INTENS CRIT CARE NUR 85 (2024) 103766

Contents lists available at ScienceDirect

Intensive & Critical Care Nursing

journal homepage: www.sciencedirect.com/journal/intensive-and-critical-care-nursing

Review Article

Upper limb peripheral nerve injuries in patients with ARDS requiring prone positioning: A systematic review with proportion meta-analysis

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ARTICLE INFO

Keywords:
Brachial plexus neuropathies
COVID-19
Intensive care units
Peripheral nerve injuries
Prone position
Respiratory distress syndrome

ABSTRACT

Objective: To investigate the prevalence of upper limb peripheral nerve injuries (PNI) in adult patients admitted to the intensive care unit (ICU) with acute respiratory distress syndrome (ARDS) undergoing prone positioning.

Methods: This systematic review with meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. Four electronic databases including PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library, and EMBASE were searched from inception to January 2024. The quality of the included studies was evaluated according to the Joanna Briggs Institute Critical Appraisal Tools. A proportion meta-analysis was conducted to examine the combined prevalence of upper limb PNI among patients requiring prone positioning.

Results: A total of 8 studies (511 patients) were pooled in the quantitative analysis. All studies had a low or moderate risk of bias in methodological quality. The overall proportion of patients with upper limb PNI was 13% (95%CI: 5% to 29%), with large between-study heterogeneity ($I^2 = 84.6\%$, $P<0.001$). Both ulnar neuropathy and brachial plexopathy were described in 4 studies.

Conclusion: During the COVID-19 pandemic, prone positioning has been used extensively. Different approaches among ICU teams and selective reporting by untrained staff may be a factor in interpreting the large variability between studies and the 13% proportion of patients with upper limb PNI found in the present meta-analysis. Therefore, it is paramount to stress the importance of patient assessment both after discharge from the ICU and during subsequent follow-up evaluations.

Implications for clinical practice: Specialized training is essential to ensure safe prone positioning, with careful consideration given to arms and head placement to mitigate potential nerve injuries. Therefore, healthcare protocols should incorporate preventive strategies, with patient assessments conducted by expert multidisciplinary teams.

Introduction

Prone positioning has been used since the 1970s to improve oxygenation in adult patients with acute respiratory distress syndrome (ARDS) [1] and has been extensively applied in the intensive care unit (ICU) during the COVID-19 pandemic [2]. The use of this maneuver was found to be associated with a significant survival benefit [3,4]. However, some complications due to the maneuver are well recognized [5],

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https://doi.org/10.1016/j.iccn.2024.103766
Received 1 April 2024; Received in revised form 6 June 2024; Accepted 6 July 2024
Available online 10 August 2024

including pressure ulcers [6], unplanned extubation [7], severe desaturation, airway obstruction, hemodynamic instability, accidental removal of vascular catheters [8], facial edema, ocular damage [9] and peripheral nerve injury (PNI), such as brachial plexopathy [10].

Prone position increases the risk of nerve complications due to prolonged exposure to localized injuries in specific body areas [11]. Applying the principles of tissue biomechanics and injury mechanisms [12], it is reasonable to assume that compression and traction are the major causes of upper limb PNI [13]. The degree of severity can vary widely, from neurapraxia, in which full recovery would be expected, to more severe axonal injuries, which can result in significant functional disability [14].

At this time, the epidemiology of upper limb PNI related to prone positioning is not fully known. The German Society of Anesthesiology and Intensive Care Medicine guideline reports that nerve compression injury after prone positioning is a rare complication [15]; however, during the pandemic period, several cases of upper limb PNI associated with prone positioning have been documented [16–18]. The last available systematic review reports weakness, pain, and motion deficits after prone positioning, identifying brachial plexopathy as a significant clinical finding during the COVID-19 pandemic [19]. So far, the literature does not provide an overall prevalence of upper limb PNI in patients admitted to ICU with ARDS undergoing prone positioning; therefore, we propose a proportion meta-analysis of all available studies on upper limb PNI.

Materials and methods

The Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA) statement [20] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [21] reporting guidelines were followed for conducting this proportion meta-analysis. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42024501190).

