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Noninvasive Respiratory Strategies in Patients with Acute Hypoxemic Respiratory Failure and COVID-19 in Gabon: A Prospective Observational Study

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Abstract

Importance: The best respiratory support technique to reduce intubation and mortality in patients with respiratory failure due to COVID-19 is controversial. **Objective:** To determine the respiratory support technique that could reduce the need for tracheal intubation and mortality in patients with respiratory failure due to COVID-19 admitted to intensive care units (ICUs) of Military's Hospital (HIAOBO) in Gabon. **Design, Setting, and Participants-Methodology:** Prospective observational study over 10 months (January 2021-October 2021). We included patients admitted to intensive care for SARS Cov2 pneumonia who had benefited from available ventilatory support: high concentration face mask, High Flow Nasal cannula (HFNC), NIV (Non Invasive Ventilation), Continuous Positive Airway Pressure (CPAP). The choice was guided by the clinical condition, and the choice of the prescribing physicians. Recourse to mechanical ventilation was decided when faced with a Glasgow score of less than 13, an SpO_2/FiO_2 ratio ≤ 300, a FR ≥ 35/min, the impossibility of drainage of secretions. **Main Outcomes and Measures:** The primary outcome was the proportion of patients requiring intubation. The secondary outcomes were mortality in ICU. **Results:** The sample included 97 patients, the average age was55.6 years, hypertension was the main comorbidity (51.1%). Mean respiratory rate (RR) was 30.8 cycles/min, admission SpO2 was 83%, respiratory alkalosis was present in 63% of patients, mean CT involvement was 51%.Respiratory support was NIV (56.7%), CPAP (21.65%), high concentration face mask (18.55%). Sixteen percent (16%) of patients

were intubated, 93% of them following failure of NIV. Mortality was 30%, mechanical ventilation was an independent risk factor for mortality. **Conclusions:** Non Invasive Ventilation, CPAP, and high-concentration face mask were frequently used in patients with COVID-related acute respiratory failure. The CPAP has reduced the need for intubation. Mechanical ventilation is a risk factor for death.

Keywords

Respiratory Failure, COVID 19-Intensive Care Units, Military Hospital, Gabon

1. Introduction

Oxygenation is essential in patients admitted to intensive care for SARS-CoV-2 pneumonia. Oxygen therapy performed with different interfaces ranging from high concentration masks to mechanical ventilation, the frequency of use varies between centers and depends on the clinical picture. In Yang's study carried out at the start of the pandemic, mechanical ventilation and non-invasive ventilation were the most used, followed by the nasal cannula with a high mortality rate [1]. The strategy for using the interfaces is progressive, depending on the initial clinical picture. In many centers, a patient who arrives in the emergency room with hypoxia is put on a single nasal cannula (NC) or face mask (FM). Patients who present with a clinical picture ranging from "normal" to "tachypneic" with normal oxygen saturation generally have an outpatient pulse oximetry recording for 60 s to screen for exertional hypoxia (*i.e.* say silent or occult) [2] [3]. Patients with hypoxemic acute respiratory failure unresponsive to simple nasal cannula and/or face mask (FM) oxygenation may benefit from high flow nasal cannula (HFNC). In some centers, some patients are initially placed under the high-flow nasal cannula (HFNC) without resorting to endotracheal intubation. This approach is controversial by some centers which favor non-invasive ventilation (NIV) as first intention. In our intensive care unit, 04 techniques are used gradually depending on the availability of devices and the training of paramedical teams and the prescription habits of medical teams.The aim of the study was to assess the effectiveness of different various respiratory assistance techniques available, Facial Mask(FM), High Flow Nasal Cannula (HFNC) type Optiflow®, Boussignac® CPAP (Continuous Positive Airway Pressure), Non Invasive Ventilation (NIV) and the use of mechanical ventilation (MV) in the management of SARS COV 2 pneumonia at Omar Bongo Ondimba Army Training Hospital (HIAOBO).

2. Material and Method

The study received approval from the ethics committee of the Omar Bongo Ondimba Army Training Hospital, Gabon.

