Received: 16 February 2021 | Revised: 2 December 2021 | Accepted: 4 December 2021

DOI: 10.1002/ejp.1897

ORIGINAL ARTICLE

Characteristics and influence on quality of life of new-onset pain in critical COVID-19 survivors

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Abstract

Background: Pain is a clinical feature of COVID-19, however, data about persistent pain after hospital discharge, especially among ICU survivors is scarce. The aim of this study was to explore the incidence and characteristics of new-onset pain and its impact on Health-Related Quality of Life (HRQoL), and to quantify the presence of mood disorders in critically ill COVID-19 survivors.

Methods: This is a preliminary report of PAIN-COVID trial (NCT04394169) presenting a descriptive analysis in critically ill COVID-19 survivors, following in person interview 1 month after hospital discharge. Pain was assessed using the Brief Pain Inventory, the Douleur Neuropathique 4 questionnaire and the Pain Catastrophizing Scale. HRQoL was evaluated with the EQ 5D/5L, and mood disorders with the Hospital Anxiety and Depression Scale (HADS).

Results: From 27 May to 19 July 2020, 203 patients were consecutively screened for eligibility, and 65 were included in this analysis. Of these, 50.8% patients reported new-onset pain; 38.5% clinically significant pain (numerical rating score ≥3 for average pain intensity); 16.9% neuropathic pain; 4.6% pain catastrophizing thoughts, 44.6% pain in ≥2 body sites and 7.7% widespread pain. Patients with new-onset pain had a worse EQ-VAS and EQ index value ($p < 0.001$). Pain intensity was negatively correlated to both the former (Spearman ρ: −0.546, $p < 0.001$) and the latter (Spearman ρ: −0.387, $p = 0.001$). HADS anxiety and depression values equal or above eight were obtained in 10.8% and 7.7% of patients, respectively.

Conclusion: New-onset pain in critically ill COVID-19 survivors is frequent, and it is associated with a lower HRQoL.

Trial registration No.: NCT04394169. Registered 19 May 2020. https://clinicaltrials.gov/ct2/show/NCT04394169.

Significance: A substantial proportion of severe COVID-19 survivors may develop clinically significant persistent pain, post-intensive care syndrome and chronic ICU-related pain. Given the number of infections worldwide and the unprecedented size of the population of critical illness survivors, providing

Antonio Ojeda and Andrea Calvo first authorship shared.

information about the incidence of new-onset pain, its characteristics, and its influence on the patients' quality of life might help establish and improve pain management strategies.

1 | INTRODUCTION

Long-term physical or mental health status problems are common in critically ill patients after discharge from ICU. In 2012, a new medical term,'post-intensive care syndrome' (PICS), was adopted by the Society of Critical Care Medicine to refer to this entity (Elliott et al., 2014). Currently, survivors 1 year after ICU admission outnumber the deceased by three to one (Brinkman et al., 2013). However, this success has come at the cost of increasing disability and decreasing survivors' quality of life (QoL), which also impacts negatively on caregivers (Cameron et al., 2016; Herridge et al., 2003, 2016; Torres et al., 2017). Critical illness survivors display a high prevalence of moderate to extreme chronic pain, with the latter entailing a significant limitation in work and social activity, and becoming a major cause of disability in Europe (Barbaglia et al., 2017; Baumbach et al., 2016; Mäkinen et al., 2020). Components of the PICS such as depression, anxiety, posttraumatic stress disorder (PTSD) and cognitive impairment are also prevalent in chronic pain. These problems show a bi-directional relationship and have been associated with a worse prognosis (Fishbain et al., 2017; Linton & Bergbom, 2011).

COVID-19 has led to a large number of hospital admissions. As of 5 October 2021 more than 237 million cases of COVID-19 have been reported worldwide (WHO Coronavirus Disease [COVID-19] Dashboard, n.d.), with up to 5% of patients requiring re-admission to the ICU (Ferrando et al., 2020; Hozhabri et al., 2020). Despite this large number of individuals that could be potentially affected by PICS and chronic ICU-related pain, there are no prospective studies to date reporting data on critically ill COVID-19 patients' pain, its characteristics, and its relationship with self-perceived QoL. Moreover, pain is a common symptom after acute COVID-19, and chronic pain could be another consequence of this disease (Carfì et al., 2020; Kemp et al., 2020; Meyer-Frießem et al., 2021). Although scientific evidence is insufficient, prevention and early pain management could improve medium or long-term outcomes, so it is imperative to call for proper identification and management of this condition (Katz et al., 2015; Mills et al., 2019).

The hypothesis was that survivors of critical COVID-19 would often present with pain and display a decrease in self-perceived QoL, as well as an increased incidence of anxiety and depression disorders (Inoue et al., 2019). The aim of the study is to investigate the prevalence and characteristics of new-onset pain in COVID-19 ICU survivors 1 month after hospital discharge. Additional objectives include the assessment of the relationship between new-onset pain and pain intensity with QoL via the Health-related Quality of Life (HRQoL) questionnaire and the quantification of the presence of mood disorders.

2 | METHODS

2.1 | Study design

This is a preliminary descriptive report of an ongoing single-centre clinical trial aiming to assess the efficacy of a combined intervention program to mitigate chronic pain in COVID-19 ICU survivors (NCT04394169). The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (approval number HCB/2020/0549) on 14 May 2020. The study protocol has been submitted for publication (Ojeda et al., 2021). Participants were enrolled 1 month after hospital discharge after giving their written informed consent. All study procedures were performed following the ethical standards of the Declaration of Helsinki. This study followed the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)' statement guidelines for observational cohort studies (von Elm et al., 2007).

