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Acute Respiratory Distress Syndrome (ARDS) Caused by the Novel Coronavirus Disease (COVID-19): A Practical Comprehensive Literature Review

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Abstract

Introduction: The exponential growth of the SARS-CoV-2 virus transmission during the first months of 2020 has placed substantial pressure on health systems worldwide. The complications derived from the novel coronavirus disease (COVID-19) vary in due to comorbidities, sex and age, with more than 50% of the patients who require some level of intensive care developing acute respiratory distress syndrome (ARDS).

Areas covered: Various complications caused by SARS-CoV-2 infection have been identified, the most lethal being the acute respiratory distress syndrome, caused most likely by the presence of severe immune cell response and the concomitant alveolus inflammation. The authors carried out an extensive and comprehensive literature review on SARS-CoV-2 infection, the clinical, pathological and radiological presentation as well as the current treatment strategies.

Expert Opinion

Elevation of inflammatory biomarkers is a common trend among seriously ill patients. The information available strongly suggests that in COVID-19 patients, their altered immune response, including a massive cytokine storm, is responsible for the further damage evidenced among ARDS patients.

The increasingly high number of scientific articles and evidence available can only suggest that the individualization of each case is the norm, not all patients with acute respiratory failure due to COVID-19 meet the Berlin definition and therefore ARDS should be considered as a heterogeneous disease, with a wide range in the expression of its severity and clinical manifestations.

Keywords: ARDS; COVID-19; Berlin Criteria; Respiratory Failure

Introduction

Coronaviruses belong to the extensive family of viruses that can cause disease in both animals and humans. Three coronaviruses have been identified which display a jump from

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animal reservoirs to humans, including the SARS-CoV virus in 2002, the MERS-CoV virus in 2012 and the SARS-CoV-2 virus in 2020 (1). These zoonotic viruses are responsible for causing severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the most recently discovered novel coronavirus disease during 2019 (COVID-19)(2).

SARS-CoV-2 is a spherical-shaped beta coronavirus, with a diameter of 60 to 140nm. The nucleocapsid has helical symmetry and a glycoprotein structured envelope. The virus particles have distinctive peaks of approximately 9 to 12nm that give virions the appearance of a solar corona (3). The complete SARS-CoV-2 genome was described on January 12th, 2020, by Chinese scientists (4) and subsequently shared with the scientific community.

Seven types of coronaviruses have been identified that can infect humans, of which HCoV-NL63, HCoV-229E, HCoV-OC43 and HKU1 are usually responsible for 10 to 30% of upper respiratory tract infections in people(5). The remaining three viruses, SARS-CoV, MERS-CoV and SARS-CoV-2 can cause serious respiratory infections with high morbidity and mortality rates (3, 5).

Table 1. Main characteristics of SARS, MERS and COV2.

	SARS	**MERS**	**COVID-19**
Pathogen	SARS-CoV	MERS-CoV	SARS-CoV-2
Origin	China	Saudi Arabia	China
Incubation (in days)	5 (2-10)	2-14	2-14
Transmission Mode	Drops produced by coughing, sneezing, talking, or breathing.	Drops from person to person	Drops produced by coughing talking or breathing
Key Symptoms	Cough (dry at first), fever and diarrhea in the first or second week of illness, or both	Fever, cough, dyspnea	Fever, dry cough, dyspnea, sore throat
Risk Factors	People with underlying conditions	Men over the age of 60, particularly those with underlying medical conditions such as diabetes, high blood pressure, and kidney failure.	High blood pressure, diabetes, coronary heart disease, over 65 years

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R0	2 to 4 people	Less than 1 person	2 to 2.5 people
Body count (as of May 14th)	774	858	224.172
Lethality Rate	9.6%	34.4%	7.1%

Epidemiology

Acute respiratory distress syndrome (ARDS) represents 10 to 15% of current hospitalizations in the Intensive Care Unit (ICU) and 5% of all hospitalizations; with incidences in South America being 10.1 per 100,000 person-years, Europe with 17.9 per 100,000 person-years, Australia with 34 per 100,000 person-years and the United States with 78.9 per 100,000 person-years (6, 7)

According to the results of the LUNG SAFE study, the incidence of ARDS was the highest in Oceania, with 0.57 cases/ICU bed/year and the lowest in Asia with an ARDS occurrence of 0.27 cases/ICU bed/year (8).

Most studies have shown that rates of mild ARDS (PaO_2/FiO_2 200–300mmHg) represent only 25% of patients with ARDS. Around 75% of patients with moderate or severe ARDS (9), taking into account PaO_2/FiO_2, show incidences of 86 per 100,000 person-years in people with PaO_2/FiO_2 ≤300mmHg and 64 per 100,000 in those people with ≤200mmHg (6, 8).

The incidence increased with the age of the patient, from 16 per 100,000 person-years among individuals aged 15 to 19, to 306 per 100,000 person-years among individuals aged 75 to 84 years (7).

Physiopathology

Based on the care of patients with COVID-19 pneumonia and acute respiratory failure in intensive care units, clinical and radiological information and autopsy reports have been collected. These suggest that at the initial disease stage, primary lung damage was related to a pulmonary vascular disorder, with particularities such as the dissociation between

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hypoxemia and compliance, which is why some authors suggest classifying it into two groups, L and H-phenotypes (9, 10).

