Academic Journal of
Pediatrics & Neonatology
ISSN 2474-7521

Juniper Publishers
key to the Researchers

Review Article
Volume 12 Issue 5 - October 2023
DOI: 10.19080/AJPN.2023.12.555905

Acad J Ped Neonatol


# Does the Timing of Intubation and IMV Impact Clinical Outcomes in Adult COVID-19 Patients with ARDS: A Systematic Review and Meta-Analysis

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**Submission:** February 03, 2023; **Published:** October 02, 2023

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## Abstract

**Background/Aim**: COVID-19 can rapidly develop into acute lung injury, and even acute respiratory distress syndrome (ARDS), which has a high risk of death. Patients with ARDS often require intubation. However, the timing of intubation and its effect on clinical outcomes in COVID-19 ARDS (CARDS) patients remains unclear. Thus, the authors explored the impact of intubation time on clinical outcomes in COVID-19 patients with ARDS through a systematic review and meta-analysis.

**Materials and Methods:** Research articles from PUBMED, CINAHL, MEDLINE, ProQuest Covid database, and Web of Science were searched through December 2021. All patients in the research met the Berlin criteria for ARDS. For the purposes of this review, "Early" intubation was defined as intubation within 24 hours of an ARDS diagnosis, while "Late" was defined as 24 or more hours after diagnosis. The primary outcome was ICU mortality, and secondary measures included length of ICU stay and duration of mechanical ventilation. The meta-analysis was performed using a random-effects model. The quality of cohort studies was assessed using the Newcastle-Ottawa Scale. The methodological quality of the overall evidence in this review was evaluated using the GRADE approach.

**Results:** After an extensive search, six cohort studies were ultimately included in the systematic review, altogether encompassing 2,739 patients with CARDS. A meta-analysis revealed statistically significant differences in mortality [risk ratio (RR)=0.78; 95% confidence interval (CI),0.69-0.88; Z=3.91, P < 0.0001)]. The mortality rate was 36.2% (817 deaths) in the early group and 48.2% (229 deaths) in the late group, respectively. Results of the narrative analysis showed that early intubation resulted in shorter ICU stays, which was statistically significant. However, no statistical difference was found in the duration of mechanical ventilation.

**Conclusions:** Early intubation can reduce mortality and length of ICU stay in adult COVID-19 patients with ARDS. However, the timing of intubation did not affect the duration of continuous mechanical ventilation.

**Keywords:** COVID-19; ARDS; Timing of Intubation; Invasive Mechanical Ventilator; Systematic Review; Mortality

## Introduction

In December 2019, COVID-19 was identified as a new clinical syndrome caused by a novel coronavirus. The virus is transmittable through the respiratory tract and is highly contagious. Despite significant efforts to control the spread of COVID-19, it triggered a global pandemic [1-4], an epidemic of scale across international borders [5]. COVID-19 pneumonia may develop rapidly into acute respiratory distress syndrome (ARDS) with a high risk of death [6]. ARDS is an acute respiratory failure caused by increased pulmonary capillary permeability secondary to inflammatory oedema. It leads to alveolar flooding and subsequent deep hypoxemia, in which intrapulmonary shunt is the most important underlying mechanism [7]. However, ARDS caused by COVID-19 is different from ARDS with any other underlying cause. According to Huang et al. (2020) [8], the onset of ARDS associated with COVID-19 is between 8-12 days. There are two distinct phenotypes of COVID-19-associated ARDS (CARDS), L-type and H-type. Type L presents as pneumonia and is limited to mild inflammation of the subpleural interstation.

It is characterized by low elasticity, atelectasis, normal compliance, and low lung weight. On the other hand, patients with Type H meet typical ARDS criteria, including decreased lung compliance, hypoxemia, bilateral lung infiltration, and increased lung weight [9]. Li and Ma [10] have been reporting on respiratory support strategies for patients with CARDS during the past two years, but how exactly the timing of tracheal intubation and use of invasive mechanical ventilation impacts clinical outcomes is still unclear in patients with CARDS. Delayed intubation can cause autologous lung injury (SILI) due to high respiratory drive pressure [11]. However, intubating patients too early can also be associated with some complications, including ventilator-associated pneumonia, airway injury, ventilator-induced lung injury, and hemodynamic disorders due to positive pressure ventilation [12]. Six primary studies [13-18] have indicated different results regarding the timing of intubation for patients with CARDS, and currently there is no systematic review relevant to this topic. Therefore, a systematic review is necessary to further explore how the timing of intubation impacts outcomes for these patients.

## Materials and Methods

The PRISMA statement, which contains a 27-item checklist and four-phase flow chart [19], is used to help authors report systematic reviews and meta-analyses.

### Eligibility Criteria

The population included in this systematic review was defined as adult patients (≥18 years old) with PCR-confirmed COVID-19 diagnoses who also had ARDS. ARDS was defined by the Berlin Criteria or American-European Consensus Conference (Table 1) [20]. Early intubation was defined as being intubated within 24 hours of being diagnosed with ARDS; Late intubation was defined as being intubated 24 or more hours after an ARDS diagnosis. The timing of intubation was also defined by authors of four original studies [21]. Systematic reviews and meta-analyses are in the upper echelon of the evidence-based medicine hierarchy of evidence, followed by randomized, controlled, double-blind studies, followed by cohort studies, case-control studies, case series, and case reports [2] (Figure 1). Randomized trial studies were not permitted due to potential ethical issues regarding the timing of intubation of COVID-19 ARDS patients [22]. Therefore, existing cohort studies and case-control studies were sought out to provide high-quality research evidence for this systematic review [23], (Figure 1).

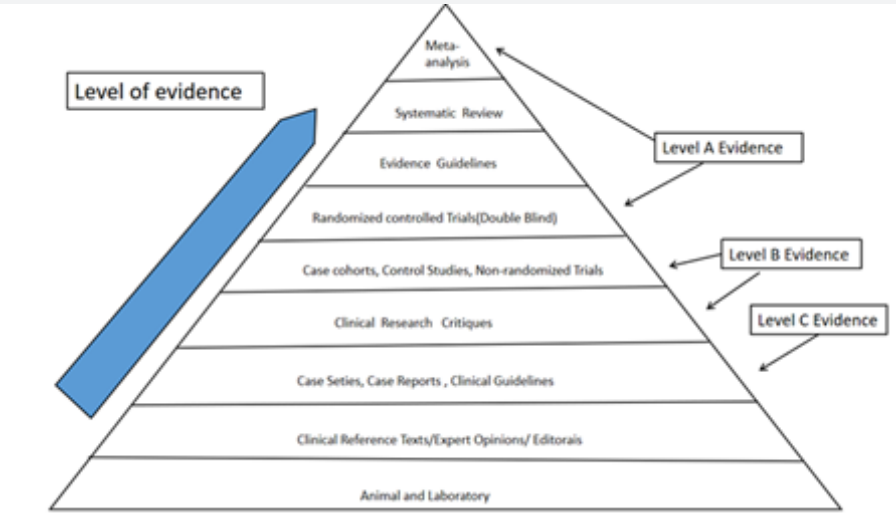


**Figure 1:** The level of research evidence is shown in a pyramid diagram [2].

### Search Strategy

The authors only searched relevant scientific databases, which included PUBMED, CINAHL, MEDLINE, ProQuest Covid Databases, and Web of Science. Articles were retrieved from December 2019 to December 2021, and the language was restricted to English. In this systematic review, the search strategy developed by the authors consisted of a combination of keywords, medical subject headings (MeSH), free-text words, wildcards, acronyms, synonyms, and transatlantic terms. Boolean operators ("AND" "OR" and "NOT") were used to combine the terms entered in each search field. Search strategy and keywords are described as follows (Table 2).

### Study Selection

Two authors independently searched for relevant literature by executing the above search strategy and browsing abstracts or full texts to find potential articles. Detailed inclusion and exclusion


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criteria were used to screen the articles, and six primary research articles were finally selected as suitable for review.

### Data Extraction and Risk of Bias Assessment

Two reviewers independently extracted and examined data from each included study. Extracted data included article title, author name(s), the date of publication, language, country, characteristics of participants, type of study, and data pertaining to the study's outcome. Outcomes included mortality, length of ICU stay, and duration of ventilator use. The Newcastle-Ottawa Scale (NOS), developed by the University of Newcastle in Australia and the University of Ottawa in Canada, is a quality assessment tool for the systematic evaluation of non-randomized studies, especially for cohort and case-control studies [24]. The NOS cohort study version consists of eight multiple-choice questions involving topic selection and comparability, as well as outcome assessment or exposure. A star rating system is used to indicate the quality of the study, up to a maximum rating of nine stars. One star is awarded for each criterion if the reporting methodology is appropriate. Separate scales have been developed for cohort and case-control studies, which can help authors identify low-quality studies and inform sensitivity analyses or meta-regression [25]. NOS developers have examined NOS face and standard validity, reliability among evaluators, and evaluator burden. Surface validity has been assessed as strong by comparing each assessment item with its stem problem [26]. Therefore, NOS can be a helpful tool in assessing the quality of studies included in systematic reviews.

