

Alternatives to Invasive Mechanical Ventilation for Acute Respiratory Distress Syndrome due to Viral Pneumonia: Systematic Review and Meta-analysis

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1. ABSTRACT

Introduction: SARS-CoV2 is a viral infection whose main pathology is COVID-19, a viral pneumonia with a mortality rate between 1% and 5%. Initially identified in the city of Wuhan, China in December of 2019, it quickly turned into a pandemic in February of 2020. Therefore, one of the greatest challenges presented in all countries worldwide, was the high demand for artificial ventilators due to the acute respiratory distress syndrome (ARDS) produced by this pathogen. However, there was a shortage of these medical equipment which further complicated the pandemic.

Methods: In this work, a systematic review of the literature will be carried out to determine the efficacy and safety of high-flow cannulae, continuous positive pressure, non-invasive mechanical ventilation by face mask, low-cost ventilators and ventilator spacers compared with conventional invasive mechanical ventilation treatment for the management of ARDS due to viral pneumonia. A systematic search of the literature will be carried out without date restrictions, focused on pandemics and epidemics caused by respiratory viruses such as SARS, H1N1, MERS and COVID-19, in the following databases: Medline, Embase, Cochrane Controlled Registered Trials (CENTRAL) and Scielo. The gray literature will include open source codes, ongoing clinical trials, official reports on low-cost ventilators and ventilator splitters. Randomized clinical trials and non-randomized studies (cohort and cases and controls) will be included.

Results: We hope to identify at least 2 published randomized clinical trials per ventilatory alternative and one ongoing clinical trial for low-cost ventilators and ventilator splitters. Also, we hope to identify that patients with the highest blood pressure oxygen / inspired oxygen fraction (PaO_2 / FiO_2) ratios are those who will benefit the most from these alternatives.

2. JUSTIFICATION

At the end of December 2019, the SARS-CoV2 virus which belongs to the β coronavirus family, was identified in the city of Wuhan, China. In this group, there are other coronaviruses that have emerged in the last 20 years, such as SARS between 2002 and 2003 and the Middle East Respiratory Syndrome (MERS) in 2012 (1). The main pathology caused by SARS-CoV2 is a viral pneumonia called COVID-19. This pathology has taken a great importance worldwide as it can cause acute respiratory failure that seriously compromises human body functioning and can lead to death. By taking this into account, on March 11, 2020, the WHO established COVID-19 as a pandemic. Since then and to this day it has spread rapidly to multiple countries. According to the latest WHO situation report, on May 12, 2020, 4,088,848 confirmed cases and 283,153 deaths were reported worldwide, which represents a fatality rate of 6.9% (2). Although

global data provides an estimate of the current situation, the distribution of cases and mortality varies considerably between different countries and regions. An example is the United States, Spain and Italy, which are currently the most affected countries, as they present the highest number of confirmed cases and the highest number of deaths with 78,652, 26,744 and 30,739 deaths respectively (2).

One of the greatest difficulties in controlling this pathology is the speed of its dissemination and transmission in the population. COVID-19 has a basic reproductive number (R_0) that ranges between 1.5 and 3.5. This means that, on average, an infected person will affect 1.5 to 3.5 people with whom they have contact (3-4). Taking this value into account is important because it allows us to know how the virus will behave in the population and, with the current results, it is most likely that the number of infected will continue to increase exponentially. Due to the foregoing, it is important to carry out early containment measures to avoid the saturation of health systems as much as possible, since one of the main causes of mortality is the inability to respond that can be generated due to an overload and depletion of available resources (5).

According to a study by the Chinese Center for Disease Control and Prevention, in which 44,500 confirmed cases were studied, the severity of the disease is classified as moderate, severe and critical, with a frequency of 81%, 14% and 5% of the cases respectively. This occurs dynamically in infected individuals, since those who initially had moderate manifestations can progress to critical ones in an average time of one week (6). Of those infected, about 20% will require hospital management. Of the hospitalized patients, 25% will require ICU management, which represents 5 to 8% of all infected (7-8). One of the major complications of critical illness is the onset of acute respiratory distress syndrome (ARDS) which can lead to rapid respiratory deterioration and death of those infected. This is important, since between 42 and 100% of the patients who develop this complication will require mechanical ventilation (9-10). Taking into account the above, if there's an excessive increase in cases, as is currently being reported in some countries, the number of people who will need the use of mechanical ventilation will exceed the capacity and availability of equipment in health care centers.

