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Non-Invasive Ventilation (CPAP) in Patients with Moderate ARDS Second Stage to SARS-CoV-2: Decrease in Mortality

Karen Yemina Uitzil Eb*, Raúl Jesús Zavala Sánchez, Ivett Asucena García Ávila, Saul May Uitz and Esmeralda Robledo Espinosa

Nursing School, Universidad Autónoma de Yucatán, Mexico

***Corresponding author:** Karen Yemina Uitzil Eb, Nursing School, Universidad autónoma de Yucatán, Mérida, Yucatán, México, E-mail: karenyemina95@gmail.com

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ABSTRACT

Objective: To analyze the factors that predispose the success or failure of Non-Invasive Ventilation (CPAP) by monitoring an adult patient with moderate ARDS secondary to SARS-CoV-2 for mortality reduction, through a systematic review.

Material and Methods: Quantitative research, systematic review question design structured by PIO, terms were identified, translated to scientific language through DeCS, MeSH and Elsevier topics, sources consulted: Epistemonikos, PUBMED, EBSCO, Google Academic, BMJ, Springer, as a research strategy the Boolean operators AND and NOT were used, articles with systematic review design were considered as criteria, primary studies from the observational type, cohorts, cases and controls not older than 5 years, excluding studies in pediatric patients.

Results: 1571 articles were located, 1515 were eliminated for not having a direct relationship with the use of CPAP in SARS-CoV-2, 56 articles were selected for critical reading (files 3.0). 44 were eliminated for not meeting the eligibility criteria and 12 were selected. They were ranked by the SING scale assigning a level of evidence and grade of recommendation.

Conclusions: Non-invasive ventilation with CPAP has been used to treat patients with respiratory insufficiency due to secondary ARDS to SARS-CoV-2. This review proves that mortality is directly related to different influential variables, among which the following stand out: comorbidities, age, PaO2/FiO2 and the no intubation order.

Abbreviations: CPAP: Continuous Positive Airway Pressure; NIV: Non-Invasive Ventilation; NMV: Non- Invasive Mechanical Ventilation; ARDS: Acute Respiratory Distress Syndrome; PaO_2: Arterial Oxygen Pressure; FiO_2: Fraction of Inspired Oxygen; PEEP: Positive End-Expiratory Pressure; ACE2: Angiotensin- Converting Enzyme 2; IOP: Question, Intervention, Outcome; DeCs: Descriptors in Health Sciences; MeSH: Medical Subject Headings; WHO: World Health Organization; ICU: Intensive Care Unit; SING: Scottish Intercollegiate Guidelines Network

Introduction

SARS-CoV-2 infection, is a health problem that caused a global pandemic, has its beginnings in Wuhan, a province belonging to Hubei, China, where it developed an outbreak of pneumonia of unknown cause, which generates tension to international level. Coronavirus was declared as an international public health emergency, there have been registered around 458 million confirmed positive cases of COVID-19 and a total of 6.04 million of world-wide deaths [1,2]. SARS-CoV-2 uses the spike (S) protein, densely glycosylated to enter the host´s cellules, binding with great affinity to the receptor of the enzyme convertor of angiotensin (ACE2), said enzyme is found in type II alveolar cells. The Coronavirus-2019 (COVID-19) cases present asymptomatic patterns, low, moderated, and serious ones, including: pneumonia, Acute Respiratory Distress Syndrome (ARDS) sepsis, and septic shock, which would have the main impact on respiratory insufficiency, therefore, it would demand major interventions and more complexity to a point where the affected patients would require hospitalization in the "Unidad de Cuidados Intensivos" (UCI for its initials in Spanish) to receive appropriate treatment and avoid severe complications that would put in risk the patient's life [3].