**Table 1:** Berlin Definition of acute respiratory distress syndrome (ARDS).

| Criteria | Rationale |
|---|---|
| Onset within 7 days after a known clinical insult or new or worsening respiratory symptoms | Observational data suggest that ARDS will develop within 72 hr in the majority of patients at risk for the syndrome and within 1wk. in nearly all patients at risk |
| Bilateral opacities that are "consistent with pulmonary edema" on chest radiographs or chest CT | There is poor interobserver reliability in interpreting the chest radiograph for the presence of edema. To address this issue, the Berlin definition offers more explicit criteria (e.g., opacities should not be fully explained by effusions, lobar or lung atelectasis, or nodules or masses), with illustrative radiographs provided |
| Categorization of ARDS severity | A patient-level meta-analysis validated three thresholds for hypoxemia, all consisting of a Pao2:Fio2 ratio ≤300 mm Hg |
| Mild | Pao2: Fio2, 201 to 300 mm Hg; mortality, 27% (95% CI, 24–30) |
| Moderate | Pao2: Fio2, 101 to 200 mm Hg; mortality, 32% (95% CI, 29–34) |
| Severe | Pao2: Fio2, ≤100 mm Hg; mortality, 45% (95% CI, 42–48) |
| Minimum PEEP setting or CPAP, 5 cm of water; Pao2:Fio2 assessed on invasive mechanical ventilation (CPAP criterion used for the diagnosis of mild ARDS) | Estimates of Fio2 are not accurate with oxygen-delivery systems other than invasive or noninvasive ventilation (with a tight-fitting mask), except for nasal high-flow oxygen delivery systems (at flow rates ≥45 liters per minute); requiring higher PEEP settings does not increase predictive validity of the Berlin severity strata and adds complexity |
| * The definition and the quotation about opacities are from Ferguson et al. [20] CI denotes confidence interval; CPAP, continuous positive airway pressure; Pao2: Fio2, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; and PEEP, positive end-expiratory pressure. | |

**Table 2:** Search Strategy and Keywords.

| | |
|---|---|
| **Population (P)** | "coronavirus2019" OR "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2" OR "novel coronavirus" OR "SARS-CoV-2" OR "nCoV disease" OR "COVID19" OR "2019nCoV" OR "coronavirus disease-19" OR "coronavirus disease 2019" OR "2019 novel coronavirus" |
| | "Acute Respiratory Distress Syndrome" OR "ARDS" OR "Severe pneumonia" OR "Respiratory Distress Syndrome" OR "acute respiratory failure" OR "acute lung injury" OR "ALI" |
| **Intervention (I)** | "Intubation" OR "tracheal Intubation" OR "tracheal tube" OR "Endotracheal intubation" OR "mechanical ventilation" OR "invasive mechanical ventilation" OR "IMV" OR "MV" OR "NIV" OR "Non-invasive ventilation" OR "high flow" |
| | Tim* OR early OR late OR delay |
| **Design of Study (D)** | "Cohort study" OR "Study" OR "Randomized Controlled Trials" OR "Randomized Controlled Trials as Topic" OR "Randomized Controlled Trials" OR "Trials, Randomized Clinical" OR "Controlled Clinical Trials, Randomized" |

### Data Synthesis

Stroup et al. published criteria for conducting and reporting meta-analyses of observational studies to improve the quality of reporting. Dichotomous data and risk ratio (RR) were chosen for data synthesis. The most common, a 95% confidence interval, is used to analysed mortality and favourable outcomes. Narrow confidence intervals are used to indicate that treatment estimates are relatively accurate [27]. In the second stage, the pooled (combined) intervention effect estimates are calculated as a weighted average of the estimated intervention effects in a single


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study. There are four methods for binary results meta-analysis, including three fixed-effect methods (Mantel-Haenszel, Peto, and inverse variance) and one random-effects method (Der Simonian and Laird inverse variance) [28]. For this systematic review, Rev Man software from the Cochrane Review was used for data analysis. The results were presented using forest maps.

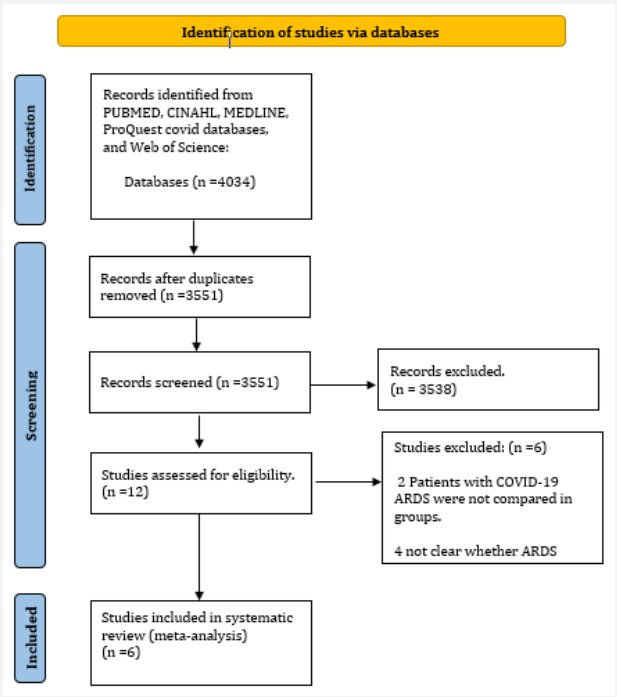


**Figure 2:** Studies Flow Diagram [3].

## Results

### Study Selection

**Table 3:** Characteristics of the Six Studies Included in the Systematic Review.

| First author | Country | Type of study | Patient populaion (N) | Early definition (h) | Late definition (h) | Early intubation (N) | Late intubation (N) | Mortality (Early) | Mortality (Late) |
|---|---|---|---|---|---|---|---|---|---|
| Lee et al. [13] | Daegu, Korea | Multi-center, retrospective, observational study | 47 | <24 | >24 | 23 | 16 | 13 (56.5) | 7 (43.8) |
| Schmidt et al. | France, Belgium, and Switzerland | Multi-center, prospective cohort study | 2233 | <24 | >24 | 2003 | 230 | 724(37%) | 96 (42%) |
| United States | United States | Retrospective cohort study | 54 | 4h- 24h | >24 | 30 | 24 | 2 (6%) | 7 (29%) |
| Zirpe et al. [16] | India | Retrospective observational study | 147 | <48 | >48 | 75 | 72 | 45 (60%) | 56 (77.7%) |
| Pandya et al. [17] | United States | Retrospective study | 75 | ≤1.27 days | (>1.27 days) | 37 | 38 | 17 (45.95%) | 20 (54.05%) |
| Vera et al. [18] | Chile | Observational, prospective, single-center study | 183 | <48 | >48 | 88 | 95 | 16 (18%) | 43 (43%) |


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Six cohort studies met the criteria to be included in this systematic review. In total, these studies encompassed 2,739 patients with COVID-19 ARDS [29-31], (Figure 2). All the studies compared patients who experienced early intubation with patients who experienced late intubation. The characteristics of all studies are shown in detail in (Figure 2), (Tables 3, 4).

**Table 4:** Additional Characteristics of Studies that were Included in the Systematic Review.

| First author | Country | Type of study | Length of ICU stay, Days (Early) | Length of ICU stay, Days (Late) | MV days (Early) | MV Days (Late) | Male sex (%) | Age (years) | SOFA at ICU admission (Early) | SOFA at ICU admission (Late) |
|---|---|---|---|---|---|---|---|---|---|---|
| Lee et al. [13] | Daegu, Korea | Multi-center, retrospective, observational study | 13 (7–33) | 47 (13–74) | 10 (4–24) | 20 (9–57) | 28 (59.6%) | 70 (IQR, 63–77) | 3 (2–7) | 3 (2–4) |
| Schmidt et al. | France, Belgium, Switzerland | Multi-center, prospective cohort study | | | | | | 63 (54–71) | 5 (3–8) | |
| Bavishi et al. [15] | United States | Retrospective cohort study | 12 (5–17) | 15 (10–19) | 10 (5–15) | 10 (7–19) | 37 | 60 (42-69) | 6 (3-8) | 4 (1-7) |
| Zirpe et al. [16] | India | Retrospective observational study | 14 (9.7–21) | 16 (7–21.7) | 7 (4–12) | 6 (2–12) | 109 (74.1%) | 59 (51-67) | 1 (1–2) | 1 (1–2) |
| Pandya et al. [17] | United States | Retrospective study | 7.38 (3.88-10.21) | 12.31 (7.75-19.96) | 5.86 | 10.30 | 43 (57.33%) | 65 | | |
| Vera et al. [18] | Chile | Observational, prospective, single-center study | 31 (17–45) | 36 (24–62) | 13 (8–25) | 16 (9–33) | 132 | 61.5 (53-71) | 6 (4–8) | 4 (2–8) |


**Figure 3:** Risk of bias assessment using Newcastle-Ottawa Score1. Risk of bias assessment for each study according to its NOS. Plots created using risk-of-bias visualization (robvis) tool [30].



