Respiratory management of Acute Respiratory Distress Syndrome (ARDS) in the Intensive Care Unit from Early Diagnosis: Narrative Review

Battalian Théo[1*]

1. Universidad CEU San Pablo, Madrid, Spain
* Correspondence: Théo Battalian (theobattalian@gmail.com)

Abstract:
This study aims to determine the optimal ventilatory technique for different levels of acute respiratory distress syndrome (ARDS) severity to reduce the need for endotracheal intubation (ETI) in the ICU. Secondary objectives include identifying predictors of failure of non-invasive ventilation (NIV), assessing the role of physiotherapists in the ICU across countries, and identifying areas for further investigation. A review of articles from 2013 to 2023 involving adults with ARDS in the ICU was conducted. The PEDro scale assessed article quality, and exclusion criteria included specific aetiologies of acute respiratory failure, extreme obesity, and pregnancy, as well as case series and case study designs. Data were extracted from PUBMED, EBSCO, and ScienceDirect, and a validated questionnaire was administered to physiotherapists in Chile, Spain, and France. Eight studies (number of patients n = 883) were included, and a questionnaire was completed by 22 physiotherapists (6 from France, 6 from Spain, 10 from Chile). Findings highlighted the management of high flow nasal cannula (HFNC) and NIV in different patient populations. Helmet NIV had an 18.2% failure rate and better outcomes than facemask interface. NIV non-response correlated with increased mortality rates. Cox analysis identified predictors of NIV failure. Caution is advised in NIV use, considering predictors of failure, and HFNC may be beneficial in mild ARDS. The majority of included studies had small sample sizes, limiting generalizability. The questionnaire results were constrained by a small sample size and lack of meta-analysis.

Keywords: Acute respiratory distress syndrome, high flow nasal cannula, non-invasive ventilation, endotracheal intubation, predictors of failure, physiotherapy.

Citation: Battalian T. Respiratory management of Acute Respiratory Distress Syndrome (ARDS) in the Intensive Care Unit from Early Diagnosis: Narrative Review. Proceedings of Socratic Lectures. **2024**, 10, 8-37. https://doi.org/10.55295/PSL.2024.II2

1. Introduction

ARDS is a syndrome characterized by acute respiratory failure due to increased permeability of the alveolar-capillary membrane, leading to non-cardiogenic pulmonary oedema, hypoxemia, and respiratory system compliance impairment. (Thompson et al., 2017; Grasselli et al., 2023). The pathophysiology of ARDS is complex and involves various inflammatory mediators and cellular mechanisms.

The initial insult to the lungs can be caused by pulmonary or extrapulmonary factors. Pulmonary ARDS is often caused by direct injury to the lungs, such as pneumonia, inhalation of toxic gases or fumes, aspiration of gastric contents, non – protective ventilation (i.e., Ventilator induced Lung Injury) or drowning (Saguil and Fargo, 2020). In these cases, the inflammatory response is initiated within the lungs, leading to damage to the alveolar-capillary membrane and resulting in pulmonary oedema and hypoxemia.

Extrapulmonary ARDS, on the other hand, is caused by systemic inflammation due to a variety of factors such as sepsis, trauma, pancreatitis, or transfusion-related acute lung injury (Kassirian et al., 2020).

One of the primary treatments for ARDS is invasive mechanical ventilation (Fan et al., 2017; Tasaka et al., 2022) which involves the use of a ventilator to provide mechanical support to the lungs. The use of invasive ventilation in ARDS has been a topic of extensive research and debate in recent years, with the goal of optimizing patient outcomes and minimizing complications.

On the other hand, non-invasive therapies such as NIV and HFNC have been used more extensively in the treatment of ARDS. NIV is a respiratory support technique that aims to deliver positive pressure to the lungs without the need for an endotracheal tube. It is typically delivered through a mask, nasal prongs or a helmet and the positive pressure helps to improve oxygenation and reduce carbon dioxide retention (Peter et al., 2006; Thompson et al., 2017).

There is already strong level of evidence for NIV effectiveness in case of exacerbation of Chronic Obstructive Pulmonary Disease (COPD) (Rochwerg et al., 2017) and for cardiogenic oedema (Peter et al., 2006).

HFNC is a type of respiratory support that delivers heated and humidified air or oxygen to the patient through a nasal cannula at a flow rate of up to 60 litters per minute (Tasaka et al., 2022). The high flow rates and humidification make it a comfortable and well-tolerated alternative to conventional oxygen therapy or NIV. The use of HFNC is based on the principle that high flow rates and humidification can improve gas exchange, reduce work of breathing, and Positive End Expiratory Pressure (PEEP) to prevent atelectasis. HFNC can be used in a variety of clinical settings, including acute respiratory failure, post-extubation support, pre-oxygenation, and bronchiolitis in infants (Frat et al., 2015; Tasaka et al., 2022).

It is known that invasive ventilation through endotracheal intubation can lead to complications such as barotrauma, ventilator-associated pneumonia, and hemodynamic instability (Saguil and Fargo, 2020; Coleman and Aldrich, 2021).

In the realm of professions to treat it, ARDS requires many of them. It is important to note that medical and nursing care are usually the ones described when considering the approach.

Physical therapy is a cornerstone in the re-education of patients, starting in the ICU. Little is known about the implication of physiotherapists in interventions regarding patients with ARDS in the ICU. Even less is known about the differences that could exist in this same level of implication according to different countries.

Therefore, this narrative review proposes to determine - according to the grade of severity of the pathology - which ventilatory technique should be adopted from the early diagnostics, to avoid as much as possible ETI as a primary objective. Additionally, the best non-invasive ventilation support interface discernment will be the secondary objective.

To start understanding physiotherapist's role in the ICU according to the country will be the primary objective of the questionnaire that has been produced during this study.

2. Methods

For the narrative review, the search was done from October 2022 until December 2022 in the following databases: PubMed, EBSCO, Science Direct. The identification process retrieved a total of 296 articles (13 from PubMed, 135 from EBSCO and 148 from Science Direct). The software Mendeley was used as a reference tool. The following data in addition to the reasons of exclusion in the assessment of eligibility are represented in **Figure 1**.

The updated preferred reporting items for systematic reviews and meta-analyses (PRISMA) has been used to report the following study.

The eligibility criteria encompass individuals aged 18 or older diagnosed with acute respiratory distress syndrome (ARDS), with consideration given to articles published between 2013 and 2023. Inclusion requires adherence to a PEDro scale score of 22 or 23 greater than 5/10 for randomized controlled trials and a focus on the intensive care unit (ICU) population. Conversely, exclusion criteria encompass individuals with other pathologies leading to acute respiratory failure, hypercapnic conditions such as Chronic Obstructive Pulmonary Disease (COPD), clinically extremely obese patients (BMI > 35 kg/m2), or those who are pregnant. Additionally, case series and case studies are excluded from consideration. The 2012 Berlin classification being the updated version of the AECC (American European Consensus Conference) for the diagnosis of ARDS is used by each article.

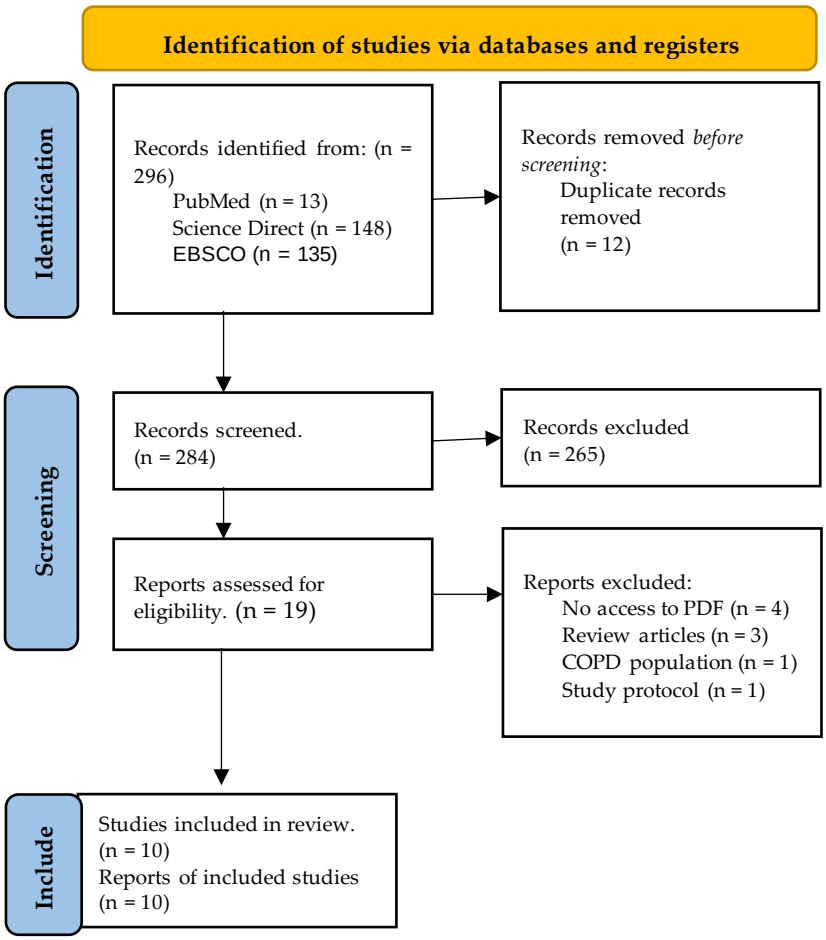

Figure 1. PRISMA Flow chart.