2.2 | Study population and data collection

Adult survivors from critically severe COVID-19 infection—confirmed by polymerase chain reaction-based tests on respiratory tract samples—with at least one of the following inclusion criteria were eligible for participation: (i) an Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU admission >14; (ii) an ICU length of stay over 10 days; (iii) ICU-acquired Weakness; (iv) delirium during ICU admission. These criteria were in accordance with those previously recommended for critical illness monitoring and rehabilitation program (Busico et al., 2019); delirium was added as it has been associated with long-term cognitive and functional deficits in multiple studies (Rengel et al., 2019; Sampson et al., 2020). The exclusion criteria were the following: (i) central nervous

system degenerative disease; (ii) terminal illness; (iii) insufficient understanding of the Spanish language; (iv) difficulty in completing follow-up due to a living distance >50 km from the Hospital Clínic of Barcelona; (v) not providing informed consent for the study (for details, see Methods S1).

The site's clinical database allowed identification of all the patients who were discharged from the intensive care units, and those who met the inclusion criteria were recruited.

One month after their discharge from hospital, these patients were contacted via a phone call to check whether they would be interested in participating in this trial and were invited to an introductory interview in which they received information about the study.

After enrolment, a baseline in person interview was conducted by researchers (AC, TC, OC-T, JA, MA) 1 month after hospital discharge. Demographic and socioeconomic data along with medical history—including mental health and chronic pain disorders—were collected. The presence of previous chronic pain was evaluated using the definition proposed by Baumbach et al. (2018): 'more than occasional pain (e.g. short headache/toothache) in the last 4 weeks before ICU admission' (see Methods S1). Information regarding their recent ICU stay also was included. Finally, questionnaires were self-administered to assess pain, QoL and mood disorders (see Methods S1 for demographic and patient characteristics variables definitions).

2.3 | Study definitions and outcomes

2.3.1 | New-onset pain and its characteristics

Pain was evaluated via the Brief Pain Inventory short form questionnaire (BPI-SF) (Cs & Km, 1994) (see Appendix S1). The definition of new onset-pain was an affirmative answer to the first question of the BPI-SF questionnaire: 'Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain?'. If the answer was positive, the Investigator confirmed the presence of new-onset pain after verifying that the pain was not present before admission to ICU or prior to Covid-19 infection. The patients were instructed not to consider acute covid symptoms when asked whether they had pain prior to ICU admission.

Pain location, intensity and interference in daily life activities were registered using the specific BPI-SF questionnaire. Following the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT) recommendations, clinically meaningful pain was defined by a numerical rating score (NRS) ≥3 for average pain intensity (Gewandter et al., 2015). Widespread pain was also assessed (see Methods S1.) Every time new-onset pain was detected, neuropathic pain (NP) and pain catastrophizing were screened and assessed with the Douleur Neuropathique 4 interview questionnaire (DN4-interview) (see Appendix S2) and the Pain Catastrophizing Scale (PCS) (see Appendix S3), respectively (Bouhassira et al., 2005; Darnall et al., 2017). A score ≥30 in the PCS was considered as a clinically relevant level of catastrophizing (Darnall et al., 2017). Once a positive NP screen was obtained, the affected anatomical area was confirmed by the Investigator.

2.3.2 | HRQoL

HRQoL, as assessed by the EQ 5D/5L (Herdman et al., 2011) (see Appendix S4), determines the QoL according to a descriptive system, a visual analogic scale (VAS) and an index value. The descriptive system evaluates five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each scored according to a scale of 1 (no problems) to 5 (extreme problems). Responses are coded as single-digit numbers expressing the severity level selected for each dimension. The digits for the five dimensions can be combined in a 5-digit code that describes the respondent's health state. The VAS measures the patient's perception of their overall current health, from 0—the worst imaginable health—to 100—the best imaginable health. An index value can also be obtained by applying a formula that attaches values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111) (EuroQol Research Foundation, 2019). The index was obtained by using the EQ 5D/5L Index Value Calculator (Developed by the EuroQol Group Version 2.0.) (Van Hout et al., 2012).

2.3.3 | Relationship between new-onset pain and health-related quality of life

The EQ-VAS and index values between individuals presenting with pain and those without pain were compared. The relationship between pain intensity and HRQoL was also assessed.

2.3.4 | Anxiety and depression

The presence of anxiety and/or depression was assessed by the Hospital Anxiety and Depression Scale (HADS)

(Bjelland et al., 2002) (see Appendix S5). According to Bjelland's review, values equal or greater than a cut-off point of 8 were considered abnormal anxiety or depression values (Bjelland et al., 2002). Additionally, the relationship between anxiety, depression, HRQoL, and new-onset pain was also assessed.

2.4 | Statistical analysis

No sample size calculation was carried out for this preliminary analysis. Notably, during this descriptive project analysis, no outcomes for the ongoing clinical trial were assessed. Continuous variables were expressed as median (interquartile range), and categorical variables were presented as numbers (percentages). Missing data were minimal (below 0.5%) and missing observations were not imputed. Comparisons between groups were conducted with either the Fisher or the Mann–Whitney test. Correlations between ordinal variables were analysed with Spearman's Rho without accounting for any order interactions. A threshold of 0.05 was used for statistical significance. All reported tests are two-sided. The R software was used for all the analysis (R Foundation for Statistical Computing).