Figure 1. SARS-CoV-2 Pathophysiology of ARDS

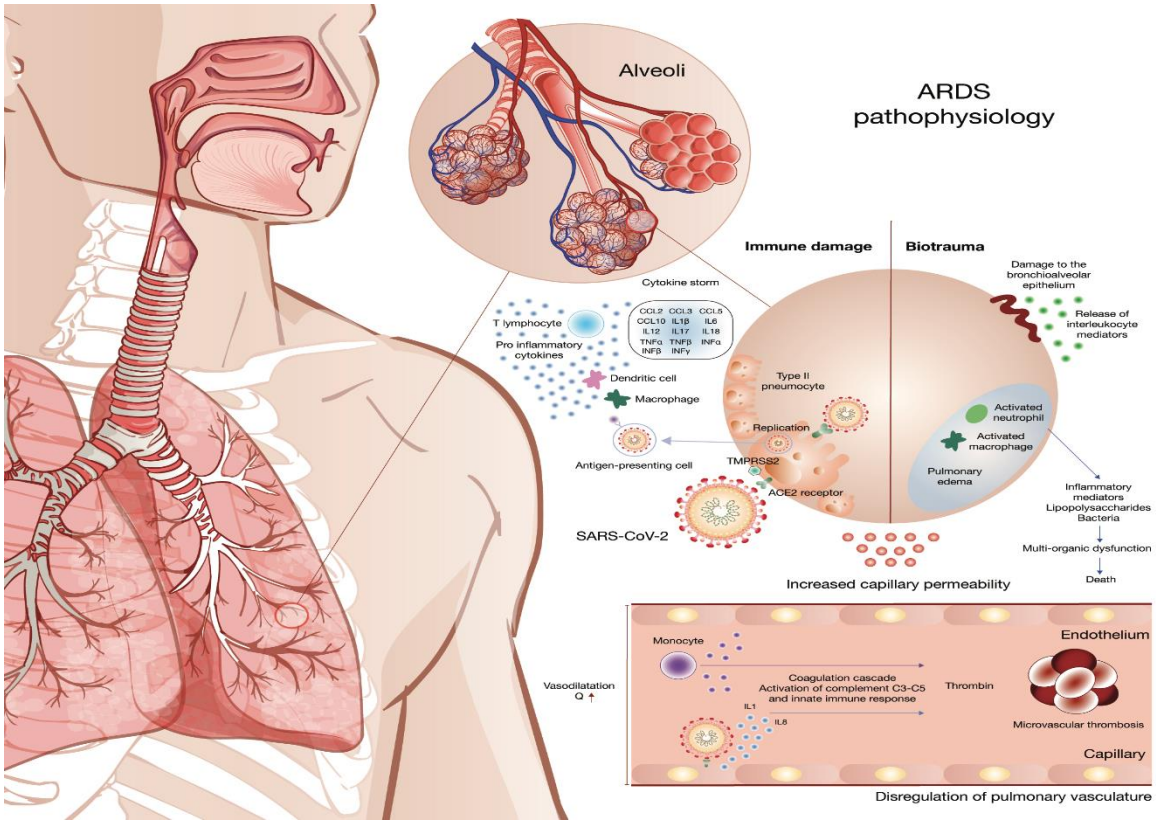

Figure 1 Proposed physiopathology for the development of ARDS due to SARS-COV-2 infection

1. *L (low) phenotype.*

This phenotype presents in an early stage as pneumonitis, where there is mild inflammation that is limited to the sub-pleural interstitium, in nonhomogeneous areas of the lung with different elastic properties, appearing like ground glass lesions under radiographic imaging. However, CT scans of the lung in these patients confirm that there are no significant areas to recruit, indeed type L is low recruitment, low elastance, with nominal compliance and low lung weight (11–15). As hypoxemia is secondary to the alteration of the ventilation/perfusion ratio (V/Q), and rather than an intrinsic problem of the pulmonary

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alveoli, the deviation of the flow towards poorly oxygenated alveolar units is considered a pulmonary vascular dysregulation. (9–13). This is possibly attributed to the affinity of SARS-CoV-2 for the receptor for angiotensin-converting enzyme 2 (ACE2) located on the surface of endothelial cells and arterial smooth muscle cells(15). Under normal conditions, these receptors are related to the natural ability of the pulmonary vasculature to produce local vasoconstriction (16). As this physiological reflex is lost, the smooth muscle of the pulmonary blood vessels does not contract and does not cause hypoxic vasoconstriction due to the decrease in alveolar oxygen pressure (PaO_2), evidencing a state of vasoplegia that finally allows blood flow without adequate oxygenation to the left side of the heart, decreasing the arterial oxygen pressure (PaO_2) (17).

