, symptom burden, functional impairment, and lower HRQoL ($p < 0.05$). These participants reported higher average pain scores across all body regions and greater radiating pain (76%) compared to other groups. Functional disability and anxiety were significant factors associated with pain severity. **Conclusions:** Pain is highly prevalent in LC, with neuropathic pain representing a distinct and more severe phenotype associated with substantial functional and quality-of-life impacts. This study provides novel comparative evidence on pain phenotypes and their differential burden, highlighting the need for targeted pain assessment and management strategies in LC.

Keywords: Long COVID; musculoskeletal pain; nociceptive pain; neuropathic pain; health-related quality of life

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1. Introduction

Post-COVID-19 syndrome or Long COVID (LC) is a multi-organ syndrome defined as a persistence of symptoms around three months after a probable or confirmed SARS-CoV-2 infection and lasting at least 2 months in the absence of alternative diagnoses [1–6]. There are currently more than 2 million individuals with LC in the UK alone and more than 200 million individuals worldwide.

Over 200 symptoms have been reported in LC, the most common ones being fatigue, pain, sleep problems, brain fog, anxiety and depression. Symptoms fluctuate over time in response to physical cognitive and emotional exertion [7,8]. Musculoskeletal (MSK) pain, particularly chronic pain, is a frequently reported symptom in LC [9,10].

Frequently reported body areas affected by MSK pain in people with LC include upper and lower back, followed by peripheral joints (e.g., leg, arm and neck) [10,11]. In addition to MSK pain, there is a growing body of evidence of neuropathic pain developing in LC following the post-acute stage [12]. Estimates for the frequency of neuropathic pain, that is, pain which is a direct consequent of disease (or lesion) affecting the nervous system [13], range from 19% to 34% [11,12,14,15]. Neuropathic pain may manifest as tingling and numbness in joints and limbs [13,16,17] and occurs along with sleep disorders and cognitive impairment (memory and concentration problems) in LC [17]. These pain syndromes may have significant detrimental impact on individuals' health-related quality of life [16].

Whilst previous studies have reported the frequency of MSK and neuropathic pain in LC, there is limited research directly comparing pain phenotypes [17] (neuropathic vs. nociceptive vs. ambiguous) and quantifying their relative impact on symptom burden, function, and health-related quality of life (HRQoL). Furthermore, factors associated with pain severity across these phenotypes remain poorly understood.

A number of predisposing factors have been proposed as being associated with LC-associated pain and specifically neuropathic pain, including female gender [12,18], previous or coexistent depressive symptoms [18,19], previous or coexistent anxiety [18], and elevated body weight [13].

To our knowledge, few studies have directly compared PD-Q-defined pain phenotypes in Long COVID and examined their differential associations with musculoskeletal burden, health-related quality of life, employment outcomes, and symptom severity.

Therefore, the aims of this study were to (i) provide a detailed characterisation of joint, muscle, and nerve pain in LC, (ii) compare pain phenotypes and their associated burden, and (iii) identify factors associated with pain severity and their impact on health-related quality of life and work.

2. Methods

2.1. Data Collection and Ethics

Data were collected as part of the University of Leeds (UK) sponsored study: "Joint, Muscle and Nerve Pain in Patients with long term effects of COVID-19 (Long COVID)" and received Health Research Authority approval on 2 December 2021 by South West Research Ethics Committee (REC) [IRAS ID: 297393; REC Number: 21/SW/0175].

2.2. Participants and Recruitment

A number of recruitment approaches were adopted. Firstly, potential participants already under the care of Leeds Community Health Care (LCHT) with symptoms of LC were contacted via letter from their clinical team outlining the study and inviting them to take part, along with a copy of the patient information sheet (PIS), consent form and questionnaires (see Instruments below).

Secondly, participants newly referred into the LC clinic in LCHT were provided with an outline of the study by their initial assessment appointment. These patients were then provided with a copy of the PIS, consent form and study questionnaire to take away with them.

The third approach involved recruitment directly through social media platforms (e.g., Facebook, Twitter) and via administrators on patient forums (e.g., LC patient forums). The social media posts contained the eligibility criteria for the study along with contact details for the study team. Individuals interested were invited to contact the study team for more information. An invitation letter, PIS, consent form and questionnaire were then sent by post to the potential participant.

The PIS included detailed information regarding the rationale, design and personal implications for the study. Participants (aged 18 or over) with LC (clinician diagnosed or participant self-report of clinician diagnosis) and current or previous joint, nerve, and/or muscle pain which may have been associated with their LC, who were interested in participating in the study were asked to complete the consent form (including an eligibility questionnaire and contact details) and then the study questionnaire.

LC status was based on clinician diagnosis or participant report of clinician diagnosis.

3. Instruments

Participants were asked to provide basic sociodemographic details, including date of birth, gender, ethnicity, details of employment, activity and work-related health before and after COVID-19 and time since LC diagnosis. In addition, participants completed the following instruments.

3.1. C19-YRS

The C19-YRS is an LC-specific patient-reported outcome measure (PROM) [19,20] capturing the symptoms (e.g., breathlessness, fatigue, pain, cognition) and functional disability (e.g., activities of daily living, mobility, personal care) of LC. Items are scored on an 11-point Likert scale (0, no problems to 10 severe problems). Ten symptom items are summed to produce the Symptom Severity (SS) subscale, and five function items form the Functional Disability (FD) subscale. Higher scores indicate greater symptomatology (range 0–100) and functional disability (0–50). Participants rated each item on their current as well as pre-COVID-19 levels. In addition to the domain scores, for each item relating to pain (five items: chest, joint, muscle and abdominal pain as well as headache), participants were also asked whether this was a new symptom post-COVID-19. In addition to this, participants also rated pain severity for each item.