Search strategy

The literature search was performed by searching into four databases: PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library and EMBASE. The search was performed in January 2024 (last search on January 12, 2024): to obtain a comprehensive overview of the evidence, no time limit was set for the publication period. The search strategy was developed using Medical Subject Headings (MeSH) and text-words, then adapted to each database. The following MeSH terms and text-words were used for the condition, context, and population/patients [22]: ("Respiratory Distress Syndrome" [MeSH Terms]) AND ("Prone Position" [Mesh Terms] OR "Prone Position Ventilation" [Text Word]) AND ("Peripheral Nerve Injuries" [MeSH Terms] OR "Brachial Plexus Neuropathies" [Mesh] OR "Brachial Plexus/Injuries" [MeSH Terms]). Additional articles were identified using hand searching through citation chasing. A detailed description of the search strategy is presented in the Supplementary materials (Table S1).

Eligibility criteria

Studies reporting the occurrence of patients with brachial plexus injury or with any related nerve complications of the upper limb after ARDS that required prone positioning during mechanical ventilation were eligible for inclusion. Articles written in languages other than English were excluded as well as studies without full-text. All types of publications, except systematic reviews, describing adult patients with or without upper limb PNI detected with clinical evaluation or diagnostic examinations via electromyography (EMG) and/or magnetic resonance imaging (MRI) were considered. Articles in which the presence of upper limb PNI was not clearly assessed and/or diagnosed and case series reporting complications of patients undergoing awake prone positioning were also excluded.

Study selection

The initial phase of the study selection process was performed blindly based on titles and abstracts. All the results from the search strategies were imported using the Rayyan tool [23]; then, two authors (FB and FM) independently screened the titles and abstracts and selected potential articles for inclusion based on the inclusion and exclusion criteria. Finally, all articles that appeared relevant to this systematic review's topic were retrieved as full-text, and subsequently reviewed by two investigators (FB and FM) who independently applied inclusion and exclusion criteria to full-text articles for final eligibility. In both phases (screening of the articles and full-text analysis), a third researcher (VR) resolved disagreements over articles eligibility. In cases of overlapping populations (i.e., different papers reporting data from the same patients), the article with the largest sample size or greatest data granularity was selected for inclusion in the review.

Data extraction

All the selected studies were entered into an electronic Microsoft Excel spreadsheet (Microsoft® Excel® for Microsoft 365 MSO – Version 2404). Data were extracted by one reviewer (FB) and double-checked for accuracy by other two reviewers (FM and SG): any disagreements were resolved by consensus. Extracted data included details on the author, year of publication, country, study design, total sample, age, sex, number of patients with upper limb PNI, diagnostics (i.e., instrumental and/or clinical evaluation), comorbidities (i.e., obesity, diabetes and arterial hypertension) and presence of swimmer position. This position involves one upper arm abducted above head and the opposite one at side, ensuring the head position with face toward the abducted upper arm [24]. When the information was not directly available, it was calculated if possible. In seven studies, to obtain more details about the use of prone positioning, authors were contacted; six of them responded providing useful data for the quantitative analysis.

Quality assessment

The quality of the studies was independently assessed by two authors (FB and FM) according to the Joanna Briggs Institute (JBI) Critical Appraisal Tools [25] for case-report, cross-sectional study, and case series [26]. Disagreements between the two authors were resolved by consensus with the help of a third reviewer (VR). A detailed description of risk of bias evaluation is available in the Supplementary materials (Tables S2, S3 and S4).

Statistical analysis

Characteristics of the studies retrieved from the systematic review are summarized as mean and ± 1 standard deviation (SD) or counts and percentages (%). Considering that we could not retrieve the total number of patients treated with prone positioning in all studies, we did not include in the meta-analysis the studies where numerator equals the denominator.

A proportion meta-analysis using DerSimonian-Laird model was employed to analyze the pooled proportions of patients with upper limb PNI among patients placed prone. The logit-transformation was used to estimate overall effect size (proportion), computed as weighted average of study-specific effect sizes. Wilson 95% confidence intervals (CI) were used for individual studies. The I^2 statistic was calculated to evaluate heterogeneity of included studies. The risk of publication bias was visually inspected through funnel plot. For all tests, a 2-sided $P<0.05$ was considered statistically significant. Statistical analyses were performed using STATA software (StataCorp. 2023. Stata Statistical

Software: Release 18. College Station, TX: StataCorp LLC).