A questionnaire on the topic of the role of physiotherapists in ICU wards on the management of ARDS and the decision-making process has been conducted. This questionnaire has been answered by physiotherapists who work or used to work in ICUs from France, Spain, and Chile. The primary objective of the later was to determine whether the role of the professional was drastically different between countries, secondarily to have a state of the current practice, and lastly to determine if the COVID 19 pandemic changed the approach.

The answers got collected from October 2022 to February 2023. The confection of the questionnaire is based on the current literature and guidelines about the management of ARDS (Arcelo et al., 1998; Peter et al., 2006; Ranieri et al., 2012; Slutsky and Ranieri, 2013; Fan et al., 2017; Munshi et al., 2017; Rezoagli et al., 2017; Thompson et al., 2017; Dries, 2019; Saguil and Fargo, 2020; Grasselli et al., 2020; Grieco et al., 2020; Coleman and Aldrich, 2021; Tasaka et al., 2022) and has been validated in October 2022 by a panel of one experimented teacher in cardiorespiratory physiotherapy of the CEU San Pablo, and the two head of intensive physiotherapy of the Clínica Dávila Vespucio de Santiago de Chile. It has been created with the platform *Google Forms*, in three languages (Spanish, French and English). Chilean and Spanish answers were collected on two distinct versions.

The questionnaire (see **Appendix 1**) is divided in four sections for a total of 30 questions: Section 1: Personal information – 7 questions; Section 2: Diagnosis of the pathology – 4 questions; Section 3: Management of the pathology – 13 questions; Section 4: Physiotherapist involvement – 6 questions.

Overall, the questionnaire got a total of 22 answers (n = 10 from Chile, n = 6 from France, n = 6 from Spain).

3. Results

Based on the questionnaire, interpretations can be drawn. While 100% of French physiotherapists found the Berlin classification relevant, 33.3% of Spanish physiotherapists and 40% of Chilean physiotherapists did not. 60% of patients in Chile received between 3 – 5 sessions of physiotherapy per day, but nor Spanish neither French patient exceeded 3 sessions. Respectively 50% of physiotherapists in Spain and Chile did not include the exclusion of cardiogenic oedema as a diagnosis criterion, while only 26.7 of physiotherapists in France did not. 60% of Chilean physiotherapists believed that COVID 19 pandemics changed the diagnostic method while only 33.3% of Spanish and 16.7% of French physiotherapists did not. All the participants used protective factors when setting up mechanical ventilation. However, only 50% of Spanish physiotherapists considered the driving pressure, while 100% of Chilean and French professionals did. Additionally, only 83,3% of French physiotherapists but 100% of Spanish and Chilean physiotherapists considered tidal volume between 6 – 8 ml/kg as a protective factor. From Chilean practice, 70% considered they were completely in charge of HFNC (5/5 points), and 60% considered themselves completely in charge on NIV (5/5 points). Both of those parameters are dropping to 33% for French physiotherapists, and 16% for Spanish ones. 50% of French physiotherapists considered their role in the daily gestation of ventilation parameters as a 3/5, when the majority (70%) of Chilean professionals graded it between 3 and 4/5, and 50% of Spanish graded it 0/5. 100% of Spanish physiotherapists graded 0/5 on their implication in ETI manoeuvre, 66% graded 0/5 and 33 graded 1/5 in France, 40% graded 2/5 and 30% graded 3/5 in Chile. 66% of Spanish physiotherapists graded between 0 and 1/5 of involvement in the decision-making process for evolution between treatment strategies, 70% in Chile graded between 2 and 3/5, 33% in France graded 4/5, and 33% as a 2/5. Lastly, 100% of Chilean physiotherapists but only 33% of French and 66% of Spanish physiotherapists considered that their role in those points were more important after the pandemic.

This review is including 7 observational studies ((Frat et al., 2015; Messika et al., 2015; Sehgal et al., 2015; Chawla et al., 2016; Bellani et al., 2017; Menzella et al., 2021; Yaroshetskiy et al., 2022) and one randomized control trial (Patel et al., 2016). They are classified in three categories according to the technique of their investigation. The first

category regards the use of HFNC as a treatment method and includes two articles (Frat et al., 2015; Messika et al., 2015). The second one regards NIV and includes 4 articles (Sehgal et al., 2015; Patel et al., 2016; Bellani et al., 2017; Menzella et al., 2021). Lastly, the third category regards predictors of NIV failure and includes 2 articles (Chawla et al., 2016; Yaroshetskiy et al., 2022). We decided to separate group 2 and 3 since group 2's results are enhancing the focus on the facts and group 3's results are focused on drawing conclusions about the failure predictors of NIV. Firstly, we will present the results of the articles, in order to analyse those in a critical way.

3.1. Group 1: Publications on treatment with High Flow Nasal Canula (HFNC)

The summary of the characteristics along with the study design, the intervention, and a brief view of the results of the publications in Group 1 can be found in **Table 1**.

3.1.1. Article characteristics

Two studies evaluated the effect of HFNC on ARDS patients. Both publications dated from 2015. The population of interest in each of the article is based on the Berlin classification from 2012 and is scoping patients with approved diagnosis of ARDS, that are above 18 years old and are admitted to the ICU. However, Messika et al. (2015) are not taking into consideration in their diagnosis the parameter that requires a PEEP of 5 cm/H_2O on NIV since the treated population would be with HFNC. The sample size of the studies was 23 (Frat et al., 2015) and 45 (Messika et al., 2015).

Table 1: The summary of the characteristics, the study design, the intervention and a brief view of the results of the Publications on treatment with High Flow Nasal Canula (HFNC) (Group 1).

	Population characteristics	Study design	Intervention	Results
Frat et al. (2015)	- n = 23 within a year - ARDS patients from Berlin classification - Male gender 78% - Median age 61 years - SAPS II 36 points - Pneumonia 64% - Severity (mild 34%, moderate 61%, severe 4%)	Prospective observational	2 hours session of HFNC, then 1 hour session of NIV for a total of 16 hours of HFNC and 8 hours of NIV per day	Failure rate of 8/23 subjects (35%) requiring ETI No ETI for intolerance reasons Increase of PaO_2 in comparison standard oxygen Increase of PaO_2/FiO_2 ratio only in NIV Decrease of RR and HR HFNC better tolerated than NIV, although second session of NIV was better than the first
Messika et al. (2015)	- n = 45 within a year - ARDS from Berlin classification without considering the NIV criterion. - Male gender 49% - Median age 57.9 years - SAPS II 36 points - Pneumonia 80% - Severity (mild 29%, moderate 38%, severe 33%)	Prospective observational single centre	Use of HFNC for first line treatment of ARDS when need >9L/min of oxygen to maintain SpO_2 > 92%	Failure of 18/45 subjects (40%) requiring secondary ETI Success of 26 subjects only with HFNC and one in combination with NIV Additional organ failure increases HFNC failure rate

3.1.2. Methodology

Each study is based on a prospective observational approach, with a (STrengthening the Reporting of OBservational studies in Epidemiology) score of 19 out of 22. On the STROBE score, the lack of study's funding sources and assessment of the generalizability of the study findings, are the items downgrading them to 19 points (**Table A2.1** in **Appendix 2**).

3.1.3. Population characteristics
It is quite similar on the following points: median age (61 years (Frat et al., 2015) vs 57.9 years (Messika et al., 2015)) and the Simplified Acute Physiology Score II of 36 in both cases. However, the aetiology is different since population in Messika et al. (2015) were treating cases from pneumonia in 80% of the patients, and Frat et al. (2015) were treating 64% of pneumonia-induced ARDS. The severity of the pathology in the patient group from Messika and al. (2015) is notably homogenous, when the other population is focused to 61% of patients with moderate ARDS.

3.1.4. Results of the therapy
Messika et al. (2015) are describing the use of HFNC as first line treatment in 29% of the subjects admitted for acute respiratory failure. Additionally, HFNC was used at all stages of the pathology, from first line treatment to pre-ETI, post-extubation or palliative care. The study of Frat et al. (2015) that is combining HFNC and NIV, points out that PaO_2 increased in 20 out of 28 patients included in the study for acute respiratory failure, and that it was even higher when in combination with NIV in comparison with standard oxygen therapy. On the other side, only NIV caused a decrease in the PaO_2/FiO_2 ratio. Moreover, remaining stable throughout the entire HFNC/NIV sessions, respiratory rate and heart rate significantly decreased after the initiation of the therapy.

3.1.5. Tolerance of the therapy
HFNC was better tolerated than NIV, according to a lower score on the visual analogue scale of 16 mm versus 61 mm (P=0.004). However, comfort was better on the second session of NIV at 49 mm on the scale (Frat et al., 2015).