3.2. Nordic Musculoskeletal Questionnaire (NMQ)

The Nordic Musculoskeletal Questionnaire (NMQ) is a standardised questionnaire designed to assess musculoskeletal complaints across body regions [21] and includes a shaded manikin highlighting regions of the body. Participants were asked to indicate (yes or no) which regions they experience trouble (ache, pain or discomfort). For the purposes of this study, the additional items were included alongside the NMQ to determine if the pain was new onset or worse post-COVID-19 (yes/no) and to rate the overall (average) severity of the pain per region in the past week on a 0–10 numerical rating scale (NRS), where 0 is no pain and 10 is pain as bad as it can be.

3.3. Pain Detect (PD-Q)

PainDetect (PD-Q) [22] is a PROM designed primarily to screen for the presence of neuropathic pain. Although originally developed in patients with low back pain, PD-Q has subsequently been applied across a range of chronic pain conditions and has been used in

studies examining post-COVID-19 pain phenotypes [18]. Three items assess current, worst ("strongest") and average pain on a 10-point Likert scale (ranging from 1, "None" to 10, "Maximum"). A single item assesses whether the individual is experiencing radiating pain. Seven additional items are scored on a 6-point descriptive scale (0, "Never" to 5, "Very strongly"); these scores are combined with a further four descriptive scales (persistent pain with slight fluctuations/pain attack and pain attacks with/without pain between them) to derive a score ranging from -1 to 38. A score ≥ 19 indicates the pain is likely to have a neuropathic component. A score ≤ 12 indicates neuropathic pain is unlikely, therefore reflecting other pain mechanisms, e.g., nociceptive pain. A score of 13–18 is considered ambiguous (or reflecting a "possible" neuropathic component). These categories were selected in accordance with established PD-Q scoring recommendations and have been used previously in studies examining pain phenotypes in Long COVID and other chronic pain populations. As PD-Q is a screening rather than diagnostic instrument, the categories should be interpreted as reflecting the likelihood of neuropathic pain features rather than definitive pain mechanisms.

3.4. Musculoskeletal Health Questionnaire (MSK-HQ)

The Musculoskeletal Health Questionnaire MSK-HQ [23] is a brief PROM designed to capture the impact of musculoskeletal conditions (e.g., on daily activities, sleep, symptom management) on those affected. It contains 14 questions scored on a 5-point scale from 'not at all' to 'very severe', with an additional question about physical activity levels in the last week. Higher MSK-HQ scores indicate greater musculoskeletal burden and poorer musculoskeletal health status (range 14 to 70).

3.5. EQ-5D-5L

The EQ-5D-5L is a preference-based measure of health-related quality of life [24]. The instrument comprises five single-item dimensions: Mobility; Self-care; Usual activity; Pain or Discomfort; and Anxiety or Depression. Response categories on each dimension range from 1 (no problems) to 5 (severe problems). These profile scores are converted to health utilities using country-specific value sets. Profile scores in this study were converted using the UK value set (range -0.594 to 1) [25].

3.6. Statistics

Summary statistics were derived consisting of the mean and standard deviation for continuous variables and frequency and percentage for discrete variables. Participants were categorised according to PD-Q scores suggestive of neuropathic pain, unlikely neuropathic pain, or an ambiguous pain phenotype. Summary measures were calculated for the PD-Q, NMQ, MSK-HQ, C19-YRS and EQ-5D-5L by pain group. For the C19-YRS, analyses of the individual pain, fatigue, cognition, anxiety and depression items were also included. Pearson's Chi-squared and Fisher's exact tests were applied for discrete data; continuous data were analysed using Kruskal–Wallis rank sum test for comparisons across pain groups, and Wilcoxon signed-rank tests were applied to evaluate differences pre- and post-COVID-19 (in C19-YRS). Bonferroni post hoc tests were applied to determine subgroup differences. A backward stepwise ordinary least squares (OLS) regression model was applied to evaluate factors associated with overall pain score (PDQ Total), i.e., likely neuropathic pain. Potential factors were identified from the summary analysis (those achieving statistical significance $p < 0.10$) as well as those identified from the literature (e.g., mental health, cognition, fatigue) [12,18,19]. All data were analysed in R Studio (version 2024.12.0).

4. Results

4.1. Participants

A total of 198 respondents (145 females, 73%) participated with a mean age of 52 years (standard deviation, SD: 12.7 years). The majority of participants self-identified as White British, White Irish, or another White ethnic background (96%); 38 (19%) participants had been admitted to hospital for COVID-19, and 7 (4%) had been admitted to intensive care (Table 1). Virtually all participants (97%) reported current comorbidities, with the most frequently reported being anxiety (48%) and depression (39%); 72% were attending healthcare services for their current health problems and 85% were on current medications. The mean duration of LC was 2.4 years (SD = 310 days; 857 days).

Table 1. Sociodemographics, work and activities by pain type (PD-Q).