Results

Study selection

The PRISMA flow diagram summarizing the study selection process is reported in Fig. 1. The initial search retrieved 2150 published records. After screening the title and abstracts, 1242 duplicates and 866 records were excluded based on title and abstract screening. A total of 42 full-text articles underwent evaluation for eligibility and 2 were not retrieved. After the examination of the 40 full-text articles, 26 studies were excluded because 12 reported a wrong topic, 11 reported missing data, 2 examined a wrong population and 1 was written in Russian language. A total of 14 publications fulfilled eligibility. Additionally, 4 records were identified by searching for citations and a total of 18 articles were included in the review. Details on the article selection are available in Supplementary materials (Table S5).

Study characteristics

The characteristics of the included studies are summarized in Table 1. All studies, but one [27], were published between 2020 and 2023 in different types of journals (critical care medicine, rehabilitation, or generalist journal) and were conducted in different world regions (Europe, United Kingdom, North and South America, East Asia, and Oceania). Among the included studies, all were observational, including 11 (61.1%) case series, 5 (27.8%) case reports, and 2 (11.1%) cross-sectional studies. Overall, 256 adults with the sample sizes ranging from 1 to 81 participants were included. The majority of the participants were males (184/256, 71.9%) with age ranging from a mean of 39.7 to 80 years. All studies, except one [27], included adult patients with COVID-19 ARDS. Nine studies reported the mean duration of prone positioning, ranging from 27 to 240 hours. Only 6 studies (33.3%) described the use of swimmer position during prone positioning [27–32]. Regarding the types of diagnostic examinations for the upper limb PNI, 4 studies (22.2%) used EMG, 10 studies (55.6%) used both the MRI and EMG, and 4 studies (22.2%) used clinical evaluation.

Critical appraisal

Supplementary materials (Tables S2, S3 and S4) summarize the findings from the critical appraisal. Based on the results, articles were grouped into three categories: low risk of bias (result 75%-100%),