Viral replication causes direct cellular injury to both the pulmonary epithelium and the endothelium, releasing pro-inflammatory cytokines, thus excessive activation of the innate immune system causes damage to the microvascular system. Furthermore, the activation of the complement cascade through the lectin pathway not only causes direct endothelial damage but also recruits leukocytes through the formation of C3a and C5a, responsible for a massive local release of proinflammatory cytokines (18). On the other hand, COVID-19-induced thrombosis includes a local or systemic hypercoagulable state, leading to the formation of large numbers of microthrombi blocking blood flow to oxygenated alveolar units, preventing adequate hematosis (19).

2. *Phenotype H (High).*

About 20-30% of patients admitted to the ICU develop a classic ARDS, this is low compliance that determines such low values of partial oxygen saturation (SPO_2) (17). Several causes explain the development of lung injury, the first is directly related to the disease, SARS-CoV-2 encodes 4 structural proteins, the spike (S) protein, the envelope (E) nucleocapsid (N), membrane (M) and various accessory proteins.

Protein S is a determinant for entry into the host cell, by binding to the ACE2 receptor that is highly expressed in type II alveolar cells (AT2). Once bound, the host serine protease type 2 (TMPRSS2) cleaves the protein S and results in the fusion of the viral and cellular membranes, later the SARS-CoV-2 will release its genomic material in the cytoplasm that will help it in its replication; the lungs appear to be particularly vulnerable due to their large

 doi:10.20944/preprints202006.0045.v1

surface area and because type 2 alveolar epithelial cells act as a reservoir for virus replication (20). The entry of the virus into the host cell triggers the stimulation of the host immune response, as the first line is the innate immune system through antigen-presenting cells (APCs), dendritic cells and macrophages, later transcription factors IRF3 and NF-κB will induce the excess release of proinflammatory cytokines such as interferon (IFN) α and INF-β, IFN-γ, IL-1β, IL-6, IL-12, IL-17, IL-18, IL-33, tumor necrosis factor-alpha (TNF-α), tumour necrosis factor-beta (TGFβ) and chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10. These cytokines recruit neutrophils and monocytes at the site of infection and activate other proinflammatory cytokines and chemokines, including IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1. Combined, this will generate hyperinflammation responsible for direct injury to the lung tissue and will eventually lead to ARDS (20–24).

A second possibility is known as self-inflicted patient lung injury (P-SILI) caused by the respiratory effort made by patients with respiratory failure when breathing spontaneously or with the support of non-invasive mechanical ventilation (NIMV), since the high respiratory impulse generates large tidal volumes (VT) with potential to cause transpulmonary pressure changes. Zones closed by lung damage are temporarily opened and closed again, generating stress injury (pressure changes) and strain injury (changes by deformation), which is known as a ‘Pendelluft phenomenon’ (25). The different forces generated by muscular work cause damage to already injured lungs, increasing vascular leakage by increasing transmural pulmonary vascular pressure. The high respiratory drive may be due to increased stimulation of juxtacapillary receptors or inhibition of slowly adapting pulmonary stretch receptors (Hering-Breuer reflex) (26).

The third cause is an injury caused by invasive mechanical ventilation (VILI), which can lead to new injuries to already injured lungs or worsen current injuries. Injuries generated by mechanical ventilation leads to what is known as biotrauma, the cellular injury generates a local and systemic inflammatory response that will cause more damage. Laceration of the lung endothelium and epithelium results in a flooding of the air space with protein-rich lung edema, macrophages, and activated neutrophils, with loss of aeration, increased concentrations of hydroxyproline, β-growth factor, and interleukin-8 and release of proinflammatory mediators IL-1b, TNF-α, IL-8 and IL-6 at the pulmonary and systemic

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level. Translocation of inflammatory mediators, lipopolysaccharides, and bacteria into the systemic circulation can lead to multiple organ dysfunction and possibly death (25, 26)

Clinical Presentation.

Presentation is highly variable, between asymptomatic and severe. Severe symptoms can warrant hospital admission with potential critical care involvement, characterized by a rapid deterioration in the general condition and an acute worsening of respiratory failure within the first week of symptoms. The average time for the development of ARDS was rapid, on average 2 days from hospital admission or 9 to 12 days after the onset of symptoms (27, 28). General severity characteristics such as age over 65 years, the presence of chronic comorbidities, especially hypertension and diabetes mellitus, the presence of lymphopenia, abnormal liver tests, abnormal coagulation tests, especially with lengthening of prothrombin time (TP) and elevation of the D-dimer, increase in serum ferritin values were also predictive of the development of ARDS and death (31).

Patients admitted to ICUs with severe COVID-19 and who later developed ARDS met the criteria established in the Berlin consensus, including acute onset, presence of abnormalities on lung imaging exams, and severe abnormalities in lung imaging tests. Oxygenation values (32), recognizing this disorder promptly has implications for prognosis (33), does not accurately reflect damage at the cellular level in the alveolar-capillary unit.