3.1.6. Failure rate
In the study of Messika et al. (2015) is about 40% of the patients, and the main reasons for ETI were worsening of hypoxemia in 72%, onset of hemodynamic failure with 22% and onset of neurological failure with 6%. The subjects included in the failure of HFNC group had significantly higher SAPS II scores in comparison to the success group. The failure rate on the combined treatment in the study of Frat et al. (2015) is 35% for ARDS patients and 36% for acute respiratory failure, and the reasons for ETI are worsening of distress in 70% patients, shock for 20% of them, and respiratory arrest for the last 10%

3.1.7. Predictors of failure
It is associated to lower PaO_2/FiO_2 ratio after initiation of HFNC (115.3 vs 145.3 mmHg, P=0.26), SAPS II scores (46 vs 29), and hemodynamic failure in the univariate analysis, but only the SAPS II score in the multivariate analysis according to Messika et al. (2015). In the case of Frat et al. (2015) failure was associated to a breathing frequency of >30 breaths/min at 1 hour after initiation of the first HFNC session with a sensitivity of 94.1% and a specificity of 87.5%.

3.1.8. Mortality rate
According to Messika et al. (2015) mortality rate was 50% in patients in whom the treatment failed ($p = 0.001$ for the failed treatment) and 4% in patients in whom the treatment was successful. Therefore, meaning that mortality rate was much lower in successful patients. Frat et al. (2015) are reporting a mortality rate of 20% for the population in which the treatment failed, but it was not statistically significantly relevant ($p = 0.12$). Consequently, it does not precisely represent the percentage of deceased patients caused by the failure of the non-invasive treatment.

3.2. Group 2: Publications on treatment with non-invasive ventilation
The summary of the characteristics along with the study design, the intervention, and a brief view of the results of the publications in Group 2 can be found in **Table 2**.

Table 2. The summary of the characteristics, the study design, the intervention and a brief view of the results of the Publications on treatment with non-invasive ventilation (NIV)(Group 2).

	Population characteristics	Study design	Intervention	Results
Bellani et al. (2017)	- n = 436 for 4 weeks - ARDS patients from Berlin classification aged > 16 years - Male gender 58.9% - Median age 68 years - non-pulmonary SOFA 3 points - No etiology - Severity (mild 27.3%, moderate 53.2%, severe 19.5%)	Prospective observational multicentre international cohort	NIV with any type of interface or ventilatory mode for at least 1 or 2 days to be enrolled as NIV patients	Failure rate of 131/436 subjects (37.5%) requiring ETI. Greater severity of ARDS associated with an increase of recognition of ARDS and worsening in outcomes including LOS and ICU mortality but not hospital mortality. Use of NIV didn't vary according to the severity category of ARDS. NIV patients had lower PEEP and higher respiratory rate in comparison to IMV. NIV failure in case of higher SOFA, lower PaO_2/FiO_2 ratio and % of increase of $PaCO_2$ within first 2 treatment days.
Sehgal et al. (2015)	- n = 41 for one year - ARDS from AECC classification, >18 years - Exclusion of severe ARDS patients - 65.7% women - Median age 30.9 +/- 11.4 years - APACHE II 18 points - Malaria 26.8%, Typhus 19.5% - Severity (mild 56.1%, moderate 43.9%, severe 0%)	Prospective observational	NIV using ICU ventilators. First 24 hours, off only for oral intakes, then depending on patient, increase of off periods.	Failure of 23/41 subjects (56%) requiring ETI. NIV failure group had significantly higher APACHE II. Duration of ventilation higher in IMV. Significant decrease of respiratory rate in both groups. Predictors of NIV failure: no improvement of $PaCO_2/FiO_2$ within 1 hour and higher baseline APACHE II.
Menzella et al. (2021)	- n = 79 over a month - COVID 19-ARDS patients - Male gender 56(71%) - Median age 66.5 +/- 11.4 years - SOFA 4.3 points - Charlson comorbidity index 3.4 - Severity (mild 0%, moderate 100%, severe 0%)	Retrospective observational	Use of NIV on patients with a PaO_2/FiO_2 ratio >100 and <200 mmHg	Failure of 41/79 subjects (51.9%) requiring ETI in 21(26.6%) and death in 20(25.3%). 18/20 deceased were not eligible for ETI. Failure predictors according to a multivariate COX regression model: SOFA score. No higher mortality rate for failed NIV patients.
Patel et al. (2016)	- n = 83 for 3 years - ARDS with mask NIV>8 hours, >18yo, berlin criteria - Male gender 54% face mask, 55% helmet - Median age 60.9 years face mask, 58 helmet - APACHE II 26 points face mask, 25 points helmet. - Pneumonia 36% - Severity (60% PaO_2/FiO_2 < 200 mm Hg)	Single centre randomized clinical trial.	After 8 hours of face-mask NIV Control (39/83): continue with face mask on a single limb ventilator. Intervention (44/83): switch to helmet interface with double limb ventilator.	ETI rate of 61.5% in face mask group, 18.2% in helmet group. PEEP of 8.0 (median) in intervention group VS 5.1 in control. Reduction of tachypnoea from face mask to helmet interface. Helmet group had more ventilator-free days (28 vs 12.5) and less ICU LOS (4.7 vs 7.8 days). Hospital and 90-days mortality significantly lower in helmet group. Independent association of APACHE II with 90-days death rate (still lower for helmet group)

3.2.1. Articles characteristics

The second part of the review consists of four articles, one randomized control trial (Patel et al., 2016) and three observational studies (Sehgal et al., 2015; Bellani et al., 2017; Menzella et al., 2021). The publication dates are ranging from 2015 to 2021 and they are all investigating the effect of NIV on ARDS patients.

3.2.2. Methodology

Two studies are using the Berlin classification as a diagnosis method (Bellani et al. (2017) and Patel et al. (2016), Menzella et al.(2021) are not specifying the diagnosis criteria but are mentioning the treatment of moderate to severe cases. In the case of Sehgal et al. (2015) they are using the now changed classification of the American European Consensus Conference (AECC) (Villar and Kacmarek, 2012) as a diagnostic criterion. Sehgal et al. (2015) are reporting cases of ARDS from tropical diseases such as malaria in 26.8% and typhus in 19.5% of the patients, only 9.7% was pneumonia related. The sample sizes are 436 patients in 4 weeks in Bellani et al. (2017), 41 patients in one year in Sehgal et al. (2015), 79 patients in one month in Menzella et al. (2021), and 83 patients in 3 years in Patel et al. (2016).

3.2.3. Patient's characteristics

Bellani et al. (2017) describe their population as being older, with a lower non-pulmonary SOFA score when comparing to intubated population. Additionally, they report that the NIV population is more prone to suffer from comorbidities such as chronic renal failure, congestive heart failure, and chronic obstructive pulmonary disease compared to intubated patients. Finally, they didn't find any significant difference about immunocompromised patients between both groups but was still an important number of subjects in each. Patel et al. (2016) are comparing their control and intervention group at baseline, and the findings are related to what Bellani et al. (2017) are stating. It was found that more than half of the overall non-invasive population are immunocompromised by virtue of cancer or transplant, and about one third had an immunocompromised pneumonia.

3.2.4. NIV failure

Regarding the outcomes, focusing on the failure of the treatment method, Sehgal et al. (2015) are reporting a rate of 56% of failure, 51.9% of failure for Menzella et al. (2021) with 26.6% requiring ETI, and 25.3% being deceased, 61.5% for face-mask group (control) and most importantly only 18.2% for helmet group (intervention) according to Patel et al. (2016). Lastly, Bellani et al. (2017) are reporting a rate of 37.5% of failure with a bigger sample size than any other of the studies. APACHE II has a high median value in the study of Patel et al. (2016) when looking closer to the same value in the study of Sehgal et al. (2015) (18 vs 25-26 points). Additionally, population in Sehgal et al. (2015) has a median age of 30.9 in comparison to the three other population ranging from 60.9 to 68 years.

3.2.5. Ventilation and patient's parameters

When comparing NIV with invasive ventilation, NIV had significantly lower levels of PEEP, and higher respiratory rates than the second one (Bellani et al., 2017). Moreover, measured tidal volumes and minute ventilation were greater in population treated by NIV. However, the latter and the former were not affected by ARDS severity in patients treated with NIV compared to patients treated with invasive ventilation. Patel et al. (2016) are reporting that patients from their control group had a median sustained PEEP level of 5.1 cm H_2O (face mask group) and that their intervention group was at a level of 8.0 cmH_2O (helmet group) ($p = 0.006$ for both values). PEEP titration in the case of face-mask interface was a challenge because patients did not tolerate it well and because of excessive air-leak. Lastly, tachypnoea significantly decreased when patients got randomly assigned from the facemask to the helmet interface (from 27.7 breaths/min to 24.5 breaths/min) ($p<0.001$). It was pointed out in the study of Bellani et al. (2017) that in their consequent study population, NIV was used almost as frequently in the three severity groups of ARDS, 14.3% for mild, 17.3% for moderate and 13.2% for severe cases of the pathology.

