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# Mechanical Ventilation Management for Aneurysmal Subarachnoid Hemorrhage in ICU Settings: A Literature Review

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**A B S T R A C T**

Aneurysmal Subarachnoid Hemorrhage (aSAH) is one of the challenging neurologic emergencies with a high mortality rate along with various permanent disabilities. In order to provide the patient with the most appropriate and accurate treatment, as well as to prevent further complications, a multidiscipline approach is required. This study aimed to review the various mechanisms, indications, management, and sedation of mechanical ventilation in aSAH, along with a review of prone positioning and acute respiratory distress management in aSAH. Although the main injured organ is the brain, aSAH also affects the respiratory system through various mechanisms. The usage of mechanical ventilation plays an important part in brain oxygenation and perfusion and helps prevent related complications. Levels of oxygen and carbon dioxide in the blood might play some roles in aSAH patients. No significant difference was found in using various sedative regimens. Prone positioning is indeed beneficial for the oxygenation of aSAH patients, provided that continuous monitoring is done. Blood glucose and calcium levels might be able to help predict the outcome of aSAH patients. Mechanical ventilation plays an important part in aSAH management. Clinicians must be aware of the impact of mechanical ventilation on neurological organs and the cardiopulmonary system. Balancing between oxygenation, ventilation, and sedation must be in line with aSAH condition. Several prognostic factors and tools can help predict aSAH mortality that might be able to help the clinician tailor aSAH management to their patient's needs.

## 1. Introduction

Aneurysmal Subarachnoid Hemorrhage (aSAH) is one of the challenging neurologic emergencies with diverse complications and contributes up to 5% of stroke incidents. aSAH is one of the major problems with high mortality rates along with various permanent disabilities. In order to provide the patient with the most appropriate and accurate treatment, as well as to prevent further complications, management of aSAH requires a multidiscipline approach, including neurology, neurocritical care, neuroradiology, and neurosurgery.[1]

The incidence of aSAH is estimated to reach 9.1 cases per 100,000 people per year. The numbers are even higher in developed countries like Japan and Finland. In the United States, aSAH incidence is estimated at up to 10-15 cases per 100,000 people per year. Lower incidence was found in South Africa, with 4.2 cases per 100,000 people per year. Though aSAH has a lower incidence rate compared to the other types of strokes, aSAH has a high mortality rate. A study done in Norwegia showed that 30-day mortality of aSAH reached up to 38% of the cases.[1,2] The aSAH

mortality rate in Indonesia is 20.8-53.1% which is higher than in other Southeast Asian countries.[3]

Mechanical ventilation helps reduce the respiratory system effort by giving positive oxygen pressure and fulfilling the partial oxygen ($PO_2$) and carbon dioxide ($PCO_2$) pressures. Mechanical ventilation is generally used for critical patients with inadequate ventilation, compromised airway, and/or respiratory failure. For patients with brain injury, mechanical ventilation helps the oxygen delivery to the brain and prevents ongoing or further ischemia. The demand for mechanical ventilation is particularly high for aSAH compared with other types of stroke, which happens because of high pulmonary complications in aSAH. Mechanical ventilation for patients with aSAH is a major challenge faced by the physician and intensivist in preventing delayed cerebral ischemia that could lead to poor prognosis.[2,4] This study aimed to review the various mechanisms of aSAH pathophysiology and mechanical ventilation strategies in aSAH management.

