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José Geraldo De Andrade Neto, 6th Year, Group 3

INTEGRATED STUDY MASTER'S THESIS

Long-Term Outcomes in Mechanically Ventilated Patients

Supervisor Dr., MD PhD, Tomas Jovaiša

Head of clinic Prof. Dr. (HP) Jūratė Šipylaitė

Advisor MD, Raimundas Stasiūnaitis

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geraldo.de@mf.stud.vu.lt

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General Thesis Introduction

Mechanical ventilation is a critical treatment used by hospitals round the world. This thesis consists of two parts.

The first part consists of a literature review that will explore the physiology, historical background, evolution of mechanical ventilators, evolution of techniques involved in mechanical ventilation, differentiate a standard ventilated patient from a long term ventilated one, explore different outcomes such as mortality, healthcare costs, the biomechanics involved in mechanical ventilation, analyse the clinical impact of mechanical ventilation, different control methods and alternatives to mechanical ventilation.

The second part of the thesis includes a scoping review of the Long-Term Outcomes in Mechanically Ventilated Patients. This review attempts map and synthesise available data of the outcomes of mechanically ventilated patients, identify and analyse the resources that are currently available for the topic, identify current knowledge gaps and describe relevant characteristics of the relevant studies presented.

This thesis is separated in two parts in order to clearly differentiate the narrative synthesis performed in Part I in terms of mechanically ventilated patients from the systematic mapping conducted in the Part II scoping review. This structure allows for a comprehensive exploration of the topic by first tracing the historical development of mechanical ventilation, examining its evolution in clinical practice, and analysing key advancements that have shaped current approaches. This approach provides foundational understanding that aids the synthesis and analytical component presented in Part II, that additionally uses a broader scope of literature to assess trends and areas that are in need of further investigation.

Finally, a comprehensive conclusion will finalize the thesis, summarizing key facts presented in both parts, and highlight issues relating to both parts of the thesis.

Keywords

Ventilation; outcomes; literature review; scoping review

Abbreviations

ICU: Intensive Care Unit

OR: Operating Room

RR: Respiratory Rate

FiO2: Fraction of Inspired Oxygen

PMV: Prolonged Mechanical Ventilation

LTACH: Long Term Acute Care Hospital

Pplat: Plateau Pressure

PO2: Partial Oxygen Pressure

ARDS: Acute Respiratory Distress Syndrome

VILI: Ventilator Induced Lung Injury

COPD: Chronic Obstructive Pulmonary Disease

NIV: Non-Invasive Ventilation

HFNC: High Flow Nasal Cannula

OSAS: Obstructive Sleep Apnoea Syndrome

PEEP: Positive End Expiratory Pressure

Further abbreviations may be present in the body of the thesis and have been kept to aid readability.

Part I: Mechanically Ventilated Patients: Literature Review

Definition of ventilated patients.

Mechanically ventilated patients are those that underwent an intubation procedure by a qualified health care professional such as an emergency medicine physician, and are now connected to a ventilation machine that provides respiratory support(1).

Before initiating mechanical ventilation, it is necessary to intubate the patient. Previous preparation is necessary for this procedure, which includes procuring items such as adequate personal protective equipment, functional suction equipment, endotracheal tube, endotracheal blade, and stethoscope(2). While routinely performed, the endotracheal tube should be carefully positioned, taking care to avoid certain complications associated with endotracheal intubation, such as unrecognized oesophageal intubation, which may be life threatening(2).

Therefore, endotracheal intubation can be considered one of the highest risk procedures in the ICU. Further, there are significant differences in the purpose of endotracheal intubation between different patients, for example: The main purpose of endotracheal intubation and subsequent ventilation in an operating room (OR) is to prepare a patient to receive anaesthesia, whereas in the ICU, this procedure is medically necessary in order to address life threatening conditions such as acute respiratory failure.(3)

During endotracheal intubation a variety of medicines are administered, in order to assure a safe and pain free procedure for the patient. Some of the commonly used drugs include sedative agents such as propofol and ketamine, each which depress a patients awareness and consciousness, while other agents such as muscle relaxants may also be used in certain cases.(3)

Definition of long-term ventilated patients

There exists a significant minority of patients that require mechanical ventilation outside the ICU. Those patients are defined as ventilator dependent, or long-term ventilated patients. While various timeframes ranging from 2 to 29 days of continuous ventilation have been proposed to define when a patient will be consider to be under Prolonged Mechanical Ventilation (PMV), international consensus defined PMV as at least six hours of ventilation per day for 21 consecutive days(4,5).

Historical development of mechanical ventilation

Breathing, though a universal action among animals, was poorly understood before the advent of modern advancements in medicine. Therefore, many scientists conducted experiments in order to better understand it.

Galen of Pergamon (129-216AD) was one of the first scientists to theorize about the purpose and functioning of the breathing apparatus. Responsible for impactful experiments in the medical field, his experiments with animals yielded valuable results that pointed towards the importance of breathing as basic requirement of life. (6)

It would only be much later, in the 15th century, that Galen's findings would be refined by another scientist. Andries von Wezel (1514-1564), better known as Andreas Vesalius, described for the first time in his book a "De Humani Corporis Fabrica", how blowing air through a tube inserted in the trachea, would cause an animal's lung to be inflated again. Though extremely useful nowadays, this technique only became commonplaces centuries later.(7)

Robert Hooke (1635-1703) went further, and challenged one of Galen's theories that movement of the lungs was necessary to sustain life. He devised an experiment with a dog, where he cut two openings on the surface of the dog's lungs, and connected the trachea to a set of bellows in order to provide a flow of air that would escape via through the openings. The dog would stay conscious when the air was being pumped through the bellows, but would start convulsing when the flow of air would cease.(8)

However, as stated by Hooke, he and other scientists did not understand at the time why humans breathed, as it was thought at the time that a lack of consciousness or breathing was due to a lack of stimulus to the patient.(7)

The discovery of oxygen attributed simultaneously to Joseph Priestley (1733-1804) Antoine-Laurent Lavoisier (1743-1794) and Carl Wilhelm Scheele(1742-1786)(9,10), resulted in greater understanding of the purpose of respiration, which in turn would set up the theoretical foundations towards the development of the first prototype ventilators in the late 19th century.(7,9).

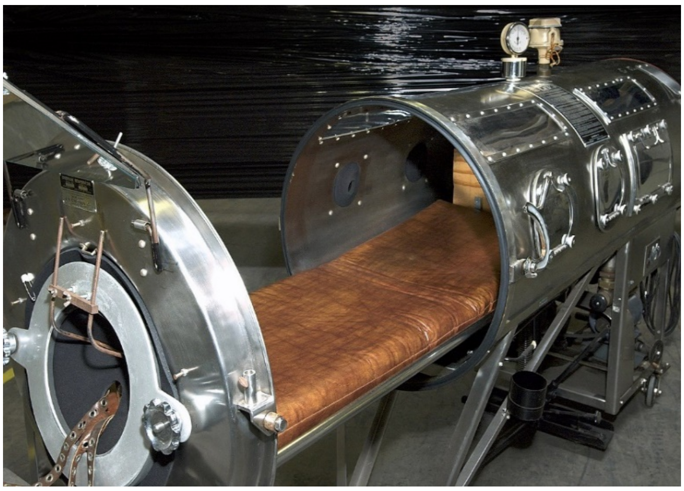
It would only be decades later, that the first machine for mechanical ventilation would be used in a more widespread capacity. (11)

An important catalyst for the medical interest in mechanical ventilation was the surge of Polio infections closing years of the 19th century. Though Poliovirus infections were already a common occurrence then, changing socioeconomic trends led to increased incidence of the virus in older children, which corresponded to an increasing number of children with paralytic poliomyelitis.(12)

Louis Agassiz Shaw Jr (1886-1940) together with Phillip Drinker (1894-1972), were encouraged by staff at the Boston’s Children’s Hospital to develop a ventilation machine that could be used to treat children infected with the Polio virus, which had a high mortality at the time. This machine would be known at the time as the Iron Lung. (13)

Weighing over 650 pounds, the Iron Lung was a large, cylindrical device that would completely envelop a patient, leaving only the head outside the machine, whereas the neck would be attached to the machine via a rubber seal. It would work by reducing the pressure around one’s body and lungs, forcing air inside the lungs making it the first practical negative pressure ventilator. (14)

The first patient to use an iron lung was an 8-year-old girl, which was suffering from the effects of a Polio virus infection. As her capacity to breathe was rapidly diminishing, the decision was made to test the functionality of the machine with her. Though her clinical picture markedly improved, she still succumbed to the disease a few days later.(15)



Left: Photograph shows an opened artificial respirator commonly known as the iron lung. (A)

Right: A boy with polio in the Emerson Respirator (Iron Lung) viewing the photographer (Joe Clark) in the machine's mirror. Herman Kiefer Hospital, Detroit, MI. (B)

Though a valuable tool, the Iron Lung was not a panacea for the treatment of Polio. The bulky, expensive machine precluded hospital staff from having access to a patient’s body, with everyday tasks such as drawing blood or moving patients inside the machine nearly impossible. The machine was also expensive, precluding many hospitals from acquiring the machines before a polio epidemic struck the region.(14)

With expanding use of iron lungs worldwide, steps were taken to address some of the machines known limitations.

