Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Early identification of acute respiratory distress syndrome in times of the COVID-19 pandemic

Acute respiratory distress syndrome (ARDS) was reported for the first time in 1967 in 12 patients with sudden respiratory failure due to a non-cardiogenic pulmonary edema.[1] Even though these patients had no underlying pulmonary disease, they rapidly developed severe hypoxemia, stiff lungs, and pulmonary bilateral infiltrates within a few days after a precipitating factor. Autopsy revealed a characteristic histological pattern of diffuse alveolar damage involving hyaline membranes, edema, necrosis, and cell proliferation.[2,3] The definition of ARDS evolved markedly over time and the Berlin definition, which was proposed in 2012, is currently the most recent one.[4] First, acute onset of respiratory symptoms appearing or worsening within 7 days of a clinical insult, thereby excluding patients who develop respiratory failure over more prolonged periods due to idiopathic pulmonary fibrosis, non-specific interstitial pneumonitis, organizing pneumonia, or pulmonary vasculitis. [5] Second, hypoxemia is classified according to severity as mild when the partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio is between 201 mmHg and 300 mmHg, moderate when between 101 mmHg and 200 mmHg, and severe when ≤100 mmHg. The PaO_2/FiO_2 ratio is obligatorily measured with a positive end-expiratory pressure level of at least 5 cmH_2O. Third, respiratory failure must not be fully explained by cardiogenic pulmonary edema (as judged by the clinician or confirmed by echocardiography). Fourth, bilateral infiltrates (which are not atelectasis or nodules) must be seen on chest radiography or lung computed tomography. Applying the Berlin definition, the large-scale international LUNG SAFE study showed that ARDS represented >20% of intubated patients in intensive care units (ICUs), and that in-ICU mortality approximated 35%, ranging from 30% in mild ARDS to >40% in severe ARDS.[6]

Before the Berlin definition was established, ARDS was considered only in patients intubated under invasive mechanical ventilation. This definition specified that patients receiving continuous positive airway pressure of at least 5 cmH_2O while breathing spontaneously may be considered as having only mild ARDS. However, several studies have shown that the greater the severity of hypoxemia under non-invasive ventilation (NIV), the higher the risk of intubation and mortality. Therefore, patients treated with NIV should be considered as having moderate or even severe ARDS.[7–10] In the LUNG SAFE study, the in-ICU mortality of patients with ARDS treated with NIV was 28%, i.e., very close to the 32% rate reported in patients intubated without prior NIV, and ranged from 22% in mild ARDS to 40% in patients with severe ARDS under NIV, i.e., exactly like in patients with severe ARDS under invasive mechanical ventilation.[6,7] In a recent observational cohort study including 131 patients treated with NIV for respiratory failure due to coronavirus disease 2019(COVID-19), only 4% patients who needed intubation lost ARDS criteria after initiation of invasive mechanical ventilation.[11] Patients could even be identified at an earlier stage while breathing spontaneously under conventional oxygen therapy. In an observational cohort study that included 219 patients treated first with conventional oxygen therapy and then with NIV for acute hypoxemic respiratory failure, 94% patients with pulmonary bilateral infiltrates and PaO_2/FiO_2 ≤300 mmHg under conventional oxygen therapy fulfilled the criteria for ARDS once NIV was applied with a positive-end expiratory pressure level of at least 5 cmH_2O. This meant that almost all patients admitted to ICU with pulmonary bilateral infiltrates and a PaO_2/FiO_2 ≤300 mmHg under conventional oxygen therapy met the ARDS criteria.[12] In this study, the in-ICU mortality rate was 29% and very close to the 30–35% reported in intubated patients with ARDS criteria as per the Berlin definition.[4,6] However, FiO_2 is not measured with conventional oxygen therapy, and to assess PaO_2/FiO_2, the FiO_2 may need to be accurately estimated using the following 3% formula: FiO_2 estimated = 3% per liter of oxygen + 21%.[13] Although the most recent clinical practice guidelines do not recommend NIV in patients with acute hypoxemic respiratory failure,[14,15] NIV has been widely used in patients with respiratory failure due to COVID-19,[16] even outside ICUs.[17] Several studies have shown a decreased risk of intubation with NIV or continuous positive airway pressure as compared with conventional oxygen therapy in patients with respiratory failure due to COVID-19.[18,19] NIV is frequently used in clinical practice for management of respiratory failure in ICUs, and the mortality rate of patients meeting the criteria

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for ARDS under NIV is similar to that of patients under invasive mechanical ventilation. Consequently, patients treated with NIV should probably be considered as ARDS when all the other criteria are fulfilled, and should be classified as mild, moderate, or severe according to their degree of hypoxemia.

