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COVID-19: Does the Timing of Intubation Affect Overall Outcomes

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COVID-19: DOES THE TIMING OF INTUBATION AFFECT OVERALL OUTCOMES

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Abstract

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COVID-19 also known as coronavirus disease of 2019 is a viral illness caused by novel coronavirus SARS-CoV2 that was discovered in December 2019 in Wuhan, China. To date, there have been over 250 million cases worldwide. The severity of COVID-19 ranges from mild symptoms to critical illness warranting hospitalization within an intensive care unit to death. Current treatment modalities include supportive cares, monoclonal antibodies, interleukin inhibitors, convalescent plasma, therapeutic anticoagulants, anti-inflammatory medications and/or corticosteroids. A common complication due to COVID-19 is acute respiratory failure resulting in pulmonary insult which start as cough but progress to the need for supplemental oxygen and/or mechanical ventilation. There are varying modalities to provide supplemental oxygen as well as processes to support such processes including proning. Patients that become critically ill typically require increased amounts of supplemental oxygen to avoid hypoxia which included early intubation. Based on a literature review, the recommendations have shown that early intubation may not be key and that critically ill patients should be maintained on alternative oxygen-supplying modalities to avoid hypoxia and potential intubation. For patients who warranted intubation, literature reveals that timing of intubation did not have significant impact on clinical outcomes. Based on the literature, an algorithm called Ventnet, has been developed and should be utilized to assist in prediction of intubation in patients with acute respiratory distress syndrome secondary to COVID-19.

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Introduction

In December 2019, a plethora of pneumonia cases emerged in Wuhan, China rapidly spreading worldwide causing a pandemic. The virus causing this type of pneumonia was found to be severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 also known as COVID-19). As of November 2021, COVID-19 has caused over 5 million deaths worldwide (Worldometer, 2021). Despite a significant amount of research and the fact that COVID-19 is a viral process, there is no curative treatment for COVID-19. There are supportive treatment methods including corticosteroids, therapeutic anticoagulants, anti-inflammatory medications, monoclonal antibodies, interleukin inhibitors and convalescent plasma which have been utilized and have been shown to decrease the severity and duration of symptoms of COVID-19 (Gupta et al., 2020). In December 2020, vaccines for COVID-19 became available in the United States. Priority was given to healthcare workers and high-risk patients such as those with comorbidities, eventually being offered to the public, greater than 5 years of age. Given the respiratory compromise secondary to the COVID-19 disease process, many patients require supportive cares, medications, antivirals, and pulmonary support. Those who require pulmonary support, may require supplemental oxygen via a simple nasal cannula but pulmonary status can progress in severity to the point in which mechanical ventilation is warranted. The need for mechanical ventilation carries its own risks and benefits. Such as ventilator induced injury, ventilator associated pneumonia, sedation, and associated delirium (Shashikumar et al.,2020). Although patients may require mechanical ventilation, there lacks supportive evidence as to the timing of such an intervention and how that affects clinical outcomes.

Background and Rationale

COVID- 19 is a viral illness that became apparent in December 2019 and progressed to a worldwide pandemic in the subsequent months. COVID-19 is transmitted via droplet transmission which consists of direct spray of large droplets onto the mucous membranes of a host when an infected individual sneezes, coughs, or talks. COVID-19 can affect any individual, whether it be a healthy child or frail, elderly adult, causing the individual to develop symptoms of COVID-19 that can range from mild to severe in nature (Berlin, 2020). Atkins et al. (2020) studied preexisting comorbidities and their association with COVID-19. Those with a prior diagnosis of dementia, type 2 diabetes, chronic obstructive pulmonary disease, pneumonia, depression, atrial fibrillation, and hypertension were the most likely to be hospitalized if diagnosed with COVID-19. COVID-19 presents with similar symptoms of upper respiratory infection including fever, chills, cough, sore throat, loss of taste or smell, fever, fatigue, muscle aches, headache, congestion or runny nose, nausea, vomiting, and/or diarrhea. With COVID-19, there is a wide spectrum of severity of symptomology from being asymptomatic to those warranting hospitalization and potentially care in the intensive care unit (ICU).

The National Institutes of Health (NIH) developed criteria for identifying the severity of COVID-19 illness according to clinical manifestations (2021). To be considered asymptomatic individuals test positive using a virologic or an antigen test but remain without symptoms (NIH, 2021). Mild symptomology includes those with symptoms such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell (NIH,2021). Typically, patients of mild symptomology category lack any significant pulmonary symptoms including shortness of breath, dyspnea, or abnormal chest imaging (NIH, 2021). Moderate symptomology includes those with lower respiratory disease on clinal assessment or imaging that shows some pneumonia (NIH, 2021). Those with moderate symptomology typically have an oxygen saturation of equal to or greater than 94% without supplemental oxygen (NIH, 2021). Severe symptomology is defined as those who have an oxygen saturation equal to or less than 94% without supplemental oxygen, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen less than 300 mm Hg, a respiratory rate more than 30 breaths per minute, and/or lung infiltrates in more than 50% of lung space (NIH, 2021). Those with severe symptomology have the potential to progress to acute respiratory failure, septic shock or multiple organ failure (NIH, 2021).

As a result of COVID-19, there is the possibility that patients could develop pneumonia which can lead to hypoxemic respiratory failure resulting in acute respiratory distress syndrome (ARDS) (Berlin et al., 2020). Berlin et al. defines ARDS as “the acute onset of bilateral infiltrates, severe hypoxemia, and lung edema that is not fully explained by cardiac failure or fluid overload” (2020). As COVID-19 progresses through its course, patients develop ARDS typically have a tenuous pulmonary status and mechanical intubation is most often warranted. Of the critically ill patients admitted to the ICU with COVID-19, 67-85% develop ARDS (Pan et al, 2020). Based on the literature, mechanical ventilation was performed if the patient clinically decompensated warranting pulmonary support although is some studies, intubation was delayed due to being considered an aerosolized procedure. Given COVID-19 is still rather new and there is limited data, timing of intubation and mechanical ventilation remains unclear (Berlin et al., 2020).

Patients with severe symptomology related to COVID-19 were more likely to require intubation due to their tenuous respiratory status. Autopsies performed on patients with severe

COVID-19 showed diffuse alveolar damage, the hallmark sign of ARDS (Berlin et al., 2020). In many cases of ARDS, which has many similarities to COVID-19 pneumonia, literature shows providing early intubation decreases lung trauma, which ais in the healing process (Berlin et al, 2020). With early intubation, protective ventilation strategies can be utilized which include low tidal volumes and moderate positive end-expiratory pressure or PEEP are the basis of treatment for ARDS (Ferrando et al., 2020). In patients who developed ARDS, delaying of intubation increased a patients' mortality risk (Matta et al., 2020). By delaying intubation whether it be in a patient with severe COVID-19 or without COVID-19 but experiencing an ARDS type situation, can cause increased self-induced lung injury. (Tobin et al., 2020). This brings forward the thought for comparison of ARDS in a non-COVID-19 to severe COVID-19 with an ARDS type clinical picture and further thoughts if the disease processes should be treated the same in regard to timing of intubation.