The development of cuirass ventilators in the 1950s, created a ventilation system that did not require the whole body of a patient to be inside of tank like the Iron Lung, but the device also had its own inefficiencies. It relied on the passive recoil of a patient’s lungs during expiration, making the machine not suitable in cases where the patient had no muscular function.(16)

Bjørn Aage Ibsen (1915-2007) observed that patients were doing well while under positive pressure ventilation during surgeries and sought to apply the concept to polio patients that needed continuous ventilation. With the assistance of a surgeon that performed a tracheostomy, he proved his theory with a critically ill pediatric patient, that later experienced an improved clinical picture. He then sought to replicate his technique on other patients, which sharply reduced mortality amongst polio patients in his hospital of practice.(17)

At the time, positive pressure mechanical ventilators were not yet widespread, which meant every patient that was ventilated by Ibsen’s method had to be ventilated manually with a bag. This created logistical difficulties, as a large number of staff members were required in order to provide round the clock care to all the patients.(7)

Conversely, this led Ibsen to create at the Copenhagen Municipal Hospital what was retroactively is considered the first Intensive Care Unit (ICU) in the world, concentrating polio patients from the whole hospital in a single ward, called the Observation Room.(18)

In the 1970s, solutions such as portable ventilators were made available to the public. This allowed ventilated patients that could not be weaned off from mechanical ventilation to be discharged home, not only decreasing costs to patients and healthcare institutions, but also giving ventilated patients a chance to return to a more normal environment.(19)

Another possibility for long term ventilated patients arose in the development of Long-Term Acute Care facilities (LTACs). There are significant challenges of maintaining those patients in ICU facilities, such as high costs and the necessity of having open ICU beds for those who are acutely ill.(4)

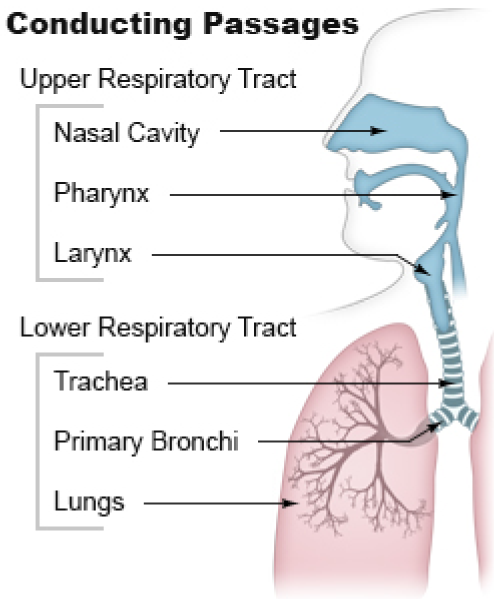
Future advancements in the field of mechanical ventilation technology are underway. One example are innovative technologies that may in the future allow the adjustment of ventilator settings in an environment away from the patient. (20)

Anatomical and histological components of respiration

In order to describe the physiological process of mechanically ventilating a patient, one must first understand the fundamentals of the human respiratory system, and how it relates to the functioning of a mechanical ventilation system.

A functioning respiratory system is a basic requirement to sustain human life. It works in tandem with the circulatory system, being responsible for the uptake of oxygen and elimination of carbon dioxide that takes place in our body.

The respiratory pact can be roughly divided into 2 parts: The upper respiratory tract and the lower respiratory tract. (21)



Respiratory conducting passages. (C)

The upper respiratory tract is composed of the nasal and oral cavities, pharynx and larynx. Air is usually inhaled through the nose, being filtered, humidified and warmed as it passes through the nasal structures, and continues its way through the pharynx. (22) In cases of infection or other nasal obstructions, breathing can also be accomplished through the mouth, though this is not optimal. (23)

Other features of note in the upper respiratory tract are the epiglottis, and the vocal cords. They are responsible for the protection of the airways from ingested food content. The epiglottis sits above the laryngeal inlet, preventing food from entering the trachea. The vocal cords close tightly when swallowing for the same reason, though their main function is related to the production of sounds also known as phonation. (24)

The lower respiratory tract consists of the trachea, bronchi, bronchioles and alveoli and diaphragm. The lower respiratory tract serves both a conducting function directing air to the sites of gas exchange, but also has structures such as the diaphragm that are mechanically responsible for both the inspiration and expiration.(24)

The trachea is a flexible tube that begins just below the larynx, roughly from the level of the sixth or seventh cervical vertebra. It is responsible for the conduction of air between the larynx and the bronchi, while at the same time exchanging heat and moisture with the environment, and removing particles form the inhaled air. (25)

The wall of the trachea consists of a muscle layer that is surrounded by up to 20 rings composed of cartilaginous hyaline that ensure the trachea remains open during respiration. It is usually 1.5 to 2 cm wide, 10 to 13 cm long. (25)

In the inferior part of the trachea at the level of the fourth thoracic vertebra, an anatomical part called the carina marks the bifurcation of the trachea into right and left primary bronchi, with each primary bronchi extending towards their respective lungs. (26)

The right primary bronchus is shorter and wider compared to the left primary bronchus. This is why aspirated foreign objects are more likely to get stuck in the right primary bronchus. The right primary bronchus branches into the three secondary bronchi, serving the upper, middle and inferior lobes of the right lung. (27)

The left primary bronchus is longer and narrower, going underneath the aortic arch in order to enter the left lung. It branches into two secondary bronchi, supplying the upper and lower lobes of the left lung. (27)

Further branching of the secondary bronchi continues to occur. Secondary bronchi will branch into tertiary bronchi, which in turn branch further into bronchioles, with bronchioles marking the transition between the conducting zone and the respiratory part of the trachea, the end of which alveoli are located, facilitating the actual gas exchange taking place in the lungs. (28)

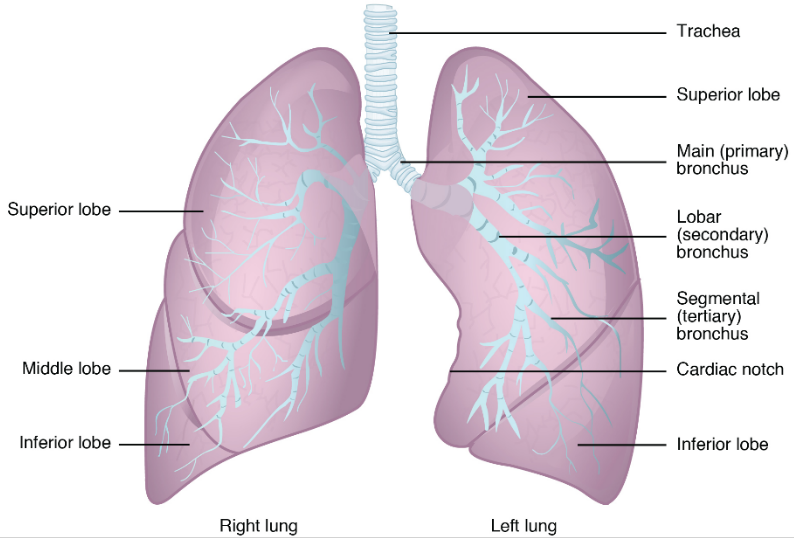
The respiratory muscles and the pleura are also important parts of the lower respiratory system.

The main muscles involved in breathing are the diaphragm and the intercostal muscles. The diaphragm is located on the lowest part of the thoracic cavity, separating the abdomen from the thorax. It is the principal muscle involved in respiration, contracting and moving downward during inspiration, increasing the volume of the thoracic cavity, allowing the lungs to inflate. The intercostal muscles, help expand the ribcage and stabilize its expansion, aiding the diaphragm during inspiration.(29)

The pleurae are elastic membranes that envelop and line the lungs, forming a sac-like structure. The inner surfaces of this structure secrete a lubricating fluid called pleural fluid, which reduces friction between the lungs and the thoracic wall during respiration.(30)

Other secondary breathing muscles that can be engaged during respiration are the abdominal, sternocleidomastoids, scalene, pectoralis and serratus anterior muscles. They are mostly used only in situations of greater oxygen demand or during respiratory distress. (31)

The most important organs of the respiratory system are the lungs. The lungs are located in the thoracic cavity, on either of the heart. Their shape is cone-like, while their lower part rests on the diaphragm. (32)



Gross Anatomy of the Lungs (D)

Though they are functionally identical to one another, the right lung is slightly larger compared to the left lung. The left lung also has a structure called the cardiac indentation, where the lung is slightly depressed in order to make room for the heart. (32)

The lungs have lobes that function as anatomically separate parts of the same organ. The right lung is divided in 3 lobes: the superior, middle and inferior lobes. The left lung on the other hand has only two, the superior and the inferior lobes, due to the necessary accommodation for the heart. (32)

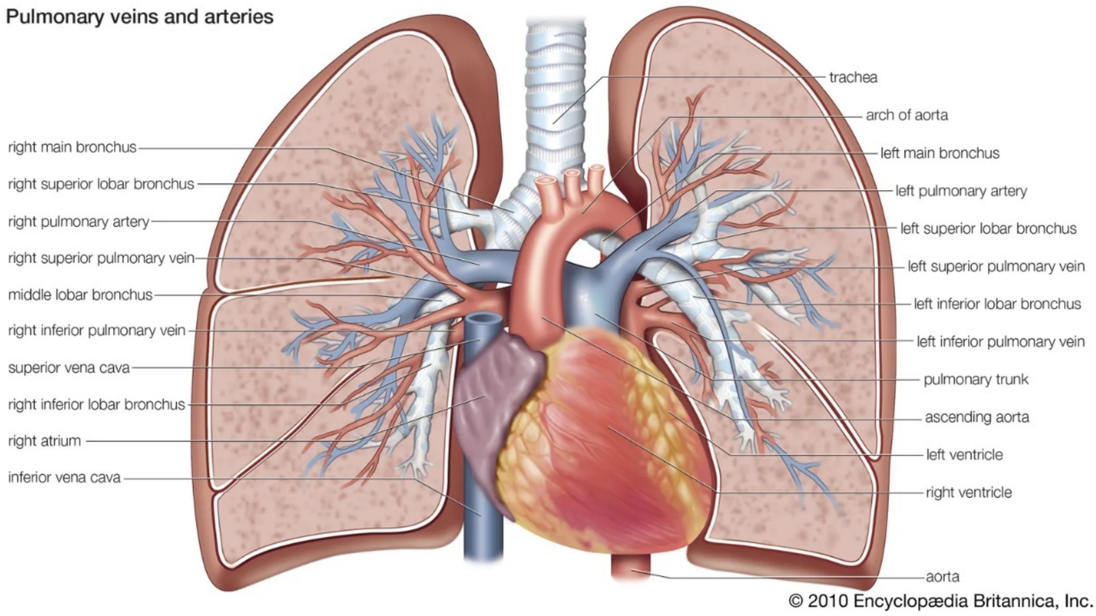
The proximity of the lungs with the heart also extends to the circulatory system. A variety of vessels such as arteries, veins and capillaries are responsible for ensuring the constant flow of blood, both oxygenated and otherwise to maintain the functions of both organs. (33)

