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REVIEW ARTICLE

Neuropathic Pain in Critical Covid-19 illness Survivors: A Narrative Review

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ABSTRACT:

Introduction: The COVID-19 pandemic has resulted in a significant number of cases worldwide, leading to a substantial increase in Intensive care unit (ICU) admissions. Survivors of critical illness are known to experience long-term physical, cognitive, and psychological impairments. Chronic pain is also a prevalent complication, and specifically, neuropathic pain (NP) is strongly linked to a diminished quality of life. This narrative review aims to investigate the incidence, causes and manifestations of NP in critical illness COVID survivors.

Methods: A comprehensive search of the Pubmed database was conducted on May 31, 2023, using the keywords "Covid-19" OR "Sars-cov-2" combined with "neuropathic pain" and "critical care" OR "intensive care unit" to identify relevant publications in English or Spanish pertaining to adult human subjects. The search process adhered to the recommended flowchart format outlined in the PRISMA 2020 statement.

Results: The primary search yielded 26 results. Eight results were excluded as they did not pertain to COVID-19 pain.

Discussion: Intensive care survivors can develop new onset pain and chronic pain though various mechanisms. In the case of critical illness COVID-19 survivors, pain may arise due to viral neurotropic potential, immune-mediated reactions, and microvascular complications. Studies have reported new-onset upper extremity NP, with ulnar neuropathy being the most prevalent, followed by brachial plexus, axillary, and median neuropathies. Lower limb NP particularly sciatic neuropathy has also been documented, along with peroneal nerve, meralgia paresthetica, and femoral neuropathy. Cranial neuropathies, such as facial palsy and trigeminal neuralgia, have been observed in case series. Additionally, widespread pain frequently associated with critical illness neuromyopathy may be present. Notably, COVID-19 survivors with critical illness may experience nociplastic pain and conditions related to central sensitization, posing challenges in distinguishing them from those with Long-COVID syndrome.

Conclusion: Further research is crucial to gain a comprehensive understanding of the neurological consequences arising from critical COVID-19 illness. Healthcare professionals should maintain a high suspicion index for NP in this population. Advancing our knowledge of NP in COVID-19 survivors can help develop effective strategies to enhance overall patient outcomes.

Keywords: Critical Care Outcomes, Critical Illness survivors, COVID-19, Neuropathic Pain, Chronic Pain, Post Intensive Care Unit Syndrome

Introduction

COVID-19 pandemic has been a major challenge for healthcare systems all around the world. As of March of 2023, 761 million cases had been reported globally [1]. Before the vaccines, when most of the studies were generated, estimations were that from laboratory confirmed COVID-19 patients, 80% of cases were mild to moderate (including pneumonia and non-pneumonia cases), around 14% severe cases, and 6.1% cases were critical requiring ICU admission [2]. Mortality had been estimated around 1% after the first waves. In vaccinated patients, COVID illness severity and mortality are known to diminish [3]. Despite vaccines have changed the initial situation, last winter COVID-19 was still frequently seen in hospital wards. Even after vaccines became available, there are still survivors to COVID critical illness suffering admission sequelae and in need of medical care [4].

Critical illness survivors from any disease can be affected by the "Post Intensive Care Syndrome" (PICS), a term that was defined in 2012 and accepted by the Critical Care Society for patients that has long-term symptoms after and ICU admission[5,6].
Health-Related Quality of Life (HRQoL) can be significantly impacted in this population and pain has a remarkable incidence [7,8] .

Some viruses are known to be able to produce post infection pain syndrome. It can be caused by direct damage (Human Herpes Virus, e.g.) or by inmunomediated mechanisms. Coronaviruses are known to have neurotropism [9] . Neuropathic pain (NP) is characterized by pain resulting from a lesion or disease of the somatosensory nervous system, which can be confirmed through diagnostic tests. In contrast, nociplastic pain refers to pain that arises from altered nociception, despite the absence of clear evidence of tissue damage or disease affecting the somatosensory system [10].

The concept of "Long COVID" has recently been introduced to define post-acute infection symptoms that persist for at least 3 months after the initial infection, lasting for a minimum of 2 months with either a recurrence of initial symptoms or the development of new ones [11]. These symptoms commonly include chronic fatigue, shortness of breath, brain fog, headache, dizziness, mood, and sleep disturbances, among others. Additionally, chest pain, fatigue, dyspnea, cough, and sputum production are among the most recognized symptoms [12]. Despite evidence of multisystemic alterations, the underlying pathophysiology of this phenomenon remains unclear[13]. Due to Long COVID's vague symptomatic and temporal definition, distinguishing between various causes for continued symptoms in patients can be challenging.

This narrative review aims to synthesize the available data about the incidence, possible causes and factors that can lead critical COVID infection survivors to suffer from NP. For didactical reasons, we divided NP in 3 groups: superior limb pain, lower limb pain, and other types. The focus on NP stems from its well-known impact on HRQoL, particularly when peripheral NP is present[14] . Compared to other types of pain, NP has been associated with higher intensity pain scores, longer pain duration, greater need for pain management, impaired physical function, disrupted sleep, and increased levels of anxiety and depression [15,16,17].