3.2.6. Reasons for ETI

When coming to the decision to intubate, refractory hypoxemia and tachypnoea caused by the face mask are reported as being the main reasons (Patel et al., 2016, Sehgal et al., 2015). In one case, neurologic failure was described as altered sensorium

and in one case the Richmond Agitation Sedation *Scale* (RASS) dropped below 8 points. However, when comparing those results with the intervention group of the randomized control trial, the first reason for ETI is neurologic failure and not respiratory failure. This can easily be correlated to the failure rate from the intervention group with the helmet interface. Lastly, Bellani et al. (2017) are reporting that PaO_2/FiO_2 ratio was increasing more rapidly in patients treated with invasive mechanical ventilation in comparison to NIV.

3.2.7. Secondary outcomes

Regarding the hospital length of stay Bellani et al. (2017) are reporting worsening of this outcome along with ICU mortality according to the severity of the ARDS, although it was also correlated with a higher clinical recognition. According to Patel et al. (2016) the helmet group spent only 4.7 days in the ICU compared to the 7.8 days for the facemask groups, and helmet group had more ventilator free days than the facemask group (28 vs 12.5 days). However, statistically, hospital length of stay was not different. Menzella et al. (2021) reported a longer duration of NIV for successful subjects compared to failed ones and deceased ones (8.7 vs 2.9 vs 6.3 days respectively). In the case of Sehgal et al. (2015) the total ventilation duration was recorded (non-invasive and invasive), with a result of 2.75 days for NIV success, and 5.2 days for failure. Additionally, only regarding the NIV ventilation, the duration was 2.75 days in success patients and 3 hours for failure subjects. However, there was no significant difference in the ICU stay between each group.

3.2.8. Mortality rates

According to Menzella et al. (2021) mortality rate was not significantly different between both groups of NIV (failure and success) (43% vs 36%, p=0.61). However, Sehgal et al. (2015) reported that out of the 23 subjects who failed NIV, 19 got deceased (82.6% of NIV failure death), and out of the 18 patients of success, none got deceased. The total percentage of death of the study reached 46.3%. Patel et al. (2016) are reporting that hospital and 90-days mortality was significantly lower in the helmet group compared to the facemask group (48.7% vs 27.3% for hospital, 56.4% vs 34.1% for 90-days). Additionality they found that APACHE II was independently associated to 90 days death with a confidence interval of 95%. Bellani et al. (2017) are reporting relevant data on the mortality rates. Firstly, between NIV and invasive ventilation, there was no significant difference in ICU and hospital mortality. However, in the case of failed NIV patients, the rates are reaching 42.7% of ICU mortality compared to the 10.6% for the success subjects ($p<0.001$). After performing a multivariate COX regression model adjusting covariates significantly associated with outcomes; NIV use was independently associated with increased ICU but not hospital mortality with a 95% confidence interval. Another multivariate COX regression analysis was performed on baseline characteristic of NIV group, that showed that chronic heart failure, hematologic or neoplastic disease, chronic liver failure, age, ARDS severity, percentage decrease of PaO_2/FiO_2 ratio between days 1 and 2, total respiratory rate and non-pulmonary SOFA score were each independently associated to in-hospital death.

3.2.9. Predictors of failure for NIV

Sehgal et al. (2015) performed a univariate logistic regression analysis and found out that failure of improvement in the PaO_2/FiO_2 ratio within an hour of treatment, and a higher baseline APACHE II scores, were associated with failure of NIV. It should be taken into consideration that this analysis in only univariate. Menzella et al. (2021) conducted a univariate and multivariate COX regression model on those parameters associated with NIV failure, and out the two analyses, only SOFA admission score was significantly correlated with failure, leaving PaO_2/FiO_2 ratio out. This can show that COVID ARDS might behave in a different manner. Bellani et al. (2017) conducted a multivariate COX regression analysis that revealed that higher non pulmonary SOFA score, lower PaO_2/FiO_2 ratio, and the percentage increase of $PaCO_2$ over the first days of treatment were independently associated to NIV failure within 28 days. The

sample size of this article gives a higher scientific weight, and on the contrary, the small sample size from Sehgal et al. (2015) is dragging its conclusions to a lower level.

3.3 Group 3: Publications on predictors of NIV failure

The summary of the characteristics along with the study design, the intervention and a brief view of the results of the publications in Group 3 can be found in **Table 3**.

3.3.1. Articles characteristics

The analysis of two articles was done in the third part of this study. Yaroshetskiy et al. (2022) gathered a population of 80 patients within 6 months of study, and Chawla et al. (2016) gathered a population of 96 patients within 3 years of study.

All the patients were treated with NIV, through a full-face mask. Chawla et al. (2016) are using the Berlin classification as a diagnosis method for the patients, knowing that the aetiology of the ARDS is coming from pneumonia in 55.3% of the patients. However, Yaroshetskiy et al. (2022) are evaluating patients with COVID 19-ARDS complying with at least one of the following criteria: fatigue, excessive visible WOB assessed by the Patrick scale (Patrick et al., 1996) (4-5 points), $SpO_2 < 92\%$. Precise ARDS classification diagnosis was not reported and only moderate to severe patients were included **(Table 3).**

Table 3. The summary of the characteristics along with the study design, the intervention, and a brief view of the results of the publications in Group 3

	Population characteristics	Study design	Intervention	Results
Yaroshetskiy et al. (2022)	- n = 102 within 6 months, 80 with NIV - COVID 19 ARDS with at least one of the following criteria: fatigue, excessive visible WOB assessed by Patrick scale(Patrick et al., 1996) (4-5 points), SpO2<92% - Male gender overall 54(56.3%) - Median age overall group 71.5 - SOFA overall 4 points - Severity only from moderate to severe ARDS	Prospective observational clinical	Use of oxygen therapy <15 L/min or CPAP outside ICU as screening. 2 hours NIV trial as entrance test. Then, if tolerated, NIV, if not, ETI	Failure rate of 57/80 subjects (71.3%) requiring ETI After 48 hours of NIV, if PaO_2/FiO_2 < 112 mmHg, ROX < 5.02, $P_{ET}CO_2$<19.5mmHg and Patrick score >= 2 then failure can be predicted. Respiratory rate can also be considered. NIV failure higher in older and/or more frailer patients, longer COVID duration without NIV
Chawla et al. (2016)	- n = 170 within three years, 96 with NIV - ARDS from Berlin classification - > 18 years - Male gender overall 61.8% - Median age overall 47.54 years - SOFA overall 8 points - APACHE II overall 17.42 points - Pneumonia 55.3% - Severity overall (mild 34.7%, moderate 41.8%, severe 23.5%)	Prospective observational	NIV through a non-vented full-face mask with and ICU ventilator using a dedicated NIV mode	Failure of 42/96 subjects (43.8%) requiring ETI Failure rate higher in severe (83.3%) and moderate (73%) Low PaO_2/FiO_2, septic shock and severity of ARDS as factors associated to failure. Higher mortality in failure of NIV patients. Longer LOS in NIV patients ICU mortality: 30.2% for NIV, 45.9% for IMV

3.3.2. Methodology

Yaroshetskiy et al. (2022) is an observational prospective clinical study with a score of 20 out of 22 points on the STROBE scale. Chawla et al. (2016) is a prospective observational study with a STROBE score of 21 out of 22. Study's funding source and an assessment of the generalizability of the study findings is lacking for Yaroshetskiy et al. (2022) and only the assessment of the generalizability of the study findings is lacking for Chawla et al. (2016).

3.3.3. Failure and mortality rates

According to Yaroshetskiy et al. (2022), out of 80 patients, 57 (71.3%) failed the treatment. Among those patients, they were all intubated and 3 were put under extracorporeal membrane oxygenation (ECMO). The other ones were not eligible for ECMO because of exclusion criteria (mostly >65 years old). The mortality rate was 100% for this group. According to Chawla et al. (2016) out of 96 patients, 42 (43.8%) failed NIV by requiring invasive mechanical ventilation. Depending on the severity of the ARDS, the failure rate was higher. In moderate ARDS the failure rate was 27/37 (73%) and in severe ARDS it was 5/6 (83.3%) as compared to mild ARDS with 10/53 (18.9%) (p=0.000). Among the patients who failed NIV, 69% (29/42 patients) of them died, with 7/10 (70%) for mild, 18/27 (66.7%) for moderate and 4/5 (80%) for severe ARDS.

3.3.4. NIV failure predictors

In the study of Chawla et al. (2016) the univariate analysis showed that admission APACHE II and SOFA scores along with low admission PaO_2/FiO_2 ratio, presence of severe sepsis or septic shock or multiorgan dysfunction, presence of confusion, absence of H_1N_1 influenza A infection, and severity of ARDS were the 9 factors for prediction of NIV failure. In the multivariate analysis however, only low admission PaO_2/FiO_2 ratio ($p = 0.049$), presence of septic shock ($p = 0.001$) and severity of ARDS ($p = 0.007$) were validated. According to a ROC analysis, Yaroshetskiy et al. (2022) have stated that after 48 hours of treatment the following parameters can be described as predictors of failure of NIV: 1) ROX index <5.02 ($p < 0.001$), 2) $PaO_2/FiO_2 < 112$ mmHg ($p < 0.001$), 3) $P_{ET}CO_2 < 19.5$ mmHg, 4) Patrick scale ≥ 2. Lastly, they concluded that the probability of failure was higher in older/frailer patients and in patients with a longer duration of COVID 19 without NIV.