The pulmonary arteries will carry deoxygenated blood to the lungs. They originate from the right ventricle of the heart, from which they bifurcate into the left and right pulmonary arteries. The left pulmonary artery then branches into two lobar arteries, each supplying one of the two lobes of the left lung. The right pulmonary artery branches into superior, middle, and inferior lobar arteries, each supplying one of the three lobes of the right lung. In both lungs, the lobar arteries further subdivide into segmental arteries, supplying individual bronchopulmonary segments. (34)

Pulmonary capillaries arise from the further branching of the segmental arteries. These will eventually form capillaries, creating a dense web of vessels that surround the alveoli. The pulmonary veins will then collect oxygenated blood from the capillaries and return the oxygenated blood to the heart. (35)

Separate bronchial vessels exist to supply blood directly to the tissues involved in the conductive and structural parts of the respiratory system, in order to meet their metabolic demands. (36)

Bronchial arteries arise from the thoracic aorta, supplying oxygen rich blood to the bronchial walls, bronchioles, connective tissue, pleura and other supporting structures of the lungs. (26) Finally, bronchial veins collect deoxygenated blood from the lung tissues and carry it into the superior vena cava and further into the right atrium of the heart. (36)



Pulmonary veins and arteries. (E)

Gas exchange in the respiratory system: Physiological and functional components

The alveoli are the structures where the actual gas exchange will take place during respiration. They are very small in size and surrounded by blood rich capillaries, hollow, and a pair of human lungs has about 480 million alveoli, providing the lungs with a large surface area for the exchange of gases.(37)

Many cells make up the alveoli. They are lined predominantly by thin, flat Type I pneumocytes, which form part of the respiratory membrane responsible for gas exchange and Type II pneumocytes, specialized cells that secrete surfactants, which is a substance that is crucial for lubrication and reducing surface tension within the alveoli, preventing their collapse during expiration. (38)

Oxygen exchange is the primary purpose of alveolar function. During inhalation, air fills the alveoli, bringing oxygen into close proximity with blood circulating in pulmonary capillaries. Due to the higher partial pressure of oxygen (PO_2) in the alveolar air compared to the deoxygenated blood, oxygen diffuses across the thin alveolar-capillary barrier into the blood plasma and then into erythrocytes. (39)

Inside the erythrocytes, oxygen binds to hemoglobin, forming oxyhemoglobin. This binding is reversible and influenced by several factors including pH, temperature, and carbon dioxide concentration. Once bound, oxygen is carried by the erythrocytes through the systemic circulation to tissues throughout the body. (39)

Carbon dioxide is produced as a waste product during cellular metabolism during aerobic respiration. Accumulation of carbon dioxide in the body can lead to respiratory acidosis, a dangerous condition where the blood pH becomes lower, with adverse effects to homeostasis. Proper ventilation ensures that CO_2 levels are kept within a narrow, safe range. (40)

Ventilator parameters and controls explained

Mechanical ventilators have a variety of controls and modes that may be used by different healthcare professionals in different settings. For doctors, this usually means that intensive training in anaesthesiology and critical care is crucial to understanding the safe operation of mechanical ventilators. (41)

There are a few common settings and values to all mechanical ventilator machines:

Respiratory Rate (RR): Usually represents how many breaths per minute the patient is doing at the moment.

Tidal volume: The volume of air moved in and outside the lungs in each respiratory cycle.

Fraction of Inspired Oxygen (FiO2): FiO2 is the concentration of oxygen that is being currently delivered to the patient's air supply.

Inspiratory to expiratory ratio: (I:E ratio) Expresses the timing of each breathing phase. Usual I:E rations range between 1:3 up to 1:5. (42)

Positive End-Expiratory Pressure (PEEP) is another very important parameter regarding ventilation settings. This is defined as the pressure applied by the ventilator at the end of expiration to keep the alveoli open. In physiological breathing, a small amount of PEEP exists, but in mechanical ventilation, additional PEEP is usually employed to keep the alveoli open, in this way improving oxygenation and eventually oxygen saturation in the blood. PEEP can be adjusted to meet demands

Interface of a typical mechanical ventilator. (F)

in patients with more severe conditions, however, excessive PEEP can reduce venous return to the heart, leading to hypotension, and can also damage alveoli, causing barotrauma, a lung injury caused due to excessive pressure in the lungs. Therefore, care should be exercised when changing PEEP parameters. (43)

Lung protective ventilation strategies have been developed specifically with the intention of avoiding lung injuries that can occur if patients are improperly mechanically ventilated. Those types of injuries are called ventilator-induced lung injury (VILI). (44)

These strategies usually employ a few tactics. A low tidal volume ventilation may significantly reduce mortality compared to higher tidal volumes. Lower tidal volumes help prevent the overdistension of alveoli. Hypercapnia may occur when ventilating a patient with lower tidal volumes, so this must be carefully balanced. (45)

Observing the plateau pressure (Pplat) dynamic is also important in order to avoid lung injury. This is defined as the pressure measured after a breath is delivered but before exhalation begins, reflecting alveolar pressure. It is generally recommended to keep plateau pressures below 30 cm H_2O. If plateau pressures are high even with low tidal volumes, further adjustments may be needed, such as decreasing tidal volumes further or adjusting PEEP levels. (46)

Finally, permissive hypercapnia may also be considered. This involves accepting higher levels of carbon dioxide ($PaCO_2$) in the blood to allow the use of lower tidal volumes and avoid excessive pressures. This may be tolerated to a degree, as long as organ perfusion and function are maintained. Overall, the aim should be to achieve a significant improvement in oxygen saturation, but that does not necessarily mean that a normal value should be used as a goal of mechanical ventilation. (47)

Injuries that may require mechanical ventilation

There exists a variety of conditions and complications that may lead to the need of an endotracheal intubations and the initiation of mechanical ventilation.

Commonly, protocols and guidelines recommend initiation non-invasive ventilation first, before escalation to the initiation of invasive mechanical ventilation, taking into account the severity of a patient's condition and vital parameters such as blood oxygenation to determine when/if the escalation of care should take place. (48)

Mechanical ventilation in the operating room setting has been demonstrated to be safe and useful for use during surgery. Nowadays, A large majority of surgical procedures, be it laparoscopic or otherwise, will make use of invasive mechanical ventilation, usually started and supervised by an anaesthesiologist and his team.(49,50)

One of the more common conditions leading to invasive mechanical ventilation, acute respiratory distress syndrome (ARDS) is a serious condition characterized by low lung compliance and oxygenation, which presents with alveolar damage and capillary injuries. While this syndrome is usually associated with an infectious aetiology, other intra and extra pulmonary sources may lead to ARDS. (51)

Acute stroke patients, especially ischemic ones, also frequently undergo mechanical ventilation. When this emergent condition happens, oxygen supply to cerebral tissues is interrupted, which causes cell damage and death. Mechanical ventilation usually comes into place whenever damage to areas of the brain that control consciousness and breathing, such as the thalami, the limbic system, pons medulla or respiratory centres in the cortex. (52)

Severe traumatic injuries may also warrant mechanical ventilation. In cases where there are significant injuries to the chest cavity, such as penetrating wounds with severe bleeding, the loss of blood occurring from the injury may rapidly lead to hypovolemic shock, a life threatening condition where there will be a generalized lack of oxygen in the tissues, where the initiation of mechanical ventilation may be use as one of many tools to manage the condition. (53) Trauma to other areas such as the brain itself, may also be addressed this way. (54)

Infections are one of the leading causes of ARDS. Normally, the immune system will counteract any infectious agents in a said organism with a variety of tools, both innate and adaptive. However, in cases of sepsis, the immune response to the infectious agent may become excessive, triggering a generalized inflammatory reaction that will damage organs and systems throughout the body. This in turn leads to a decreased functioning of the respiratory system, where the gas exchange may become impaired, leading to ARDS, whereupon the need for mechanical ventilation may arise. Nevertheless, mortality regarding this condition is high. (55,56)

Chronic Obstructive Pulmonary Disease (COPD) is another common condition that requires respiratory support, though the usage of invasive mechanical ventilation for these patients is declining. This disease is characterized by chronic bronchitis combined with emphysema, and recurrent episodes of exacerbation, where the usual intervention is made with NIV. However, as a progressive disease, in cases where the damage to the lung tissues and alveoli are substantial, a more aggressive approach with invasive mechanical ventilation can be performed. (57)

Anaphylactic shock is another life-threatening condition that evolves quickly and may be treated with mechanical ventilation. Similarly to sepsis, it involves an exaggerated and excessive response to a foreign agent, with the difference being that while sepsis relates to infectious aetiologies, Anaphylaxis involves allergic components, either environmental or foodborne. Since this condition has a broad spectrum of triggering agents, and there exists a substantial variation in reactions between affected people, the necessity of respiratory support may vary. Usually, NIV Support is used as a first line therapy, but in cases where the reaction was quite severe, and the patient has a diminished consciousness and vital status, admission to the ICU with invasive respiratory support is also a possible approach.(58)

Carbon monoxide (CO) is a colourless, toxic gas. CO poisoning can also be treated with mechanical ventilation. In this setting, Carbon monoxide binds to haemoglobin in the erythrocytes, creating a chemical bond that is much stronger than that of oxygen with haemoglobin. This leads to a distributed tissue hypoxia and CO mediated damage. To act against this, treatment often includes administering oxygen via high flow nasal cannulas or hyperbaric oxygen therapy, both of which helps to displace carbon monoxide from haemoglobin more rapidly. Mechanical ventilation may be necessary in cases of severe poisoning to support breathing and ensure adequate oxygenation while the carbon monoxide is cleared from the body. (59) Mechanical Ventilation may also be used in other types of poisoning, such as those with organophosphates for example. (60)

More generally, mechanical ventilation also plays a crucial role in the management of patients in a medically induced coma, especially when their ability to maintain adequate spontaneous breathing is impaired due to some other condition. In this comatose state, neurological dysfunction can compromise the brain's control over respiratory functions. This necessitates the initiation of mechanical ventilation, in order to preserve a patient's life as long as the patient is unable to breathe independently. (61)

