META-ANALYSIS

Assessing the Impact of Prone Positioning on Mortality and Adverse Events Among Patients with Acute Respiratory Distress Syndrome: A Meta-Analysis

Wangeng Yue, MM; Xiaohua Ai, MM; Yalan Li, MM; Huilin Ye, MM

ABSTRACT

Background • Prone positioning has evolved as a therapeutic intervention for patients with acute respiratory distress syndrome (ARDS). ARDS remains a critical condition, with a mortality rate of approximately 40%. Prone positioning, which involves placing patients in a face-down position, has the potential to enhance gas exchange and improve lung mechanics, possibly leading to better patient outcomes.

Objectives • This comprehensive review aims to evaluate the impact of prone positioning on mortality (primary outcome) and the occurrence of adverse events (secondary outcome) in patients with ARDS compared to conventional supine positioning.

Methods • We conducted an extensive systematic review, including studies published from 2000 to 2022. We searched databases including PUBMED, MEDLINE, EMBASE, CENTRAL, and WEB OF SCIENCE. Only randomized controlled trials (RCTs) that compared the outcomes of patients with ARDS in prone and supine positions were included. We employed the Cochrane risk of bias instrument to assess the methodological quality of the included RCTs.

Results • Our review included a total of twelve RCTs involving 2736 patients, with 1401 patients in the prone position. The meta-analysis demonstrated a lower mortality rate among patients in the prone position compared to those in the supine position (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.52-0.98; P = .04). Notably, there was a higher incidence of pressure sores in patients placed in the prone position (OR, 0.15; 95% CI, 0.09-0.20) compared to those in the supine position. However, there were no statistically significant differences in the occurrence of arrhythmias, unplanned extubation, or pneumothorax between the two positioning strategies.

Conclusions • Prone positioning offers potential benefits for patients with ARDS by reducing mortality rates. However, it is important to note that there is an associated risk of pressure sores. Further research and clinical consideration are needed to optimize the use of prone positioning in ARDS management. (*Altern Ther Health Med.* 2024;30(4):76-81)

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INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a medical condition characterized by respiratory failure due to decreased lung compliance, impaired oxygenation, and pulmonary congestion. This condition typically manifests in severely ill patients, often resulting from lung injuries such as pulmonary viral infections or because of systemic inflammatory responses, such as those seen in polytrauma or sepsis.[1]

The prone position induces changes in alveolar ventilation distribution, enhances ventilation-perfusion matching at a local level, decreases the prevalence of regions with low ventilation-perfusion ratios influenced by gravitational effects, and reduces the risk of ventilator-induced lung injury.[2] Numerous studies have demonstrated that placing patients with ARDS in a prone position can lead to improvements in gas exchange and disease progression.[3]

In a study conducted by Valter et al.,[4] four awake hypoxemic patients were placed in a prone position without the need for sedation or intubation. This maneuver led to a rapid improvement in PaO_2 levels in all patients, and it was well-tolerated. In recent years, there has been a noticeable rise in patients undergoing prone positioning and noninvasive respiratory support.[5,6] Adopting the prone position in patients with ARDS improved oxygenation levels and reduced intubation rates.

Additionally, during the COVID-19 outbreak, this approach contributed to delayed or decreased hospital admissions.[7] These studies collectively suggest that prone positioning may offer significant benefits to patients with

ARDS, particularly in reducing the need for invasive mechanical ventilation.

Currently, research in patients with ARDS placed in the prone position primarily consists of observational studies, cohort studies, and case reports. There is a notable shortage of large-sample randomized controlled trials (RCTs), and the existing findings are marked by inconsistency. This meta-analysis examined the impact of prone positioning on mortality and adverse events in patients with ARDS. This study aimed to offer valuable insights for optimizing the management of ARDS patients.