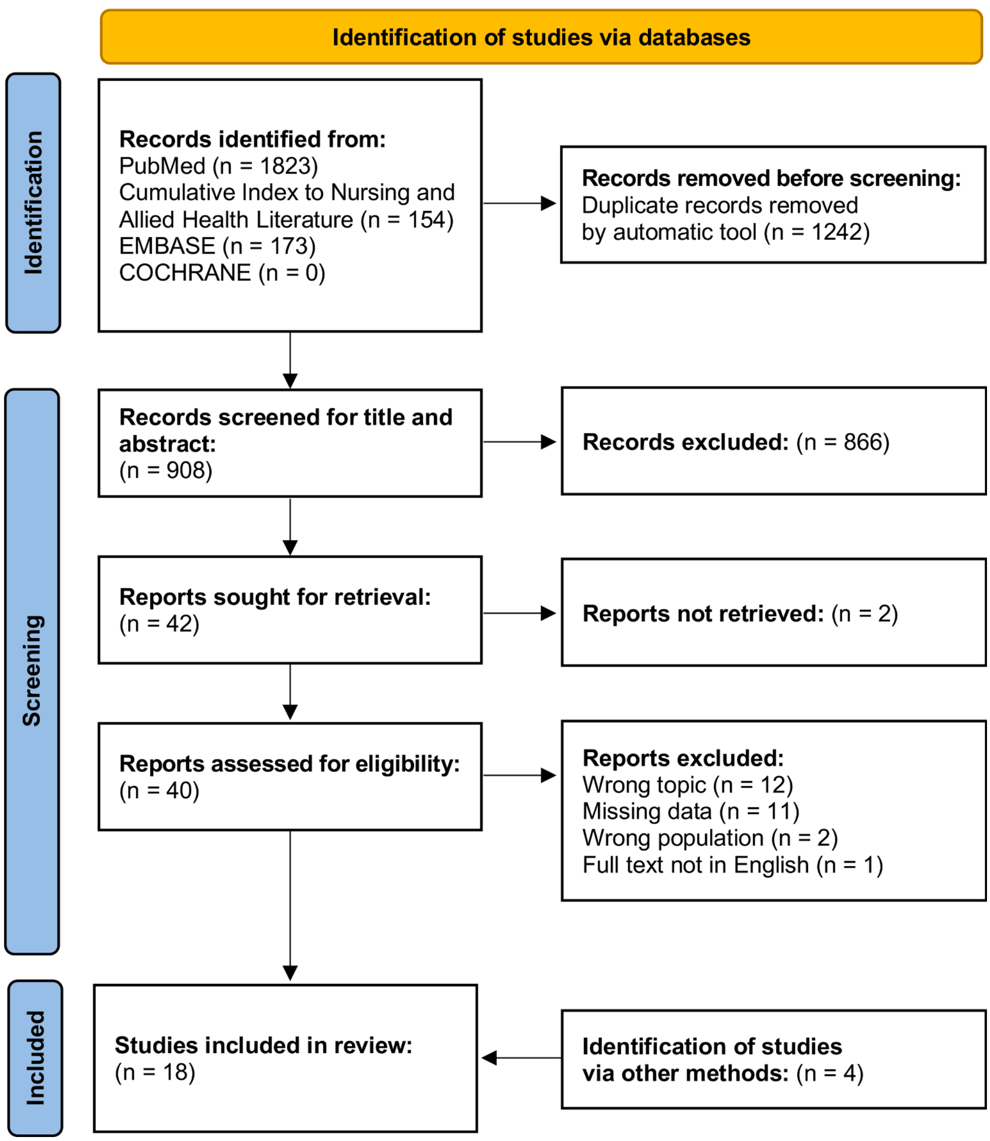

Fig. 1. Diagram of the study selection process for the systematic review and meta-analysis.

Table 1
Characteristics of included studies.

Study	Country	Study design	Sample size	Age (years)	Sex (male) (%)	Patients with PNI/Prone positioning patients
Barton (2023)*	UK	Case series	35	56 (47 – 60)	24 (68.6%)	3/24
Brugliera (2021)*	Italy	Case series	7	53.3 (12.3)	7 (100%)	6/132
Diprose (2021)	New Zealand	Case report	1	55	0 (0%)	1/1
Douglas (2021)	USA	Cross-sectional	61	56.7 (13.5)	44 (72.1%)	5/61
Goettler (2002)	USA	Case report	2	43 (12.7)	1 (50.0%)	2/2
Guthrie (2021)	USA	Case series	2	60 (0)	2 (100%)	2/2
King-Robson (2021)	UK	Case report	2	56.5 (2.1)	2 (100%)	2/2
Li (2023)*	USA	Case series	11	48.7 (12.9)	9 (81.8%)	6/6
Malik (2020)*	USA	Case series	12	60.3 (15.7)	7 (58.3%)	9/11
Mano (2022)	Japan	Case report	1	80	1 (100.0%)	1/1
Miller (2021)*	UK	Case series	15	54.5 (9.5)	13 (86.7%)	12/114
Needham (2021)	UK	Case series	11	58 (21 – 53)	8 (72.8%)	4/5
Omar (2021)	USA	Case series	3	39.7 (20.1)	3 (100%)	3/3
Sánchez-Soblechero (2020)	Spain	Case report	1	69	1 (100%)	1/1
Sayegh (2021)	USA	Case series	3	55.7 (4.7)	1 (33.3%)	2/2
Torres (2022)	Brazil	Case series	5	55.6 (17.5)	1 (20.0%)	1/1
Walter (2022)	France	Cross-sectional	81	60 (51 – 67)	58 (71.6%)	1/81
Wunder (2023)*	Canada	Case series	3	60.3 (3.8)	2 (66.7%)	3/83

Note: Data are expressed as mean (±1 SD); median (IQR) or count and percentage (%); (*) information retrieved from the authors.

moderate risk of bias (50%-74%), and high risk of bias (0%-49%). Among the 18 studies, 9 (50.0%) were classified as low risk and 9 (50.0%) as moderate risk of bias.