Clinical and societal impact of mechanical ventilation

Mechanical ventilation has had a major impact across a variety of clinical conditions, many of those which were very likely fatal before mechanical ventilation was developed. Nowadays, millions of patients undergo mechanical ventilation every year, across many countries. Global pandemics, such as the COVID-19 pandemic, have also cast the impact of mechanical ventilation in a spotlight. (62)

The COVID-19 virus, officially named SARS-CoV-2, is a novel coronavirus that emerged late 2019 in China. This virus spread rapidly to other countries across the globe, culminating in a pandemic that was declared by the World Health Organization (WHO) on March 11, 2020. (63) An infection with this virus may cause a variety of symptoms ranging from a mild respiratory infection, to even a critical ARDS, which necessitates treatment with invasive mechanical ventilation. (62)

Withing this context, during the COVID-19 pandemic, the reliance on mechanical ventilation became particularly critical. As the number of cases rose, more ventilators were needed to treat patients with severe infection. This created a significant shortage of mechanical ventilators, with doctors being forced to implement triage procedures to decide which patients would have the better odds of survival, a decision that comes with a significant emotional burden on the physician. (64,65)

Though mechanical ventilation is lifesaving, it may also have negative consequences. One of the most serious complications associated with it is ventilator-associated pneumonia (VAP), a type of lung infection that occurs 48 hours or more after endotracheal intubation. VAP is caused by bacterial colonization of the lower respiratory tract via the endotracheal tube. VAP is associated with a poor prognosis, especially in immunocompromised patients. It may also prolong the time needed under ventilation. (66)

Common pathogens responsible for VAP include Pseudomonas aeruginosa, Staphylococcus aureus, methicillin-resistant Staphylococcus aureus, and other organisms. VAP prevention is a major focus of ICU protocols, including measures such as proper hospital hygiene, head-of-bed elevation, sedation interruption to attempt extubation of the patient (SBTs), intensive oral nursing care and other measures. (67)

Antibiotic therapy is critical for suspected VAP, but overuse of broad-spectrum antibiotics can promote resistance. Therefore, while initial antibiotic therapy may be administered with broad spectrum antibiotics, a change to narrow spectrum antibiotic therapy should be considered once a clear pathogen has been identified. (68)

Once the patient is on a clear pathway to recovery, weaning of the patient from mechanical ventilation may be attempted.

Weaning refers to the gradual reduction and eventual removal of ventilator support. The ability to successfully wean from mechanical ventilation varies across conditions and patients, and repeated attempts may be necessary before a successful weaning can be achieved. (69)

Several factors favour successful weaning: improvement of the underlying cause of respiratory failure, stable hemodynamics, adequate oxygenation, stable neurologic function to ensure the patient's airway is sufficiently protected, and sufficient respiratory muscle strength. (70)

Extubation failure is usually associated with worse outcomes, with increased mortality. Predictors of extubation failure include weak cough, excessive secretions, impaired mental status, and cardiac dysfunction. (71)

If weaning is successful, and discharge from the ICU has been achieved, most patients will undergo some sort of rehabilitation therapy, depending on how long mechanical ventilation was performed and how severe the condition was. (72)

Most stays in an intensive care unit will come with significant consequences to a patients cognitive, physical and respiratory conditions. This is a process called deconditioning, where even if the patient is expected to make a full recovery from the disease, the patient status is not the same as it was before hospital admission. A common feature of deconditioning for example, is a loss of muscle mass during a hospital stay. (73)

Physical therapy will typically involve both passive and active range of motion exercises to recover muscle strength and stability. Sitting at the bedside, standing, and eventually ambulation as tolerated are usual goals of physical rehabilitation. Early mobilization has been demonstrated to shorten hospital stays, reduce the risk of ICU acquired weakness, and improve functional outcomes. (74)

Respiratory rehabilitation is also crucial. After extubation, healthcare staff may make use of techniques such as spirometry, breathing exercises, and airway clearance techniques to prevent atelectasis and other complications. Patients may experience mild inspiratory muscle weakness after extubation, and targeted breathing exercises can help strengthen respiratory muscles. (75)

Mental health support is also useful for patients for rehabilitation purposes. Patients may experience distress, especially if they cannot return to their previous level of functioning or quality of life as they had previous to the ICU stay. Psychological support may also be offered to family members that are involved in the care of these patients. (76,77)

Prognostic factors for mechanically ventilated Patients

Patients who require invasive ventilation are typically among the most severely ill in the hospital, and their outcomes depend on a complex relationship between clinical, physiological, and systemic factors.

One of the strongest predictors of outcomes in mechanically ventilated patients is the severity of the underlying illness. Scoring systems like the APACHE II (Acute Physiology and Chronic Health Evaluation), SOFA (Sequential Organ Failure Assessment), provide estimates of condition severity at ICU admission and may be used to predict mortality. Patients with higher scores are more likely to experience poor outcomes, or significant long-term disability. (78,79)

Age is a major independent predictor of outcome. Elderly patients tend to have worse outcomes when requiring mechanical ventilation, and patient frailty may impact prognosis after discharge. (80)

The underlying diagnosis a patient presents when requiring mechanical ventilation strongly affects prognosis. Patients ventilated for reversible conditions like pneumonia, or drug overdose typically have better outcomes. In contrast, those intubated due to conditions like advanced interstitial lung disease, extensive metastatic cancer, or massive stroke have much poorer prognoses. (81)

The duration of mechanical ventilation is another critical prognostic factor. Generally, the longer a patient remains ventilated, the worse the prognosis. Prolonged mechanical ventilation is associated with increased risks of ventilator-associated pneumonia, ICU-acquired weakness, and multi-organ failure. Patients who fail early weaning trials often require tracheostomy and prolonged ICU stays, leading to more complex recovery processes or transition to long-term care facilities. (82)

Alternatives to mechanical ventilation

While invasive mechanic ventilation with positive pressure is the method of choice to use with critically ill patients, in many cases a less aggressive initial intervention with non-invasive ventilation methods is preferred, due to the complexity and risks associated with invasive mechanical ventilation. (83)

Non-Invasive ventilation (NIV) is a method of positive pressure ventilation that avoids tracheal intubations by using masks or other interfaces to provide respiratory support and oxygen delivery to a patient. (84)

There are two widespread modes of NIV:

Continuous positive airway pressure (CPAP) is a method of NIV that maintains a steady supply of air flow into a patient's lungs, in order to maintain the alveoli permanently inflated in spontaneously breathing patients. CPAP delivers PEEP at while maintain a set pressure both during inspiration and expiration. (85)

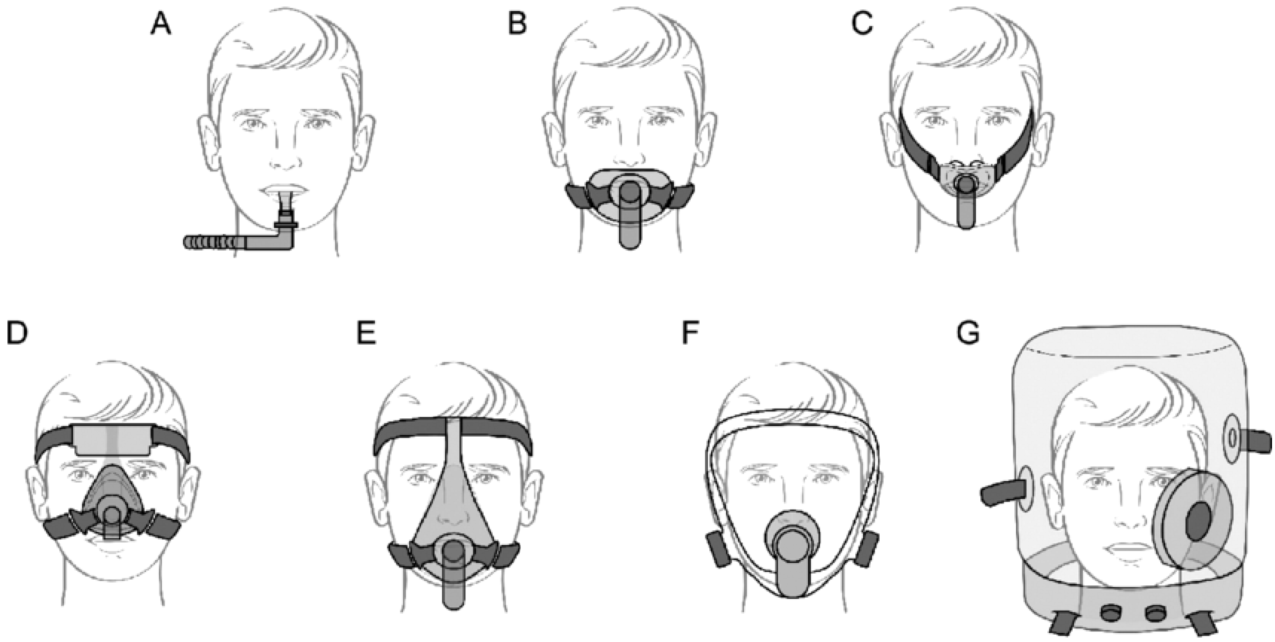
One of the most common uses cases for CPAP is that of the treatment of obstructive sleep apnoea (OSA) patients. With the CPAP machine maintaining the steady flow of air by design, this directly helps patients to keep their upper airway open while they are sleeping during the night, improving oxygenation, reducing sleep disturbances, and significantly enhancing sleep quality. (86)

Bilevel positive airway pressure (BiPAP) operation differs significantly from CPAP. While CPAP maintains continuous pressure during inspiration and expiration, BiPAP allows for separate configuration of an IPAP (Inspiratory Positive Airway Pressure) and EPAP (Expiratory Positive Airway Pressure). EPAP is typically set lower than IPAP, enhancing patient comfort during expiration and supporting airway patency, while the higher IPAP increases tidal volume and ventilation, thereby promoting greater clearance of CO_2 (87)