- Study Design

This is a prospective observational study over 10 months (January 2021-October 2021). Study carried out in intensive care unit Omar's Bongo Ondimba Army Training Hospital in Gabon.

- Participant

Patients could be enrolled if they have all the following criteria: age older than 18 years, suspected or confirmed diagnosis of COVID-19 (via reverse transcriptase-polymerase chain reaction test from a nasopharyngeal swab), a pulmonary infiltrate, and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) equal to or below 200 mm Hg while breathing oxygen at a flow rate of 10 L/min or more for at least 15 minutes. Fio2 was estimated as follows: $FiO_2 = 0.03 \times$ (oxygen flow L/min) + 0.21.

Inclusion criteria: adult patients with respiratory failure due to COVID-19 were included

Non inclusion criteria : The exacerbation of chronic lung disease, cardiogenic pulmonary edema, hemodynamic instability defined by signs of hypoperfusion or use of vasopressors, Glasgow Coma Scale score equal to or below 12 points, urgent need for endotracheal intubation and refusal to participate.

- Protocol

The Optiflow® was initiated in patients with a respiratory rate (RR) ≥ 30 and an $SpO_2 \leq 93\%$. Under Optiflow®, the flow rate was set to the minimum value of 30 L/min and the FiO_2 titrated for $SpO_2 > 92\%$. NIV or CPAP were immediately initiated when RR > 35 and $SpO_2 < 92$. The management objectives were $SpO_2 \geq 92\%$, RR ≤ 35, a SpO_2/FiO_2 ratio ≥ 300 in patients who had or had not benefited from an arterial blood gas measurement [4]. The choice of technique was left to the discretion of the clinician. The NIV (with Spontaneous Ventilation with inspiratory support) and CPAP of Boussignac® were carried out for one hour every 4 hours, between the sessions, the patient was put under a high concentration mask at 12 L/min. The Optiflow® was put on continuous. Mechanical ventilation was performed in the event of failure of NIV/CPAP defined by the need for continuous NIV/CPAP, the occurrence of impaired consciousness (Glasgow score less than 13), severe hypoxia with an SpO_2/FiO_2 ratio ≤ 300. Failure of HFNC treatment was defined by the need for intubation. For decision to intubate the clinician was left to the discretion of the clinician could use the following criteria: 1/Glasgow score < 12; 2/Cardiac arrest—haemodynamic instability, 3/Respiratory criteria with at least two of the following criteria ($PaO_2 < 60$ mmHg or $SpO_2 < 90\%$ under $FiO_2 = 1$, Respiratory acidosis with pH < 7.25, Respiratory rate > 35 Cycles/min, impossibility of drainage of secretions. All patients had received antibiotic therapy with Ceftriaxone and Azithromycin, curative dose low molecular weight heparin (LMWH), vitamin C, Zinc.

- Outcomes

The primary outcome was the proportion of patients who required endotracheal intubation. The secondary outcomes: included the mortality in the ICU.

- Statistical Analysis

Using SPSS version 25 software. Categorical variables were expressed as percentages and quantitative variables were expressed as mean and standard deviation. The association between categorical variables was evaluated by the Chi2 or Fisher test for small numbers. The significance threshold was set at 5%.

3. Results

Of 105 patients admitted for SARS-COV-2 pneumonia, 97 patients were included. The sample was between 15 and 85 years old, with an average age of 55.6 ± 14.6 years. The most representative age was 50-60 years old, comprising 30% of patients. There were 47 women (48.5%) and 50 men (51.5%), giving a sex ratio of 1.06. High blood pressure and diabetes were the main medical histories. 33% of patients admitted to intensive care had at least 2 defects. The association HTA/Diabetes was the most found (20%). 28% of patients had no history. Only 43 patients had undergone gas analysis on admission. The majority of patients were in respiratory alkalosis (63%). The severity of the respiratory impairment was assessed with the SpO_2/FiO_2 ratio for everyone. 86 patients had performed a chest CT scan, the ground glass appearance was predominant (80%).

Table 1 summarizes the patient characteristics.

Table 1. Patients' characteristics.