**Pathophysiology of aneurysmal subarachnoid hemorrhage**

Aneurysmal subarachnoid hemorrhage is the most serious form of spontaneous subarachnoid bleeding. This counts as an emergency condition that requires quick and accurate assessment with proper management. Risk factors for aSAH are generally grouped into modifiable and non-modifiable risk factors. The modifiable risks are smoking, hypertension, and alcohol consumption, and the non-modifiable risks are age, gender, familial history, and previous history of subarachnoid hemorrhage (SAH). Out of all modifiable risks, hypertension is the most influential one. An increase in systolic blood pressure equal to or higher than 10 mmHg and/or diastolic blood pressure equal to or higher than 5 mmHg above the normal level will increase the risk of aSAH around 20%.[1]

Intracranial aneurysms are generally saccular (90%), whereas the other forms like fusiform and mycotic are less common. Brain aneurysm starts when there is hemodynamic stress that triggers local inflammation and causes endothelial dysfunction, resulting in a weaker arterial wall and more susceptible to aneurysm. Brain aneurysm could happen in both anterior and posterior circulation, but about 85% happens in the anterior. The anterior circulation includes anterior cerebral arteries and posterior communication artery that originates from the internal carotid artery and bifurcation of the cerebral medial artery. Hemorrhage in the posterior circulation is associated with a higher risk of rupture and a worse neurological prognosis, along with a higher mortality rate.[5]

Progression of aSAH is grouped into 3 phases, acute (within 24 hours), subacute (where early brain injury happens), and advanced/chronic phase (where there are vasospasms and delayed cerebral ischemia (DCI)). In the acute phase, rupture happens and blood starts flowing into the subarachnoid space, increasing the intracranial pressure (ICP), and hindering the cerebral blood flow (CBF) which will lead to ischemia and hydrocephalus. Increased sympathetic nerve activities are happening in aSAH, which will affect the heart, lungs, and other organ systems. This could cause acute lung injury, lung edema, takotsubo cardiomyopathy, and other systemic inflammatory responses. Furthermore, parasympathetic nerve impairment could cause arrhythmia and systemic inflammation in the blood vessels. If the ischemia persists, this will lead to brain cell death and early brain injury (EBI).[6,7]

Damaged cells and blood components will produce damage-associated molecular patterns (DAMPs) that will induce an inflammation cascade. The receptors involved with DAMPs are toll-like receptors (TLRs), cytoplasmic NOD-like receptors (NLRs), and non-pattern recognition receptors (non-PPRs) like CD44, integrin, and CD91. Hemoglobin along with other DAMPs products (methemoglobin, heme, heme chloride, and oxygenized hemoglobin) are toxic in nature and could cause EBI and delayed brain injury. Oxyhemoglobin is one of the main sources of reactive oxygen species (ROS) that could cause oxidation of lipid cells, proteins, and DNA that will lead to cell death. Hemoglobin will also impair the reaction of nitric oxide (NO) in the blood vessel which will lead to vasoconstriction of the blood vessel.[8]

Early brain injury is the condition of brain damage after the acute phase within 72 hours. Various things happen within EBI, including global ischemia, inflammation, cortical spreading depolarization (CSD), impairment of the blood-brain barrier (BBB), cerebral edema, and necrosis of the brain tissue. Global ischemia happens when there is elevated ICP and a decrease in cerebral perfusion pressure (CCP), leading to oxygen insufficiency of the brain tissue (ischemia). This starts transiently but will widen as the ischemia persists. Furthermore, the oxyhemoglobin that escaped the arterial wall will induce the release of endothelin and other arachnoid metabolites, impairing the reaction of NO which will lead to cerebral vasoconstriction.[6,9,10]

Inflammatory cytokines such as Interleukin-1b (IL-1b), Interleukin-6 (IL-6), and Tumor Necrosis Factor α (TNF-α) are involved in the progression of aSAH. These cytokines are produced by the microglia and astroglia. IL-1b induces the secretion of IL-6, IL-8, and colony-stimulating factors (CSF). IL-6 and TNF-α are known to have pathophysiological roles in vasospasm of aSAH and DCI. IL-1 is also associated with fever, leukocytosis, and impairment of NO synthesis in aSAH. A high level of CSF in aSAH is correlated with brain damage. Other cytokines such as IL-10 and Transforming Growth Factor-β (TGF-β) are also involved in immunosuppression in aSAH, which could lead to nosocomial infection.[11]

