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.

Vaccine 39 (2021) 3028–3036

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Acute respiratory distress syndrome (ARDS) as an adverse event following immunization: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data

Nathan A. Serazin [a], Bassey Edem [b], Sarah R. Williams [c], Justin R. Ortiz [d], Anand Kawade [e], Manoj Kumar Das [f], Maja Šubelj [g], Kathryn M. Edwards [h], Shreemanta K. Parida [i], T. Anh Wartel [j], Flor M. Munoz [k], Patricia Bastero [a,*]

[a] Department of Pediatrics, Section of Critical Care Medicine, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA
[b] Department of Vaccines and Immunity, Medical Research Council the Gambia Unit at the London School of Hygiene and Tropical Medicine, UK
[c] Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
[d] Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
[e] King Edward Memorial Hospital Research Centre, Vadu Rural Health Program Pune, India
[f] The INCLEN Trust International, New Delhi, India
[g] National Institute of Public Health, University of Ljubljana, Slovenia
[h] Division of Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA
[i] CureVac AG, Frankfurt, Germany
[j] International Vaccine Institute, Seoul, Republic of Korea
[k] Departments of Pediatrics, Section of Infectious Diseases, and Molecular Virology and Microbiology, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA

ARTICLE INFO

Article history:
Received 8 January 2021
Accepted 20 January 2021
Available online 28 January 2021

Keywords:
ARDS
Acute respiratory distress syndrome
Adverse event
Immunization
Guidelines
Case definition
Pediatric
Adult
COVID-19

ABSTRACT

This is a Brighton Collaboration Case Definition of the term "Acute Respiratory Distress Syndrome – ARDS" to be utilized in the evaluation of adverse events following immunization. The Case Definition was developed by a group of experts convened by the Coalition for Epidemic Preparedness Innovations (CEPI) in the context of active development of vaccines for SARS-CoV-2 vaccines and other emerging pathogens. The case definition format of the Brighton Collaboration was followed to develop a consensus definition and defined levels of certainty, after an exhaustive review of the literature and expert consultation. The document underwent peer review by the Brighton Collaboration Network and by selected Expert Reviewers prior to submission. The comments of the reviewers were taken into consideration and edits incorporated in this final manuscript.

Contents

* Corresponding author.
E-mail addresses: pxbaster@texaschildrens.org, bc-coordinator@taskforce.org (P. Bastero).

https://doi.org/10.1016/j.vaccine.2021.01.053
0264-410X/

1. Preamble

1.1. Introduction and existing definition of acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening condition resulting from acute inflammatory lung injury. It is characterized by diffuse alveolar damage with hypoxemia and poor lung compliance. While multiple insults can result in ARDS, the final common pathway ends in direct epithelial pulmonary injury with or without injury to the endothelium. This process increases permeability of the lung epithelial barrier, filling of the alveolar spaces with inflammatory fibrinous exudates, and collagen deposition with minimal interstitial edema.

Although the condition was first reported in 1821 [1], the term ARDS was first used in the biomedical literature in 1967 [2]. Since then, it has been described using multiple other terminologies including acute lung injury, adult respiratory distress syndrome, non-cardiogenic pulmonary edema, and increased-permeability pulmonary edema. In efforts to standardize terminology and diagnosis, clinical definitions have been proposed and revised to reflect improved understanding of ARDS pathogenesis. The first clinical definition was proposed in 1988 [3], revised in 1994 [4], and revised again in 2012. The 2012 "Berlin Definition," named for the site of the expert convening, defines the most current and widely used diagnostic criteria for ARDS in adults [5,6].

While the Berlin Definition is the most widely used, several other definitions have been developed to improve recognition

Table 1
Comparison of the ARDS definitions- Berlin Definition Kigali Definition, and PALICC Definition.