While both methods are widely used, different patient groups may benefit more from CPAP or BiPAP. CPAP is mostly indicated for patients with diseases involving only obstructive and hypoxic conditions such as Obstructive Sleep Apnoea Syndrome (OSAS) while BiPAP is preferred with conditions that involve significant CO2 retention and require ventilatory support, such as COPD patients with acute hypercapnic respiratory failure and patients with neuromuscular disorders.(87) BiPAP may also be used with patients that are unable to comply with CPAP therapy.(88)

High-Flow Nasal Cannula (HFNC) is also a commonly used type of NIV. HFNC provides heated and humidified oxygen at very high flow rates through special nasal cannulas. Though it may generate a small amount of positive airway pressure, it is still considered a type of non-invasive ventilation. It is commonly used in hypoxic patients where the escalation to invasive mechanical ventilation may not yet be necessary or desirable, though persistent respiratory distress with HFNC may be grounds to initiate mechanical ventilation. (89)

Another important aspect of NIV is the choice of interface. Several types of masks are available, including nasal masks, full-face masks, and helmet-based systems. Nasal masks are generally more comfortable but less effective in acute respiratory failure due to the risk of leakage trough the mouth. Full-face masks are more commonly used in acute care settings such as emergency departments or ambulances since they may provide better seals and more effective ventilation. Other interfaces such as helmets also exist but are not commonly used. (90)



Types of noninvasive ventilation interfaces. A: Mouthpiece, B: oral (lip-seal mouthpiece) mask, C: nasal pillows, D: nasal mask, E: oronasal mask, F: total face mask, and G: helmet. (G)

Also important to consider when using NIV, is patient tolerance. This can be a significant barrier to NIV success. Mask discomfort, skin issues, and other discomforts are commonly described by patients. Sometimes, patient comfort may be improved by providing breaks from the mask when possible, using humidification, and adjusting ventilator settings to increase tolerability. (90)

Contraindications to NIV methods do exist, however. Conditions that may cause improper airway protection, impaired consciousness, facial trauma, recent upper airway surgery, excessive mucus, severe upper gastrointestinal bleeding, or agitation or confusion may make patients unsuitable to use NIV. Patients with high risk of aspiration, are also usually poor candidates for NIV. (91)

On the other end, Extracorporeal Membrane Oxygenation (ECMO) exits as a highly advanced life support technique used for patients with severe respiratory or cardiac failure, where even aggressive mechanical ventilation alone may not be enough to ensure the survival of the patient. While ECMO cannot be considered as a standalone alternative to mechanical ventilation, it can rather actually be used as a coadjutant, last resort tool to be deployed in cases where the patient would otherwise expire. (92)

Ethical considerations of mechanically ventilated patients

Prolonged mechanical ventilation raises complex ethical considerations that touch on patient autonomy, quality of life, resource allocation, and the emotional burden on families. An important part to these discussions is the principle of respecting patient autonomy: the right of individuals to make informed decisions about their own care. (93)

In cases where patients are unable to express their wishes, as often occurs during prolonged unconsciousness or severe neurological impairment, healthcare staff must often rely on advanced directives, previously agreed upon treatment routines, or external decision-makers to guide care. The lack of clear directives can generate ethical tension, especially when families and medical teams disagree about the goals of care. (94)

Expected quality of life after an intervention also plays a big role in the ethical considerations regarding mechanical ventilation. Prolonged mechanical ventilation can lead to poor outcomes with low weaning rates, sometimes leading to ventilator dependency, a shorter life expectancy, increased costs and burden among patients and their families. Often, physicians must carefully consider a patient's overall health status and consider whether initiating mechanical ventilation on a patient might bring more harm than good. (95)

The emotional and psychological burden on families and healthcare staff is also a topic worth paying attention to. Families often experience grief, guilt, and psychological distress when faced with decisions about withdrawing life support. Clinicians, too, may suffer from the emotional impacts when they feel forced to continue treatments they believe are not in the patient's best interests, or that the initiation of mechanical ventilation will only lead to a poor outcome shortly in the future. (96)

Another issue faced is the topic of resource allocation. Intensive care units are costly, resource intensive, and most health systems have either a limited capacity or even a shortage of beds depending on the region. Further, prolonged mechanical ventilation patients can further consume those limited healthcare resources. In those health systems with limited resources, prolonged life support for patients with extremely poor prognoses can potentially deny access to others with better chances of recovery. This way, a balanced and sensible approach to each patient should be considered, in order to maximize of life saving resources available, especially during crises such as pandemics. (97)

Costs are also a significant ethical factor in mechanical ventilation.

In countries with public health systems like many European nations the government or government funded health system typically compensates the costs associated with mechanical ventilation through taxation. In this case, costs are then a societal burden, shared with all of those in a healthcare system. (98)

This means that healthcare staff have to consider sustainability, particularly when prolonged care may be needed that may leave a patient ventilated but with no clear signs of recovery. The cost components include expensive ventilators, general healthcare items, sedatives and other medication, diagnostic imaging and laboratory tests, and intensive staffing requirements. Mechanical ventilation mandates around-the-clock monitoring by specialized healthcare professionals, including ICU nurses, intensivists, anaesthesiologists and other support staff. (99)

In countries where healthcare is primarily privatized costs are borne directly by patients or their health insurance. Mechanical ventilation in the United States is considerably more expensive than in most other countries, and cases involving prolonged ventilation easily exceeding thousands of dollars. (100)

For patients with no insurance, these costs can be very high, leading to medical debts, or leading to significant financial strain for family members. Additionally, other services such as medical prescriptions may not be covered or be costly, further increasing expected costs. Therefore, hospitals and healthcare workers may also need to evaluate this perspective in countries where healthcare access is not taxpayer funded. (101)

Part II: Long Term Outcomes in Mechanically Ventilated Patients: Scoping Review

Abstract

Many studies have focused on the outcomes of mechanically ventilated patients, but there are few studies that report data on long term outcomes of those patients over longer time frames. Therefore, analysing studies that report mortality and other outcomes in mechanically ventilated patients is worthwhile in order to identify potential knowledge gaps. This scoping review analysed 140 studies, that reported mortality in time frames ranging from in-hospital mortality and other time points such as 60-day, 90-day, 6-month, 12-month, 2 Year and 5 Year. Secondary outcomes such as quality of life, health costs, comparisons of early vs late tracheostomy, and outcomes associated with weaning success were observed. It was found that there seems to be no consensus on what time frame is best suited to report long term mortality in mechanically ventilated patients.

Introduction

Invasive mechanical ventilation is one of the flagship procedures that are performed in an Intensive Care Unit (ICU) setting. Patients usually undergo mechanical ventilation when it is necessary to preserve their life due to a critical illness, though outcomes vary across countries and health care systems.

This scoping review aims to investigate which mortality outcomes are reported in studies involving mechanically ventilated patients, if data for the long-term outcomes of those patients is available, other secondary outcomes reported by those studies, and whether this data provides any valuable insights relevant to current medical practice.

Methods

As part of our search strategy for this scoping review, a Medical Subject Headings (MeSH) search on Medline was performed, with the terms ("Intubation, Intratracheal"[Mesh] OR "Respiration, Artificial"[Mesh]) AND ("Outcome Assessment, Health Care"[Mesh] OR "Respiration, Artificial/statistics and numerical data"[MAJR] OR "Intensive Care Units/statistics and numerical data"[MeSH] OR "Hospitalization/statistics and numerical data"[MAJR] OR "Health Care Costs/statistics and numerical data"[MAJR] OR "Critical Illness/mortality"[MAJR]).

For this search, a publication time criterion was specified. Only studies published from January 1st, 2010 up to and including December 31st 2024 were included.

The inclusion criteria were based on studies that reported long term mortality in patients that were mechanically ventilated. For the purposes of this study and its inclusion criteria, long term mortality was specified as mortality at least 30 days post discharge from department and/or hospital facility.

Exclusion criteria were studies that included paediatric patients, did not involve ventilated patients or involved patients with non-invasive methods of ventilation.

An online software tool marketed as Covidence, was chosen to perform the analysis of the studies. Two reviewers participated in the selection and review of studies. Disagreements regarding exclusion of studies and reason of exclusion were resolved through consensus between reviews. The main author was responsible for the data extraction stage.

Results

Following the search, 3485 studies were identified for screening.

One study was identified as duplicate and removed. Out of the 3485 remaining studies, a title and abstract screening was performed in order to access relevance to the study.

The title and abstract screening yielded 300 studies identified as relevant, whereas 3185 studies were excluded as not being relevant for the analysis.

A subsequent full text analysis was performed from the remaining 300 studies. 160 studies were excluded at this stage. 77 studies were excluded due to not including mechanically ventilated patients, 22 studies were excluded due to issues related to the availability of the studies, 39 studies were excluded due to not reporting mortality outcomes or any relevant outcomes to the study, 12 studies were excluded due to having a wrong study design that did not meet the inclusion criteria. Additionally, 10 studies were flagged upon closer analysis at the full text review stage as not relevant, due to not meeting inclusion criteria specified at the previous review stage.

140 studies remained and were included in the scoping review, out of which 17 were excluded during the data analysis, due to lack of reportable mortality data or otherwise not meeting earlier inclusion criteria, for a final count of 123 studies analysed with valid data.

From 140 studies analysed, the longest mortality data that could be extracted followed as such: In-hospital mortality from 40 studies, 90-day mortality from 7 studies, 6-month mortality from 12 studies, 12-month mortality from 41 studies, 2-year mortality from 7 studies, 5-year mortality from 9 studies.

A few of the most common countries of recruitment for patients was the United States with 42 studies, followed by Taiwan with 17 studies, Germany with 15 studies, France and Israel with 8 studies each, Japan with 7 studies, and South Korea with 6 studies. Other countries where patients were recruited had 4 or less studies each.

Studies reported outcomes other than mortality. Most common secondary outcomes are noted as following: 16 studies reported outcomes related to quality of life and functional outcomes after mechanical ventilation. 5 studies reported outcomes or analysis of the costs related to prolonged mechanical ventilation and the utilization of healthcare resources related to it. Finally, 8 studies reported outcomes related to tracheostomy timing in mechanically ventilated patients.

