# Mechanical Ventilation in Patients with Acute Brain Injury: Recommendations of a European Society of Intensive Care Medicine and Neurocritical Care Society Consensus

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**Word count:** 4249
**Abstract word count:** 250
**Figures:**0
**Tables:**2
**ESM:**1
**Short title:** Mechanical ventilation in ABI
**Keywords**: Mechanical ventilation; respiratory failure; ARDS; traumatic brain injury; acute stroke; subarachnoid haemorrhage.
**Funding:** None
**Endorsement:** This project is endorsed by the Executive Committee of the European Society of Intensive Care Medicine and by the Board of Directors of the Neurocritical Care Society.
**Conflict of interest:** GC is Editor in Chief of ICM. MS received speaker fee and travel grant from BARD Medical (Ireland) and a research grant from GE Healthcare. JB received Speaker

honoraria and travel support from Boehringer Ingelheim, Medtronic, Zoll, Sedana Medical. DS is PI of the SETPOINT2 trial on early tracheostomy in ventilated cerebrovascular ICU patients and participant in a PCORI Award for SETPOINT2. SE has support from Zoll, Siemens and Medtronic, research funding from Oridion, Diasorin, Haemonetics, participation in multicenter trials for Artisanpharma, Ely Lily, Takeda, Astra Zeneca, Eisai. The other authors have no COI to declare.

**PROSPERO registration:**
**https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=141604**

**Author contributions:**

- RS, CR: Conception of the work, supervision of the consensus development, participation in literature review and interpretation, drafting the article, critical revision of the article, final approval of the version to be published.
- GC, KA, DP, MM: Participation in the supervision of the consensus development, participation in literature review and interpretation, drafting and critical revisions of the manuscript, final approval of the version to be published.
- DP, MM: Assisted with literature data extraction, methodological rating, and biostatistical tasks including meta-analysis and analysis of voting results.
- All Authors: Participation in literature review and appraisal, online consensus statement voting, critical review of the manuscript and approval of the final version of the manuscript.

**Abstract**

*Purpose:* To provide clinical practice recommendations and generate a research agenda on mechanical ventilation and respiratory support in patients with acute brain injury (ABI).

*Methods:* An international consensus panel was convened including 29 clinician-scientists in intensive care medicine with expertise in acute respiratory failure, neurointensive care, or both, and two non-voting methodologists. The panel was divided in seven subgroups, each addressing a predefined clinical practice domain relevant to patients admitted to the intensive care unit (ICU) with ABI, defined as acute traumatic brain or cerebrovascular injury. The panel conducted systematic searches and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used to evaluate evidence and formulate questions. A modified Delphi process was implemented with four rounds of voting in which panellists were asked to respond to questions (rounds 1-3) then recommendation statements (final round). Strong recommendation, weak recommendation, or no recommendation were defined when >85%, 75%-85%, and <75% of panellists respectively agreed with a statement.

*Results:* The GRADE rating was low, very low, or absent across domains. The consensus produced 36 statements (19 strong recommendations, 6 weak recommendations, 11 no recommendation) regarding airway management, non-invasive respiratory support, strategies for mechanical ventilation, rescue interventions for respiratory failure, ventilator liberation, and tracheostomy in brain-injured patients. Several knowledge gaps were identified to inform future research efforts.

*Conclusions:* This consensus provides guidance for the care of patients admitted to the ICU with ABI. Evidence was generally insufficient or lacking, and research is needed to demonstrate the feasibility, safety, and efficacy of different management approaches.

## Introduction

Patients with acute brain injury (ABI) admitted to the intensive care unit (ICU) frequently require mechanical ventilation or other forms of respiratory support [1-6]. These patients can experience respiratory failure due to loss of airway protective reflexes or decreased respiratory drive and are at risk for pulmonary complications such as pneumonia and acute respiratory distress syndrome (ARDS) [3-6]. Mechanical ventilation is used as a mechanism to ensure reliable oxygen delivery and modulate cerebral hemodynamics through control of arterial carbon dioxide tension [1-6]. At the same time, mechanical ventilation can exert harmful effects on the brain due to complex physiological interactions between intrathoracic, central venous and intracranial compartments [1-6]. Lung-protective ventilation, widely implemented in critically ill patients, may be withheld from brain-injured patients due to such concerns [1-7]. There is lack of clarity not only about strategies of ventilation but also regarding decisions on tracheal intubation, ventilator liberation, extubation, and tracheostomy in the ABI population [5-9]. Additionally, the safety and efficacy of advanced rescue therapies for severe respiratory failure such as prone positioning, alveolar recruitment manoeuvres (ARMs), and extracorporeal membrane oxygenation (ECMO) are not established in this population [5].

To address these questions, we established a consensus panel with two primary tasks. First, to provide evidence-based recommendations on best clinical practices for mechanical ventilation in patients with ABI. And second, to identify knowledge gaps and suggest an agenda for research in this area. The panel addressed seven domains of clinical practice relevant to the target population: (1) indications for endotracheal intubation;(2) non-invasive interventions to ensure oxygenation and ventilation; (3) settings of mechanical ventilation; (4) targets for arterial blood gases; (5) rescue interventions in patients with concurrent ABI and severe respiratory failure; (6) criteria for ventilator liberation and tracheal extubation; and (7) criteria and timing for tracheostomy.

## Methods

*Panel Selection and Governance*

A multidisciplinary international consensus panel was assembled with 29 intensivists who were selected for their established clinical and scientific expertise in neurointensive care and/or in acute respiratory failure and mechanical ventilation. Additional criteria for panel selection included representation from scientific societies and individuals with proven

experience in consensus generation and guideline development. The consensus panel also included two non-voting methodologists who were invited to assist with literature data extraction, methodological rating, and who performed biostatistical tasks including meta-analysis and analysis of voting results.

The consensus was led by two chairpersons (RS, CR) who conceived of the project, established the aims, deliverables, milestones and timeline; engaged with European Society of Intensive Care (ESICM) and Neurocritical Care Society (NCS) leadership to obtain endorsement; organized and set the agenda for meetings; ensured communications with the panel; and drafted this report. The chairs worked closely within a six-member steering committee that included two methodologists (DP and MM) and two members of the panel (GC and KA). The consensus panel met by one teleconference and once in person, respectively in July and in October 2019, the latter organized in conjunction with the ESICM LIVES Conference in Berlin, Germany. The steering committee met monthly by teleconference. The steering committee identified seven domains of clinical practice and generated a list of questions to be addressed by the panel (Table 1).

*Consensus Subgroups*

The consensus panel was divided in seven subgroups, each tasked with one of the domains. Subgroups nominated a lead who served in a coordinating role, and subgroup communications were undertaken by email and teleconferences. Subgroup members refined the proposed question, generated the search strategy, performed the systematic search, and screened titles and abstracts based on predetermined inclusion and exclusion criteria.

*Article Selection, Data Extraction and Reporting*

Systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. A systematic search was performed by two experts in each subgroup, using MEDLINE, up to the dates indicated for each query in the Electronic Supplementary Material (ESM). The search codes for each subgroup are presented in the ESM. The search was set by including only original studies published in English in peer-review journals. Additionally, reference lists of the pre-screened studies were manually checked, using an iterative approach. Disagreements were discussed with the panel methodologists (DP, MM).

Studies were eligible for inclusion if they reported on adult patients with ABI, defined as an acute cerebral disorder consequent to trauma or to a cerebrovascular event (specifically subarachnoid haemorrhage, intracranial haemorrhage, or acute ischemic stroke). Studies on mechanical ventilation in other critically ill neurological populations (e.g. brain tumour, status epilepticus, anoxic-ischemic brain injury) were excluded. Significant intracranial pressure elevation was defined as >20 mmHg when invasive monitoring was available, or as clinical or radiological signs of intracranial hypertension [10].

Articles were included in the analysis if they met the following criteria: studies of adults (>18 years) admitted to the ICU with ABI, defined as above; clearly defined intervention and control groups; reported data on relevant outcome measures, such as clinical endpoints (survival, neurological or cognitive function, functional status) and/or physiological endpoints (intracranial pressure, cerebral oxygenation, cerebral blood flow, cerebral perfusion pressure, measures of lung function). Data from articles selected for full-text analysis were extracted using a standardized electronic form structured according to the population, intervention, comparison, and outcomes (PICO) model. Categorical variables were presented as event rates in treatment arms and controls, and absolute risks, absolute risk reductions, and relative risks computed. Continuous variables were reported as means or medians, standard deviation (SD) or interquartile ranges (IQR). Absolute and relative risks from randomized controlled trials (RCTs) were represented in Forest plots. Reporting on evidence rating, consensus methodology, statistical analysis and generation of the research agenda are in the ESM. Statements were classified as a *strong recommendation, weak recommendation,* and *no recommendation* when respectively >85%, 75-85% and <75% of votes were in favour.

**Results**

Results of the literature search, article selection, systematic review, GRADE rating and meta-analyses (when possible) for each domain are presented in the ESM. Overall, evidence was of low quality or lacking in nearly all domains and questions studied. The panel generated a total of 36 statements which are described hereafter, grouped according to the preestablished clinical practice domain (Table 1). Based on pre-established voting thresholds (ESM), 19 statements were strong recommendations, 6 were weak recommendations, and 11 were no recommendations. Ten of the 36 statements were based on some level of scientific evidence, while the remaining 26 were expert-determined (Table 1).

1. *What are the indications for endotracheal intubation in patients with ABI?*

*Rationale*

Despite the lack of scientific evidence, clinical experience in brain-injured patients and in critically ill patients helped the panel define a composite of factors that should inform the decision to intubate brain-injured patients. There was consensus regarding specific neurological factors as well as general factors such as acute respiratory or circulatory failure.

*Recommendations*

- We recommend that in patients with ABI, the decision to proceed with endotracheal intubation should be guided by a combination of factors including the level of consciousness, severe agitation and combativeness, loss of airway protective reflexes, significant ICP elevation (strong recommendation; no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who are comatose (Glasgow Coma Scale [GCS] ≤8) (strong recommendation; no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI when there is a loss of airway protective reflexes (strong recommendation, no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who have a significant elevation in intracranial pressure (strong recommendation, no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who have clinical evidence of brain herniation (strong recommendation, no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who have non-neurological indications for intubation (strong recommendation, no evidence; good practice statement).
- We suggest that endotracheal intubation should be considered in patients with ABI who have severe agitation and combativeness (weak recommendation, no evidence).

*2. Is it safe and effective to use non-invasive respiratory support in patients with ABI?*

*Rationale*

The panel noted that the quality of evidence was very low and did not reach consensus on the use of non-invasive ventilation in acute brain injured patients with TBI. Based on clinical experience and data in other populations, the following was stated:

*Recommendations*

- We are unable to provide a recommendation on the use of non-invasive positive pressure ventilation in patients with ABI who have hypercapnic or mixed hypercapnic/hypoxemic respiratory insufficiency (no recommendation, low evidence in favour).
- We suggest that high flow nasal cannula oxygen therapy may be considered in patients with ABI who have hypoxemic respiratory failure that is refractory to conventional supplemental oxygen (weak recommendation, no evidence).

*3. Should we use specific mechanical ventilation settings in patients with ABI?*

*Rationale*

The aim in this domain was to determine if specific ventilator settings (e.g. tidal volume, positive end expiratory pressure [PEEP]) would be beneficial in patients with ABI. An extensive review of the literature (ESM) revealed only marginal evidence for a specific strategy.

*Recommendations*

- We recommend that in mechanically ventilated patients with ABI without ARDS who do not have clinically significant ICP elevation, the same level of PEEP should be used as in patients without brain injury (strong recommendation, very low evidence in favour).
- We recommend that in mechanically ventilated patients with ABI without ARDS who have clinically significant ICP elevation that is PEEP-insensitive (patients who do not experience ICP elevation after increase of PEEP), the same level of PEEP should be used as in patients without ABI (strong recommendation, no evidence; good practice statement).
- We recommend that in mechanically ventilated patients with concurrent ABI and ARDS who do not have clinically significant intracranial pressure (ICP) elevation, a strategy of

lung protective mechanical ventilation should be used (strong recommendation, no evidence, good practice statement).

- We suggest that in mechanically ventilated patients with ABI without ARDS without clinically significant ICP elevation, a strategy of lung protective mechanical ventilation should be considered (weak recommendation, no evidence).
- We are unable to provide a recommendation regarding lung protective mechanical ventilation in mechanically ventilated patients with ABI without ARDS who have clinically significant ICP elevation (no recommendation, no evidence).
- We are unable to provide a recommendation regarding lung protective mechanical ventilation in mechanically ventilated patients who have concurrent ABI, ARDS, and clinically significant ICP elevation (no recommendation, no evidence).

4. *Should we target specific values of partial pressure of oxygen ($PaO_2$) and partial pressure of carbon dioxide ($PaCO_2$) in patients with ABI?*

*Oxygen levels*

*Rationale*

The panel concluded that there is enough data to suggest that both hypoxemia and hyperoxia should be avoided in ABI patients as both may have an unfavourable impact on clinical outcomes. Although specific targets for PaO2 would optimally need to individualised on the basis of disease-, context- and patient-specific features, the panel agreed on a general recommendation of normoxia.

*Recommendations*

- We recommend that the optimal target range of $PaO_2$ in patients with ABI who do not have clinically significant ICP elevation is 80-120 mmHg (strong recommendation, low-quality evidence).
- We recommend that the optimal target range of $PaO_2$ in patients with ABI who have clinically significant ICP elevation is 80-120 mmHg (strong recommendation, no evidence; good practice statement).

*PaCO2 and short-term hyperventilation*

*Razionale*

The panel considered at some length the question of $PaCO_2$ targets in ABI, including existing guidelines which recommend short-term mild hyperventilation in the management of TBI patients who have increased intracranial pressure [29]. Despite the overall low level of evidence on this topic, there was agreement to recommend targeting a normal range of $PaCO_2$ values in the absence of increased ICP and hyperventilation as a therapeutic option in patients with brain herniation. Conversely, panel members expressed differing views regarding hyperventilation as a therapeutic option in patients who have clinically significant ICP elevation, and a consensus was not obtained regarding this question.

*Recommendations*

- We recommend that the optimal target range of $PaCO_2$ in patients with ABI who do not have clinically significant ICP elevation is 35-45 mmHg (strong recommendation, low quality evidence).
- We recommend short-term hyperventilation as a therapeutic option in patients with ABI who have brain herniation (weak recommendation, no evidence).
- We are unable to provide a recommendation regarding the use of short-term hyperventilation as a therapeutic option in patients with ABI who have clinically significant ICP elevation (no recommendation, no evidence).

5. *Is it safe and effective to use rescue interventions to support severe respiratory failure in patients with ABI?*

*Alveolar recruitment manoeuvres*

*Rationale*

The panel felt that the issue was insufficiently investigated, and attention should be paid to achieving a balance between expected improvements in oxygenation and potentially detrimental effects on ICP and CPP.

*Recommendations*

- We are unable to provide a recommendation regarding the use of alveolar recruitment manoeuvres in mechanically ventilated patients who have concurrent ARDS and ABI who do not have significant ICP elevation (no recommendation, very low evidence in favour).

- We are unable to provide any recommendations regarding the use of alveolar recruitment manoeuvres in mechanically ventilated patients who have concurrent ARDS and ABI who have significant ICP elevation (no recommendation, very low evidence in favour).