Methods

A literature search was conducted on the Pubmed database using the free text terms "Covid-19" OR "Sars-cov-2" combined with "neuropathic pain" and "critical care" OR "intensive care unit" on May 31, 2023. Relevant Spanish or English publications involving human adults were included. The search results were obtained and presented in Figure 1, following the recommended flowchart format outlined in the PRISMA 2020 statement [18]. Upon analysis of the primary search results, the reference lists were reviewed, and studies deemed relevant were included in the review. Publication type was not used as an exclusion criterion.

Results

The primary search yielded 26 results. Eight search results were excluded as they were not related to COVID-19 pain: three of them focused on trigeminal neuralgia and chronic pain management in the context of the pandemic, the fourth was about herpes zoster neuralgia, and the fifth about discomfort related to wearing facemasks. A study about pathologic role of renin-angiotensin system, another about cutaneous manifestations of COVID-19 and the last one about vaccine-related neuropathies were also excluded. The study designs of the included studies were eight narrative reviews, five case reports or series, three cohort studies, one systematic review, and a preliminary report of a randomized controlled open trial.

Figure 1. Flowchart based on the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) statement.

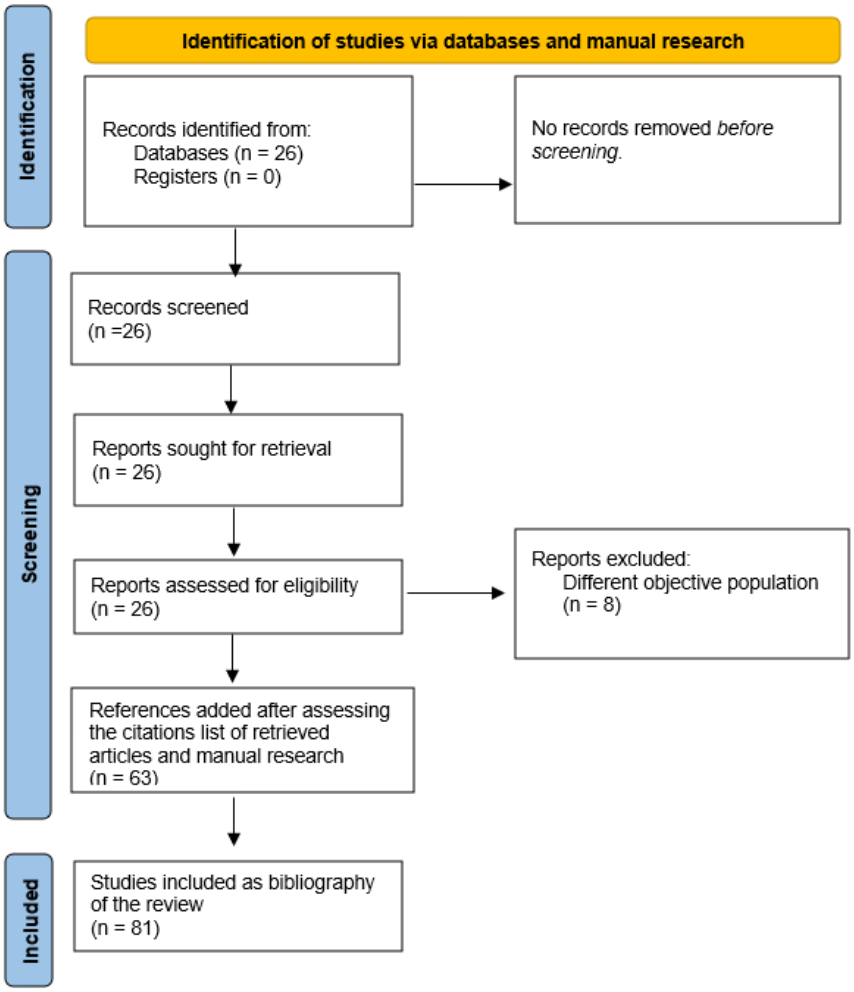


Table 1. Studies found in the primary literature search on the Pubmed database.

Authors	Type of study design	n	Observations
Kemp et al 2020[4]	Editorial / Narrative review	-	Adresses rehabilitation implications of COVID pandemics.
Mitsikostas et al 2022[19]	Narrative review	-	Review of NP including COVID.
Fernandez de las Peñas et al 2022[20]	Narrative review	-	Proposal of an algorithm to phenotype post-covid pain.
Novak et al 2022[13]	Narrative review	-	Reviews COVID multisystemic consequences.
Miller et al 2021[21]	Retrospective case series	15	Case series of brachial plexopathy.
Ojeda et al 2022[22]	Preliminary report of a Randomized controlled trial	65	Multi-disciplinary intervention to impact on pain and mental health on COVID ICU admission survivors.
Guerrero et al 2022[23]	Narrative review	-	Latin american perspective of pain management during COVID pandemics
Meyer-Friessen et al	Narrative review	-	COVID pandemics in Germany and the world,