	Number (%)
Mean age (years)	55.6
Sex	
- Men	50 (51.5)
- Women	47 (48.5)
Comorbidities	
- hypertension	50 (51.1)
- Diabetes	33 (34)
- None	27 (27.8)
Number of comorbidities	
- 1:	38 (39.2)
- 2:	24 (24.7)
- 3:	7 (7.2)
- 4:	41 (1)
Respiratory rate (cycle/min)	
- Mean	30.8 ± 7
- <24	8 (8.2%)
- 24 - 30	45 (46.4%)
- >30	44 (45.4%)

Continued

SPO_2 (%)	
- Mean	83 ± 12.5
- <90%	61 (62.9)
- 90% - 95%	30 (30.9)
- >95%	6 (6.2)
Blood gas (N = 43)	
- Respiratoryalkalosis	63%
- Respiratoryacidosis	16%
- Metabolicacidosis	13%
- Metabolicalkalosis	5%
Chest CT scan (N = 86)	
- Mean:	51% ± 6%
- <30%	18 (20.9%)
- 30% - 60%	38 (44.2%)
- >60%	30 (34.9%)
Signs of respiratory struggle	
- Presence of signs	56 (526%)
- Absence of signs	41 (47.4%)

Biological examinations

There was mainly acute renal failure and an increase in thrombosis markers. Table 2 summarizes the biological constants.

Ventilatory assistance: The frequency of use of the techniques depended on the clinician and the availability of the devices (02 Optiflow® devices were available) (Table 3).

Evolution: Favorable evolution in 68.05% of patients. Mortality was 30% (n = 30). Due to lack of available space, 1% of patients were transferred to another hospital. The average length of stay was 6.51 days with extremes of 1 and 32 days

Prognostic factors (Table 4, Table 5)

The risk factors for mortality were the degree of lung invasion measured by chest CT scan (Table 4).

Mechanical ventilation was significantly correlated with mortality (Table 5).

4. Discussion

Our study aimed to compare the effectiveness of different ventilatory assistance techniques, their impact on mortality and the use of mechanical ventilation in patients with SARS Cov 2 pneumonia. In our prospective observational study, 56.70% of patients benefited from NIV, 21.65% from CPAP and 3.10% from Optiflow.

Table 2. Biologic results.

Mean ± Standard Deviation		*Extremes*
Leukocytes (103/mm^3)	12 ± 4.5	3.9 - 24
Hemoglobin (g/dl)	11.9 ± 2.1	6.1 - 15.5
Hematocrit (%)	33.9 ± 8.3	15.1 - 66.1
Platelets (103/mm^3)	210.1 ± 87.2	33.0 - 399.0
D-Dimers (ng/l)	7668.2 ± 22615.4	100.0 - 123329.0
Urea (mmol/l)	10.5 ± 12.4	2.9 - 73.3
Creatinine (µmol/l)	163.0 ± 292.1	2.7 - 1534.0

Table 3. Distribution according to ventilatory assistance.

	Number	**Percentage (%)**	**Use of orotrachealintubation**	
			NNumber	**%**
Facial Mask alone	18	18.55	0	0
NIV	55	56.70	15	93,75
Optiflow®	3	3.10	1	6,25
Boussignac CPAP	21	21.65	0	0
Total	97	100.00	16	100

Table 4. Prognostic factors.

Factors	Death n(%)	OR [95% CI]	**p**
CT > 60% achievement	**13 (43.3)**	**13 [1.53 - 110.74]**	**0.007**
RR > 31 cycles/min	**21 (47.7)**	**5.93 [2.09 - 16.85]**	**<0.001**
Signs of respiratory struggles	**22 (43.1)**	**5.06 [1.82 - 14.05]**	**0.001**

Table 5. Prognosis according to the technique of respiratory assistance.