*Prone positioning*

*Rationale*

Despite the low level of evidence, the panel recommended prone positioning when ICP is not increased, given the favourable effect on ARDS outcome and the potentially beneficial increases in brain oxygenation. However, questions remain regarding significant ICP elevation since prone position could mediate detrimental effects on intracranial physiology.

*Recommendation*

- We recommend that prone positioning may be considered in mechanically ventilated patients who have concurrent moderate or severe ARDS (PaO2/FiO2 ratio<150) and ABI, but do not have significant ICP elevation (strong recommendation, very low evidence in favour).
- We are unable to provide any recommendations regarding the use of prone positioning in mechanically ventilated patients who have concurrent moderate or severe ARDS (PaO2/FiO2<150), ABI and significant ICP elevation (no recommendation, no evidence).

*Neuromuscular blockers*

*Rationale*

The panel found no studies on the use of neuromuscular blockers as a rescue therapy for patients with concurrent ABI and ARDS. However, based on evidence suggesting beneficial effects in severe ARDS [11-13], the panel ruled in favour of short-term use of neuromuscular blocker infusions.

*Recommendation*

We recommend that short-term treatment with a neuromuscular blocker, in combination with appropriate sedation, may be considered in mechanically ventilated patients who have concurrent ABI and severe ARDS (strong recommendation, no evidence; good practice statement).

*Extracorporeal Life Support*

*Rationale*

Experience with ECMO and extracorporeal $CO_2$ removal ($ECCO_2R$) in ABI with severe respiratory failure patients is limited due to serious concerns regarding the safety of these techniques in patients with, or at risk of, intracranial haemorrhage and cerebral ischemia following ABI. Small case series and case reports were identified evaluating ECMO in patients with both ABI and ARDS, none which reported serious neurological complications [ESM - Group NV5]. However, after discussion, the panel did not reach a consensus on the use of these techniques.

*Recommendations*

- We are unable to provide a recommendation regarding the use of ECMO in mechanically ventilated patients who have concurrent ARDS and ABI (no recommendation, very low evidence in favour).
- We are unable to provide a recommendation regarding the use of $ECCO_2R$ in mechanically ventilated patients who have concurrent ARDS and ABI (no recommendation, no evidence).

*6. What are the criteria for ventilator weaning and extubation in patients with ABI?*

*Rationale*

The panel identified variables that should be considered in the decision to wean and extubate this subpopulation including neurological and non-neurological features. A consensus was not reached regarding a specific GCS threshold to guide the decision to extubate.

*Recommendations*

- We recommend that the decision to extubate patients with ABI should be guided by several factors including the expected clinical trajectory of the underlying neurological condition, the level of consciousness, the presence of airway protective reflexes, and factors relevant to the extubation of non-neurological patients (strong recommendation, moderate evidence in favour).
- We recommend that the neurological status should be accounted for in making the decision to wean mechanical ventilation in patients with ABI (strong recommendation, no evidence; good practice statement).

- We recommend that the decision to extubate patients with ABI should account for the expected clinical trajectory of the underlying neurological condition (strong recommendation, no evidence; good practice statement).
- We suggest that the decision to extubate patients with ABI should account for the level of consciousness (weak recommendation, no evidence).
- We recommend that the decision to extubate patients with ABI should account for airway protective reflexes (cough, gag, swallowing) (strong recommendation, no evidence; good practice statement).
- We are unable to provide any recommendations regarding a specific GCS threshold to be considered in the decision to extubate mechanically ventilated acute brain injured patients (no recommendation, no evidence).

*7. What are the indications for and optimal timing of tracheostomy in patients with ABI?*

*Indications for tracheostomy*

*Rationale*

Despite the lack of high quality evidence, based on clinical experience and on the literature from the general ICU population, the panel determined that a major determinant in the decision to perform tracheostomy should be one or more failed attempts of extubation trials and persistently depressed responsiveness.

*Recommendations*

- We recommend that tracheostomy should be considered in mechanically ventilated patients with ABI who have failed one or several trials of extubation (strong recommendation, no evidence; good practice statement).
- We suggest that tracheostomy should be considered in mechanically ventilated patients with ABI who have persistently reduced level of consciousness (weak recommendation, contradictory low-level evidence).

*Timing of tracheostomy*

*Rationale*

The panel noted that the decision regarding timing of tracheostomy varies considerably across countries and medical institutions and may depend considerably on local practices and policies. Therefore, the panel did not reach a consensus.

*Recommendation*

We are unable to provide a recommendation regarding the optimal timing of tracheostomy in patients with ABI (no recommendation, contradictory low-quality evidence).

**Discussion**

The recommendations contained in this document are intended as guidance to clinicians managing patients admitted to the ICU with ABI. These recommendations were generated via a rigorous methodology that included a comprehensive systematic review and grading of available evidence, the engagement of a multidisciplinary, international expert panel, and the iterative refinement of consensus statements using the modified Delphi method. The principal limitation encountered was the paucity or lack of robust scientific evidence on many of the clinical questions posed, which means that several of the recommendations are based on the collective expert opinions of the panel [14-19]. As a corollary of this limitation, several knowledge gaps were identified, which have helped to establish an agenda for research (Table 2).

The decision to intubate a patient with isolated ABI in the absence of intrinsic respiratory failure is very common in emergency and intensive care medicine, yet scientific evidence is lacking to support specific approaches. Intubation is lifesaving in severe ABI patients and not beneficial in milder forms of ABI, yet the role of intubation in intermediate severity ABI remains unclear [18]. Intubation commits patients to a course of mechanical ventilation and sedation, which significantly curtails the ability to clinically assess neurological function at the bedside. Studies are needed to explore strategies (including timing) regarding endotracheal intubation in the ABI population. These studies should be stratified according to ABI aetiology (TBI, SAH, ICH, AIS) and consider the relative importance of clinical factors such as neurological severity (e.g. GCS), presence of airway protective reflexes, agitation or combativeness, ICP elevation, predicted clinical trajectory (e.g. likelihood and time-course of neurological worsening, the need for surgery or interventional management), and non-neurological injury or organ failure.

Invasive ventilation is used in patients with severe ABI to counter dysregulated breathing patterns and to maintain $PaO_2$ and $PaO_2$ within physiological ranges [19]. This enables effective and reliable oxygen delivery to the brain and provides a mechanism to indirectly control cerebral perfusion via adjustment of minute ventilation and PaCO2. Yet these principles, well-established in neurointensive care, seem at variance with lung protective strategies which aim to reduce ventilator induced lung injury (VILI) via settings in which relative hypercapnia and hypoxemia may be permitted. Lung protective ventilation has been associated with significantly higher survival in clinical trials of patients with ARDS [20-24]

and with improved outcomes in mechanically ventilated ICU and surgical populations who do not have ARDS [25,26]. Although patients with ABI have consistently been excluded from these trials, the Consensus recommended that patients with ABI who do not have ICP elevation should receive lung protective ventilation and PEEP as other mechanically ventilated patients would. Clinical trials are needed to determine the safety and efficacy of different lung protective ventilation strategies in ABI patients, both with and without ARDS. These trials should be stratified by ABI aetiology and neurological severity and consider a range of different endpoints both proximal (neurophysiological impact, biomarkers of VILI) and more distal (mortality, neurological outcome, duration of mechanical ventilation and stay in the hospital).

Regarding arterial blood gases, the consensus recommended avoidance of hyperoxia and hypoxia, both associated with poor outcome after ABI. The panel recommended maintaining PaO2 80—120 mmHg, higher compared to the range commonly targeted in the general ICU population (55—80 mmHg)[27]. Overall, research is warranted to identify optimal PaO2 targets in this population. One approach will be to leverage large-scale multi-site observational studies using multivariable modelling, to precisely determine associations between specific PaO2 thresholds or target ranges and clinically significant outcomes in stratified ABI populations.

The panel recommended normocapnia in ABI patients without ICP elevation. It also recommended short-term hyperventilation in patients with cerebral herniation. However, there was a lack of agreement on the use of short-term mild hyperventilation (PaCO2 target 30-35 mmHg) to treat elevations in ICP. Although it is part of the staircase approach for the management of ICP, hyperventilation causes cerebral vasoconstriction and has been associated with poor outcome in the Lung Safe cohort[28], perhaps due to an increase in mechanical power[29]. While early studies have explored this issue [30], contemporary trials are needed to investigate the effect of short courses of hyperventilation, in conjunction with other measures, on physiological endpoints and clinical outcomes in patients who have intracranial hypertension.

Little is known about how ventilator liberation should be accomplished in the setting of ABI [31]. Available evidence and clinical experience suggest that decisions on ventilator weaning and tracheal extubation must integrate neurological features with other systemic variables,

and this is the approach recommended by the panel. Mechanical ventilation may be prolonged unnecessarily, or tracheostomy performed prematurely, in a subset of patients who could have been successfully extubated. Studies are needed to investigate more precise approaches for ventilator weaning and extubation in the target population. Multivariable models should be tested and validated to individualize management based on patient-specific clinical and physiological features. Clinical trials should evaluate the effectiveness and efficacy of different liberation strategies. These trials could be designed to integrate tracheostomy either as a treatment arm or as an outcome variable.

Timely tracheotomy represents a means of effectively weaning sedation and discontinuing mechanical ventilation in patients who require an artificial airway but are otherwise able to breathe independently. Yet studies indicate that the selection of ABI patients for tracheostomy is highly variable, often dependent on regional or institutional factors [31,32]. Our panel recommended consideration of this procedure in mechanically ventilated ABI patients who are persistently unconscious (but with an expected acceptable quality of life) or when one or several trials of extubation have failed; however, there was no consensus on the optimal timing of tracheostomy. Carefully designed studies would be needed to validate tracheostomy decision algorithms for patients with ABI, and to determine the optimal timing of this procedure based on patient-specific factors. Trials should consider stratification by ABI aetiology, severity and predicted natural history.

The management of patients with concurrent ABI and acute respiratory failure is a specific scenario which merits further discussion. In the general ICU population, there is extensive evidence supporting non-invasive strategies, such as BiPAP and high-flow nasal canula oxygen, for patients who have acute respiratory failure and an underlying cause that can be effectively treated in a relatively short time frame [33]. Randomised trials in carefully selected respiratory failure patients show that when compared to invasive ventilation, non-invasive techniques can significantly improve outcomes including survival [34]. Importantly, preserved consciousness and airway protective reflexes are generally viewed as prerequisites for the successful use of these methods. The consensus panel found very limited evidence on the use of non-invasive respiratory support in patients who have acute respiratory failure in the setting of ABI, however it did recommend consideration of high-flow oxygen therapy in selected patients with hypoxemia. These results are likely a reflection of clinical observations among members of the panel that high flow nasal cannula oxygen therapy might be beneficial

and is associated with a low risk of adverse effects. Studies are needed to determine the indications, safety, and efficacy of non-invasive strategies in selected ABI patients.

One additional clinical scenario which needs special consideration is that of patients who have ARDS in the setting of neurological injury. It has been reported that up to one third of mechanically ventilated patients with ABI can develop ARDS [5]. Several interventions have been validated as effective rescue therapies to increase survivability in patients with ARDS refractory hypoxemia [5,22]. These interventions, which include alveolar recruitment manoeuvres, prone positioning, neuromuscular blocking agents, and ECMO, are increasingly used as part of a stepwise algorithm for patients in the severe ARDS stratum, however their feasibility and safety in ABI patients with ARDS is undetermined. A significant subset of ABI patients have concurrent spinal injuries and prone positioning might be unsafe in this group. ECMO generally requires systemic anticoagulation which could have catastrophic consequences in patients with recent ABI[35-36]. The consensus panel recommended consideration of prone positioning and neuromuscular blocking drug infusions, but it was unable to provide a recommendation on the use of alveolar recruitment or ECMO. Studies are needed to guide clinicians in selecting patients with concurrent ABI and ARDS who are most likely to benefit, and least likely to be harmed, by these therapies.

In summary, this consensus statement proposes guidance for clinicians on mechanical ventilation and respiratory support in critically ill ABI patients. As with all guidelines, the recommendations provided here must implemented in a treatment plan that is individualized and considers not only physiological parameters but patient co-morbidities and clinical trajectory. The panel found deficiencies in the scientific evidence across the domains studied, underscoring an urgent need for innovative and high-quality research to improve the care and outcomes in this population. Well-designed randomized controlled trials are needed to explore the role of different ventilator strategies and physiologic targets in this specific population. A promising direction is the possibility of personalizing therapy based on patient-specific clinical and physiological features, for example data from multimodal neuromonitoring techniques.

**Table 1. Domains Addressed by the Consensus and Recommendations.**

| Domain | Consensus Recommendation | Level of Recommendation | Level of Evidence |
|---|---|---|---|
| 1.What are the indications for endotracheal intubation in patients with ABI? | 1. We recommend that in patients with ABI, the decision to proceed with endotracheal intubation should be guided by a combination of factors including the level of consciousness, severe agitation and combativeness, loss of airway protective reflexes, significant ICP elevation (strong recommendation; no evidence; good practice statement). | Strong Recommendation | No evidence |
| | 2. We recommend that endotracheal intubation should be considered in patients with ABI who are comatose (GCS≤8) | Strong Recommendation | No evidence |
| | 3. We recommend that endotracheal intubation should be considered in patients with ABI when there is a loss of airway protective reflexes | Strong Recommendation | No evidence |
| | 4. We recommend that endotracheal intubation should be considered in patients with ABI who have significant elevation in intracranial pressure | Strong Recommendation | No evidence |
| | 5. We recommend that endotracheal intubation should be considered in patients with ABI who have clinical evidence of brain herniation | Strong Recommendation | No evidence |
| | 6. We recommend that endotracheal intubation should be considered in patients with ABI who have non-neurological indications for intubation | Strong Recommendation | No evidence |
| | 7. We suggest that endotracheal intubation should be considered in patients with ABI who have severe agitation and combativeness | Weak Recommendation | No evidence |
| 2.Is it safe and effective to use non-invasive respiratory support (e.g. high-flow nasal canula, NIPPV) in patients with ABI? | 8. We are unable to provide a recommendation on the use of noninvasive positive pressure ventilation in patients with ABI who have hypercapnic or mixed hypercapnic/hypoxemic respiratory insufficiency | No Recommendation | Low evidence in favor |
| | 9. We suggest that high flow nasal cannula oxygen therapy may be considered in patients with ABI who have hypoxemic respiratory failure that is refractory to conventional supplemental oxygen, provided there are no contraindications | Weak Recommendation | No evidence |
| 3.Should we use specific mechanical ventilation settings (e.g. tidal volume/PBW; PEEP; FiO2) and target specific respiratory physiologic parameters (e.g. Pplat) in patients with ABI? | 10. We recommend that in mechanically ventilated patients with ABI who do not have clinically significant ICP elevation, the same level of PEEP should be used as in patients without brain injury | Strong Recommendation | Very low evidence in favour |
| | 11. We recommend that in mechanically ventilated patients with ABI who have clinically significant ICP elevation that is PEEP-insensitive, the same level of PEEP should be used as in patients without ABI | Strong Recommendation | No evidence |
| | 12. We recommend that in mechanically ventilated patients with concurrent ABI and ARDS who do not have clinically significant ICP elevation, a strategy of lung protective mechanical ventilation should be used | Strong Recommendation | No evidence |
| | 13. We suggest that in mechanically ventilated patients with ABI without clinically significant ICP elevation, a strategy of lung protective mechanical ventilation should be considered | Weak Recommendation | No evidence |