The SDRA it's a form of pulmonary edema with no cardiogenic cause that comes from an alveolar injury, which is caused by an inflammatory process of local origin or systematic one [4]. The classic diagnosis is made based on The Berlín criteria that works to evaluate the temporality, the obtained radiography, the edema's origin, and the oxygenation, classifying it low with a Blood Oxygen Pressure (PaO_2) / Fraction of inspired oxygen (FiO_2) of 300-200 mmHg, moderated with PaO_2/FiO_2 de 100-199 mmHg and severed with PaO_2/FiO_2 <100mmhg, all of them with Positive-end expiratory pressure (PEEP) >5cmH_2O [5]. Cornaviru's patients and patients with severe respiratory insufficiency are hospitalized in the UCI with hypoxemia that most of the time requires a way of respiratory support. One of the most common therapies is the "Ventilación No Invasiva" (VNI for its initials in Spanish) which consists of the administration of the ventilatory support without an artificial airway, such as an endotracheal tube or a tracheostomy, instead, they do it through a facial mask, nasal or a hull system [6]. The considered criteria for introducing non-invasive respiratory support in the acute respiratory failure are the Clinical criteria: Moderate-severe Dyspnea accompanied by signs of labored breathing, use of accessory musculature or paradoxical abdominal movement, Tachypnea higher than 30 rpm, and Gasometric criteria: PaO_2/FiO_2 <200 mmHg and Acute ventilatory failure with pH< 7,35 with $PaCO_2$ > 45 mm Hg) [7].

The VNI for Continuous Positive Pressure in the Airway (CPAP for its initials in Spanish) as applicable therapy in adult patients with COVID 19 reduces the necessity of intubation concerning conventional oxygen therapy [8]. We have to take into account that not all patients benefit from the Invasive Mechanical Ventilation (VMI), for this reason, it is important to establish the opportune time for the implementation of CPAP, evaluating the deterioration or increase of the PaO_2/FiO_2, as the principal determinant of the hypoxia correction. This investigation is relevant for the timely attention that we can give to patients that go through an infection of SARS CoV-2 in hospitalization. The objective is to analyze the factors that predispose the success or failure of the non-invasive ventilation (CPAP) through the monitoring of the adult patient with SDRA secondary to SARS-CoV-2 for the decrease of mortality, by a bibliographic review.

Material and Methods

Quantitative research was conducted, a kind of systematic revision through the phases of Nursing Based in Evidence using the PRISMA declaration, the question of the investigation was formulated based on the PIO model, the characteristics of the population needed for this investigation were senior patients whose clinical condition was: SDRA secondary to SARS-CoV-2. Carried out in a phase from September 1, 2021, to March 2022.

Researching Strategy

A question was formulated in the PIO (Patient, Intervention, Outcome) format. The analysis process and preparation for research was realized in a list of natural language terms, for its localization and traduction to a documental language a Descriptor en Ciencias de la Salud (DeCS) was used [9], el Medical Subject Headings (MeSH) [10] and Topics de la editorial Elsevier (Table 1) [11]. As a strategy for precise searching terms with the proper language were used to form research chains (CPAP AND covid-19 AND Mortality, COVID-19 AND Non- invasive Ventilation AND CPAP NOT CNAF AND Mortality, CPAP AND COVID 19) using the booleans AND and NOT. Free terms were used for the sensitive search. The used sources of information were databases (Epistemonikos, PUBMED and EBSCO), Search engines (Google academic), Electronic journals (BMJ, Editorial: Springer). The Sci-Hub tool was used for the recovery of the full-text articles, while the title and abstract were read for the initial selection of the articles. Articles both in English and in Spanish were published about the adult patients with ARDS secondary to SARS-CoV-2 and the mortality factors; the articles that were used are systematic designs and primary observational case studies.

Descriptive observational studies, case reports and letters to the editor, evidence published with more than 5 years, studies in populations under 18 years of age and in animals, as well as those for which the full text could not be accessed, were excluded. For

the synthesis and interpretation of the evidence and to answer the research question formulated, the 12 scientific articles included in this review were ranked using the SIGN (Scottish Intercollegiate Guidelines Network) with the purpose to assign the level of evidence based on the design and the degrees of recommendation to assess the reliability of the intervention to be recommended (Table 1). To evaluate the risk of bias and the quality of the studies included in this analysis we evaluated based on the characteristics of each design (Table 2). In this article, the main bias analyzed it's been selected mainly due to the predominance of observative studies of cohort. These biases were addressed by doing a triangulation of critical reading, getting to an agreement of shared opinions in case of discordance. This strategy consisted in reviewing at least by three autors each study that was included. So in this way we can get more reliable information.

Table 1: Translation of free terms into documentary language.