METHODS

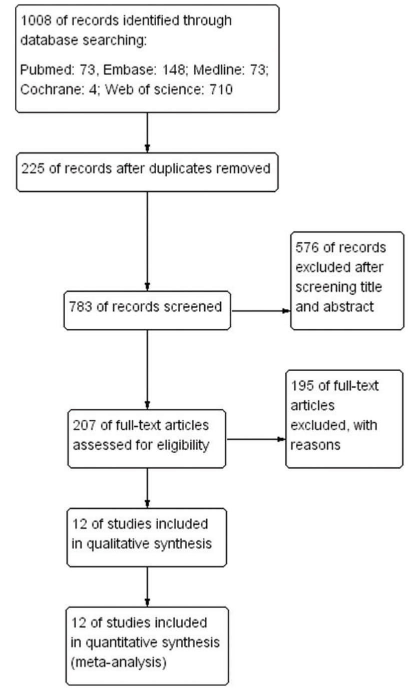
Study Design

We employed a systematic review and meta-analysis study design. This approach allowed us to systematically gather and critically evaluate a wide range of existing studies on prone positioning in patients with ARDS. This study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines to ensure a comprehensive and structured review process.

Search Strategy

Our search strategy involved entering the following terms: ("prone position" OR "prone positioning") AND ("acute respiratory distress syndrome" OR "ARDS"), with a specific focus on randomized controlled trials. This comprehensive search yielded a total of 1008 references. These references were carefully organized and stored using EndNote. Subsequently, we identified and removed 225 duplicate references from the database. Following this initial screening, the remaining 783 original references were thoroughly reviewed, guided by our predefined inclusion criteria (as illustrated in Figure 1).

Figure 1. Selection of Studies for the Meta-Analysis



Note: This figure illustrates the process of study selection for the meta-analysis, including the initial identification of relevant studies, screening, eligibility assessment, and the final inclusion of studies in the analysis. It provides a visual representation of the study selection flowchart.

Inclusion and Exclusion Criteria

Two independent researchers thoroughly reviewed the full texts of all studies. Each reviewer independently assessed the relevance of the studies and determined their eligibility for inclusion. In disagreements, consensus was reached among the researchers through discussion and mutual agreement.

The inclusion criteria for study selection encompassed the following: (1) randomized controlled trials (RCTs); (2) studies comparing prone positioning to supine positioning in patients with ARDS; and (3) studies reporting data on mortality rates and adverse events. The exclusion criteria were as follows: (1) Studies not published in English, including commentaries, reviews, and duplicate publications from the same study; (2) Studies where data could not be extracted through statistical methods; and (3) Studies that did not address the specific outcomes of interest.

Data Extraction and Assessment of Study Quality

Data were independently extracted and recorded in an Excel spreadsheet, focusing on key aspects such as the study details, groupings, interventions, and outcomes. We utilised the Cochrane Collaboration risk of bias instrument to evaluate the quality and potential bias within each study. This comprehensive instrument facilitated the assessment of various elements, including random sequence generation, allocation concealment, blinding of caregivers, outcome assessment, handling of incomplete outcome data, and selective reporting.[8]

Selected Outcomes for Evaluation

We carefully selected a set of outcomes established through consensus among our content experts. These outcomes were deemed critical and substantial in assessing the impact of prone positioning. Our primary focus was on mortality, recognizing its utmost significance. In addition, we also examined adverse events, which included unplanned extubation or catheter displacement, arrhythmias, pressure sores, and pneumothorax.

Statistical Analysis

We employed odds ratios (OR) for the analysis of dichotomous outcomes. Qualitative and quantitative heterogeneity were assessed using the I^2 measure to evaluate clinical heterogeneity across studies. Statistical significance was established with a $P < .05$. Additionally, we examined funnel plots, plotting treatment effects against study quality, to assess the potential presence of publication bias.

All statistical analyses were conducted using RevMan 5.2, a software tool from the Cochrane Collaboration based