The situation mentioned above has generated an international need to take economic and administrative measures to face this pandemic. Some of the measures taken have been to increase ICU beds numbers by adapting places that previously served other purposes. Despite these efforts, most countries do not have the necessary inputs and tools to face this pandemic. One of the most important examples is the shortage of ventilators, which are essential for the management of patients with critical illness as we have mentioned. In fact, according to a study conducted at the John Hopkins Hospital Health Security Center, an estimated 160,000 ventilators are available in the United States, 580,000 fewer than are needed to adequately manage the pandemic (11). Due to the above, it has become necessary to use other strategies to face the shortage of ventilators in the world.

3. RESEARCH QUESTION

What is the efficacy and safety of alternative ventilation strategies compared to conventional invasive mechanical ventilation for the treatment of patients with ARDS due to viral pneumonia?

PICO Strategy

- *Population*
 - Patients with SARS-CoV2, SARS, MERS or H1N1, diagnosed by serological or molecular tests, without specifying the manufacturer of the tests, and with oxygen requirement given by an ARDS of viral origin and a PaO₂/FiO₂ less than 300 mmHg
- *Interventions*
 - High-flow nasal cannulas: continuous flow equal to or greater than 20 ml / min and that the research team specify the temperature and the humidification of the oxygen dilution.
 - Continuous positive pressure: continuous pressure greater than or equal to 5 mmHg, by nasal, nasopharyngeal or mask administration and that the research team reports on the inspiratory flow rate used.
 - Low-cost ventilators: Mechanical compression of the resuscitation bags and that the research team reports the positive pressure at the end of expiration (PEEP), the PICO pressure, the rate and the inspiration / expiration ratio used.
 - Ventilation splitters: with or without resistance valves and that the research team reports the positive pressure at the end of expiration (PEEP), the PICO pressure, the rate and the inspiration / expiration ratio used.
 - Non-invasive mechanical ventilation: either with a mask or helmet and the research team to report the positive pressure at the end of expiration (PEEP), the PICO pressure, the rate and the inspiration / expiration ratio used.
- *Comparator*
 - Conventional invasive mechanical ventilation: The research team should report the positive end expiratory pressure (PEEP), the PICO pressure, the rate and the inspiration / expiration ratio used.
- *Main outcome:*
 - All-cause mortality: patient who dies from any cause in the intensive care unit (Dichotomous variable)
- *Secondary outcomes:*
 - Days of stay in ICU: days of stay in intensive care units, ranging from the day of admission to the day of transfer (continuous variable)

- o Arterial blood gases in the first 24 hours
- o Arterial partial pressure of oxygen (PaO₂): amount of oxygen dissolved in blood in millimeters of mercury and not bound to hemoglobin (continuous variable)
- o Fraction of inspired oxygen (FiO₂): fraction of oxygen that the patient inspires (continuous variable)
- o PaO₂/FiO₂ : relationship between arterial oxygen pressure and inspired fraction of oxygen (continuous variable)
- o SOFA: Scale used to determine the possibility of sepsis in a patient (continuous variable).
- o APACHEII: Scale used in the intensive care unit to determine the severity of a disease in a patient (continuous variable).
- o Barotrauma: Lesion in the alveoli characterized by microvascular hemorrhage and that is the product of inadequate pressure management (nominal variable)
- o Nosocomial superinfection: Infection acquired in intensive care unit (nominal variable)

4. THEORETICAL FRAMEWORK

SARS-CoV2 is a new type of coronavirus initially detected in December 2019 in the Hubei province, in the city of Wuhan China (12). This virus, like other pathological coronaviruses for humans, is part of the beta subfamily of coronaviruses, characterized by four main structural genes that encode the nucleocapsid protein, the spike protein, a small membrane protein and the membrane glycoprotein with an additional membrane (13-14). On the other hand, this new coronavirus has been genetically sequenced, demonstrating an animal and chimeric origin (15). In fact, like SARS from 2002, SARS-CoV2 has the ability to bind to ACE2 receptors and is so far the main candidate to explain pathophysiology (16). Given the characteristics of the subfamily to which SARS-CoV2 belongs, the main pathology it generates in humans is COVID-19, a viral pneumonia.