During the early COVID 19 pandemic, there was a perceived shortage of mechanical ventilators which led to a drastic change in how healthcare providers determined when a patient warranted intubation. Initially, COVID-19 patients were intubated once their need for supplemental oxygen exceeded more than 6 liters via nasal cannula. With the perceived shortage of mechanical ventilators, healthcare providers were forced to utilize subsequent modalities of supplemental oxygen delivery including non-invasive measures such as high flow nasal cannula (HFNC), continuous positive airway pressure or bilevel positive airway pressure (Schünemann et al., 2020). According to Matta, "the optimal threshold regarding when to intubate patients with COVID-19 pneumonia remains unclear" (2020).

Purpose

The primary purpose of this integrative literature review was to assess the literature to determine if early versus delayed intubation in patients with COVID-19 has an impact on overall patient outcomes. Identifying the optimal timing for intubation and mechanical ventilation is imperative for patients with COVID-19 due to the high mortality rate among those critically ill with the viral process.

Clinical Question

Based on the provided information, a clinical question was developed to guide the literature search. The clinical question to guide this integrated literature review is the following: For patients with severe COVID-19, does timing of intubation and mechanical ventilation affect overall outcomes? The term overall outcomes could be defined as a range of aspects which could include from survival at 28 days post admission, development of ARDS, comparing SOFA scores, oxygenation, ICU days/length of stay, ventilator-free days and P/F ratios, and mortality.

Method of Inquiry

An integrative literature review of the current literature was the method of inquiry conducted for this scholarly inquiry paper. This method gives a comprehensive review of the evidence to aid in a better understanding of the clinical question and knowledge of the interventions available. Given this topic, COVID-19, is a very up and coming topic, much of the literature is current although smaller studies. The outcome of the literature review is to provide recommendations to the clinical question discussed.

Literature Review

Introduction

A literature review was completed using multiple search engines with multiple different key words. This method was utilized to find a larger understanding of the research studies present on the subject of COVID-19, the timing of intubation with initiating mechanical ventilation and the effect on clinical outcomes.

Search Strategy

Multiple search engines were used to perform a thorough literature search on the topic. Continuous searches were performed throughout the development of this paper as COVID-19 has been an everchanging topic. Search engines used included: Cochrane library, Google Scholar, Pubmed, Ebscohost, CINAHL. Keywords to guide this search included: COVID-19, covid, intubation, timing, early, late, ARDS, and criteria. The searches took place between December 7, 2020, through April 1, 2021. All articles used were published between 2020 and 2021 and written in the English language. See Table 1 for search engines used.

Studies chosen for this literature review can be viewed in Table 2. Articles that were excluded were studies including patients with mild COVID-19 and not treated with mechanical ventilation. Levels of evidence included in this review ranged from I to IV including one systematic review, meta-analysis, and multiple retrospective studies.

Levels of Evidence

Articles were chosen, reviewed, and then rated on levels of evidence based on the Ackely et al. (2008) evidence framework. See table 3. The levels of evidence used in the literature review are as follows: one systemic review and meta- analysis (level I) and 13 retrospective cohort studies (level IV).

Review of Evidence

Themes

Common themes were found throughout the literature to help guide the clinical question whether early versus late intubation has an impact in overall clinical outcomes of patients with severe COVID-19. The term clinical outcomes could be defined as a range of clinical outcomes including survival at 28 days post COVID-19 diagnosis, to development of ARDS, comparing SOFA scores, oxygenation status, ICU days/length of stay, ventilator-free days and P/F ratios, and mortality. However, mortality as an outcome for patients with severe COVID-19 was the most frequent theme in articles chosen related to COVID-19 and intubation. The two most common themes used to separate the articles were as follows, intubation timing makes no difference in overall outcomes and timing of intubation affects mortality.

Intubation Timing Makes No Difference in Mortality

In review of COVID- 19 and timing of intubation, mortality is a repeating theme. Hernandez et al. (2020), Hyman et al. (2020), Lee et al. (2020), Matta et al. (2020), Patoutsi et al. (2021), and Siempos et al.(2020), all found no evidence that increased amount of time to intubation had any effect on the mortality of these patients. According to Siempos et al. (2020), the early intubation strategy was not associated with fewer ventilator days or fewer ICU days. With this evidence, Matta et al. (2020) suggests that COVID-19 could be managed similarly to hypoxic respiratory failure not caused by COVID-19. While continuing to point out that the optimal management of COVID-19 has not been established, Paptousi et al. (2021) suggests a "wait-and-see approach" which could lead to fewer intubations. Lee et al. (2020) also supported the theme that early intubation was not associated with improved survival, nor did it show the late intubation increased mortality. This information may help with the limited medical resources such as mechanical ventilators and personal protective equipment that was problematic early in the COVID-19 pandemic.

Voshaar et al. (2021) encouraged conservative management of COVID-19 hypoxemia, consisting of a primary goal of maintaining the patient's own spontaneous breathing, if possible, by using oxygen therapy, non-invasive ventilation, and patient positioning techniques such as prone or lateral position. To decrease the mortality rate that was a trend with COVID-19 patients, an escalation protocol was developed that only increased respiratory support with increased dyspnea, allowing permissive hypoxemia (Voshaar et al., 2021). The study noted that invasive ventilation may correct the initial hypoxemia in the short term but can cause a ventilatory associated lung injury or oxygen induced ARDS at any point during the mechanical ventilation (Voshaar et al., 2021). The study found that this more restrictive use of intubation as a more beneficial strategy for severe COVID-19 patients resulting in a lower rate of mortality and fewer patients needing supplemental oxygen at discharge (Voshaar et al., 2021).