Question	Language	
	Español	Inglés
P: Paciente adulto con SDRA secondaries a SARS-CoV-2	-Covid-19	-Covid 19
	-SARS-COV-2	-SARS-COV-2
	-Síndrome de Dificultad Respiratoria del Adulto	-Respiratory Distress Syndrome, Adult
I: Monitorización de la Ventilación No Invasiva (CPAP)	-Presión de las Vías Aéreas Positiva Continua	-Continuous Positive Airway Pressure
	-Ventilación no invasiva	-Noninvasive ventilation
O: Reducción de la mortalidad	-Mortalidad	-Mortality

Note: ARDS: Acute Respiratory Distress Syndrome, CPAP: Continuous Positive Airway Pressure.

Table 2: Risk of bias on the articles.

Design	Risk of bias
Sistematic reviews	Analysis of continuous or not continuous variables.
Cases and controls	Layered Cox proportional hazards model for grouped data.
Cohort	Analysis of independent, multivariate, categorical continuous, qualitative, parametric and multiparametric variables, as well as the use of regression techniques

Results

According to the research done by Epistemonikos, EBSCO, Google scholar, BMJ and SPRINGER, 1571 articles have been found, from which 56 were selected by title and summary for the recuperation of the full text, while having in mind the inclusion and exclusion criteria mentioned before and having them evaluated with the FLC 3.0 platform (Figure 1 & Table 3) [12-23].

Table 3: Evidence synthesis.

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Evidence/Designe	**Result**	**Conclusion**	**SING grade**
Non-invasive Respiratory support out of intensive care unit due to acute respiratory insufficiency in relation to corona disease/ systematic metanalysis revision [12]	NIRS with CPAP was applied in 2764 out of 3047 patients. In patients who failed NIRS and were subsequently intubated, in-hospital mortality reached 45% [36-54%], whereas in those subjects on NIRS who did not undergo IMV, in-hospital mortality was 30% [23-37%].	Despite concerns arising from the crisis response of hospital and the lack of clinically effective therapy, delivery of NIRS outside the ICU were generally revealed as a feasible strategy to cope with the demand creating massive respiratory support even for those patients with care limitations	1++/A
CPAP management of Respiratory insufficiency of COVID-19/Observational cases and controls [13].	CPAP was found to be associated significantly (HR 0.38, CI 95%: 0.36 to 0.40) with a lower risk of death in patients with a hospital stay equal to or less than 7 days. However, for longer hospitalization, CPAP was found to be associated with an increased risk of death (HR 1.72, 95% CI 1.40 to 2.12). When CPAP was started within 4 days of hospital admission, the probability of survival was greater than 73% (95% CI 53% to 99%).	CPAP is a simple and cost- effective intervention. It has been established for the care of other respiratory disorders, but not for COVID-19 respiratory failure. This evaluation establishes that CPAP is a potentially viable treatment option for this group of patients during the first days of hospital admission.	2+/C