4. Discussion

The HFNC is a relatively new technique that has been incorporated into ICUs for good reasons. However, the findings of this review about the use of the latter as an effective treatment option for patients with ARDS are fragile. There are lots of limitations and precautions to consider when interpreting results from those articles. Starting by the study design of both, which is observational, and the fact that they don't comply with the entirety of the items in the STROBE score. This is additional to the population sample size, that even though growing in comparison to previous case series or case studies, stays low.

Moreover, the HFNC technique presents a limitation when referring to ARDS. It is thought to generate low levels of PEEP, depending on the volume applied (between 35 and 60 L/min) and most importantly depending on if the patient stays mouth closed. This lack of precise knowledge about the PEEP level, confronts itself with the essence of diagnosis method of ARDS. The Berlin classification is including one crucial parameter that makes it the evolution of the AECC, the minimum PEEP level of 5 cmH_2O. In this case, HFNC cannot provide such information and then block ARDS proper identification by health professionals. A post hoc analysis from two prospective studies by Coudroy et al. (2018) comes in line to defend this position and try to revise the Berlin classification on this very precise point of minimum level of PEEP. However, even though debates are forming, in this precise time, minimum level of PEEP is required to consider a diagnosis of ARDS.

On the level of failure rate, it is clearly stated that the use of HFNC is related to less failure of the treatment with 35% (Frat et al., 2015) and 40% (Messika et al., 2015), in comparison to studies on the use of NIV that reports failure rate in between 37.5% and 61.5% in the case of full-face interfaces (Sehgal et al., 2015; Patel et al., 2016; Bellani et al., 2017; Menzella et al., 2021). However, one of the greatest concerns in any non-invasive ventilatory support, is not the failure rate itself, but the hospital/ICU mortality for the subjects that are part of the failure group. This is shown by Bellani et al. (2017) when taking as a study population, the largest ARDS database available nowadays. They reported with a ROX regression analysis that NIV was associated with mortality, and the use of HFNC on this matter remains unknown. If considering the

results of the two articles of this review, Messika et al. (2015) are reporting 50% of deceased patients from the failure group, but this result is drawn from a sample of 18 subjects in the failure of the treatment, which is really low. Frat et al. (2015) are not reporting such data. Lack of power of both studies on such matters prevents any conclusions from being properly deduced.

Messika et al. (2015) concluded that HFNC was not improving the PaO_2/FiO_2 ratio itself but only the FiO_2, which can prove that levels of PEEP provided by HFNC is not sufficient to improve the overall gas exchange. Frat et al. (2015) with their approach of combination of both techniques with NIV, is then using the beneficial effect of oxygenation improvement from the NIV.

In the combined use of HFNC and NIV, is has been found that tolerance levels were significantly better in the case of HFNC rather than NIV, and a previous study by Antonelli et al. (2007) depicted an ETI rate due to NIV intolerance of 25% (Antonelli et al., 2007) in patients with ARDS. However, when considering that patients have to keep their mouth closed to benefit from the effectiveness of HFNC, another concern can be drawn on whether the tolerance level assessment was made respecting this criterion. To continue the positive sense of combination of HFNC and NIV, Frat et al. (2015) have reported that no ETI due to interface intolerance was conducted, knowing that the interface used in this study is a full-face mask. Patel et al. (2016) have proven the efficacy of helmet interface in comparison to full-face mask on multiple level, such as failure rate and mortality. This could be a good opening for next research, evaluating the efficacy and failure rate of combined HFNC and Helmet NIV alternatively.

It is advanced that HFNC have an effect on decreasing the respiratory rate (Frat et al., 2015). However, it is important to keep in mind which are the predictors of failure of NIV (Table 3) since this study is using both HFNC and NIV. As a matter of fact, respiratory rate is never going further in the predictors than a univariable analysis. By relying on multivariable analysis, then HFNC doesn't have any substantial/statistical effect on avoiding failure of NIV. When conducting their multivariable analysis on the predictors of mortality Bellani et al. (2017) found that respiratory rate was one of them. Thus, statistically, HFNC has an effect on reducing mortality, but not on reducing failure rate. This conclusion can be turned into a positive sense, since as mentioned before, one of the greatest concerns from the analysis of the entire articles is focused on the mortality rate of the failure group.

Messika et al. (2015) are observing the use of HFNC at any stage of ARDS, 33% as severe, 38% as moderate and 29% as mild. However, SAPS II scores are relatively low (median of 36 for all subjects, 29 for success and 46 for failure) and the majority of patients did not present with an additional organ failure. The use of HFNC can be done at any stage if the ETI timing is respected. The need for further research on the exact population of application is needed to establish a clear view.

The questionnaire conducted in this study gives multiple information on the management of ARDS in the ICU. HFNC is designed as the major first line treatment for mild ARDS for physiotherapists in Spain (along with standard oxygen therapy), France and Chile, and the first with NIV in the case of moderate ARDS but only for physiotherapists in Spain. Limitations are multiple to this questionnaire, such as lack of power due to sample size, or lack of statistical analysis of the results. However, the conclusion of this survey is that in nowadays practice, HFNC is used broadly as the first line therapy in mild ARDS.

NIV in its turn is an older technique that has been used for a long time in acute respiratory failure from COPD or cardiogenic oedema. Healthcare professionals in the ICUs are highly trained for the technique. However, in the case of ARDS, the studies of this review are creating a brand-new perspective.

Results from the studies are reporting many deductions, but one crucial point here is to point out which outcome should be the main one to be analysed. Failure rate of the therapy is the first one that would seem logical, in the sense that if the patient doesn't fail the therapy, then the outcomes are positive, which seems to be the case. (Bellani et al., 2017) is the largest study population sample of all the articles and has a failure rate of only 37.5% out of the 436 subjects enrolled. Sehgal et al. (2015) reported a failure rate of 56%, but this study presents a couple of limitations that deserves to be pointed

out. The study sample is clearly different from all of the other studies, by its small sample size of 41 patients, by its aetiology of ARDS coming in most of the cases from tropical diseases (extra-pulmonary ARDS) and leaving pneumonia for less than 10% of the patients, and most importantly, including in the research patients that are staying under NIV for extremely short period of time, hence the median timing of ventilation of 3 hours for patients who failed the treatment. A limitation of this study is also the exclusion of severe ARDS patients. Failure rates in other studies are around 50% for NIV, which can be positively interpreted by saying that in case of both extra-pulmonary and pulmonary ARDS, NIV is effective in half of the patients.

The results of Yaroshetskiy et al. (2022) are conflicting to interpret since they report a failure rate of 73%. In this case it is important to note that they only included moderate to severe ARDS population and that is has been shown in the predictors of failure that lower PaO_2/FiO_2 at baseline was highly associated with NIV failure (Chawla et al., 2016; Bellani et al., 2017). This leads towards the fact that the use of NIV on more severe population leads to higher failure rates. However, Bellani et al. (2017) stated that the use of NIV was not different in practice between the three severity groups, against the current state of evidence on the subject. This raises questions on whether this "non-adequate" use of the therapy is deliberate or if lack of precision and sharpness of knowledge could be at the origin. As a result of the questionnaire, it is clear that Spanish physiotherapists are not in complete osmosis with the current knowledge since none of the participants considered ETI as a first line treatment for moderate ARDS and shows that Chilean professionals are more prone to take a scientifically based decision, with 40% of them considering ETI as first line treatment, and 60% for NIV as first line. On the contrary, most participants of the questionnaire apart from one Spanish subject (HFNC), and 2 French ones (depends on the patient) did not consider other possibilities than invasive ventilation in the case of severe ARDS, which clearly seem to be the best option when evoking failure rates and improvement of parameters.

One result that points out from the studies is the comparison in the randomized control trial of Patel et al. (2016) of facemask and helmet NIV. The failure rate in the facemask group is 61.5% when in the helmet group drastically drops to 18.2%. This result is conclusive on the net effect and difference of the two interfaces when regarding the failure rate.