Cortical spreading depolarization (CSD) happens because of the disruption of ion homeostasis, disorder of vascular response, and lower electrical brain impulse due to the injury. CSD in aSAH might be induced by brain ischemia that contributes to EBI. CSD causes loss of brain activity through excitotoxicity, along with microvascular spasms that lead to vasoconstriction. This causes hypoperfusion and worsens the brain ischemia. Disruption of BBB in aSAH is influenced by the elevated ICP, decrease of CBF, neuroinflammation, and oxidative reaction within 24-48 hours. These will lead to an increased permeability of BBB and facilitate the entry of other fluids and molecules into the brain parenchyma, which will lead to cerebral edema, microthrombosis, inflammation, and disruption of brain metabolism.[10,12]

Delayed cerebral ischemia happens in the advanced phase, which starts 3-14 days after aSAH onset. DCI is defined as a neurological deficit (either focal or decrease in Glasgow coma scale (GCS) more than 2 points) that persists for more than 1 hour without any other explainable cause. It is known that DCI is associated with cerebral vasospasm, including the narrowing of brain arteries that happens a few days after aSAH, along with microthrombi, infarct, and microvascular collapse. The mechanisms in DCI are directly associated with EBI. Risk factors of DCI and EBI are generally similar, including massive brain hemorrhage and, a history of early complications such as recurrent bleeding, hydrocephalus, seizures, cerebral edema, and prolonged loss of consciousness.[6,10]

Complications in aSAH could also affect the respiratory system. Pneumonia, acute lung injury (ALI), neurogenic pulmonary edema (NPE), and ARDS could also happen due to aSAH. Lung complication results in mortality for up to 50% of aSAH patients. The possible mechanism is that patient with DCI tend to get more aggressive fluid therapy, which potentially could cause congestive heart failure and leads to lung complications. Another possible mechanism is that when aSAH occurs, a sympathetic surge causes systemic vasoconstriction and increases blood pressure. This will facilitate the migration of fluid in the systemic intravascular system to the pulmonary blood vessels due to its lower pressure.[6,13]

**Mechanical ventilation indication**

In general, the primary indication for mechanical ventilation usage is inadequate airway patency, hypoventilation, increased ventilatory demand, and hypoxemic respiratory failure. Inadequate airway patency can be caused by airway obstruction (e.g., angioedema, bronchospasm, trauma) or decreased consciousness. Hypoventilation can cause accumulation in arterial carbon dioxide level ($PaCO_2$) and hypercapnic respiratory failure. The etiology of hypoventilation is decreased central respiratory drive, respiratory muscle weakness (e.g., muscular dystrophy), peripheral nervous system disturbances (e.g., myasthenia crisis, Guillain-Barré Syndrome),

and ventilatory restrictive disease. Hypoxemic respiratory failure can be caused by alveolar disruption (pneumonia, acute respiratory distress syndrome, lung edema), V/Q mismatch, and lung fibrosis. Patients with sepsis, shock, and severe metabolic acidosis require mechanical ventilation to fulfill the increase in ventilatory demand.[14]

Positive pressure generated by mechanical ventilator devices affects human normal physiology. Ventilator positive pressure will occupy from the upper airway to the alveoli. That positive pressure will be transmitted to the alveolar space and thoracic cavity, causing pleural space pressure less negative. Less negative pressure in the pleural space will cause an increase in the right atrium, which will then decrease venous return. A decrease in venous return will decrease cardiac output and mean atrial pressure (MAP).[15]

One of the primary functions of mechanical ventilation is to manage patient oxygenation and ventilation. The rule of thumb to manage oxygenation is to adjust the fraction of inspired oxygen ($FiO_2$%) and/or the positive end-expiratory pressure (PEEP), and for ventilation is to adjust the minute ventilation. Higher $FiO_2$% and PEEP means higher oxygenation for the patient, whereas higher ventilation means more carbon dioxide exhalation. $PaO_2$ and $PaCO_2$ will greatly affect patient outcomes, especially in brain-injured patients. $PaO_2$ is essential to maintain brain oxygen demand and neurological function, whereas $PaCO_2$ will affect cerebral blood flow, affecting intracranial pressure.[15]