Characteristic/Pain Type	Overall	Neuropathic [2]	Nociceptive	Unclear
Age [1]	51.8 (12.7)	52.9 (11.3)	51.2 (14.1)	51.8 (11.9)
Gender (n (%))				
Female	145 (73)	45 (82)	51 (65)	49 (77)
Male	49 (25)	8 (15)	28 (35)	13 (20)
Non-binary	3 (1.5)	2 (3.6)	0 (0)	1 (1.6)
Not recorded	1 (0.5)	0 (0)	0 (0)	1 (1.6)
Ethnicity (n (%))				
White—English/ Welsh/Scottish/Northern Irish/ British/Irish/Other	191 (96.4)	52 (94.6)	77 (97.5)	62 (96.9)
Asian/Asian British—Indian	3 (1.5)	2 (3.6)	0 (0)	1 (1.6)
Mixed/Multiple ethnic groups	3 (1.5)	1 (1.8)	1 (1.3)	1 (1.6)
Other	1 (0.5)	0 (0)	1 (1.3)	0 (0)
Co-morbidities (n (%))				
Hypertension (self-reported)	53 (27%)	18 (33%)	21 (27%)	14 (22%)
Diabetes Mellitus	14 (7.1%)	4 (7.3%)	6 (7.6%)	4 (6.3%)
Angina or previous myocardial infarction	4 (2.0%)	1 (1.8%)	1 (1.3%)	2 (3.1%)
Chronic obstructive pulmonary disease	5 (2.5%)	3 (5.5%)	1 (1.3%)	1 (1.6%)
Asthma	43 (22%)	11 (20%)	16 (20%)	16 (25%)
Depression	78 (39%)	30 (55%)	22 (28%)	26 (41%)
Anxiety disorder/symptoms	96 (48%)	31 (56%)	38 (48%)	27 (42%)
Other	97 (49%)	37 (67%)	31 (39%)	29 (45%)
Pre-COVID BMI (kg/m^2) [1]	29.0 (7.5)	31.5 (9.0)	27.9 (6.7)	28.0 (6.6)
Post-COVID BMI (kg/m^2) [1]	29.9 (7.6)	32.0 (8.4)	29.1 (7.2)	29.0 (7.2)
Duration LC (days) [1]	856.7 (310.0)	890.9 (317.6)	806.8 (300.1)	888.6 (312.1)
Hospital admission (Yes) (n (%))	38 (19)	16 (29)	10 (13)	12 (19)
ICU admission (Yes) (n (%))	7 (3.6)	1 (1.8)	4 (5.1)	2 (3.2)
Pre-COVID employment (n (%))				
Full-time	115 (58)	27 (49)	49 (62)	39 (61)
Part-time	53 (27)	17 (31)	19 (24)	17 (27)

Table 1. *Cont.*

Characteristic/Pain Type	Overall	Neuropathic [2]	Nociceptive	Unclear
Retired	14 (7.1)	4 (7.3)	6 (7.6)	4 (6.3)
Unemployed	12 (6.1)	5 (9.1)	3 (3.8)	4 (6.3)
Not recorded	4 (2.0)	2 (3.6)	2 (2.5)	0 (0)
Post-COVID employment (n (%)**)**				
Full-time	52 (26)	8 (15)	23 (29)	21 (33)
Part-time	63 (32)	15 (27)	28 (35)	20 (31)
Retired	35 (18)	10 (18)	13 (16)	12 (19)
Unemployed	41 (21)	18 (33)	12 (15)	11 (17)
Not recorded	7 (3.5)	4 (7.3)	3 (3.8)	0 (0)
Employment change (n (%)**)**				
Yes	119 (60)	39 (71)	38 (48)	42 (66)
No	64 (32)	13 (24)	32 (41)	19 (30)
Not recorded	15 (7.6)	3 (5.5)	9 (11)	3 (4.7)
Pre-COVID Physical activity (n (%)**)**				
Heavy Activity	72 (36)	16 (29)	31 (39)	25 (39)
Moderate activity	109 (55)	32 (58)	40 (51)	37 (58)
Mild Activity	15 (7.6)	6 (11)	7 (8.9)	2 (3.1)
Not active	1 (0.5)	0 (0)	1 (1.3)	0 (0)
Not recorded	1 (0.5)	1 (1.8)	0 (0)	0 (0)
Current Physical activity (n (%)**)**				
Heavy Activity	2 (1.0)	1 (1.8)	0 (0)	1 (1.6)
Moderate activity	31 (16)	5 (9.1)	18 (23)	8 (13)
Mild Activity	115 (58)	31 (56)	46 (58)	38 (59)
Not active	49 (25)	17 (31)	15 (19)	17 (27)
Not recorded	1 (0.5)	1 (1.8)	0 (0)	0 (0)
Future work ability (n (%)**)**				
Relatively certain	45 (23)	4 (7.3)	27 (34)	14 (22)
Not certain	77 (39)	21 (38)	29 (37)	27 (42)
Unlikely	73 (37)	29 (53)	21 (27)	23 (36)
Not recorded	3 (1.5)	1 (1.8)	2 (2.5)	0 (0)
MSKHQ Physical Impact (n (%)**)**				
None	2 (1.0)	0 (0)	2 (2.5)	0 (0)
1 Day	26 (13)	2 (3.6)	20 (25)	4 (6.3)
2 Days	61 (31)	11 (20)	33 (42)	17 (27)
3 Days	72 (36)	22 (40)	22 (28)	28 (44)
4 Days	37 (19)	20 (36)	2 (2.5)	15 (23)

[1] Mean (SD); [2] Suggestive of neuropathic pain Key: LC, Long COVID; ICU, Intensive Care Unit; BMI, Body Mass Index; MSKHQ, Musculoskeletal Health Questionnaire.

4.2. Musculoskeletal and Other Pain: Overall Burden and Affected Areas

All participants registered a high degree of symptom burden on the MSK-HQ (30.3, SD: 10.2) (Table 2). Only two participants (1%) had not experienced MSK pain during the last 3 months or any new and/or worsening pain (NMQ) since their COVID-19 infection (Table 3). This number closely matched the number of participants reporting new (MSK and non-MSK) pain on the individual C19-YRS pain question (N = 190, 96%) (Table 3).

Table 2. Musculoskeletal Health Questionnaire and Pain Detect Questionnaire.