Table 1. Baseline Characteristics of Included Studies

Study	Sample (T/C)	Grouping (T/C)	Intervention	Mortality	Adverse events
Alhazzani et al. 2022[9]	205/195	awake prone positioning/usual care	8 h/d to 10 h/d with 2 to 3 breaks (1-2 hours each)	46/46	Unintentional removal of intravenous access:1/0
Beuret et al. 2002[10]	25/26	prone position/ supine position	positioned prone for 4 h once daily	7/12	NA
Chiumello et al. 2012[11]	13/13	Prone position/ Supine position	Prone position	8/7	NA
Fernandez et al. 2008[12]	21/19	Prone/Supine	Prone/Supine	8/10	Pneumothorax: 0/1; Unplanned extubation:1/1;
Gattinoni et al. 2001[13]	152/152	Prone/Supine	prone group: kept prone for at least six hours per day for a period of 10 days;	32/38	Pressure ulcers:54/42; Displacement of tracheal tube:12/15
Guerin et al. 2013[14]	237/229	Prone/ Supine	prone position: at least 16 consecutive hours	38/75	Non-scheduled extubation: 31/25; Cardiac arrest: 16/31
Guerin et al. 2004[15]	413/378	Prone/Supine	Prone: at least 8 hours per day; Supine: a 30° angle semi-recumbent position	134/119	Unplanned extubation: 44/47; Cardiac arrest: 87/88; Pressure sores: 208/157; Pneumothorax: 22/28
Jayakumar et al. 2021[16]	30/30	Prone/ Standard care	Prone: more than 6 hours in a day; Standard care: As per their comfort, they may change their position	3/2	Intubated: 4/4
Lu et al. 2021[17]	40/40	PPV/SPV	Prone; Supine: mechanical ventilation in a semi-supine position with the head of the bed raised 30-40°	5/9	NA
Mancebo et al. 2006[18]	76/60	Prone/Supine	Prone/Supine	33/35	Pneumothorax: 7/4; Unplanned tracheal extubation: 6/1
Taccone et al. 2009[19]	168/174	Prone/ Supine	Prone positioning was applied using a rotational bed	52/57;	Hypotension, arrhythmias, increased vasopressors:121/95 Displacement of endotracheal tube:18/8
Voggenreiter et al. 2005[20]	21/19	Prone/ Supine	Prone positioning: During nighttime. Supine group: positioned according to standard care guidelines	5/16	Pressure sores and skin lesions: 19/12; Displacement of an endotracheal tube: 1/1; Brady- or tachyarrhythmias: 8/3

Note: This table provides an overview of the baseline characteristics of the included studies, including the study name, sample size, grouping, intervention, mortality rates, and adverse events observed in both the prone and supine positions. "T/C" denotes the patient count in the treatment and control groups. Adverse events are listed with corresponding occurrences in the prone (T) and supine (C) groups. "NA" signifies data not available for certain studies.

in Oxford, UK. The results were analyzed, and forest plots were generated, utilizing either a fixed-effect or random-effect model, depending on the level of heterogeneity. A fixed-effect model was chosen for values of I^2 less than 50%, indicating low heterogeneity, while values exceeding 50% were considered moderate heterogeneity and thus required a random-effects model. Furthermore, we utilized funnel plots to aid in assessing publication bias. A significant difference was determined to exist when the $P < .05$.

RESULTS

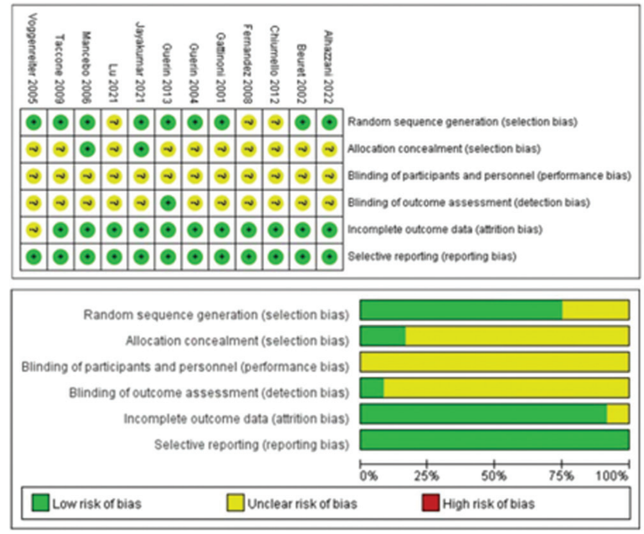
Search Outcomes

Our search across various databases initially yielded a total of 1008 publications that were considered relevant to our study's focus. Subsequently, these publications underwent careful screening, resulting in the identification of 12 articles from the year 2000 to 2023. These 12 articles collectively comprised data from 2736 patients with ARDS, of which 1401 were placed in the prone position. A comprehensive summary of all the articles included in this study is presented in Table 1, providing key insights into their main characteristics ($P = .05$).