Patients with aSAH that require mechanical ventilation are 38.5-65%. Usual indications for aSAH patient requiring mechanical ventilation are respiratory failure, airway protection, altered mental status, seizures, severe brain injury, and need for analgesia and sedation.[16] Mechanical ventilation in this aSAH patient provides a challenge to intensivists because of potential pulmonary complications such as pulmonary aspiration, neurogenic pulmonary edema, cardiogenic pulmonary edema, and pneumonia. That complication can occur in up to 22% of aSAH patients. Mechanical ventilation management plays an important part in brain oxygenation and perfusion. Mechanical ventilation management in patients with aSAH must realize the potential of delayed cerebral ischemia (DCI) and increased intracranial pressure from hydrocephalus.[2,17]

**Mechanical ventilation oxygenation and $CO_2$ clearance management**

Mechanical ventilation management is essential to support brain recovery and avoid neurological complications. Brain oxygenation in aSAH is very crucial to prevent brain ischemia. Hypoxemia can cause hypoxic brain injury. Patients with subarachnoid hemorrhage (SAH) commonly experience brain tissue hypoxia, indicated by brain tissue oxygen tension ($PbtO_2$) levels of less than 20 mmHg, which is associated with unfavorable outcomes.[18,19] Because the brain is an organ that requires a large amount and constant supply of oxygen, a decrease in its supply will disrupt the brain's intracellular adenosine triphosphate production. This disruption will affect energy-dependent ion channels that will cause intracellularly sodium accumulation and brain cytotoxic oedema. A prolonged hypoxic state can cause brain neuronal cell death.[20]

Cerebral vasospasm can caused DCI event cerebral infarction. One of the theories of cerebral vasospasm in aSAH patients is a spasmogenic effect of blood deposits in subarachnoid space. When blood clot resolution happens, extracellular cell-free hemoglobin (CFH) will accumulate in the subarachnoid space. CFH is known as an inflammatory mediator and can cause oxidative tissue injury. CFG has vascular spasmogenic properties. High levels of blood oxygen partial pressure (hyperoxemia) can increase CFH oxidation, which will then cause lipid and protein oxidation. These mechanisms will cause neuronal cell apoptosis and brain injury. Another proposed explanation of hyperoxemia's effect on cerebral vasospasm is mitochondria respiration disorder, uncoupling of nitric oxide (NO) synthase, and disruption of intrinsic oxidative signaling pathways. Research done by Reynolds et al in 345 patients with aSAH showed patients with cerebral vasospasm have higher $PaO_2$ in the first 72 hours after admission.[21] Recent systematic reviews suggest that even though evidence for the

hyperoxemia effect in aSAH patients is limited, brain tissue oxygen pressure monitoring should be used for a fraction of inspired oxygen titration.[2]

Abnormal levels of $PaCO_2$ have been identified as a major contributor to changes in cerebral blood flow through cerebral vasoconstriction and vasodilation processes. Hypocapnia will decrease cerebral blood flow, meanwhile, hypercapnia will increase cerebral blood flow which will then increase intracranial pressure. These changes may potentially exacerbate brain injuries. In general, intensivists attempt to maintain the $PaCO_2$ target at 35-40 mmHg.[22] Theoretically, hypocapnia can help reduce intracranial pressure, however aSAH patient with a level of $PaCO_2$ less than 35 mmHg is associated with Glasgow coma scale (GCS) less than 4 and delayed cerebral ischemia (DCI). In general, hypocapnia is best to avoid in aSAH patient unless there is an acute rise in intracranial pressure.