This viral pneumonia initially presents fever (98%), cough (76%), dyspnea (55%) and myalgia or fatigue (44%), although other symptoms such as gastrointestinal ones observed in patients from the city of Wuhan (17). Similarly, the median time from onset of symptoms to first hospital admission was 7.0 days (IQR 4.0–8.0). On the other hand, radiological findings may not appear after 2 days of symptom onset since up to approximately 50% of COVID-19 patients may have normal CT scans (18). Therefore, the main diagnostic test is the real time polymerase chain reaction (RT-PCR). (19) In addition, the vast majority of COVID-19 cases are mild cases, with the possibility to be managed at home. However, some of these cases will evolve in severity due to the respiratory distress syndrome that produces COVID-19.

Of the total number of cases of COVID-19, 6.1% of them will be classified as critical cases based on the experience acquired by China in patients who developed ARDS (20). Similarly, patients with this pathology present histopathological patterns similar to those acquired by other

infections, such as exudate and polymorphonuclear infiltrate to the alveoli (21-22) as it's seen seen in other viruses such as influenza viruses, especially H1N1 (23). It is for this reason that the presence of fluid can lead to hypoxemia and that ICU management is essential to provide the ventilation needed as inflammatory response decreases (24). In the same way, it is necessary to be able to adjust the necessary and specific ventilators parameters to provide adequate oxygenation to the tissues, according to each individual's needs, and avoid a possible barotrauma (25). This is due to the fact that the inflammatory response itself leads to the lung being more prone to barotrauma, as we have seen in other pathologies that produce ARDS. In conclusion, and despite its limitations, the use of mechanical ventilators is indicated for ARDS and the ones secondary to COVID-19 are no exception. However, given the spread and high number of critical cases of COVID-19 in the world, mechanical ventilators are in short supply and alternatives are necessary.

In 2010, the first article on a low-cost ventilator was published, detailing the design of the prototype, as well as its functionality and limitations (26). In addition to this, the use of manual resuscitation bags stands out as the main element to generate positive pressure. Similarly, materials made from acrylics ensure that these fans are inexpensive and portable. Finally, this prototype was intended in the future to include an inspiration-to-expiration ratio control, a pressure relief valve, end-expiratory pressure (PEEP) capabilities, and an LCD display. All of this would bring the prototype to a value of \$ 420, making it easily accessible. Unfortunately, this prototype was not even tested in computer models. For 2019, another prototype was presented in which it was evaluated in an artificial lung, demonstrating basic functions for a patient with SARS (27). Despite these results, there are no pre-pandemic studies that show their effectiveness in real life scenarios, making it necessary to evaluate them during the COVID-19 pandemic.

5. OBJECTIVES

General

To determine the efficacy and safety of alternative ventilation strategies compared with conventional invasive mechanical ventilation in patients with ARDS of viral pneumonia.

Specific:

- To determine the efficacy of alternative ventilation strategies to conventional mechanical ventilation
- To know the safety of alternative ventilation strategies to conventional mechanical ventilation

6. METHODOLOGY

A. Design

This systematic review will be registered in the international prospective registry of PROSPERO systematic reviews, and will be developed following the reporting elements for the systematic review and the meta-analysis protocol guide (PRISMA-P) (28).

B. Literature

- Search and selection of indexed literature

We will carry out a systematic search of the literature in different databases including Medline, Embase, Web of Science, Cochrane Controlled Registered Trials (CENTRAL) and Scielo without date restriction. The search terms and relative variants were as follows:

- Categories, search terms and search strategy
 - Disease: "acute respiratory distress syndrome" OR "Critical ill patient" OR "Acute respiratory failure"
 - Therapy: AND "High Flow Nasal Cannula" OR "High Flow Nasal Cannula Oxygen" OR "HFNO" OR "HFNCO" OR "Continuous Positive Airway Pressure" OR "CPAP" OR "" Non-invasive ventilation "OR" Noninvasive ventilation "" OR "Ventilators splitters" OR "mechanical ventilation splitters "OR" Low-cost ventilator "OR" automated bag valve mask "OR" emergency ventilator "OR" emergency resuscitator "OR" Open source ventilator "
 - Pathogen: AND" COVID-19 "OR" SARS "OR" SARS-CoV2 " OR "H1N1" OR "Influenza" OR "MERS" OR "Middle East respiratory syndrome" OR "viral pneumonia"
 - Terms to exclude: NOT "Bacterial pneumonia"
- Combination of terms

The following is the combination of terms used for MEDLINE and will be adapted to other search engines or databases.