Timing of Intubation affects Mortality

On the other side of the spectrum, Rhee et al. (2020) found that significant hypoxemia and a worsened ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen also known as a P/F ratio surrounding intubation, the more likely the patient was to experience cardiac arrest peri-intubation. A limitation of this study was that it was performed from data collected early in the pandemic and ways of preoxygenating the patient prior to intubation safely without viral aerosolization of disease to the staff was unknown. Therefore, preoxygenation was not done prior to intubation thus increasing the likelihood of peri-intubation complications such as cardiac arrest. That fact may have increased the number of cardiac arrests and complications surrounding intubation early in the pandemic. Hyman et al. (2020) concluded that intubation earlier in the hospital course may be associated with improved outcomes" (p. 7). This conclusion was made from data that each additional day after admission, before being intubated, was significantly associated with higher in-hospital death rates (Hyman et al., 2020). Again, this data was taken from early on in the pandemic, January 30, 2020, to May 1, 2020, when safety of noninvasive measures of respiratory support was less known. The use high- flow nasal cannula, continuous positive airway and bilevel positive airway pressure was not as common due to the unknown of how to protect the exposure of healthcare workers against the viral aerosolization of these devices. It is also noted in this study that the lack of ICU beds and ventilators available may have played a part in the increased amount of mortality and time to intubation thus patients who warranted earlier intubation could possibly have experienced better outcomes due to receiving better care (Arulkumaran et al., 2020).

Pandya et al. (2021) revealed data that supported patients with increased mortality had delayed and prolonged intubation and prolonged ICU stays. Also noted in this study was worse compliance on ventilator, increased fraction of inspired oxygen (FI02) needs and increased age thus whether the increased mortality rate is caused by delayed intubation or disease progression is unknown (Pandya et al., 2021).

Zhang et al. (2020) also found that increased time to intubation increased mortality. The study took this data farther by discovering that when these patients had an Acute Physiology and Chronic Health Evaluation II (APACHE II) score less than 10 or a pneumonia severity index (PSI) of less than 100, intubating in less than 50 hours from admission could decrease mortality to 60% or less (Zhang et al., 2020). The APACHE II score is based form 0-100, the higher the score the more the mortality rate increases (Zhang et al., 2020). The PSI score is the estimated severity of pneumonia which is used to predict mortality risk (Zhang et al., 2020). Showing that each case needs to be looked at individually to take in for account individual risk factors and comorbidities.

A Deeper Look into Mortality

Zuccon et al. (2020) and Gupta et al. (2020) were two articles that looked deep into factors that increased mortality. In the Zuccon et al. (2020) study, multiple factors that did affect mortality were noted, including onset of symptoms, age, and number of days in the ICU. In addition to those, Gupta et al. (2020) also noted that males, patients with higher body mass index (BMI), active cancer, presence of hypoxemia, liver, and kidney dysfunction, level of dysfunction not noted, and being admitted to a hospital with minimal ICU beds available had a higher risk of mortality. Zuccon et al. (2020) found that the most severely ill COVID-19 patients had diffuse alveolar damage, thrombotic microangiopathy along with an associated focus of alveolar hemorrhage, which progressed into organ failure going into a phase of lung consolidation, interstitial and intralobular fibrosis. Zuccon et al. (2020) continues to note that these processes are not well understood, and it is unknown if this is a part of the super inflammation by release of cytokines or the mediated effect of COVID-19. Neither of these studies focused on the timing of intubation with patients with COVID-19 or how this affected mortality.

Need an Algorithm

Shashikumar et al. (2020) researched the best possible way to predict the need for mechanical ventilation in patients with COVID-19. They concluded that “a generalizable and transparent deep-learning algorithm improves on traditional clinical criteria to predict the need for mechanical ventilation in hospitalized patients, including those with COVID-19. Such an algorithm may help clinicians with optimizing timing of endotracheal intubation, better allocation of mechanical ventilation resources and staff and improve patient care” (Shashikumar et al., 2020, p. 3). The developed algorithm was created with information taken directly from the electronic health record of no COVID-19 and COVID-19 (Shashikumar et al., 2020). The goal of this model was to end emergent intubations and to avoid unnecessary intubation (Shashikumar et al., 2020). Shashikumar et al. (2020) was able to identify the top 15 factors most contributed to the high-risk score 12 hours prior to intubation. These factors included respiratory rate, oxygen saturation, heart rate, total bilirubin, platelet count, temperature, aspartate aminotransferase (AST), fraction of inspired oxygen FIO2, any change in platelets, fibrinogen, phosphate, any change in temperature, any change in alkaline phosphate, and any change in white blood count which is calculated in 4 to 24 hour increments. See appendix A which shows the VentNet algorithm the intubation prediction model example that spans 67 hours. This guides providers to when intubation need is coming.

Summary of Evidence

Going forward with synthesizing the evidence, the literature supports the need for a better system to determine the need for intubation for severe COVID-19 patients. There are many articles, Hernandez et al. (2020), Hyman et al. (2020), Lee et al. (2020), Matta et al. (2020), Patoutsi et al. (2021), and Siempos et al. (2020), that all support theory that intubation timing makes no difference in clinical outcomes. Voshaar et al. (2021) suggested that permissive hypoxemia should allow for delayed intubation until clinical presentation deteriorates. Rhee et al. (2020) suggests the opposite, which is that lower oxygen levels cause an increase cardiac arrests and complications surrounding intubation. Data from Pandya et al. (2021) and Zang et al. (2020) supports that timing of intubation does make a difference in rates of mortality. This could also be dependent on other factors such as disease progression, age, or comorbidities. Gupta et al. (2020) and Zuccon et al. (2020) dive deeper into the many other factors that affect mortality, suggesting timing of intubation not being one of them. Shashikumar et al. (2021) supports a specific algorithm to determine need for intubation, streamlining the process.

Conceptual Framework

The conceptual framework most appropriate to guide the answer to this clinical question would be the John Hopkins Nursing Evidence Based Practice Model (JHNEP). The JHNEP is described as a "powerful problem-solving approach to clinical decision making" (Dang & Dearholt, 2017). The model uses a three-step guide to problem solving, using the practice question, evidence, and translation (PET) method (Dang & Dearholt, 2017). See appendix B to see framework. The framework begins the process with the practice question which in this case was related to the severe COVID-19 patients related to timing of intubation and the affect this has on overall clinical outcomes. The next step is evidence for which the available evidence was reviewed in detail, although limited, for guidance. Based on the evidence, there was not one clear outcome that was found to be more superior than another. Research showed that there were more factors that needed to be considered such as the patients hemodynamic status, pulse oximetry, and levels such as oximetry, blood gas, and lower d-dimers which often predicted patient mortality.

For the translation step, recommendation for changes in clinical practice are made based on the evidence. After reviewing and synthesizing the evidence, there is not one clear recommendation for practice. Although one promising piece of evidence was an algorithm called VentNet that could be used to determine which patients are at highest risk for acute respiratory failure or respiratory failure related to severe COVID-19. Permission was granted by John Hopkins Nursing to utilize their model.