3 | RESULTS

From 27 May to 19 July 2020, 203 critically ill COVID-19 ICU survivors were consecutively screened; 65 patients were finally included in the study and they completed the questionnaires. These cases belong to the first wave of the COVID-19 pandemic in Spain. Patients´ flowchart is shown in Figure 1. A summary of demographics and characteristics for patients without new-onset pain, patients with new-onset pain, and for both groups are presented in Table 1.

Comparison between 'No pain' and 'New onset pain' patients identified as factors significantly associated with the development of new onset pain among severe COVID-19 survivors: a younger age, a lower Charlson Comobirdity Index Score, a higher SOFA, mechanical ventilation, use of neuromuscular blocking agents and the use of vasopressor therapy (Table 1).

3.1 | New-onset pain and characteristics

Thirty-three (50.8%) patients presented new-onset pain; 25 (38.5%) reported clinically significant pain (NRS ≥3 for average pain intensity); 18 (27.6%) had a BPI-SF intensity score ≥3 and a BPI-SF interference score ≥3; 10 (15.4%)

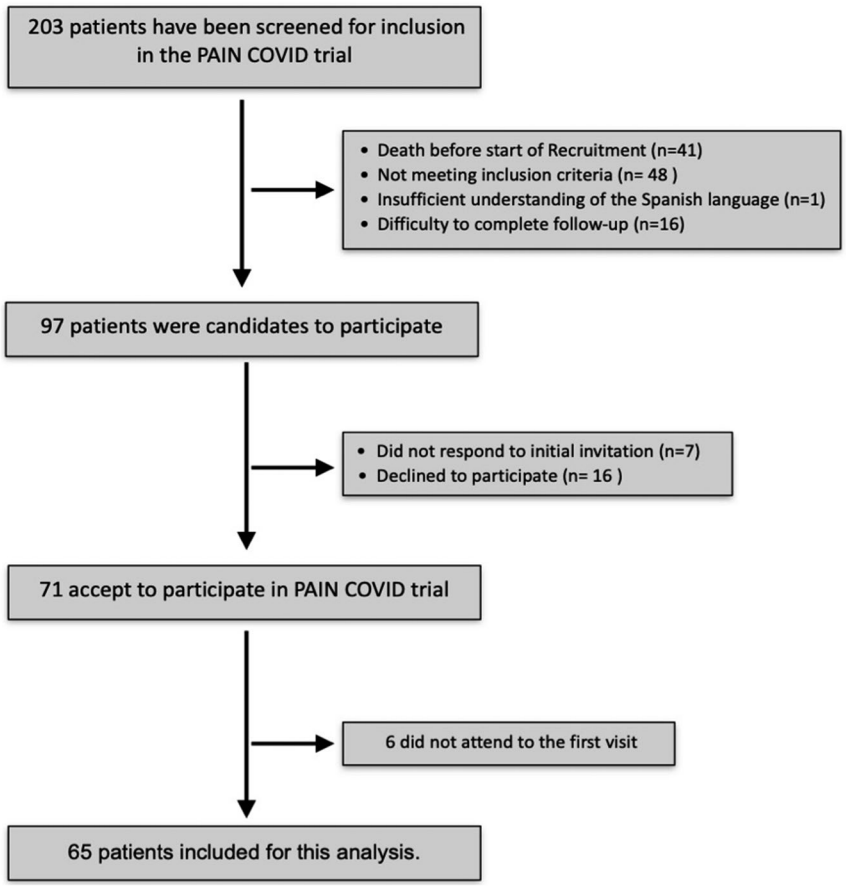

FIGURE 1 Patient inclusion flowchart. Covid-19 ICU Survivors meeting PAIN-COVID trial inclusion/exclusion criteria were contacted before 1 month after hospital discharge. A total of 65 patients were included for the analysis. Difficulty in completing follow-up: home distance over 50 km from the Hospital Clinic of Barcelona

TABLE 1 Summary of demographics and characteristics of patients without new onset pain, with new onset pain, and for both groups (all patients)

Characteristics	All patients ($n = 65$)	No pain ($n = 32$)	New onset pain ($n = 33$)	p value
Age (years)	65 (57–70)	68 (61–76)	60 (55–69)	**0.005**
Male sex	48 (73.8)	25 (78.1)	23 (69.7)	0.574
Current tobacco smoking status	25 (38.5)	11 (34.4)	14 (42.4)	0.612
Body mass index (kg/m^2)	27 (25–31.4)	26.5 (24.9–30.2)	28.3 (25–32)	0.434
History of psychiatric disease	10 (15.4)	4 (12.5)	6 (18.2)	0.733
History of chronic pain	8 (12.3)	2 (6.2)	6 (18.2)	0.258
Opioid tolerance patient	4 (6.2)	0	4 (12.1)	0.114
Barthel Index	100 (95–100)	100 (95–100)	100 (95–100)	0.46
Charlson Comorbidity Index Score	3 (2–4)	3 (2–4)	2 (1–3)	**0.033**
S.O.F.A	5 (3–7)	4 (3–6)	6 (3–8)	**0.043**
A.P.A.C.H.E II	12 (9–15)	12 (10–15.2)	12 (8–15)	0.594
Mechanical ventilation	50 (76.9)	21 (65.6)	29 (87.9)	**0.042**
Mechanical ventilation (days)	15 (9–22)	13 (8–17)	16.5 (10–23.2)	0.161
Tracheostomy	34 (52.3)	13 (40.6)	21 (63.6)	0.084
Use of neuromuscular blocking agents	31 (47.7)	10 (31.2)	21 (63.6)	**0.013**
Non-invasive ventilation	20 (30.8)	12 (37.5)	8 (24.2)	0.29
Hypoxemia >24 h	60 (92.3)	30 (93.8)	30 (90.9)	1
Sepsis	42 (64.6)	18 (56.2)	24 (72.7)	0.2
Vasopressor therapy	49 (75.4)	20 (62.5)	29 (87.9)	**0.023**
Total corticoids dose (mg)	1968 (1267–2700)	881.5 (334–1250)	850 (625–1300)	0.52
Sedation (total days)	15 (9 −20)	14 (9 −18)	17 (10–20.5)	0.213
Acute renal injury	28 (43.1)	10 (31.2)	18 (54.5)	0.08
Replacement renal therapy	5 (7.7)	3 (9.4)	2 (6.1)	0.672
D-Dimerum maximum (ng/ml)	6400 (3400–10,000)	7350 (3700–10,000)	6100 (3300–10,000)	0.59
Ferrityn maximum (ng/ml)	1968 (1267–2700)	1943 (1149.8–2475)	2200 (1267–2900)	0.276
C-reactive protein maximum (mg/dl)	20.3 (12–27)	17.1 (11.3–25.2)	22.0 (17–29)	0.094
Days with increased C-reactive protein	8 (5–18)	6.5 (3.8–14)	8 (5–18)	0.275
LOS $_{ICU}$ (days)	25 (15–33)	19.5 (11.8–30.5)	28 (16–34)	0.203
LOS $_{Hospital}$ (days)	36 (25–47)	33 (23–45.2)	40 (30–50)	0.141
Delirium	25 (38.5)	12 (38.7)	13 (39.4)	1
ICU acquired weakness	41 (63.1)	17 (53.1)	24 (72.7)	0.127
Days after discharge from the ICU	72.5 (63.75–82.75)	67 (62.5–81.5)	78 (65–84)	0.189