Authors	Type of study design	n	Observations
2022[24]			narrative review.
Shanthanna et al. 2022[25]	Narrative review	-	Reviews pandemics consequences on chronic pain.
Cohen et al. 2022 [26]	Narrative review		Addresses infectious causality of chronic pain
Petrucci et al 2022[27]	Retrospective cohort	123	Retrospective study describing pain and characteristics at admission and discharge of ICU COVID.
Luchinni et al 2022[28]	Retrospective cohort	96	Describes critical COVID survivors after prone positioning without neuropathy.
Xiong et al 2022[29]	Multicenter retrospective cohort study	917	Describes neurologic symptoms reported on COVID patients. Pain not specifically described.
Bohania et al 2021[30]	Case report and Narrative review	4	Report on cranial neuropathies (2 facial palsy and 2 trigeminal neuropathy).
Mahmood et al. 2022[31]	Case report	1	Peroneal mononeuropathy after severe COVID pneumonia.
Raahimi et al 2020[32]	Case report	1	Gillian Barré after COVID case.
Woltsche et al. 2022[33]	Case report	1	Reports corneal neuropathic pain after non-critical COVID.
Correia et al 2020[34]	Systematic review	409	Reviews neurological manifestations of COVID-19 and other coronaviruses.

Studies of the primary search classified by study design type, number of patients (n) if applicable, and brief description.

Chronic Intensive Care - related pain

Post Intensive Care Syndrome is typically diagnosed based on psychological, cognitive, and physical disturbances [5]. While pain is not a core diagnostic criterion, there is evidence of a higher prevalence of chronic pain in this population [35], ranging from 14% to 77% depending on the specific illness, timeframe and diagnostic tools used for assessment [7]. The term chronic ICU-related pain (CIRP) has been suggested to describe pain that persists for at least 3 months after discharge from the ICU [36]. More than 50% of patients with CIRP may refer moderate to intense pain with high levels of interference in their daily activities. HRQoL is usually lowered in ICU survivors related to all areas of health, and CIRP adds an additional decrement [7]. Although differentiating between worsening chronic pain and new-onset pain is challenging due to unplanned admissions and memory bias, the incidence of the latter has been estimated between 17% and 33%[7,23]. The cohort study conducted by Koster-Brouwer with 1864 ICU survivors shows that half of the patients with newly acquired chronic pain experienced pain with neuropathic characteristics [37].

CHRONIC INTENSIVE CARE - RELATED PAIN ETIOLOGY:

Repetitive noxious stimulation and uncontrolled acute pain can lead to persistent and intense pain, contributing to the development of central sensitization and subsequent CIRP [38,39]. Certain surgical procedures and nerve compression due to factors such as muscle atrophy, immobility, and contracture have also been associated with NP [39–41]. Furthermore, although evidence is contradictory, there is a suggestion that inflammatory states can activate nociceptors, potentially increasing the risk of chronic pain in patients with systemic inflammatory response syndrome (SIRS) [36,42].

ICU acquired weakness (ICUAW) can also lead to various types of pain, including NP, joint-related pain, and contractures [42,43] . ICUAW is a prevalent condition, impacting around half of the individuals who survive an ICU admission for any reason, and can manifest as Critical Illness Neuropathy (CIN), Critical Illness Myopathy (CIM), or a combination of both, referred to as Critical Illness NeuroMyopathy (CINM). Its diagnosis typically involves electrophysiologic tests and muscle or nerve biopsy.

Several risk factors have been identified, including SIRS, multiple organ dysfunction, immobilization, hyperglycemia, sepsis, female sex, prolonged mechanical ventilation, catecholamine infusion [44].

The role of steroids as a risk factor remains controversial, with conflicting evidence [40,45,46]. Furthermore, the prolonged use of neuromuscular blocking agents (infusions longer than 48 hours, especially when coadministered with steroids) and certain antibiotics (such as vancomycin and aminoglycosides) have been associated with an increased risk [40,47]. It is worth noting that tight glycemic control has been shown to have and inverse relationship with the incidence of ICUAW [45]. COVID-19 survivors have shown a higher prevalence CIN compared to non-COVID-19 ICU survivors [48]. The exact cause of this increased incidence is not yet fully understood, but it may be associated with the severity of the disease. In the studied cohort, COVID-19 patients who survived experienced a more severe disease course compared to those without COVID-19 [48]. Additionally, no distinct patterns of CIN have been observed in patients with COVID-19 when compared to individuals admitted to the ICU for other reasons [49]. It is important to mention that COVID-19 patients with ICUAW experience a decline in HRQoL. Zupanc et al conducted a prospective cohort study, including 157 critical COVID survivors diagnosed with CIN or CIM, who underwent a 2-year rehabilitation program. The study assessed HRQoL using the EQ5D questionnaire. Upon admission to the program, the median EQ VAS score was 48. The most reported issues were mobility limitations (96% of patients), followed by difficulties in self-care (87%) and pain or discomfort (54%). Although there was an improvement in HRQOL parameters at discharge (median EQVAS=80), 61% of patients still reported some or extreme problems with mobility, 61% with usual activities, 45% with pain or discomfort, 29% with self-care, and 12% with anxiety or depression [50].

It is also important to note that certain drugs administered in the ICU have been associated with the potential for neurotoxic and myotoxic effects and in the case of critical COVID-19 patients, there are several recognized drugs that carry these risks, including hydroxychloroquine, steroids, tocilizumab, daptomycin, linezolid, clindamycin, and ritonavir [51–53].