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### Assessment Quality

The Newcastle-Ottawa Scale was used to evaluate the quality of the six studies [32] (see Appendix 3). There are detailed evaluation records for each study, as well as summary tables for each of the six studies. The traffic-light plots and summary bar plots were created using the robvis tool (Figure 3), which is a web application for visualizing deviation risk assessment as part of a system assessment [33]. Selection criteria, comparability, and outcome (cohort) or exposure (case-control) were scored on a scale up to 9 (Figure 3).

### Main Outcome

The forest plot showed that 2,731 participants across six studies were included in the meta-analysis with a combined RR = 0.78 (95% CI 0.69 to 0.88, Z=3.91, P < 0.0001) (Figure 4). Overall, the results showed that the mortality of the early intubation group was lower than the late intubation group, and the difference was statistically significant. Significant heterogeneity was observed (I2=63%), which indicated a large degree of variation between effect sizes in the included studies (Figure 4).

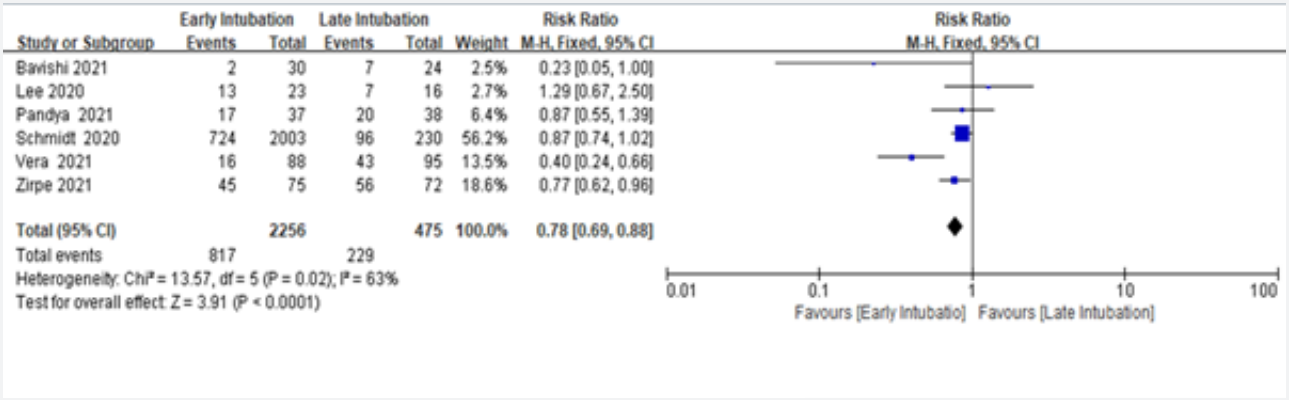


**Figure 4: The mortality of all patients with CARDS in the 6 studies undergoing early intubation versus (VS) late intubation. Pooled risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random effects model. I2: Heterogeneity.**

### Length of ICU Stay

Schmidt et al. failed to extract the length of ICU stay of participants. No statistically significant differences were found between groups regarding the number of days spent in the ICU in three of the other studies (P > 0.05) [34,35]. Two studies indicated that there were significant differences between the groups (P< 0.05). Overall, since analysis found that early intubation results in shorter ICU stays, this was seen as statistically significant (Table 5).

### Duration of Ventilation

Ventilation time was not extracted for the participants in one study Schmidt et al. The other five studies reported no significant difference in the duration of mechanical ventilation between the early intubation group and the late intubation group (P□0.05). Overall, the timing of intubation does not appear to impact the duration of mechanical ventilation of CARDS patients in the ICU (Table 5).

### Complications

Patient complications were not reported separately in one study. Lee et al. observed that among patients treated with MV, the incidence of ventilator-associated pneumonia (VAP) in the early intubation group was often higher than that in the late intubation group, but no statistical significance was found (30.4%; N = 7 vs 6.2%; N = 1; P = 0.109). In research by the secondary infection rate was 13.3% in the early intubation group, while it was 22.2% in the late intubation group (P = 0.6). Additionally, AKI/RENAL failure was 21.3% in the early group and 18% in the late group (P = 0.1). A total of 16% of patients underwent tracheostomy in the early group, while the percentage rose to 25% in the late group (P = 0.1). Therefore, no statistically significant differences were found regarding secondary infection, Acute kidney injury (AKI), and interventional tracheotomy between intubation within 48 hours (early group) and intubation 48 hours after ICU admission (late group). Two studies did not describe patient complications.

## Discussion

The purpose of this systematic review was to explore the effects of intubation time on clinical outcomes in COVID-19 patients with ARDS. Questions to investigate included whether late intubation increases ICU mortality, length of ICU stay, and duration of ventilator use. Results indicated that early intubation could reduce mortality and length of ICU stay in patients with CARDS. However, intubation time did not affect the duration of continuous mechanical ventilation in patients. There were obvious differences between the definitions of early intubation


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and late intubation in the six included studies. In three studies early intubation was defined as intubation within 24 hours after diagnosis of ARDS. Two studies defined early intubation as within 48 hours of diagnosis, while defined it as within 1.27 days. Most studies defined the early intubation time as within 24 hours after admission to an ICU [36,37]. However, according to the systematic review reported by the definition of early/late intubation time had no statistical difference in all-cause mortality between the two groups and did not influence the clinical outcomes of COVID-19 patients. Therefore, for the sake of homogeneity, early intubation group and late intubation group data was extracted for analysis according to the respective definitions included in the current study. However, the definition of early/late intubation time directly affected the number of participants between the two groups.

**Table 5:** The Length of ICU Stays Among Patients in the Six Included Studies.

| First author | Country | Type of study | Patient population (N) | Early definition (h) | Late definition (h) | Early intubation (N) | Late intubation (N) | Median length of ICU stays (IQR) (Early) | Median length of ICU stays (IQR) (Late) | P-Value |
|---|---|---|---|---|---|---|---|---|---|---|
| Lee et al. [13] | Korea | Multi-center, retrospective, observational study | 47 | ＜24 | ＞24 | 23 | 16 | 13 (7–33) | 47 (13–74) | 0.101 |
| Schmidt et al. | France, Belgium, Switzerland | Multi-center, prospective cohort study | 2233 | ＜24 | ＞24 | 2003 | 230 | | | |
| Bavishi et al. [15] | United States | Retrospective cohort study | 54 | 4–24 | ＞24 | 30 | 24 | 12 (5–17) | 15 (10–19) | 0.13 |
| Zirpe et al. [16] | India | Retrospective observational study | 147 | ＜48 | ＞48 | 75 | 72 | 14 (9.7–21) | 16 (7–21.7) | 0.9 |
| Pandya et al. [17] | United States | Retrospective study | 75 | ≤1.27 days | ＞1.27 days | 37 | 38 | 7.38 (3.88-10.21) | 12.31 (7.75-19.96) | 0.001 |
| Vera et al. [18] | Chile | Observational, prospective, single-center study | 183 | ＜48 | ＞48 | 88 | 95 | 31 (17–45) | 36 (24–62) | 0.003 |

**The Effects of Early and Late Intubation**

The high mortality associated with late intubation may be related to lung injuries (P-SILI) unintentionally caused by the patients themselves. When COVID-19 patients' respiratory support was insufficient, their lung function deteriorated in the first week [38]. ARDS is characterized by non-cardiogenic pulmonary oedema, decreased exchange volume of hypoxic blood, and normal gas related to V/Q imbalance, which leads to low respiratory compliance. Hypoxemia may cause patients to inhale spontaneously and violently, leading to lung injury caused by high trans-pulmonary pressure. Early intubation with pulmonary protective ventilation can prevent P-SILI [39]. In a study including 457 ARDS patients, the 60-day mortality rate of the late intubation subgroup (56%) was significantly higher than that of the early intubation group (36%) [40]. The mortality rate of the late intubation group continued to rise during the 2-year follow-up period, which was consistent with the results of the current study.

Chinese critical care experts also suggested that tracheal intubation should be done when critically ill patients are asymptomatic (persistent respiratory distress and/or hypoxemia) after standard oxygen therapy, which was also referred to in the COVID-19 guidelines for patient treatment [41]. Given the high risk of non-invasive respiratory support failure and the risk of virus particle atomization [42], Brown et al. also recommended that early tracheal intubation be performed for patients with respiratory failure who need ventilation support. Other factors influencing death included BMI, age, Sequential Organ Failure Assessment (SOFA) Score, and (Acute Physiology, Age, and Chronic Health Evaluation (APACHE)); however, no statistical difference was found between the two groups in the early/late stage. In a study by Pandya et al. The included population was characterized by a nasopharyngeal swab-confirmed COVID-19 patient with a mean age of 65 years. A median BMI of 31 was observed in the study, and all patients were more than 50% of the standard BMI and could be categorized as 'obese'.

These were risk factors associated with mortality. In this study, the mortality rate of patients with mechanical ventilation was as high as 49%. The median age of non-survivors was higher than that of survivors (70 VS 59, p = 0.0006). The median ages of


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patients in the six included studies were 70, 63, 60, 59, 65, and 61.5, all of which were higher than 59. Therefore, elderly COVID ADRS patients were found to have a higher mortality rate. Compared with the United States, whose patients had a mortality rate of 16.6%, India's mortality rate was much higher at 68.7%, which may be related to the level of economic development and medical care [43]. Overall, this systematic review found that patients with early intubation were prone to more severe illness, organ dysfunction, and higher SOFA and APACHE scores when diagnosed with ARDS compared to those with late intubation. These results may have great significance in clinical practice, by providing strong evidence for researchers and clinicians to consider when choosing when to intubate COVID-19 ARDS patients. This can assist in rationalizing the allocation of medical resources and reduce the mortality of patients.