A peculiar characteristic observed in some of these patients is the presence of disparity between hypoxemia that reaches severe levels and the relative preservation of respiratory mechanics. These differences suggest the existence of two groups with distinctive clinical characteristics. Type 1 develops severe hypoxemia, but lung compliance is normal or close to normal (low lung elasticity), low ventilation-perfusion ratio (low VA/Q), tomographic images characterized by peripheral ground glass lesions with large areas of pulmonary aeration that would entail a low net lung weight, called by Gattinoni "L phenotype" (Low). Type 2 is characterized by large pulmonary edema resulting in more rigid lungs with low compliance (high elasticity) and the presence of wide right-left shunt (shown in the images by wide bilateral consolidations). With few aerated areas, the lung weight in this group is high, characteristics related to an "H-phenotype" (High) (15, 32). The recognition of clinical characteristics may have important implications in the final management of the

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patient (Table 2). The lack of recognition of sub-phenotypes and their clinical manifestations lead to delayed management with worse results.

Table 2. Distinctive clinical characteristics of clinical behavior in patients diagnosed with Acute Respiratory Distress Syndrome in patients with SARS-CoV-2.

Characteristic	Type 1 Low phenotype	Type 2 High phenotype
Hypoxemia	Severe	Severe
Lung compliance * (C)	Normal	Engaged
Pulmonary elasticity ** (E)	Low	High
Pulmonary tomography image	Bilateral frosted glass peripheral infiltrates.	Wide lung consolidations
Net lung weight	Low	High

Notes: (*) Lung Compliance (Lung Compliance); (**) Lung elasticity (Lung Elastance; E = 1/C)

DIAGNOSIS

There is still heterogeneity for ARDS diagnosis and treatment. Among the general criteria for its diagnosis, the following have been considered:

Table 3. General diagnostic criteria for ARDS.

Severity of acute respiratory distress syndrome	Mild	Moderate	Severe
Time	Acute onset within 1 week of known clinical damage or new respiratory symptoms / worsening respiratory symptoms.		
Pulmonary imaging *	Bilateral opacities - not explained by effusions, lobar collapse, or lung nodules.		
Oxygenation **	PaO_2/FiO_2 201-300mmHg with PEEP/CPAP≥5cmH_2O***	PaO_2/FiO_2 101-200mmHg with PEEP/CPAP≥5cmH_2O	PaO_2/FiO_2 ≤100 with PEEP/CPAP≥5cmH_2O
Origin of edema	Respiratory failure not explained by heart failure or fluid overload (objective evaluation is required if no ARDS risk factor is present)		

* Chest x-ray or computed tomography
** If the altitude is greater than 1000m; the correction should be done like this (PaO_2/FiO_2 x (barometric pressure/760)].
*** Could be administered non-invasively in the mild ARDS group.

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Pulmonary imaging

Computed tomography (CT) is regarded as the 'gold standard', with greater sensitivity than RT-PCR (35), (98% vs. 71%, p <0.001), becoming one of the pillars of the diagnosis overshadowed by the difficulty to perform. The most common findings are ground-glass opacity (86%), bilateral infiltrates (75%), involving multiple lobes in 71% and consolidations in 29% of cases (34, 35).

Ultrasound in the diagnosis of ARDS

Ultrasound (US), with portability and ease of use, allows for an assessment at the foot of the patient's bed, aiding in rapid study; US can visualize and evaluate pleural and pulmonary structures. In the PEEP qualification, the step of consolidation to coalescing B lines, or from B lines to A-lines, reflects successful alveolar recruitment; even verifying an improvement in lung aeration could dynamically establish what the best plateau could be to maintain adequate conduction pressure(38). A limitation of ultrasound is the impossibility of visualizing deep consolidations, which reduces its diagnostic capacity (39–41)

PaO_2/FiO_2

The PaO_2/FiO_2 oxygenation indices are one of the simplest to perform and analyze (42). There is a nonlinear relationship between PaO_2 and FiO_2 because other non-pulmonary factors such as intrapulmonary shunt, $PaCO_2$, respiratory quotient, and hemoglobin can modify their values. It also presents variations according to FiO_2 and Positive end-expiratory pressure (PEEP) (43). Its use in heights above 1500 m above sea level has been questioned, an adjustment has been determined for its calculation considering a constant of 0.71, however, some works have raised doubts on the accuracy of the calculation (44).

$PaCO_2$ - $ETCO_2$ ($PaETCO_2$)

The gradient between the arterial pressure of carbon dioxide ($PaCO_2$) and end-tidal carbon dioxide ($ETCO_2$) can be used in the evaluation of ARDS progression, considering a Pa-$ETCO_2$ cut-off value of 10.6mmHg, with a sensitivity of 77.8%, a specificity of 85.7% and

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an area under the curve of 0.84 (45–47). The value elevation may be useful, among others, in monitoring patients with pneumonia and interstitial edema due to ischemia-reperfusion phenomena (48).

Physiological dead space ventilation (VD/VT)

The physiological dead space (RV/RV) has a prognostic value for survival during the first week of ARDS initiation, independent of oxygenation (49), and also helps in ventilator programming. Other predictors of mortality, impaired ventilation or increased CO_2 production includes alveolar oxygen pressure (PaO_2), obtained by volumetric capnography (V cap) and respiratory quotient (VR) (50–52).

Management of Acute Respiratory Insufficiency and ARDS.