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|---|---|---|---|
| | 14. We are unable to provide a recommendation regarding lung protective mechanical ventilation in mechanically ventilated patients with ABI who have clinically significant ICP elevation | No Recommendation | No evidence |
| | 15. We are unable to provide a recommendation regarding lung protective mechanical ventilation in mechanically ventilated patients who have concurrent ABI, ARDS, and clinically significant ICP elevation | No Recommendation | No evidence |
| 4.Should we target specific values of pH, PaO2 and PaCO2 in patients with ABI? | 16. We recommend that the optimal target range of PaO2 in patients with ABI who do not have clinically significant ICP elevation is 80-120 mmHg | Strong Recommendation | Contradictory low-quality evidence |
| | 17. We recommend that the optimal target range of PaO2 in patients with ABI who have clinically significant ICP elevation is 80-120 mmHg | Strong Recommendation | No evidence |
| | 18. We recommend that the optimal target range of PaCO2 in patients with ABI who do not have clinically significant ICP elevation is 35-45 mmHg | Strong Recommendation | Low quality evidence |
| | 19. We recommend hyperventilation as a therapeutic option in patients with ABI who have brain herniation | No Recommendation | No evidence |
| | 20. We are unable to provide a recommendation regarding the use of hyperventilation as a therapeutic option in patients with ABI who have clinically significant ICP elevation | Weak Recommendation | No evidence |
| 5.Is it safe and effective to use rescue interventions (e.g. neuromuscular blockade, prone positioning, extracorporeal membrane oxygenation) to support respiratory failure in patients with ABI? | 21. We are unable to provide a recommendation regarding the use of alveolar recruitment manoeuvres in mechanically ventilated patients who have concurrent ARDS and ABI who do not have significant ICP elevation | No Recommendation | Very low evidence in favour |
| | 22. We are unable to provide any recommendations regarding the use of alveolar recruitment manoeuvres in mechanically ventilated patients who have concurrent ARDS and ABI who have significant ICP elevation | No Recommendation | Very low evidence in favour |
| | 23. We recommend that prone positioning may be considered in mechanically ventilated patients who have concurrent ARDS and ABI, but do not have significant ICP elevation | Strong Recommendation | Very low evidence in favour |
| | 24. We are unable to provide any recommendations regarding the use of prone positioning in mechanically ventilated patients who have concurrent ARDS, ABI and significant ICP elevation | No Recommendation | No evidence |
| | 25. We recommend that short-term treatment with a neuromuscular blocker, in combination with appropriate sedation, may be considered in mechanically ventilated patients who have concurrent ABI and severe ARDS | Strong Recommendation | No evidence |

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|---|---|---|---|
| | 26. We are unable to provide any recommendations regarding the use of ECMO in mechanically ventilated patients who have concurrent ARDS and ABI | No Recommendation | Very low evidence in favour |
| | 27. We are unable to provide any recommendations regarding the use of $ECCO_2R$ in mechanically ventilated patients who have concurrent ARDS and ABI | No Recommendation | No evidence |
| 6.What are the criteria for ventilator weaning in patients with brain injury? What are the criteria for extubation in patients with brain injury? | 28. We recommend that the decision to extubate patients with ABI should be guided by several factors including the expected clinical trajectory of the underlying neurological condition, the level of consciousness, the presence of airway protective reflexes, and factors relevant to the extubation of non-neurological patients | Strong Recommendation | Moderate evidence in favour |
| | 29. We recommend that the neurological status should be accounted for in making the decision to wean mechanical ventilation in patients with ABI | Strong Recommendation | No evidence |
| | 30. We recommend that the decision to extubate patients with ABI should account for the expected clinical trajectory of the underlying neurological condition | Strong Recommendation | No evidence |
| | 31. We suggest that the decision to extubate patients with ABI should account for the level of consciousness | Weak Recommendation | No evidence |
| | 32. We recommend that the decision to extubate patients with ABI should account for airway protective reflexes (cough, gag, swallowing) . | Strong Recommendation | No evidence |
| | 33. We are unable to provide any recommendations regarding a specific GCS threshold to be considered in the decision to extubate mechanically ventilated acute brain injured patients. | No Recommendation | No evidence |
| 7.What are the indications for tracheostomy in patients with ABI? What is the optimal timing of tracheostomy in in patients with ABI? | 34. We recommend that tracheostomy should be considered in mechanically ventilated patients with ABI who have failed one or several trials of extubation | Strong Recommendation | No evidence |
| | 35. We suggest that tracheostomy should be considered in mechanically ventilated patients with ABI who have persistently reduced level of consciousness | Weak Recommendation | Contradictory low-quality evidence |
| | 36. We are unable to provide a recommendation regarding the optimal timing of tracheostomy in patients with ABI | No Recommendation | Contradictory low-quality evidence |

ABI, acute brain injury; ARDS, acute respiratory distress syndrome; ECCO2R, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation; ICP, intracranial pressure; GCS, Glasgow Coma Scale; LPV, lung protective ventilation; NMB, neuromuscular blocker ; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide;PEEP, positive end expiratory pressure.

## Table 2. Proposed Scientific Agenda on Mechanical Ventilation and Respiratory Support in ABI

| Clinical Context | Knowledge Gaps | Study Design Considerations | Endpoints of Interest |
|---|---|---|---|
| **ABI** | Clinical indications for intubation | Pragmatic trials comparing different strategies/algorithms (including timing) regarding intubation in ABI patients stratified by aetiology and severity | Mortality, neurological outcome<br>Duration of MV<br>Length of stay in ICU and hospital |
| | Optimal PaO2 and PaCO2 levels | Adequately powered observational data<br>Pragmatic trials comparing different PaO2 and PaCO2 targets in selected ABI patients/settings<br>Use of prognostic enrichment strategies | Physiological effects<br>Mortality, neurological outcome |
| | Role of lung protective ventilation | Explanatory and pragmatic trials comparing LPV with conventional ventilation, or different intensities of LPV, in in ABI patients stratified by aetiology and severity | Physiological effects<br>Markers of VILI<br>Mortality, neurological outcome<br>Duration of mechanical ventilation<br>Length of stay in ICU and hospital |
| | Ventilator liberation | Statistical models exploring factors independently associated with successful extubation<br>Explanatory and pragmatic trials comparing different strategies for ventilator liberation in selected ABI patients/settings | Tracheostomy<br>Mortality, neurological outcome<br>Duration of mechanical ventilation<br>Length of stay in ICU and hospital |
| | Clinical indications for tracheostomy | Explanatory and pragmatic trials comparing tracheostomy vs extubation strategies in selected ABI patients/settings<br>Use of predictive enrichment strategies to optimize patient selection | Mortality, neurological outcome<br>Duration of mechanical ventilation<br>Length of stay in ICU and hospital |
| | Timing of tracheostomy | Explanatory and pragmatic trials comparing tracheostomy at different timepoints in selected ABI patients/settings | Mortality, neurological outcome<br>Duration of mechanical ventilation<br>Length of stay in ICU and hospital |
| **ABI and ICP elevation** | Role of short-term hyperventilation | Analysis of high-resolution physiological time series data<br>Pragmatic trials evaluating hyperventilation strategies/durations for the management of clinically significant ICP elevation | Safety<br>Efficacy in reducing ICP<br>Mortality, neurological outcome |
| **ABI and acute respiratory failure** | Role of non-invasive ventilation | Analysis of observational data<br>Pragmatic trials comparing non-invasive ventilation with invasive ventilation in selected ABI patients/settings stratified by aetiology and severity<br>Use of predictive enrichment strategies to optimize patient selection | Safety (e.g. risk of aspiration)<br>Physiological effects<br>Conversion to invasive ventilation<br>Mortality, neurological outcome<br>Length of stay in ICU and hospital<br>Sedative use in ICU<br>Barriers to clinical neurological assessment in ICU |
| | Role of high flow oxygen therapy | Analysis of observational data<br>Pragmatic trials comparing high flow oxygen therapy with other invasive ventilation in selected ABI patients/settings<br>Use of predictive enrichment strategies to optimize patient selection | Safety (e.g. risk of aspiration)<br>Physiological effects<br>Conversion to invasive ventilation<br>Mortality, neurological outcome<br>Length of stay in ICU and hospital<br>Sedative use in ICU<br>Barriers to clinical neurological assessment in ICU |
| **ABI and ARDS** | Role of lung protective ventilation | Explanatory and pragmatic trials comparing LPV with conventional ventilation, or different intensities of LPV, in in ABI patients stratified by aetiology and severity | Physiological effects<br>Sedative use in ICU<br>Mortality, neurological outcome<br>Duration of mechanical ventilation<br>Length of stay in ICU and hospital |
| | Role of neuromuscular blocker therapy | Analysis of observational data<br>Explanatory and pragmatic trials evaluating NMB therapy in selected patients with concurrent ABI and severe ARDS | Physiological effects<br>Mortality, neurological outcome<br>Duration of mechanical ventilation<br>Length of stay in ICU and hospital<br>Barriers to clinical neurological assessment in ICU |

| | | | |
|---|---|---|---|
| | Role of prone positioning | Analysis of observational data<br>Pragmatic trials evaluating prone positioning in selected patients with concurrent ABI and severe ARDS<br>Use of predictive enrichment strategies to optimize patient selection | Safety<br>Physiological effects<br>Mortality, neurological outcome<br>Duration of mechanical ventilation<br>Length of stay in ICU and hospital<br>Sedative use in ICU<br>Barriers to clinical neurological assessment in ICU |
| | Role of ECMO | Analysis of observational data<br>Pragmatic trials evaluating management with and without ECMO in selected patients with concurrent ABI and severe ARDS<br>Use of predictive enrichment strategies to optimize patient selection | Safety<br>Neurological complications (e.g intracranial haemorrhage)<br>Physiological effects<br>Mortality, neurological outcome<br>Length of stay in ICU and hospital |

ICP, intracranial pressure; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ECCO2R, extracorporeal carbon dioxide removal; VILI, ventilator induced lung injury; LPV, lung protective ventilation; NMB, neuromuscular blocker

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# Mechanical Ventilation in Patients with Acute Brain Injury: Recommendations of a European Society of Intensive Care Medicine and Neurocritical Care Society Consensus

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## Electronic Supplementary Material

***Index***

***Evidence Rating***

The study was conducted according to the PRISMA guidelines[1]. The evidence reported in RCTs and observational studies was rated by the Consensus Methodologists in accordance with Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [2]. GRADE ranks evidence on a four-level scale ranging from "high" to "very low", expressing confidence on the estimates of the effect. RCTs provide default "high" quality that can be downgraded if bias or other limitations are present. Observational studies, instead, are initially rated as "low" quality but can be up- or down-graded depending on specific methodological features. According to GRADE rating, "very low" quality indicates that uncertainty of the documented effects is so high as to be compatible with substantially different true effects (including absence of any effect). The GRADE system emphasizes adequate control for confounding which implies that when a model purpose is explanatory, all known prognostic factors should be measured and included in the model [2-5]. Although the GRADE rating was developed for bodies of evidence, we applied its evidence quality criteria first to single studies, along with the criteria below, and then proceeded with body evidence analysis as a subsequent step. The GRADE rating was performed after having verified that individual studies met these additional criteria:

1. High quality reporting (rated "partial" or "sufficient for quality assessment") according to the Consolidated Standards of Reporting Trials (CONSORT) statement for RCTs[6] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (https://www.strobe-statement.org/index.php?id=strobe-home).
2. Absence of methodological and statistical flaws not detailed by the GRADE system such as risk of over-fitting when less than 10 outcomes per variable are available, bivariate statistics tests used to screen variables for multivariable analysis, abuse of automatic variable selection procedures, not accounting for immortal-time bias when dealing with time-dependent treatments, not balancing the probability of receiving a specific treatment with propensity scores [7-13].
3. Absence of external validity issues, such as specificity of case-mix, of treatment protocols, of health-care settings [14].

The GRADE rating of studies not meeting one or several of these criteria was further downgraded.

***Consensus Methodology***

We implemented a modified Delphi method since a phase of literature systematic review and grading preceded the consensus phase. The aim of the consensus was to reduce the heterogeneity of the different points of view to reach, in the end, the highest possible degree of convergence. Consensus panel members were instructed to review the literature summary statements and quality of evidence assessments, and then express their degree of agreement with a series of questions or statements using a 10-point Likert scale distributed as four sequential online surveys from January to May 2020. Each panel member voted independently and was able to annotate their responses with specific comments during the first three voting rounds. We incorporated an iterative approach aimed at generating a set of questions most relevant to the panel, and modified questions in round two and three based on comments from the prior round. In the final round of voting, only minor rewording of statements was allowed, rather than intervention or contextual changes to content. In each round, we provided members of the panel with the frequency distribution of responses recorded in the previous round, inviting the members to evaluate their previous answers and revise as needed. Panel members were not shown the individual responses of their peers at any time until the final iteration was reached.

The objective was to reach consensus and not agreement, meaning that the final choice of the group may not have been the first choice of an individual member who, according to *cooperative* behaviour, should adopt whenever possible a *stand-aside* position. No blocking positions were permitted. After each round, we analysed answers to spot heterogeneity and inconsistent patterns of individual member answers. In these cases, individual members were contacted by email or by phone to verify the correct understanding of the questions and query whether they wanted to maintain or modify their answers. The analysis of voting results was performed by a non-voting member Methodologist (DP) on the Panel. Since evidence was lacking or insufficient in many instances, the majority of recommendations were based on expert opinion, and a decision rule was predefined to ascertain the degree of consensus required to provide a recommendation.

***Statistical Analysis***

*Analysis of Published Literature*

When indicated, we combined studies in meta-analyses applying random-effects model using restricted maximum-likelihood for the estimation of variance (REML)[15]. Heterogeneity was measured with $I^2$, the percentage of total variation attributable to true heterogeneity and not to chance[16, 17], performing the Cochran's Q statistical test under the null hypothesis of homogeneity [18]. Although some authors consider $I^2$ as a descriptive statistics more than a point estimate [19], we reported $I^2$ 95%-confidence intervals, an approach which is considered important by some authors for the assessment of heterogeneity [20-22].

*Analysis of Consensus Voting*

Percentages and correspondence analysis mapping were used to assess the distribution of answers. We analysed the data with hierarchical clustering to develop dendrograms and used multiscale bootstrap resampling (with 1000 samples randomly generated) to calculate p-values [15]. This approach helped identify subgroups with homogenous distribution patterns accounting for random variation. At the individual level this allowed detection of heterogeneous voting patterns, which could be connected with misunderstanding of questions or truly heterogeneous positions. In both cases this enabled refinement of the questionnaires in terms of intelligibility or in terms of contents, respectively. These analyses helped define clusters according to the prevalent opinions in the panel, creating the basis for the final statements.

***Research Agenda generation***

Based on the knowledge gaps identified in the systematic reviews as well as specific observations provided by members of the consensus, the steering committee proposed a set of items for a scientific agenda (Table 2). Members of the consensus reviewed and commented on the agenda during manuscript preparation.