	Death	OR [95% CI]	**p**
CPAP	2 (11.8)	0.28 [0.06 - 1.30]	0.139
OPTIFLOW®	1 (33.3)	1.24 [0.11 - 14.26]	1.000
NIV	22 (40)	1.75 [0.44 - 11.08]	1.005
Mechanical ventilation	**16 (75)**	12.19 [3.47 - 42.83]	**<0.001**

Regarding the first outcome, it appears that CPAP in first intention made it possible to avoid the use of intubation because no patient on CPAP benefited from orotracheal intubation, unlike patients on NIV and Optiflow® or mechanical ventilation was used in 15 patients on NIV and 1 patient on Optiflow®. It is possible that the lower rate of tracheal intubation in the CPAP group is linked to a recruitment bias, in fact, practitioners were likely to offer CPAP in less serious patients and reserve NIV for patients in very critical condition, for example, Co-

simo Franco's study found a PaO_2/FiO_2 ratio of 166 in patients placed on ONHD, 151 in the CPAP group and 138 in the NIV group, similarly, the SOFA score was 4 in the NIV group, 3.3 in the CPAP group and 2.5 in the ONHD group these results show that NIV is immediately reserved for the most serious patients [5], so it is not surprising that NIV has more failures than other techniques. Similarly, the low rate of intubation observed in patients on Optiflow® is also linked to this bias because this technique has been used very little because it is very recent and not very available in our structure.

Our results show that NIV is the technique most used in first intention in patients with severe impairment in intensive care units. This treatment option is common with some efficacy and failures. The study by NardiTetaj *et al*. on 307 COVID patients in ARDS, 224 benefited from NIV as first intention, there was failure in 84 patients with the use of intubation, the statistical analysis showed that the main factor of risk of NIV failure was a PaO_2/FiO_2 ratio below 200 when starting NIV [6].

The superiority of support in reducing the need for intubation is controversial. A systematic review and meta-analysis of 25 randomized clinical trials (3804 patients) showed that non-invasive ventilation and HFNO were superior to conventional oxygen therapy on the use of orotracheal intubation and 90-day mortality in patients with acute respiratory failure due to COVID-19 [7]. The Colombian study by Gustavo A Ospina-Tascón finds that among patients with severe COVID-19, use of high-flow oxygen through a nasal cannula significantly decreased need for mechanical ventilation support and time to clinical recovery compared with conventional low-flow oxygen therapy [8]. Domenico Luca Grieco's meta-analysis of 109 patients with COVID-19 and moderate to severe hypoxemia, shows that treatment with non-invasive helmet ventilation (Helmet), compared to nasal high-flow oxygen, did not resulted in no significant difference in the number of days without respiratory support in the 28 days [9]. Wesla Neves da Silva Costa *et al*. compared NIV and nasal cannula, there was no significant difference in the use of intubation and mortality [10].

Our study is not the only one to show the effectiveness of first-line CPAP in reducing the need for intubation. The RECOVERY trial compares 3 groups of COVID patients with hypoxemic acute respiratory failure having an initial strategy of either CPAP or NIV or conventional oxygen therapy finds that an initial strategy with CPAP significantly reduced the risk of tracheal intubation or mortality compared to conventional oxygen therapy, but there was no significant difference between an initial strategy with HFNO compared to conventional oxygen therapy. The trial was stopped prematurely due to falling numbers of COVID-19 cases in the UK [11]. Our study is in line with the RECOVERY trial with a low use of intubation in patients on CPAP and high-flow mask oxygen therapy despite our small sample. ORANGER *et al*. treated 38 patients with CPAP in a respiratory intensive care unit, although the study included a limited number of patients, CPAP made it possible not to resort to intubation in pa-

tients, the study presents a bias because some of the patients were not to benefit from intubation after multidisciplinary staff [12].

Regarding the second endpoint, our study found mechanical ventilation as an independent risk factor for mortality .In our study, 100% of intubated patients died. Faraone found a mortality of 33% of intubated patients [13]. Of 1260 admissions to 24 Italian intensive care units, Zanella found an overall mortality of 34% with a mortality of 38% in patients on mechanical ventilation [14]. Too late intubation and the difficulties related to the management of the intubated patient with the occurrence of nosocomial respiratory infections explain our results.