Note: Data are in number and proportions (%) for categorical variables and in median and interquartile range (IQR) for continuous variables. Non-invasive ventilation: patients without intubation all along the process. p value refers to the statistical comparison between 'No pain' and 'New onset pain' patients. Bold values are statistically significant values.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; LOS, length of stay; S.O.F.A, Sequential Organ Failure Assessment Score.

patients reported NP, and 3 (4.6%) patients had a clinically relevant level of catastrophizing.

Among those experiencing new-onset pain, median BPI average pain item was 4 (IQR 3–5), median BPI-SF score was 3 (IQR 2–4) for intensity and 3 (IQR 1–5) for interference. Figure 2 shows the BPI average pain item and its self-perceived impact on daily life activities.

3.1.1 | Pain location

Twenty-nine (44.6%) patients reported pain in two or more body locations, and 5 (7.7%) reported widespread pain. Upper extremities were the most affected body location (18 [27.7%] patients), followed by lower extremities (12 [18.5%] patients); 10 (15.4%) patients reported shoulder pain. Figure 3

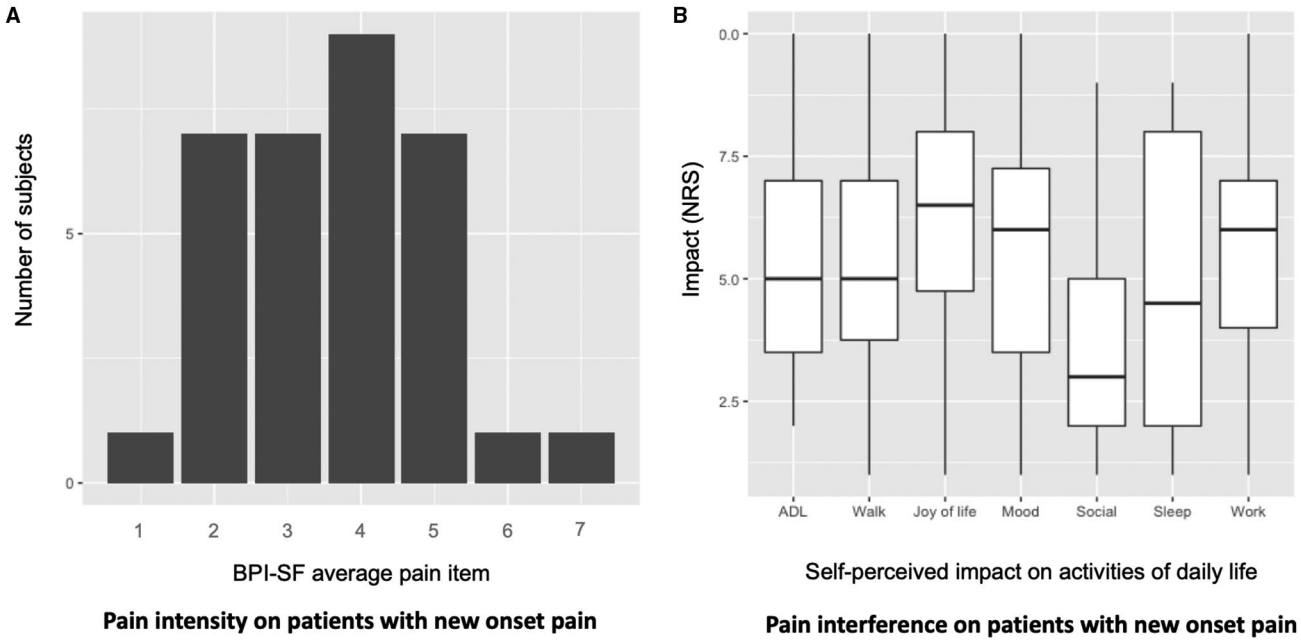

FIGURE 2 Pain intensity and pain interference in daily life activities on those patients with new onset pain. (a) BPI average pain intensity item (0–10) (b) BPI Self-perceived impact on activities of daily life in patients with new-onset pain. The box plots indicate the median interquartile range. ADL, activities of daily life; BPI-SF, Brief pain inventory Short Form; NRS, numeric rating scale