Management is described through a protocol considering a comprehensive and individualized evaluation, monitoring and systemic support over time, with the main objective of reducing the risk of VILI (Figure 3). COVID-19 results in hypoxemia and the absence of specific treatment, providing adequate monitoring and ventilatory support at the correct time is vital for patient care (11). The recommendations made should be modified as new information becomes available.

Non-Invasive Mechanical Ventilation, NIV

In those patients who do not need immediate intubation, they may benefit from supplemental oxygen if SpO_2/FiO_2 >200, respiratory rate (RR) <25 per minute and without evidence of dyspnea (51, 52). In this case, the available options are nasal cannula with a maximum flow of 6L/min and the facial mask with a reservoir with a maximum flow of 15L/min. If after 30 minutes there is compliance with SaO_2/FiO_2 ≤200, RR <25 and respiratory work is absent, regular surveillance should be maintained (53).

With SaO_2/FiO_2 ≤200 mmHg, RR ≥25 per minute, it is possible for CNAF, eventually CPAP or NIV with pressure support and PEEP (51, 52).

1. *High flow nasal cannula (HFNC)*

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Nasal cannula affects the inspiratory pressure without increasing the tidal volume (CV), an important advantage over NIV (53, 54). It reduces respiratory work and tachypnea; the effect of PEEP improves mechanical properties, increases lung compliance and decreases intrapulmonary short circuit, improving PaO_2, which will decrease respiratory work (53, 54). The CO_2 washing product of the application of the high flow reduces the anatomical dead space, with better alveolar ventilation and optimization of the gas exchange (54, 55).

Studies show that patients with AKI and P/F <200 mmHg are less likely to require intubation compared to those who used conventional oxygen therapy and NIV, 35%, 53%, and 58%, respectively (58). A meta-analysis published in 2019 reported a decreased risk of requiring intubation (RR: 0.85, CI: 0.74-0.99) or of scaling therapy with either NIMV or IMV (RR: 0.71, CI: 0.51-0.98) in the group of patients managed with CNAF; no impact on mortality, ICU stay or hospital stay has been demonstrated (59).

2. *HFNC for COVID-19 patients* .

HFNC benefits include easy handling, versatility, quick familiarization, the possibility of use in other hospital services (54), decreased the need for intubation and is particularly useful where resources such as ICU beds and ventilators can be limited (58, 59).

- Initial programming:
  - Start with high flows, 60L/min
  - FiO2 to achieve SpO2 >90%
  - Ideal temperature of 37C and high humidification.
- Monitoring:
  - The use of the ROX index, Formula 1, measured at the time of initiation of the therapy, a cut-off point of 4.88 is recommended to predict the possibility of intubation with a PPV of 89.4%. A ROX ≤4.88 indicates failure (59, 60).
  - Intubation is recommended in the first 2 hours if there is a failure in CNAF (53). Increased mortality of up to 67% has been reported in late intubation versus 39% early intubation(63).
  - Failure is related to presentation severity, in a retrospective study of 318 patients in China, failure of 64% was observed among those with P/F less than 200 mmHg (64).

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- Formula 1. (61)

  $ROX = (SpO_2/FiO2)/FR$

Risks for the health team:

- The CNAF has not been shown to increase the risk of contamination compared to conventional oxygen therapy (1), the maximum distance of dispersion of exhaled air is less than 17cm at a maximum flow of 60L/min, while with oxygen therapy by nasal cannula, simple oronasal mask or Venturi, 100cm, 40cm and 33cm respectively (51, 64).
- The risk of aerosolization can be significantly reduced with the use of a surgical mask (63, 64), the ideal size and correct placement of the cannula must be ensured (66).

3. *Non-Invasive mechanical ventilation (NIV) and Continuous positive airway pressure (CPAP)*
   - The mechanisms of action in the management of ARDS are achieved by applying support pressure to increase the VC, decrease the RR and the ventilation of the dead space, with the consequent increase in alveolar ventilation, decrease in $PaCO_2$ and respiratory work. On the other hand, PEEP increases lung compliance and decreases the intrapulmonary shunt, which ultimately increases PaO_2 (67).
   - The unpredictable increase in CV is questioned, with the potential risk of self-induced lung injury (SILI) in the patient (53, 66). The probability that safe volumes are applied is around 20% in hypoxemic acute respiratory failure (ARF) patients, with most receiving injurious volumes (26). An expired CV of about 9.5ml/kg BMI predicts failure in strategy; however, the LUNG SAFE study showed that NIV is frequently used in these patients and that the failure rate is directly associated with the severity of ARDS, reporting between 42% and 47% in the moderate and severe, respectively, with mortality of almost 50% associated with failure (24, 67).

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- NIV in acute hypoxemic failure, has a limited indication, must be evaluated individually, as it can increase SILI lung damage and delay intubation by providing a false sense of security (52, 68). Its use is controversial, associated with the risk of biological exposure by aerosolization.
- Initial programming:

  - PS: 8, PEEP: 5

  - FiO_2 to achieve SpO_2> 90%

- We recommend the use of the HACOR score (Table 4) measured at the time of starting therapy, a cut-off point of 5 to predict failure and the need for intubation, AUC 0.88 (71).
- It is recommended not to delay intubation in case of HACOR failure >5, as it is associated with higher mortality (68).