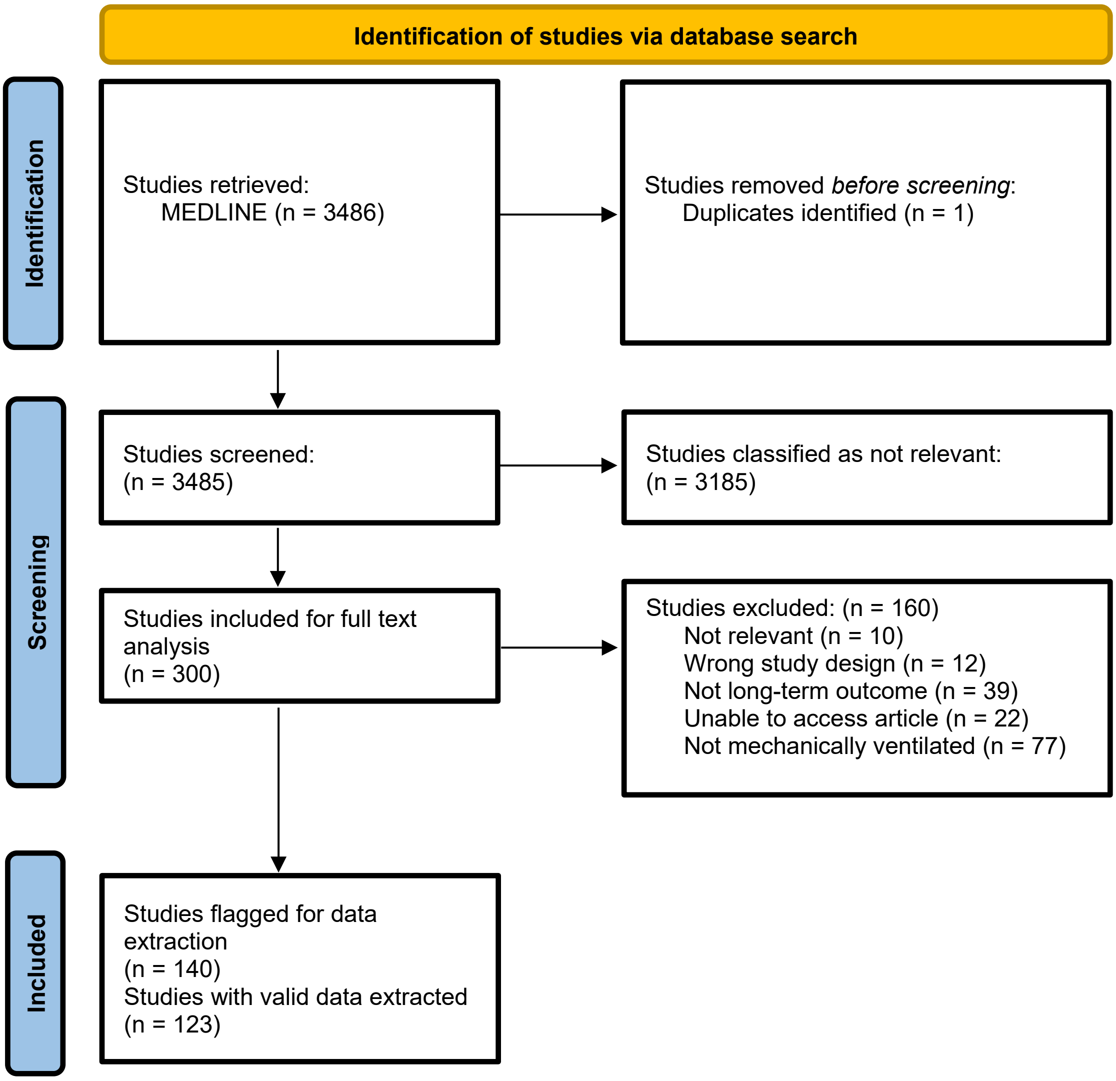
Other secondary outcomes were also reported: Studies reported outcomes related to nutrition during mechanical ventilation, association between sedation depth and outcomes in mechanically ventilated patients, association of depressive disorders with outcomes of mechanically ventilated patients, frailty of patients, and correlation of clinical scores such as APACHE II and ASIA motor scores with patient survival.

The intensive care unit was the most common unit where patients were recruited. Over 80 studies reported recruiting patients in an ICU setting, with the remainder recruiting patients from a long-term acute care hospital, or other specialized units.

While the majority of studies observed a varied pool of patients, some studies had specific groups of patients such as Covid-19, neurological and oncological patients. A significant proportion of the studies analysed involved patients with prolonged mechanical ventilation.

Full data to each analysed study is provided as a table in the annex of this thesis. Mortality data was either extracted directly from study or when possible calculated from underlying data. Results from studies where data was calculated were rounded to the nearest whole number: Up when 5 or more, down when 4 or below, with the raw unrounded values additionally included in brackets.

A Prisma flowchart is provided demonstrating the study flow.



Discussion

The data analysed in this study yields some valuable insights. The mortality data extracted from the studies shows that while in-hospital and shorter-term outcomes are more readily available, there is a significant decrease in studies with reported longer term mortality, specifically 2-year and 5-year mortality. Understanding longer term outcomes in mechanically ventilated patients may be useful to guide clinical decision making and patient expectations. (102)

Secondary outcomes reported in those studies also show concerns related to patients' functional capacity and quality of life, as a significant part of those studies reported additional data related to this topic. This remains an area of considerable interest, as many patients may need rehabilitation and continuing care, after being discharged from an intensive care unit. (103)

Another insight of this study was the observed lack of agreement on what patients can be considered long term mechanically ventilated. While there is a consensus opinion on the topic, (104) it seems that inconsistencies remain across countries and healthcare systems, as demonstrated by how studies in this scoping review had different parameters on what patients should be classified as such.

Limitations

This study has several potential limitations. There is a risk of bias due to the involvement of only two reviewers, which may affect the objectivity and consistency of the data selection and interpretation.

Second, the research relied solely on a single database, which may have limited the scope of the literature and excluded relevant studies available elsewhere.

Third, some articles were not accessible in full text, potentially leading to incomplete data extraction and analysis, and therefore also increasing the risk of bias.

Fourth, as a scoping review, the review did not include a formal appraisal of the methodological quality of the included studies, which limits the ability to assess the strength or reliability of the evidence.

Fifth, the broad scope of the review may have resulted in a more superficial analysis of individual topics, reducing the depth of insight into specific areas.

Sixth, due to time constraints, newer studies published after the search date have not been captured.

Finally, variability in how studies reported their data posed challenges to synthesis and comparability, potentially impacting the consistency of the review's conclusions.

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Comprehensive Thesis Conclusion

This thesis aimed to explore in detail the establishment and evolution of mechanical ventilation procedures, especially in a context outside the operating room, its usefulness for society, clinical impact and ethical considerations that impact care for mechanically ventilated patients.

Further, it also details the biological processes pertaining to the respiratory function of healthy and mechanically ventilated patients, function of alveoli and other components of the respiratory tract.

The functioning and the technical disposition of mechanical ventilators was also discussed. Additionally, the existence of alternative ventilation methods was also addressed, and explained in detail.

Clinically important conditions and injuries were also addressed, elaborating further on the necessity and consequences of using mechanical ventilation in such cases. Attention was paid to the therapeutic reasoning, expectations, and complications associated with mechanical ventilation.

Ethical considerations, a crucial aspect in the context of end-of-life decisions, were also elaborated upon, yielding important insights that helped guide this thesis. As noted in this thesis, these decisions may come with significant emotional burden for both patients and care providers.

Additionally, the scoping review included with this thesis provides an overview into long term mortality associated with mechanical ventilation, other outcomes as those that were reported during other studies, and what conclusions can be drawn from such an analysis.

Moreover, this thesis reaffirms the importance of continuous research in this field, as advancements in technology and clinical protocols continue to evolve. By understanding not only how mechanical ventilation works but also when and why it is applied, healthcare professionals can make more informed decisions.

Ultimately, this thesis contributes to a growing body of literature aimed at improving outcomes, promoting ethical practice, and fostering a deeper understanding of an important tool of modern medicine.

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Annex A: Scoping Review Dataset

Author	Year of Publication	Country of Recruitment	Patient Type	Case Type	Study Population	Mortality: Longest Reported	In-hospital	30 Day	60 Day	90 Day	6 Month	12 Month	2 Year	5 Year	Additional Outcomes
Tripp DG; et al.	2014	New Zealand	ICU	Varied	58003	2 Year	11,137	X	X	X	X	14154	15832	X	N
Chao CT; et al.	2012	Taiwan	ICU	PMV/AKI	47754	4 Year	17889	X	X	X	X	X	X	X	N
Muzaffar SN; et al.	2017	India	ICU	PMV	176	12 Month	95	X	X	X	X	17	X	X	N
Roquilly A; et al.	2014	France	ICU	Acute Traumatic Tetraplegic Patients	164	12 Month	19	42{41.68}	54{54.08}	56{56.31}	59{58.99}	65{65.22}	X	X	Y,ASIA Motor Scores
Skazel T; et al.	2021	Germany	WC	Varied	61	In-Hospital	2	X	X	X	X	X	X	X	Y, Outcomes and necessary care after weaning
Subramaniam A; et al.	2023	Australia/New Zealand	ICU	COVID-19	4028	2 Year	X	X	X	X	1383	2792	3737	X	Y, Frailty+Mortality,
Nagata I; et al.	2019	Japan	ICU,HCU	PMV	93	6 Month	52	X	X	X	54{54.31}	X	X	X	Y,Repeated MV
Cinotti R; et al.	2019	France/Belgium	ICU	PMV/Varied	615	12 Month	X	X	X	X	X	307	X	X	Y, Quality of life, Psychological Outcomes
Law AC; et al.	2023	USA	LTACH	PMV	8084	90 Day	3291	X	X	5170	X	X	X	X	Y,PMV costs, Mortality after LTAC closure
Windisch W; et al.	2020	Germany	SWC	PMV/Varied	11424	In-Hospital	1658	X	X	X	X	X	X	X	Y,Variables associated with Increased PMV Mortality, Weaning Failure, NIV after weaning
Sumiya R; et al.	2022	Japan	ICU	COVID-19	11	In-Hospital	2	X	X	X	X	X	X	X	Y, Apache II Score association with weaning
Corona A; et al.	2022	Italy	ICU	COVID-19	248	In-Hospital	106	X	X	X	X	X	X	X	Y, Survival associated with Tracheostomy
Abunasser JJ; et al.	2023	USA	ICU	COVID-19	164	12 Month	X	35	51	49	66	73	X	X	N
Ben-Avi R; et al.	2014	Israel	Cardiac ICU	Post-OP Cardiac	199	2 Year	X	33	X	96	119	131	136	X	Y,Mortality associated with Early vs Late Tracheostomy
Lin WC; et al.	2015	Taiwan	ICU	PMV/Varied	508	In-Hospital	222	X	X	X	X	X	X	X	Y,Outcomes asscoiated with tracheostomy vs translaryngeal intubation
Carenzo L; et al.	2024	Italy	ICU	COVID-19	246	In-Hospital	77	X	X	X	X	X	X	X	Y, Health related quality of life, physical function, and cognitive performance
Jackson JC; et al.	2010	USA	ICU	Varied	180	In-Hospital	54	X	X	X	X	X	X	X	Y,Cognitive, psychological, and functional quality-of-life outcomes
Slingerland-Boot R; et al.	2023	Netherlands	ICU	Varied	839	6 Month	213	X	X	258	272	X	X	X	Y,"Association between first-week propofol administration and longterm outcomes of critically ill mechanically ventilated patients"
Carpenè N; et al.	2010	Italy	RICU	Varied	49	90 Day	8	X	X	11	X	X	X	X	Y, Cost benefit of RICS and WC