Depression, anxiety, post-traumatic stress disorder (PTSD), and cognitive impairment are commonly observed in patients recovering from critical illness[54], as well as in individuals recovering from COVID-19[55]. These issues frequently coexist with chronic pain, exhibit a reciprocal relationship and have been linked to a poorer prognosis [56,57].

The literature about CIRP in COVID-19 critical survivors is limited. A specific meta-analysis of COVID-19 related NP proposes as risk factors for development of NP the treatment with azithromycin, diagnostic of depression, COVID-19 illness severity in hospitalized cohorts, and prone positioning[58].

In a retrospective study by Petrucci et al. examined a cohort of 123 critical COVID-19 survivors and found a high prevalence of pain at discharge, with 96% of patients experiencing pain. Among them, 38% had pain with neuropathic features, either exclusively or in combination with somatic pain. Risk factors associated with pain development were identified, including female sex, cardiologic comorbidity, sedoanalgesia with propofol and remifentanil (compared to propofol and ketamine), and non-invasive ventilation [27]. Ojeda et al. conducted a study to investigate the occurrence of new-onset pain one month after hospital discharge in patients with very severe COVID-19. They found that half of the patients (50.8%) experienced this issue, with 38.5% reporting clinically significant pain intensity (Numeric Rating Scale (NRS) ≥3). The study used the self-reported EQ visual analogue scale (EQ-VAS), ranging from 0 to 100, to assess HRQOL. At the 1-month follow-up, the median EQ-VAS score was 70. Patients with new-onset pain had significantly lower EQ-VAS scores (65 [50–75] vs. 80 [69–86], $p < 0.001$). Additionally, there was an inverse correlation between pain intensity and EQ-VAS scores, indicating that higher pain intensity was associated with lower HRQOL scores [22].

Neurotropic and Neurodamaging potential of COVID-19

The SARS-CoV-2 virus, along with other members of the Coronaviridae family such as MERS-CoV, HCoV-229E and HCoV-OC43 have been found to have neurotropic and neuroinvasive properties in humans[59]. A wide variety of neurological diseases have been related to COVID-19 including encephalitis, encephalopathy, acute cerebrovascular disease, ischemic stroke, polyneuropathy, epileptic seizures, Guillain-Barré syndrome, and others [23]. Different pathologic mechanisms have been proposed.

The spike protein of the SARS-CoV-2 virus has been found to interact with angiotensin-converting enzyme 2 (ACE2) receptors, which are present not only in endothelial cells but also in nervous system cells, including neurons and microglia in the spinal cord[9]. ACE2 receptor has also been identified in

muscle cells, which could explain high myalgia prevalence in COVID-19. For example, a study involving 45 in patients with acute COVID-19 infection reported that 44% experienced myalgias. Plasma Creatin-Kinase (CK) levels were measured, finding elevation in 33% of the patients [60].
Neuropilin-1 (NRP1) is another transmembrane receptor that may facilitate the entry of the virus to the brain from the olfactory epithelium[61]. NRP1 is also expressed in nociceptors such as neurons in the Dorsal Root Ganglia[62,].

Endothelitis provoked by the invasion of the endothelium via ACE2 receptor that leads to elevation of pro-inflammatory cytokines, creates a hyperinflammatory state. This can cause disruption of the blood-brain barrier and intrusion of pro-inflammatory mediators and innate immune cells into the brain[63].

Although there is evidence of neuroinvasive mechanisms associated with the SARS-CoV-2 virus, its presence in cerebrospinal fluid (CSF) has been observed in only a small percentage of cases[63]. Therefore, it has been suggested that although transient neural infection may occur, most of the consequences are likely due to parainfectious phenomena[63]. Inmune mediated processes such as molecular mimicry between viral proteins and neural proteins may also be present [26].

Neurofilament Light Chain (NFL) is a neuronal protein that has shown potential as a biomarker for neurodamage in various neurological conditions. Although its association with peripheral neuropathy requires further investigation, elevated NFL levels have been observed in conditions such as multiple sclerosis, stroke, dementia, and traumatic brain injury [64]. In the case-control study by Magdy et al[65] , patients with post COVID-19 pain exhibited higher serum NFL levels, suggesting its potential as a biomarker for neuropathic pain following COVID-19. These elevated NFL levels were also correlated with positive screening for NP, allodynia, and the intensity of pain. Similarly, in the observational study by Frithiof et al[48], patients who developed CIN showed higher NFL plasma levels during the early phase of ICU, indicating NFL as a potential predictor of neuropathy. Additionally, Glial Fibrillary Acidic Protein (GFAp) plasma levels were measured in this study and also demonstrated a relationship with CIN, suggesting its potential as a neurodamage biomarker [48].

Saif et al. [66] conducted a study involving 400 patients, including those with and without neuromuscular symptoms, and 30 healthy volunteers as controls, to investigate the involvement of peripheral nerves and muscles following COVID-19 infection. The study found significant differences in clinical signs and electrophysiological findings compared to the control group. Risk factors for neuromuscular complications included hospitalization, severe respiratory symptoms, and long-lasting symptoms. These findings indicate that muscle and peripheral nerve problems are common, even in asymptomatic patients, particularly when accompanied by risk factors. However, that the study did not provide information about the severity of the disease, which limits the ability to rule out overlapping symptoms between PICS and COVID-19.