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***Group NV1: What are the indications for endotracheal intubation in patients with acute brain injury (ABI)?***

No articles meeting inclusion criteria was identified.

***Group NV2: Is it feasible, safe, and effective to use non-invasive respiratory support (e.g. high-flow nasal canula, NIPPV) in patients with ABI?***

The NV2 group addressed two different issues: feasibility of non-invasive respiratory support after ABI, and effectiveness on clinically relevant outcomes. Of the 125 titles retrieved, 13 advanced to full-text screening, where an additional 9 were excluded [22-30], resulting in only 4 matching the inclusion criteria [31-34].

*Randomized Controlled Trials*

Three RCTs met inclusion criteria: one study evaluated feasibility [10], while the remaining two studies examined effectiveness of different noninvasive support on patient outcomes [11-12]. Feasibility of continuous positive airway pressure (CPAP) initiated on the first night after stroke for three consecutive nights was evaluated among a cohort of 50 patients, with 25 randomized to CPAP, and the remaining 25 randomized to a control group. Feasibility end points included apnea-hypoapnea index (AHI) reduction, nursing workload, and CPAP adherence. Results indicate a significant decrease in API scores from night 1 to night 4 among the group receiving CPAP (32.2-9.8, p=0.0001); however, the AHI index for the control group was not reported. Overall polysomnography results and nursing workload were similar between groups, and adherence varied: 40% of patients had excellent CPAP use, 56% had moderate use, and 4% had no use. Methodological quality was limited by lack of allocation concealment and blinding, and serious limitations with regards to indirectness and imprecision, resulting in downgrading of evidence regarding feasibility to low quality.

Among the remaining two RCTs, one investigated effectiveness of nasal continuous positive airway pressure (nCPAP) on functional outcome [11]; the second RCT evaluated effectiveness of 100% oxygen for the first 24 hours after stroke on patient mortality and disability [12]. The study investigating effectiveness of nCPAP on functional outcome [11] randomized acute ischemic stroke patients with newly detected, moderate-severe sleep apnea to receive nCPAP (*n*=71), or conventional treatment (*n*=69). Of those assigned to the treatment group, *n*=20 (28.2%) refused the nCPAP mask and abandoned the study (*n*=14 refused immediately, and *n*=6 refused after hospital discharge), leaving *n*= 57 for analysis. While results report modest increases in functional outcome at 1 month post-discharge for the nCPAP group, differences are not sustained at additional follow up points. Methodological assessment of the study indicates an absence of an intention to treat (ITT) analysis, likely due

to the high early attrition rate, which also presents a confounding effect not controlled by randomization. In addition, the study lacks allocation concealment and blinding, resulting in downgrading evidence to low quality. The second RCT [12] utilized a modified randomization scheme by birth number among patients with acute stroke onset. Patients presenting with acute stroke were allocated to treatment group that received supplemental 100% oxygen treatment (*n*=292) for 24 hours, or the control group (*n*=258), which received usual care. The primary outcome was survival at one year, which was similar between groups (68.8% for treatment group, 72.9% for control group, p=0.300). The randomization approach limits allocation concealment and favors selection bias. In this study design, blinding was not possible, resulting in downgrading quality of evidence to low.

*Observational Studies*

Only one observational study met inclusion criteria for data extraction. The study investigated the safety and tolerability of noninvasive ventilatory correction (NIVC) among patients with acute ischemic stroke [13]. Noninvasive ventilatory correction was applied as standard of care to eligible patients, with settings titrated to maintain tidal volumes between 5-7ml/kg. A total of 64 patients received NIVC, with four patients not tolerating the treatment. The in-hospital mortality rate among those receiving NIVC was 8%, compared to 11% for the remaining population not receiving NIVC; however, stroke severity and morbidity were higher among those in the NIVC group. Inadequate measurement of exposure, lack of allocation concealment, and poor adjustment for confounding variables contributed to serious ratings for bias, imprecision and indirectness, resulting in downgrading of the evidence to very low.

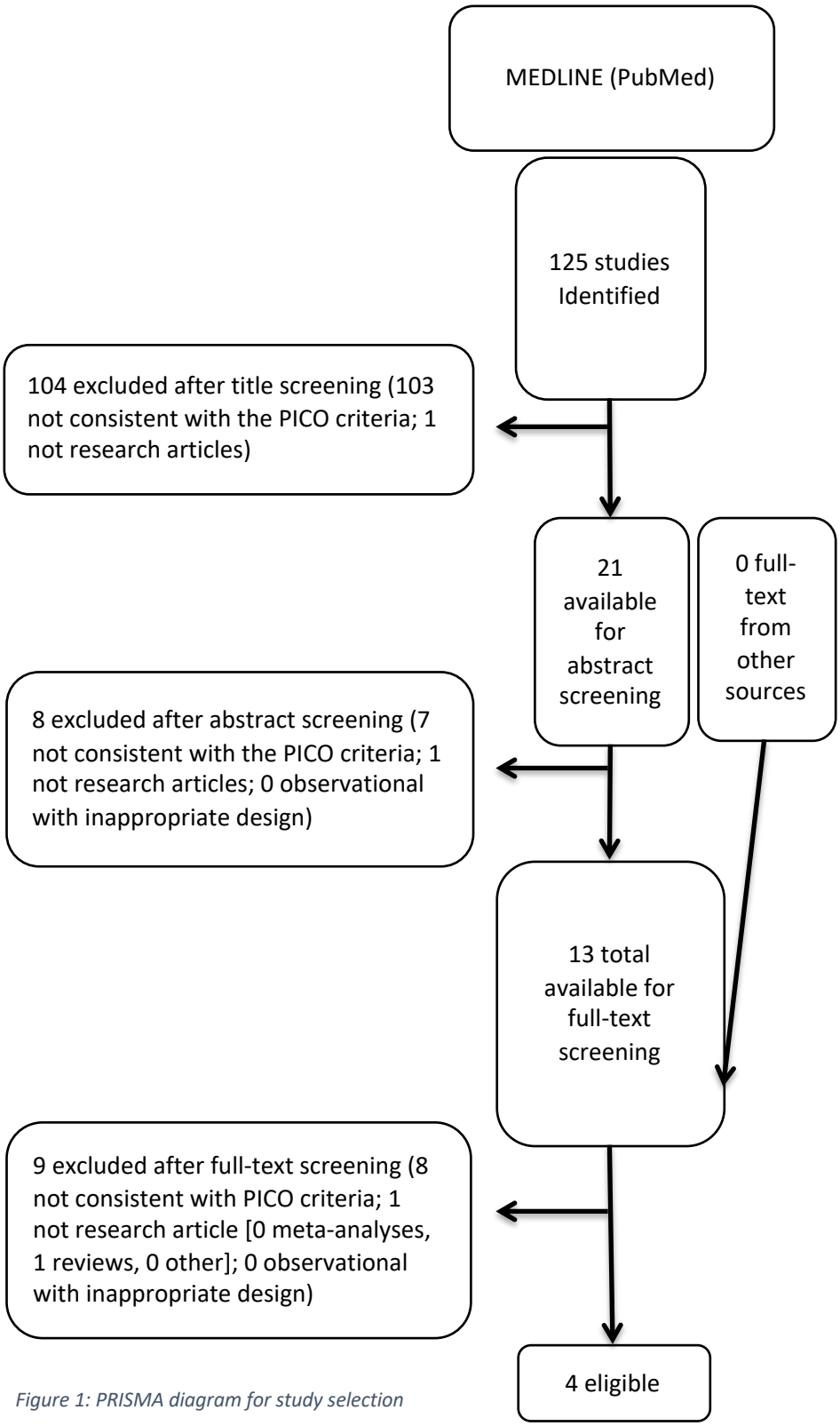


*Figure 1: PRISMA diagram for study selection*

NV2 search code, run on August 14, 2019
125 hits

("brain injury" OR "head injury" OR "head trauma" OR “brain trauma” OR "ischemic stroke" OR “ischaemic stroke” OR “hemorrhagic stroke” OR “haemorrhagic stroke” OR "cerebral infarction" OR “brain infarction” OR "subarachnoid hemorrhage" OR "subarachnoid haemorrhage" OR "intracerebral hemorrhage" OR "intracerebral haemorrhage" OR "cerebral hemorrhage" OR "cerebral haemorrhage" OR "intracranial hemorrhage" OR "intracranial haemorrhage")

AND

(("noninvasive ventilation” OR “non-invasive ventilation” OR “noninvasive positive pressure ventilation” OR “non-invasive positive pressure ventilation”) OR “continuous positive airway pressure” OR “CPAP” OR “Bilevel positive airway pressure” OR “BIPAP” OR “high flow nasal canula” OR “high-flow nasal canula” OR “supplemental oxygen”)

NOT

(child OR children OR infant OR infantile OR pediatric OR paediatric)

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***Group NV3: Should we use specific mechanical ventilation settings (e.g. tidal volume/PBW; PEEP; FiO2) and target specific respiratory physiologic parameters (e.g. Pplat) in patients with ABI?***

The PubMed search provided 494 articles, 59 were selected for full text assessment and 23 were included in the review [35-60]. Of the studies included, 7 were randomized controlled trials (RCTs), and 16 were observational trials.

*Randomized Controlled Trials*

There were 7 RCTs comparing different mechanical ventilation approaches among critically ill patients with ABI [1, 10-11, 14, 20-21, 24]. The majority of these trials (*n*=5) included patients with traumatic brain injury (TBI) [1,11,20-21, 24], while one study investigated subarachnoid hemorrhage (SAH) patients with acute respiratory distress syndrome (ARDS) [14], and one reported a heterogenous cohort with "brain injury"[10]. Three studies investigated pressure control ventilation settings [1, 14,24]; two evaluated PEEP [10,14], two investigated hyperbaric and normobaric approaches [20-21], and one trial evaluated normoxia and hyperoxia [11].

Pressure Control Ventilation

Two studies investigated pressure control ventilation (PCV) among TBI patients [1, 24]. Aghadavoudi [1] compared pressure regulated volume control (PRVC) and synchronized intermittent mandatory (SIMV) among a cohort of 100 patients and reported the SIMV group experienced higher rapid shallow breathing test indices and slightly lower oxygenation values. The study was downgraded to low quality evidence due to lack of blinding, low methodological quality and imprecision. Similarly, Schirmer [24] compared PCV and PRVC settings for effect on intracranial pressure (ICP) among TBI patients. The study was a randomized crossover trial, where *n*=11 patients received alternating 2 hour periods of PC and PRVC. Findings indicated no difference in ICP and $PaCO_2$ values between groups, and all patients in the study had normal values of ICP before and throughout the study period. The study was downgraded to very low quality evidence due to high risk of bias, no blinding, poor allocation concealment, and high indirectness and imprecision. Only one study investigated ventilation strategies among SAH patients with ARDS [15], and compared pressure control recruitment maneuver (pressure control ventilation/15 PEEP/CPAP35) to continuous positive airway pressure (CPAP) recruitment maneuver (alveolar recruitment

maneuver/CPAP15). While the CPAP recruitment group experienced higher ICP and lower cerebral perfusion pressure (CPP) values, they had only slightly lower oxygenation levels. The study was limited by lack of blinding and intention to treat, and there was poor methodological quality due to imprecision and indirectness, resulting in very low level of evidence rating.

Positive End Expiratory Pressure

Only one study compared levels of positive end expiratory pressure (PEEP) among patients with brain injury [10]. The study population was heterogenous, and poorly defined as patients presenting with "brain injury with no acute lung injury". A total of 10 subjects received PEEP=0, while 11 subjects received PEEP=8. The group with PEEP=0 had higher levels of static elastance and minimal resistance of the respiratory system on days 1-5 when compared to the PEEP=8 group, suggesting presence of low lung volume injury. The study was rated low level of evidence due to no allocation concealment or blinding, and serious indirectness and poor control of confounders.

Hyperbaric Oxygenation

Two studies compared hyperbaric or normobaric hyperoxia to usual care among TBI patients for effect on cerebral metabolism, ICP, mortality, and functional outcome [20-21]. In the first study, a cohort of TBI patients (*n*=69) were randomized to hyperbaric, normobaric hyperoxia, or usual care treatments [20]. The hyperbaric oxygen and normobaric oxygen groups had higher brain tissue $PO_2$ levels when compared to controls. Indices of cerebral metabolism (lactate concentration, dialysate lactate and microdiaylsis lactate/pyruvate ratio) and ICP were also slightly decreased in hyperbaric and normobaric groups, although degree of change in ICP values were not clinically significant (range 0.2-0.8mmHg). There were not consistent and significant benefits for hyperbaric over normobaric; however both approaches appeared to have positive impact when compared to usual care. Unfortunately, the management approaches and treatments in the usual care group were not described or standardized, resulting in significant methodological flaws. As such, the study was rated low quality. In a related study by the same author group, a combination of a hyperbaric and normobaric hyperoxia treatment regimen were compared to usual care for impact on cerebral metabolism, ICP, mortality and functional outcome [21]. In this study of 42 TBI patients, *n*=20 received 60 minutes of hyperbaric treatment, followed by 3 hours of normobaric treatment with 100% FiO2 once daily for 3 days. The brain tissue partial pressure of oxygen

levels remained higher during and after the hyperbaric/normobaric treatments. Cerebral metabolism (microdiaylsate/pyruvate ratio, microdiaylsate glycerol, cerebral spinal fluid (CSF) F2 isoprostane) and ICP values were lower in the treatment group when compared to values in the usual care group. The treatment group also experienced a 26% reduction in mortality and 36% improvement in favorable outcome. However, care in the usual care group was poorly defined with no protocol, and absolute differences in ICP values were not clinically significant. The study had poor allocation concealment, no blinding, and serious concerns for indirectness, resulting in low level of evidence rating.

Hyperoxia

Only one trial compared normoxia and hyperoxia approaches among traumatic brain injured (TBI) patients in a multicenter pilot study [11]. Oxidative stress levels were compared between patients receiving $FiO_2$=40 (*n*=19) or $FiO_2$=70 (*n*=27). While there were no differences in oxidative stress levels reported between groups, there was poor control over treatment protocols across sites, no allocation concealment or blinding, and high numbers lost to follow up, resulting in low level evidence rating.

*Observational Trials*

There were 16 observational studies that investigated relationships between various ventilation settings and outcomes among critically ill patients with ABI.

Ventilation Ratios

Of the 16 observational trials, 2 included evaluations of ventilation ratios among small cohorts of TBI (*n*=18) [5], and stroke (*n*=16) [8]. Among TBI patients, use of a pressure-controlled, inverse ratio ventilation (PC-IVR) was compared to pressure-controlled normal ratio ventilation for each patient for effect on ICP. All patients had stable ICP values at baseline and were exposed to two rounds of each ventilation strategy. While results indicated no discernable effect on ICP values, the study was limited by inadequate measurement exposure, minimal control of confounders, and risk of bias, resulting in a very low quality of evidence rating. Similarly, an evaluation of I:E ratios of 1:2 or 1:1 with either 5 or 10 of PEEP resulted in no significant changes to ICP values among stroke patients with normal baseline ICP values [8], which was also rated at very low level of evidence.