Instrument/Pain Type	Overall	Neuropathic	Nociceptive	Unclear
	N = 198	N = 55	N = 79	N = 64
MSKHQ [1]	30.3 (10.2)	37.7 (7.8)	23.6 (8.6)	32.2 (8.5)
Pain Detect Questionnaire (PDQ)—Total	14.4 (7.5)	23.7 (3.6)	7.1 (3.8)	15.5 (1.8)
Pain now	5.5 (2.4)	7.1 (1.8)	4.1 (2.1)	6.0 (2.0)
Strongest pain	7.8 (1.8)	8.9 (1.3)	6.8 (1.8)	8.1 (1.6)
Average pain	6.1 (2.0)	7.3 (1.5)	5.0 (1.8)	6.5 (1.9)
Radiating pain [2]	121 (61)	42 (76)	29 (37)	50 (78)
PDQ—Pain description [2]				
Pain attacks with pain between them	53 (27)	17 (31)	19 (24)	17 (27)
Pain attacks without pain between them	27 (14)	4 (7.3)	17 (22)	6 (9.4)
Persistent pain with pain attacks	64 (32)	23 (42)	14 (18)	27 (42)
Persistent pain with slight fluctuations	54 (27)	11 (20)	29 (37)	14 (22)

[1] Mean (SD); [2] n (%). Key: MSKHQ, Musculoskeletal Health Questionnaire; PDQ, Pain Detect Questionnaire.

Table 3. C19-YRS pain items by pain group.

C19-YRS Items	Overall	Neuropathic	Nociceptive	Unclear	*p*-Value [2]
	N = 198	N = 55	N = 79	N = 64	
New pain [1]	190 (96)	53 (100)	75 (96)	62 (100)	0.12
Chest pain	111 (56)	33 (67)	40 (57)	38 (63)	0.5
Joint pain	166 (84)	47 (94)	62 (87)	57 (92)	0.4
Nerve pain	130 (66)	45 (87)	37 (52)	48 (80)	<0.001
Muscle pain	173 (87)	50 (100)	66 (92)	57 (92)	0.077
Headache	130 (66)	38 (76)	47 (64)	45 (74)	0.3
Abdominal pain	77 (39)	27 (55)	24 (35)	26 (44)	0.09
Other pain	53 (27)	21 (47)	16 (24)	16 (29)	0.03
Chest pain—worst	21 (11)	7 (13)	8 (10)	6 (9.4)	0.8
Joint pain—worst	86 (43)	23 (42)	31 (39)	32 (50)	0.4
Nerve pain—worst	33 (17)	20 (36)	2 (2.5)	11 (17)	<0.001
Muscle pain—worst	64 (32)	16 (29)	21 (27)	27 (42)	0.12
Headache—worst	24 (12)	8 (15)	11 (14)	5 (7.8)	0.4
Abdominal pain—pain	12 (6)	3 (5.5)	2 (2.5)	7 (11)	0.1
Other pain—worst	12 (6)	5 (9.1)	4 (5.1)	3 (4.7)	0.6

[1] n (%); [2] Fisher's exact test; Pearson's Chi-squared test.

The majority of participants were experiencing joint and muscle pain on all body areas on the NMQ (e.g., "upper back" 62% to "shoulders" 83%) with the exception of "elbow" (38%). This pain or discomfort was described as either new or having worsened in most joints since COVID-19 infection (60–70%), again with the exception of elbow (36%).

In line with these results, the C19-YRS pain items indicated the most commonly reported pain was muscle pain (87%) and joint pain (84%). Nerve pain (65.7%) was also frequently reported and described as the worst pain by 17% of participants. Headache was assessed through the C19-YRS rather than the NMQ because it is not captured by the NMQ body-region framework: 65.7% of participants reported headache, with 12% reporting this as the worst pain (Table 3).

4.3. Levels and Types of Pain

Around 28% of the participants were categorised with scores suggesting neuropathic pain (N = 55); 40% were likely nociceptive pain (N = 79), and 32% were in the ambiguous group (N = 64) on the PD-Q. Musculoskeletal burden (MSK-HQ) was more pronounced in the neuropathic pain group compared to the other two pain groups ($p < 0.05$) (Table 2).

Participants with likely neuropathic pain demonstrated significantly greater musculoskeletal burden (MSK-HQ), with higher mean scores compared to both nociceptive and ambiguous groups ($p < 0.05$).

Participants in the group suggesting neuropathic pain reported higher overall pain on the PDQ ($p < 0.001$), as well as greater levels of current pain ($p < 0.001$), worst pain ($p < 0.001$) and average pain ($p < 0.001$) relative to both the "nociceptive" pain and "ambiguous" groups ($p < 0.05$) (Table 2).

The average pain reported on the NMQ in all joints was also higher for those participants in the likely neuropathic pain group (Table 4). In general, the levels of pain reported on the NMQ were lower than those for the PD-Q.

Table 4. Nordic Musculoskeletal Questionnaire (NMQ).