Other studies have also found neuropathy in COVID-19 patients [67] but mainly are case reports, related to Gillian Barré and usually with lower frequency. Peripheral neuropathy incidence, to our knowledge, has not been widely measured [68].

Neuropathic Pain in critical COVID-19 survivors.

Small fiber deficits, which can be identified through temperature sensitivity tests as part of Quantitative Sensory Testing[7,35] or assessed through skin biopsies to evaluate the Intraepidermal Nerve Fiber Density[62] , have been reported in ICU survivors and can potentially manifest as NP. Moreover, it has been demonstrated that neuropathic symptoms and abnormalities in nerve conduction studies could persist for up to five years after discharge from the ICU[69].

In 2017 Baumbach et al.[35], conducted a cross-sectional study were investigated somatosensory functions in critical illness survivors compared to a control group and explored the associations between small fiber deficits, pain, HRQoL, and clinical data. The study included 84 critical illness survivors and 44 controls. The results demonstrated that the patients who had previously experienced critical illness exhibited reduced small fiber functioning, as evidenced by elevated thermal detection thresholds and abnormal thermal testing values. Notably, patients with significant small fiber deficits reported higher levels of pain intensity, pain-related disability, and diminished physical HRQoL[35].

In another study conducted by Koster-Brouwer et al [37]. in 2020, which focused on new-onset CIRP, it was found that 50% of the patients experienced pain predominantly of neuropathic origin, as indicated by a DN4 score equal to or greater than 4. Among these patients, 57% reported multiple affected body sites. Furthermore, pain intensity during the

last week prior to the visit was significantly higher in patients with NP compared to those with nociceptive pain, as measured by the median Visual Analogue Scale (VAS) (5 [IQR, 3–6] vs. 3 [2–5], p = 0.036) and NRS (6 [4–7] vs. 4 [3–6], p = 0.030), respectively[37].

As previously mentioned, human coronaviruses possess the ability to target the nervous system, and extensive research has established their association with neuroinflammation and various neurological disorders[70]. Furthermore, it has been observed that the COVID-19 virus can trigger a cytokine storm in specific populations, leading to immediate effects on the nervous system and potential long-term consequences[71]. While evidence regarding the persistence of neuroinflammation in COVID-19 survivors is currently limited, the presence of NP may potentially serve as an indication of this underlying process.

In a demographic study that examined patients with chronic pain, it was found that 7% of them had NP [16]. Interestingly, although we did not come across a specific comparative study, in individuals who have contracted COVID-19, this prevalence appears to be higher, particularly among patients who were previously hospitalized and now experience new-onset post-COVID pain, reaching nearly 25%. Additionally, the presence of NP has been linked to elevated levels of anxiety and kinesiophobia, which is the fear of movement[72].

In a cohort study by Fernandez de las Peñas et al, 146 post-COVID patients previously hospitalized were evaluated 18.8 ± 1.8 months after discharge using the S-LANSS and PainDETECT questionnaires to assess NP symptoms. The results revealed that 26% of individuals with post-COVID pain exhibited neuropathic symptoms according to the S-LANSS (cut-off ≥ 12 points), while 12.2% displayed likely neuropathic symptoms based on the PainDETECT (cut-off > 18 points). Discrepancies between the questionnaires may be attributed to variations in terminology or specific questions. The study identified an association between the S-LANSS score and symptom duration, as well as weight, suggesting that longer pain duration and higher weight may contribute to the development of NP. The importance of early pain treatment in long-haulers to mitigate the risk of NP symptoms is emphasized, along with the recommendation to incorporate exercise programs as part of a multimodal therapeutic approach for long-COVID patients. However, it should be noted that the study had limitations, including the absence of electrophysiological tests to diagnose NP, the inclusion of a range of severity levels but excluding ICU patients, and the lack of collection of clinical measurements during hospitalization[73].

A positive screening for NP was found in 30% of severe COVID-19 survivors experiencing new-onset pain. Among those with NP, 33% exhibited allodynia or hyperesthesia in one foot and leg, indicating possible peroneal nerve injury. Peroneal nerve compression can occur due to factors such as prolonged immobility, muscle atrophy, and contracture[22].

In COVID-19 survivors, pain has been observed to be more common in joints (27%), along with occurrences in the thorax, myalgia, and headache [74].

In patients affected by PICS following mixed-cause ICU admissions, chronic pain was reported to be most prevalent in the shoulders (22%), followed by the lower limbs, lumbar spine, and cervical spine[7]. However, there is a lack of studies specifically describing pain location in critical illness COVID-19 survivors. The PAINCOVID study indicated that after a one-month follow-up, the most frequent location of pain was in the upper limbs (27% of total patients), followed by the lower limbs (18%) and shoulders (15%). Furthermore, 47% of patients reported pain in multiple sites[22].