Positive End Expiratory Pressure

There were 7 observational studies that examined levels of PEEP and impact on respiratory compliance and oxygenation, and ICP/CPP [2, 3-4, 7, 9, 14, 26]. Three studies evaluated PEEP values from 0-15 and reported: increases from 0-12 PEEP resulted in increases in central venous pressure (CVP) and jugular pressure, but reduced MAP among *n*=21 SAH patients, with no effect on ICP [2]; increases from 5-15 PEEP resulted in slight increases in esophageal pressure among patients who had fluctuating ICP values among *n*=15 SAH patients; and 15 PEEP did not impact chest wall elastance among *n*=30 TBI patients with or without respiratory failure [7]. All three studies were rated as providing only very low quality evidence due to poor methodological quality. The remaining 4 studies evaluated changes in PEEP values from 0-15 on ICP and/or CPP [9, 12, 14, 26] on TBI [9,12, 14] or mixed neurocritical care populations [26]. The studies report varying results: one study reported decreased levels of ICP (from 14 to 13) and increasing levels of CPP as PEEP increased to a maximum value of 15 [9], while a second study reported increases in ICP from 11.6-14.6 with PEEP at 10 and 15, with no associated decrease in CPP values [26]. The remaining two studies reported no changes in ICP or CPP with PEEP values ranging from 5-15 [14], and both reported an increased ICP response (from 12-17) or a decreased response (from 13-11) which were dependent on chest wall elastance [12]. Across these studies, all ICP values remained within normal limits, and fluctuations in values in either direction were not deemed to be of clinical significance. These four studies were rated as providing very low quality evidence due to small sample size (range *n*=12-20), high risk of bias, and low methodological and statistical quality.

Oxygenation

A total of 5 observational studies investigated various oxygenation settings among TBI patients [13, 16, 17, 23, 25]. All five studies evaluated the relationship between increasing levels of $FiO_2$ and either brain $PbtO_2$ [13, 16, 17], cerebral blood flow [23], or ICP [25]. Effects of sustained high $FiO_2$ on $PbO_2$ were variable: two studies reported elevated levels of $PbtO_2$ [13, 16] after higher $FiO_2$ levels among samples of *n*=12 and *n*=36 TBI patients; while a separate study reported no change in brain partial tension of oxygen ( $PbtO_2$ )levels among a sample of 36 TBI patients [17]. These three studies were rated as providing low quality evidence due to lack of control for confounding and poor methodological and statistical quality. Only one study evaluated relationship between increased $FiO_2$ ($FiO_2$=0.4, 0.6, 1.0) and cerebral blood flow (CBF), as measured by transcranial Doppler velocities [23] among *n*=50 TBI patients and reported no difference in CBF. The study was rated very low quality

evidence as a result of indirectness and imprecision. The final study investigating $FiO_2$ levels was conducted among *n*=52 TBI patients who were treated with 100% $FiO_2$ for 24hours within 6 hours of admission. Data from the treatment group was prospectively gathered and compared to a historical control group treated with standard of care. The hyperoxia group experienced improved markers of cerebral metabolism and modest decreases in ICP (from 15 to 12), although the study was deemed low quality evidence.

Evidence Based Ventilation Bundles

Two of the observational studies employed quality improvement, before/after approaches to evaluate use of protocolized ventilation bundles on mortality [2] and duration of mechanical ventilation [22]. The first bundle included low tidal volumes, moderate PEEP, and early extubation among a nationwide sample of *n*=744 TBI patients [2]. Protocol adherence in the first 90 days was poor and did not result in differences in ventilator free days; however ,as adherence increased, there was an increase in ventilator free days among the protocolized group (*n*=60) when compared to the usual care group (*n*=684). However, the study was downgraded to low quality evidence due to poor exposure control in the pre-protocol group and indirectness. The second study was also a quality improvement initiative evaluating implementation of a bundle that included protective ventilation, early enteral nutrition, standardization of antibiotic therapy for hospital-acquired pneumonia, and a systematic approach to extubation among patients with TBI, SAH, stroke, cancer, or meningitis [22]. There were *n*=299 patients in the pre-protocol cohort, and *n*=200 in the protocol intervention cohort. The protocol cohort experienced a decrease in duration of mechanical ventilation (from 14.9 days to 12.6 days, *p*=0.02). However, there was poor control and reporting of exposure in the pre-protocol cohort, and limitations of indirectness and imprecision, resulting in a low quality of evidence rating.

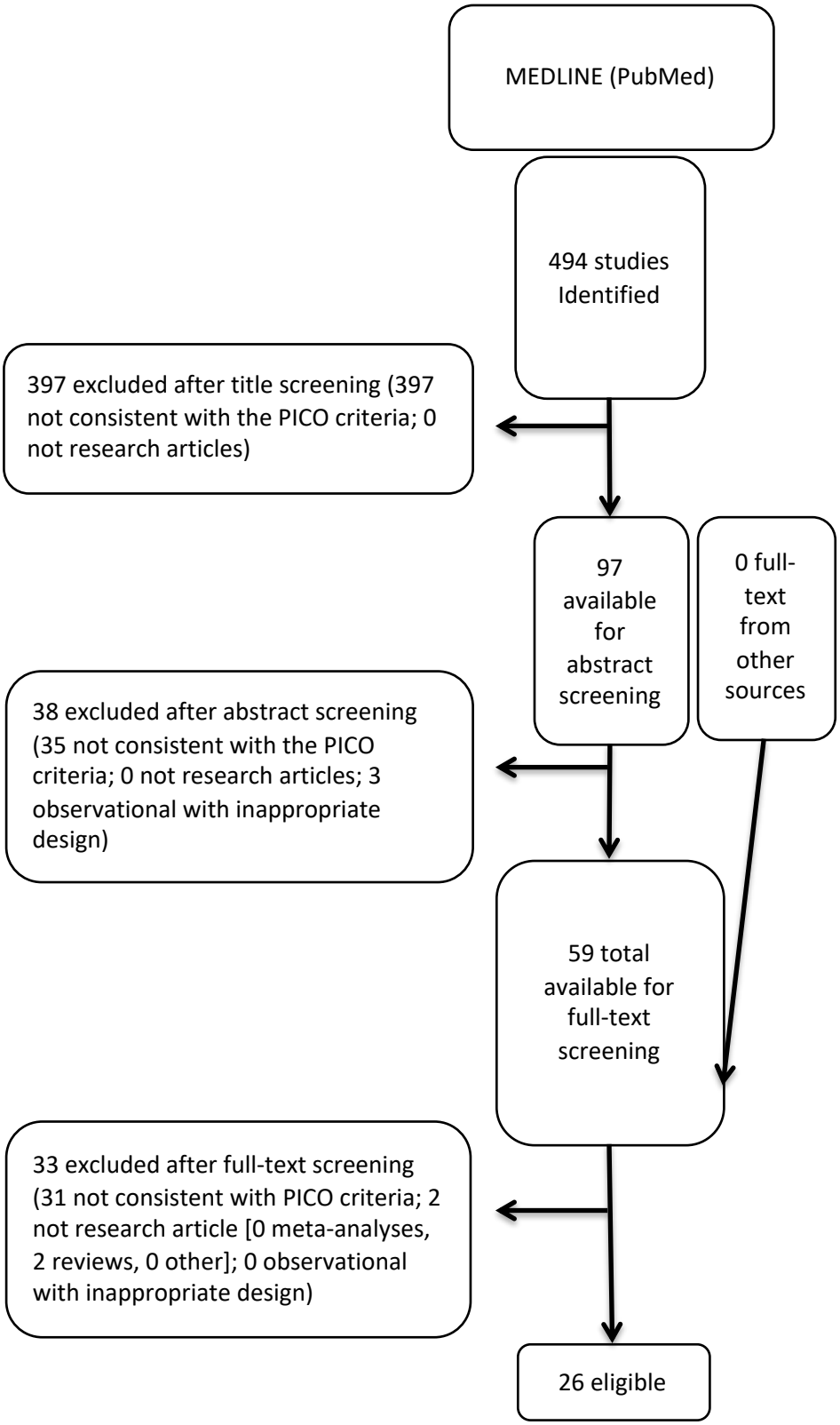


*Figure 2: PRISMA diagram for study selection, group NV3*

NV3 search code, run on July 13, 2019
494 hits

("Craniocerebral Trauma/drug therapy"[MeSH Terms] OR "traumatic brain injury"[All Fields] OR "head trauma"[All Fields] OR "head injury"[All Fields] OR "intracranial haemorrhage"[All Fields] OR "intracranial hemorrhages"[MeSH Terms] OR "intracerebral hemorrhage"[All Fields] OR "intracerebral haemorrhage"[All Fields] OR "cerebral hemorrhage"[All Fields] OR "cerebral haemorrhage"[All Fields] OR "intraventricular hemorrhage"[All Fields] OR "subarachnoid haemorrhage"[All Fields] OR "subarachnoid hemorrhage"[MeSH Terms] OR ("subarachnoid"[All Fields] AND "hemorrhage"[All Fields]) OR "subarachnoid hemorrhage"[All Fields] OR "Infarction, Middle Cerebral Artery"[Mesh] OR "middle cerebral artery infarction"[All Fields] OR (("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND "middle cerebral artery"[All Fields]) OR "brain injuries"[MeSH] OR "brain injury"[All fields] OR "acute brain injury"[All fields] OR "stroke"[MeSH] OR "Stroke/diagnosis"[MeSH Terms] OR "hemorrhagic stroke"[All Fields] OR "cerebral infarction"[All Fields] OR "brain infarction"[All Fields] OR "ischemic stroke"[All Fields] OR "ischaemic stroke"[All Fields])
AND
((ZEEP OR “zero end expiratory pressure” OR PEEP OR “positive end expiratory pressure” OR “continuous positive airway pressure” OR “CPAP” OR "Positive-Pressure Respiration/methods"[MAJR])
OR
(“tidal volume” OR “protective ventilation”)
OR
(FiO2 OR “fraction of inspired oxygen”))
NOT
Animals[Mesh:noexp]
AND
English[lang]
NOT
(child* OR infant* OR pediatrics)

*References*


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***Group NV4: Should we target specific values of pH, PaO2 and PaCO2 in patients with ABI?***

The PubMed search provided 2125 titles, after title and abstract selection 23 studies were available for full-text assessment, 8 were excluded [61-68] and 15 remained after further selection [40, 52, 53, 69-80]. Of the final studies meeting inclusion criteria, all were observational trials.

*Observational Trials*

Among the included observational trials, a total of 13 investigated specific values of $PaO_2$ or surrogate metric and its relationship to patient outcomes at discharge [10-13; 16; 20-21; 23] and/or three month [17-18] or six months [9,15,19] post-discharge intervals. Patient populations included TBI [9-13; 19, 21], SAH [16,17,23], [15, 18, 20] and stroke [15,18,20].

Partial pressure of oxygen (PaO2) and Mortality at Hospital Discharge

There were six studies that evaluated the relationship between $PaO_2$ levels and mortality or survival at hospital discharge [10-13, 20-21]. There was wide heterogeneity in operational definitions for hyperoxemia across studies, ranging from $PaO_2$ >150mmHg to $PaO_2$>300mmHg. Five of the studies evaluated PaO2 values in TBI patients [10-13, 21], and one study included stroke patients (acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), SAH) [20]. Across studies, higher values of $PaO_2$ were associated with higher mortality rates at hospital discharge [11-13, 20-21], although various thresholds were used to define hyperoxemia. Similarly, normoxemia among patients with severe TBI [11-13, 20] and AIS [21] appear to have had a neutral or positive effect on mortality. However, specific normoxemia targets ranged from $PaO_2$=60-250mmHg [10], 100-200mmHg [11], 60-299 mmHg [12], 110-487 mmHg [13], or 60-330 mmHg [20-21]. Overall, the quality of evidence of these studies was rated as either moderate [11-13] or low quality [20-21] due to issues of poor measurement of treatment exposure and control for confounding variables.

PaO2 and Clinical Outcomes

Two studies examined hyperoxemia among SAH patients and relationship to either delayed cerebral ischemia (DCI) [16] or functional outcome at discharge [23]. The first study included 252 SAH patients and reported three-fold higher odds of DCI among patients with

hyperoxemia [16]; however, there was a large degree of imprecision in the trial, with inadequate measures of outcome and no control for confounding variables. As such, the evidence was rated low quality due to serious indirectness and imprecision. The second study investigated the association between $PaO_2$ thresholds of 60-120 mmHg, 121-200 mmHg, 201-300 mmHg, and >300 mmHg and relationship to functional outcome at discharge [23]. Hyperoxemia was associated with poor functional outcome at discharge, but values for specific thresholds were not reported, and there was poor exposure to treatment, control for confounding, and imprecision, resulting in rating the study as very low quality evidence.

PaO2 and Post-Discharge Outcomes

There were five studies evaluating specific $PaO_2$ targets and relationship to post-discharge outcomes, including mortality [9,15,17,19], or functional outcome at 3 months [17, 18] or 6 months [9, 19]. One study evaluated hyperoxemic thresholds ($PaO_2$=100 mmHg, 150 mmHg, 250 mmHg, or 350 mmHg) and impact on 6 month Glasgow Outcome Scale Extended (GOSE) scores among TBI patients [9]. The study was rated low quality evidence due to risk of bias, but reported that patients with $PaO_2$ levels ranging from 150-200 mmHg experienced better functional and cognitive outcomes at 6 months, with no improvement in overall mortality rates. Higher levels of hyperoxemia offered no benefit on functional outcomes or mortality. Similarly, Raj [19] examined varying levels of hyperoxemia, measured by $PaO_2$ levels of 10 kPa, 10-13 kPa, or >13.3 kPa on 6 month mortality among TBI patients, and reported no benefit on mortality rates among the hyperoxemia groups. While the study did control for confounders, it was limited by lack of measurement of treatment exposure and rated low quality evidence.

The remaining three studies evaluated relationships of $PaO_2$ thresholds among patients with SAH [17], ICH [15], and AIS after thrombectomy [18]. Two studies included $PaO_2$ thresholds of <97.5 mmHg, 97.5-150 mmHg, and >150 mmHg [15,17]. In the first study, oxygenation levels among SAH patients were examined with primary end points of 3 months mortality and functional outcome. Findings indicate higher mortality rates within the low oxygenation cohort, comparable mortality between the normoxemia ($PaO_2$ 97.5-150 mmHg) and hyperoxemia ($PaO_2$>150 mmHg) groups [17], and no discernable impact on functional outcome. The study was rated low quality evidence due to poor measurement of exposure and control of confounding variables. In the second study, the same $PaO_2$ thresholds were

examined within an ICH cohort, and reported those with hyperoxemia ($PaO_2$>150 mmHg) experienced higher mortality rates at 6 months; although these rates across the 3 thresholds remained comparable after controlling for confounding variables [15]. The study included a sample of 1100 patients from 21 sites, and was rated moderate quality evidence. The third study investigated $PaO_2$ thresholds of >120 mmHg or <120 mHg among AIS stroke patients after thrombectomy and relationship to modified Rankin scores after 90 days [18]. Findings indicate those in the hyperoxemia group had higher modified Rankin scores and mortality rates; however this cohort also had higher National Institutes of Stroke Scale (NIHSS) scores and intensive care unit (ICU) length of stay. The study was rated low quality due to imprecision and limitations regarding measurement of treatment exposure.