Parameters	Berlin Definition (2012) [5]	Kigali modification of Berlin Definition (2017) [8]	PALICC Definition (2015) [7]
Onset timing	Within one week of a known clinical insult or new or worsening respiratory symptoms	Within one week of a known clinical insult or new or worsening respiratory symptoms	Within one week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation status (defines disease severity)	$PaO_2/FiO_2 \leq 300$[a]	$SpO_2/FiO_2 \leq 315$	Non-intubated patients: PaO_2/FiO_2 ratio ≤ 300 or $SpO_2/FiO_2 \leq 264$ Intubated Patients: OI ≥ 4
Mild severity	200 mm Hg < $PaO_2/FIO_2 \leq 300$ mm Hg with PEEP or CPAP ≥ 5 cm H_2O [b]	Not mentioned	For intubated patients only $4 \leq OI < 8$ $5 \leq OSI < 7.5$
Moderate severity	100 mm Hg < $PaO_2/FIO_2 \leq 200$ mm Hg with PEEP ≥ 5 cm H_2O	Not mentioned	$8 \leq OI < 16$ $7.5 \leq OSI < 7.5$
Severe severity	$PaO_2/FIO_2 \leq 100$ mm Hg with PEEP ≥ 5 cm H_2O	Not mentioned	OI ≥ 16 OSI ≥ 12.3
PEEP requirement	Minimum 5 cm H_2O CPAP for non-intubated patients or PEEP ≥ 5 for intubated patients.	No PEEP requirement	Minimum 5 cm H_2O CPAP for non-intubated patients or PEEP ≥ 5 for intubated patients.
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules	Bilateral opacities not fully explained by effusions, lobar/ lung collapse, or nodules	Chest imaging of new infiltrates consistent with parenchymal disease (does not have to be bilateral)
Imaging Modality sufficient for diagnosis			
Chest Radiograph (CXR)	Yes	Yes	Yes
Chest Ultrasound	Not included [d]	Yes	Not included
CT scan	May be used to make diagnosis but not required	May be used to make diagnosis but not included	Not included
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present.[e]	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present.	Respiratory failure not fully explained by cardiac failure or fluid overload. Echocardiography only recommended if suspected cardiac disease / dysfunction.

Abbreviations: CT, computerized tomography; CXR, chest x-ray; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; OI oxygenation index; OSI, Oxygen Saturation Index; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] If altitude is higher than 1000 m, the correction factor should be calculated as: [PaO_2/FiO_2 X (barometric pressure/760)].

[b] This may be delivered noninvasively in the mild ARDS severity group.

[d] Ultrasound was not mentioned in the Berlin Definition.

[e] Though mentioned as an example to rule out hydrostatic edema in the initial definition, echocardiography is not necessary longer required to make the diagnosis of ARDS, and clinical evaluation/judgment is sufficient.

and diagnosis for other specific patient populations. Important examples include the Pediatric Acute Lung Injury Consensus Conference (PALICC) Definition [7], and the Kigali Modification to the Berlin Definition for use in resource-limited settings [8] (Table 1).

1.2. Epidemiology

ARDS is responsible for substantial morbidity and mortality worldwide. However, quantifying this burden can be challenging and depends on the morbidity measure used, such as intensive care unit (ICU) prevalence or incidence, ICU/hospital prevalence, or population incidence (Table 2). Regardless, a population-based incidence estimate of ARDS is not available, and the available disease burden estimates are likely underestimates.

1.3. Pathology

The pathological features of ARDS are typically described as passing through three overlapping and progressive phases – an inflammatory or exudative phase, a proliferative phase, and a fibrotic phase. The inflammatory or exudative phase occurs within the first 7 days from initial insult and is characterized by interstitial edema, acute inflammation, type II alveolar pneumocyte hyperplasia, and hyaline membrane formation. The proliferative stage begins around 10 days after the initial trigger (2–4 weeks), is characterized by resolution of pulmonary edema, proliferation of type II alveolar cells, squamous metaplasia, interstitial infiltration by myofibroblasts, and early deposition of collagen. It lasts about two to three weeks. Lastly, the fibrotic stage, starting approximately 2–4 weeks into the insult, is characterized by obliteration of normal lung architecture, fibrosis, and cyst formation. The degree of fibrosis can range from minimal to severe in patients who reach this third phase [36].

1.4. Pathophysiology

ARDS is caused by a complex interplay between the immune and inflammatory systems. The inflammatory or exudative phase begins shortly after an inciting insult activates and amplifies the response of the innate immune system. Complement activation, release of proinflammatory mediators (e.g., TNF, IL6, IL17), and chemokines (e.g., IL8, CCL2, CCL7) drive activation of innate lymphoid cells, adaptive immune cells, and recruitment of neutrophils. This leads to damage of the epithelial-alveolar barrier and increased permeability [37], resulting in interstitial and intra-alveolar edema with concurrent deactivation of surfactant. The process manifests clinically as heterogeneous areas of pulmonary edema and atelectasis that cause mismatch of lung ventilation and blood perfusion (V/Q mismatch) and hypoxemia. In the proliferative phase, there is proliferation of fibroblasts, myofibroblasts, and locally generated pluripotent mesenchymal progenitor cells that begin the repair process. This response marks the proliferative phase. Endothelial and progenitor cell proliferation restore endothelial barrier function [38]. In the fibrotic phase, expression of multiple pro-fibrotic mediators (e.g., PDGF, TGF-β, IGF-1 etc.) results in dramatic expansion and differentiation of resident fibroblasts into highly synthetic myofibroblasts [39]. This final phase of ARDS may not occur in all patients.