Table 4. HACOR score, non-invasive mechanical ventilation failure scale.

Variable	Value	Score
HR	≤ 120	0
	≥ 121	1
pH	≥ 7.35	0
	7.30-7.34	2
	7.25-7.29	3
	< 7.25	4
Glasgow	15	0
	13-14	2
	11-12	5
	≤ 10	10
PaO_2/FiO_2	>201	0
	176-200	2
	151-175	3
	126-150	4
	101-125	5
	≤ 100	6
RR	≤ 30	0
	31-35	1
	36-40	2
	41-45	3
	≥ 46	4

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- The use of CPAP is based on favorable anecdotes during the initial management of SARS-CoV-2 ARI, however, the evidence is limited (51, 52, 64) and may play a promising role in post-extubation patients.

General considerations

- Risks for the health team
    - Due to a lack of tightness, attempts have been made to limit its use (55). Air dispersion has been observed at significant distances depending on the interface and the applied support pressure, with a face mask it can reach up to 91.6cm. The use of Helmet as an interface reduces it to 27cm and becomes undetectable if a neck is added air (51, 64). CPAP via an oronasal mask, the dispersion is undetectable, and the nasal route reaches a distance of 33cm (66)

- Recommendations to decrease the risk of contamination (54):
    - Use interfaces and elbows to connect to the circuit without leakage.
    - Exhalation port in the circuit
    - Viral/bacterial filter (before exhalation)
    - Minimize the disconnections of the fan, in case it is necessary to do it with the fan in STANDBY (54)
    - Avoid nebulization therapy, if necessary, with pressurized nebulizers (52, 64)
- Recommendations of NIV in context COVID-19 (63, 64):
    - Entrance to the care units always with PPE (according to international guidelines)
    - Constant supervision of the proper use of PPE and hand washing
    - Maintain patients with surgical mask or N95 (51, 52).
    - Negative pressure in the work area.
- Individual rooms or with a minimum separation of 2 meters between patients (65).

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- Non-invasive ventilatory support in the prone vigil position:

  - Physiological rationality, therefore, seems to be promising.
  - Low quality of evidence so far.
  - Continuous monitoring is essential.
  - The implementation of protocols is necessary.

- Invasive Mechanical Ventilation Management (VMI)

- All patients are suspected or confirmed diagnosis of COVID-19 who present with ARF and require an emergent definitive airway or those patients who present with data on the failure of NIV or CNAF should be managed on IMV.
- It is recommended to adhere to the recommendations for the safe management of the patient's airway with COVID-19 (72).
- Proper hemodynamic management in the initial phase will be a priority.
- Initial setting of mechanical ventilation
- Driving in a prone position
- It will be the fundamental pillar in the management of patients with a P/F ≤150, the recruitment of posterior areas, the gravitational distribution of the lesion, the homogeneous redistribution of stress and strain with optimization of the V/Q ratio are considered the determining factors most important to decrease VILI, which in turn has been shown to decrease mortality, especially when applied early (73), additionally it helps to mitigate the harmful effect of the use of high PEEP values alone by reducing regional hyperinflation by optimizing recruitment potential (10).
- Minimum time in the prone position of 16 hours a day (74) although extended treatments are just as effective; a premature withdrawal may again lead to the development of VILI. Staff training and protocol implementation should be part of each institution.
- Sedation Analgesia and use of Muscle Relaxer

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- Recent studies have not shown a decrease in mortality with its use (75).
- Its administration will be carried out in continuous infusion for patients with ARDS managed in the prone position, who maintain high airway pressures or present asynchronies; it is recommended to use the lowest dose and time possible, ideally no more than 48 hours (76).

Figure 2 indicates guidelines for sedation and analgesia throughout the process.