In our study, no respiratory assistance technique was correlated with death, results that are controversial in the literature. Describing a population of COVID-19 patients treated with CPAP outside of intensive care, Vaschetto found significantly higher 60-day in-hospital mortality in patients receiving CPAP for more than 3 days compared to those receiving CPAP for less than 3 days [15]. Cosimo Franco found no significant difference in mortality at 30 days by comparing NIV and HFNC after adjusting for confounding factors. In this study, NIV and HFNC were performed outside intensive care [5]. In Ferrayro's study's, across 14 trials (1275 patients), noninvasive ventilation via a face mask was significantly associated with a lower risk of both mortality and tracheal intubation. In contrast, HFNO was significantly associated with a lower risk of tracheal intubation (5 trials; 1479 patients), but not mortality (3 trials; 1279 patients) [7] while The RECOVERY-RS trial found that CPAP significantly reduced tracheal intubation, but not mortality, although the wide 95% CI precludes the drawing of a specific conclusion about the effect on mortality [11].

Thus, mortality related to ventilatory assistance techniques is not clearly defined. In all cases, studies show that late intubation is harmful; these techniques should not delay mechanical ventilation when necessary.

5. Limitations of the Study

Our study presented limitations, essentially a possible selection bias in patients considered hypoxemic on the basis of an SpO_2 of less than 95% and not on gasometry (P/F ratio), similarly, a small population benefited gas analysis, the extrapolation to the rest of the sample can be a confounding factor. However, some results are supported by the literature. The absence of randomization is for the allocation of the ventilatory assistance technique.

6. Conclusion

Our study shows the effectiveness of different ventilatory assistance techniques in the management of severe Sars Cov-2 pneumonia. No technique is clearly superior in reducing the need for intubation and mortality. Mortality linked to mechanical ventilation remains high in our study. Mortality reduction is multifactorial. Studies show the effectiveness of prone position associated with non-

invasive ventilation or high-flow nasal cannula [16].

Agreement

a) All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript.

b) This submitted article is an original work that is not being considered or reviewed by any other publication and has not been published elsewhere in the same or a similar form.

Authors' Contributions

EDJO NKILLY G: principal investigator HIAOBO, drafting the manuscript.
Fernande MANGA: inclusion and follow-up patients.
OKOUE ONDO R: inclusion and follow-up of HIAOBO patients.
Christian NZE OBIANG: follow-up patients.
Stéphane OLIVEIRA: follow-up patients.
Ulysse MAYEGUE: follow-up patients.
Jean Marcel MANDJI-LAWSON: reading of the manuscript.
TCHOUA R: reading and final approval of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., *et al.* (2020) Clinical Course and Outcomes of Critically Ill Patients with SARS-CoV-2 Pneumonia in Wuhan, China: A Single-Centered, Retrospective, Observational Study. *The Lancet Respiratory Medicine*, **8**, 475-481. https://doi.org/10.1016/S2213-2600(20)30079-5

[2] Murthy, S., Gomersall, C.D. and Fowler, R.A. (2020) Care for Critically Ill Patients with COVID-19. *JAMA*, **323**, 1499-1500. https://doi.org/10.1001/jama.2020.3633

[3] Alhazzani, W., Møller, M.H., Arabi, Y.M., Loeb, M., Gong, M.N., Fan, E., *et al.* (2020) Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Medicine*, **46**, 854-887. https://doi.org/10.1007/s00134-020-06022-5

[4] Rice, T.W., Wheeler, A.P., Bernard, G.R., *et al.* (2007) Comparison of the Spo_2/Fio_2 Ratio and the Pao_2/Fio_2 Ratio in Patients with Acute Lung Injury or ARDS. *Chest*, **132**, 410-417. https://doi.org/10.1378/chest.07-0617

[5] Franco, C., Facciolongo, N., Tonelli, R., *et al.* (2020) Feasibility and Clinical Impact of Out-of-ICU Non-Invasive Respiratory Support in Patients with COVID-19 Related Pneumonia. *European Respiratory Journal*, **56**, 2002130. https://doi.org/10.1183/13993003.02130-2020