Risk of Bias in Included Studies

A comprehensive evaluation of each study's risk of bias was conducted, and the findings are presented in Figure 2, providing a graphical summary of assessments. Our analysis revealed that most studies demonstrated a low risk of bias in terms of "selective reporting," "incomplete outcome data," and "random sequence generation." However, it is worth noting that our assessment of "blinding of participants and personnel" across all studies resulted in an outcome of "unclear risk." Furthermore, a total of ten studies fell into this category due to the absence of clear descriptions regarding allocation concealment.

Figure 2. Risk of Bias Graph and Bias Summary

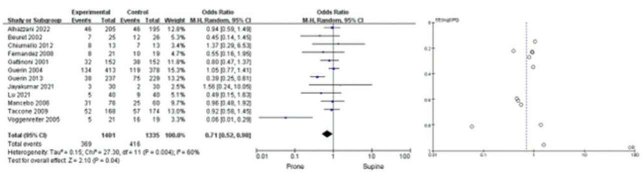


Note: This figure presents a graphical representation of the risk of bias assessment for the included studies. It provides an overview of the assessment results, indicating the potential sources of bias in each study. Additionally, it includes a bias summary, presenting a concise summary of the overall risk of bias in the included studies.

Primary Outcome: Mortality

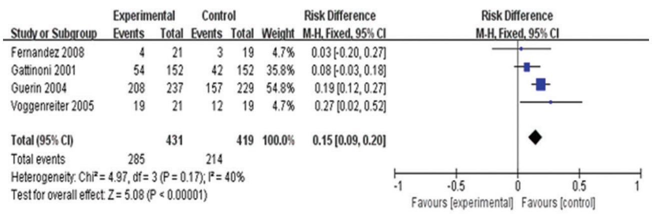
A total of twelve studies involving 2736 participants contributed data on mortality. The analysis resulted in an odds ratio (OR) of 0.71 (95% CI: 0.50 to 0.98; $P = .04$), signifying a lower mortality rate among patients in the prone positioning group, see Figure. 3. This study's findings provide compelling evidence that prone positioning holds the potential to mitigate the risk of mortality in individuals afflicted with ARDS.

Figure 3. Primary Outcome: Mortality Comparison between Prone and Supine Positions



Note: This figure visually depicts the primary outcome of the comparison of mortality rates between patients placed in the prone position and those in the supine position. It presents the relevant data and statistical analysis related to mortality outcomes in a clear graphical format.

Figure 4. Secondary Outcome: Pressure Sores Comparison between Prone and Supine Positions



Note: This figure provides a visual representation of the secondary outcome related to the comparison of pressure sore incidence between patients in the prone and supine positions. Each data point on the plot represents an individual study included in the analysis. Squares represent the study's estimated odds ratio, while horizontal lines indicate the corresponding confidence intervals (CI). The vertical line at the center signifies the null effect, indicating no difference.

Secondary Outcome: Pressure Sores

In the evaluation of pressure sores, a total of four studies involving 850 patients were analyzed. It was observed that patients placed in the prone position exhibited an elevated aggregate rate of pressure sores in comparison to those in the supine group (OR=0.15; 95% CI: 0.09-0.20). Detailed data is presented in Figure 4.

Secondary Outcome: Arrhythmia

The assessment of arrhythmia encompassed data from five studies involving a total of 2039 patients. Our meta-analysis revealed that concerning the incidence rate of arrhythmia occurrence, no statistically significant difference was observed between prone positioning and supine positioning (OR = 1.19, 95% CI: 0.59-2.39, P = .62, I^2 = 80%). Detailed findings are presented in Figure 5.

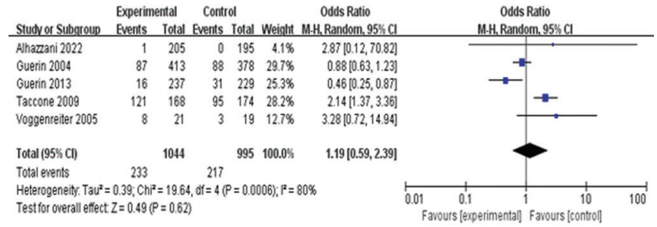
Secondary Outcome: Unplanned Extubation

Our meta-analysis results conclude that no statistically significant difference exists between prone positioning and supine positioning concerning the occurrence rate of unplanned extubation (OR = 1.12, 95% CI: 0.84-1.48, P = .45, I^2 = 14%). Refer to Figure 6.