Studies done on permissive hypercapnia are still inconclusive. The arterial partial pressure of carbon dioxide of more than 37.5 mmHg in the first 24 hours is associated with a decreased risk of unfavorable outcomes (GCS of 1-3).[2] A study done by Reiff et al disagrees with the study mentioned before. A study done by Reiff et al showed that $PaCO_2$ of more than 40 mmHg is associated with higher Hunt-Hess score, pneumonia, and longer length of stay.[23] Recent systematic reviews suggest that permissive hypercapnia is possibly tolerated in aSAH patients and its implementation should be done with intracranial pressure monitoring.[2]

To this day, the best mechanical mode of ventilation for neurological patients is always debated. Researchers try to study the best mechanical ventilation mode to improve neurological outcomes and reduce mortality in patients with brain injury. A randomized cohort study done by Mourão et al tried to compare volume control ventilation (VCV), pressure control ventilation (PCV), and pressure-regulated volume control (PRVC) in neurological patients. They found that VCV and PRVC mode has better outcome (mechanical ventilation duration, survival, ICU length of stay) than PVC mode.[24]

**Sedation in aSAH with mechanical ventilation**

Sedation and analgesia play an important role and complement each other in mechanically ventilated patients. Sedatives are usually indicated in mechanically ventilated patients for relieving discomfort, decreasing the work of breathing, and improving patient breath synchrony with the ventilator. Relieving and controlling pain before using sedatives in mechanically ventilated patients is essential. Uncontrolled sedation in mechanically ventilated patients is associated with less early mobilization, prolonged use of mechanical ventilation and ICU stay, incidence of delirium, and long-term cognitive dysfunction. Pain and sedation monitoring in critically are associated with less pain and sedative medications, shorter length of stay and mechanical ventilation duration, and reduced cost. Several tools are available for pain assessment in critical care situations for example behavioural pain scale (BPS) and critical-care pain observation tool (CPOT). However, its evidence on performance and reliability use in aSAH patients is limited. Depth of sedation can be measured objectively using auditory evoked potential and bispectral index.[25]

Patients with aSAH usually need deep sedation in the early course of the disease to help control brain edema, increase seizure threshold, and control brain oxygen consumption.[26] Patients under deep sedation are usually under control or assisted with mechanical ventilators. Sedative drugs commonly used in intensive care settings are benzodiazepine (e.g., midazolam, lorazepam), propofol, dexmedetomidine, and opioid (e.g., fentanyl, remifentanil, morphine).[27]

Generally in mechanically ventilated patients, nonbenzodiazepine sedatives (propofol or dexmedetomidine) are preferred to improve clinical outcomes. Recently dexmedetomidine has gained a lot of attention in critical care settings. A recent systematic review comparing dexmedetomidine with another sedative agent in mechanically ventilated ICUs. This review found that dexmedetomidine reduced the risk of delirium (RR: 0.67, 95% CI: -2.89 to -.0.71; moderate certainty), mechanical ventilation duration (MD: − 1.8 hours, 95% CI: − 2.89 to − 0.71; low certainty), and duration of ICU stay (MD: − 0.32 days,

95% CI −0.42 to −0.22; low certainty). However. Its usage is associated with increased bradycardia risk (RR: 2.39, 95% CI: 1.82 to 3.13; moderate certainty) and hypotension (RR: 1.32, 95% CI: 1.07 to 1.63; low certainty).[28]

Till now there are no specific recommendations regarding sedative drug regimens in patients with aSAH. Chelsea et al try to compare sedative regimens in SAH patients (including aSAH). A retrospective cohort study including 240 SAH patients shows no differences in vasospasm rate, sedative drugs adverse events, and ICU mortality in patients who receive dexmedetomidine (alone or combined with other sedative drugs) compared with other sedative drugs (midazolam, propofol, or no sedation).[29]

**Patient positioning in aSAH**

Brain cerebral blood flow is influenced by body positioning. Head-up position increases the distance of the head from the heart, so brain arterial blood pressure is supposedly decreased. However normal physiological reflexes enable the brain's systemic arterial pressure to be maintained. In a normal person, head up position reduces head arterial perfusion pressure along with improved cerebral venous drainage so that intracranial is maintained, this mechanism along with cerebral autoregulation will lead to minimal changes in cerebral blood flow. Patients with impaired cerebral autoregulation (e.g., intracranial hemorrhage, ischemic stroke) lose this regulatory mechanism.[30]