**Agreements and Disagreements with Other Studies and Reviews**

No similar systematic reviews were found pertaining to the topic of this article. Navas-Blanco and Dudaryk (2020) agreed that early intubation can prevent adverse consequences due to delayed intubation in patients with CARDS. Two studies recommend early intubation for COVID-19 ARDS patients. However, a recent review by Papoutsi et al. found no statistically detectable difference in all-cause mortality between patients undergoing either early or late intubation (3981 deaths; 45.4% versus 39.1%; RR 1.07 95% CI 0.99-1.15 p = 0.08). The same was true of MV duration (1892; MD-0.58 days, 95% CI -3.06 to 1.89 days, p = 0.65). Intubation time may have had no effect on the mortality and morbidity of critically ill COVID-19 patients, which was inconsistent with the results summarized in this systematic review. In a study by Papoutsi et al. (2021), participants were critically ill patients with COVID-19. However, the population in this systematic review included ARDS patients with COVID-19.

## Critique and Limitation

There are a few notable limitations to this study. For one, the reviewers only searched English-language articles, which can potentially lead to language bias. There may perhaps be articles related to this topic in other languages, but if so, these would have been excluded from the current review. In terms of secondary outcome data extraction, we contacted the authors of the six included studies by email, but failed to obtain specific data on length of ICU stays and MV duration. Therefore, the reliability of secondary measurement results may be reduced.

## Conclusion

The findings of this systematic review conclude that early intubation for mechanical ventilation is beneficial to patients with COVID-19 ARDS. However, it appears that early intubation cannot reduce the overall duration of mechanical ventilation. The authors recommend immediate tracheal intubation for patients with moderate to severe COVID-19 ARDS. The treatment and management strategies of ARDS patients have been the continuing focus of researchers. In the face of COVID-19 pandemic, decreasing COVID-19 ARDS patients' mortality remains an unsolved problem that needs further investigation. Further work is needed to improve research design and solve the problem of high heterogeneity and provide higher quality evidence.



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## Appendix 1

**Cinahl Search Strategy**

| Search ID# | Search Terms | Search Options | Last Run Via | Results |
|---|---|---|---|---|
| S24 | S6 AND S10 AND S17 AND S23 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 29 |
| S23 | S18 OR S19 OR S20 OR S21 OR S22 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 1,096,190 |
| S22 | "delay" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 39,485 |
| S21 | "late" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 72,941 |
| S20 | "early" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 345,693 |
| S19 | "Time-to-Treatments" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 0 |
| S18 | (MH "Time") OR "time" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 768,665 |
| S17 | S11 OR S12 OR S16 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 29,372 |
| S16 | S11 AND S15 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 637 |
| S15 | S13 OR S14 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 2,480 |
| S14 | "High flow nasal cannula" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 769 |
| S13 | "Noninvasive ventilation" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 1,821 |
| S12 | (MH "Ventilators, Mechanical") OR "invasive mechanical ventilation" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete | 4,356 |



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| | | | | |
|---|---|---|---|---|
| S11 | (MH "Intubation, Intratracheal") OR "intubation" | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 25,428 |
| S10 | S7 OR S8 OR S9 | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 17,318 |
| S9 | (MH "Acute Lung Injury") OR "Acute Lung Injury" | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 3,768 |
| S8 | "Acute respiratory distress syndrome" | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 11,266 |
| S7 | (MH "Respiratory Distress Syndrome") OR (MH "Severe Acute Respiratory Syndrome") | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 6,126 |
| S6 | S1 OR S2 OR S3 OR S4 OR S5 | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 51,948 |
| S5 | "Sars-cov-2" | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 9,333 |
| S4 | "Coronavirus 2019" | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 512 |
| S3 | "Covid-19 pandemic" | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 32,864 |
| S2 | (MH "SARS-CoV-2") | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 582 |
| S1 | (MH "COVID-19") | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete | 19,567 |

**Medline Search Strategy**

| Search ID# | Search Terms | Search Options | Last Run Via | Results |
|---|---|---|---|---|
| S25 | S6 AND S11 AND S18 AND S24 | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 174 |
| S24 | S19 OR S20 OR S21 OR S22 OR S23 | Expanders - Apply related words; Apply equivalent subjects.<br>Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - MEDLINE | 6,009,819 |


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| | | | | |
|---|---|---|---|---|
| S23 | "delay" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 194,650 |
| S22 | "late" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 450,850 |
| S21 | "early" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 1,707,963 |
| S20 | (MH "Time-to-Treatment") | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 8,957 |
| S19 | (MH "Time") OR "time" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 4,411,143 |
| S18 | S12 OR S13 OR S17 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 93,573 |
| S17 | S12 AND S16 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 966 |
| S16 | S14 OR S15 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 4,027 |
| S15 | "High flow nasal cannula" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 1,483 |
| S14 | (MH "Noninvasive Ventilation") | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 2,867 |
| S13 | (MH "Ventilators, Mechanical") OR "invasive mechanical ventilation" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 12,659 |
| S12 | "intubation" OR (MH "Intubation, Intratracheal") | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 82,217 |



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| | | | | |
|---|---|---|---|---|
| S11 | S7 OR S8 OR S9 OR S10 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 56,467 |
| S10 | (MH "Acute Lung Injury") OR "Acute Lung Injury" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 16,754 |
| S9 | "Acute respiratory distress syndrome" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 36,176 |
| S8 | (MH "Severe Acute Respiratory Syndrome") | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 5,619 |
| S7 | (MH "Respiratory Distress Syndrome") | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 21,903 |
| S6 | S1 OR S2 OR S3 OR S4 OR S5 | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 156,116 |
| S5 | ""sars-cov-2" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 116,207 |
| S4 | "Coronavirus 2019" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 1,269 |
| S3 | "Covid-19 pandemic" | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 55,842 |
| S2 | (MH "SARS-CoV-2") | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 87,085 |
| S1 | (MH "COVID-19") | Expanders - Apply related words; Apply equivalent subjects. Search modes - Boolean/Phrase | Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE | 111,529 |



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**ProQuest Search Strategy**

| Set# | Searched for | Databases | Results |
|---|---|---|---|
| S1 | main subject (COVID-19) | Coronavirus Research Database | 51710 |
| S2 | SARS-CoV-2 | Coronavirus Research Database | 46791 |
| S3 | covid-19 pandemic | Coronavirus Research Database | 77037 |
| S4 | coronavirus 2019 | Coronavirus Research Database | 55624 |
| S5 | main subject (COVID-19) OR SARS-CoV-2 OR (Covid-19 pandemic) OR (coronavirus 2019) | Coronavirus Research Database<br>These databases are searched for part of your query. | 102656 |
| S6 | main subject (coronavirus 2019Respiratory Distress Syndrome) OR main subject (severe acute respiratory syndrome) | Coronavirus Research Database | 20723 |
| S7 | acute respiratory distress syndrome | Coronavirus Research Database | 12883 |
| S8 | main subject (Acute Lung Injury) OR (acute lung injury) | Coronavirus Research Database | 8946 |
| S9 | (Main subject (coronavirus 2019Respiratory Distress Syndrome) OR main subject (severe acute respiratory syndrome)) OR (acute respiratory distress syndrome) OR (main subject (Acute Lung Injury) OR (acute lung injury)) | Coronavirus Research Database<br>These databases are searched for part of your query. | 31230 |
| S10 | main subject (Intubation, Intratracheal) OR Intubation | Coronavirus Research Database | 4198 |
| S11 | main subject (Ventilators, Mechanical) OR (invasive mechanical ventilation) | Coronavirus Research Database | 3795 |
| S12 | (Noninvasive ventilation) OR (high flow nasal cannula) | Coronavirus Research Database | 2017 |
| S13 | (Main subject (Intubation, Intratracheal) OR Intubation) AND ((noninvasive ventilation) OR (high flow nasal cannula)) | Coronavirus Research Database<br>These databases are searched for part of your query. | 947 |
| S14 | (Main subject (Intubation, Intratracheal) OR Intubation) OR (main subject (Ventilators, Mechanical) OR (invasive mechanical ventilation)) OR ((main subject (Intubation, Intratracheal) OR Intubation) AND ((noninvasive ventilation) OR (high flow nasal cannula))) | Coronavirus Research Database<br>These databases are searched for part of your query. | 6593 |
| S15 | main subject (Time) OR Time | Coronavirus Research Database | 94492 |
| S16 | Time-to-treatment | Coronavirus Research Database | 141 |
| S17 | early | Coronavirus Research Database | 63514 |
| S18 | late | Coronavirus Research Database | 69675 |
| S19 | delay | Coronavirus Research Database | 14656 |
| S20 | (Main subject (Time) OR Time) OR Time-to-treatment OR early OR late OR delay | Coronavirus Research Database<br>These databases are searched for part of your query. | 103112 |