Cabrio D; et al.	2022	Switzerland	ICU	Varied	80	In-Hospital	19	X	X	X	X	X	X	X	N
Chalard K; et al.	2021	France	ICU	Neuro(aSAH)	236	12 Month	86	X	X	X	X	32(31.82)	X	X	N
Sansone GR; et al.	2016	USA	LTACH	PMV/Varied	370	In-Hospital	114	X	X	X	X	X	X	X	Y, PMV reinstitution, Perfecting PMV definition
Lee H; et al.	2021	South Korea	ICU	Varied	158712	12 Month	58133	X	X	X	X	86721	X	X	Y, Effect of Sedatives on In-hospital and Long-term Mortality in MV patients. ICU LOS, hospital LOS
Wilson ME; et al.	2017	USA	ICU	Varied	743	5 Year	103	X	X	X	X	157	X	258	Y, Functional Impairment after MV
Rodriguez Lima DR; et al.	2024	Colombia	ICU	COVID-19	898	In-Hospital	613	X	X	X	X	X	X	X	Y, Quality of Life after MV
Nakamura K; et al.	2022	Japan	ICU	COVID-19	414	In-Hospital	77	X	X	X	X	X	X	X	Y, nutrition therapy in the acute phase and outcomes of ventilated patients with COVID-19 infection
Lin MS; et al.	2013	Taiwan	ICU	PMV	633	12 Month	X	X	X	253(253.2)	355(354.5)	443(443.1)	X	X	N
Lai HH; et al.	2021	Taiwan	ICU	PMV	1342	5 Year	X	X	X	X	X	X	X	346	Y, PMV Costs
Kojicic M; et al.	2011	USA	ICU	PMV/Varied	65	12 Month	19	X	X	X	X	29	X	X	N
Heinemann F; et al.	2011	Germany	SWC	PMV	117	12 Month	8	X	X	X	X	37(37.02)	X	X	N
Brummel NE; et al.	2014	USA	ICU	Varied	187	12 Month	54	88	X	X	X	100	X	X	Y,Delirium in the ICU and Subsequent Long-Term Disability in MV patients
Bulic D; et al.	2020	Australia	ICU	Varied	140	12 Month	12	X	X	X	26	29	X	X	Y,Cognitive and psychosocial outcomes of MV patients with or without Delirium
Keng LT; et al.	2017	Taiwan	ICU	Cancer	112	12 Month	49	X	X	X	X	83*	X	X	Y,Associated clinical factors in Oncological Patients in terms of long term mortality
Hannan LM; et al.	2012	Australia	VWU	PMV/Varied	81	12 Month	8	X	X	X	X	26	X	X	Y, Ventilator Weaning success
Dermot Frengley J; et al.	2014	USA	LTACH	PMV	540	In-Hospital	343	X	X	X	X	X	X	X	Y,Effects of Increasing Age on Clinical Outcomes and Survival
Frengley JD; et al.	2018	USA	LTACH	PMV/Varied	866	In-Hospital	493	X	X	X	X	X	X	X	Y,Comorbitities asscoiated with weaning outcomes
Huang C	2024	Taiwan	RCC	PMV	428	12 Month	145	X	X	X	X	262	X	X	Y,Age association with mortality
Heidler MD; et al.	2018	Germany	ERC	PMV/Neuro+Varied	831	In-Hospital	62	X	X	X	X	X	X	X	Y, Outcomes associated with decannulation of patient

Hill AD; et al.	2016	Canada	ICU	PMV/Varied	152778	5 Year	60902	X	X	X	X	X	X	84624	Y, Health care utilization after PMV
Datta D; et al.	2017	USA	LTACH	PMV/AKI	167	In-Hospital	57	X	X	X	X	X	X	X	Y, Weaning from Ventilation
Stein D; et al.	2022	Israel	LTACH	PMV	308	In-Hospital	140	X	X	X	X	X	X	X	Y, Outcomes associated with age, consciousness and cognitive state
Demiralp B; et al.	2021	USA	STACH	PMV	13622	90 Day	X	X	X	5954	X	X	X	X	N
Peñuelas O; et al.	2021	Spain	ICU	COVID-19	868	6 Month	335	X	X	X	X	X	X	X	N
Keizman E; et al.	2023	Israel	Cardiac ICU	PMV/Cardiac Surgery	407	5 Year	X	103	X	X	X	217	231	265	Y, Outcomes of Early tracheostomy after cardiac surgery
Matsunashi A; et al.	2023	Japan	ICU	IPF	28	90 Day	15	X	X	18	X	X	X	X	N
Sonneville R; et al.	2023	France	ICU	Acute Stroke	364	12 Month	167	X	X	176	182	190	X	X	Y, Mortality associated with different Stroke subtypes
de Koning MLY; et al.	2019	Netherlands	ICU	Sepsis/PMV	423	6 Month	116	X	X	X	153	X	X	X	Y,Association of PROtein and CAloric Intake and Clinical Outcomes in PMV
Needham DM; et al.	2012	USA	ICU	Varied	485	2 Year	X	X	X	X	X	X	311	X	Y, Association of Lung Protective Ventilation with mortality
Gamberini L; et al.	2021	Italy	ICU	COVID-19	470	In-Hospital	188	X	X	X	X	X	X	X	Y, Quality of life after ICU discharge
Kahn JM; et al.	2018	USA	LTACH	PMV/Varied	9447	In-Hospital	3283	X	X	X	X	X	X	X	Y, Variations in Mortaality Rates between different LTACHS
Lin Z; et al.	2022	USA	ICU	Varied	16775	3 Year	X	X	X	X	X	X	X	X	N
Melero R; et al.	2022	Spain	ICU	COVID-19+AKI	30	In-Hospital	19	X	X	X	X	X	X	X	Y, Renal Long Term Outcomes
van den Berg B; et al.	2018	Netherlands	ICU	PMV+GBS	144	6 Month	X	X	X	X	10	X	X	X	Y, PMV vs Non PMV Outcomes
Fernando SM; et al.	2019	Canada	ICU	Varied	8110	In-Hospital	2638	X	X	X	X	X	X	X	Y, Frailty association with outcomes
Zhang C; et al.	2024	China	ICU	Unknown	132	90 Day	11	X	X	25	X	X	X	X	Y, High Intensity Early Mobilization Outcomes
Na SH; et al.	2019	South Korea	ICU	Varied	3679	12 Month	X	X	X	X	X	493	X	X	N
Huang C	2021	Taiwan	ICU	PMV+Weaned	243	5 Year	X	X	X	X	X	182(182.493)	185(184.923)	191(191.24)	N
Carson SS; et al.	2012	USA	ICU	PMV/Varied	260	12 Month	71	X	X	X	X	124	X	X	N

Sole ML; et al.	2014	USA	ICU	PMV/Varied	323	In-Hospital	32	X	X	X	X	X	x	X	Y, Cost and resource utilization,Early vs Late Tracheostomy
Saad M; et al.	2022	USA	LTACH	COVID-19	158	In-Hospital	15	X	X	X	X	X	X	X	N
Steffling D; et al.	2012	Germany	Neuro ICU	Neuro	201	17 Month	31	X	X	X	X	X	X	X	Y, Quality of life
Bostock IC; et al.	2017	USA	Unknown	Cardio(Post EVAR)	209	30 Day	X	8(8.15)	X	X	X	X	X	X	N
Jubran A; et al.	2010	USA	LTACH	PMV/Varied	336	In-Hospital	54(53.92)	X	X	X	X	X	X	X	Y, Association of depressive disorders on outcomes
Davies MG; et al.	2017	United Kingdom	SPW	PMV	458	5 Year	41	X	X	X	X	187(186.6)	286(286.44)	336(336.36)	N
Fradkin M; et al.	2024	Israel	Rehab-Hospital	PMV	124	12 Month	X	X	X	X	X	32	X	X	Y, Association of weaning with long term survival
Chatterjee K; et al.	2020	USA	PCH	PMV+Surgical+Palliative Care	664765	In-Hospital	167021	X	X	X	X	X	X	X	N
Kim WY; et al.	2021	South Korea	ICU	PMV	124	12 Month	X	X	X	29	44	59	X	X	Y, Association of Mortality with HMV on discharge
Huang C	2022	Taiwan	ICU	PMV/Varied	296	5 Year	X	X	X	X	213(212.99)	236(235.96)	253(252.85)	265(265.23)	Y, Association of Survival with Gender with PMV
Koch T; et al.	2012	Germany	ICU	PMV/Varied	100	In-Hospital	21	X	X	X	X	X	X	X	Y, tracheostomy decreases ventilation time but has no impact on mortality of intensive care patients
Mamary AJ; et al.	2011	USA	VRU	PMV/Varied	182	In-Hospital	35	X	X	X	X	X	X	X	N
Surani S; et al.	2020	USA	LTACH	PMV	162	In-Hospital	43	X	X	X	X	X	X	X	N
Trudzinski FC; et al.	2024	Germany	ICU	PMV/Varied	7758	In-Hospital	1954(1954.22)	X	X	X	X	X	X	X	Y, Risk factors leadning to Invasive Mechanical Ventilation
Mineshita M; et al.	2024	Japan	ICU	COVID-19	133	90 Day	X	28(27.93)	43(42.56)	45	X	X	X	X	N
Al-Alwan A; et al.	2014	USA	ICU	Unknown	471962	2 Year	385123	X	X	X	X	X	439553	X	Y,Survival after discharge following in-hospital CPR
Ouchi K; et al.	2020	USA	ICU	Varied	415	12 Month	152(151.89)	X	X	X	X	311	X	X	Y, Association of Older age with survival
Zirpe KG; et al.	2017	India	Neuro ICU	Neurotrauma	164	In-Hospital	54	X	X	X	X	x	X	X	Y, Early vs Late Tracheostomy
Taran S; et al.	2023	USA	ICU	Varied	463	12 Month	80	X	X	92	96	104	X	X	Y, Functional Outcomes