Head positioning effects in intracranial hemorrhage patients remain a debate. Theoretically flat/supine position will lead to improved cerebral blood flow but an increase in intracranial pressure. Meanwhile, a head-up position will reduce intracranial pressure and brain cerebral blood flow. Patients with SAH especially with vasospasm usually maintain with supine position to improve cerebral blood flow and avoid brain hypoperfusion. Transcranial Doppler assessment at SAH patient showed no consistent changes from the effect of the head of bed elevation. Head of bed elevation does not significantly impact cerebral blood flow velocity or regional cerebral blood flow. Supine position can also reduce tidal volume and impair lung secretion clearance ability, making patients prone to atelectasis and pneumonia.[30]

Prone positioning is one of the methods that can be used in patients with respiratory failure, but this position is rarely used in patients at risk of increased intracranial pressure. In a study conducted by Leppert et al, patients with aSAH who underwent prone positioning showed a significant increase in mean arterial oxygenation and brain tissue oxygenation ($PbrO_2$). This study showed an increase in median intracranial pressure (ICP) in the prone position, but there was no significant change in cerebral perfusion pressure (CPP). The effect of prone positioning on ICP makes this procedure not recommended for patients with elevated baseline ICP and reduced intracranial compliance. Prone positioning is indeed beneficial for the oxygenation of aSAH patients provided that continuous monitoring is done.[31] Recent guidelines from American Heart Association (AHA) and American Stroke Association (ASA) recommended prone positioning in aSAH patients with ARDS.[32]

**Mechanical ventilation management for ARDS in aSAH patients**

Patients with aSAH have a risk of pulmonary complications, one of which is acute respiratory distress syndrome (ARDS). ARDS incidence in aSAH patient is 11-50%.[33] Development of lung injury in an aSAH patient is hypothesized caused by adrenergic surge and systemic inflammation triggered by an acute neurologic injury, and also from nonneurological stressors such as infection, transfusions, and mechanical ventilation. It usually happens in a median of 3 days from admission. The key pathological problem in ARDS is alveolar collapse. Alveolar collapse causes intrapulmonary shunting. Positive end-expiratory pressure (PEEP) enables the opening of the collapsed alveoli at the end of expiration, thereby maintaining functional residual capacity and improving oxygenation. This method is called the alveolar recruitment maneuver. Theoretically, PEEP can decrease mean arterial pressure and increase intracranial pressure.[2]

ARDS Network trial for mechanical ventilation strategies to reduce mortality is tidal volume 6-8

mg/kg of predicted body weight and to keep plateau pressure equal to or below 30 $cmH_2O$. However, this study excluded participants with elevated intracranial pressure.[2] Mechanically ventilated patients with acute brain injury under protocol of lower tidal volume (≤ 7mL/kg), moderate PEEP (6-8 $cmH_2O$), and early extubation were associated with a shorter course of mechanical ventilation duration and decrease in mortality.[34] This study is used as supporting evidence for recommendations in AHA/ASA 2023 guidelines for the management of patients with aSAH.[32]

Recent systematic reviews suggest the implementation of acute respiratory distress protocol with higher PEEPs in the early bleeding course and after the aneurysm has been secured. Advanced intracranial monitoring should be used to balance oxygenation, ventilation, PEEP, and cerebral perfusion.[2]

A multicentric retrospective cohort study done by Mazeraud et al that included 855 aSAH patients showed that ARDS was associated significantly with a poor outcome at ICU discharge (univariate analysis). Multivariate analysis done in this study also showed that ARDS was associated with worse neurological outcomes (OR = 3.00, 95% CI: 1.16–7.72; p = 0.023). Brain injury can affect the pulmonary system. Brain-injured patients usually have swallowing problems which then will increase aspiration pneumonia risk. Another possible mechanism is immune and catecholamine abnormality that might increase intrapulmonary pressure and activate the pulmonary immune system, both will increase lung susceptibility to lung injury. A possible mechanism of association of ARDS with poor outcomes in aSAH patients is poor brain oxygenation that causes cerebral hypoxia and neuronal cell death.[33]