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| | | | |
|---|---|---|---|
| S21 | (main subject(COVID-19) OR SARS-CoV-2 OR (covid-19 pandemic) OR (coronavirus 2019)) AND ((main subject(coronavirus 2019Respiratory Distress Syndrome) OR main subject(Severe Acute Respiratory Syndrome)) OR (acute respiratory distress syndrome) OR (main subject(Acute Lung Injury) OR (acute lung injury))) AND ((main subject(Intubation, Intratracheal) OR Intubation) OR (main subject(Ventilators, Mechanical) OR (invasive mechanical ventilation)) OR ((main subject(Intubation, Intratracheal) OR Intubation) AND ((noninvasive ventilation) OR (high flow nasal cannula)))) AND ((main subject(Time) OR Time) OR Time-to-treatment OR early OR late OR delay) | Coronavirus Research Database<br>These databases are searched for part of your query. | 4304 |
| S22 | (main subject(COVID-19) OR SARS-CoV-2 OR (covid-19 pandemic) OR (coronavirus 2019)) AND ((main subject(coronavirus 2019Respiratory Distress Syndrome) OR main subject(Severe Acute Respiratory Syndrome)) OR (acute respiratory distress syndrome) OR (main subject(Acute Lung Injury) OR (acute lung injury))) AND ((main subject(Intubation, Intratracheal) OR Intubation) OR (main subject(Ventilators, Mechanical) OR (invasive mechanical ventilation)) OR ((main subject(Intubation, Intratracheal) OR Intubation) AND ((noninvasive ventilation) OR (high flow nasal cannula)))) AND ((main subject(Time) OR Time) OR Time-to-treatment OR early OR late OR delay) AND steeplejack("Scholarly Journals") | Coronavirus Research Database<br>These databases are searched for part of your query. | 4023 |
| S23 | (main subject(COVID-19) OR SARS-CoV-2 OR (covid-19 pandemic) OR (coronavirus 2019)) AND ((main subject(coronavirus 2019Respiratory Distress Syndrome) OR main subject(Severe Acute Respiratory Syndrome)) OR (acute respiratory distress syndrome) OR (main subject(Acute Lung Injury) OR (acute lung injury))) AND ((main subject(Intubation, Intratracheal) OR Intubation) OR (main subject(Ventilators, Mechanical) OR (invasive mechanical ventilation)) OR ((main subject(Intubation, Intratracheal) OR Intubation) AND ((noninvasive ventilation) OR (high flow nasal cannula)))) AND ((main subject(Time) OR Time) OR Time-to-treatment OR early OR late OR delay) AND (stype.exact("Scholarly Journals") AND pd(20191201-20211028)) | Coronavirus Research Database<br>These databases are searched for part of your query. | 3973 |
| S24 | (main subject(COVID-19) OR SARS-CoV-2 OR (covid-19 pandemic) OR (coronavirus 2019)) AND ((main subject(coronavirus 2019Respiratory Distress Syndrome) OR main subject(Severe Acute Respiratory Syndrome)) OR (acute respiratory distress syndrome) OR (main subject(Acute Lung Injury) OR (acute lung injury))) AND ((main subject(Intubation, Intratracheal) OR Intubation) OR (main subject(Ventilators, Mechanical) OR (invasive mechanical ventilation)) OR ((main subject(Intubation, Intratracheal) OR Intubation) AND ((noninvasive ventilation) OR (high flow nasal cannula)))) AND ((main subject(Time) OR Time) OR Time-to-treatment OR early OR late OR delay) AND (stype.exact("Scholarly Journals") AND la.exact("ENG") AND pd(20191201-20211028)) | Coronavirus Research Database<br>These databases are searched for part of your query. | 3971 |
| S25 | (Cohort study) OR (Randomized Controlled Trials) | Coronavirus Research Database | 30239 |
| S26 | ((main subject(COVID-19) OR SARS-CoV-2 OR (covid-19 pandemic) OR (coronavirus 2019)) AND ((main subject(coronavirus 2019Respiratory Distress Syndrome) OR main subject(Severe Acute Respiratory Syndrome)) OR (acute respiratory distress syndrome) OR (main subject(Acute Lung Injury) OR (acute lung injury))) AND ((main subject(Intubation, Intratracheal) OR Intubation) OR (main subject(Ventilators, Mechanical) OR (invasive mechanical ventilation)) OR ((main subject(Intubation, Intratracheal) OR Intubation) AND ((noninvasive ventilation) OR (high flow nasal cannula)))) AND ((main subject(Time) OR Time) OR Time-to-treatment OR early OR late OR delay) AND (stype.exact("Scholarly Journals") AND la.exact("ENG") AND pd(20191201-20211028))) AND ((Cohort study) OR (Randomized Controlled Trials)) | Coronavirus Research Database<br>These databases are searched for part of your query. | 3033 |


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## Web of Science Search Strategy

S24 #5 AND #10 AND #17 AND #23 | TimeSpan: 2019-12-01 to 2021-10-29 (Publication Date)
Web of Science Core CollectionShow editionS464
S23 #18 OR #19 OR #20 OR #21 OR #22 Web of Science Core CollectionShow editionS1, 754, 072
S22 ALL=(delay) Web of Science Core CollectionShoweditionS
107, 405
S21 ALL=(early) Web of Science Core CollectionShoweditionS
3, 215, 413
S20 ALL=(late) Web of Science Core CollectionShoweditionS
1, 474, 144
S19 ALL=(Time-TO-Treatment) Web of Science Core CollectionShow
editionS4, 211
S18 ALL=(Time) Web of Science Core CollectionShow editionS8, 727, 652
S17 #11 OR #12 OR #16 Web of Science Core CollectionShoweditionS
63, 920
S16 #15 AND #11 Web of Science Core CollectionHide editionS2, 007
S15 #13 OR #14 Web of Science Core CollectionShow editionS10, 955
S14 ALL=(high flow naSal cannula) Web of Science Core CollectionShow editionS2, 302
S13 ALL=(NoninvaSive Ventilation) Web of Science Core Collection
Show editionS9, 296
S12 (ALL=(VentilatorS, Mechanical)) OR ALL=(invaSive mechanicalventilation) Web of Science Core
CollectionShow editionS18, 124
S11 (ALL=(intubation)) OR ALL=(Intubation, Intratracheal) Web of Science Core CollectionShow
editionS47, 894
S10 #6 OR #7 OR #8 OR #9 Web of Science Core CollectionShow
editionS99, 930
S9 ALL=(Acute Lung Injury) Web of Science Core CollectionShow editionS42, 195
S8 ALL=(acute reSpiratorydiStreSSSyndrome) Web of Science Core CollectionShow editionS27, 618
S7 ALL=(Severe Acute ReSpiratorySyndrome) Web of Science Core CollectionShow editionS33, 104
S6 ALL=(ReSpiratoryDiStreSSSyndrome) Web of Science Core CollectionShoweditionS47, 754
S5 #1 OR #2 OR #3 OR #4 Web of Science Core CollectionShoweditionS200, 600
S4 ALL=(coronaviruS 2019) Web of Science Core CollectionShoweditionS40, 642
S3 ALL=(covid-19 pandemic) Web of Science Core CollectionShow
editionS94, 203
S2 SARS-CoV-2 (All FieldS) Web of Science Core CollectionShoweditionS56, 088
S1 COVID-19 (All FieldS) Web of Science Core CollectionShoweditionS186, 863

