

Relationship between brachial plexus injury and intensive care unit-managed COVID-19 patients requiring prone ventilation: A scoping review

Relación entre lesión del plexo braquial y ventilación en decúbito prono en pacientes con COVID-19 manejados en la unidad de cuidados intensivos: una revisión exploratoria

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ABSTRACT

Introduction: Brachial plexus neuropathy is a rare complication of therapeutic pronation at the intensive care unit. Few studies explore the association between ICU-managed COVID-19 and the development of plexopathies of the upper limbs.

Objective: Synthesize the medical literature on the relationship between COVID-19 requiring prone ventilation and brachial plexus neuropathy.

Methods: A scoping review including observational studies in PubMed and Scopus. Results were summarized based on the general characteristics of each included article.

Results: Eleven full-text articles were included, identifying case series (n = 4), case reports (n = 3), retrospective (n = 2) and prospective (n = 2) cohort studies, with a total sample of 361 patients. The brachial plexus injury is a rare complication of prone ventilation in the ICU. Males with a history of high blood pressure, diabetes mellitus and obesity are more likely to develop this injury. The main clinical manifestations were weakness, paresthesia, and neuropathic pain with an onset time from one to four weeks after the end of pronation.

Conclusion: Prone ventilation in the treatment of patients with severe COVID-19 has been increasing along with neurological complications such as brachial plexus neuropathy.

Keywords: neuropathy; brachial plexus; SARS-CoV-2; COVID-19; pronation.

RESUMEN

Introducción: La neuropatía del plexo braquial es una complicación rara de la pronación terapéutica en la Unidad de Cuidados Intensivos. Pocos estudios exploran la asociación entre la COVID-19 manejada en la UCI y el desarrollo de plexopatías de las extremidades superiores.

Objetivo: Sintetizar la literatura médica sobre la relación entre el COVID-19 que requiere ventilación en decúbito prono y la neuropatía del plexo braquial.

Métodos: Una revisión de alcance que incluye estudios observacionales en PubMed y Scopus. Los resultados se resumieron en función de las características generales de cada artículo incluido.

Resultados: Se incluyeron 11 artículos a texto completo; se identificaron series de casos (n = 4), reportes de casos (n = 3), estudios de cohortes retrospectivos (n = 2) y prospectivos (n = 2) con muestra total de 361 pacientes. La lesión del plexo braquial es una complicación rara de la ventilación en decúbito prono en la UCI. Los varones con antecedentes de hipertensión arterial, diabetes *mellitus* y obesidad

son más propensos a desarrollar esta lesión. Las principales manifestaciones clínicas fueron debilidad, parestesia y dolor neuropático con un tiempo de aparición de una a cuatro semanas después del final de la pronación.

Conclusión: La ventilación de prono en el tratamiento de pacientes con COVID-19 grave ha ido en aumento junto con complicaciones neurológicas como la neuropatía del plexo braquial.

Palabras clave: neuropatía; plexo braquial; SARS-CoV-2; COVID-19; pronación.

Recibido: 22/12/2022

Aceptado: 20/10/2023

Introduction

Brachial plexus neuropathy (BPN) accounts for 14% of neurological injuries of the upper limbs. Its main cause is trauma to the limbs and to a lesser extent neoplastic compression, ischemic lesions, autoimmune diseases, and viral infections.^(1,2) BPN generates paresthesia, pain, and weakness of the upper extremity. It is associated with a temporary or permanent neurological dysfunction that can even involve absolute paralysis.^(1,3,4)

COVID-19 promotes a multisystemic inflammatory response mainly in the respiratory system, causing pneumonia and acute respiratory distress syndrome (ARDS).^(5,6) In some cases, patients with COVID-19 who develop ARDS require invasive ventilatory support in prone position (PP) with sessions lasting 16 to 18 hours a day.^(7,8) Pronation has been associated with the development of pressure ulcers, musculoskeletal and peripheral nerve pressure injuries, and overstretching of the extremities during a prolonged stay in the intensive care unit (ICU).^(8,9)

A relationship between COVID-19 and BPN has recently been suggested. Miller et al analyzed 114 patients with a history of ICU-managed COVID-19 with PP and suspected peripheral nerve injury, reporting that 13.1% of patients presented clinical findings of neuropathic pain and muscle atrophy associated with BPN.⁽¹⁰⁾ The authors proposed a pathophysiological relationship between pronation and

brachial plexus injury. They did not rule out, however, other mechanisms such as the tropism of SARS-CoV-2 on the peripheral nervous system facilitated by the inflammatory state during the disease.^(11,12,13) Few studies explore the association between COVID-19 with in-hospital management and the development of plexopathies of the upper limbs. The purpose of this scoping review is to synthesize the medical literature on the relationship between ICU-managed COVID-19 requiring prone ventilation and BPN.