((((((Acute respiratory failure [Text Word])) OR (Critical ill patient [Text Word])) OR (acute respiratory distress syndrome [Text Word])) OR (Respiratory Insufficiency [Text Word])) OR (Respiratory failure [Text Word])) OR (Respiratory failure [MeSH Terms])) AND (((((((((((High Flow Nasal Cannula [Text Word]) OR (High Flow Nasal Cannula Oxygen [Text Word])) OR (CPAP ventilation [MeSH Terms])) OR (High Flow Nasal Cannula [MeSH Terms])) OR (HFNO [Text Word])) OR (HFNCO [Text Word])) OR (Continuous Positive Airway Pressure [Text Word])) OR (CPAP [Text Word])) OR (Non-invasive ventilation [Text Word])) OR (Noninvasive ventilation [Text Word])) OR (Ventilators splitters [Text Word])) OR (mechanical ventilation

splitters [Text Word])) OR (Low-cost ventilator [Text Word])) OR (automated bag valve mask [Text Word])) OR (emergency ventilator [Text Word])) OR (emergency resuscitator [Text Word])) OR (Open source ventilator [Text Word])) AND (((((((COVID-19 [Text Word]) OR (SARS [Text Word])) OR (SARS-CoV2 [Text Word])) OR (H1N1 [Text Word])) OR (Influenza [Text Word])) OR (MERS [Text Word])) OR (Middle East respiratory syndrome [Text Word])) OR (viral pneumonia [Text Word])) OR (Middle East respiratory syndrome [MeSH Terms])) NOT (Bacterial pneumonia)

- *Gray Literature Search*

We will carry out a gray literature search in the different regulatory agencies of multiple Anglo-Saxon or Spanish speaking countries, as well as in databases on registration of clinical trials. These agencies are:

- Food and Drug Administration (FDA)
- Emergency Department Critical Care (EMCrit)
- American Association for Respiratory Care (AARC)
- Clinical Evidence Assessment (ECRI)
- National Institute of Vigilance for Medicines and Food in Colombia (INVIMA)
- MedRxiv
- clinicaltrial.gov
- Spanish Agency for Medicines and Sanitary Products (AEMPS)
- the General Direction for Medicine, Supplies and Drugs in Peru (DIGEMID)
- National Administration for Medicaments, Food and medical Technologies in Argentina (ANMAT)
- Central Drugs Standard Control Organization in India (CDSCO)

C. Eligibility criteria

The search for studies will be limited to randomized clinical trials (RCTs) and non-randomized studies (NRS) (cohort and case-control) evaluating the effectiveness and safety of the different alternative ventilation strategies compared to conventional invasive mechanical ventilation for the treatment of patients with ARDS due to viral pneumonia in patients over 18 years old, diagnosed with SARS-CoV2, SARS, MERS or H1N1 by serology, molecular or clinical test and with respiratory distress syndrome due to a PaO₂/FiO₂ less than 300 mmHg at the time of admission to the ICU. There will be no restrictions for publication date; however, at minimum articles must include mortality as an outcome. Alternative intervention strategies should include at least one of the following:

- a) High-flow nasal cannulas

- b) Continuous positive pressure
- c) Low-cost ventilators
- d) Ventilator separators
- e) Non-invasive mechanical ventilation.

Articles in languages other than Spanish or English will be excluded and studies of the cited references of the selected articles will be included.

D. Selection of articles

The search results from the different sources will be combined, using a reference management software. Duplicate records will be removed. The titles and abstracts of each of the articles will be reviewed to eliminate studies that do not meet the inclusion criteria, trying to be inclusive at this stage. This process will be carried out by two reviewers who will work independently. For potentially relevant studies, the full texts will be retrieved. Any disagreement will be solved through discussion and in the event of not reaching an agreement, it will be referred to a third peer. The screening process for full-text articles will be carried out by two independent reviewers. Before starting the screening process, the agreement between the reviewers will be measured using the statistical kappa coefficient, applying the inclusion criteria on a sample of articles. After measuring the agreement between the reviewers, the study selection process will be carried out, verifying that they meet the inclusion criteria. This process will be carried out by two authors who will work independently. The reviewers will discuss the disagreeing studies among themselves and will define or not their inclusion. In case of not reaching an agreement between them, a third reviewer will define the inclusion or not of the study. In studies where it is not possible to obtain the full text, the researchers will be contacted in order to request the information necessary to carry out the final inclusion process.