Proportion of upper limb peripheral nerve injury

Given the sample sizes of the included studies, only 8 [29,31–37] provided sufficient data for pooling in a meta-analysis. Fig. 2 presents the pooled proportion estimate of the included studies using a forest plot. After retrieving information from the authors, the overall proportion of patients with upper limb PNI is estimated to be 13% (95%CI: 5% to 29%, P=0.002). Furthermore, there is large evidence of between-study heterogeneity (P<0.001): the 84.6% of the variability in the effect-size estimates is due to the differences between studies. The estimated between-study variance τ^2 is 1.62: we then expect that in some 90% of all populations, the true proportion will fall in the approximate range of 1% and 68%.

The main characteristics of patients and risk factors of upper limb PNI among the included studies are extracted in Table 2. All studies included in the meta-analysis reported enrollment during the first wave of the COVID-19 pandemic. Few studies reported data on comorbidities in patients with upper limb PNI: only 4 authors [31,32,34,35] collected data on arterial hypertension, diabetes, and obesity. In studies with available information on the anatomical site of the upper limb PNI, 5 of them [31,33–36] also reported the presence of ulnar neuropathy. A total of 2 studies [31,36] detected upper limb PNI during the follow-up period, while 2 studies [34,35] conducted specific diagnostic investigations along the rehabilitation period. Only 2 studies [29,37] reported that a dedicated multidisciplinary team (consisting of intensivists, nurses, and respiratory therapists) performed the prone positioning maneuver and the swimmer position was explicitly described in 3 different studies included in meta-analysis [29,31,32]. Visual inspection of the funnel plot shows smaller studies as less precise (Fig. 3). Specifically, 2 studies reported a high occurrence of upper limb PNI as equal or greater than 80% [35,36].

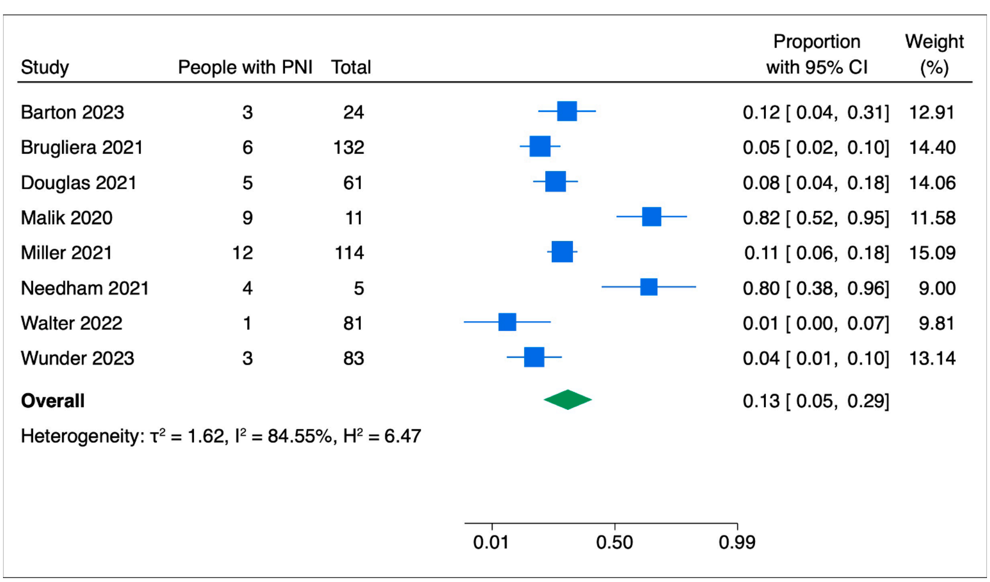

Fig. 2. The forest plot of the overall pooled proportion of upper limb PNI. A blue square is plotted for each study, with the size of the square being proportional to the study weight. The estimate of the overall effect size is depicted by a green diamond: its width represents the corresponding CI. τ^2 = between-study variance; I^2 = between-study heterogeneity; H^2 = heterogeneity statistic. Studies are presented in alphabetic order. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Characteristics of the patients with upper limb PNI included in meta-analysis.