Pain During Last 3 Months (Yes) (N, %)					Pain New or Worse Since COVID-19 (Yes) (N,%)				Overall Pain Rating by Body Area (Mean, (SD))			
Site/Pain Type	**Overall**	**Neuropathic**	**Nociceptive**	**Unclear**	**Overall**	**Neuropathic**	**Nociceptive**	**Unclear**	**Overall**	**Neuropathic**	**Nociceptive**	**Unclear**
Neck	150 (76)	46 (84)	51 (65)	53 (83)	129 (66)	41 (75)	41 (53)	47 (73)	3.87 (2.98)	5.29 (3.18)	2.68 (2.50)	4.11 (2.78)
Shoulders	163 (83)	53 (96)	56 (71)	54 (86)	140 (72)	47 (85)	44 (57)	49 (78)	4.14 (2.82)	6.02 (2.23)	2.82 (2.54)	4.16 (2.71)
Upper back	123 (62)	43 (78)	37 (47)	43 (68)	110 (56)	38 (69)	30 (39)	42 (67)	3.36 (3.11)	4.96 (3.25)	2.05 (2.52)	3.60 (2.97)
Elbow	74 (38)	28 (52)	22 (28)	24 (39)	68 (36)	26 (49)	20 (27)	22 (35)	1.99 (2.88)	3.17 (3.58)	1.06 (1.89)	2.13 (2.86)
Wrist/hands	148 (76)	49 (89)	45 (58)	54 (86)	136 (70)	44 (80)	41 (55)	51 (81)	4.33 (3.27)	5.80 (3.03)	2.76 (2.97)	5.00 (3.02)
Low back	149 (76)	48 (87)	50 (63)	51 (81)	116 (60)	40 (74)	33 (43)	43 (68)	4.55 (3.38)	6.69 (3.03)	2.92 (3.06)	4.73 (2.97)
Hips/thighs	145 (74)	47 (87)	52 (67)	46 (73)	128 (67)	40 (75)	45 (60)	43 (68)	4.58 (3.29)	6.16 (3.18)	3.38 (2.82)	4.69 (3.37)
Knees	144 (73)	43 (78)	49 (62)	52 (83)	124 (64)	37 (69)	39 (51)	48 (76)	4.20 (3.31)	5.22 (3.60)	2.80 (2.84)	5.10 (2.98)
Ankles/feet	143 (73)	46 (84)	46 (59)	51 (81)	133 (68)	41 (75)	42 (55)	50 (79)	4.13 (3.25)	5.71 (3.32)	2.69 (2.83)	4.52 (2.95)

A majority (61%, N = 121) of participants reported radiating pain with higher levels observed in the neuropathic (42/55, 76%) and ambiguous (50/64, 78%) pain groups (Table 2). Pain was characterised by the potential neuropathic pain group as comprising "pain attacks with pain between attacks" and "persistent pain with pain attacks" (Table 2). This was also

seen in the "ambiguous" pain group. On the other hand, pain was described as persistent with slight fluctuations by 37% of participants with nociceptive pain.

4.4. Employment, Physical Activity and Health-Related Quality of Life

Although a longer duration of LC (2.4 years or 891 days) was observed for participants in the potential neuropathic pain group, this difference was not statistically significant ($p = 0.3$) (Table 1). A majority of participants reported employment changes following COVID-19 (60%), and 76% were either not certain about their future ability to work or felt unlikely to be able to work in the future. The proportion of respondents able to participate in physical activity decreased from 91% (heavy or moderate activity) pre-LC to current levels of 17%, although 44% had undertaken 1–2 days physical activity in the last 7 days (MSK-HQ Physical Impact).

Overall HRQoL on the EQ-5D-5L and EQ-5D VAS (Table 5) was low across all pain groups; however, this was significantly lower for those participants in the potential neuropathic pain group ($p < 0.001$). Overall, low levels of symptom burden and functional disability were reported pre-COVID-19 (Table 4). Participants in the potential neuropathic pain group reported higher levels of symptoms, but these were not statistically different to the other pain groups ($p = 0.3$). The potential neuropathic pain group reported higher functional impairment (FD) pre-COVID-19 which was statistically significant ($p < 0.006$).

Table 5. C19-YRS and EQ-5D.

Pain Type	Overall	Neuropathic [2]	Nociceptive	Unclear
C19-YRS Domains [1]				
Symptom Severity PC	11.08 (11.76)	14.47 (15.81)	9.34 (8.43)	10.18 (10.53)
Symptom Severity Now	48.18 (17.69)	58.52 (17.79)	38.25 (13.69)	51.59 (15.73)
Symptom Severity change	36.80 (19.71)	43.71 (24.53)	28.86 (15.30)	40.68 (16.50)
Functional Disability PC	3.04 (6.81)	5.50 (9.59)	2.03 (4.29)	2.19 (6.06)
Functional Disability Now	25.17 (12.11)	33.00 (11.52)	19.72 (10.41)	25.31 (10.94)
Functional Disability change	22.14 (13.04)	27.50 (15.62)	17.70 (10.64)	23.15 (11.46)
C19-YRS Individual Items				
Pain—PC	1.09 (1.87)	1.51 (2.25)	0.91 (1.62)	0.94 (1.75)
Pain—Now	6.94 (2.38)	8.13 (1.97)	5.85 (2.40)	7.27 (2.11)
Fatigue PC	1.56 (2.37)	1.95 (2.70)	1.30 (2.20)	1.56 (2.25)
Fatigue now	7.58 (2.17)	8.27 (2.38)	6.87 (2.03)	7.86 (1.90)
Cognition PC	0.94 (1.80)	1.36 (2.50)	0.77 (1.39)	0.78 (1.45)
Cognition now	6.46 (2.34)	7.45 (2.04)	5.49 (2.07)	6.80 (2.47)
Anxiety PC	2.01 (2.33)	2.51 (2.64)	1.95 (2.34)	1.64 (1.95)
Anxiety now	5.45 (3.08)	7.11 (2.77)	4.03 (2.93)	5.78 (2.73)
Depression PC	1.56 (2.21)	2.05 (2.64)	1.33 (1.86)	1.43 (2.18)
Depression now	4.52 (3.40)	5.85 (3.35)	3.41 (3.11)	4.76 (3.36)
EQ-5D-5L	0.44 (0.26)	0.24 (0.25)	0.58 (0.21)	0.45 (0.22)
EQ5D VAS	48.09 (20.02)	39.00 (18.21)	54.76 (18.91)	47.66 (19.97)

[1] Mean (SD); [2] Potential neuropathic pain.