Methods

A scoping review was carried out following the steps described by Arksey and O'Malley⁽¹⁴⁾ and later enhanced by Levac.⁽¹⁵⁾ These steps include describing the research question, finding the most important documents, selecting the articles, extracting the data, and summarizing and reporting the results. The review answered the question: What is the nature of the scientific evidence on the relationship between ICU-managed COVID-19 requiring prone ventilation and BPN?

Eligibility Criteria

Observational studies that evaluate the relationship between ICU-managed COVID-19 requiring prone ventilation and BPN were included. Publications in English and Spanish were considered. Narrative reviews, letters to the editor, systematic reviews, articles without access to the abstract and/or full document were excluded.

Search strategy, study selection and data extraction

We used PubMed and Scopus. The search strategy used Boolean operators and keywords according to each database. The last update of this search was made on January 30, 2022. Rayyan web application allowed independent researchers to screen the title and abstracts according to the eligibility criteria.⁽¹⁶⁾ Discussion and consensus were then carried out for the final inclusion of documents where people involved went over the main findings on each study that met the eligibility criteria and showed reasoning about why various documents were not suitable for this review, it was decided to exclude works that even if meeting the required type of study weren't fully available online for their proper reading and analysis, and several

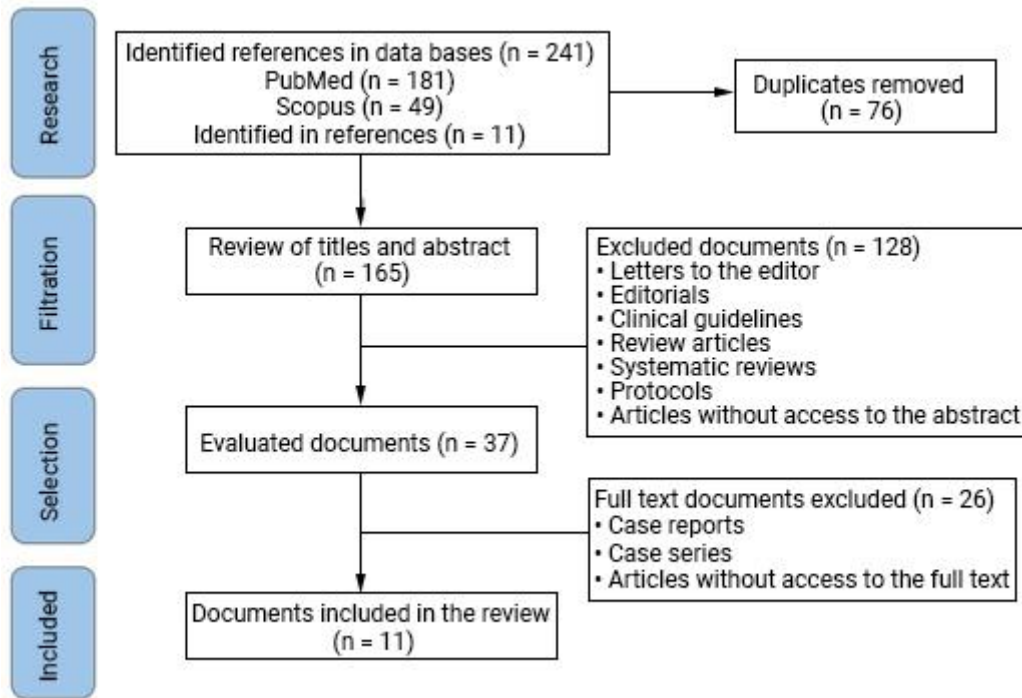
case reports and case series that didn't fully focus on BNP and mechanical ventilation, and instead lightly mention the topics without going into full detail into this relation, or that mainly focused in other conditions related to the current topic, therefore not meeting the inclusion criteria; the information was extracted using a predesigned format. During this process, several meetings were held to adjust the data extraction form. The final version included the following variables: authors, type of document, study type, population characteristics, objective, country of the authors, and main findings.