E. Data extraction

Three review authors will independently extract relevant data from each included study. The results of the data extraction will be compared and any discrepancies will be resolved through discussion and consensus. The following information will be extracted from the studies: study population, sample size, methodological characteristics, systematic biases and limitations, as well as information on results and outcomes. Additionally, a narrative summary will be included detailing those studies that met the eligibility criteria, but were excluded and the reason for this exclusion.

F. Data analysis

Initially, the results will be described in a narrative manner and where possible the evidence will be pooled in a meta-analysis. As we expect clinical and statistical heterogeneity between studies, we will pool direct evidence for each outcome using a random effects model (REM). Relative estimates of effects together with 95% confidence intervals will be estimated using the relative risk (RR) for binary outcomes, and the mean difference for continuous outcomes. If continuous outcomes are reported using different metrics, the standardized mean difference will be used.

G. Assessment of heterogeneity

We will assess heterogeneity by estimating the magnitude of the variance between studies and using the statistic I^2 to quantify the percentage of variability that is due to true differences between studies rather than sampling error. We will interpret the I^2 using the thresholds established by Cochrane (29), and it will be used as a criterion to pool the results and perform the subgroup analyzes. In this regard, the thresholds are:

- 0% to 40%: heterogeneity may not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: heterogeneity considerable

If there is a heterogeneity greater than 50%, we will use meta regression to explain it if we have enough data to do so. Otherwise, we will perform subgroup analyzes. We propose 10 a priori hypotheses to explain the variability (heterogeneity) between the studies and therefore, as possible modifiers of the effect:

1. The difference in mortality between the selected viruses generates a wide variability.
2. Patients with mild PaO₂ / FiO₂ benefit more from the alternatives than those with severe PaO₂ / FiO₂.
3. Younger patients benefit more from the alternatives than those with older age.
4. Patients who received additional therapeutic treatments show greater improvement than those who did not receive them.
5. Patients with smoking habits benefit the least from ventilatory alternatives than non-smokers.
6. Patients with comorbidities benefit the least from ventilatory alternatives than those without comorbidities.

7. Patients with a severe APACHE II score on admission will have worse outcomes than those with a better APACHE II score.
8. Patients who have a better ROX index and are using high-flow nasal cannulas will have better outcomes than those with poorer ROX index and are using high-flow nasal cannulae
9. Patients receiving non-invasive mechanical ventilation by helmet will have better results than those patients who they receive non-invasive mechanical ventilation by mask.
10. Patients using low-cost ventilators in which positive pressure is generated by resuscitation bags will have worse outcomes than those using low-cost ventilators with a different mechanism for generating positive pressure.

Also, the following strategies will be implemented to corroborate and study the heterogeneity obtained which are suggested by the Cochrane manual for systematic reviews and meta-analyses:

- The database created will be reviewed and the data it contains are those published in the corresponding studies.
- A change will be made in the measurement of dichotomous outcomes. That is, instead of quantifying the RR, the odds ratio (OR) will be quantified.
- It will be preferred to analyze the results with a REM rather than with a fixed model.
- An analysis by subgroups will be carried out.
- A sensitivity analysis will be carried out from the risk of bias per study.

H. Subgroup analysis for heterogeneity study

The following subgroups were selected based on our clinical experience and the knowledge that we have about ARDS due to viral pneumonia. It should be noted that the analysis by subgroups will be used for all the outcomes and for each one of them a REM will be made using the RR for the binary outcomes, and the mean difference for the continuous outcomes. Similarly, there are subgroups that will be used for all ventilatory alternatives and subgroups that will be for the exclusive use of some ventilatory alternatives.