FIGURE 3 Body map of pain locations completed by patients in the BPI-SF. BPI-SF, Brief Pain Inventory Short Form

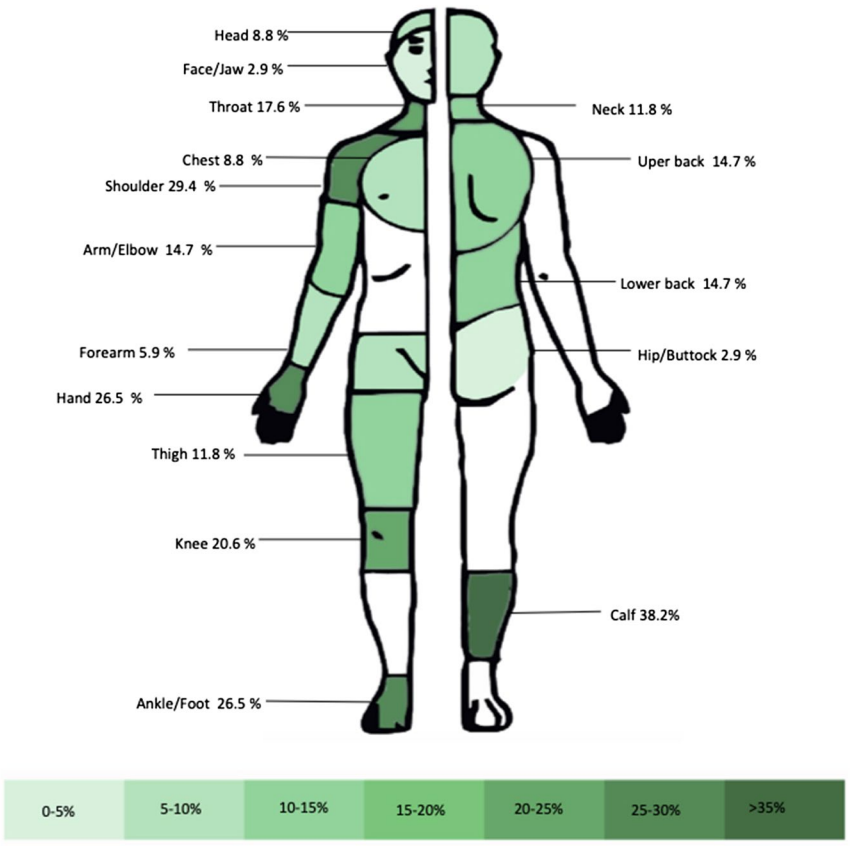

TABLE 2 Chronic pain patients characteristics

Patient ID	3	13	14	23
Age	68	47	60	60
Gender	Male	Female	Male	Male
Previous pain diagnosis	Politopic osteoarthritis: hands, back and knees	Abdominal pain: Polycystic disease	Cervical pain	Postherpetic neuralgia
Psychiatric pathology	None	None	None	None
EQ pain/discomfort dimension	2 (slight problems)	3 (moderate problems)	2 (slight problems)	2 (slight problems)
BPI-SF: first question	No	Yes	Yes	No
New onset pain confirmed by researcher	No	Yes	Yes	No
BPI average pain item	—	5	4	—
BPI intensity score	—	7	3.75	—
BPI interference score	—	7.14	6.29	—
PCS ≥30	—	Yes	Yes	—
DN4 Interview	—	Yes	No	—
HADS anxiety ≥8	Yes	Yes	Yes	No
HADS depression ≥8	Yes	Yes	No	No
Chronic pain worsening	No	No	Yes	No
Observations		*New pain:* myofasial neck and right shoulder girdle pain. Foot and left leg neuropathic pain	*New pain:* mechanical low back pain radiating to lower extremities	

Note: BPI-SF questionnaire first question: 'Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain?'. BPI-SF intensity score: mean of the 4 intensity questions. BPI-SF interference score: mean of the 7 interference questions.

Abbreviations: BPI-SF, Brief Pain Inventory Short Form; DN4, Douleur Neuropathique 4 Questionnaire; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale.

TABLE 3 Neurophatic pain patients characteristics

Patient ID	6	13	17	26	31
Neurophatic pain localization and characteristics	Numbness of the upper right limb	Left foot allodynia	Dysesthesia in both feet	Hyperesthesia left forearm and hand. Right hand paresthesias	Dysesthesias in the right thigh
Age	49	47	77	49	72
Gender	Male	Female	Female	Male	Male
Psychiatric pathology			Depression		
Chronic pain	No	Yes	No	No	No
ICU acquired weakness	No	Yes	Yes	Yes	Yes
EQ 5D Index	0.838	0.378	0.484	0.649	0.818
EQ VAS	90	50	50	85	40
BPI average pain item	4	5	7	2	5
BPI intensity score	4.25	7	4.25	2	4.75
BPI interference score	6.14	7.14	6.57	1	3.86
PCS >30	No	Yes	No	No	No
HADS anxiety ≥8	No	Yes	No	No	No
HADS depression ≥8	No	Yes	Yes	No	No

Note: BPI-SF intensity score: mean of the 4 intensity questions. BPI-SF interference score: mean of the 7 interference questions.

Abbreviations: BPI-SF, Brief Pain Inventory Short Form; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale.