Synthesis and presentation of results

The results of this scoping review are presented based on the categories proposed by Grudniewicz et al: a summary of the characteristics and distribution of the documents included, as well as a narrative synthesis of the results.⁽¹⁷⁾ The PRISMA extension for scoping reviews (PRISMA-ScR) was used to report our findings.⁽¹⁸⁾

Results

Of 241 documents identified in the search, 11 full-text articles evaluating the relationship between ICU-managed COVID-19 requiring prone ventilation and BPN were included (fig. 1). Case series (n = 4), case reports (n = 3), retrospective (n = 2) and prospective (n = 2) cohort studies were identified, with a total sample size of 361 patients. The general characteristics of the documents are found in table 1.



Fuente: Copied and adapted from: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al.⁽¹⁸⁾

Fig. 1 – PRISMA flowchart.

Table 1 - Explored article characteristics

Authors	Document type	Demographic data	Objective	Country of origin	Main findings
Miller et al ⁽¹⁰⁾	Cases series	12 male and 3 females; mean age was 54.5 years. The prone position for 16 hours returning to supine for 8 hours	Report observations and to explore the challenges in patients that use the prone position with COVID-19 pneumonia who are critically ill and mechanically ventilated	United Kingdom	The most commonly injured nerve was the ulnar nerve and cords of the brachial plexus, the patients reported neuropathic pain and motor weakness. Three patients had evidence of a glenohumeral joint dislocation
Lucchini et al ⁽¹⁹⁾	Retrospective cohort study	96 patients, 22 female/74 male. mean age 59 years. Prone position for about 18 hours per day (taking in account standard pp <24 hours and extended pp > 24 hours)	Investigate complications due to extended and standard prone positioning in COVID-19 patients.	Italy	3 months after being in the ICU patients did not report any kind of neuropathic pain or sensory loss in the upper limbs

Douglas et al ⁽²⁰⁾	Retrospective cohort study	61 patients, 15 female, 46 males. Mean age 56,7 years. Prone position for 0.28 days (6.72 hours), however patients were not repositioned until needed	To determine the safety of prone position treatment without daily repositioning in patients with ARDS due to COVID-19	United States of América	The main concern with this treatment is pressure wounds due to extended proning time, however, limb weakness was present in 58% of patients and 8,2% of patients presented brachial plexus palsies due to prone positioning
Binda et al ⁽²¹⁾	Prospective cohort study	87 patients, 23 females, 64 males. 34/87 were prone, 8 female, 26 male. Mean age 58 years. 106 pronation circles, median duration 72 hours, 22/34 patients were prone for longer than 16 hours	Evaluate muscle strength levels and other aspects in patients that were in a prone position during their stay in the ICU due to COVID-19 infection.	Italy	Muscular strength between prone and not prone patients was not significantly different in either wrist, elbow or shoulder. Strength levels were mainly related to age, being older patients more susceptible to having weaker upper limbs
Portela-Sánchez et al ⁽²²⁾	Prospective cohort study	50 males, 21 females. Mean age 69 years. Unknown proning time	To describe several neurological complications associated with covid19 treatment in the ICU	Spain	Three patients were diagnosed with brachial plexopathies, two of which acquired it after being placed in a prone position, characterized mainly by a generalized weakness in the limb either due to stretching or compression on the nerve
Michaelson et al ⁽²³⁾	Cases series	14 male patients (out of 25) with peripheral nerve damage. 4 out of 14 with brachial plexopathy, one of which was prone. Mean age 57. Unknown prone position time	Present a case series of patients who developed several peripheral neurological complications due to covid19 treatment in the ICU.	United States of América	The prone patient with brachial plexopathy developed a compressive neuropraxic plexopathy caused by shoulder hyperabduction during proning.
Sánchez-Soblechero et al ⁽²⁴⁾	Cases report	Male, 69 years old. Prone position for the first 27 hours in	Present a case of a patient who acquired brachial plexopathy after	Spain	Brachial plexopathies are uncommon in the ICU context but