Spontaneous Hyperventilation

Two studies investigated the effect of spontaneous hyperventilation (SHV) on outcomes [22-23]. The first study included 207 SAH patients and included DCI as the primary endpoint [22]. Findings indicate a three-fold higher risk of DCI among patients who experienced SHV (carbon dioxide, $CO_2$<35 mmHg), but there was a high degree of imprecision and lack of treatment effect, resulting in downgrading of the evidence to low quality. The second study examined relationship between SHV and functional outcome at 6 months among a cohort of 110 TBI patients [23], and reported a higher incidence of poor functional outcomes among patients with SHV. The study was limited by imprecision and inadequate measurement of exposure, and was therefore rated as low quality evidence.

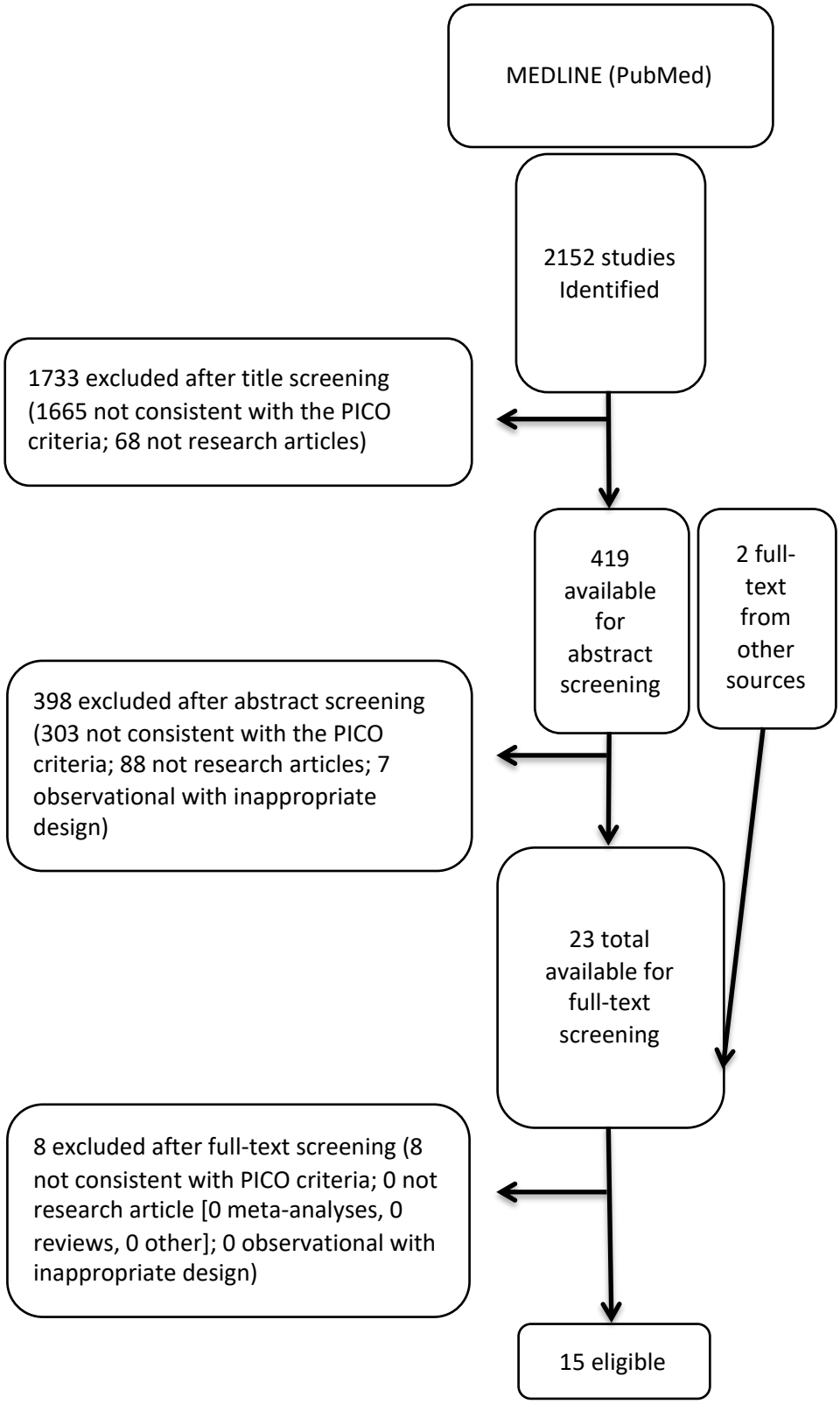


*Figure 3: PRISMA diagram for study selection, group NV4*

NV4 search code, run on July 13, 2019
2147 hits

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AND
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NOT
Animals[Mesh:noexp]
AND
English[lang]
NOT
(child* OR infant* OR pediatrics)

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19. Raj R, Bendel S, Reinikainen M, Kivisaari R, Siironen J, Lang M, Skrifvars M, (2013) Hyperoxemia and long-term outcome after traumatic brain injury. Crit Care 17: R177
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***Group NV5: Is it feasible, safe, and effective to use rescue interventions (e.g. neuromuscular blockade, prone positioning, extracorporeal membrane oxygenation) to support respiratory failure in patients with ABI?***

The NV5 group addressed two different issues. Besides the effectiveness on clinically relevant outcomes, also feasibility of rescue interventions to support respiratory values in ABI patients was investigated. For this reason, case series and case reports were also included in the list of selected articles as reported in the PRISMA selection flow-chart in figure 1. The string used to search the PubMed, is reported at the end of this document. Overall, 27 studies reporting 72 patients who received rescue treatments including prone position ventilation, extra-corporeal membrane oxygenation (ECMO), inhaled nitric oxide (iNO), and high frequency oscillatory ventilation (HFOV), were retrieved.[81-107] Instead, 9 studies were selected investigating HVOF, ECMO, alveolar recruitment maneuvers, on surrogate outcomes such as ICP and CPP, while no studies concerning ECMO, neuromuscular blocking agents, or iNO [48, 108-115]. Obviously, these studies also contributed to provide evidence in support of the feasibility issue investigated by NV5. The forms providing the synthesis of our grading analysis are reported in the NV5 grading report file. No mortality and neurological disability outcomes were investigated in the retrieved literature, but only unvalidated surrogates such as ICP, CPP, and PbtO2.

*High frequency oscillatory ventilation*

We meta-analyzed the three observational studies with before/after dealing with the influence of HFOV on ICP in patients with TBI.[109, 113, 115] Overall only 54 patients were studied, and a statistically significant ICP reduction was found with either the most conservative and optimistic assumptions regarding correlation (Figure 2, top boxes), but high heterogeneity was found. However, a stratification according to the initial ICP value (the largest the greater ICP reduction) would have been a reasonable hypothesis to be investigated with meta-regression to reduce heterogeneity, but the studies were too few to perform such analysis. Oxygenation improved in two of three studies. Overall, evidence was graded *very low* in favor of HVOF, for the improvement of surrogate outcomes and oxygenation.

*Prone position ventilation*

The four available observational studies investigated both ICP and CPP, and one PbtO2, in different kind of cerebral injuries, performing repeated measures on same patients in most cases without accounting for this in the statistical analysis.[110-112, 114] We, thus, could not

combine their results in a meta-analysis but reported the results in the Forest plots in figure 2 (bottom boxes), which suggest a possible increase of ICP and substantial stability of CPP. The only study that measured PbtO2 found a statistically significant increase of this parameter from 26.8 to 31.6 mmHg. All the studies showed a clinically relevant increase of oxygenation with pronation. In this case, overall evidence regarding prone position ventilation benefit/risk balance, was graded *very low* in favor.

*Alveolar recruitment maneuvers*

We found a trial randomizing 16 patients with SAH, comparing continuous positive airway pressure (CPAP) and pressure control alveolar recruitment maneuvers showing the greater impact of the former on ICP (7.3 mmHg increase) and CPP (15.1 mmHg reduction)[48]. The quality of this study was downgraded to *very low.* An observational study with a before/after design recruiting only 11 mixed neurointensive patients showed a statistically significant but clinically irrelevant ICP increase. CPP decreased from 72 to 60 mmHg ($p < 0.01$).[108]. We downgraded the quality of this study to *very low*, but the results of the study were inconclusive neither in support nor against the maneuver. Overall evidence was rated *low*, but the findings were insufficient to conclude in favor or against these procedures. The issue was insufficiently investigated and attention should be paid on the balance between ICP and CPP decrease and oxygenation improvement.

*Feasibility studies*

Small case series and case reports concerning ECMO, HFOV, Prone position ventilation, iNO did not report serious neurological side effects (tables 1 and 2). Studies providing evidence for main outcomes did not report serious side-effects besides two cases in prone ventilation studies that required rapid patient supination for dangerous ICP increases.

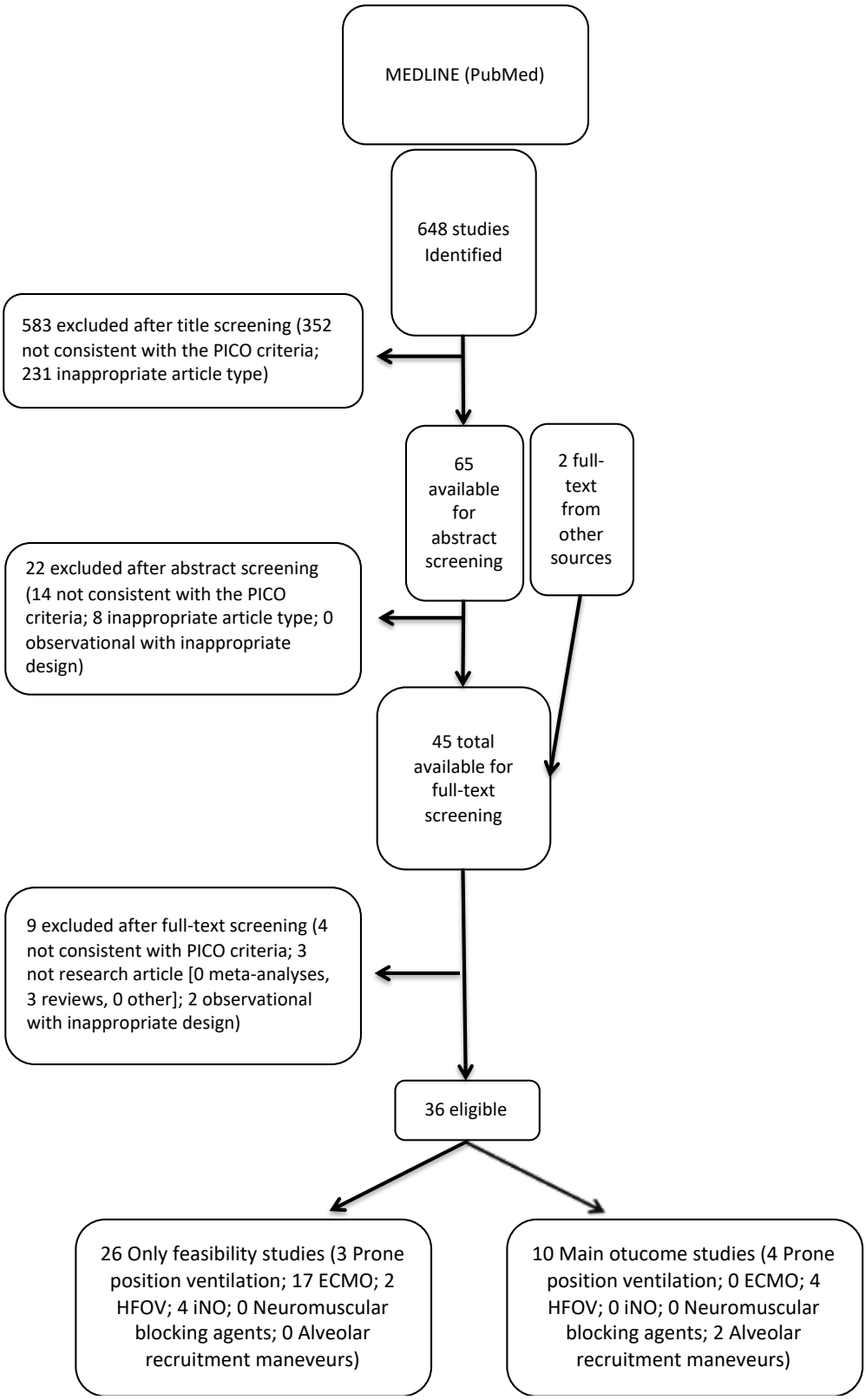


*Figure 4: PRISMA flow chart for article selection, group NV5.*

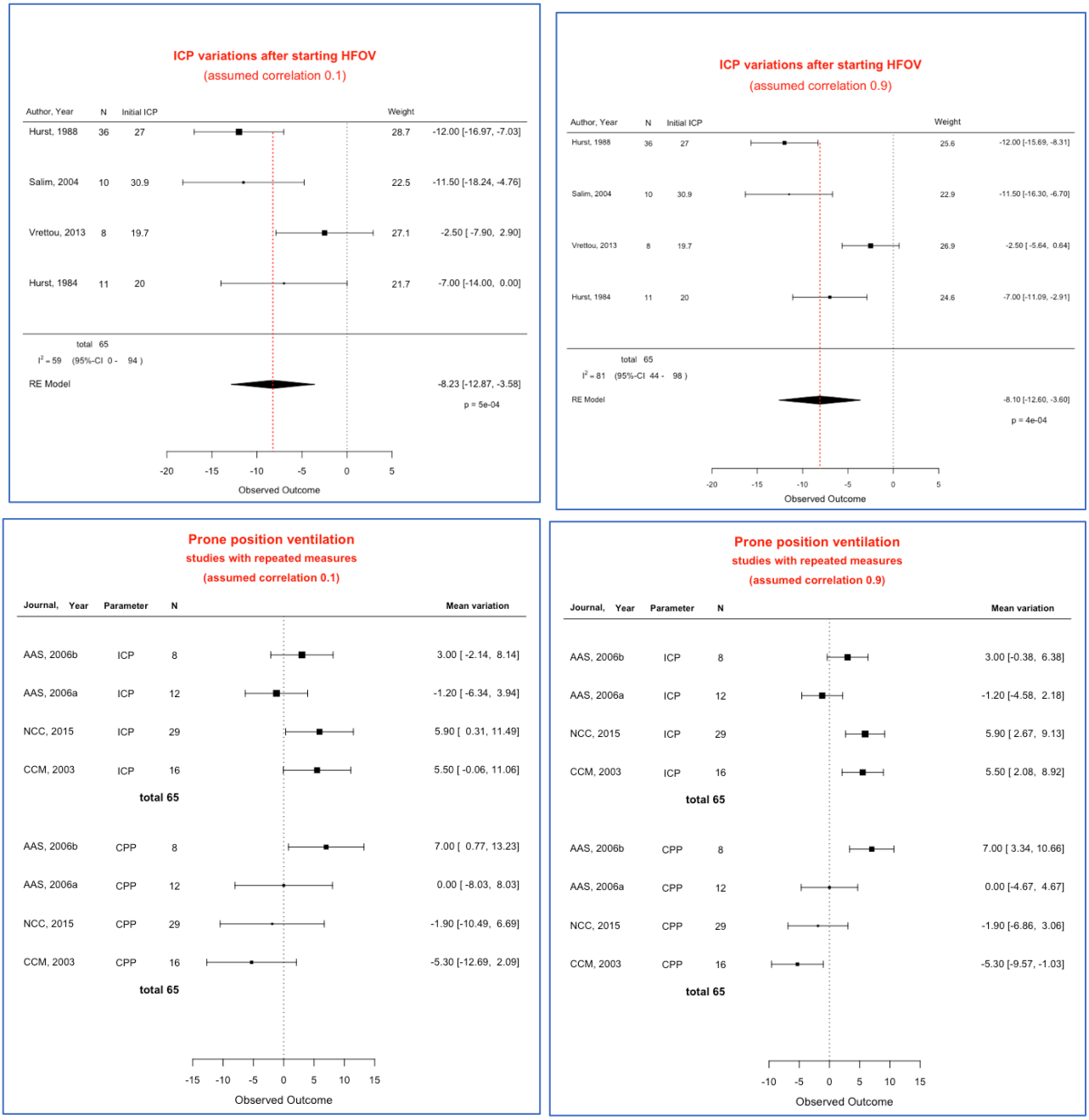


*Figure 2: ICP variations in patients with TBI submitted to HFOV (top boxes, meta-analysis assuming low and high correlations). ICP and CPP variations in patient with brain injury undergoing prone position ventilation (bottom boxes, Forest plots assuming low and high correlations).*