Following a logical interpretation of the results, the focus of the question in NIV should not only be on the failure rate but also on the mortality rates (ICU, Hospital, 90-days). This concern has been raised in previous articles (Antonelli et al., 2001; Rana et al., 2006) and the results of this review are going in this sense. Bellani et al. (2017) reported 42.7% of mortality among the subjects who failed NIV which stands as the smallest and most optimistic value. Sehgal et al. (2015) reported 82.6% of mortality, Yaroshetskiy et al. (2022) 100%, Chawla et al. (2016) 69%, and Patel et al. (2016) 48.7% vs 27.3% for hospital, 56.4% vs 34.1% for 90-days, respectively in the case of facemask and helmet. Chawla et al. (2016) enhance this statistics by giving details depending on the severity of the pathology, and moderate and severe results are above 70% of mortality. Bellani et al. (2017) used multivariate COX analysis is linking NIV and ICU mortality indicating that NIV in the case of moderate and severe cases seem to lead towards high mortality rates. This link could be explained by the fact that patients under NIV are according to two studies of this review older, frailer, and with a greater number of comorbidities. Although these parameters are defending the treatment technique, it is important to be aware of the risks of delayed ETI, and the consequences it can have. By showing that NIV was used for any severity of the pathology, Bellani et al. (2017) are unrevealing some points that could include persistence of NIV against ETI criteria, thus leading to the late ETI. Lastly, the same study is showing that mortality in patients with a PaO_2/FiO_2 of less than 150 mmHg was 36.2% for NIV and 24.7 with IMV. This opens a new window of research in the field and calls for answers on what is the current state of practice on the ETI level. Being able to pick the right population when implementing any non-invasive technology could reduce failure rate, but mostly could allow mortality in this category to decrease.

In the case of NIV, outcomes are clearly differing when using a full-face mask in comparison to the helmet interface. In the ETI reasons, Patel et al. (2016) and Sehgal et al. (2015) are pointing out respiratory failure as the first reason for ETI in the case of full-face mask NIV. As an example, this includes refractory hypoxemia or tachypnoea. As a correlation, tachypnoea can be associated to worsening of the respiratory failure, but can also be coming from psychological reasons, and most importantly stress itself (Gerritsen and Band, 2018). Frat et al. (2015) clearly showed that full-face mask comfort for the patient is not optimal, and the grades given to it on the visual analogue scale are going in this way. This would be the first conclusion drawn from the randomized control trial, that helmet is more comfortable and less aggressive for the patient, thus can have an effect on tachypnoea. Moreover, the randomized control trial shows that helmet ventilation is providing higher levels of PEEP by 3 cm H_2O more than the mask. This allows the tachypnoea to be reduced as well and to correct even better the PaO_2/FiO_2 ratio level. Bellani et al. (2017) found that provided levels of PEEP were more important in invasive mechanical ventilation rather than NIV, but if the study had been done on helmet interfaces, the outcome would have changed, and possibly reaching the same levels. This outline one limitation of NIV through face-mask, since they are not able to provide high levels of PEEP, the management of severe and even moderate ARDS patients will be far from optimal, and ETI would be recommendable. However, in the case of using helmet interfaces, the titration of PEEP is not limited by air leak and patient discomfort, which would allow successful management of this more severe population of ARDS.

Continuing on the beneficial effect of helmet NIV, Patel et al. (2016) are showing that ICU length of stay (4.7 vs 7.8 days) and ventilator-free days (28 vs 12.5 days) are significantly and effectively reduced in the helmet group, and even though total hospital length of stay is not significantly different, being out of the ICU means avoidance of ICU related complications such as ICU – acquired weakness, or ventilatory related complications such as V-ILI or P-ILI or nosocomial infections.

Predictors of NIV failure are then crucial. They are bringing the answer to how and when to stop the non-invasive technique to switch the patient to ETI and avoid the delay of the latter. Almost each article is reporting its set of predictors but Sehgal et al. (2015) as an example are only treating data into a univariate COX regression model and not in the multivariate model. Thus, those data are not significant enough to be considered relevant. However, 4 studies are reporting multivariate COX analysis, and their conclusions are the following. Menzella et al. (2021) only achieved to bring the SOFA score at this position, and not have the low PaO_2/FiO_2 ratio. This can be interpretated that it is one of the differences between ARDS and COVID-ARDS since the general systemic state will apparently weight more than the severity of the ARDS alone. Bellani et al. (2017) are reporting higher non-pulmonary SOFA score, lower PaO2/FiO2 ratio, percentage of increase of $PaCO_2$ over the first days as failure predictors within 28 days. SOFA score is then cited in two of the articles. Chawla et al. (2016) are then using low admission PaO_2/FiO_2 ratio, presence of septic shock and the severity of ARDS as predictors in their multivariate analysis.

Lastly, Yaroshetskiy et al. (2022) are the most precise by stating that if after 48 hours of ventilation, 1) ROX index < 5.02, 2) PaO_2/FiO_2 < 112 mmHg, 3) $P_{ET}CO_2$ < 19.5 mmHg (using a capnometer) and 4) Patrick score ≥ 2, then failure can be predicted.

Therefore, predictors can be uncovered before applying the therapy thanks to the SOFA score, lower PaO_2/FiO_2 ratio, presence of septic shock, severity of ARDS and can be effectively assessed after 48 hours of ventilation with the protocol established by Yaroshetskiy et al. (2022) .

These findings are limited by the lack of precise information on the correlation between SOFA score, PaO_2/FiO_2 and severity of ARDS and failure prediction. Further investigation should be performed in order to determine the optimal limitation values when predicting failure. **Figure 2** is depicting the knowledge drawn from this review. The questionnaire is limited by lack of power due to sample size. Moreover, additional statistical data interpretation would allow the aforementioned to gain power. The latter is limited knowing that it serves only as informative data. The objective of this questionnaire is to have a global idea of the actual involvement and management of

the pathology of and by physiotherapists; therefore, conclusions can't be properly drawn. They can lead to further research on the topic to provide areas of involvement of the profession.

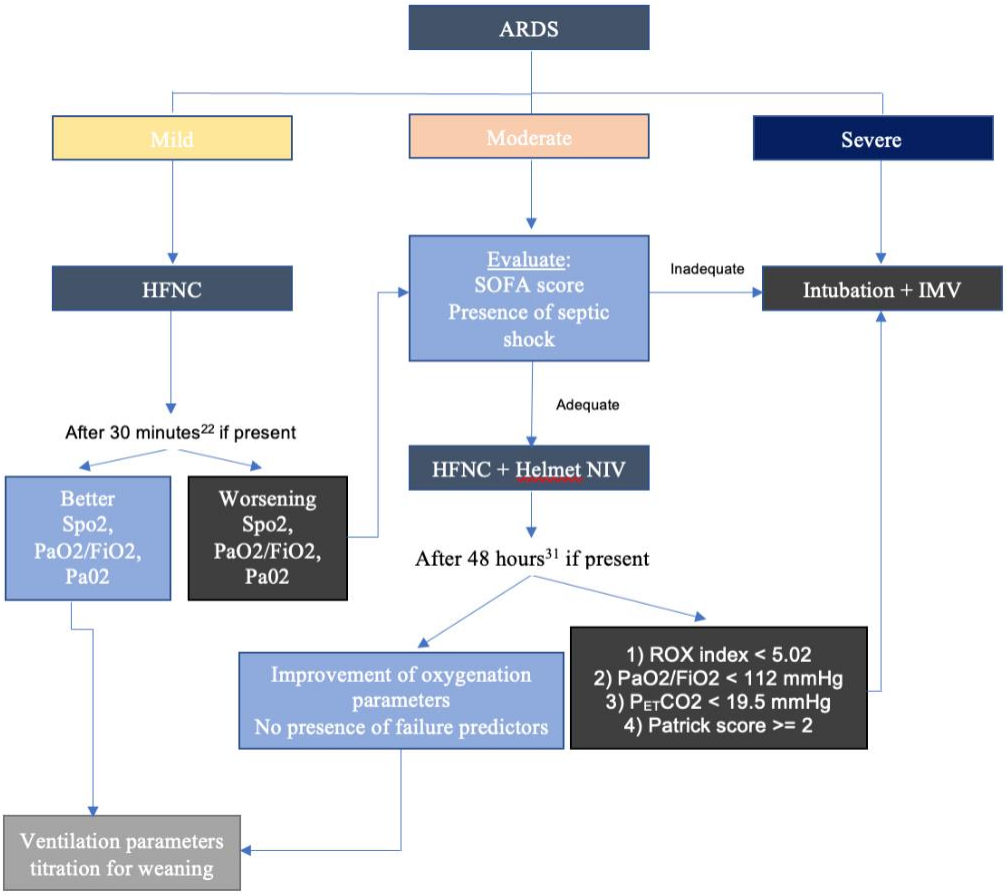

Figure 2. ARDS early ventilatory management scheme

5. Conclusions

To conclude, the effective use of High-Flow Nasal Cannula (HFNC) in conjunction with Non-Invasive Ventilation (NIV) is recommended for treating mild to moderate Acute Respiratory Distress Syndrome (ARDS), but caution is advised, and HFNC should be avoided in cases of severe ARDS. NIV application in moderate and severe ARDS requires careful consideration, with a thorough assessment of predictors of failure both before and during therapy. Notably, NIV shows an association with a higher failure rate in more severe ARDS cases. Survey responses indicate widespread utilization of HFNC as a primary treatment for mild ARDS.

Helmet NIV demonstrates superior outcomes in terms of mortality rates, failure rates, secondary outcomes, and patient comfort when compared to full-face masks. The use of helmet NIV is associated with enhanced comfort for patients compared to full-face masks.