[6] Tetaj, N., Piselli, P., Zito, S., De Angelis, G., Marini, M.C., Rubino, D., Gaviano, I., Antonica, M.V., Agostini, E., Porcelli, C., Stazi, G.V., Garotto, G., Busso, D., Scarcia, S., Navarra, A., Cimaglia, C., Topino, S., Iacomi, F., D'Abramo, A., Pinnetti, C., Gualano, G., Capone, A., Villanacci, A., Antinori, A., Palmieri, F., D'Offizi, G., Ian-

niello, S., Taglietti, F., Campioni, P., Vaia, F., Nicastri, E., Girardi, E., Marchioni, L. and on behalf of the ReCOVeRI Study Group (2022) Timing and Outcomes of Noninvasive Ventilation in 307 ARDS COVID-19 Patients: An Observational Study in an Italian Third Level COVID-19 Hospital. *Medicina*, **58**, 1104. https://doi.org/10.3390/medicina58081104

[7] Ferreyro, B.L., Angriman, F., Munshi, L., *et al.* (2020) Association of Noninvasive Oxygenation Strategies with All-Cause Mortality in Adults with Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis. *JAMA*, **324**, 57-67. https://doi.org/10.1001/jama.2020.9524

[8] Ospina-Tascón, G.A., Calderón-Tapia, L.E., García, A.F., *et al.* (2021) HiFLo-Covid Investigators. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients with Severe COVID-19: A Randomized Clinical Trial. *JAMA*, **326**, 2161-2171. https://doi.org/10.1001/jama.2021.20714

[9] D.L., Grieco, L.S., Menga, M., Cesarano, *et al.* (2021) Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure. The HENIVOT Randomized Clinical Trial. *JAMA*, **325**, 1731-1743. https://doi.org/10.1001/jama.2021.4682

[10] da Silva Costa, W.N., Miguel, J.P., Dos Santos Prado, F., de Mello Lula, L.H.S., Amarante, G.A.J., Righetti, R.F. and Yamaguti, W.P. (2022) Noninvasive Ventilation and High-Flow Nasal Cannula in Patients with Acute Hypoxemic Respiratory Failure by Covid-19: A Retrospective Study of the Feasibility, Safety and Outcomes. *Respiratory Physiology & Neurobiology*, **298**, 103842. https://doi.org/10.1016/j.resp.2022.103842

[11] Perkins, G.D., Chen, J., Connolly, B.A., *et al.* (2022) Effect of Noninvasive Respiratory Strategies on Intubation or Mortality among Patients with Acute Hypoxemic Respiratory Failure and COVID-19. The RECOVERY-RS Randomized Clinical Trial. *JAMA*, **327**, 546-558. https://doi.org/10.1001/jama.2022.0028

[12] Oranger, M., Gonzalez-Bermejo, J., Dacosta-Noble, P., *et al.* (2020) Continuous Positive Airway Pressure to Avoid Intubation in SARS-CoV-2 Pneumonia: A Two-Period Retrospective Case-Control Study. *European Respiratory Journal*, **56**, 2001692. https://doi.org/10.1183/13993003.01692-2020

[13] Faraone, A., Beltrame, C., Crociani, A., Carrai, P., Lovicu, E., Filetti, S., Sbaragli, S., Alessi, C., Smith, M.C., Angotti, C. and Fortini, A. (2020) Effectiveness and Safety of Noninvasive Positive Pressure Ventilation in the Treatment of COVID-19-Associated Acute Hypoxemic Respiratory Failure: A Single Center, Non-ICU Setting Experience. *Internal and Emergency Medicine*. https://doi.org/10.21203/rs.3.rs-73781/v1

[14] Zanella, A., Florio, G., *et al.* (2021) Time Course of Risk Factors Associated with Mortality of 1260 Critically Ill Patients with COVID-19 Admitted to 24 Italian Intensive Care Units. *Intensive Care Medicine*, **47**, 995-1008.

[15] Vaschetto, R., Barone-Adesi, F., Racca, F., *et al.* (2021) Outcomes of COVID-19 Patients Treated with Continuous Positive Airway Pressure outside ICU. *ERJ Open Research*, **7**, 00541.

[16] Ding, L., Wang, L., Ma, W. and He, H. (2020) Efficacy and Safety of Early Prone Positioning Combined with HFNC or NIV in Moderate to Severe ARDS: A Multi-Center Prospective Cohort Study. *Critical Care*, **24**, Article No. 28. https://doi.org/10.1186/s13054-020-2738-5