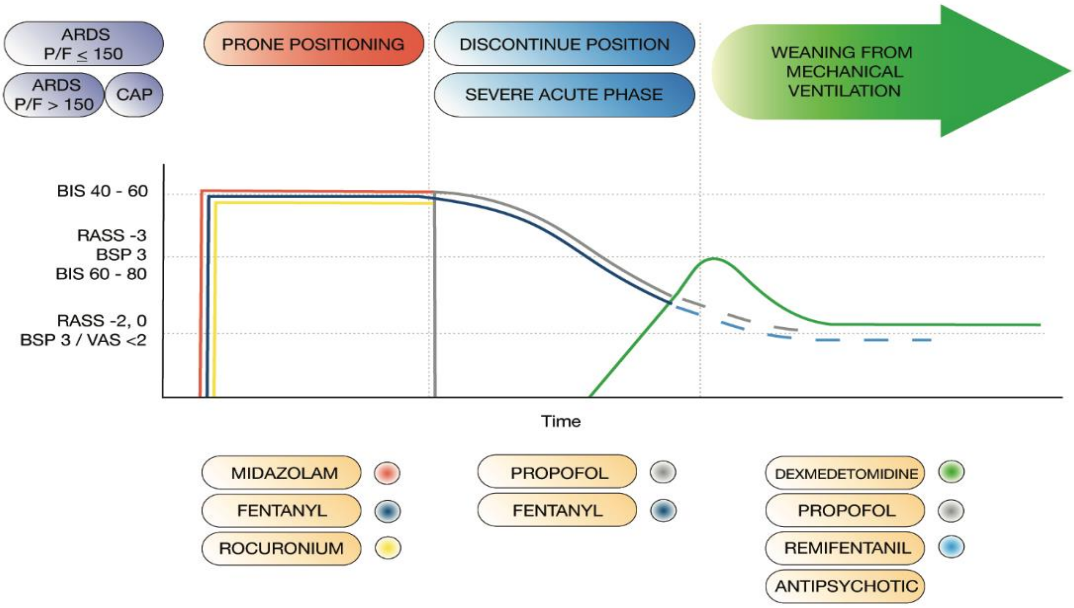

Figure 2 Management of Analgesia, Sedation and Use of Muscle Relaxants

The recommendations for sedation analgesia management and use of the muscle relaxant available in the environment are detailed. The guidelines are intended to optimize resources during the time of the pandemic, emphasizing objective titration in each phase to avoid adverse effects associated with overuse, it recommends a sequential guideline over time to minimize the use of benzodiazepines. Regarding the use of antipsychotics, it is recommended to use it in the weaning phase to control agitation whenever pain control has been optimized.

4. *Recruitment Potential, Lung Recruitment and PEEP Titration*

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The recruitment potential will be evaluated before a lung opening maneuver and/or the PEEP titration. Some patients maintain significant recruitment potential and improvement in the prone position (9, 75). A Recruitment-to-Inflation ratio (R/I ratio) value of ≥0.5 is considered favorable (78).

There is no consensus on the most effective method to titrate PEEP (79–81), the improvement in oxygenation is not always associated with anatomical recruitment. The objective is to identify the optimal PEEP, which is considered the PEEP value by which the highest lung recruitment is obtained without producing overdistension.

Routine lung recruitment is not recommended as part of the management of the patient with ARDS, the evidence is controversial and not free of complications (82,83); we recommend its application in hemodynamically stable patients who maintain a P/F ≤150 and a favorable recruitment potential (84).

Recommendations for a safe procedure: do not exceed an airway pressure greater than 40, maintain a DP of 15 and pause time in the high pressure of at least 10 seconds. Once performed, it must be ensured that the lung is kept open with optimal PEEP (85).

The evaluation of the maneuvers performed will be considered favorable if the patient presents a SpO_2 ≥88% and/or a P/F> 150.

It is recommended at this time to use the ACP risk score to identify patients at risk of developing a pulmonary embolism (86); the prone position is not a contraindication to perform cardiac ultrasound (85, 86).

Management of the patient in a severe initial phase, removal of the prone position and weaning.

Achieved oxygenation objectives and always ensuring protective ventilation, the FiO_2 will be decreased to a target value between 40-60%, it is recommended to decrease 5 points every 30 minutes; if desaturation appears below the indicated range, the previous FiO_2 value will be maintained and evaluated in 1 hour. During the first 24 hours of handling, it is recommended not to modify the optimal PEEP value to maintain alveolar stability.

Once the FiO_2 objective has been achieved, after 24 hours the PEEP will begin to decrease by 1 cmH_2O every 6 hours to a value of 10 cmH_2O, ensuring the oxygenation objectives in each intervention; if the SpO_2 or P/F decrease below the aforementioned values, it will return to the previous value.

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With a FiO_2 40-60% and PEEP 10, if you maintain a P/F>150 for 4 hours, the prone position will be removed; the output values should not be altered in supine, FiO_2 40-60% and PEEP in 10; if in the following 4 hours the P/F >150 is considered "successful withdrawal"; otherwise "failed withdrawal" and the patient must be placed in the prone position again. Prone removal will be evaluated every 24 hours until achieving a P/F>150 if failed.

Once the patient is in the supine position, they are considered stable and with the disease process in resolution, the release will begin, describing an average time in IMV of up to 16 days, despite a favorable initial evolution (89).