Comparatively, physiotherapists in Chile exhibit greater involvement in the daily care of ICU patients with ARDS than their counterparts in France and Spain. Some responses from French and Spanish professionals deviate from current guidelines on ARDS management and are identified as areas for improvement.

Ongoing research is needed to investigate the potential combination of helmet NIV with HFNC in reducing mortality rates. Further exploration is required to enhance the precision of NIV predictors. Additionally, there is a need for research focusing on the use of helmet NIV in the moderate to severe ARDS population.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Antonelli M, Conti G, Moro M, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med. 2001; 27:1718-1728. DOI:10.1007/S00134-001-1114-4
2. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med. 2007; 35:18-25. DOI:10.1097/01.CCM.0000251821.44259.F3
3. Arcelo M, Ritto B, Assos P, et al. Effect of a Protective-Ventilation Strategy on Mortality in the Acute Respiratory Distress Syndrome. 1998; 338:347-354. DOI:10.1056/NEJM199802053380602
4. Bellani G, Laffey JG, Pham T, et al. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome: Insights from the LUNG SAFE Study. Am J Respir Crit Care Med. 2017; 195:67-77. DOI:10.1164/rccm.201606-1306OC
5. Chawla R, Mansuriya J, Modi N, et al. Acute respiratory distress syndrome: Predictors of noninvasive ventilation failure and intensive care unit mortality in clinical practice. J Crit Care. 2016; 31:26-30. DOI:10.1016/J.JCRC.2015.10.018
6. Coleman MH, Aldrich JM. Acute Respiratory Distress Syndrome: Ventilator Management and Rescue Therapies. Crit Care Clin. 2021; 37:851-866. DOI:10.1016/J.CCC.2021.05.008
7. Coudroy R, Frat JP, Boissier F, Contou D, Robert R, Thille AW. Early identification of acute respiratory distress syndrome in the absence of positive pressure ventilation: Implications for revision of the Berlin criteria for acute respiratory distress syndrome. Crit Care Med. 2018; 46: 540-546. DOI:10.1097/CCM.0000000000002929
8. Dries DJ. ARDS From Syndrome to Disease—Treatment Strategies. Air Med J. 2019; 38:64-67. DOI:10.1016/J.AMJ.2018.12.003
9. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of intensive care medicine/society of critical care medicine clinical practice guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017; 195:1253-1263. DOI:10.1164/RCCM.201703-0548ST
10. Frat JP, Brugiere B, Ragot S, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: An observational pilot study. Respir Care. 2015; 60:170-178. DOI:10.4187/respcare.03075
11. Gerritsen RJS, Band GPH. Breath of Life: The Respiratory Vagal Stimulation Model of Contemplative Activity. Front Hum Neurosci. 2018; 12:397. DOI:10.3389/FNHUM.2018.00397
12. Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020; 8:1201-1208. DOI:10.1016/S2213-2600(20)30370-2
13. Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023; 49: 727-759. DOI:10.1007/S00134-023-07050-7
14. Grieco DL, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. Crit Care. 2020; 24: 529. DOI:10.1186/s13054-020-03253-2
15. Kassirian S, Taneja R, Mehta S. Diagnosis and management of acute respiratory distress syndrome in a time of COVID-19. Diagnostics. 2020; 10:1053. DOI:10.3390/DIAGNOSTICS10121053
16. Macedo LG, Elkins MR, Maher CG, Moseley AM, Herbert RD, Sherrington C. There was evidence of convergent and construct validity of Physiotherapy Evidence Database quality scale for physiotherapy trials. J Clin Epidemiol. 2010; 63:920-925. DOI:10.1016/J.JCLINEPI.2009.10.005
17. Messika J, Ahmed K Ben, Gaudry S, et al. Use of high-flow nasal cannula oxygen therapy in subjects with ARDS: A 1-year observational study. Respir Care. 2015; 60:162-169. DOI:10.4187/respcare.03423
18. Menzella F, Barbieri C, Fontana M, et al. Effectiveness of noninvasive ventilation in COVID-19 related-acute respiratory distress syndrome. Clinical Respiratory Journal. 2021; 15:779-787. DOI:10.1111/CRJ.13361
19. Moseley AM, Sherrington C, Elkins MR, Herbert RD, Maher CG. Indexing of randomised controlled trials of physiotherapy interventions: a comparison of AMED, CENTRAL, CINAHL, EMBASE, Hooked on Evidence, PEDro, PsycINFO and PubMed. Physiotherapy. 2009; 95:151-156. DOI:10.1016/j.physio.2009.01.006

20. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone position for acute respiratory distress syndrome: A systematic review and meta-analysis. Ann Am Thorac Soc. 2017; 14: S280-S288. DOI:10.1513/AnnalsATS.201704-343OT
21. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome A Randomized Clinical Trial Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT. JAMA. 2016; 315:2435-2441. DOI:10.1001/jama.2016.6338
22. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome a randomized clinical trial. JAMA - Journal of the American Medical Association. 2016; 315:2435-2441. DOI:10.1001/jama.2016.6338
23. Patrick W, Webster K, Ludwig L, Roberts D, Wiebe P, Younes M. Noninvasive positive-pressure ventilation in acute respiratory distress without prior chronic respiratory failure. Am J Respir Crit Care Med. 1996 ; 153:1005-1011. DOI: 10.1164/ajrccm.153.3.8630538
24. Peter JV, Moran JL, Phillips-Hughes J, Graham P, Bersten AD. Effect of Non-Invasive Positive Pressure Ventilation (NIPPV) on Mortality in Patients with Acute Cardiogenic Pulmonary Oedema: A Meta-Analysis. Lancet. 2006; 367:1155-1163. DOI: 10.1016/S0140-6736(06)68506-1
25. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. Crit Care. 2006; 10: R79. DOI:10.1186/CC4923
26. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA. 2012; 307:2526-2533. DOI:10.1001/jama.2012.5669
27. Rezoagli E, Fumagalli R, Bellani G. Definition and epidemiology of acute respiratory distress syndrome. Ann Transl Med. 2017; 5:282. DOI:10.21037/atm.2017.06.62
28. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure TASK FORCE REPORT ERS/ATS GUIDELINES. Eur Respir J. 2017; 50:1602426. DOI:10.1183/13993003.02426-2016
29. Saguil AMM, Fargo MV. Acute Respiratory Distress Syndrome:Diagnosis and Management. AmFam Physician. 2020; 101:730-738.
30. Sehgal IS, Chaudhuri S, Dhooria S, Agarwal R, Chaudhry D. A study on the role of noninvasive ventilation in mild-to-moderate acute respiratory distress syndrome. Indian Journal of Critical Care Medicine. 2015; 19:593-599. DOI:10.4103/0972-5229.167037
31. Slutsky AS, Ranieri VM. Ventilator-Induced Lung Injury. New England Journal of Medicine. 2013; 369:2126-2136. DOI:10.1056/NEJMra1208707
32. Tasaka S, Ohshimo S, Takeuchi M, et al. ARDS clinical practice guideline 2021. Respir Investig. 2022; 60:446-495. DOI:10.1016/J.RESINV.2022.05.003
33. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome: 50 years. Drazen JM, ed. New England Journal of Medicine. 2017; 377:562-572. DOI:10.1056/NEJMra1608077
34. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. Epidemiology. 2007; 18:805-35. DOI: 10.1097/EDE.0b013e3181577511.
35. Villar J, Kacmarek RM. The American-European Consensus Conference definition of the acute respiratory distress syndrome is dead, long live positive end-expiratory pressure! Med Intensiva. 2012; 36:571-575. DOI:10.1016/j.medin.2012.08.010
36. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. J Clin Epidemiol. 2008; 61:344-349. DOI: 10.1016/j.jclinepi.2007.11.008.
37. Yaroshetskiy AI, Merzhoeva ZM, Tsareva NA, et al. Breathing pattern, accessory respiratory muscles work, and gas exchange evaluation for prediction of NIV failure in moderate-to-severe COVID-19-associated ARDS after deterioration of respiratory failure outside ICU: the COVID-NIV observational study. BMC Anesthesiol. 2022; 22: 307. DOI:10.1186/S12871-022-01847-7

6. Apendixes

6.1. Appendix 1

Management of Acute Respiratory Distress syndrome in the ICU

Dear ones,

In the process of my 4th year's final year project in physiotherapy in the CEU San Pablo in Madrid, I am realizing a bibliographic review about the management of Acute Respiratory Distress Syndrome (ARDS) in the ICU from early diagnosis.

As a French student, studying in Spain and doing an international exchange in Chile, I would like to gather information about the management of the pathology according to the country, and put it int perspective as a discussion.

From a personal experience, ARDS is a pathology that is not perfectly understood yet and treated empirically, without a proper protocol. Furthermore, the role of respiratory physiotherapy is primordial in the prognostic of each individual patient and is not clearly established in each country.

Based upon those, I am kindly asking you to share you experience through this questionnaire that is completely anonymous and will last about 5 minutes.

I am available for any question or doubt at the following email: b.theo@usp.ceu.es

Thank you for your participation,

Théo Battalian

*mandatory

Section 1: Personal information

1. Are you or have you been physiotherapist in Intensive care units (ICU)? *

   If the answer is negative, you don't need to continue answering.