		ICU	being placed in a prone position while being treated for ARDS		due to the pandemic some cases have appeared. These can most likely be associated with comorbidities such as obesity, mispositioning and mishandling during the procedure
Diprose et al ⁽²⁵⁾	Cases report	Female, 55 years old. Prone position for 16 to 18.5 hours per day for 7 days	To present a case of bilateral upper limb neuropathies in a patient with covid19 managed with prone position ventilation	New Zealand	The patient was unable to lift her arms, there was bilateral weakness of shoulder abduction and external rotation, no pain was reported. There was partial denervation of both deltoid muscles and of both ulnar nerves
Saif et al ⁽²⁶⁾	Cases report	Male in his 60s. Unknown prone position time	Describe the case of a patient with sensor and motor polyneuropathy in upper limbs following covid19 treatment	United Kingdom	The patient developed left hand oedema, reduced ability to grab and was unable to flex the left elbow, however after an MRI there was no evidence of focal injury in the brachial plexus due to the pronation maneuver.
Álvarez et al ⁽²⁷⁾	Case series	7 male, 13 females. Mean age of 63,16 years. Mean mechanical ventilation time 26,5 days, mean pronation time 5,81 days	Quantify and describe the presence of shoulder pain in covid19 patients after leaving the ICU.	Chile	Patients present pain during repose and during activity, patients showed diminished glenohumeral joint flexion and abduction ranges. The main affected nerves were the median and the ulnar. Tendinosis and tendinopathy were also a common finding
Brugliera et al ⁽²⁸⁾	Cases series	7 males; mean age 53.28 years. Prone position for about 16 hours	Present and report complications related to prone position in	Italy	Male patients and patients with conditions such as diabetes, obesity and

		per day	critically ill patients with SARS-CoV-2		anatomic abnormalities contribute to the risk of developing compression neuropathies in the upper limbs. The technique used by the physician heavily influences this outcome
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Legend: ICU: intensive care unit; ARDS: Acute Respiratory Distress Syndrome.

Source: Self made.

Retrospective cohort studies

Lucchini *et al*/evaluated the relationship between PP in 96 patients with ARDS due to COVID-19 and the development of pressure ulcers and peripheral nerve injury during a follow-up of 3 months after hospital discharge. Peripheral muscle strength was assessed using the *Medical Research Council* scale and manual dynamometry. "Standard pronation" was defined as any cycle greater than 16 hours and less than 24 hours. "Extended pronation" was defined as any cycle greater than 24 hours. The characteristics of the participants included a mean age of 59 years (IQR: 53-66), an average stay in the ICU of 15 days (IQR: 7-25) and an average time elapsed since admission to the ICU. The median time for each cycle of pronation was 18 hours (IQR: 16-32).

Some 31% of patients had one cycle, 22% two cycles, 17% three cycles, and 30% three or more cycles. In 38% of the patients, at least one cycle of extended pronation was implemented. The investigators reported a prevalence of pressure ulcers of 51% for patients with extended pronation and 32% for patients with standard pronation ($p = 0.032$). No differences were found in the *Medical Research Council* score in patients undergoing standard pronation compared to extended pronation (60 IQR points: 59-60 *versus* 60 IQR points: 58-60) ($p = 0.395$) and none reported sensory loss or the presence of neuropathic pain in the upper limbs. Finally, no difference was reported between groups in the results of manual dynamometry, a technique for measuring hand grip strength (33 kg-force IQR:25.0-37 *versus* 29 kg-force IQR:20-39) ($p = 0.679$).⁽¹⁹⁾

Douglas and colleagues explored the safety and efficacy of prolonged PP in patients who developed COVID-19-related ARDS. Patients were only repositioned to

supine position when the inspired fraction of oxygen was less than 60% (with positive pressure at the end of expiration less than 10 cmH₂O for 4 hours or more). The characteristics of the study sample included a mean age of 56.7 (SD: 13.5) and a body mass index of 33.39 (SD: 8.9). Some 57.4% of the study population had a history of diabetes mellitus. The average time from intubation to the initial episode of PP was 0.28 days (IQR: 0.11-0.80). Some 75.4% of patients had a pronation cycle (75.4%) and the remaining 24.6% two or more cycles. Objective weakness in all four limbs was present in 95.1% of the patients, and 8.2% of the patients had true brachial plexus palsy.⁽²⁰⁾