30	41	46	51
54	60	70	71
Female	Female	Female	Male
Quervain tendinitis; heel pain; low back pain; migraine	Right knee osteoarthritis	Migraine	Ankylosing Spondylitis Axial pain Knee and hip osteoarthritis
Major depressive disorder	Major depressive disorder	None	None
3 (moderate problems)	3 (moderate problems)	4 (severe problems)	2 (slight problems)
Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes
5	2	5	4
6	1.5	4	3.5
7	2.75	3.29	1.29
No	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Yes	Yes	Yes	No
New pain: knees, and hands arthralgia, generalized myalgia	*New pain:* left thoracic pain	*New pain:* mechanical neck pain	*New pain:* right feet (decubitus ulcer)

38	43	47	54	69
Right shoulder girdle pain	Left leg and foot hyperesthesia	Bilateral tingling in both feet	Bilateral tingling in both feet	Left leg and foot hyperesthesia
59	69	55	25	54
Male	Male	Male	Male	Female
No	No	No	No	No
Yes	No	Yes	Yes	Yes
0.576	0.818	0.527	0.813	0.549
65	80	50	70	80
3	2	5	3	6
3.5	2	2.5	2	5.75
2.43	1.57	3	1.29	3
No	No	No	No	No
No	No	No	No	No
No	No	No	No	No

shows a body map with the percentage of pain reported in each anatomical area.

3.1.2 | Chronic pain patients

Of the 8 (12.3%) patients who reported previous chronic pain, 6 (9.2%) had new-onset pain, and 4 (6.2%) experienced worsening of their previous chronic pain. The main features of these patients are shown in Table 2.

3.1.3 | Neuropathic pain

Ten of 33 (30%) patients with new-onset pain had a positive screen for NP, the affected areas being: Both feet ($n = 3$), leg and foot ($n = 2$), foot ($n = 1$), thigh ($n = 1$), shoulder girdle ($n = 1$) and upper limb ($n = 1$). Table 3 summarizes the characteristics of these patients. It should be noted that 8 of 10 patients with NP presented ICU-acquired weakness.

3.2 | HRQoL

Only 9 (5.8%) patients reported self-perceived full health status. Median EQ Index Value was 0.8 (IQR 0.57–0.87), and median EQ VAS was 70 (IQR 60–80). (See Table S1 for EQ 5D/5L frequencies and proportions reported for each dimension and level.)

3.3 | New-onset pain and HRQoL

As expected, individuals displaying new-onset pain had a significantly worse EQ VAS (65 [50–75] vs. 80 [69–86], $p < 0.001$). In addition, these individuals showed a worse EQ index value (0.65 [0.55–0.80] vs. 0.87 [0.80–1], $p < 0.001$). Pain intensity was negatively correlated to EQ VAS measurements (Spearman ρ: −0.41, $p < 0.001$) and EQ index value (Spearman ρ: −0.55, $p < 0.001$), as shown in Figure 4.

3.4 | Anxiety and depression disorders

In 7 (10.8%) patients a HADS anxiety value ≥ of 8 was reported, and 5 (7.7%) patients displayed a HADS depression value ≥8. Anxiety was related to a worse HRQoL in the EQ index value (0.49 [0.36–0.63] vs. 0.82 [0.60–0.87], $p = 0.006$), but not in the EQ VAS (60 [45–75] vs. 72 [60–80], $p = 0.19$). Regarding depression, it was related to worse HRQoL both in the EQ index value (50 [40–50] vs. 75 [60–81], $p = 0.007$) and in the EQ VAS (0.42 [0.38–0.48] vs. 0.82 [0.60–0.87], $p = 0.02$).

New-onset pain occurred in 3 of the 7 patients with a HADS anxiety value ≥8 ($p = 0.71$), and in 4 of the 5 patients with a HADS depression value ≥8 ($p = 0.36$).

4 | DISCUSSION

To the best of our knowledge, this is the first study that prospectively assesses the incidence of new-onset pain, its characteristics, and its influence on the QoL in very severe COVID-19 survivors.

Murat et al. exanimated the characteristics of pain in COVID-19 (Murat et al., 2020). However, prospective studies evaluating the incidence and characteristics of persistent pain after infection are non-existent (Meyer-Frießem et al., 2021).

Pain research after COVID-19 is starting, so it is necessary to establish an appropriate terminology. Soares et al. proposed a classification (Pain not related to COVID-19; Pain directly related to COVID-19; and Pain aggravated by COVID-19) (Soares et al., 2021), that could not be adapted to the current study because it could not be assumed that new-onset pain was related to COVID-19 in all patients since it is also frequent in other critical illness survivors (Baumbach et al., 2016; Koster-Brouwer et al., 2020).

Most studies assessing pain in ICU survivors, and after COVID-19, use a subdomain of the QoL scales (Kemp et al., 2019; Taboada et al., 2020). Consensus statement on physical rehabilitation in ICU survivors recommend to assess pain using the VAS (Major et al., 2016). However, given the multidimensional nature of pain, appropriate management will only be achieved after detailed assessment with specific instruments (Bendinger & Plunkett, 2016).

Half of the critical COVID-19 survivors reported new pain in the first month after hospital discharge, and that was frequently associated with a significantly worse QoL.

Studies evaluating new-onset pain in ICU survivors reported an incidence between 18% and 44% (Battle et al., 2013; Baumbach et al., 2016; Koster-Brouwer et al., 2020). In COVID-19 patients, a prevalence of new-onset pain of around 19% had been informed (Caronna et al., 2020; Soares et al., 2021). Comparison of the current results with the previously reported ones is difficult, due to the impossibility to assess chronic pain according to widely used criteria, also because of the short period of time allocated to pain assessment (Treede et al., 2015), and due the characteristics of the study population (severe critical illness survivors).