| Journal | Year | Pts | Lung disease | N | Treatment | Respiratory Condition 1 | Effect | Respiratory Condition 2 | Effect | Neurologic Condition | Effect | Severe neurological side effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **JNA** | 2014 | TBI | pulmonary embolism | 1 | ECMO | | | hypoxia | Improved | nr | | no events reported |
| **JTACS** | 2013 | TBI | thoracic trauma | 7 | ECMO | Hypercapnia | nr | hypoxia | nr | nr | | no events reported |
| **Perfusion** | 2015 | TBI | severe ARDS | 2 | ECMO | | | severe hypoxia | nr | nr | | no events reported |
| **JT** | 2008 | TBI | pulmonary embolism | 1 | ECMO | | | hypoxia | Improved | nr | | no events reported |
| **AN** | 2005 | TBI | pulmonary contusion | 1 | ECMO | | | severe hypoxia | Improved | nr | | no events reported |
| **BJA** | 2015 | TBI | pulmonary contusion | 1 | ECMO | | | severe hypoxia | Improved | | | no events reported |
| **ASAIO** | 2014 | TBI | ARDS | 1 | ECMO | | | severe hypoxia | Improved | nr | | no events reported |
| **JT** | 2012 | TBI | ARDS | 3 | ECMO | | | severe hypoxia | Improved | nr | | no events reported |
| **AJEM** | 2014 | TBI | severe ARDS | 1 | ECMO | | | severe hypoxia | Improved | nr | | no events reported |
| **CNN** | 2008 | TBI | severe ARDS | 1 | ECMO | | | severe hypoxia | Improved | ICP | improved or stable | no events reported |
| **Perfusion** | 2015 | TBI | pulmonary contusion | 1 | ECMO | | | severe hypoxia | Improved | nr | | no events reported |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **JTACS** | 2013 | TBI | thoracic trauma | 7 | ILA | Hypercapnia | nr | hypoxia | nr | nr | | no events reported |
| **Anaesthesia** | 2007 | ICH | ARDS | 1 | pumpless extracorporeal CO2 removal | Hypercapnia | Improved | | | nr | | no events reported |
| **Anaesthesia** | 2008 | TBI | pulmonary contusion | 1 | pumpless extracorporeal CO2 removal | Hypercapnia | Improved | | | | | no events reported |
| **JT** | 2005 | TBI | moderate to severe ARDS | 5 | pumpless extracorporeal lung assist system | Hypercapnia | improved or stable | Hypoxia | improved or stable | ICP | unmodified | no events reported |
| **CC** | 2015 | TBI | moderate to severe ARDS | 10 | pumpless extracorporeal lung assist system | Hypercapnia | Improved | hypoxia | unmodified | nr | | no events reported |
| **Perfusion** | 1999 | TBI | severe ARDS | 1 | pumpless extracorporeal lung assist system | | | severe hypoxia | Improved | nr | | no events reported |

Table 1. Feasibility studies on extracorporeal respiratory rescue treatments.

| Journal | Year | Pts | Lung disease | N | Treatment | Respiratory Condition 1 | Effect | Respiratory Condition 2 | Effect | Neurological Condition1 | Effect | Severe neurological side effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **BJA** | 2011 | TBI | severe ARDS | 1 | PRONE ventilation | Hypercapnia | Improved | Hypoxia | Improved | ICP | worsened | no event reported |
| **RBTI** | 2014 | SAH | severe ARDS | 2 | PRONE ventilation | | Improved | Hypoxia | Improved | ICP | unmodified | no event reported |
| **BJA** | 2003 | SAH | pulmonary edema | 1 | PRONE ventilation | | Improved | Hypoxia | Improved | nr | | no event reported |
| **NCC** | 2007 | BI | ARDS | 5 | HFOV | Hypercapnia | Improved or stable | Hypoxemia | Improved | ICP | improved or stable | no event reported |
| **AAS** | 2005 | TBI | ARDS | 5 | HFOV | Hypercapnia | unmodified | Hypoxemia | Improved | ICP | unmodified | no event reported |
| **JA** | 2012 | TBI | severe ARDS | 1 | iNO | | | Hypoxemia | Improved | ICP | no clear relation to ICP | no event reported |
| **JNA** | 1999 | SAH | ARDS | 1 | iNO | | | Hypoxemia | Improved | ICP | no clear relation to ICP | no event reported |
| **SJTREM** | 2008 | TBI | ARDS | 1 | iNO | | | Hypoxemia | Improved | ICP | no clear relation to ICP | no event reported |
| **RC** | 2012 | ICH | ARDS | 1 | iNO | | | Hypoxemia | Improved | ICP | ICP decreased from 41 to 5 mmHg after iNO was started in one case | no event reported |
| **AJEM** | 2011 | TBI | severe ARDS | 9 | Alveolar recruitment maneuvers | | | Hypoxemia | Improved | ICP | no clear relation to ICP | no event reported |

Table 2: Feasibility studies on respiratory rescue treatments.

NV5 search code, run on July 12, 2019
648 hits

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AND
(("Extracorporeal Circulation/instrumentation"[MeSH Terms] OR "Extracorporeal Circulation/methods"[MAJR] OR "Extracorporeal Membrane Oxygenation"[MeSH Terms] OR “ECMO”[All Fields])
OR
(“Nitric oxide” AND (“ARDS” OR “adult respiratory distress syndrome” OR “acute lung injury”))
OR
("Neuromuscular Nondepolarizing Agents/therapeutic use"[MAJR] OR "Neuromuscular Nondepolarizing Agents"[nm] OR “Neuromuscular Blocking agents”[All Fields] OR "Atracurium"[nm] OR "Vecuronium Bromide"[nm])
OR
("prone ventilation"[All Fields] OR ("prone position"[All Fields] AND ("ARDS"[All Fields] OR "acute respiratory distress syndrome"[All Fields] OR "acute lung injury"[All Fields] OR "ventilation"[All Fields] OR "respiration"[All Fields])))
OR
(“Alveolar recruitment maneveur”[All Fields] OR “Alveolar recruitment”[All Fields] OR “Lung recruitment maneveur”[All Fields] OR “Lung recruitment”[All Fields])
OR
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OR
(“end-expiratory positive pressure” OR PEEP))
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NOT
(pediatrics)

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37.

***Group NV6: What are the criteria for ventilator weaning in patients with ABI? What are the criteria for extubation in patientins with ABI?***

The NV6 group investigated two similar but different issues. Actually, weaning indicates the capacity of breathing autonomously, which means even through a tracheostomal cannula, while extubation consists in the removal of any kind of tube from the trachea. Tracheostomy enables care providers to remove secretions while extubation implies a greater autonomy keeping airways clear. After running the PubMed search code (available at the end of this document) 34 articles were retrieved for full-text screening, 18 were excluded[36, 116-132] and among the 16 matching the inclusion criteria, 3 were randomized controlled trials[133-135] and 13 observational studies [56, 136-147] (figure 1).

*Randomized Controlled Trials*

Two RCTs investigated the influence of a weaning protocol vs. standard practice on extubation failure but the definition of the outcome was different (any reintubation or within 48 hours reintubation). Thus, we could not perform a meta-analysis and an overall grading of evidence [134, 135]. However, one RCT provided “moderate” evidence in favor of the weaning protocol ability to improve autonomous ventilation for at least 24 hours after intubation, bearing, however, large imprecision (NNT between 16 and 1031)[135] which raises some perplexities on the clinical relevance. The other RCT, that was rated “low” in terms of evidence quality because of serious shortcomings [134]. Since it did not provide any statistically significant finding and the study was not powered to detect a clinically meaningful difference, we considered that the study did not provide evidence neither in favor nor against the weaning protocol. The third trial investigated only weaning (e.g. spontaneous breathing for more than 72 hours), did not provide any statistically significant finding and was underpowered to detect any meaningful difference. Thus, its quality was rated “low” without providing any indication to support or not a weaning protocol for weaning [133].

*Observational studies*

Of the thirteen studies retrieved, 10 developed predictive models for extubation [56, 136, 138-145], 2 were external validation studies of previously developed models for extubation [137, 147], and one was a predictive model focused on weaning and not specifically extubation [146] (table 1). The quality of prognostic models was evaluated according to the PROGRESS (Prognosis Research Strategy) recommendations [148]. These guidelines require

that three criteria are matched for reliable models: development on a large and high-quality database, the use of sound statistical analyses, and external validation on an independent dataset. Moreover, it is suggested that clinical impact should be assessed, in terms of effectiveness in improving patients' outcomes and/or in reducing healthcare costs. The 10 prognostic models proposed were all developed on small samples and from datasets that were not specifically designed for prognostic purposes. The models were also all overfitted since the ratio between the number of outcomes and of screened variables was always less than 10 (table 2). We also reported the same ratio for the variables that remained in the final model, 3 of 9 models (for one information required was not available) were overfitted. We should however remember that the ratio should be referred to the variables screened, with bivariate or automatic procedures, and not on those selected in the final model [5]. The prognostic model for weaning had the same shortcomings [146]. Besides these limitations, the reporting of the methodology used to develop the scores, including goodness-of-fit and homogeneity of fit measures, was scanty or null. In conclusion, the statistical design of the prognostic models we scrutinized was poor, and we rated the quality of these studies "very low". Moreover, the predictive ability of these studies was not tested on independent samples and, consequently, no clinical impact studies were available. Of the two validation studies of preexisting scores, the one validating the Time Inspiratory Effort (TIE)[149] score reported an area under the ROC curve of 0.94 in discriminating those that breathed more than 48 hours autonomously, but it was carried out on a very small sample, did not provide any cut-off for clinical decision making, and concerned a heterogeneous group of patients including cervical medullary lesions [147]. While the other showed a very low discriminative ability of the rapid shallow breathing index (RSBI) score[137, 150]. Evidence provided by these two studies was also rated "very low".