Conclusion, Recommendations, Implications for Nursing

Introduction

The purpose of this integrative literature review was to determine if early versus delayed intubation in severe COVID-19 patients would have an impact on overall clinical outcomes. Identifying the optimal timing for intubation and mechanical ventilation for patients with severe COVID-19 is important due to the high mortality rate among severe COVID-19 patients. This knowledge could potentially improve mortality outcomes in severe COVID-19 patients. This section will go over practice implications and provide recommendations on optimal timing of intubation and mechanical ventilation of severe COVID-19 patients as well as the need for an algorithm for timing of intubation of severe COVID-19 patients.

Conclusion

Ideal timing of intubation of severe COVID-19 patients to allow for the best possible clinical outcomes is yet to be determined. Delayed intubation or lack of intubation can result in an increase in mortality rates (Voshaar et al. 2021).

Implications for Nursing

Nurses are on the forefront when caring for patients, in this case, specifically those that are severely ill with COVID-19. Nurses are the first to recognize a change in vital signs, deterioration in clinical status, and the need to alert the medical team that the next necessary steps will need to be taken to care for the patient, in this case, intubation. Given a lack of supportive evidence to determine if early versus delayed intubation is more effective; an algorithm could be developed that could not only guide healthcare providers, but nurses as well could use the algorithm as a guide to alert a healthcare provider as to when a patient may warrant intubation versus relying on clinical judgement alone. This will aid in better communication among nurses and healthcare providers as well as empower nurses to have a voice when caring for these severely ill patients.

Recommendations

A recommendation for practice is for a specific algorithm aimed at patients with severe COVID-19 to identify ideal intubation timing. By using Shashikumars' et al. (2021) algorithm, the need for intubation could be predicted within the 24 hours of the procedure occurring. The algorithm is described as a generalizable and transparent deep learning process. Goals of the algorithm model include minimizing the number of urgent intubations therefore reducing hemodynamic instability (Shashikumar et al., 2021). The algorithm could assist in decreasing unnecessary intubations, which itself carries risk such as a ventilator induced lung injury, ventilator associated pneumonia and unnecessary sedation (Shashikumar et al., 2021).

The Shashikumars et al. (2021) algorithm takes input from the electronic medical record to predict need for intubation. The variables used are all found in the electronic medical record which consist of laboratory studies and vital signs. The VentNet algorithm was used in the Shashikumars' et al. study (2021). This algorithm outperformed other similar modalities in the study (Shashikumars' et al., 2021). The VentNet algorithm used in Shashikumars et al. (2021) study uses 40 clinical variables including heart rate, pulse oximetry, temperature, systolic blood pressure, mean arterial pressure, diastolic blood pressure, respiration rate and end tidal carbon dioxide, laboratory values such as bicarbonate, measure of excess bicarbonate, fraction of inspired oxygen or FiO_2, pH, partial pressure of carbon dioxide from arterial blood, oxygen saturation from arterial blood, aspartate transaminase, blood urea nitrogen, alkaline phosphatase, calcium, chloride, creatinine, bilirubin direct, serum glucose, lactic acid, magnesium, phosphate, potassium, total bilirubin, troponin, hematocrit, hemoglobin, partial thromboplastin time, leukocyte count, fibrinogen and platelets (Shashikumar et al., 2021). For each vital sign and laboratory variable, the slope of change since its last measurement is included (Shashikumar et al., 2021). This highly sensitive algorithm was able to provide a 24-hour prediction of intubation needs for severe COVID-19 patients (Shashikumar et al., 2021).

As described in the literature review, outcomes for severe COVID-19 patients were not worsened by delayed intubation. Maintaining these patients' oxygen levels in any way possible with non-invasive measures is best. By using the VentNet algorithm tool to predict intubation needs in the next 24 hours, providers can avoid urgent intubations.

Summary

COVID-19 is a viral illness that emerged in December of 2019, turning into a world-wide pandemic. Currently there is no curative treatment. There are pharmacologic interventions that could shorten the duration and decrease severity of the illness. As of December 2020, COVID-19 vaccines were made available to help control the spread of COVID-19. Despite these interventions, COVID-19 has not become obsolete. COVID-19 is still prevalent in a spectrum of severity ranging from asymptomatic patients to those who are severely ill. Severely ill patients with COVID-19 often require intubation but the timing of this procedure in this patient population is not clear. A review of the literature shows that early intubation versus delayed intubation does not influence mortality outcomes. In fact, some literature supported delayed intubation with the end goal that patients may not need intubation at all. With implementation of VentNet, an algorithm that takes vital signs and laboratory values into account, intubations could be predicted within 24 hours of occurring. Therefore, decreasing unnecessary intubations and urgent intubations all while decreasing mortality outcomes in severe COVID-19 patients.

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Zhang, Q., Shen, J., Chen, L., Li, S., Zhang, W., Jiang, C., Ma, H., Lin, L., Zheng, X. & Zhao, Y. (2020). Timing of invasive mechanic ventilation in critically ill patients with coronavirus disease 2019. *Journal of Trauma and Acute Care Surgery*. 89 (6), 1092-1098. https://www-ncbi-nlm-nih-gov.wsuproxy.mnpals.net/pmc/articles/PMC7687875/

Table 1
Databases Searched and Data Abstraction

Date of Search	**Keyword Used**	**Database source**	**Listed**	**Reviewed**	**Used**
12/7/2020	Covid intubation	Cochrane Library	42	3	1
12/7/2020	covid	CINAHL	28,047	4	1
1/27/2021	Covid intubation timing	PubMed	75	3	1
2/1/2021	Covid intubation criteria	Ebscohost	3	1	0
2/1/2021	Covid intubation timing	Ebscohost	1	0	0
2/1/2021	Covid intubation	Ebscohost	18	1	1
3/15/2021	Covid intubation guidelines	Winona library “everything”	722	1	1
3/26/2021	ards covid intubation early vs late	Google scholar	7640	5	2
3/30/2021	Covid intubation timing	Cochrane library	186	6	1
4/1/2021	Covid intubation timing	PubMed	86	3	1