Prospective cohort studies

Binda and colleagues evaluated the muscle strength of 87 ICU-managed COVID-19 patients with and without PP. Pronation in the *swimmer's* position was used in 39.1%, with a total of 106 pronation cycles and a median duration of 72 hours (IQR: 60-83). 64.7% of the patients were in PP for more than 16 hours. In this study, pronation was not associated with changes in muscle strength at the shoulder level (OR: 1.34; 95% CI: 0.61–2.97; $p = 0.468$). The elderly patients, however, presented a loss of strength (OR: 1.06; 95% CI: 1.02-1.10) compared to the supine position.⁽²¹⁾ Portela et al described the neurological complications observed in 71 patients who survived COVID-19 infection. The characteristics of the population included a mean age of 69 years (SD: 23.9) and 56.3% had a history of high blood pressure. Some 33.7% of the patients experienced neuromuscular complications. Three were diagnosed with BPN and two of these presented weakness after PP in ARDS management. A prevalence of neurological complications of 2.6% was reported.⁽²²⁾

Case series

Michaelson and colleagues described a case series of 14 hospitalized patients with COVID-19 who presented peripheral neurological complications. The patients were evaluated by a neurologist after an electromyography and magnetic resonance imaging, as well as nerve and muscle biopsies in selected patients. A total of ten patients presented entrapment neuropathy, six patients presented with peripheral neuropathy and four had BPN. In this last group, only one patient was managed with mechanical ventilation and PP due to ARDS in COVID.⁽²³⁾

Miller et al described the demographic characteristics, comorbidities, and presentation of peripheral neuropathies in a series of 15 COVID-19 survivors undergoing physical rehabilitation. The characteristics of the sample included a mean age of 54.5 years (IQR: 39-69) and 80% had a history of high blood pressure. The median duration in the ICU was 32.5 days (IQR: 20-46) and the number of times in PP was 7.3 (IQR: 2-15). Thirty lesions of the peripheral nerves of the upper extremities were identified. 11 of them affected the brachial plexus.⁽¹⁰⁾

Case reports

Sánchez et al presented the clinical case of a 69-year-old man with a history of obesity, type 2 diabetes mellitus and atrial fibrillation who was hospitalized for COVID-19. The patient developed ARDS with ventilatory support and PP during the first 27 hours of hospitalization. The treatment he received was lopinavir/ritonavir, hydroxychloroquine, ceftriaxone, methylprednisolone, and tocilizumab. One week after ICU discharge, the patient reported right upper extremity weakness with decreased strength for humeral rotation, shoulder abduction, and elbow flexion. In addition, the patient reported hypoesthesia on the skin over the right deltoid muscle. At three weeks, needle electromyography was performed showing fibrillation potentials, enlarged polyphasic motor unit potentials, and decreased recruitment of the right supraspinatus, deltoid, and biceps brachii muscles. Based on these findings, the authors reported a postganglionic axonal injury affecting C5 and C6 levels suggesting BPN. The patient partially improved his symptoms one month after discharge from ICU, persisting however with hypoesthesia.⁽²⁴⁾

Discussion

This scoping review summarizes the available information on the relationship between ICU-managed COVID-19 and the development of plexopathies of the upper limbs. Post-pronation brachial plexus injury is a rare complication. However, it has been reported that mechanical ventilatory support in patients with COVID-19 increases the probability of the use of PP and BPN in ICUs.^(23,24,25,26,27) Males with a history of high blood pressure, diabetes mellitus and obesity are more likely to

develop this lesion. In these patients, the main clinical manifestations were weakness, paresthesias, and neuropathic pain. The onset time was one to four weeks after the end of pronation.^(9,22,23,24,25,26,27,28) Protocols and techniques that reduce peripheral nerve involvement are therefore essential to prevent and/or reduce associated complications in pronated patients.^(24,25,26,27) However, in several cases it's not clearly stated if the development of BPN in this kind of patients is directly related to their preexisting conditions or if it was most likely related to the difficult pronation maneuver in patients with larger bodies, heavier and therefore harder to manage in this context or that already had reduced mobility due to their physical condition.

Before the COVID-19 pandemic, a prevalence of 0.14% of BPN had been reported in the management of pronated patients in the ICU and after spinal surgery.⁽²⁹⁾ Currently, an increase in patients requiring PP management has increased the prevalence of peripheral nervous system injuries to 13.1% and 14.5%, most of which involve the brachial plexus and the ulnar nerve.⁽³⁰⁾

The nerve bundle that arises from the cervical spine and controls upper extremity function is called the brachial plexus. Brachial plexus injuries are classified as supraclavicular, retroclavicular, and infraclavicular, depending on the anatomical structures affected.^(31,32,33) Prolonged periods of immobility due to PP can cause nerve damage through mechanical compression and traction mechanisms, generating transient or persistent hypoxic damage on certain occasions.^(34,35) Peripheral nervous tissue can stretch or extend up to 8% of its normal size without presenting any injury. When exceeding 10%, however, permanent damage is generated due to traction and decreased intraneural blood perfusion, which leads to structural damage, the release of pro-inflammatory cytokines, dysfunction of the sodium-potassium ATPase pump and demyelination.^(36,37)