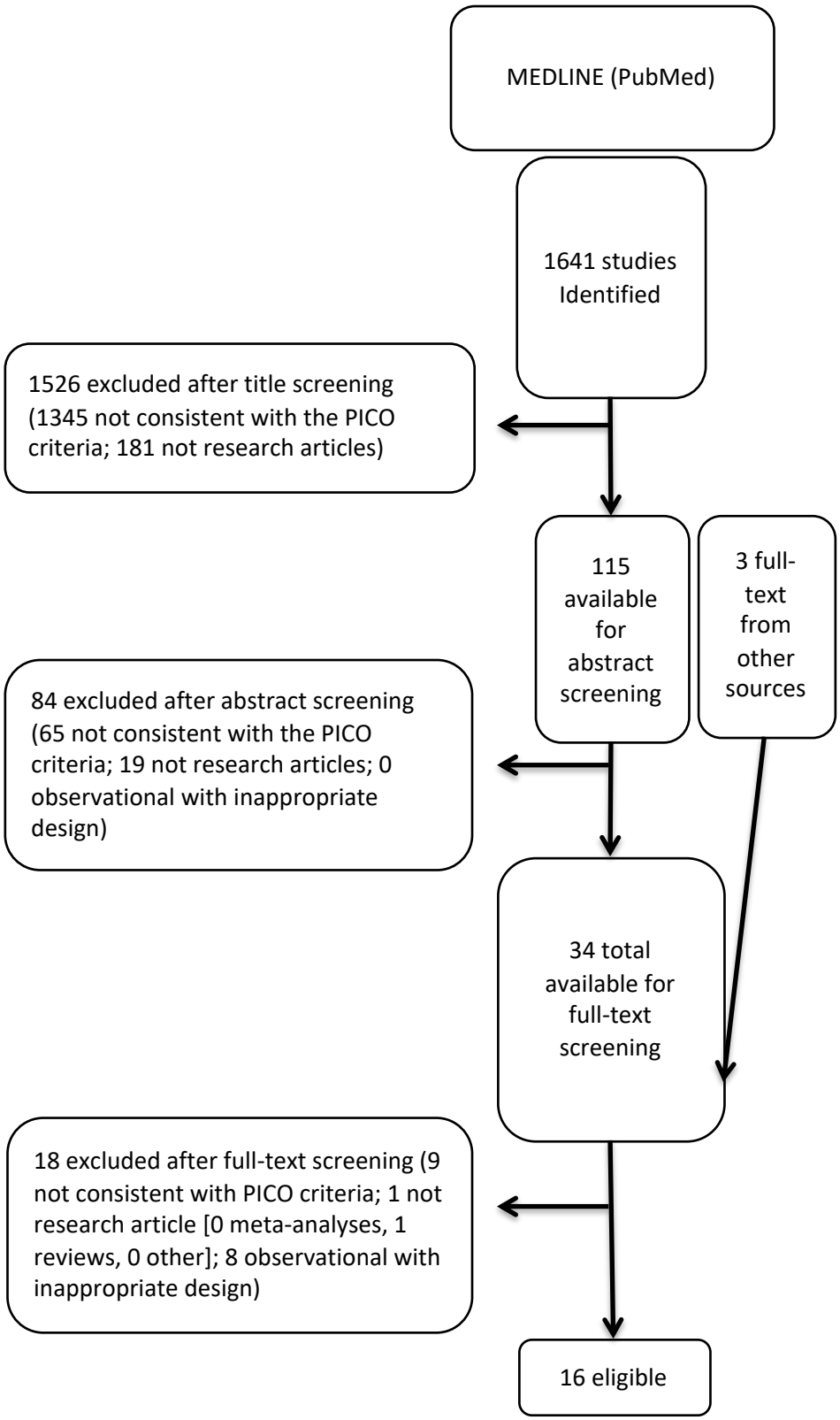


*Figure 5: PRISMA flow chart for article selection, group NV6.*

| Journal - year | study type | n centres | n pts | pts | duration years | pts/year/centre | outcome | outcome definition | predictors in the final model |
|---|---|---|---|---|---|---|---|---|---|
| RC - 2015 | validation (TIE score) | 1 | 43 | TBI, stroke, neuromuscular dis., cervical medullary injuries | 1.0 | 14 | extubation success | spontaneous breathing for more than 48 hours | TIE score variables |
| RBTI - 2013 | validation (RSBI score) | 1 | 119 | TBI, at time of extubation GCS > 7 and passed SBT | 0.8 | 48 | extubation success | no reintubation within 48 hours | RSBI score variables (n.s.) |
| ICM - 2009 | prognostic model | 1 | 42 | Brain stem injuries | 1.2 | 12 | weaning success | independence from mechanical ventilation for 7 consecutive days | age (n.s.), high vs. low response to hypercapnic challenge |
| AJRCCM - 2013 | prognostic model | 3 | 499 | TBI, SAH, stroke, tumour, infection | 3.0 | 55 | extubation failure | definition not provided | extubation readiness bundle (n.s.) |
| JBP - 2015 | prognostic model | 1 | 135 | TBI, SAH, brain tumour | 2.5 | 18 | extubation success | no reintubation within 48 hours | APACHE II (n.s.), VT (n.s.), MEP (n.s.), MIP (n.s.), duration of MV (n.s.), RSBI (n.s.), Reflex cough PEF, GCS |
| NCC - 2016 | prognostic model | 1 | 150 | Posterior fossa stroke | 10.0 | 5 | extubation success | Independence from mechanical ventilation for 7 consecutive days | GCS score >6 mechanical ventilation for less than 7 days, surgical evacuation of a hematoma |
| JNSc - 2016 | prognostic model | 1 | 112 | Ischemic stroke | 3.6 | 10 | extubation success | no reintubation within 48 hours (trachetomy and terminal extubation were considered "extubation failures") | NIHSS score ≤ 15, absence of dysarthria prior to intubation |
| Anesthesiol - 2017 | prognostic model | 3 | 437 | SAH, TBI, ICH, MS | 3.5 | 42 | extubation success | no reintubation within 48 hours | AGE < 40, visual pursuit, swallowing attempts, GCS < 10 |
| JCC - 2017 | prognostic model | 1 | 311 | TBI | 2.2 | 48 | extubation failure | no reintubation within 48 hours | female, secretions, inability to cough, GCS < 6, mechanical ventilation > 9 days |
| Anesthesiol - 2017 | prognostic model | 1 | 140 | SAH, TBI, ICH, stroke | 1.7 | 27 | extubation failure | NIV or need for intubation during ICU stay | cough, gag reflex, deglutition, neurologic status |
| ATS - 2017 | prognostic model | 3 | 152 | TBI | 1 | 51 | extubation success | no reintubation within 72 hours | presence of cough, fluid balance in prior 24 hours, age |
| WN - 2018 | prognostic model | 1 | 107 | Good grade SAH | na | na | extubation failure | reintubation within 48 hours | no statistically significant predictor |

***Table 1:*** *Characteristics of the observational studies investigating weaning protocol for extubation or weaning. TBI = traumatic brain injury; GCS = Glasgow Coma Scale; SBT = spontaneous breathing trial; SAH = subarachnoid hemorrhage; ICH = intracranial hemorrhage; MS = malignant stroke; MEP = maximum expiratory pressure; MIP maximum inspiratory pressure; NIV = non-invasive ventilation; PEF = peak expiratory flow.*

| Journal - year | study type | n pts | n of variables screened | n of variables selected | large dataset | high quality dataset | model | discrimination ROC | score | Proposed threshold | Sens | Spec | PPV | NPV | GOF overall | GOF subsets | external validation | n pts/n screened | n pts/n selected | clinical impact |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RC - 2015 | validation (TIE score) | 43 | not applicable | not applicable | no | no | not applicable | 0.96 | no | not applicable | na | na | na | na | not applicable | not applicable | not applicable | not applicable | not applicable | no |
| RBTI - 2013 | validation (RSBI score) | 119 | not applicable | not applicable | no | no | not applicable | 0.64 | no | not applicable | na | na | na | na | not applicable | not applicable | not applicable | not applicable | not applicable | no |
| ICM - 2009 | prognostic model | 42 | 12 | 3 | no | no | logistic regression | na | no | none | na | na | na | na | na | no | no | 1.7 (overfitted model) | 6.7 (overfitted model) | no |
| AJRCCM - 2013 | prognostic model | 499 | 6 | na | no | no | Cox proportional hazards | na | no | none | na | na | na | na | na | no | no | 9 (overfitted model) | na | no |
| JBP - 2015 | prognostic model | 135 | 8 | 2 | no | no | logistic regression | na | no | none | na | na | na | na | na | no | no | 11.3 (overfitted model) | 22.5 (not overfitted model) | no |
| NCC - 2016 | prognostic model | 150 | 14 | 4 | no | no | logistic regression | na | no | none | na | na | na | na | na | no | no | 3.7 (overfitted model) | 13 (not overfitted model) | no |
| JNSc - 2016 | prognostic model | 112 | 6 | 2 | no | no | logistic regression | 0.75 | no | none | na | na | na | na | na | no | no | 9.3 (overfitted model) | 28 (not overfitted model) | no |
| Anesthesiol - 2017 | prognostic model | 437 | 13 | 4 | no | no | logistic regression | 0.75 | yes | ≥3 | 62 | 79 | 90 | 39 | HL p = 0.77 | no | no | 26 (overfitted model) | 24.8 (not overfitted model) | no |
| JCC - 2017 | prognostic model | 311 | 7 | 5 | no | no | logistic regression | 0.81 | yes | ≥8 | na | na | 43 | na | HL p = 0.78 | no | no | 6.1 (overfitted model) | 8.6 (overfitted model) | no |
| Anesthesiol - 2017 | prognostic model | 140 | 13 | 4 | no | no | logistic regression | 0.82 | yes | ≥9 | 84 | 75 | 89 | 66 | na | no | no | 3.3 (overfitted model) | 10.8 (not overfitted model) | no |
| ATS - 2017 | prognostic model | 152 | 7 | 4 | no | no | logistic regression | na | no | none | na | na | na | na | na | no | no | 17.1 (overfitted model) | 8 (overfitted model) | no |
| WN - 2018 | prognostic model | 107 | 5 | 5 | no | no | logistic regression | na | no | none | na | na | na | na | na | no | no | 2.6 (overfitted model) | 2.6 (overfitted model) | no |

***Table 6:*** *Statistical features of prognostic model for extubation and weaning in our review. GOF = goodness of fit; HL = Hosmer – Lemeshow.*

NV6 search code run on July 13, 2019
1632 hits

("Craniocerebral Trauma/drug therapy"[MeSH Terms] OR "traumatic brain injury"[All Fields] OR "head trauma"[All Fields] OR "head injury"[All Fields] OR "intracranial haemorrhage"[All Fields] OR "intracranial hemorrhages"[MeSH Terms] OR "intracerebral hemorrhage"[All Fields] OR "intracerebral haemorrhage"[All Fields] OR "cerebral hemorrhage"[All Fields] OR "cerebral haemorrhage"[All Fields] OR "intraventricular hemorrhage"[All Fields] OR "subarachnoid haemorrhage"[All Fields] OR "subarachnoid hemorrhage"[MeSH Terms] OR ("subarachnoid"[All Fields] AND "hemorrhage"[All Fields]) OR "subarachnoid hemorrhage"[All Fields] OR "Infarction, Middle Cerebral Artery"[Mesh] OR "middle cerebral artery infarction"[All Fields] OR (("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND "middle cerebral artery"[All Fields]) OR "brain injuries"[Mesh] OR "brain injury"[All fields] OR "acute brain injury"[All fields] OR "stroke"[Mesh] OR "Stroke/diagnosis"[MeSH Terms] OR "hemorrhagic stroke"[All Fields] OR "cerebral infarction"[All Fields] OR "brain infarction"[All Fields] OR "ischemic stroke"[All Fields] OR "ischaemic stroke"[All Fields] OR "Nervous System Diseases/therapy"[MAJR])
AND
("Extubation"[All Fields] OR "weaning"[MeSH] OR "weaning"[All fields] OR "ventilator weaning"[All fields] OR "mechanical ventilation weaning"[All fields] OR "weaning mechanical ventilation"[All fields] OR "extubation failure"[All fields] OR "extubation success"[All fields] OR "mechanical ventilation"[All fields])
NOT
(“External Ventricular Drain” [All fields] OR “EVD” [All fields] OR “hydrocephalus” [All fields])
AND
("humans"[MeSH Terms] AND English[lang])
NOT
(child* OR infant* OR pediatrics)

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***Group NV7: What are the indications for tracheostomy in patients with ABI? What is the optimal timing of tracheostomy in in patients with ABI?***

The NV7 groups addressed both the indications for tracheotomy, seeking for evidence in to support it compared to endotracheal intubation, and the timing of tracheotomy, trying to verify the hypothesis that early interventions improve the outcome. We retrieved 37 articles from the literature and discarded 27, ten remaining for grading, as illustrated in the article selection diagram in figure 1.[151-160] The string used to search the PubMed, is reported at the end of this document.

*Tracheotomy indications*

Only one study comparing tracheotomy performed on day 5-6 from admission (the day of randomization) with intubation was found.[153] It was a small RCT with very serious methodological bias, that was clearly underpowered to detect any minimally clinical meaningful difference in terms of mechanical ventilation duration. Moreover, the *p* value reported as significant (*p* 0.02) according to our calculation, instead, using the same statistical test *p* was 0.20. Overall evidence provided by literature in this field was thus graded *very low*, and inconclusive in regard to effectiveness because the issue was insufficiently investigated.

*Timing of tracheostomy*

We selected three randomized controlled trials (RCTs) [152, 155, 159] and six observational studies[151, 154, 156-158, 160] comparing early vs. late tracheostomy. We were unable to meta-analyze the RCTs due to substantial differences in treatment, control arms, and outcomes. One RCT focused on patients with ICH or AIS, showed a 35% 6-month mortality and 25% poor neurologic outcome reduction, comparing tracheotomy performed between day 1 and 3 vs. day 7 to 14.[152] The sample size was small, the quality of the study “low”, and the very large although statistically significant finding suggested the possibility of an exaggerated finding according to the “winner curse” theory.[161] The other two RCTs,[155, 159] dealing with TBI, provided non-significant findings concerning both clinically relevant and surrogate outcomes, but were underpowered and of very poor quality. Among observational studies there was one, with a large sample, and a propensity score matching analysis, reporting no differences in hospital mortality, but statistically significant reduction in pneumonia and deep venous thrombosis rates.[151] However, the study did not account for the time-dependent nature of tracheotomy, which requires the correct weighting of the exposure to treatment. Moreover, we had concerns about potential selection bias and external

validity issues. Thus, the study was not upgraded and was rated “low” in term of quality of evidence. The other observational studies were all downgraded to “very low” level of evidence because of methodological and statistical issues. Although studies included different mechanisms of brain injuries, this was not a contraindication for their combination. However, there was wide heterogeneity in definition of early and late tracheotomy and in characteristics of control groups, which prevented data pooling and analysis across studies. Cumulatively, the studies reported inconsistent evidence for impact of tracheotomy on mortality, poor neurologic outcome, and complications incidence. Overall evidence provided by literature in this field was rated *low*, with inconclusive findings and an insufficient investigation of the subject.

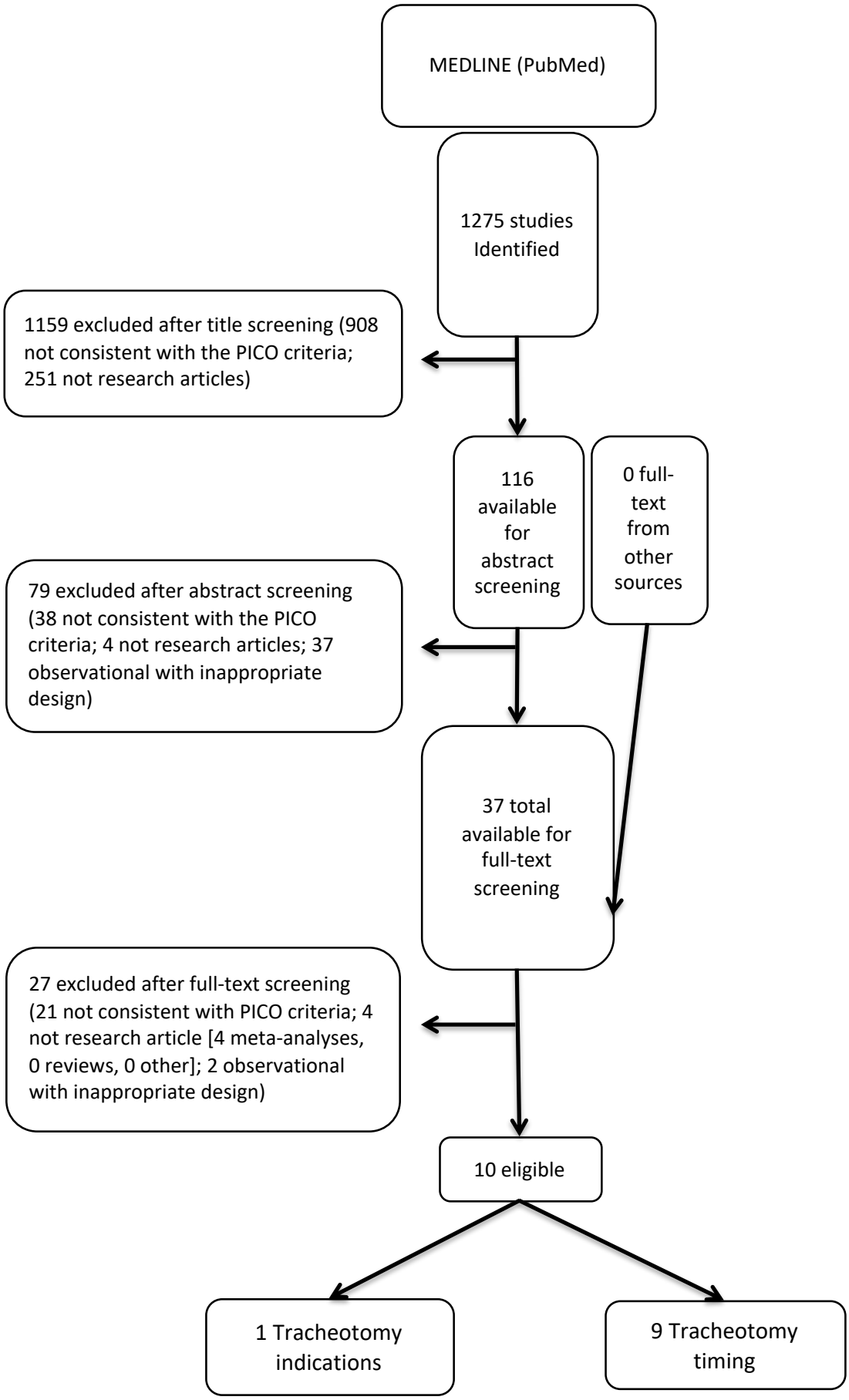


*Figure 7: PRISMA flow chart for article selection, group NV7.*

NV7 search code, run on July 13, 2019
1268 hits

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AND
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Animals[Mesh:noexp]
AND
English[lang]
NOT
(child* OR infant* OR pediatrics)

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