As with the subscales, the potential neuropathic pain group also recorded higher levels of pre-COVID-19 pain, cognitive impairment, fatigue, anxiety and depression on the individual C19-YRS items. However, these were not statistically different compared to the other two pain groups.

In terms of current symptoms and functional impairment, large deteriorations (i.e., increased scores) were observed for both the SS ($p < 0.001$) and FD ($p < 0.001$) subscales. Similarly, significant worsening of individual C19-YRS symptoms ($p < 0.001$) was also reported.

Across all pain groups, the potential neuropathic pain group showed significantly higher overall levels of symptoms (SS), functional impairment (FD), as well as greater levels of pain, fatigue, cognitive impairment and mental health problems compared to the other two groups ($p < 0.05$). However, a more granular analysis of the individual cognitive items on the C19-YRS did not reveal any statistically significant differences across the pain groups (Supplementary Table S1).

4.5. Factors Associated with Pain Category and Current Pain Levels

Variables meeting the prespecified inclusion criterion ($p < 0.10$) in univariable analyses were gender, hospital admission, and pre-COVID-19 functional disability. Based on the previous literature, post-COVID-19 BMI, MSK-HQ score, symptom severity, functional disability, anxiety, depression, fatigue, and cognition were additionally entered into the multivariable model. In the final model, current functional disability ($p = 0.03$) and anxiety ($p = 0.02$) were independently associated with higher PD-Q scores. Post-COVID-19 BMI ($p = 0.08$) and previous hospitalisation ($p = 0.07$) demonstrated borderline associations. The model explained 36% of the variance in PD-Q scores.

5. Discussion

The aim of this study was to characterise pain experienced by individuals with LC and its impact on health-related quality of life and work activities.

The results showed that the majority of LC participants in this study had experienced new-onset pain subsequent to their COVID-19 infection. For a significant proportion this involved joint and muscle pain with a consequent high MSK pain burden, supporting previous studies that have evidenced MSK involvement in LC [10]. The shoulder and lower arm were areas where pain was reported as either new or worse since COVID-19 infection for most participants. Two-thirds of participants also reported nerve pain and headache. Both results are in agreement with other studies [11,12,26].

Pain across all measures could best be described as moderate overall. Nevertheless, in line with previously reported frequencies [11,12,14,15], PD-Q scores suggestive of neuropathic pain was identified in over 25% of the respondents. These participants reported significantly higher levels of pain (across all measures) compared to both those in the ambiguous group and, particularly, those participants in the nociceptive pain group. However, it should be noted that although the PD-Q is widely used as a screening tool for neuropathic pain, elevated scores may also reflect nociplastic pain mechanisms and central sensitisation rather than definite neuropathic pathology alone. This may be particularly relevant in LC, where overlapping nociceptive, neuropathic and nociplastic mechanisms are increasingly recognised. However, importantly, PD-Q categories should not be interpreted as representing pure neuropathic or nociceptive mechanisms. Contemporary pain science recognises nociplastic pain as a third mechanistic descriptor arising from altered nociception despite no clear evidence of ongoing tissue damage or somatosensory lesion [27]. Long COVID may involve overlapping nociceptive, neuropathic and nociplastic mechanisms, includ-

ing central sensitisation processes. Consequently, some participants classified as having neuropathic or ambiguous pain phenotypes may also have experienced nociplastic pain.

The relatively high proportion of participants with PD-Q scores suggestive of neuropathic pain may reflect the fact that pain in Long COVID is often considered within broader symptom clusters and may therefore be under-recognised in routine clinical assessment. Furthermore, overlap between nociceptive, neuropathic and nociplastic mechanisms may make classification difficult. Greater awareness and systematic pain phenotyping may improve identification of individuals experiencing more severe symptom burden.

LC was associated with a considerably higher degree of symptom burden (SS) and functional impairment (FD) relative to pre-COVID-19 levels. This was also reflected in greater levels of cognitive impairment, fatigue and mental health problems. Those participants with PDQ scores suggesting neuropathic pain experienced greater symptom burden and dysfunction, which was also evident in the pre-COVID-19 functional disability scores.

There was also a significant impact of MSK pain with a majority of participants with LC having undergone employment changes post-COVID-19, moving from full-time employment as well as becoming unemployed.

Current anxiety levels were associated with higher levels of overall pain, which accords with other studies [13,18,28]. However, unlike previous studies there was no statistically significant association of BMI, sex (female gender), fatigue and cognitive disorders with pain levels [12]. A statistically significant association was nevertheless demonstrated with functional disability. However, it should also be noted that a substantial proportion of participants also reported pre-existing anxiety and depression. These conditions are recognised risk factors for chronic pain development and maintenance and may have contributed to the high symptom burden observed in this cohort.

Finally, the results from the EQ-5D-5L showed very low levels of HRQOL across all groups with health utilities significantly lower than the UK norms for the associated age-group (50–54 years, females 0.798; males, 0.836) [29], highlighting the significant burden of MSK pain and LC on individuals affected.

There are a number of potential limitations, the main one of which is the fact that the participants' responses were entirely reliant on self-report with the additional potential for recall bias; therefore, a LC diagnosis could not be independently verified. Recall periods differ between the instruments (e.g., 7 days for the NMQ and 4 weeks for the PD-Q). This may have potentially impacted on the levels of pain reported by participants on the pain instruments. There was also a large proportion of female respondents, which may have masked the gender effect for neuropathic pain observed in other studies [11]. Furthermore, the sample was predominantly composed of participants from White ethnic backgrounds, limiting the generalisation of results to other ethnicities. Finally, participants were recruited through both clinical services and community-based approaches and therefore may not be representative of the wider Long COVID population. In addition, Long COVID status was based on clinician diagnosis or participant report of clinician diagnosis and could not be independently verified.