Severity of respiratory failure at admission and hospital mortality in patients with COVID-19/ Observational cohort, prospective, multicenter [14].	CPAP was prescribed in emergency rooms in 9.7% of cases, while only three patients were immediately intubated (severe group). Mortality was 25.5%. It increased proportionally with lower PaO_2/FiO_2 values, being higher in the severe group (55.6%) and lower in patients with PaO_2/FiO_2> 300 mm Hg (6.5%; p <0.0001). The number of days from admission to death was lower in the severe group and higher in patients with normal PaO_2/FiO_2 at admission (p = 0.0001).	A moderate to severe deterioration in PaO_2/FiO_2 was independently associated with a three-fold increase in the risk of in-hospital mortality. The Severity of respiratory failure is useful to identify patients at increased risk of mortality.	2+/C
Non-invasive CPAP in low SDRA and moderate SARS-CoV-2. /Observational cohort, prospective [15].	11 patients died (61%), 4 of NI- CPAP and 7 of non-responders (40% vs 87%, p value=.004). NI-CPAP has a beneficial impact on the prognostic. In fact, the ones who do not respond had double increase in chance of dying instead to the ones who respond.	NI -CPAP it's a valid therapeutic option in SDRA mild and moderated secondary SARS-CoV-2, that seems to be related only with increased lung recruitment detected by pulmonary ultrasound is a relevant but not exclusive mechanism underlying therapeutic efficacy of NI-CPAP in this clinical setting.	2+/C
Effectiveness of non-invasive ventilation on the syndrome of breathing difficulties due to Covid-19. / Observational cohort, prospective [16].	The VNI-CPAP evaluated 79 patients, which 38 (48.1%) were successful. EOT was necessary in 21 (26.6%) patients. 20 (25.3%) patients died. Related to the ones who continued VNI, there was no increase in mortality. (43% to 36%, PAG = .61). When analyze the survivor results in the UCI of the patient group who were intubated after the VNI, the 57% of the patients were discharged. While de rest, 43%, died. The successful VNI tests happened for 8.7 days. EOT tests lasted 2.9 days and in the dead patients 6.3 days.	This preliminary data shown that VNI-CPAP worked in almost half of the patients. Also, it reduced the UCI pression in dramatic scenarios. Avoiding an over number of patients in the IOT. The use of the VNI could potentially help reduce the progressive and inevitable of the UCI resources in case of a huge bed demand.	2+/C
Effectiveness and safety of non-invasive positive pressure ventilation in the treatment of acute hypoxemic respiratory failure associated with COVID-19. /Single-center retrospective observational cohort study [17].	Increased PaO_2/FiO_2 ratio measured 24-48 h after initiation of NIPPV-CPAP (OR 1.02, CI 1-1.03, p 0.015) was independently associated with NIPPV success, while the presence of a treatment limitation decision (OR 0.03, CI 0.001-0.57, p0.020), was a predictor of NIPPV failure. Overall hospital mortality among patients treated with NIPPV was 50% (25/50).Mortality was significantly higher among patients with a treatment limitation decision than among patients without STI exclusion (88% vs. 12%, p<0.0001,).	Apart from elderly patients with limited life expectancy, NIPPV was effective in a substantially high percentage of patients with AHRF associated with COVID-19 in this study. The SARS-CoV-2 infection rate among healthcare workers caring for COVID-19 patients receiving NIPPV was quite low, suggesting that NIPPV is a safe practice, as long as strict adherence to the measures is ensured, adequate infection prevention and control.	2++/B
Outcomes of COVID-19 Patients Treated with Continuous Positive Airway Pressure Outside the Intensive Care Unit/ Retrospective, Multicenter Cohort Study [18].	According to the predefined therapeutic goal of CPAP, 397 patients were included in the full treatment subgroup with the possibility of escalating to IMV and 140 in the no intubate subgroup. Mortality was 42% for the 45% of patients who failed CPAP and required intubation, while it was 73% for patients ordered not to intubate. On the other hand, hospital mortality was higher in patients who received CPAP for more days, compared to those who received CPAP for fewer days. Mortality appeared to increase in patients with lower PaO_2/FiO_2 at the start of CPAP.	The CPAP failure rate was 45%, indicating that effective treatment occurred in more than half of the patients, who avoided invasive ventilation through an endotracheal tube, which is a life-saving procedure, but it is also prone to various side effects and complications. It is concluded that CPAP is a feasible treatment. It was determined that hospital mortality is closely related to the therapeutic objective, patients who have an order not to intubate are affected by much more mortality. It is confirmed that delayed intubation is a risk factor for mortality.	2+/C
Severity of respiratory failure and outcome of patients requiring ventilatory support in the Emergency Department during the outbreak of the novel Italian coronavirus SARS-CoV2/ Retrospective observational cohort study [19].	Of the patients who started with CPAP (54.9%) died before intubation; (36.6%) were intubated and 15 of them (57.7%) died after intubation. NIV-CPAP failure occurred in 88.5% of patients. Mortality was lower in younger patients (<60 years) compared to older patients (>60 years), ranging from 44.4% in patients <60 years to 85% in those older than 60 years.	The strategy with NIV-CPAP is feasible for the treatment of patients with severe hypoxia who cannot be intubated due to lack of intensive care resources. In our experience, it did not lead to higher mortality rates compared to other studies in patients with similar clinical features.	2+/C
The role of CPAP as a potential bridge to invasive ventilation and as a ceiling of care for hospitalized patients with Covid-19/ Retrospective cohort study [20].	Unlike patients who had CPAP as a potential bridge to IMV, high mortality was observed among patients who received CPAP as the upper limit of care. Older age was strongly associated with a higher risk of death from Covid-19.	The implications of our findings are that the use of CPAP prior to intubation appears to be an effective treatment strategy in selected patients. Mortality among patients who required and received borderline CPAP was slightly higher than that of those who received IMV, reflecting both disease severity as well as frailty, age, and comorbidities in this cohort.	2+/C