Kaya H; et al.	2015	USA	ICU	Varied	178	12 Month	X	41 (40.95)	49 (48.60)	54 (53.88)	57 (56.97)	71 (71.15)	X	X	Y, Association of Race with Mortality of ventilated patients
Kisil I; et al.	2024	Israel	GRC	Varied	73	In-Hospital	6	X	X	X	X	X	X	X	Y,outcomes after successful weaning in extremely prolonged mechanical patients
Depuydt P; et al.	2016	Belgium	ICU	PMV	114	12 Month	14	28	X	X	X	33(33.1)	X	X	Y, Association between quality of life and ventilator dependency
Saccheri C; et al.	2020	France	ICU	Varied	76	2 Year	X	X	X	X	X	X	23	X	Y, ICU-acquired weakness, diaphragm dysfunction
Jacobs JM; et al.	2020	Israel	Home/LTACH	PMV	120	6 Month	X	X	X	X	23(23.2)	X	X	X	Y, Home vs LTACH PMV Outcomes
Lin C; et al.	2023	Taiwan	ICU	PMV/Varied	5709	12 Month	1576(1575.68)	X	X	1954(1953.67)	X	2757(2757.44)	X	X	Y, Association of Prolonged use of neuromuscular blocking agents with mortality
Bouvet P; et al.	2019	France	ICU	Neuro(Stroke)	274	In-Hospital	144	X	X	X	X	X	X	X	Y, Association of Stoke type with Mortality, Functional Outcomes
Kung SC; et al.	2017	Taiwan	ICU/RCC	PMV+Major Trauma	93	In-Hospital	6	X	X	X	X	X	X	X	N
Huang C	2019	Taiwan	RCC	PMV/Varied	574	12 Month	95	X	X	X	X	435(434.51)	X	X	N
Tsukinaga A; et al.	2020	Japan	ICU	PMV+Cardiovascular Surgery	172	12 Month	X	8	X	X	X	40	X	X	Y, Asssociation of Low Hematocrit levels with Mortality
Gupta N; et al.	2023	India	ICU	Varied	111	30 Day	X	18	X	X	X	X	X	X	Y Association of Early vs Late Tracheostomy with Mortality
Hodgson CL; et al.	2022	Australia	ICU	Varied	888	6 Month	197	X	X	213	222	X	X	X	Y, association of Sepsis with Mortality in Ventilated Patients
Rose L; et al.	2022	Canada	SWC	Varied	402	2 Year	131	X	X	X	X	200	223	X	Y, Health costs, SWC vs Prolonged ICU Outcomes
Dolinay T; et al.	2022	USA	LTACH	PMV/COVID-19	165	In-Hospital	17	X	X	X	X	X	X	X	Y,Covid vs Non covid respiratory failure outcomes.
Galiatsatos P; et al.	2017	USA	LTACH	PMV/Varied	141	12 Month	58	X	X	X	X	113	X	X	N
Leroy G; et al.	2014	France	ICU	Varied	201	12 Month	83	X	X	X	X	120	X	X	Y,ProVent score evaluation
Romain M; et al.	2020	Israel	ICU/Wards	Varied	170	6 Month	63	X	X	112	X	X	X	X	Y, Outcomes of Tracheostomy ICU vs Wards
Medrinal C; et al.	2016	France	ICU	Varied	124	12 Month	14	X	X	X	X	25(24.8)	X	X	Y,Respiratory weakness after mechanical ventilation is associated with one-year mortality
Bickenbach J; et al.	2018	Germany	SWU	PMV/Varied	430	In-Hospital	53(53.32)	X	X	X	X	X	X	X	Y,Impact of multidrug-resistant bacteria on outcome

Ge M; et al.	2020	China	ICU	PMV/ aortic dissection repairment	582	30 Day	X	71	X	X	X	X	X	X	N
Shehabi Y; et al.	2013	Malaysia	ICU	Varied	259	6 Month	82	X	X	X	X	110	X	X	Y, association between sedation depth and long term mortality
Detsky ME; et al.	2017	USA	ICU	Varied	303	6 Month	72	X	X	X	130	X	X	X	Y, Functional Outcomes
Haviland K; et al.	2020	USA	Post ICU	PMV/Cancer	122	In-Hospital	101	X	X	X	X	X	X	X	N
Kornblith LZ; et al.	2013	USA	ICU	Spinal Cord Injury	344	In-Hospital	32	X	X	X	X	X	X	X	Y, Association of Tracheostomy and Ventilation requirements with Discharge outcomes
Huang C	2022	Taiwan	ICU	Varied	296	5 Year	X	X	X	185(185)	213(213.12)	236(235.91)	245(245.4)	264(264.03)	Y, Association of weaning, tracheostomy, age with mortality outcomes.
Wei X; et al.	2015	US/CA/Europe	ICU	PMV/Varied	457	6 Month	151	X	X	155	173	X	X	X	Y,Association Between Nutritional Adequacy and Long-Term Outcomes
Huang C; et al.	2021	Taiwan	RCC	PMV/Intracranial Hemorrhage + weaned	69	12 Month	X	X	X	X	X	39	X	X	Y,Survival of Intracranial Hemorrhage Patients Successfully Weaned from PMV
Shehabi Y; et al.	2012	AUS/NZ	ICU	Varied	251	6 Month	53	X	X	X	64	X	X	X	Y, Association of sedation depth with long term mortality
Huttmann SE; et al.	2018	Germany	ICU	PMV/Varied	112	12 Month	10	X	X	X	X	17	X	X	Y, Quality of life, life satisfaction
Jubran A; et al.	2019	USA	LTACH	PMV	315	12 Month	X	X	X	155	X	183	X	X	Y, Functional outcomes, Quality of Life
Chen S; et al.	2011	Taiwan	ICU	PMV/Varied	34	12 Month	X	0	X	7	12	18	X	X	Y, Functional outcomes
Oehmichen F; et al.	2012	Germany	Neuro WC	Neuro/varied	1486	In-Hospital	247	X	X	X	X	X	X	X	Y,Outcomes after succesful weaning
Lamas DJ; et al.	2016	USA	LTACH	PMV	50	12 Month	3	X	X	X	X	15	X	X	Y,Quality of life
Chen CM; et al.	2015	Taiwan	ICU	End Stage Kidney Disease	38659	2 Year	X	X	X	X	5162	5469	5836	X	Y,Effect of end-stage renal disease on longterm survival
Sun Y; et al.	2020	China	ICU	PMV+Post Surgery	124	12 Month	X	X	X	X	X	92	X	X	N
Lee H; et al.	2019	South Korea	ICU	Varied	158712	5 Year	56133	X	X	X	X	86721	X	51021	Y,Effect of Institutional Case Volume on In-Hospital and Long-Term Mortality
Trouillet JL; et al.	2011	France	ICU	Post Cardiac Surgery	216	90 Day	X	58	65	X	X	X	X	X	Y, Outcomes associated with Early Versus Late Tracheotomy After Cardiac Surgery
Ohbe H; et al.	2023	Japan	ICU	Varied	4198	12 Month	X	X	X	X	X	2208	X	X	Y, Functional Outcomes, care needs after ventilation
O'Connor H; et al.	2013	USA	LTACH	PMV/Varied	80	In-Hospital	8	X	X	X	X	X	X	X	Y, outcomes associated with agitation during PMV

Bickenbach J; et al.	2011	Germany	ICU	PMV/Varied	136	12 Month	X	X	X	X	X	13	X	X	Y,Risk factors associated with Mortality
Jang H; et al.	2024	South Korea	ICU	PMV/Varied	327	12 Month	145	X	X	X	X	221	X	X	Y, ProVent score usability
Sansone GR; et al.	2016	USA	LTACH	Varied	437	In-Hospital	159	X	X	X	X	X	X	X	Y, Association of MV time with weaning success rate and discharge condition
Schmickl CN; et al.	2015	USA	ICU	Acute Lung Inury/Cardiogenic Pulmonary Edema	328	In-Hospital	60	X	X	X	X	X	X	X	Y,Comparison of Hospital Mortality Acute Lung Injury vs Cardiogenic Pulmonary Edema
Chatelain E; et al.	2023	Unknown	ICU	Lung Cancer	136	12 Month	X	88	99	99	105	114	X	X	N
Heine A; et al.	2021	Germany	WC	PMV	33	12 Month	X	3	X	6	X	9	X	X	Y, Outcomes associated with weaning success
Warnke C; et al.	2020	Germany	ICU	PMV/Varied	597	12 Month	107	X	X	X	X	183(183.19)	289(288.99)	323(323.02)	Y, Outcomes after successful Prolonged weaning