Secondary Outcome: Pneumothorax

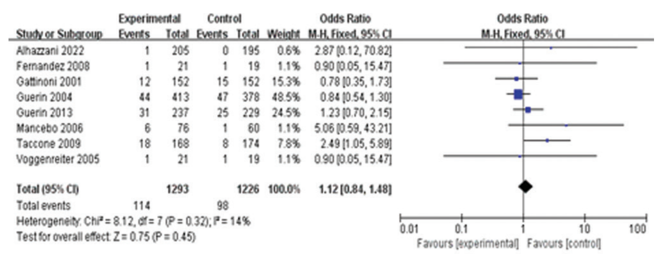
Three studies involving 967 participants were conducted under prone positioning conditions to assess the occurrence of pneumothorax. The results of our meta-analysis indicate that there are no statistically significant differences in the incidence rate of pneumothorax between patients positioned prone and those in the supine position regarding the occurrence of this condition (OR = 0.77, 95% CI: 0.46-1.29, P = .32, I^2 = 0%). Refer to Figure 7.

Figure 5. Secondary Outcome: Arrhythmia Comparison between Prone and Supine Positions



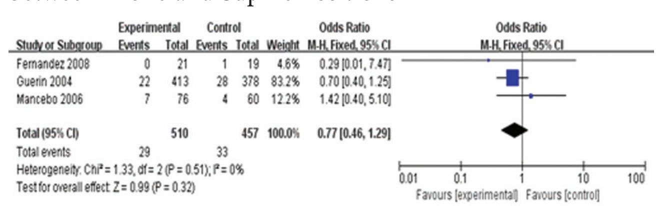
Note: This figure presents the results of the secondary outcome analysis, of the comparison of arrhythmia incidence between patients positioned in the prone and supine positions. Each data point on the plot represents an individual study included in the analysis. Squares represent the study's estimated odds ratio, while horizontal lines indicate the corresponding confidence intervals (CI). The vertical line at the center signifies the null effect, indicating no difference.

Figure 6. Secondary Outcome: Unplanned Extubation Comparison between Prone and Supine Positions



Note: This forest plot illustrates the results of a meta-analysis comparing the incidence of unplanned extubation between patients placed in the prone and supine positions. Each data point on the plot represents an individual study included in the analysis. Squares represent the study's estimated odds ratio, while horizontal lines indicate the corresponding confidence intervals (CI). The vertical line at the center signifies the null effect, indicating no difference in unplanned extubation rates between the two positions. Studies with squares to the right of the line favor the prone position, while those to the left favor the supine position.

Figure 7. Secondary Outcome: Pneumothorax Comparison between Prone and Supine Positions



Note: This forest plot presents the results of a meta-analysis assessing the incidence of pneumothorax in patients positioned either prone or supine. Each square on the plot corresponds to a specific study included in the analysis, with squares indicating the study's estimated odds ratio, and horizontal lines representing the associated confidence intervals (CI). The vertical line at the center denotes the null effect, indicating no significant difference in pneumothorax rates between the two positioning methods. Studies with squares to the right of the line favor the prone position, while those to the left favor the supine position.

DISCUSSION

This meta-analysis was based on twelve randomized trials from the past 23-year period. The initial findings from this meta-analysis indicate that patients with ARDS experience a reduced mortality rate when positioned in a prone posture. However, the rate of adverse events, particularly pressure sores, was higher in the prone group than in the supine group. Our findings indicate that prone positioning is associated with a survival benefit, aligning with consistent results from previous meta-analyses[21] and an observational study.[22] Interestingly, this finding contrasts with earlier randomized trials that did not identify a survival advantage.[23]

This meta-analysis involving ARDS studies has further demonstrated improved outcomes among patients with severe hypoxemia when placed in a prone position compared to those not in the same position. It is worth noting that despite strong evidence from large animal studies showcasing the lung-protective benefits of prone positioning, early randomized trials conducted on a non-selected population of patients experiencing oxygenation failure did not reveal a significant impact of prone ventilation on their mortality.[25]

In early studies, proning was predominantly employed as a rescue therapy for severe hypoxemia over numerous years. However, it is important to note that the methodology employed in these early studies has faced scrutiny, potentially leading to erroneous negative conclusions. One of the main challenges was that some of these early studies were not adequately powered to detect differences in mortality. Additionally, they involved limited daily periods of pronation and the excessive use of sedation.[26] It is noteworthy that ARDS patients with a propensity for hypoxemia tend to derive greater benefits from prone positioning, particularly when this approach is sustained for an extended duration.