Table 2
Literature Review

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Gupta, S., Hayek, S.S., Wang, W., Chan, L., Mathews, K.S., Melamed, M.L., Brenner, S.K., Leonberg-Yoo, A., Schenck, E.J., Radbel, J. & Reiser, J. (2020). Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA internal medicine*, *180*(11), 1436-1446. https://jamanetwork-com.wsuproxy.mnpals.net/journals/jamainternalmedicine/article-abstract/2768602 **Pubmed**	"To assess factors associated with death and to examine interhospital variation in treatment and outcomes for patients with COVID-19" (p. 1436).	2215 adults diagnosed with COVID-19 Intensive care units in New York City, NY and Seattle, WA -65 sites, from March 4 to April 4, 2020	Multicenter cohort study Retrospective control trial	Primary outcome: Mortality rates at 28 days of Intensive Care Unit (ICU) admission Those discharged prior to 28 day endpoints were considered alive Secondary outcomes: Development of respiratory failure, acute respiratory distress syndrome, congestive heart failure, myocarditis, pericarditis, arrhythmia, shock, acute cardiac injury, acute kidney injury, acute liver injury, coagulopathy, secondary infection, and thromboembolic events	35.4% of patients (784) died within the first 28 days of ICU admission, 37.2% of patients (607) remained hospitalized at 28 days. Causes of death were respiratory failure (727 [92.7%]), septic shock (311 [39.7%]), and kidney failure (295 [37.6%])	Intubation timing was not considered as a factor of death at 28 days Factors associated with 28-day death included age, male gender, morbid obesity, coronary artery disease, cancer, acute organ dysfunction, and admission to a hospital with limited intensive care unit beds.	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Hernandez-Romieu, A. C., Adelman, M. W., Hockstein, M. A., Robichaux, C. J., Edwards, J. A., Fazio, J. C., ... & Auld, S. C. (2020). Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. *Critical care medicine*. . https://www-ncbi-nlm-nih-gov.wsuproxy.mnpals.net/pmc/articles/PMC7448713/ **Pubmed**	To determine the impact of time to intubation and use of high-flow nasal cannula on clinical outcomes in patients with COVID-19	231 adult patients with COVID-19 Six ICU settings across four university affiliated hospitals in Atlanta, Georgia	Retrospective cohort study	Interventions included: High-flow nasal cannula alone High-flow nasal cannula followed by intubation Intubation without preceding high-flow nasal cannula use Patients intubated within the first 8 hours of ICU admission Patients intubated within 8-24 hours of ICU admission Patients intubated after 24 horus of ICU admission	"Seventy-six patients (43.4%) were intubated within 8 hours of ICU admission, 57 (32.6%) were intubated between 8 and 24 hours of admission, and 42 (24.0%) were intubated at greater than or equal to 24 hours after admission" (p.1). Mortality did not differ by timing of intubation (≤ 8 hr: 38.2%; 8–24 hr: 31.6%; ≥ 24 hr: 38.1%; $p = 0.7$), "There was no difference in initial static compliance, duration of mechanical ventilation, or ICU length of stay by timing of intubation. High-flow nasal cannula use prior to intubation was not associated with increased or decreased mortality" (p.1).	Neither time from ICU admission to intubation nor use of high-flow nasal cannula use were associated with increased mortality. This study provides evidence that COVID-19 respiratory failure can be managed similarly to hypoxic respiratory failure of other etiologies.	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Hyman, J.B., Leibner, E.S., Tandon, P., Egorova, N.N., Bassily-Marcus, A., Kohli-Seth, R., Arvind, V., Chang, H.L., Lin, H.M. & Levin, M.A. (2020). Timing of intubation and in-hospital mortality in patients with coronavirus disease 2019. *Critical care explorations*, *2*(10). https://www-ncbi-nlm-nih-gov.wsuproxy.mnpals.net/pmc/25rticular/PMC7587418/ **Google Scholar**	"To examine whether increasing time between admission and intubation was associated with increased mortality in patients with COVID-19 who underwent mechanical ventilation"(p.1).	755 adult patients diagnosed with COVID-19 Five hospitals within the Mount Sinai Health System in New York City, NY.	Retrospective cohort study	Cox model was used to evaluate the effect of time to intubation on in-hospital death. Time zero was defined as the time a patient was first placed on invasive mechanical ventilation. still intubated, extubated, or having had a tracheostomy.	"As of this time in follow-up, 121 patients (16%) who were intubated and mechanically ventilated had been discharged home, 512 (68%) had died, 113 (15%) had been discharged to a skilled nursing facility, and 9 (1%) remained in the hospital. The median time from admission to intubation was 2.3 days (interquartile range, 0.6–6.3 d). Each additional day between hospital admission and intubation was significantly associated with higher in-hospital death (adjusted hazard ratio, 1.03; 95% CI, 1.01–1.05)" (p.1). The adjusted hazard ratio for mortality was 1.03 (95% CI, 1.01–1.05) for each day of delay in intubation following initial hospital presentation	Intubation earlier in the hospital course may be associated with improved survival. Patients who were extubated after a more prolonged course of mechanical ventilation (> 3 to 4 weeks) had a lower hazard ratio for death relative to patients who were on mechanical ventilation for a shorter duration. The observations suggest that supportive care consisting of early intubation and conservative extubating strategy may be associated with improved outcomes.	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Lee, Y. H., Choi, K.-J., Choi, S. H., Lee, S. Y., Kim, K. C., Kim, E. J., & Lee, J. (2020). Clinical Significance of Timing of Intubation in Critically Ill Patients with COVID-19: A Multi-Center Retrospective Study. *Journal of Clinical Medicine*, *9*(9), 2847.http://dx.doi.org/10.3390/jcm9092847 **Pubmed**	To determine if early intubation is associated with the survival of COVID-19 patients with acute respiratory distress syndrome	47 adult patients diagnosed with COVID-19 Three tertiary referral hospitals in Daegu, Korea between 2/17/20-4/23/20	Retrospective	Early intubation: Intubated/mechanically ventilated and meeting ARDS criteria on the same day as intubation (within 24 hours) and Initially non-intubated: Not intubated on the day of meeting ARDS criteria. The initially non-intubated group was divided further into two subgroups: (A) never intubated (B) late intubation defined by not being intubated on day of ARDS diagnosis	Of the 47 patients, 23 (48.9%) patients were intubated on the day of meeting ARDS criteria (early intubation), while 24 (51.1%) were not initially intubated. Of those eight patients were never intubated during their in-hospital course. 21 patients (44.7%) died while in the hospital. No significant difference in in-hospital mortality rate was found between the early group and initially non-intubated groups (56.5% vs. 33.3%, p = 0.110)	Early intubation was not associated with improved survival	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Matta, A., Chaudhary, S., Lo, K.B., DeJoy III, R., Gul, F., Torres, R., Chaisson, N. & Patarroyo-Aponte, G. (2020). Timing of intubation and its implications on outcomes in critically ill patients with coronavirus disease 2019 infection. *Critical care explorations*, *2*(10). https://www-ncbi-nlm-nih-gov.wsuproxy.mnpals.net/pmc/articles/PMC7587415/ **Pubmed**	To "evaluate the association between timing of intubation and outcomes among critically ill patients with COVID-19" (p.1).	128 ICU patients diagnosed with COVID-19 from March 15, 2020 to May 30, 2020 Einstein Medical Center, Philadelphia, PA .	Observational Retrospective Study	Early intubation was defined as intubation either at hospital admission or less than 2 days since the onset of increased oxygen requirements defined by requiring more than 50% FIO2. Late intubation greater than or equal to 2 days following the onset of increased oxygen requirements defined by requiring more than 50% FIO2.	Timing of intubation does not seem to be significantly associated with poor clinical outcomes in critically ill patients with COVID-19. The timing of intubation seems to be driven mainly by disease severity and rate of progression The patients who required early intubation had significantly higher Sequential Organ Failure Assessment scores at admission (6.51 vs 3.48; $p \leq 0.0001$)	Relatively small cohort of patients	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Pandya, A., Kaur, N.A., Sacher, D., O'Corragain, O., Salerno, D., Desai, P., Sehgal, S., Gordon, M., Gupta, R., Marchetti, N., & Zhao, H. (2021). Ventilatory mechanics in early vs late intubation in a cohort of coronavirus disease 2019 patients with ARDS: a single center's experience. *Chest, 159*(2), 653-656. https://europepmc-org.wsuproxy.mnpals.net/articles/pmc7456835/bin/mmc1.pdf **GoogleScholar**	To examine ventilator mechanics in early versus late intubation for patients with COVID 19	Seventy-five COVID-19 patients Hospitalized between February and May 2020. Temple University Hospital, Phiadephia, PA	Retrospective Study	Early intubation was intubation within the first <1.27 days of admission Late intubation was intubation within >1.27 days of admission	Late intubation (median, day 4) was associated with longer ICU length of stay and longer duration of mechanical ventilation than early intubation (median, day 0). Non survivors had a longer time to intubation than survivors in our cohort.	Patients intubated who had late intubation appear to have worse compliance or ventilator ratio with potentially higher mortality. Difficult to determine if the decline in lung compliance is due to disease progression or the presence of self induced lung injury	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Papoutsi, E., Giannakoulis, V. G., Xourgia, E., Routsi, C., Kotanidou, A., & Siempos, I. I. (2021). Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. *Critical Care*, *25*(1), 1-9. https://link-springer-com.wsuproxy.mnpals.net/article/10.1186/s13054-021-03540-6 **Google Scholar**	To investigate the effect, if any, of timing of intubation on clinical outcomes of critically ill patients with COVID-19	8944 critically ill patients (hospitalized in the ICU) with COVID-19 ICU setting in Africa, Asia, Europe and America	Systematic review and meta-analysis.	Early intubation – intubation after 24 hours from intensive care unit admission Late intubation – intubation after 24 hours of ICU admission.	"There was no statistically detectable difference on all-cause mortality between patients undergoing early versus late intubation" (p.1). Of 8944 patients there were 3981 recorded deaths; 45.4% were early intubation versus 39.1% were late intubations; RR 1.07, 95% CI 0.99–1.15, $p = 0.08$	Of almost 9000 patients, timing of intubation had no effect on mortality and morbidity of critically ill patients with COVID-19.	Level I