Despite the study limitations and given the large number of patients that can be affected with this problem worldwide, the authors believe it is essential to report

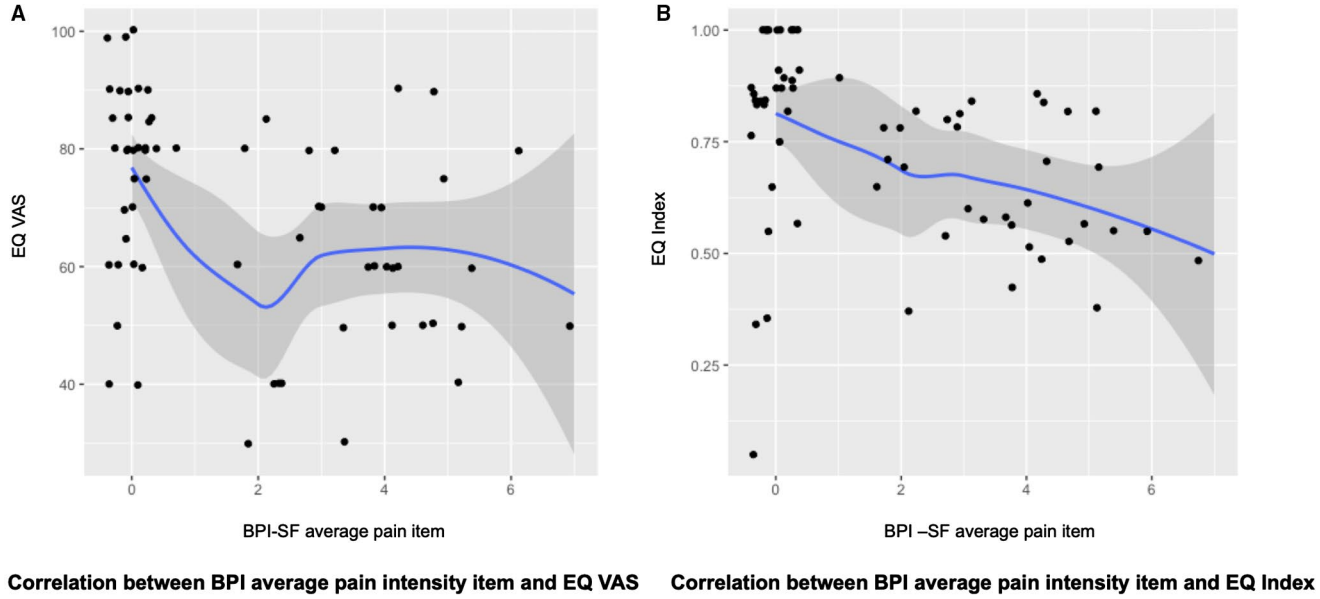

FIGURE 4 New-onset pain and Health Related Quality of Life. (a) Correlation between BPI average pain intensity item and EQ VAS. (b) Correlation between BPI average pain intensity item and EQ Index. BPI-SF, Brief Pain Inventory Short Form; VAS, visual analogue scale

these findings, that also include the identification of factors associated with new onset pain (Table 1).

4.1 | Characteristics of pain

4.1.1 | Severity

38.5% and 75.8% of patients reported clinically significant pain, and new-onset pain respectively. This is a critical finding, because pain intensity is a risk factor to develop chronic pain (Fletcher et al., 2015; Mills et al., 2019).

4.1.2 | Pain location

As it has been observed in non COVID-19 ICU survivors' studies, most subjects with new-onset pain (87.9%) reported pain in multiple body areas. Similarly, shoulder pain was frequently reported (30%) (Battle et al., 2013). The shoulder is susceptible to muscle atrophy resulting from neuromuscular relaxation, corticosteroid therapy, sedation and mechanical ventilation (Koster-Brouwer et al., 2020), implantation of invasive devices in the area (Battle et al., 2013) and/or manoeuvres used to move the patients, often depending on the pressure exerted on the joint (Yachou et al., 2020). Brachial plexus injury during prone positioning for mechanical ventilation has been identified as another potential cause (Guérin et al., 2020). Therefore, a protocol for proning procedures and the identification of pain and functional limitation after patient extubation is desirable (Quick & Brown, 2020). Widespread pain was observed in 15.2% of patients reporting new-onset pain. A chronic fibromyalgia-like symptoms after severe acute respiratory syndrome has been described (Moldofsky & Patcai, 2011), with neuroinflammation being a possible pathophysiological factor. Thus, further studies are needed to demonstrate generalized hyperalgesia (suggesting central sensitization) using quantitative sensory testing (Kemp et al., 2020).

4.1.3 | Neurophatic pain

Thirty percent of patients suffering from new-onset pain had a positive screening for NP. Chronic NP pain has been reported in non-COVID-19 ICU survivors (Baumbach et al., 2017; Koster-Brouwer et al., 2020). Despite the fact that the DN4 questionnaire is only validated for chronic pain patients (Hansson et al., 2019), NP in the early stages is linked with chronic NP development, (Beloeil et al., 2017; Martinez et al., 2012; Searle et al., 2009) and this, in turn, with QoL impairment (Colloca et al., 2017). Thus, early management of this condition is believed to be essential.