Prone positioning offers stronger physiological justifications for benefiting patients with severe lung injuries. This is because severe lung injuries tend to be more pronounced and diverse, resulting in greater ventilation-perfusion mismatch in the lower lung regions when patients are in the supine position. Placing a patient in a prone position facilitates lung recruitment and reduces compliance disparities. As a result, oxygenation is improved, and the potential for harmful ventilation is minimized.[27]

The challenges in transitioning patients smoothly from a prone to seated position can result in various complications, including loss of venous access, vomiting, inadvertent extubation, device displacement, obstruction or dislodgment of an endotracheal tube, hemodynamic instability, brachial plexus injury, pressure ulcers.[28] However, in the context of ARDS patients, there is a lack of data available on this issue. Consequently, various strategies are under investigation to prevent complications in ARDS patients requiring prolonged periods of prone positioning.[29]

Recent research indicates that barotrauma, ventilator-associated pneumonia, accidental catheter removal, and unplanned extubation do not significantly differ between the supine and prone positions. However, pressure sores and endotracheal tube obstructions tend to increase when patients are in the prone position.[29]

Our findings similarly suggest that the prone position may elevate the occurrence of pressure ulcers while exhibiting no impact on pneumothorax, arrhythmia, and unplanned extubation. For instance, there was no significant difference between the prone and supine positions concerning accidental extubation, selective bronchial intubations, and endotracheal tube obstructions during intubation.[30] Effective prevention of these complications in the future is likely achievable through staff training and collaboration. Moreover, once the patient has been positioned in the prone posture, there is no subsequent increase in complications or the nursing workload associated with maintaining this position.

However, it is worth noting that reversible facial edema is a predictable occurrence when the prone position is maintained. Studies on patients receiving extracorporeal membrane oxygenation (ECMO) have reported minor complications related to the procedure.[31] Ensuring safety is of paramount importance to maximize benefits while minimizing harm. Thus, caregivers should receive continuous education and training.[32]

Besides the duration of the prone position, several other risk factors are associated with pressure ulcers in ARDS patients. These factors include hemodynamic instability, other organ dysfunctions, patient age, ICU length of stay, nutritional status, and immobility. A study revealed that by day 7, the prone position group had a higher incidence of pressure ulcers compared to the supine position group. It is important to note that the rate of pressure ulcers among patients discharged from the ICU did not differ between the groups at discharge.[33]

Our findings highlighted that prone positioning in patients with ARDS has potential benefits and associated risks. While it demonstrates promise in reducing mortality rates, we must remain vigilant regarding the increased occurrence of pressure ulcers. Moving forward, a balanced approach that prioritizes patient safety through staff training and collaboration will be important in optimizing the outcomes of ARDS patients placed in the prone position.

Study Limitations

We acknowledge a few limitations in this study. One notable limitation is the variability in selection criteria across the included trials, which encompasses differences in the interpretation and definition of acute respiratory distress syndrome. Such variations in trial design and patient inclusion criteria may have introduced heterogeneity that could affect the study outcomes. Additionally, it is important to acknowledge that despite our efforts, statistical tests may not always detect potential publication bias, and the possibility of such bias should be considered when interpreting the results. These limitations emphasize the need for caution in drawing definitive conclusions, and future research should strive for greater standardization in trial design and patient selection criteria.

CONCLUSION

In conclusion, our systematic review and meta-analysis of 12 randomized trials reveals a significant reduction in mortality rates among patients placed in the prone position compared to those in the supine position. However, it is crucial to acknowledge that this favorable outcome is tempered by an increased risk of pressure ulcers associated with prone positioning. These findings underscore the clinical relevance and potential benefits of incorporating prone positioning in the management of ARDS while emphasizing the critical importance of vigilant pressure ulcer prevention strategies. Moving forward, healthcare providers should carefully weigh the potential advantages of prone positioning against the risk of pressure ulcers, tailoring their approach to individual patient needs and ensuring the highest standard of care.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author upon reasonable request.

FUNDING

Not applicable.

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