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Rhee, C.J.A., Castaneda, C., Karass, M., Abe, O., Elshakh, H., Kim, M., Sajid, F., Ju, T., Voronina, A., Al-Ghrairi, A. & El Marabti, E. (2020). Timing of intubation and outcome in the covid-19 pandemic: challenging the concept of permissive hypoxemia. *Chest*, 158(4), A630. https://journal.chestnet.org/article/S0012-3692(20)32780-X/fulltext **Ebscohost**	Examine the preoxygenation state of patients diagnosed with COVID-19 prior to intubation and the implications of intubation on clinical outcomes.	192 patients diagnosed with COVID-19 between March 15, 2020 and April 15, 2020 Queens, New York	Retrospective study	Preoxygenation levels of all intubated patients Subsequent groups identified included patients with normal preoxygenation levels, and those with significantly lower peri-intubation oxygen levels P/F ratio of the two groups were also looked at. The P/F ratio is the arterial pO2 from the ABG divided by the FIO2	Decreased oxygenation and P/F ratios before intubation were associated with an increase in peri-intubation complications, such as cardiac arrest 32 out of 192 patients (16.7%) with peri-intubation cardiac arrest demonstrated significantly lower pre-oxygenation levels($p = 0.03$) These 32 patients also demonstrated more days with COVID-19 symptoms prior to intubation ($p = 0.004$).	Clinical outcome was further impacted by the restriction on preoxygenation of the patients before intubation, given its risk of viral aerosolization	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Shashikumar, S. P. (2021). Development and prospective validation of a deep learning algorithm for predicting need for mechanical ventilation. *Chest*., *159*(6), 2264–2273. https://doi.org/10.1016/j.chest.2020.12.009 **Pubmed**	To develop, externally validated and prospectively test a transparent deep learning algorithm for predicting, 24 hours in advance, the need for mechanical ventilation in hospitalized patients with COVID-19 by using a field of machine learning (ML) which is an artificial intelligence that automates analytical model building to identify patterns in data to predict outcomes	402 adult patients diagnosed with COVID-19 3,888 general ICU patients January 01, 2016, to December 31, 2019 (Retrospective cohorts) February 10, 2020 to May 4, 2020 (Prospective cohorts) University of California San Diego Health and Massachusetts General Hospital	Observational cohort study	Variable used in guidance of intubation included were heart rate, pulse oximetry, temperature, systolic blood pressure, mean arterial pressure, diastolic blood pressure, respiration rate and end tidal carbon dioxide. Lab values included bicarbonate, measure of excess bicarbonate, fraction of inspired oxygen or FIO2, pH, partial pressure of carbon dioxide from arterial blood, oxygen saturation from arterial blood, aspartate transaminase, blood urea nitrogen, alkaline phosphatase, potassium, total bilirubin, troponin, hematocrit, hemoglobin, partial thromboplastin time, leukocyte count, fibrinogen, and platelets along with demographic variables. An automated program gathers the date from electronic medical record, scores it and predicts when a patient likely needs mechanical ventilation in the next 24 hours. Patients with a score of 0 were unlikely to need mechanical ventilation in the next 24 hours where a patient with a score closer to 1 was likely to need to be	intubated in the next 24 hours. A traditional algorithm improves traditional clinical criteria to predict need for mechanical intubation The area under the ROC curve model was used to check reliability of the prediction, the higher the score the better. For general ICU population 0.882 and 0.918 for patients with COVID-19 when using the 24- hour prediction horizon compared to the ROX score which was in the range of 0.772-0.810		Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Siempos, I.I., Xourgia, E., Ntaidou, T.K., Zervakis, D., Magira, E.E., Kotanidou, A., Routsi, C. & Zakynthinos, S.G. (2020). Effect of early versus delayed or no intubation on clinical outcomes of patients with COVID-19: An observational study. *Frontiers in medicine*, *7*. https://www-ncbi-nlm-nih-gov.wsuproxy.mnpals.net/pmc/articles/PMC7785771/ **Cochrane library**	To determine the optimal timing of initiation of invasive mechanical ventilation in patients with acute hypoxemic respiratory failure due to COVID-19	42 ICU patients with COVID-19 March 11, 2020 and April 15, 2020 Evangelismos Hospital, Athens, Greece	Retrospective single center study	Early intubation group Delayed or no intubation group: patients receiving non-rebreather mask for equal to or more than 24 hours or high-flow nasal oxygen for any period of time or non-invasive mechanical ventilation for any period of time in an attempt to avoid mechanical intubation	Early intubation, as opposed to delayed or no intubation, was not associated with worse clinical outcomes, such as mortality 21% vs 33%, ventilator-free days 3 versus 2 or out of ICU days compared to delayed or no intubation.	Early intubation doesn't help	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Voshaar, T., Stais, P., Köhler, D., & Dellweg, D. (2021). Conservative management of COVID-19 associated hypoxaemia. *ERJ Open Research*, *7*(1). https://openres.ersjournals.com/content/7/1/00026-2021.abstract **Googlescholar**	To evaluate a predefined protocol for restrictive use of invasive ventilation where the decision to intubate was based on the clinical presentation and oxygen content rather than on the degree of hypoxemia.	78 adult patients diagnosed with COVID-19 Kloster Grafschaft Hospital and Bethanien Moers Hospital	Retrospective study analysis	Group 1 received supplemental oxygen via nasal cannula Group 2 received nasal high-flow continuous positive airway pressure (CPAP), noninvasive ventilation or a combination of the above mentioned methods Group 3 received intubation They used Horowitz index or P/F ration to assess lung function, helpful to determine extent of damage to lungs. Which is a calculation that uses the partial pressure oxygenation and fraction of inspired oxygen.	Overall mortality was 7.7% of all groups 93% of all patients studied were discharged on room air Mortality of intubated patients was 50% The Horowitz index: Group 1: 216±8 Group 2: 157±13 Group 3: 106±15 The Horowitz index or P/F rations of greater than 300 is considered not ARDS, 200-300 is considered to be mild ARDS, 100-200 moderate ARDS and less than 100 severe ARDS	Allowing patients to become hypoxemic and basing intubation on clinical presentation decreased mortality and showed a decrease in the rate of intubation	Level IV