## Pubmed Searchhistory

| Search nu | Query | Sort By | Filters | Search Details | Results | Time |
|---|---|---|---|---|---|---|
| 31 | #23 AND #30 | | from 2019 | ((("covid 19"[MeSH Terms] AND 201 | 334 | 16:04:36 |
| 30 | #24 OR #25 OR #26 OR #27 OR #28 OF | | from 2019 | (("time"[MeSH Terms] AND 2019/12/ | 726,759 | 16:04:15 |
| 29 | Time-to-Treatment[MeSH Terms] | | from 2019 | ("time to treatment"[MeSH Terms]) | 2,470 | 16:03:41 |
| 28 | early | | from 2019 | ("early"[All Fields]) AND (2019/1 | 217,184 | 16:03:14 |
| 27 | late | | from 2019 | ("late"[All Fields]) AND (2019/12 | 47,613 | 16:02:53 |
| 26 | delay | | from 2019 | ("delay"[All Fields] OR "delayed" | 66,484 | 16:02:38 |
| 25 | time | | from 2019 | ("time"[MeSH Terms] OR "time"[All | 501,228 | 16:02:20 |
| 24 | Time[MeSH Terms] | | from 2019 | ("time"[MeSH Terms]) AND (2019/12 | 43,741 | 16:01:47 |
| 23 | #6 AND #12 AND #22 | | from 2019 | ((("covid 19"[MeSH Terms] AND 201 | 788 | 16:01:02 |
| 22 | #19 OR #21 | | from 2019 | (((("intubation, intratracheal"[M | 12,187 | 16:00:19 |
| 21 | #14 AND #20 | | from 2019 | (("intubate"[All Fields] OR "intu | 549 | 15:59:51 |
| 20 | #17 OR #18 | | from 2019 | (("noninvasive ventilation"[MeSH | 2,664 | 15:59:27 |
| 19 | #13 OR #14 OR #15 OR #16 | | from 2019 | (("intubation, intratracheal"[MeS | 12,187 | 15:59:04 |
| 18 | high-flow | | from 2019 | ("high-flow"[All Fields]) AND (20 | 2,082 | 15:58:44 |
| 17 | Noninvasive Ventilation[MeSH Terms | | from 2019 | ("noninvasive ventilation"[MeSH T | 785 | 15:58:09 |
| 16 | invasive mechanical ventilation | | from 2019 | (("invasibility"[All Fields] OR " | 3,000 | 15:57:39 |
| 15 | Ventilators, Mechanical[MeSH Terms | | from 2019 | ("ventilators, mechanical"[MeSH T | 664 | 15:57:02 |
| 14 | intubation | | from 2019 | ("intubate"[All Fields] OR "intub | 9,154 | 15:56:18 |
| 13 | Intubation Intratracheal[MeSH Terr | | from 2019 | ("intubation, intratracheal"[MeSH | 2,321 | 15:55:46 |
| 12 | #7 OR #8 OR #9 OR #10 OR #11 | | from 2019 | (("respiratory distress syndrome" | 12,991 | 15:55:06 |
| 11 | acute lung injury | | from 2019 | ("acute lung injury"[MeSH Terms] | 4,321 | 15:54:37 |
| 10 | Acute Lung Injury[MeSH Terms] | | from 2019 | ("acute lung injury"[MeSH Terms]) | 980 | 15:54:16 |
| 9 | acute respiratory distress syndrom | | from 2019 | ("respiratory distress syndrome"[ | 8,931 | 15:53:35 |
| 8 | Severe Acute Respiratory Syndrome | | from 2019 | ("severe acute respiratory syndro | 1,173 | 15:53:06 |
| 7 | Respiratory Distress Syndrome[MeSH | | from 2019 | ("respiratory distress syndrome"[ | 3,212 | 15:52:23 |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 | | from 2019 | (("covid 19"[MeSH Terms] AND 2019 | 188,853 | 15:51:23 |
| 5 | sars-cov-2 | | from 2019 | ("sars cov 2"[MeSH Terms] OR "sar | 119,091 | 15:50:51 |
| 4 | coronavirus 2019 | | from 2019 | ((("coronavirus"[MeSH Terms] OR "c | 45,209 | 15:50:11 |
| 3 | covid-19 pandemic | | from 2019 | ("covid 19"[MeSH Terms] OR "covid | 182,368 | 15:49:28 |
| 2 | SARS-CoV-2[MeSH Terms] | | from 2019 | ("sars cov 2"[MeSH Terms]) AND (2 | 89,411 | 15:48:58 |
| 1 | COVID-19[MeSH Terms] | | from 2019 | ("covid 19"[MeSH Terms]) AND (201 | 114,270 | 15:47:27 |


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## Appendix 2

| Author, Years | The reason of exclusion |
|---|---|
| Roedl et al. | It included 163 patients with COVID-19 ARDS, but which did not group these patients and describe the timing and outcomes of intubation |
| Hernandez-Romieuet al. [11] | It did not distinguish between patients with COVID-19 ARDS |
| Panadero et al. | It mainly included patients with COVID-19 ARDS who underwent endotracheal intubation after HFNC treatment failed |
| Zhang et al. [38] | It mainly compared the survival and death groups of PATIENTS with COVID-19 ARDS |
| Matta et al. | It included patients with severe COVID-19 and did not identify who met the criteria for ARDS |
| Siempos et al. | It included patients with acute hypoxemic COVID-19 and compared patients with early intubation and patients with late intubation, but they were not patients with ARDS. |

## Appendix 3

**Etailed Newcastle-Ottawa Scale of each included cohort study.**

| | Selection | | | | Comparability | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Representativeness of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Adjust for the most important risk factors | Adjust for other risk factors | Assessment of outcome | Follow-up length | Loss to follow-up rate | Total quality score |
| Lee et al. [2020] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | **8** |
| Schmidt et al [2020] | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 8 |
| Bavishi et al [2021] | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | **7** |
| Zirpe et al [2021] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | **8** |
| Pandya et al [2021] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | **8** |
| Vera et al [2021] | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | **7** |

The quality of included studies was assessed by the Newcastle Ottawa scale. A study can be awarded a maximum of one star for each. numbered item within the Selection and Outcome categories and a maximum of two stars for Comparability.

**Selection:**

1) Representativeness of exposed cohort: 1, study population truly or somewhat representative of a community/ population-based study; 0, study population was sampled from a special population, that is, population from a company, hospital patients, data from the health insurance company or health examination organization, nurses.

2) Selection of non-exposed cohort: 1, drawn from the same community as the exposed cohort.

3) Ascertainment of exposure: 1, Clearly define early intubation time and late intubation time 0, The time of intubation was not clearly. defined.

4) Demonstration that outcome was not present at start of study: 1, SOFA score or APACHE II score have not significant difference

**Comparability:**

1) Whether a study adjusted for the most important factors deliberately.


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DOI: 10.19080/AJPN.2023.12.555905

2) Whether a study adjusted for other important risk factors.

**Outcome:**

1) Assessment of outcome: 1, The mortality events were confirmed by medical records or record linkage; 0, self-reported.

2) Was follow-up long enough for outcomes to occur: 1, duration of follow-up >=3 months; 0 if duration of follow-up <3 months.

3) Loss to follow-up rate: 1, complete follow-up or loss to follow up rate <=20 %; 0, follow-up rate < 80% or no description of those lost.

**Modified Newcastle - Ottawa Quality Assessment Scale**

**Cohort Studies**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and

Outcome categories. A maximum of two stars can be given for Comparability.

Study1: Lee et al (2020)

| No. | Criterion | Decision rule | Score (*=1) no*=0) | Location in text |
|---|---|---|---|---|
| | **SELECTION** | | | |
| 1 | Representativeness of the exposed cohort | a) Truly representative of the average _____ (describe) in the community *↓<br>b) Somewhat representative of the average _____ in the community *↓<br>c) Selected group of users eg nurses, volunteers<br>d) No description of the derivation of the cohort | 1 | Data were collected from consecutive hospitalized adults (≥18 years old) with laboratory-confirmed SARS-CoV-2 infection who subsequently were admitted to ICUs at the three tertiary referral hospitals in Daegu, Korea between 17 February and 23 April 2020 |
| 2 | Selection of the non-exposed cohort | a) Drawn from the same community as the exposed cohort *↓<br>b) Drawn from a different source<br>c) No description of the derivation of the non exposed cohort | 1 | Come from ICUs at the same three tertiary referral hospitals |
| 3 | Ascertainment of exposure | a) Secure record (e.g., surgical records) *↓<br>b) Structured interview*↓<br>c) Written self-report<br>d) No description | 1 | Early intubation: intubated/mechanically ventilated and meeting ARDS criteria on the same day (within 24 h)<br>late intubation: not intubated on the day of ARDS diagnosis, but intubated on a subsequent study day |
| 4 | Demonstration that outcome of interest was not present at the start of the study | a) Yes*<br>b) No or not explicitly stated | 1 | SOFA score: Early intubation 3 (2–7); -4), P=0.336<br>Late intubation 3 (2-4), P=0.336<br>APACHE II score: Early intubation 15 (10–17) Late intubation 15 (10–17), P=0.252<br>No significant difference |
| | **COMPARABILITY** | | | |
| 1 | Comparability of cohorts based on the design or analysis | a) Study controls for age and sex (select the most important factor) *↓<br>b) Study controls for any additional factor various sociodemographic and lifestyle variables *(These criteria could be modified to indicate specific control for a second important factor.) | 1<br>1 | Age, sex, comorbid conditions, and presenting symptoms did not show significant differences between the groups. |


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DOI: 10.19080/AJPN.2023.12.555905

| | | | | |
|---|---|---|---|---|
| | OUTCOME | | | |
| 1 | Assessment of outcome | a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g., imaging, structured mortality data, etc.) * b) Record linkage (e.g., identified through medical records) * c) Self-report with no reference to original structured injury data or imaging d) No description | 1 | Mortality data were obtained from medical records by ICU physicians |
| 2 | Was follow-up long enough for outcomes to occur? | a) Yes (≥3 months) * b) No (<3 months) | 0 | Median follow-up duration was 46 days |
| 3 | Adequacy of follow up of cohorts | a) Complete follow up – all participants accounted for* b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up, or description provided of those lost) * c) Follow up rate <85% and no description of those lost provided d) No statement | 1 | At the end of the study period, four patients (8.5%) remained hospitalized, 21 (44.7%) had died in the hospital, and 22 (46.8%) had been discharged |
| | | SCORE | 8 | |