COVID 19: Respiratory Management by Non-Invasive Ventilation / Retrospective Observational Cohort Study [21].	Of 119 patients, 42 patients were successfully weaned from NIV-CPAP, while the remainder were switched to invasive mechanical ventilation. All patients who were switched to invasive ventilation died. The low PaO_2/FiO_2 ratio was related to conversion to invasive ventilation and high mortality in the group.	NIV-CPAP plays an important role in the prevention of IMV in patients with COVID-19. Although age, associated comorbidity, and the stage of ARDS at the time of presentation, play an important role in the outcome of the patient with COVID-19 infection. NIV-CPAP is more useful in preventing IMV in patients with mild-moderate respiratory distress than in patients with severe respiratory distress at presentation.	2+/C
COVID-19 and acute respiratory failure treated with CPAP/ Retrospective Observational Cohort Study [22].	Of the 44 patients who received CPAP, 12 (27%) avoided intubation, 13 (29%) were intubated, and 19 (43%) died. A positive CPAP response was observed in respiratory rate ($p = 0.002$) and oxygenation ($p < 0.001$). Advanced age and high initial oxygen demand predicted treatment failure and increased mortality.	In conclusion, CPAP in patients with COVID-19 and respiratory failure reduces work of breathing and optimizes oxygenation, thereby avoiding intubation in some cases and even reducing mortality. However, the prognosis for especially elderly patients with a high requirement of oxygen is bad.	2+/C
Results of non-invasive ventilation as treatment ceiling in patients with COVID-19/ Observational Cohort Study [23].	According to the predefined therapeutic goal of CPAP, 397 patients were included in the full treatment subgroup with the possibility of escalating to IMV and 140 in the no intubate subgroup. Mortality was 42% for the 45% of patients who failed CPAP and required intubation, while it was 73% for patients ordered not to intubate. On the other hand, hospital mortality was higher in patients who received CPAP for more days, compared to those who received CPAP for fewer days. Mortality appeared to increase in patients with lower PaO_2/FiO_2 at the start of CPAP.	Patients with COVID-19- related ARDS and a treatment ceiling of NIV have a high burden of comorbidities, limited basal organ reserve, and a poor prognostic profile, but may benefit effectively from a combination of NIV and chest physiotherapy. Poor response to treatment may be preceded in these patients by early respiratory and hemodynamic failure in the first 48 hours. Cardiovascular and hematologic morbidity, increased demand for longer NIV cycles, and deteriorating vital signs are additional risk factors for CPAP failure in patients receiving NIV and physical therapy for severe COVID-19.	2-/C

Note: NIV: Non-Invasive Ventilation, NIRS: Non-Invasive Respiratory Support, IMV: Invasive Mechanical Ventilation, ICU: Intensive Care Unit, CPAP: Continuous Positive Airway Pressure, PaO_2: Arterial Oxygen Pressure, FiO_2: Inspiratory Fraction of Oxygen, SARS-CoV-2: Severe Acute Respiratory Syndrome associated with Coronavirus 2, IOT: Endotracheal Intubation, ARDS: Acute Respiratory Distress Syndrome, NIPPV: Non- Invasive Positive Pressure Ventilation, AHRF: Acute hypercapnic respiratory failure.