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Zhang, Q., Shen, J., Chen, L., Li, S., Zhang, W., Jiang, C., Ma, H., Lin, L., Zheng, X. & Zhao, Y. (2020). Timing of invasive mechanic ventilation in critically ill patients with coronavirus disease 2019. *Journal of Trauma and Acute Care Surgery*. 89 (6), 1092-1098. https://www-ncbi-nlm-nih-gov.wsuproxy.mnpals.net/pmc/articles/PMC7687875/ **Googlescholar**	To report the cases of critical patients receiving mechanical ventilation in Wuhan, China To discuss the timing of intubation in patients diagnosed with COVID- 19 patients.	40 adult pateints diagnosed with COVID-19 January 1, 2020 to March 10, 2020 Zhongnan and Wuhan Union Hospital in Wuhan, China	Retrospective Study	Acute Physiology and Chronic Health Evaluation II (APACHE II) score is based form 0-100 the higher the score the more the mortality rate increases pneumonia severity index (PSI) score estimated the severity of pneumonia to predict mortality risk Patients with 50 hours or less of non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC)	"Early initial intubation after NIV/HFNC could have a beneficial effect in reducing mortality for critically ill patients meeting IMV indication. Considering APACHE II and PSI scores might help physicians in decision making about timing of intubation for curbing subsequent mortality" (p. 2092). 67% of survivors and 61% non survivors had APACHE II scores of between 8 and 15 at admission. Median PSI score was 78 in survivors and 98 in nonsurvivors	This study was performed early on in the COVID-19 pandemic, prior to when preoxygenation data was allowed of COVID-19 patients due to risk of aerosol particles. Early intubation was found beneficial in those with low APACHE II and PSI scores	Level V

Citation/Search Engine	Purpose/Objective	Study Population/Sample/ Setting	Design	Variables/Instruments	Results(s)/Major or Findings	Implications/Critique	Level of Evidence
Zuccon, W., Comassi, P., Adriani, L., Bergamaschini, G., Bertin, E., Borromeo, R., Corti, S., De Petri, F., Dolci, F., Galmozzi, A.& Gigliotti, A. (2020). Intensive care for seriously ill patients affected by novel coronavirus sars-CoV–2: Experience of the Crema Hospital, Italy. *The American journal of emergency medicine*. https://pubmed-ncbi-nlm-nih-gov.wsuproxy.mnpals.net/33046317/ **Ebscohost**	To determine the best treatment and management in the care of patients diagnosed with COVID-19	54 adult patients diagnosed with COVID- 19 March to June 2020. Crema Hospital in Italy	Retrospective Study	Number of days of COVID-19 symptoms Admitted days Blood chemistry (ABG), Patient age Gender Pulse oximetry	9 out of the 25 patients who received early intubation died 12 out of the 23 who were intubated late died Late intubation was defined as 24 hours of non invasive ventilation No difference in mortality of early or late intubations.		Level IV