The use of high-flow nasal oxygen for treatment of patients with acute hypoxemic respiratory failure has gained worldwide attention.[20] According to the current ARDS definition, positive end-expiratory pressure of at least 5 cmH_2O is needed to meet the criteria for ARDS, but is usually not reached using high-flow nasal oxygen, even with a flow of at least 50 L/min.[21] Although high-flow nasal oxygen may generate continuous positive airway pressure >5 cmH_2O with a particularly high flow exceeding 50 L/min and with the mouth closed,[22,23] positive end-expiratory pressure levels are often around 2–3 cmH_2O and remain lower than the levels needed to meet the ARDS criteria.[21] Consequently, patients treated with high-flow nasal oxygen still cannot be considered as having ARDS even if they fulfill all the other criteria. As for NIV, high-flow nasal oxygen has been widely used for the management of respiratory failure due to COVID-19.[24–27] In this setting, several observational studies have reported intubation rates exceeding 50%,[11,24,25] meaning that most of these patients would have met the ARDS criteria once intubated. In fact, only 7% patients with pulmonary bilateral infiltrates and PaO_2/FiO_2 ≤300 mmHg under high-flow nasal oxygen no longer fulfilled the ARDS criteria after initiation of invasive mechanical ventilation.[11] It has also been shown that biomarkers of inflammation and injury in patients treated with high-flow nasal oxygen for acute respiratory failure with pulmonary bilateral infiltrates reached values similar to those of patients with ARDS under invasive mechanical ventilation.[28] Although the mortality of patients treated with high-flow nasal oxygen for respiratory failure due to COVID-19 in ICUs was slightly lower than in intubated patients with ARDS, ranging from 10% to 30%,[19,24,25,29] all of these findings suggest that patients with pulmonary bilateral infiltrates and PaO_2/FiO_2 ≤300 mmHg under high-flow nasal oxygen could have been considered as ARDS cases as soon as high-flow nasal oxygen was initiated. Consequently, a new definition of ARDS was recently proposed, which included patients treated with high-flow nasal oxygen at a flow of at least 30 L/min.[30]

Early identification of ARDS is a major forward in the assessment of future pharmacological and non-pharmacological treatments. Numerous anti-inflammatory drugs have failed to show beneficial effects in patients with ARDS. However, treatment effects might depend on the timing in the course of the disease, and it cannot be ruled out that some treatments could be effective at an early stage and ineffective at a later stage. For example, results regarding steroid use are conflicting. While some studies have shown that steroids may have deleterious effects on outcomes when administered at a late stage in the course of ARDS,[31] others studies have shown beneficial effects with a decreased risk of death when steroids are started early in the course of ARDS.[32,33] During the COVID-19 pandemic, steroids were associated with decreased risk of death in patients under invasive mechanical ventilation or when administered at an early stage in patients breathing spontaneously under conventional oxygen therapy.[34] Although COVID-19 is characterized by a marked systemic inflammatory response, which could explain the effectiveness of steroids in this setting, it cannot be ruled out that steroids are likely to be beneficial early in the course of other causes of ARDS. Recognition of ARDS at an early stage might be paramount in future studies to initiate lung-protective measures in patients still breathing spontaneously with the aim to mitigate patient-self-inflicted lung injury.[35] Similarly, while the beneficial effects of prone positioning have been demonstrated in the management of patients with ARDS under invasive mechanical ventilation,[36] it has also recently been shown that prone positioning may be effective at an earlier stage in patients breathing spontaneously but with respiratory failure due to COVID-19.[37,38]

In conclusion, it is about time that the current definition of ARDS is updated by including patients with pulmonary bilateral infiltrates and those breathing spontaneously under non-invasive respiratory supports. Patients treated with high-flow nasal oxygen or NIV can probably be considered at an earlier stage in the course of respiratory failure as “non-invasive” ARDS cases. Expansion of the ARDS definition may enable earlier identification of ARDS and earlier initiation of therapeutic strategies. While awaiting an updated definition of ARDS, this very special issue of acute respiratory failure has led to different reviews focusing on the management of respiratory failure in COVID-19, using non-invasive respiratory supports such as high-flow nasal oxygen or NIV and awake prone positioning. Taking into account the particularities of ARDS due to COVID-19, targets of oxygenation and the decision to initiate extra-corporeal membrane oxygenation for the most severe patients have been scrutinized. Last, an original article discusses the potential for recruitment over time in patients with COVID-19 under invasive mechanical ventilation.

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