The biological mechanisms underpinning neuropathic symptoms in Long COVID remain incompletely understood. Emerging evidence suggests potential involvement of persistent neuroinflammation, blood–brain barrier dysfunction, and direct or indirect effects on cranial and peripheral nerves, including olfactory and trigeminal pathways [30–32]. Recent studies have demonstrated sustained systemic inflammation associated with blood–brain barrier disruption in patients with Long COVID-related cognitive impairment, while neuropathological and neuroimaging studies suggest that neurovascular dysfunction and cranial nerve involvement may contribute to persistent neurological symptoms, including

pain and headache [30–32]. Further research is needed to determine the extent to which these mechanisms contribute to neuropathic pain phenotypes in Long COVID.

6. Conclusions

Amongst individuals with Long COVID and a history of pain, PD-Q scores suggestive of neuropathic pain were associated with greater symptom burden, functional disability, and poorer health-related quality of life than other pain phenotypes. Anxiety and functional disability were independently associated with higher pain scores. These findings support the importance of comprehensive pain assessment in Long COVID and highlight the heterogeneity of pain experiences within this population.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/covid6070118/s1, Table S1. C19-YRS Cognitive Items by Pain Group.

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References

1. National Institute for Health and Care Excellence (NICE). COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19. 2024. Available online: https://www.nice.org.uk/guidance/ng188 (accessed on 29 July 2024).
2. Soriano, J.B.; Murthy, S.; Marshall, J.C.; Relan, P.; Diaz, J.V. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect. Dis.* **2022**, *22*, e102–e107. [CrossRef] [PubMed]
3. World Health Organization (WHO). Available online: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition#: :text=Definition,months%20with%20no%20other%20explanation (accessed on 12 March 2025).
4. Woodrow, M.; Carey, C.; Ziauddeen, N.; Thomas, R.; Akrami, A.; Lutje, V.; Greenwood, D.C.; Alwan, N.A. Systematic Review of the Prevalence of Long COVID. *Open Forum Infect. Dis.* **2023**, *10*, ofad233. [CrossRef] [PubMed] [PubMed Central]
5. Hastie, C.E.; Lowe, D.J.; McAuley, A.; Mills, N.L.; Winter, A.J.; Black, C.; Scott, J.T.; O'dOnnell, C.A.; Blane, D.N.; Browne, S.; et al. True prevalence of long-COVID in a nationwide, population cohort study. *Nat. Commun.* **2023**, *14*, 7892. [CrossRef] [PubMed]
6. Office for National Statistics (ONS). Available online: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/30march2023 (accessed on 9 May 2025).
7. Davis, H.E.; Assaf, G.S.; McCorkell, L.; Wei, H.; Low, R.J.; Re'em, Y.; Redfield, S.; Austin, J.P.; Akrami, A. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *eClinicalMedicine* **2021**, *38*, 101019. [CrossRef] [PubMed]
8. Kerzhner, O.; Berla, E.; Har-Even, M.; Ratmansky, M.; Goor-Aryeh, I. Consistency of inconsistency in long-COVID-19 pain symptoms persistency: A systematic review and meta-analysis. *Pain Pract.* **2024**, *24*, 120–159. [CrossRef] [PubMed]