Recent AHA/ASA guidelines recommend adaptation of bundled care for aSAH patients with mechanical ventilation. Those bundled care mentioned is lung protective ventilation (mentioned before), early enteral nutrition, standardization of antibiotic therapy for hospital-acquired pneumonia, and a systematic approach to extubation. Studies showed that adaptation of those bundled care is associated with earlier extubation, shorter mechanical ventilation duration, increased ventilator-free days, and increased ICU-free days.[32]

**Prognosis of aSAH patient under mechanical ventilation**

Researchers try to identify factors that can predict mortality in aSAH patient on mechanical ventilation. In-hospital mortality in aSAH patient on mechanical ventilation is up to 54.6%.[16] Based on the study available, multiple factors may affect patient aSAH mortality and lung injury incidence including ARDS. A study done by Sachdeva et al found that a higher grade of SAH (modified Hunt-Hess grade 3,4,5) is associated with a 28.56% incidence of ventilator-associated pneumonia. The possible explanation is higher grade SAH is associated with immunosuppression and, therefore higher risk of pneumonia. The catecholamine hypothesis stated that SAH might be able to trigger massive sympathetic nervous system activation that leads to a sudden increase in cerebrospinal fluid. Sudden increases in intracranial pressure along with sympathetic nervous system activation contribute to SAH-induced systemic inflammatory response syndrome (SIRS). SIRS contributes to acute lung injury and poor outcomes in SAH. SIRS incidence in SAH patients is ranging from 29-87%.[35]

A prospective observational study including 219 aSAH patients done by Chen et al found that regardless of SAH grade, aSAH patients having neutrophil to lymphocyte ratio (NLR) of more than 10 were associated with worse postoperative pneumonia survival rates. The author of this study proposes that NLR at admission might help as a postoperative pneumonia predictor in an aSAH patient. NLR might help in the identification of high-risk patients.[36]

A retrospective cohort study by Ren et al showed that deceased patients have lower blood calcium and higher blood glucose concentrations. Hypocalcemia can disturb platelet function and coagulation cascade, which will then worsen aSAH patient's condition. Hypocalcemia can increase vascular tone and potentially increase bleeding. Hypocalcemia also can decrease the anti-apoptotic pathway and disrupt blood-brain barrier integrity. Mechanisms in which hyperglycemia can affect the brain are brain edema,

inflammatory reaction, free radical injury, and cell apoptosis.[16]

Wan et al have made a tool for predicting long-term outcomes in aSAH patients requiring mechanical ventilation. This tool incorporates four clinical characteristics which include early brain injury, rebleeding, length of ICU stay, and Simplified Acute Physiology Score 2. This tool might be of help for the selection of therapeutic regimens and prognostic prediction.[37]

**Limitation**

Regarding mechanical ventilation, this review is still unable to provide evidence from several questions. We are unable to find literature about the impact of prior surgical intervention (surgical clipping or endovascular clipping) on mechanical ventilation strategies in aSAH patients. We are unable to retrieve evidence about the common comparison of mechanical ventilation mode especially in aSAH patients with ARDS. We acknowledge that in the future this study could be improved by better methodological strategy for example systematic review with or without meta-analysis to provide better certainty of evidence or less risk of bias.

## 2. Conclusion

Mechanical ventilation plays an important part in aSAH management. The pulmonary complication is not uncommon and contributes to mortality and poor outcomes in aSAH patients. Clinicians must be aware of the impact of mechanical ventilation on neurological organs and to cardiopulmonary system. Balancing between oxygenation, ventilation, and sedation must be in line with aSAH condition. Several prognostic factors and tools can help predict aSAH mortality that might be able to help the clinician tailor aSAH management to their patient's needs. In the future systematic review and meta-analysis are needed for these specific subjects.

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