Study	Patients with PNI	Sex (male)	Comorbidities			Timing of PNI assessment	Diagnostics	
			Obesity	Hypertension	Diabetes		EMG	MRI
Barton (2023)*	3	NR	NR	NR	NR	Hospital discharge	NR	NR
Brugliera (2021)*	6	6 (100%)	NR	3 (50.0%)	2 (33.3%)	Rehabilitation	6 (100%)	NR
Douglas (2021)	5	NR	NR	NR	NR	NR	NR	NR
Malik (2020)*	9	6 (66.7%)	5 (55.6%)	5 (55.6%)	5 (55.6%)	Rehabilitation	8 (88.9%)	3 (33.3%)
Miller (2021)*	12	10 (83.3%)	8 (66.7%)	10 (83.3%)	5 (41.7%)	Follow-up	11 (91.7%)	3 (25.0%)
Needham (2021)	4	NR	NR	NR	NR	Follow-up	4 (100%)	1 (25.0%)
Walter (2022)	1	NR	NR	NR	NR	NR	NR	NR
Wunder (2023)*	3	2 (66.7%)	NR	1 (33.3%)	2 (66.7%)	ICU stay	3 (100%)	2 (66.7%)

Note: Data are expressed as count and percentage (%); (*) information retrieved from the authors.
PNI = Peripheral Nerve Injury; EMG = Electromyography; MRI = Magnetic Resonance Imaging; NR = Not reported.

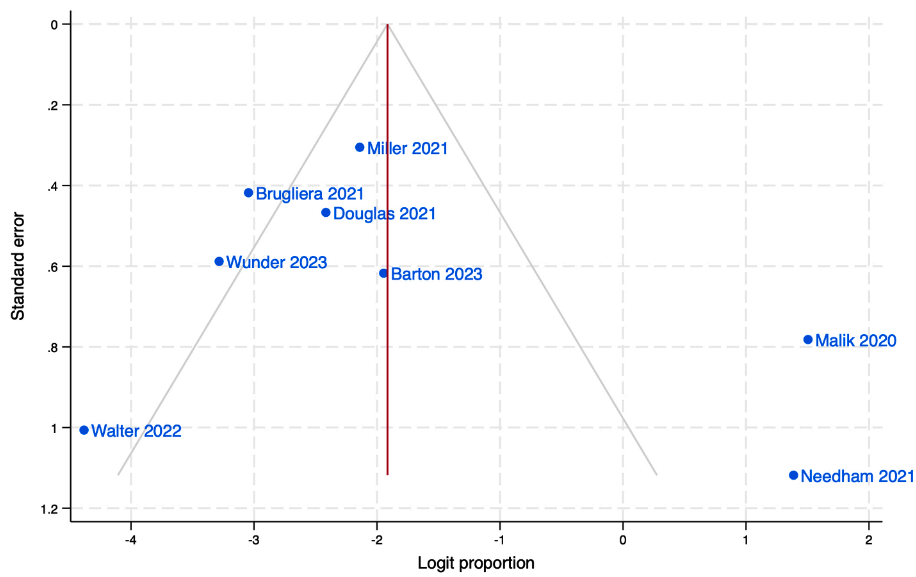

Fig. 3. Funnel plot using logit proportions scattered against their standard errors. Solid red line is the estimated effect-size line and grey lines are the corresponding pseudo 95% CIs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Discussion

This systematic review shows that prone positioning has been widely used during the COVID-19 pandemic and that this maneuver has been spuriously associated with upper limb PNI in a small group of patients. Indeed, the meta-analysis of 8 studies including 511 patients revealed that the estimated proportion of patients with upper limb PNI is 13% and rather imprecise. To our knowledge, this is the first systematic review with meta-analysis to investigate the proportion of upper limb PNI in patients with ARDS requiring prone positioning during mechanical ventilation.