**Schmidt et al (2020)**

| No. | Criterion | Decision rule | Score (*=1, no*=0) | Location in text |
|---|---|---|---|---|
| | SELECTION | | | |
| 1 | Representativeness of the exposed cohort | a) truly representative of the average _____ (describe) in the community *↓ b) somewhat representative of the average _____ in the community *↓ c) selected group of users e.g., nurses, volunteers d) no description of the derivation of the cohort | 1 | COVID-ICU is a multi-canter, prospective cohort study conducted in 138 hospitals in France, Belgium, and Switzerland. |
| 2 | Selection of the non-exposed cohort | a) drawn from the same community as the exposed cohort *↓ b) drawn from a different source c) no description of the derivation of the non-exposed cohort | 1 | Come from ICUs at the same 138 hospitals |
| 3 | Ascertainment of exposure | a) secure record (e.g., surgical records) *↓ b) structured interview*↓ c) written self-report d) no description | 1 | Early intubation: ARDS was reported in 2233 patients on mechanical ventilation (invasive or non-invasive) on ICU Day 1 late intubation: On day-1, non-invasive ventilation were applied to 230/4109 (6%) patients |
| 4 | Demonstration that outcome of interest was not present at the start of the study | a) Yes* b) No or not explicitly stated | 0 | SOFA score, APACHE II score: At ICU admission, their SAPS II, and SOFA scores were 37 (28–50), and 5 (3–8), |
| | COMPARABILITY | | | |


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| | | | | |
|---|---|---|---|---|
| 1 | Comparability of cohorts on the basis of the design or analysis | a) study controls for age and sex (select the most important factor) * ↓<br>b) study controls for any additional factor various sociodemographic and lifestyle variables *(This criterion could be modified to indicate specific control for a second important factor.) | 1<br>1 | At ICU admission, their median age was 63 (54–71) years.<br>Only 4% of patients were active smokers and only 5% had concomitant bacterial pneumonia at ICU admission. |
| | **OUTCOME** | | | |
| 1 | Assessment of outcome | a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g., imaging, structured mortality data, etc.) *<br>b) record linkage (e.g., identified through medical records) *<br>c) Self-report with no reference to original structured injury data or imaging<br>d) No description | 1 | Mortality data were obtained from medical records by ICU physicians |
| 2 | Was follow-up long enough for outcomes to occur? | a) Yes (≥3 months) *<br>b) No (<3 months) | 1 | 90-day mortality was 820/2233 (37%) |
| 3 | Adequacy of follow up of cohorts | a) Complete follow up – all participants accounted for*<br>b) Subjects lost to follow up unlikely to introduce bias (< 20%<br>lost to follow up, or description provided of those lost) *<br>c) Follow up rate <85% and no description of those lost provided<br>d) No statement | 1 | 90-day mortality was 820/2233 (37%), 90-day mortality was 96/230 (42%) in patients who received standard non-invasive ventilation at day-1 |
| | | **SCORE** | **8** | |

**Bavishi et al (2021)**

| No. | Criterion | Decision rule | Score (*=1, no*=0) | Location in text |
|---|---|---|---|---|
| | **SELECTION** | | | |
| 1 | Representativeness of the exposed cohort | a) truly representative of the average _____ (describe) in the community *↓<br>b) somewhat representative of the average _____ in the community *↓<br>c) selected group of users e.g., nurses, volunteers<br>d) no description of the derivation of the cohort | 1 | All patients intubated for coronavirus disease in Northwestern Memorial hospital ICUs on 2019 between March 2020 and June 2020. |
| 2 | Selection of the non-exposed cohort | a) drawn from the same community as the exposed cohort *↓<br>b) drawn from a different source<br>c) no description of the derivation of the non-exposed cohort | 1 | Come from the same ICU |


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| | | | | |
|---|---|---|---|---|
| 3 | Ascertainment of exposure | a) secure record (e.g., surgical records) *↓<br>b) structured interview* ↓<br>c) written self-report<br>d) no description | 1 | Data were stratified based on time from hospital admission to time of intubation. The "early intubation cohort" was defined as those subjects intubated between 4 and 24 hours after admission the "late intubation cohort" consisted of subjects intubated between 5 and 10 days after admission |
| 4 | Demonstration that outcome of interest was not present at the start of the study | a) Yes*<br>b) No or not explicitly stated | 1 | There was no difference in Sequential Organ Failure Assessment (SOFA) scores between the cohorts at time of ICU admission |
| | **COMPARABILITY** | | | |
| 1 | Comparability of cohorts on the basis of the design or analysis | a) study controls for age and sex (select the most important factor) *↓<br>b) study controls for any additional factor various sociodemographic and lifestyle variables *(These criteria could be modified to indicate specific control for a second important factor.) | 1<br>0 | Age, sex, comorbid conditions, and presenting symptoms did not show significant differences between the groups. Body mass index, Hypertension, Chronic kidney disease, End-stage renal disease and Smoking history show significant differences between the groups |
| | **OUTCOME** | | | |
| 1 | Assessment of outcome | a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g., imaging, structured mortality data, etc.) *<br>b) record linkage (e.g., identified through medical records)*<br>c) Self-report with no reference to original structured injury data or imaging<br>d) No description | 1 | Data were obtained from the electronic medical record with a combination of automatic extraction using the electronic data warehouse. |
| 2 | Was follow-up long enough for outcomes to occur? | a) Yes (≥3 months) *<br>b) No (<3 months) | 0 | length of follow-up is extracted from the time frame (2019 between March 2020 and June 2020.) |
| 3 | Adequacy of follow up of cohorts | a) Complete follow up – all participants accounted for*<br>b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up, or description provided of those lost) *<br>c) Follow up rate <85% and no description of those lost provided<br>d) No statement | 1 | Mortality: Early intubation 2 (6%) Late intubation 7 (29%) P<0.001a |
| | | **SCORE** | **7** | |

**Zirpe et al (2021)**

| No. | Criterion | Decision rule | Score (*=1, no*=0) | Location in text |
|---|---|---|---|---|
| | **SELECTION** | | | |


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DOI: 10.19080/AJPN.2023.12.555905

| | | | | |
|---|---|---|---|---|
| 1 | Representativeness of the exposed cohort | a) truly representative of the average _____ (describe) in the community *↓<br>b) somewhat representative of the average _____ in the community *↓<br>c) selected group of users e.g., nurses, volunteers<br>d) no description of the derivation of the cohort | 1 | All patients admitted to intensive care unit of a tertiary care hospital in Pune, India between April 1, 2020, and October 15, 2020 |
| 2 | Selection of the non-exposed cohort | a) drawn from the same community as the exposed cohort *↓<br>b) drawn from a different source<br>c) no description of the derivation of the non-exposed cohort | 1 | Come from ICUs at the same intensive care unit |
| 3 | Ascertainment of exposure | a) secure record (e.g., surgical records) *↓<br>b) structured interview* ↓<br>c) written self-report<br>d) no description | 1 | Early intubation: within 48 hours of admission to critical care unit<br>late intubation: after 48 hours of admission to critical care unit |
| 4 | Demonstration that outcome of interest was not present at the start of the study | a) Yes*<br>b) No or not explicitly stated | 1 | The median qSOFA score assessed on admission to critical care unit was 1 (IQR, 1–2) and was comparable in both the groups |
| | **COMPARABILITY** | | | |
| 1 | Comparability of cohorts on the basis of the design or analysis | a) study controls for age and sex (select the most important factor) *↓<br>b) study controls for any additional factor various sociodemographic and lifestyle variables *(These criteria could be modified to indicate specific control for a second important factor.) | 1<br>1 | Age, sex, comorbid conditions, and presenting symptoms did not show significant differences between the groups. |
| | **OUTCOME** | | | |
| 1 | Assessment of outcome | a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g., imaging, structured mortality data, etc.) *<br>b) record linkage (e.g., identified through medical records) *<br>c) Self-report with no reference to original structured injury data or imaging<br>d) No description | 1 | Patient data were obtained retrospectively from patient files, nursing charts, and treatment sheets |
| 2 | Was follow-up long enough for outcomes to occur? | a) Yes (≥3 months) *<br>b) No (<3 months) | 0 | length of follow-up is extracted from the time frame |
| 3 | Adequacy of follow up of cohorts | a) Complete follow up – all participants accounted for *<br>b) Subjects lost to follow up unlikely to introduce bias (< 20%<br>lost to follow up, or description provided of those lost) *<br>c) Follow up rate <85% and no description of those lost provided<br>d) No statement | 1 | Mortality was 60% in those intubated within 48 hours of critical care unit admission (early group) compared to 77.7% in those of delayed group |
| | | **SCORE:** | **8** | |