In Long-COVID, which can be a confounding condition, a wide range of symptoms is reported, including general pain, myalgias, and arthralgias, with a duration of 3-6 months. Meta-analysis and Systematic reviews studies on Long-COVID usually do not differentiate patients based on severity[58,75]. A meta-analysis found higher prevalence of anxiety, depression, sleep disturbances and fatigue in cohorts with >20% ICU admission population compared to cohorts with <20% ICU admission[76].

For didactic purposes we organized the evidence found in 3 groups: Superior limb NP, lower limb NP, and other types of pain.

SUPERIOR LIMB NEUROPATHIC PAIN

Superior limb neuropathies have been documented in various studies, primarily consisting of case series and case reports. A retrospective cohort study conducted in the UK[21] examined ICU COVID-19 survivors. Among 256 ICU patients during the first wave, 114 individuals required prone positioning, and 15 of them were diagnosed with peripheral nerve injuries in the upper limb. The prone positioning was performed in accordance with the Faculty of Intensive Care Guidelines, involving 2-hourly changes and 16-hour pronation sessions. Among the 15 patients, three had evidence of glenohumeral joint dislocation, potentially related to axillary nerve and medial cord injuries. A total of 30 anatomical nerve injuries were identified, with

the ulnar nerve being the most frequently affected (46.6% of nerve injuries), commonly at the cubital tunnel, followed by injuries to the brachial plexus cords (33.3%), most frequently at the infraclavicular level. All patients reported NP and motor weakness, with most diagnosed neuropathies classified as high grade, while the remainder were categorized as intermediate grade. It is possible that lower grade injuries may be underdiagnosed, mistaken for, or missed as CINM.

Another case series by Malik et al.[77] focused on patients admitted to a rehabilitation hospital in the UK. Among 83 survivors of COVID-19 acute respiratory distress syndrome (ARDS) who were admitted, 12 patients (14.5%) were diagnosed with peripheral nerve injuries, with all but one having a history of prone positioning. A total of 21 nerve injuries were identified, with 71.6% occurring in the upper limb. The ulnar nerve was the most affected (28.6%), followed by the radial nerve (14.3%), sciatic nerve (14.3%), brachial plexus (9.5%), and median nerve (9.5%). However, the study did not provide information about the total population of critical COVID-19 illness admissions, making it impossible to calculate the incidence of neuropathies.

Li et al.[78] conducted a case series of upper limb neuropathy in COVID-19 patients who required mechanical ventilation. Among the 11 described patients, the most frequent injury was pan-plexopathy (45%), followed by incomplete plexopathy. Notably, only 54% of the patients required prone positioning. A majority (81%) of patients with neuropathy reported NP.

Michaelson et al. [79] described 25 cases referred to a rehabilitation clinic for weakness or paresthesia. Among the 14 patients diagnosed with neuropathy, four had brachial plexopathy, two of whom had been placed in the prone position. Nerve biopsy in one patient revealed patchy areas of damage and invasion of macrophages. The authors proposed that microthrombi formed on vasa nervorum could lead to nerve ischemia, and COVID-19's impact on endothelial function and blood-nerve barrier disruption, along with reduced levels of ADAMTS-13 protein, may contribute to a procoagulant state.

Young et al. reported a case of a 52-year-old man with a medical history of hypertension and recently diagnosed type 2 diabetes. He was admitted to the ICU for critical COVID-19, required mechanical ventilation, but was not placed in the prone position. The patient developed severe weakness and neuropathic pain in one arm, along with a rash interpreted by dermatologists as COVID-induced thrombotic microvascular injury, which was consistent with previous cases observed at the center. Autoimmunity and vasculitis tests yielded negative results, except for elevated D-dimer levels. MRI revealed plexitis without signs of compression, and no other probable diagnoses were identified. Electromyography showed severe denervation in some fascicles while sparing others on the same nerve trunks, suggesting a microvascular perifascicular infarction caused by COVID-19-related hypercoagulability. Needham et al. also proposed vascular mechanisms as a potential cause for a case series of mononeuritis multiplex in COVID-19 patients [80].

Lucchini et al.[28] reports a cohort of 96 patients who were proned for critical COVID-19 hypoxemia treatment. Opposed to previously described samples, from the 58 patients who were followed-up at 3 months, none of them reported paresthesia or weakness in the upper extremities. Prone positioning was performed with both extremities along the sides of the body, as opposite to the "swimming position", without flexion neither of the shoulder nor the elbow. We understand these results with caution because of probable underdiagnose derived from lost in follow-up of a relevant percent of the sample.

In the PAINCOVID study, pain in the upper extremity was identified as the most common site (27.7%), followed by shoulder pain (15.4%). Two patients reported NP, one in the upper extremity and one in the shoulder area[22].

Although upper limb neuropathies can occur in any patient with respiratory distress requiring prone positioning, there are no comparative studies available to compare COVID-19 with other causes. Needham et al. conducted a case series of critical COVID-19 survivors and found that mononeuritis multiplex was present in 16% of discharged patients, which is a higher incidence than expected in all-cause ICU admissions [80].

As not all patients with neuropathy were placed in prone position, and even patients without neuromuscular symptoms can experience post-COVID neuromuscular impairments, the physiopathology of upper limb neuropathy appears to be multifactorial, involving mechanical and systemic factors.