Small nerve fiber pathology might present as NP with different patterns (Devigili et al., 2008) and is common in ICU survivors {Citation} (Baumbach et al., 2017; Latronico et al., 2013). Thirty-three percent of patients with NP presented with allodynia or hyperesthesia in one foot and leg, suggesting peroneal nerve injury. Prolonged immobility, muscle atrophy, and contracture can cause peroneal nerve compression (Rubinos & Ruland, 2016). To avoid compression neuropathies, proper patient positioning in bed is crucial (Grigoriadis et al., 2009). Critical

illness polyneuropathy has been previously described (Kemp et al., 2020), and the results of this study showed that 80% of patients with NP had ICU-acquired weakness. Moreover, in our study, 70% of patients with NP reported pain in the lower extremities, suggesting that polyneuropathy may explain a significant proportion of new-onset NP in this population. The presence of unilateral NP in the foot, may suggest the appearance of a mononeuropathy or early stages of a polyneuropathy.

Human coronaviruses are neurotropic, and their association with neuroinflammation and various neurological disorders is well documented (Yachou et al., 2020). Moreover, the COVID-19 virus can trigger a cytokine storm in specific populations, with immediate—but also probably lasting—effects on the nervous system (Wu et al., 2020). Although there are no conclusive data about the persistence of neuroinflammation in COVID-19 survivors, NP could be a manifestation of this process.

4.1.4 | Chronic pain patients

Seventy-five percent of patients with chronic pain had new-onset pain. This finding is in line with previous reports, with chronic pain in another location being an important risk factor for developing new chronic pain. (Mills et al., 2019). However, the use in this study of a chronic pain definition based on the work of Baumbach et al. (2016), which has broader criteria than the IASP definition (Treede et al., 2015), might lead to an overestimation of previous chronic pain incidence.

4.2 | Anxiety and depression

A lower prevalence of anxiety and depression was found in this population when compared to previously documented prevalence in non-COVID-19 ICU survivors at 2 and 3 months after hospital discharge (Davydow et al., 2009; Hatch et al., 2018). Alternatively, patients could develop a post-traumatic growth, defined as positive changes that a person can experience due to struggling with trauma (Tedeschi & Calhoun, 1996). The Polyanna Syndrome, described as being 'blind optimistic' to a bad situation (Sirgy, 2002), could also explain the unexpected low incidence of depression given the survival to the pandemic.

4.3 | HRQoL

The EQ VAS evidenced that they had a better perception of their health status than expected, which could be related to the feeling of being a survivor of the pandemic. Additionally, there is controversy about the impact of ICU-delirium on QoL after hospital discharge (Abelha et al., 2013; Luz et al., 2020). In this study, ICU-delirium was included as inclusion criteria, although not a mandatory one and it might have led to the underestimation of HRQoL scores. However, in our results, patients with ICU-delirium did not show a worse EQ index value compared to patients without ICU-delirium (0.78 [0.54–0.86] vs. 0.8 [0.58–0.88], $p = 0.55$).

4.4 | Correlation of clinically significant pain and HRQoL

Clinically significant pain was correlated with worse HRQoL, and these findings have been described for many pathologies, usually related to an injury as a trigger of pain (Langerud et al., 2018). This association sheds light on the importance of improving the characterization of physical and mental trajectories after ICU admission to provide the best long-term patient care.

4.5 | Limitations

The main limitation of this study is the small size of the cohort from a single centre and the lack of a control group of non-COVID-19 ICU survivors. In addition, this preliminary analysis of the PAIN-COVID cohort trial is purely descriptive and, as sample size was not calculated, some of the results could be unpowered.

Second, PAIN-COVID trial excludes patients with neurodegenerative diseases (Carniglia et al., 2017), and includes patients with ICU-acquired weakness and delirium, which are related to persistent pain, and could have led to an over-estimation of new-onset pain.

Moreover, data were analysed 1 month after hospital discharge and therefore some components of PICS, such as PTSD and new-onset chronic pain, were left out of the analysis. Also, the chronic pain definition used when collecting basal patient characteristics may limit the comparison of this study findings with other studies', and eventually undiagnosed persistent cognitive impairment after ICU-delirium may lead to error when completing the questionnaires.

5 | CONCLUSIONS

In this prospective, observational study, new-onset pain was found to be frequent in critically ill COVID-19 survivors 1 month after hospital discharge. Pain was associated with daily life activity limitations and with a lower

HRQoL. Characteristics of this new-onset pain were also described to help determine the best strategies for managing this healthcare problem in future studies.

ACKNOWLEDGEMENTS

The authors thank the staff of the Pain Unit and the Surgical Intensive Care Unit.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. The study was designed by Dr Ojeda. Preparation, patient recruitment and data collection were performed by Dr Calvo, Dr Cuñat, Dr Comino-Trinidad, Dr Aliaga and Dr Arias. The first draft of the manuscript was written by Dr Ojeda and Dr Calvo, who share the first authorship of this manuscript; all the authors commented on previous versions of the manuscript. Dr Mellado-Artigas performed the data analysis. Dr Dürsteler, Dr Martinez-Pallí and Dr Ferrando reviewed the different contributions of all the authors and contributed to the structure of this manuscript. All the authors read and approved the final manuscript.

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SUPPORTING INFORMATION

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How to cite this article: Ojeda, A., Calvo, A., Cuñat, T., Mellado-Artigas, R., Comino-Trinidad, O., Aliaga, J., Arias, M., Ferrando, C., Martinez-Pallí, G., & Dürsteler, C. (2022). Characteristics and influence on quality of life of new-onset pain in critical COVID-19 survivors. *European Journal of Pain*, 26, 680–694. https://doi.org/10.1002/ejp.1897