   One answer only.

   ◯ Yes
   ◯ No

2. How old are you? *

One answer only.

- ◯ 18 - 25 years old
- ◯ 26 - 35 years old
- ◯ 36 - 50 years old
- ◯ 51 - 65 years old
- ◯ 66 and above

3. What was/is your country and city of practice? *

_____

4. Which type of ICU's do/did you work in? *

Multiple answers possible.

- ☐ Neonatal
- ☐ Pediatric
- ☐ Cardiac
- ☐ Severe burns
- ☐ Polyvalent
- ☐ Post-surgical
- ☐ Other: _____

5. Which type of physiotherapy treatment are/were you applying? *

Multiple answers possible.

- ☐ Motor
- ☐ Respiratory
- ☐ Neurologic
- ☐ Other: _____

6. How many sessions of physiotherapy per 24 hours for each patient? *

One answer only.

- ◯ Less than 3
- ◯ Between 3 and 5
- ◯ More than 5
- ◯ Other: _____

7. What is/was your experience in the ICU? *

One answer only.

- ◯ Less than 1 year
- ◯ 2 - 5 years
- ◯ 5 - 10 years
- ◯ 10 - 20 years
- ◯ 20 + years

Section 2: Diagnosis of the pathology.

8. Are you aware of the Berlin classification of ARDS from 2011? *

One answer only.

- ◯ Yes
- ◯ No

9. In your personal experience, which criteria are considered in the diagnosis of ARDS? *

Multiple answers possible.

- [ ] Chest imaging
- [ ] Oxygenation level (PaFi)
- [ ] Origin of the oedema (non - cardiogenic oedema)
- [ ] Timing (> 1 week of symptomatology)
- [ ] Other: _____

10. Do you personally believe in this diagnostic method? *

One answer only.

- ◯ Yes
- ◯ No

11. Did the pandemic change the diagnostic technic of ARDS? *

One answer only.

- ◯ Yes
- ◯ No

Section 3: Management of the pathology

12. In the case of mild ARDS (PaFi 200 – 300 mmHg) which type of ventilatory treatment do you usually use as a **first line of treatment**?

One answer only.

- ◯ High Flow Nasal Canula (HFNC)
- ◯ Non - invasive ventilation (NIV)
- ◯ Oxygen therapy
- ◯ Invasive ventilation through endotracheal intubationNone
- ◯ Other: _____
- ◯

13. In the case of moderate ARDS (PaFi 100 – 200 mmHg) which type of ventilatory treatment do you usually use as a **first line of treatment**?

One answer only.

- ◯ High flow nasal canula (HFNC)
- ◯ Non - invasive ventilation (NIV)
- ◯ Oxygen therapy
- ◯ Invasive ventilation through endotracheal intubationNone
- ◯ Other: _____
- ◯

14. In the case of severe ARDS (PaFi < 100 mmHg) which type of ventilatory treatment do you usually use as a **first line of treatment**?

One answer only.

- ◯ High flow nasal canula (HFNC)
- ◯ Non - invasive ventilation (NIV)
- ◯ Oxygen therapy
- ◯ Invasive ventilation through endotracheal intubationNone
- ◯ Other: _____
- ◯

15. How do you measure the evolution after 1 hour of any ventilatory therapy or change inventilatory parameters?

One answer only.

- ◯ Clinical evaluation (monitor evaluation, signs, and symptoms)
- ◯ Gasometrical analysis
- ◯ Both
- ◯ Other: _____

16. Which are the intubation criteria in your ICU? *

One answer per line.

	Not at all important	Low importance	Neutral	Important	Very important
PaFi < 150 mmHg	◯	◯	◯	◯	◯
Glasgow coma scale < 8 points	◯	◯	◯	◯	◯
Shock with unstable hemodynamic	◯	◯	◯	◯	◯
Hyperlactatemia	◯	◯	◯	◯	◯

17. Any other intubation criteria you would consider?

_____

18. Do you use protective factors with mechanical ventilation? *

One answer only.

◯ Yes

◯ No

19. If yes, which ones?

Multiple answers possible.

☐ Control of PEEP
☐ Tidal volume according to the ml/kg (ideal weight)
☐ Driving pressure.
☐ Neuromuscular blocking agents
☐ Prone ventilation
☐ Other: _____

20. Which PEEP level would you implement in patients with **moderate** ARDS in invasive ventilation?

One answer only.

- ◯ 5 - 10 cmH2O
- ◯ 10 - 15 cmH2O
- ◯ 15 - 20 cm H20

21. Which level of PEEP would you implement in a patient with **severe** ARDS in invasive ventilation?

One answer only.

- ◯ 5 - 10 cmH20
- ◯ 10 - 15 cm H20
- ◯ 15 - 20 cm H20

22. In which type of patients neuromuscular blocking agents are usually prescribed in your ICU?

One answer only.

- ◯ Mild ARDS
- ◯ Moderate ARDS
- ◯ Severe ARDS
- ◯ Other: _____

23. In which case would you pronate a patient? *

One answer only.

- ◯ PaFi < 150 mmHg with FiO2 0.8
- ◯ Generalized Lung fibrosis
- ◯ Desaturation SpO2 < 90%
- ◯ Severe hypoxemia
- ◯ Other: _____

24. In which case would you evaluate the patient for weaning from the invasive ventilation? *

One answer only.

- ◯ PaFi > 200 mmHg; PEEP < 8 cmH20, FiO2 < 0.5
- ◯ PaFi > 150 mmHg; PEEP < 10 cmH20; FiO2 < 0.6
- ◯ PaFi > 150 mmHg; PEEP < 8 cmH2O; FiO2 < 0.6
- ◯ Other: _____

Section 4: Physiotherapist involvement

25. In the following table, cross the level of implication you have as a physiotherapist in each treatment method.
0 = no involvement; 5 = completely in charge

One answer per line.

	0	1	2	3	4	5
High flow nasal canula	◯	◯	◯	◯	◯	◯
Non - invasive ventilation	◯	◯	◯	◯	◯	◯
Oxygen therapy	◯	◯	◯	◯	◯	◯
Invasive ventilation	◯	◯	◯	◯	◯	◯
Endotracheal intubation decision taking	◯	◯	◯	◯	◯	◯
Endotracheal intubation maneuver	◯	◯	◯	◯	◯	◯
Management of ventilatory parameters	◯	◯	◯	◯	◯	◯
Weaning decision taking	◯	◯	◯	◯	◯	◯
Pronation	◯	◯	◯	◯	◯	◯
Decision between each treatment evolution	◯	◯	◯	◯	◯	◯

26. Did you notice a difference of involvement before and after the pandemic? *

One answer only.

◯ Yes
◯ No

27. If yes, in the following table, cross the level of implication you had as a physiotherapist in each treatment method **before** the pandemic.
0 = no involvement; 5 = completely in charge

One answer per line.

	0	1	2	3	4	5
High flow nasal canula	◯	◯	◯	◯	◯	◯
Non - invasive ventilation	◯	◯	◯	◯	◯	◯
Oxygen therapy	◯	◯	◯	◯	◯	◯
Invasive ventilation	◯	◯	◯	◯	◯	◯
Endotracheal intubation decision taking	◯	◯	◯	◯	◯	◯
Endotracheal intubation maneuver	◯	◯	◯	◯	◯	◯
Management of ventilatory parameters	◯	◯	◯	◯	◯	◯
Weaning decision taking	◯	◯	◯	◯	◯	◯
Pronation	◯	◯	◯	◯	◯	◯
Decision between each treatment evolution	◯	◯	◯	◯	◯	◯

28. Do you consider inter - disciplinary approach important in the management of a pathology in the ICU?

One answer only.

◯ Yes
◯ No

29. Do you generally feel satisfied with the physiotherapist role in the ICU and the decision taking?

30. Would you like to add any comment to this study?

6.2. Appendix 2

Table A2.1. Scoring of articles according to STROBE statement and PEDro scale

	STROBE score (Vandenbroucke et al., 2007; Von Elm et al., 2008)	PEDro scale (Moseley et al., 2009; Macedo et al., 2010)	Missing information/items
Frat et al. (2015)	19 out of 22	x	- Study's funding sources - Assessment of the generalizability of the study findings.
Messika et al. (2015)	19 out of 22	x	- Study's funding source - Sample size calculation - Assessment of the generalizability of the study findings.
Menzella et al. (2021)	20 out of 22	x	- Study's funding source - Assessment of the generalizability of the study findings.
Bellani et al. (2017)	22 out of 22	x	x
Sehgal et al. (2015)	16 out of 22	x	- Study's funding - Potential sources of bias - Assessment of the generalizability of the study findings
Patel et al. (2016)	x	8 out of 10	- Blinding of therapists - Blinding of assessors for mortality outcome - Treatment or "intention to treat" for mortality outcome
Yaroshetskiy et al. (2022)	20 out of 22	x	- Study's funding source - Assessment of the generalizability of the study findings.
Chawla et al. (2016)	21 out of 22	x	- Assessment of the generalizability of the study findings