- All ventilatory alternatives

Virus type (MERS, SARS, SARS-CoV2, H1N1)

PaO₂ / FiO₂ before ventilation (300-200, 200-100 and <100)

Age in years (18-30, 30-50, 50 -70,> 70)

Additional treatment (without additional treatment, antiviral, anti-inflammatory)

Habits (smoker, non-smoker)

Comorbidities (obesity due to body mass index greater than 25 kg / cm², hypertension, diabetes, asthma, Chronic Obstructive Pulmonary Disease , any malignancy)

APACHEII score on admission (<20 mild, 20-32 moderate,> 32 severe)

- High-flow cannula

ROX index for intubation (score> 4.87, score 3.85-4.87, score 2.85-3.84, score <2.85)

- Non-invasive mechanical ventilation

Interface (helmet, mask)

- Low-cost ventilators

Mechanism by which positive pressure is generated (resuscitation bags, other than resuscitation bags)

I. Assessment of risk of bias

Two reviewers will independently assess the risk of bias for studies meeting the inclusion criteria. For RCTs, the Cochrane risk of bias tool will be used (30) In this order of ideas, we will evaluate the following 6 items with three categories (low risk of bias, unclear risk of bias, high risk of bias):

- Generation of random sequence: We will evaluate the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We rate high risk if you have selection bias (biased allocation to interventions) due to improper generation of a random sequence
- Concealment or blinding of allocation: We will evaluate the method used to conceal the allocation sequence in sufficient detail to determine whether the allocations intervention could have been planned before or during enrollment. We rate it as high risk if it exhibits selection bias (biased allocation to interventions) due to inadequate allocation concealment prior to allocation.
- Blinding of participants and staff: We will assess all measures used (if any) to blind study participants and staff of knowledge of which intervention a participant received. We rate high risk if performance bias is present due to knowledge of the interventions assigned by participants and staff during the study.

- Blinding of outcome assessment: We will assess all measures used (if any) to blind outcome assessors of knowledge of which intervention a participant received. We will classify as high risk if it presents detection bias due to the knowledge of the interventions assigned by the outcome assessors.
- Incomplete outcome data: We will assess data integrity for each main outcome, including attritions and exclusions from the analysis. We will rate high risk if you have attrition bias due to the amount, nature, or handling of incomplete outcome data.
- Selective reporting: We will assess whether the reviewers examined the possibility of selective reporting of results and what was found. We rate it as high risk if it has reporting bias due to selective reporting of results.

Instead, the Newcastle-Ottawa tool will be used to assess the risk of bias in the NRS (31). In this way, we will divide the NRS between cohort and case-control studies, in which we will evaluate with three categories. Each category is subdivided into several questions and what we evaluate is whether it presents it or not.

- Cohort
 - o Selection
 - Representativeness of the exposed cohort (+1 point)
 - Selection of the unexposed cohort (+1 point)
 - Determination of exposure (+1 point)
 - Demonstration that the result of interest was not presented at the beginning of the study (+1 point)
 - o Comparability
 - Cohort comparability based on design or analysis (+1 point if it is comparable with age) (+1 point if other variables were controlled)
 - o Outcome
 - Outcome evaluation (+1 point)
 - Was the follow-up long enough for the results to occur ? (+1 point)
 - Adequacy of cohort follow-up (+1 point)
- Case-Control studies
 - o Selection
 - Is the case definition adequate? (+1 point)
 - Representativeness of the cases (+1 point)
 - Controls selection (+1 point)
 - Controls definition (+1 point)
 - o Comparability
 - Comparability of cases and controls based on design or analysis (+1 point if it is comparable with age) (+1 point if other variables were controlled)

- o Exposition
 - Determination of exposure (+1 point)
 - Non response rate (+1 point)

J. sensitivity analysis

Using the results compiled, analyzing them and assessing individual study biases, two reviewers will perform a sensitivity analysis, as stipulated in the Cochrane Handbook for Systematic Reviews of Interventions (32). To do this, an analysis will be made between studies that had the best quality and another with those of poorer quality, based on the biases evaluated. The same analysis of REM by RR will be carried out.