Given the significant level of statistical heterogeneity, the estimated effect should be interpreted with caution. Large heterogeneity (i.e., over 75%) may indicate hidden effects, such as competing populations, interventions, treatments effects, or methods [38]. Indeed, it is possible to mention a multitude of factors when exploring the clinical reasons for such large variability: the era of COVID-19 pandemic, differences in the timing and setting of PNI evaluations, specific comorbidities, sex distribution, the presence of a dedicated multidisciplinary team to perform the prone positioning maneuver and geographical distribution of included patients.

Prone positioning is part of the management of ARDS to improve oxygenation [39], and its beneficial effects on patient outcomes were reported in several trials [40]. Various complications can occur during transitions to and from prone positioning [5,41], including upper limb PNI [42]. Among the prone positioning techniques, there are different strategies among which the swimmer position is recommended by the British guidelines of the Intensive Care Society [24]. The swimmer position is traditionally adopted to reduce the difficulties in positioning the patient's head and endotracheal tube, reduce the risk of developing facial pressure ulcers, and ensure a safe intravenous access line. Alternating the positioning of the arms every 2–4 hours is a nursing intervention to prevent both pressure ulcers and musculoskeletal injuries [24]. Compared to the face-down position (which involves the head resting on a dedicated prone position foam headrest with the neck in a neutral position and the arms resting by the sides), the swimmer position was found to minimize pressure ulcers incidence in critically ill prone patients [43]. Following the principles of biomechanics and injury mechanisms [12], it is plausible to assume that the major causes of PNI when patients are positioned prone using the swimmer position could be compression and traction [44,45]. Rather than the prone position itself, it is the improper handling of patients to achieve the prone position and the care during and after positioning that potentially lead to various complications, including injuries to the brachial plexus [17,32]. Moreover, any underlying anomalies in the anatomy of upper limb can predispose some individuals to nerve injury [10]. It is worth noting that only 3 of the studies [29,31,32] included in this meta-analysis specifically report the use of the swimmer position, which may have contributed to the large heterogeneity. Patients also present with other specific comorbidities, such as obesity, diabetes, and arterial hypertension, which are already known to be associated with a greater likelihood of nerve injury. These risk factors are recognized to induce neuropathy through inflammatory processes, oxidative stress, and ischemic conditions [44]. In this meta-analysis, arterial hypertension is more commonly observed, followed by diabetes and lastly obesity. However, it is important to note that only 2 studies [31,35] included in the meta-analysis provided a comprehensive descriptions of all comorbidities. In addition to the genetic and metabolic factors already reported, sex is another risk factor, and it is known that males are more likely to develop compression neuropathies than females [46]. In any case, considering the years in which the included patients were observed, the high prevalence of males is likely influenced by the epidemiology of pandemic, which accounted for a higher number of males with severe COVID-19 [47].

The etiology of neuropathy in critically ill patients may have multiple causes, such as nutritional demands, neuroinflammatory changes, critical illness polyneuropathy, or peripheral nerve trauma, highlighting the need to harmonize diagnostic methods and timing [48]. The results of this meta-analysis also shows variability of diagnostic procedures (EMG and/or MRI) and timing of diagnosis, which could explain the different proportion of upper limb PNI [31,34–36]. Even if MRI is indicated to diagnose PNI and to detect weaknesses or sensory deficits acquired during ICU stay [49], it was used only in 4 studies [31,32,35,36]. Other authors have also observed an increased number of delayed diagnoses of upper limb PNI after prone positioning and prolonged stays in the ICU [10]. This delay often occurs due to the difficulty in distinguishing between nerve injury and ICU-acquired weakness [50]. Indeed, several studies have reported muscle weakness and poor activity level at the ICU discharge in patients with COVID-19 [31,51,52]. Another retrospective study, enrolling patients survived to ICU, shows that PNI symptoms were reported in at least one-third of them, in similar proportion whether patients suffered from severe COVID-19 or not. Interestingly, the duration of invasive mechanical ventilation, but not the prone positioning, was found to be a risk factor for PNI occurrence [42]. Without timely assessment and follow-up, it remains challenging to draw any diagnostic conclusion of upper limb PNI after prone positioning or at the ICU discharge.