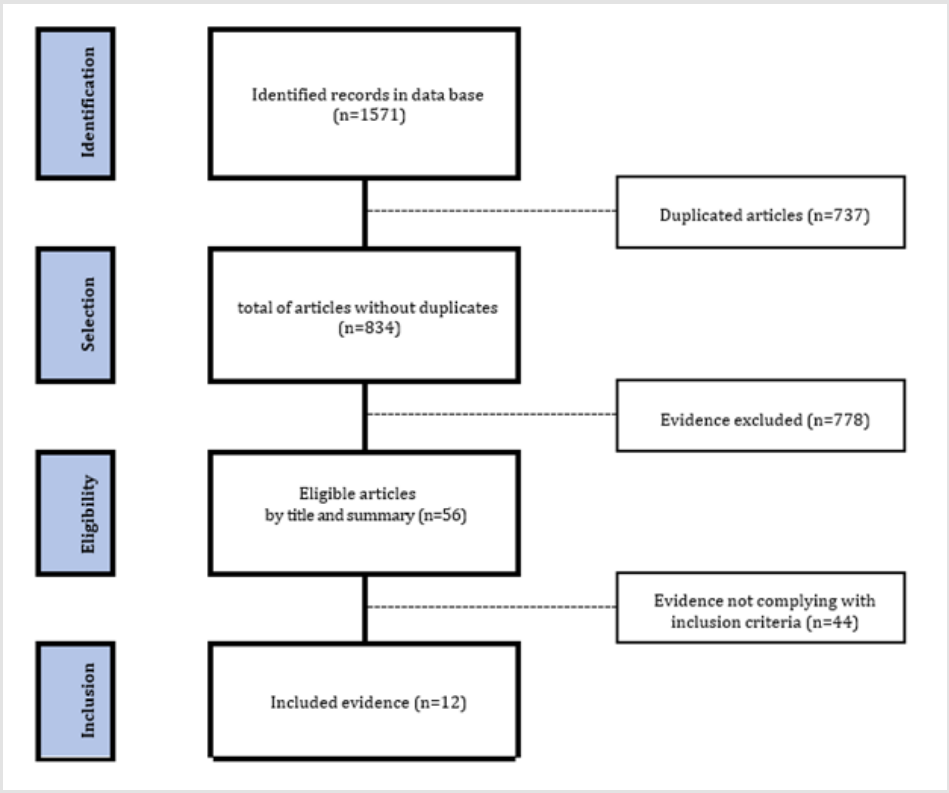

Figure 1: Evidence selection

Discussion

The main findings of this review can be summarized as follows: In all articles, mortality was higher in patients >60 years of age, who suffered from comorbidities such as hypertension, diabetes, lung, kidney and heart disease, Likewise, criteria such as male gender and a decreased PaO_2/FiO_2 ratio play an important role in the outcome of patients with COVID-19, since they were associated with greater failure of NIV-CPAP. 58% of the articles included the order of no intubation, based on criteria such as present comorbidities, chronic diseases, Cammarota, et al. [12] adds among these criteria the decision of the patient, the family and the multidisciplinary team, on the other hand, Faraone, et al. [17] includes all the aforementioned criteria, adding short life expectancy, since the patients who had a higher incidence of acquiring ARDS secondary to SARS- CoV-2 were patients aged >60 years. On the other hand, Invasive Mechanical Ventilation (IMV) was indicated in patients with NIV-CPAP failure who presented fatigue, respiratory rate >30, decreased level of consciousness, but Barone, et al. [18] Includes hemodynamic instability, defining it as a decrease in systolic blood pressure <90mmHg despite the use of vasoactive drugs, while Walker et al considered higher oxygen requirements, decreased PaO_2/FiO_2 and increased shallow breathing, in addition to other criteria already mentioned.

Regarding efficacy, all the articles agree that non-invasive CPAP ventilation is related to a greater probability of survival, however Ashish, et al. [13] It refers that when its onset is less than four days after admission and in selected patients it can have significant benefits both for the patient's well-being and for the resources of the health system and in the same way a potential benefit for patients treated with order not to intubate, as opposed to being treated with oxygen alone, on the other hand Kofod, et al. [22] reports that the prolongation of the use of CPAP for more than one week compromises successful weaning in these patients with ARDS, thus showing that the duration of CPAP time was an important predictor of mortality in patients. About the nursing care function, the evidence indicates that NIV-CPAP monitoring in these patients must be constant in order to identify changes in physiological parameters that may predispose the failure or success of NIV-CPAP therap. Patients affected by ARDS due to COVID-19. The main fears in relation to the studies were expressed by the risk of lung injury related to NIV-CPAP, in which close monitoring and individualized titration of ventilatory pressures were suggested. Another concern is the high risk of aerosol generation that can cause contagion in health personnel, so the use of bacterial filters is recommended to apply NIV-CPAP, avoiding the spread of the virus. Use of Personal Protective Equipment (PPE) when coming into contact with patient care.

Conclusion

The application of NIV-CPAP in patients with ARDS secondary to SARS-CoV-2 proves to be feasible in selected patients under 60 years of age, with few or no comorbidities, with a mild to moderate ARDS level according to the Berlin classification, reducing the mortality rate when they are treated in the first four days after hospital admission, performing continuous monitoring by qualified personnel. The limitations of our study are related, for the most part, to the observational and retrospective design of the included investigations, however, in the future, studies with a higher level of evidence are required to carry out more reliable evaluations.

Conflict of Interest

The authors declare that they have no conflict of interest in relation to this work.

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