K. Assessment of the certainty (quality) of the evidence

To assess the certainty (quality) of the evidence in the effect estimates for each outcome, we will follow the GRADE approach (33) making judgments about the risk of five aspects which are: risk of bias, inconsistency, imprecision, indirect evidence and publication bias. It should be noted that a GRADE assessment of high (++++), medium (+++), low (++) or very low (+) certainty will be given for each outcome, all summarized in an evidence table. To assess the quality of the evidence from RCTs, the GRADE assessment will start with ++++ and decrease according to the assessment of each of the Large domains. In the case of NRS, the GRADE assessment will start at ++ and will increase according to the presence of a large effect size. When there is a dose response gradient, or when all possible confounding factors or other biases increase our certainty in the effect estimator. For RCTs, the way we categorize each domain is Not Serious, Serious, or Very Serious:

- Risk of bias: this domain will be assessed across all RCTs or NRS that report Findings for each outcome.
- Inconsistency: we will study the I^2 and the variability in the results for each outcome.
- Indirect evidence: We will evaluate the variability of the PICO strategy proposed to each study, observing if the selected studies have similar populations, comparators, interventions or outcomes.
- Imprecision: We will use the information of the uncertainty of the effect estimator (95% confidence intervals) and the calculation of the optimal size of the information (OSI) that starts from the optimal sample size according to a specific statistical power.
- Publication bias: the studies will be summarized in a funnel plot and analyzed with it.

7. Expected results

We expect to find at least more than 2 randomized clinical trials per ventilatory alternative and a larger number for the COVID-19 pandemic. Similarly, we hope to find no differences between all

ventilatory alternatives and invasive mechanical ventilation, both for the main outcome and for the secondary outcomes. Finally, we hope to identify ongoing clinical trials for low-cost ventilators and ventilator splitters.

8. Presentation of findings

We plan to publish our results and recommendations in high-impact journals in intensive care and pulmonology such as the *Journal of Critical Care* or *The American Journal of Respiratory and Critical Care*. At the same time, Fredy Leonardo Carreño Hernández would use this study as a master's thesis in epidemiology at the Universidad de los Andes.

9. Researchers statement

The Fundación Santa Fe de Bogotá University Hospital and the Los Andes University are characterized by always seeking continuous improvement in their investigative processes, as well as contributing to the management of critical COVID-19 patients. Similarly, and knowing the conflicts of interest that may be generated when making recommendations on the use of one or another ventilatory alternative, we inform that none of our members has conflicts of interest with manufacturers of medical equipment that develop the equipment studied in this work.

10. Ethical considerations

Considering Law 6 of 1970, which approves the Inter-American Convention on copyright in literary, scientific and artistic works, signed in Washington on June 22, 1946, we will give the corresponding authorship of the studies compiled to their respective authors and researchers. Similarly, we assume that all published studies were duly approved by the ethics committees of each of the institutions and that due use has been made of the medical records as indicated in the resolution of the Colombian Ministry of Health number 1995 of 1999 or the respective to each country.

11. Formation and trajectory of the Research Group

Scientific production has become one of the most important quality indicators of higher education institutions in the world. In Colombia these institutions make great efforts to consolidate master's degrees and PhD programs, position their lines of investigation, research groups and increase their number of publications, projects and results. In recent years, the Fundación Santa Fe de Bogotá is part of a small group of institutions that have a tendency towards generating technological and social innovations as a strategy to build a future. Los Andes University has also been characterized by knowledge creation. These institutions have been promoting joint work for several years for the formation of new knowledge that improves well-being and that influences the best quality of care.

This is why these two institutions have directed a large part of their efforts to strengthen the scientific community. The Critical Medicine and Intensive Care Department of the Fundación Santa Fe University Hospital in Bogotá, created, four years ago, a research group for training students from different areas with clinical and research professors who are interested to coordinate and strengthen research. Also, they have the desire to contribute to solve problems that plague our community. With the creation of this research group and in search of solving questions through the development of research protocols, the secondary objective is to improve the research capacity of the professionals belonging to the Fundación Santa Fe de Bogotá University Hospital and Los Andes University.

For the above and seeing the importance of a work that can contribute to solving problems in the current pandemic, it is important to emphasize that this project will be carried out under the supervision of Dr. Yenny Rocío Cárdenas, an intensivist doctor attached to the Fundación Santa Fe de Bogotá. Additionally, it will count with the participation of Sergio Prieto rural doctor in critical research care and attached to the Fundación Santa Fe de Bogotá, Fredy Leonardo Carreño Hernández doctor graduated from Los Andes University, Daniela Abondano intern of the Fundación Santa Fe de Bogotá and Jairo Alejandro Gaitán Alfonso, ninth semester student of medicine at Los Andes University

12. Special thanks

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13. Bibliografía

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