The worldwide spread of COVID-19 [53] and the extensive use of prone positioning during the pandemic [54] might be a contributing factor to the large heterogeneity found in this study. During the pandemic, many more patients were placed in the prone positioning, perhaps by untrained staff [55]. The extensive use of this maneuver has significantly increased the workload of healthcare workers and led some hospitals to create dedicated teams to perform a safe prone positioning maneuver [56,57]. Based on the findings of this meta-analysis, only 2 studies mentioned a multidisciplinary team dedicated to perform prone positioning with the adoption of a standardized protocol, reporting a low occurrence of upper limb PNI [29,37]. The expertise of the ICU staff is fundamental, and reports in the literature suggest that the incidence of adverse events is significantly reduced with a trained team experienced in the maneuver [3,8,45]. Therefore, the increase in adverse events and neurological sequelae after prone positioning during the COVID-19 pandemic could also be easily explained by inexperienced and untrained staff performing this maneuver [58], which may have generated a biased literature towards selective reporting of exceptional cases of upper limb PNI, also poorly documented. In the face of the urgent need for information during an unprecedented health crisis, the insufficient knowledge among scientists and doctors has led to the acceptance of many articles following rapid peer review process, in order to quickly disseminate the latest discoveries and knowledge within the scientific community [59]. However, several case series [60–65] and observational studies [6,18,66,67] on complications of prone positioning published after the first pandemic wave showed that upper limb PNI remain a rare or underdiagnosed event.

Limitations and strengths

This meta-analysis has some limitations that should be taken into account for when interpreting the results. First, there was considerable heterogeneity in the meta-analysis, as reflected by the I^2 statistic. Despite the inherent substantial between-study heterogeneity in meta-analysis of single proportion, isolating all the reasons for this heterogeneity is challenging. Many characteristics of patients were not reported individually but were aggregated across all patient groups in the case series, making it difficult to assess their individual contribution to the current estimate. Additionally, detailed descriptions of the intervention, such as numbers of hours spent in prone positioning, and mechanical ventilation data were partially reported whereas the severity of nerve injury was lacking. Data on the use of steroids and nutritional supplements were also missing. This absence of information significantly limits the interpretation of the proportion of PNI. Discriminating between the causes of upper limb PNI, particularly between pronation and ICU-acquired weakness, proved challenging across multiple studies. Furthermore, most of the included studies were case series, and few reported clear consecutive inclusion of participants. These factors may limit the interpretation of the results. Although one in ten patients in the prone position may develop upper limb PNI, as indicated by the presented data, the causative link between prone positioning and subsequent neuropathies has yet to be established. Further research is required before we can reassess the safety of prone positioning in patients with ARDS.

Despite these limitations, this meta-analysis is the first to quantitively synthesize the evidence regarding the proportion of upper limb PNI among adult patients with ARDS treated with prone positioning. In addition, the comprehensive search strategies in 4 major electronic databases and application of the validated appraisal tool to evaluate the methodological quality of the included studies enhanced the internal validity of the meta-analysis.

Conclusion

Thirteen percent of patients undergoing prone positioning exhibit upper limb PNI, with high variability between the studies. Selective reporting of cases during the COVID-19 pandemic and the challenges of diagnosing nerve injuries in complex clinical settings contribute to significant uncertainty about the occurrence of upper limb PNI, which can be rare or underdiagnosed. Therefore, it remains crucial to emphasize the importance of patient assessment both at ICU discharge and during follow-up evaluations: this would help in identifying the etiological mechanisms of upper limb PNI and preventing their occurrence. Future guidelines should be developed to standardize diagnostic methods and timing for assessing upper limb PNI.

Funding source

This study was partially funded by Italian Ministry of Health – Current research IRCCS.

Ethical approval

This was a systematic review and meta-analysis. Therefore, ethical approval is not required because this study retrieve and synthetize data from already published studies.

CRediT authorship contribution statement

Filippo Binda: Writing – original draft, Project administration, Investigation, Data curation, Conceptualization. **Simone Gambazza:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Federica Marelli:** Writing – original draft, Investigation, Data curation. **Veronica Rossi:** Writing – original draft, Investigation, Data curation. **Maura Lusignani:** Writing – review & editing, Supervision. **Giacomo Grasselli:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.iccn.2024.103766.

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