9. El-Tallawy, S.N.; Perglozzi, J.V.; Ahmed, R.S.; Kaki, A.M.; Nagiub, M.S.; LeQuang, J.K.; Hadarah, M.M. Pain Management in the Post-COVID Era-An Update: A Narrative Review. *Pain Ther.* **2023**, *12*, 423–448. [CrossRef] [PubMed] [PubMed Central]
10. Gümüş, A.S.; Borman, P.; Yaman, A.; Yaşar, E. Neuropathic component of chronic musculoskeletal pain in patients with post-COVID-19: A cross-sectional study. *Arch. Rheumatol.* **2024**, *39*, 436–446. [CrossRef] [PubMed]
11. Zis, P.; Ioannou, C.; Artemiadis, A.; Christodoulou, K.; Kalampokini, S.; Hadjigeorgiou, G.M. Prevalence and Determinants of Chronic Pain Post-COVID; Cross-Sectional Study. *J. Clin. Med.* **2022**, *11*, 5569. [CrossRef] [PubMed]
12. Vu, P.D.; Abdi, S. Post-acute sequelae SARS-CoV-2 infection and neuropathic pain: A narrative review of the literature and future directions. *Pain Manag.* **2025**, *15*, 333–343. [CrossRef] [PubMed]
13. Raja, S.N.; Carr, D.B.; Cohen, M.; Finnerup, N.B.; Flor, H.; Gibson, S.; Keefe, F.J.; Mogil, J.S.; Ringkamp, M.; Sluka, K.A.; et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain* **2020**, *161*, 1976–1982. [CrossRef] [PubMed] [PubMed Central]
14. Williams, L.D.; Zis, P. COVID-19-Related Neuropathic Pain: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2023**, *12*, 1672. [CrossRef] [PubMed]
15. Tabacof, L.; Chiplunkar, M.; Canori, A.; Howard, R.; Wood, J.; Proal, A.; Putrino, D. Distinguishing pain profiles among individuals with long COVID. *Front. Rehabil. Sci.* **2024**, *5*, 1448816. [CrossRef] [PubMed]
16. Ceklarz, J. Symptom intensity of post-COVID and long COVID syndromes in patients entering rehabilitation treatment. *Reumatologia* **2024**, *62*, 18–25. [CrossRef] [PubMed]
17. Fernández-de-Las-Peñas, C.; Nijs, J.; Neblett, R.; Polli, A.; Moens, M.; Goudman, L.; Shekhar Patil, M.; Knaggs, R.D.; Pickering, G.; Arendt-Nielsen, L. Phenotyping Post-COVID Pain as a Nociceptive, Neuropathic, or Nociplastic Pain Condition. *Biomedicines* **2022**, *10*, 2562. [CrossRef] [PubMed]
18. Magdy, R.; Eid, R.A.; Fathy, W.; Abdel-Aziz, M.M.; Ibrahim, R.E.; Yehia, A.; Sheemy, M.S.; Hussein, M. Characteristics and Risk Factors of Persistent Neuropathic Pain in Recovered COVID-19 Patients. *Pain Med.* **2022**, *23*, 774–781. [CrossRef] [PubMed]
19. Sivan, M.; Halpin, S.; Gee, J.; Makower, S.; Parkin, A.; Ross, D.; Horton, M.; O'Connor, R. The self-report version and digital format of the COVID-19 Yorkshire Rehabilitation Scale (C19-YRS) for Long COVID or Post-COVID syndrome assessment and monitoring. *Adv. Clin. Neurosci. Rehab.* **2021**, *20*. [CrossRef]
20. O'COnnor, R.J.; Preston, N.; Parkin, A.; Makower, S.; Ross, D.; Gee, J.; Halpin, S.J.; Horton, M.; Sivan, M. The COVID-19 Yorkshire Rehabilitation Scale (C19-YRS): Application and psychometric analysis in a post-COVID-19 syndrome cohort. *J. M. Virol.* **2022**, *94*, 1027–1034.
21. Dawson, A.P.; Steele, E.J.; Hodges, P.W.; Stewart, S. Development and test-retest reliability of an extended version of the Nordic Musculoskeletal Questionnaire (NMQ-E): A screening instrument for musculoskeletal pain. *J. Pain* **2009**, *10*, 517–526. [CrossRef] [PubMed]
22. Freynhagen, R.; Baron, R.; Gockel, U.; Tölle, T.R. painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. *Curr. Med. Res. Opin.* **2006**, *22*, 1911–1920. [CrossRef] [PubMed]
23. Hill, J.C.; Kang, S.; Benedetto, E.; Myers, H.; Blackburn, S.; Smith, S.; Dunn, K.M.; Hay, E.; Rees, J.; Beard, D.; et al. Development and initial cohort validation of the Arthritis Research UK Musculoskeletal Health Questionnaire (MSK-HQ) for use across musculoskeletal care pathways. *BMJ Open* **2016**, *6*, e012331. [CrossRef] [PubMed]
24. Herdman, M.; Gudex, C.; Lloyd, A.; Janssen, M.; Kind, P.; Parkin, D.; Bonsel, G.; Badia, X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual. Life Res.* **2011**, *20*, 1727–1736. [CrossRef] [PubMed]
25. van Hout, B.; Janssen, M.; Feng, Y.-S.; Kohlmann, T.; Busschbach, J.; Golicki, D.; Lloyd, A.; Scalone, L.; Kind, P.; Pickard, A.S. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* **2012**, *15*, 708–715. [CrossRef] [PubMed]
26. Oguz-Akarsu, E.; Gullu, G.; Kilic, E.; Dinç, Y.; Akdag, G.; Rehber, C.; Karli, N. Beyond the acute: Pain in long COVID survivors at 1.5 years. *Neurol. Sci.* **2024**, *45*, 4109–4117. [CrossRef] [PubMed]
27. Kosek, E.; Clauw, D.; Nijs, J.; Baron, R.; Gilron, I.; Harris, R.E.; Mico, J.A.; Rice, A.S.C.; Sterling, M. Chronic nociplastic pain affecting the musculoskeletal system: Clinical criteria and grading system. *Pain* **2021**, *162*, 2629–2634. [CrossRef] [PubMed]
28. Herrero-Montes, M.; Fernández-de-Las-Peñas, C.; Ferrer-Pargada, D.; Tello-Mena, S.; Cancela-Cilleruelo, I.; Rodríguez-Jiménez, J.; Palacios-Ceña, D.; Parás-Bravo, P. Prevalence of Neuropathic Component in Post-COVID Pain Symptoms in Previously Hospitalized COVID-19 Survivors. *Int. J. Clin. Pract.* **2022**, *2022*, 3532917. [CrossRef] [PubMed]
29. McNamara, S.; Schneider, P.P.; Love-Koh, J.; Doran, T.; Gutacker, N. Quality-Adjusted Life Expectancy Norms for the English Population. *Value Health* **2023**, *26*, 163–169. [CrossRef] [PubMed]
30. Greene, C.; Connolly, R.; Brennan, D.; Laffan, A.; O'keeffe, E.; Zaporojan, L.; O'callaghan, J.; Thomson, B.; Connolly, E.; Argue, R.; et al. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. *Nat. Neurosci.* **2024**, *27*, 421–432. [CrossRef] [PubMed]

31. Kempuraj, D.; Aenlle, K.K.; Cohen, J.; Mathew, A.; Isler, D.; Pangeni, R.P.; Nathanson, L.; Theoharides, T.C.; Klimas, N.G. COVID-19 and Long COVID: Disruption of the Neurovascular Unit, Blood-Brain Barrier, and Tight Junctions. *Neuroscientist* **2024**, *30*, 421–439. [CrossRef] [PubMed]
32. Talkington, G.M.; Kolluru, P.; Gressett, T.E.; Ismael, S.; Meenakshi, U.; Acquarone, M.; Solch-Ottaiano, R.J.; White, A.; Ouvrier, B.; Paré, K.; et al. Neurological sequelae of long COVID: A comprehensive review of diagnostic imaging, underlying mechanisms, and potential therapeutics. *Front. Neurol.* **2024**, *15*, 1465787. [CrossRef] [PubMed]