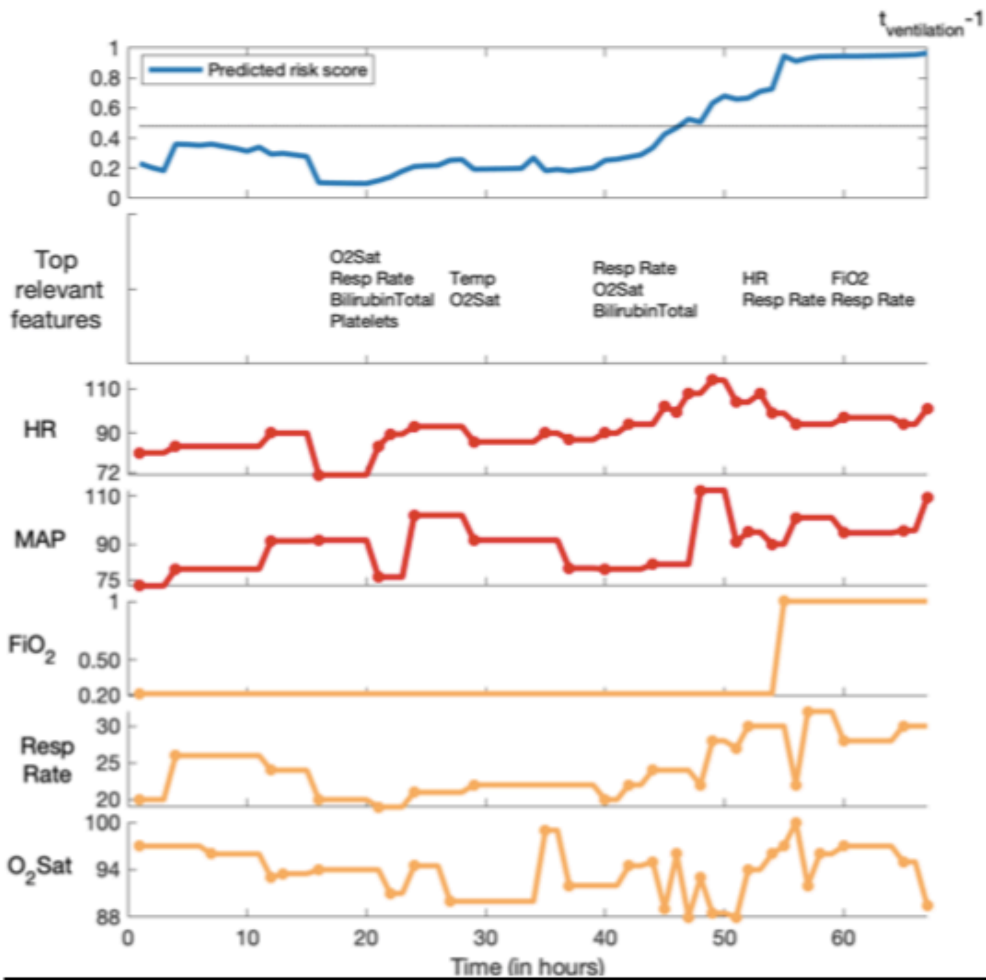
Table 3
Levels of Evidence

Level of evidence (LOE)	Description
Level I	Evidence from a systematic review or meta-analysis of all relevant RCTs (randomized controlled trial) or evidence-based clinical practice guidelines based on systematic reviews of RCTs or three or more RCTs of good quality that have similar results.
Level II	Evidence obtained from at least one well-designed RCT (e.g. large multi-site RCT).
Level III	Evidence obtained from well-designed controlled trials without randomization (i.e. quasi-experimental).
Level IV	Evidence from well-designed case-control or cohort studies.
Level V	Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis).
Level VI	Evidence from a single descriptive or qualitative study.
Level VII	Evidence from the opinion of authorities and/or reports of expert committees.

(Ackley et al., 2008)

APPENDIX A

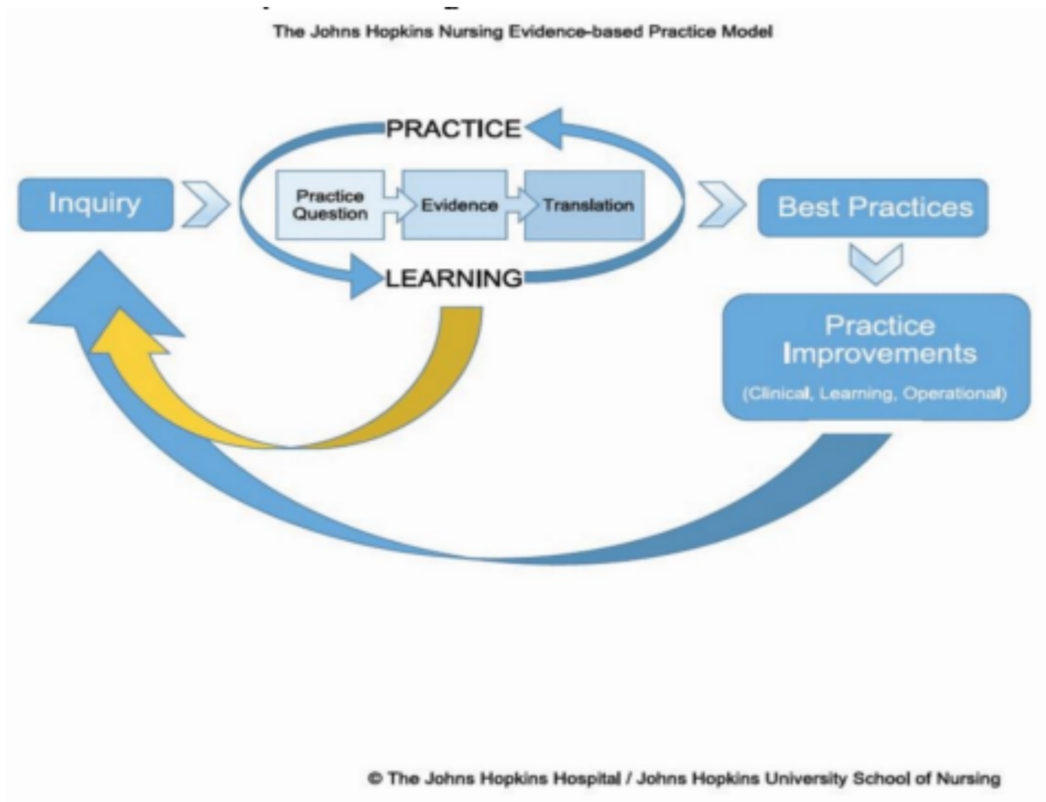
VentNet Algorithm



(Shashikumar et al., 2020)

APPENDIX B

Johns Hopkins Nursing Evidence-Based Practice Model



Practice Question
Step 1: Recruit interprofessional team
Step 2: Define the problem
Step 3: Develop and refine the EBP question
Step 4: Identify stakeholders
Step 5: Determine responsibility for project Leaders
Step 6: Schedule team meetings

Evidence
Step 7: Conduct internal and external search for evidence
Step 8: Appraise the level and quality of each piece of evidence
Step 9: Summarize the individual evidence
Step 10: Synthesize overall strength and quality of evidence
Step 11: Develop recommendations for change based on evidence synthesis

Translation:
Step 12: Determine fit, feasibility and appropriateness of recommendations
Step 13: Create action plan

Step 14: Secure support and resources to implement action plan
Step 15: Implement action plan
Step 16: Evaluate outcomes
Step 17: Report outcomes to stakeholders
Step 18: Identify next steps
Step 19: Disseminate findings