INFERIOR LIMB NEUROPATHIC PAIN

Inferior limb neuropathy has also been described in critical COVID-19 survivors in multiple studies. Meralgia paresthetica and superficial peroneal nerve neuropathy related to prone positioning were

described in a report of 2 cases, one of them was produced after a single session of 16 hours of prone [81].

The PAINCOVID study described pain in lower extremities at 1 month after discharge in 18.5% of patients with new onset pain. From 10 patients of the cohort that referred new onset pain with neuropathic features 7 of them located it on lower extremities as follows: Both feet (n = 3), leg and foot (n = 2), foot (n = 1) and thigh (n = 1) [22].

The case series discussed below report the presence of lower limb neuropathies, but specific mention of NP as the primary feature is not provided.

Michaelson et al. described four patients with sciatic neuropathy, including one individual with bilateral neuropathy caused by severe rhabdomyolysis leading to gluteal compartment syndrome [79].

In the case series by Malik et al.[77] , twelve patients with nerve injuries were identified, with three of them experiencing sciatic nerve injury, accounting for 14.3% of the patients. Eleven out of the 12 patients were placed in the prone position.

The case series of Malik et al described 12 patients with nerve injuries and 3 of them had sciatic nerve injury, accounting for 14,3% of patients. 11 of the 12 patients were proned for severe ARDS. In the post-ICU COVID case series by Needham [80] that focused on mononeuritis multiplex, eight out of 11 patients had neuropathy in the lower limbs. These patients were referred to a rehabilitation clinic and exhibited weakness related to ICUAW and neuropathy. The findings in these patients differed from the typical findings seen in critical illness neuropathy, displaying clinical and electrophysiological signs of patchy affection, suggesting the presence of a microvascular disruption mechanism.

OTHER TYPES OF PAIN

In addition to peripheral neuropathies affecting the extremities, cranial nerve disorders have also been reported in relation to COVID-19. However, these cranial nerve disorders have not been specifically associated with critical COVID-19 cases [30].

Guillain-Barré Syndrome and its variants, such as cranial neuropathy and Miller-Fisher syndrome, have been reported in association with COVID-19. However, severe pulmonary COVID-19 involvement is not commonly observed in conjunction with these neuropathies. A review by Bohania et al examined cranial neuropathies and found that they can occur at any age and affect various cranial nerves [30]. The most frequently reported cranial neuropathy was facial palsy, followed by trigeminal neuralgia. These conditions typically do not require treatment or can be managed conservatively with steroids, NSAIDs, or intravenous immunoglobulin.

A single case of neuropathic corneal pain was reported in a woman after non-critical COVID illness[33].

Chest pain has also been widely described to occur in post COVID-19 patients and it has also been linked to long-COVID[75]. Although chest-drainages and chronic coughing could derive in intercostal neuropathy, to the best of our knowledge no study has linked intercostal nerve neuropathy as the underlying cause.

Cerebrovascular events are also a risk in COVID patients, which could also lead to NP conditions as central NP, spasticity related, musculoskeletal pain, and headache[24].

Generalized pain is frequently reported as a post-COVID symptom [75] and is also observed in survivors of critical COVID illness. In the PAINCOVID follow-up study at 1 month, it was found that 15% of patients who reported new-onset pain experienced widespread pain [22].

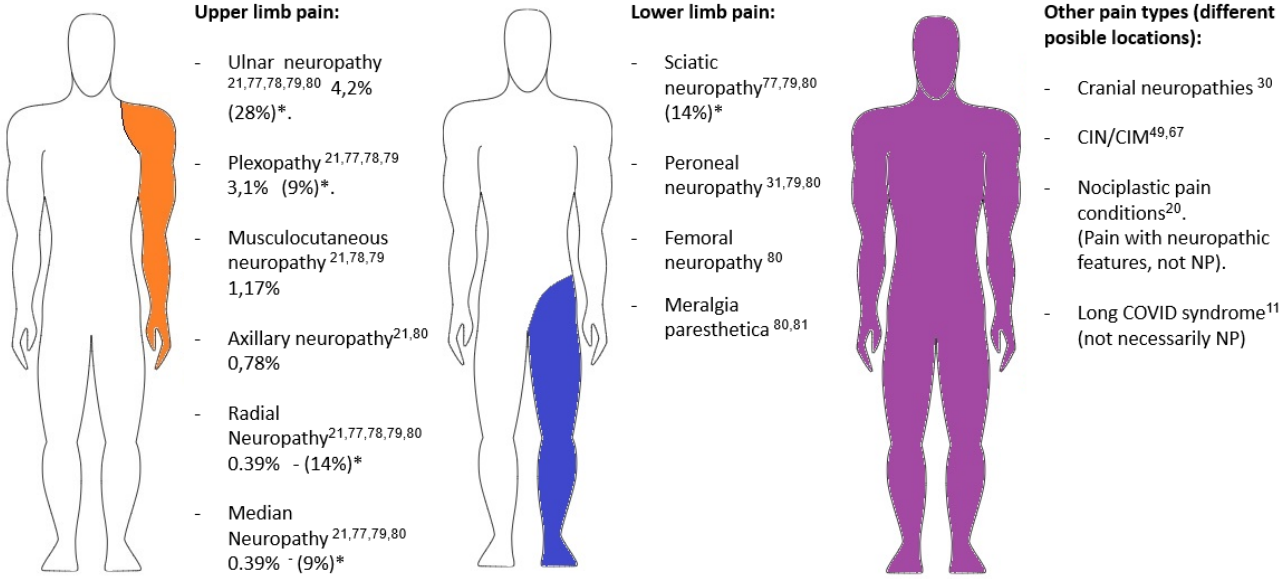
Central sensitization is defined by an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [82].This mechanism may play a role in the development of nociplastic pain and could be associated with the origin of Long-COVID symptoms.