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**Pandya et al. (2021)**

| No. | Criterion | Decision rule | Score (*=1, no*=0) | Location in text |
|---|---|---|---|---|
| | **SELECTION** | | | |
| 1 | Representativeness of the exposed cohort | a) truly representative of the average _____ (describe) in the community *↓<br>b) somewhat representative of the average _____ in the community *↓<br>c) selected group of users eg nurses, volunteers<br>d) no description of the derivation of the cohort | 1 | This retrospective study includes adult inpatients requiring invasive mechanical ventilation secondary to COVID-19 at Temple University Hospital between February and May 2020. Positive infection status was confirmed by polymerase chain reaction nasopharyngeal swab. |
| 2 | Selection of the non-exposed cohort | a) drawn from the same community as the exposed cohort *↓<br>b) drawn from a different source<br>c) no description of the derivation of the non-exposed cohort | 1 | Come from the same University Hospital |
| 3 | Ascertainment of exposure | a) secure record (e.g., surgical records) *↓<br>b) structured interview *↓<br>c) written self-report<br>d) no description | 1 | Patients were separated into an early intubation (≤1.27 days) or late intubation (>1.27 days) group for analysis. |
| 4 | Demonstration that outcome of interest was not present at the start of the study | a) Yes*<br>b) No or not explicitly stated | 1 | Lower static compliance (34.88 vs 40.68; P = .311) and higher VR (1.90 vs 1.57; P = .078) was noted in the late intubation group on day 0 |
| | **COMPARABILITY** | | | |
| 1 | Comparability of cohorts because of the design or analysis | a) study controls for age and sex (select the most important factor) *↓<br>b) study controls for any additional factor various sociodemographic and lifestyle variables *(These criteria could be modified to indicate specific control for a second important factor.) | 1<br>1 | Age and sex did not show significant differences between the groups.<br>Lower static compliance (34.88 vs 40.68; P = .311) and higher VR (1.90 vs 1.57; P = .078) was noted in the late intubation group on day 0, although these values were not statistically significant |
| | **OUTCOME** | | | |
| 1 | Assessment of outcome | a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g., imaging, structured mortality data, etc.) *<br>b) record linkage (e.g., identified through medical records)*<br>c) Self-report with no reference to original structured injury data<br>or imaging<br>d) No description | 1 | Data were collected from the electronic medical record |
| 2 | Was follow-up long enough for outcomes to occur? | a) Yes (≥3 months) *<br>b) No (<3 months) | 0 | As of data censoring on June 20, 2020 |
| 3 | Adequacy of follow up of cohorts | a) Complete follow up – all participants accounted for*<br>b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up, or description provided of those lost) *<br>c) Follow up rate <85% and no description of those lost provided<br>d) No statement | 1 | As of data censoring on June 20, 2020, 49% of all mechanically ventilated patients had died |
| | | **SCORE** | **8** | |



**How to cite this article:** Fu L, Xiaoqin Z, Long Cheng T, Lorraine M, Phillip D. Does the Timing of Intubation and IMV Impact Clinical Outcomes in Adult COVID-19 Patients with ARDS: A Systematic Review and Meta-Analysis. Acad J Ped Neonatol 2023; 12(5): 555905.
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**Study 6: Vera et al (2021)**

| No. | Criterion | Decision rule | Score (*=1, no*=0) | Location in text |
|---|---|---|---|---|
| | **SELECTION** | | | |
| 1 | Representativeness of the exposed cohort | a) truly representative of the average _____ (describe) in the community *↓<br>b) somewhat representative of the average _____ in the community *↓<br>c) selected group of users e.g., nurses, volunteers<br>d) no description of the derivation of the cohort | 1 | Patients with laboratory-confirmed SARS-CoV-2 infection and moderate to severe ARDS were consecutively included between March 17 and July 31, 2020. |
| 2 | Selection of the non-exposed cohort | a) drawn from the same community as the exposed cohort *↓<br>b) drawn from a different source<br>c) no description of the derivation of the non-exposed cohort | 1 | Came from the same ICU of the Clinical Hospital of the UC-CHRISTUS Health Network in Santiago |
| 3 | Ascertainment of exposure | a) secure record (e.g., surgical records) *↓<br>b) structured interview*↓<br>c) written self-report<br>d) no description | 1 | Early intubation: Eighty-eight patients (48%) were intubated before 48 h (early); late intubation: ninety-five (52%) after 48 h (late). According to ROC curve analyses from our data, the time of intubation was classified as early (<48 h) or late (≥48 h). |
| 4 | Demonstration that outcome of interest was not present at the start of the study | a) Yes*<br>b) No or not explicitly stated | 1 | SOFA score: Early intubation 6 [4–8]; Late intubation 4 [2–8], P=0.014<br>APACHE II score: Early intubation 12 [8–15] Late intubation 12 [8–15], P=0.354<br>Thoracic CT scan showed a predominance of ground-glass opacities, with no difference between groups. |
| | **COMPARABILITY** | | | |
| 1 | Comparability of cohorts based on the design or analysis | a) study controls for age and sex (select the most important factor) *↓<br>b) study controls for any additional factor various sociodemographic and lifestyle variables *(These criteria could be modified to indicate specific control for a second important factor.) | 0<br>1 | Early intubation: median age 59 [53–66] late intubation: 64 [55–71] P=0.013<br>comorbid conditions and presenting symptoms did not show significant differences between the groups. |
| | **OUTCOME** | | | |


How to cite this article: Fu L, Xiaoqin Z, Long Cheng T, Lorraine M, Phillip D. Does the Timing of Intubation and IMV Impact Clinical Outcomes in Adult COVID-19 Patients with ARDS: A Systematic Review and Meta-Analysis. Acad J Ped Neonatol 2023; 12(5): 555905.
DOI: 10.19080/AJPN.2023.12.555905

| | | | | |
|---|---|---|---|---|
| 1 | Assessment of outcome | a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g., imaging, structured mortality data, etc.) * b) record linkage (e.g., identified through medical records) * c) Self-report with no reference to original structured injury data or imaging d) No description | 1 | Data Collection. Data were recorded prospectively by the research team in an electronic worksheet during the patient's stay in the ICU. |
| 2 | Was follow-up long enough for outcomes to occur? | a) Yes (≥3 months) * b) No (<3 months) | 0 | length of follow-up is extracted from the time frame |
| 3 | Adequacy of follow up of cohorts | a) Complete follow up – all participants accounted for* b) Subjects lost to follow up unlikely to introduce bias (< 20% lost to follow up, or description provided of those lost) * c) Follow up rate <85% and no description of those lost provided d) No statement | 1 | Mortality was higher in patients intubated late [16(18%) versus 43(43%)], |
| | | **SCORE** | **7** | |

Cohort Studies: Very Good Studies: 9-10 points ; Good Studies: 7-8 points ; Satisfactory Studies: 5-6 points.

Unsatisfactory Studies: 0 to 4 points.




How to cite this article: Fu L, Xiaoqin Z, Long Cheng T, Lorraine M, Phillip D. Does the Timing of Intubation and IMV Impact Clinical Outcomes in Adult COVID-19 Patients with ARDS: A Systematic Review and Meta-Analysis. Acad J Ped Neonatol 2023; 12(5): 555905.
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**Appendix 4-data extraction**

| First author | Country | Type of study | Patient population(N) | Early definition (h) | Late definition (h) | Early intubation (N) | Late intubation(N) | mortality(early) | mortality(late) | Length of ICU stay, Days (Early) | Length of ICU stay, Days(late) | MV days(early) | MV Days (late) | male sex, % | Age, years | SOFA at ICU admission(early) | SOFA at ICU admission(late) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lee et al (2020) | Daegu, Korea | multi-center, retrospective, observational study | 47 | <24 | >24 | 23 | 16 | 13 (56.5) | 7 (43.8) | 13 (7–33) | 47 (13–74) | 10 (4–24) | 20 (9–57) | 28(59.6%) | 70 years (IQR, 63–77 years) | 3 (2–7) | 3 (2–4) |
| Schmidt et al (2020) | France, Belgium, Switzerland | multi-center, prospective cohort study | 2233 | <24 | >24 | 2003 | 230 | 724 (37%) | 96 (42%) | | | | | | 63 (54–71) | 5 (3–8) | |
| Bavishi et al (2021) | America | Retrospective cohort study | 54 | 4–24 | >24 | 30 | 24 | 2 (6%) | 7 (29%) | 12 (5–17) | 15 (10–19) | 10 (5–15) | 10(7–19) | 37 | 60(42-69) | 6(3-8) | 4(1-7) |
| Zirpe et al (2021) | India | retrospective observational study | 147 | <48 | >48 | 75 | 72 | 45 (60%) | 56 (77.7%) | 14 (9.7–21) | 16 (7–21.7) | 7 (4–12) | 6 (2–12) | 109（74.1%） | 59（51-67） | 1 (1–2) | 1 (1–2) |
| Pandya et al (2021) | America | retrospective study | 75 | ≤1.27 days | >1.27 days | 37 | 38 | 17 (45.95%) | 20 (54.05%) | 7.38 (3.88-10.21) | 12.31 (7.75-19.96) | 5.86 | 10.30 | 43 (57.33%)65 | | | |
| Vera et al (2021) | Chile | observational, prospective, single-center study | 183 | <48 | >48 | 88 | 95 | 16 (18%) | 43 (43%) | 31 (17–45) | 36 (24–62) | 13 (8–25) | 16 (9–33) | 132 | 61.5(53-71） | 6 (4–8) | 4 (2–8) |

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**How to cite this article:** Fu L, Xiaoqin Z, Long Cheng T, Lorraine M, Phillip D. Does the Timing of Intubation and IMV Impact Clinical Outcomes in Adult COVID-19 Patients with ARDS: A Systematic Review and Meta-Analysis. Acad J Ped Neonatol 2023; 12(5): 555905.
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**How to cite this article:** Fu L, Xiaoqin Z, Long Cheng T, Lorraine M, Phillip D. Does the Timing of Intubation and IMV Impact Clinical Outcomes in Adult COVID-19 Patients with ARDS: A Systematic Review and Meta-Analysis. Acad J Ped Neonatol 2023; 12(5): 555905.
DOI: 10.19080/AJPN.2023.12.555905

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