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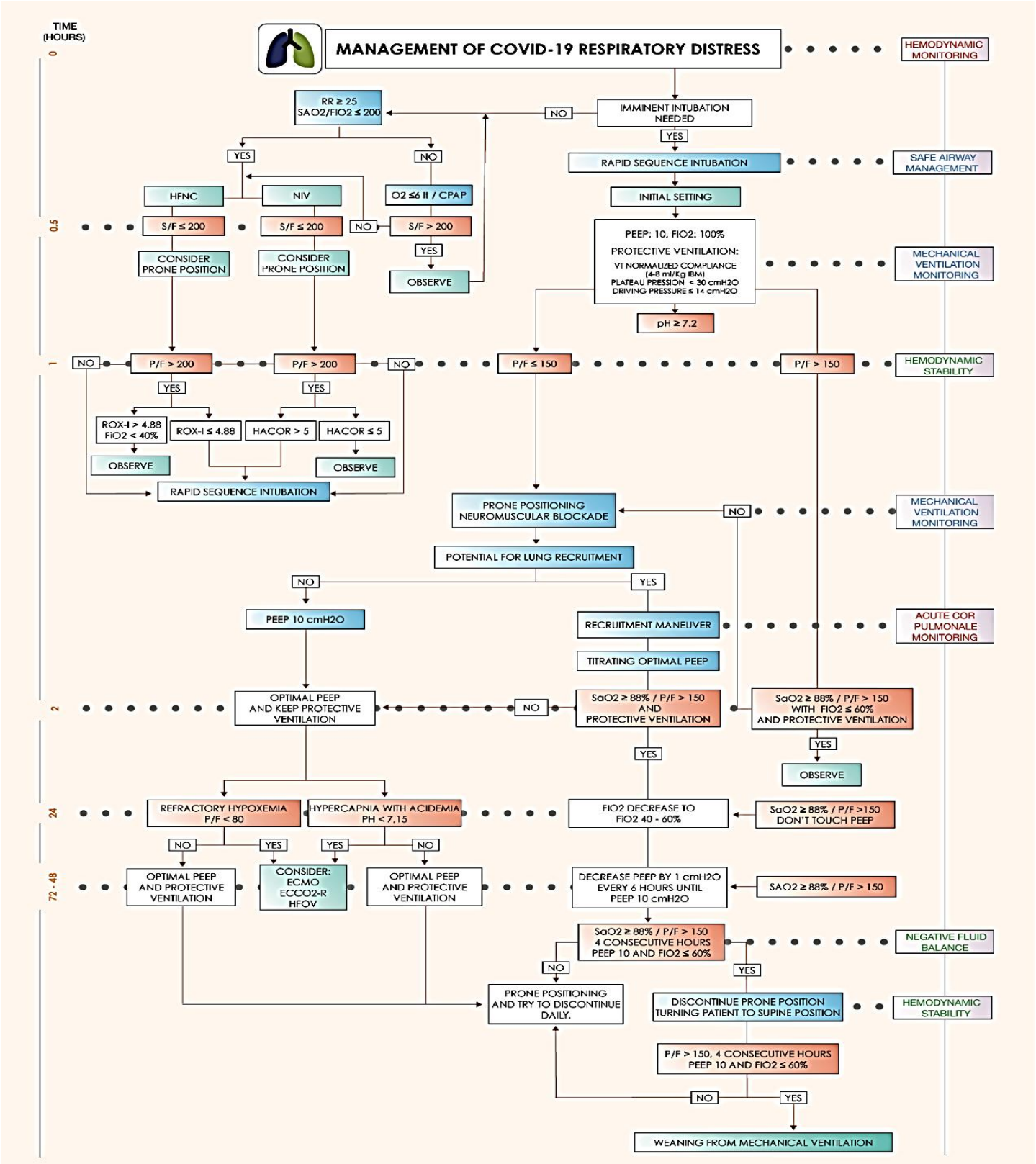

Figure 3 ARDS management flowchart COVID-19

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A protocol with all the management recommendations is detailed, prioritizing the use of the prone position and the individualization of each intervention over time. Specific recommendations on ECMO, ECCO2-R or HFOV are outside the scope of this work, however, the appropriate time is established for their consideration.

RR Respiratory Rate, HFNC High-Flow Nasal Cannula, NIV Non-Invasive Ventilation, S/F SpO2/FiO_2 ratio and P/F PaO2/FiO_2 ratio.

Pharmacological Management

To date, no specific antiviral treatment or vaccines are available for COVID-19. All therapeutic options are based on previous experiences to treat SARS, MERS or Influenza; the efficacy and safety of specific pharmacological treatments have not yet been guaranteed.

Despite the data we have, based on anecdotes or observational data, certain hypotheses have been generated and some scientific societies have defined situations in which the use of some treatment could help control multiorgan failure, although in no case is there unanimity in their proposals.

Conclusions

Patients with Covid-19 who developed pneumonia and meet the Berlin criteria for ARDS have an atypical form of this syndrome. The main characteristics seems to be caused by the dissociation between their relatively well-preserved lung dynamics and the severity of hypoxemia. A possible explanation for the severe hypoxemia that occurs within the complacent lungs is most likely attributed to pro-inflammatory state and the loss of regulation of pulmonary perfusion, causing and important vasoconstriction of the pulmonary vascular bed.

The clinical presentation varies from case to case, including asymptomatic individuals, to mild symptoms which can progress seriously. The presence of risk actors, particularly in those over 65 years, such as diabetes and hypertension, can have important implications in the final treatment of the patient. This work has reviewed the literature on managing

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patients with ARDS and provides a useful guide for clinical teams who are caring for positive patients with respiratory distress.

Declarations

Ethics approval and consent to participate

According to the local and international regulation, this project did no required ethical approval.

Consent to publish

Not Applicable.

Availability of data and materials

All the information used for this analysis can be found online throughout the several medical databases available.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

LU and LM were responsible for the full conceptualization and they were in charge of drafting the document in all of the stages. GP, TM, AR, LT, JCL, FEJ and GDP contributed with the background information and the conceptualization of the proposed guidelines. AMD, EV and DCR completed the second draft of the manuscript while ALC was responsible for the elaboration of the figures and EOP and AL critically review the entire document and reviewed the final version of the manuscript

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