In a cohort study conducted by Fernandez de las Peñas et al., which included 77 patients with new-onset post-COVID pain, high scores on the Central Sensitization Inventory (CSI) were observed in 33% of the participants. These high CSI scores were positively correlated with pain intensity, levels of depression, anxiety, catastrophism, and kinesiophobia. Additionally, 20% of the patients reported experiencing generalized pain[83].

To aid in the differentiation of nociceptive, neuropathic, and nociplastic pain in patients with post-COVID pain, Fernández de las Peñas proposed an algorithm consisting of seven steps [20]. This algorithm involves clinical assessments for allodynia, hyperalgesia, and a history of hypersensitivity to stimuli. Based on the results, pain can be categorized as non-nociplastic, possibly nociplastic, or probably nociplastic. It is important to note that nociplastic pain can coexist with NP, and repetitive stimuli associated with NP may

contribute to central and peripheral sensitization [84], thereby promoting the presence of nociplastic conditions.

Figure 2. Pain locations in critical COVID-19 survivors and frequent causes.



Frequency estimations were conducted using available data. Percentages were calculated based on the case series by Miller et al.[21], which involved counting the number of patients affected by each neuropathy and dividing it by the total number of critical COVID illness admissions to the ICU. Percentages indicated within parentheses and marked with an asterisk (*) were calculated based on the case series by Malik et al.[77], by counting the number of patients affected by each neuropathy and dividing it by the total number of patients admitted to the rehabilitation clinic. The remaining causes were reported in various case series or were not specific to the ICU population.

Conclusion

Critical Illness COVID-19 survivors are at an increased risk of experiencing pain, which can be caused by multiple factors. Nociceptive pain is commonly observed, often affecting joints or the chest. NP is also frequent and can result from CIN or other neuropathies. Nociplastic pain can develop after prolonged exposure to neuropathic or nociceptive pain. It is important to note that these three types of pain can coexist and be correlated within the same patient. Neuropathies following critical COVID illness can have various underlying causes, including systemic hypoxia or hypoperfusion, immune-mediated reactions, local compression, microvascular thrombosis, or toxicity. Direct invasion of the virus is less likely to be the primary cause. Proper management during prone positioning during mechanical ventilation is crucial to prevent local nerve compression or stretching, which could lead to neural damage[77,81].

A comprehensive assessment of pain factors, type of pain, potential underlying causes, secondary symptoms, and sensitivity impairments is important. Electrophysiological studies, muscle and nerve biopsy, skin biopsy, and blood tests should be used to rule out secondary causes and differentiate CIN/CIM or neuropathy. Psychological tests and assessment of HRQoL are also important, as comorbidity plays a significant role. A multidisciplinary approach with early referral to specialized treatments is key in managing these patients.

The diverse range of symptoms associated with Long-COVID syndrome can make it challenging to diagnose specific underlying pathologies. While nociplastic pain may exhibit neuropathic features, it is important to use diagnostic tests to differentiate between long-COVID and neuropathies, as neuropathies can also occur frequently in non-critical COVID illness survivors.

During our investigation, we came across a scarcity of studies that specifically investigated pain exhibiting neuropathic features by employing confirmatory diagnostic tests. It is imperative to underscore that in the absence of conclusive evidence regarding neural involvement, it is not possible to establish a definitive diagnosis of NP. As

a result, in most of the studies we reviewed, the classification of pain as neuropathic can only be considered as a probable NP.

This review has several limitations that need to be acknowledged. Firstly, it should be noted that this review follows a narrative approach, starting from a specific research database, which may have resulted in the omission of relevant studies. The subsequent manual search conducted by the authors introduces a potential selection bias.

Furthermore, it is important to highlight that the available literature primarily focuses on COVID-illness populations with NP through case series and cohorts with small sample sizes. Consequently, determining the frequency of reported neuropathies in most cases becomes challenging or even impossible. Additionally, caution should be exercised when considering risk factors and causal associations due to the weak level of evidence currently available.

In conclusion, this review highlights that the existing literature on critical COVID-19 illness survivors predominantly consists of reviews, small case series, and retrospective cohorts. To further our understanding of the neurological consequences associated with critical COVID-19 illness, it is imperative to conduct additional research. Healthcare professionals should maintain a high level of suspicion for NP in this population. Advancing our knowledge of NP in COVID-19 survivors will contribute to the development of effective strategies aimed at improving overall patient outcomes.

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