It is important to note that BPN in patients with COVID-19 is not exclusively due to management with PP. Han et al, for example, described the case of a 52-year-old man with a history of diabetes mellitus, who was admitted for SARS-CoV-2 pneumonia. During the hospital stay, he presented ventilatory failure, requiring management with invasive mechanical ventilation. During the period of stay in the ICU, neither PP nor axillary artery catheterization was performed. However, he

subsequently presented a rash on the left hand and forearm with findings suggestive of thrombotic microvascular injury and weakness in the left upper limb compatible with BPN. Therefore, the BPN was reported to be secondary to the development of micro thrombotic vasculopathy of the vasa nervorum with ischemia and infarction. The authors suggested the need for additional studies to determine the influence of the inflammatory process in the development of plexopathies.⁽³⁸⁾ These findings also may lead to discussion about other diseases and preexisting conditions, such as diabetes mellitus, that might as well enable the apparition of BPN and other similar nervous system injuries, due to the immune and peripheral nervous tissue damage linked to it.

There's also a lingering question, regarding the 3 Italian studies^(19,21,28) in which similar groups were evaluated, in the majority of the population, mainly those considered without comorbidities, there were no cases of muscle weakness except in patients described as older, and no sensory loss was present 3 months after the ICU stay; Presence of BNP is only described in multi-comorbid patients and it is mainly associated with the maneuver carried out by health personnel. However, it is not adequately expressed whether these patients underwent an adequate neuromuscular examination prior to the maneuver and therefore it is not known if they already had conditions that altered mobility or sensitivity, if a different maneuver was used in obese or otherwise larger patients, or whether even in patients considered healthy there were changes in mobility or sensitivity that the patient describes as normal, leaving an interview and interviewer-specific bias regarding the information both prior to pronation and after it.

It is essential to improve our understanding of the pathophysiological mechanism of neurological compromise by SARS-CoV-2. It has been reported that the virus enters the central nervous system through the olfactory nerve or the blood-brain barrier. It subsequently spreads to the peripheral nervous system. This process is mainly mediated by the union of viral protein S with the angiotensin-converting enzyme 2 receptor, generating a storm of inflammatory cytokines, decreasing the capacity of microglial cells to regenerate and modulate neuroinflammation.^(39,40,41) Although pronation-related injuries seem to be essential in the pathophysiology of

BPN, the tropism of SARS-CoV-2 and its virulence mechanisms cannot be underestimated.

The need for PP protocols in the ICU has increased in the context of the COVID-19 pandemic.^(42,43,44) Additionally, recommendations focused on reducing the risk of associated nerve injuries have been established. For example, the swimmer's position protocol, in which the patient is placed in a prone position with an upper extremity in abduction less than 70° and elbow flexion to 70.^(45,46) This protocol additionally involves placing the contralateral extremity in adduction with the patient's trunk and the head in rotation towards the side of the extremity. To avoid traction injuries, an extension of the shoulders or their subluxation towards the dorsal side should be avoided.^(10,36,47) Despite these recommendations and according to our findings, positioning is not the only factor that contributes to BPN. Therefore, despite established strategies, peripheral nerve injuries still develop.^(48,49)

Limitations

Due to the nature of scoping reviews, the quality and risk of bias of each of the included studies were not evaluated.^(14,15,18) Furthermore, this review only considered studies written in English and Spanish, probably overlooking studies in other languages. The use of the steps proposed by Arksey and O'Malley and the extension *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* for exploratory reviews, granted a clear methodological process to answer our research question.^(14,15,18)

Conclusion

The use of PP in the treatment of patients with severe COVID-19 has been increasing along with neurological complications such as BPN. This clinical presentation is common among men with comorbidities, and the main clinical manifestations are weakness, paresthesia and neuropathic pain. To avoid peripheral nerve injury, it is necessary to train health professionals in posture techniques and individualized patient care. Moreover, additional studies are necessary to determine the impact of the pronation techniques protocols and to explore the pathophysiology of COVID-19-related BPN.

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Conflict of interests

The authors declare that there is no conflict of interest.