1.5. Diagnosis of ARDS

While the understanding of ARDS has improved over time, accurate diagnosis remains a challenge. The gold standard diagnostic test is histopathology, which is infeasible in most clinical settings. Furthermore, reliable biomarkers of ARDS remain elusive [40,41]. As a result, diagnosis remains largely based on clinical criteria that focus on recognizing an acute primary pulmonary illness with diffuse parenchymal involvement and hypoxemia. The Berlin Definition of ARDS has achieved widespread use globally, and it

Table 2
Epidemiology of the ARDS in adults and children.

Population	Location [references]	Morbidity measure used	Burden	Mortality (%)	Severity level included*
Adults	North America [9–11]	Population incidence	38.3–82.4[a]	38.5–45	Adults
		ICU incidence	6.9[b]		
	South America [12]	Population incidence	10.1 [a]	49.2	All
		ICU incidence	1.8[b]	49.2	
	Europe [11,13–19]	Population incidence	7.2–48.4 [a]	42.7–47	All
		ICU incidence	3.6–23[b]	12–78	
			7.1–19[b]	32.3–54.7	
	Australia [20]	Population incidence	28 [a]	32	All
			7.3–9.3[b]	59	Mod-Sev
					All
	Asia [21–23]	Population incidence	4.5–15.7 [a]	40–57.8	All
		ICU incidence	3.5[b]	46.3	Mod-Sev
	Africa [24]	ICU incidence	4[b]	50	All
					All
	Multi-country [11,25]	ICU incidence	8.4–10.4[b]	35.3–40	All
Children	North America [26,27]	Population incidence	12.8 [a]	18	
		ICU incidence	5.8[b]	22.7	All
	Europe [28–30]	Population incidence	2.2–9.6 [a]	20.4–27.4	Children
		ICU incidence	7.7[b]		
	Australia [31]	Population incidence	1.9 [a]	35	All
		ICU incidence	2.2[b]		
	Asia [32,33]	ICU incidence	2.7–9.9[b]	44.8–57.3	–
	Multi-country [34]	ICU incidence	3.2[b]	17.1	–
	Pooled [35]	Population incidence	3.5 [a]	33.7	All
		ICU incidence	2.3[b]		
					All
					All

* Studies reported "All severity" which included mild, moderate or severe illness, or "Moderate to Severe" illness as indicated.
[a] population-based incidence: cases per 100,000 person-years; [b] ICU-based incidence per 1000 admissions

has been recommended for use by the World Health Organization (WHO) and many professional societies [5]. The Berlin Definition criteria consist of 1) new or worsening respiratory symptoms within one week of an inciting clinical insult; 2) chest radiograph or computed tomography (CT) scan showing bilateral infiltrates not fully explained by effusions, pulmonary or lobar collapse, or pulmonary nodule; 3) cardiogenic edema ruled out as an etiology of pulmonary edema; and 4) ratio of arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2), called the P/F ratio, of at most 300 mmHg and positive end-expiratory pressure (PEEP) of at least 5 cm H_2O [5].

While ARDS has a similar constellation of clinical findings in children, there is growing recognition that there are important clinical and pathologic differences between the two groups [42]. This is evidenced by the fact that direct application of the Berlin Definition to a pediatric population may miss up to 50% of cases as it requires a PaO_2 for case definition[43]. To address this limitation, a separate pediatric definition for ARDS, the Pediatric Acute Lung Injury Consensus Conference (PALICC) Definition was developed. It uses similar criteria including onset after an inciting factor, radiographic abnormalities not caused by cardiogenic edema, and hypoxemia. However, bilateral infiltrates are not required to make a diagnosis; instead, any parenchymal abnormality on chest radiograph is sufficient. Lastly, preference is given to the use of oxygenation index (OI) or oxygenation saturation index (OSI) to quantify the degree of hypoxemia rather than the P/F ratio for intubated pediatric patients. Diagnosis requires an OI $\geq$ 4 or OSI of $\geq$5. Alternatively, for non-intubated patients requiring $\geq$5 cm H_20 of continuous positive airway pressure (CPAP), hemoglobin oxygen saturation (SpO_2) to fraction of inspired oxygen (FiO_2), called the S/F ratio, may be used. In this case, an S/F of $\leq$264 is required to make the diagnosis.

A modification of the Berlin Definition has been advocated for diagnosis of ARDS in resource-limited settings. In this "Kigali modification of the Berlin Definition" of ARDS [24,44], named for the city in Rwanda where it was first used, the criteria for timing and origin of edema are kept the same, but a diagnosis can be made in the absence of mechanical or non-invasive positive-pressure ventilation (NIPPV), PaO_2 measurement, or chest CT scan. The Kigali Definition criteria regarding timing, imaging, etiology, and oxygenation are the following: 1) new or worsening respiratory symptoms within one week of an inciting clinical insult; 2) chest radiograph or pulmonary ultrasound showing bilateral infiltrates not fully explained by effusions, pulmonary or lumbar collapse, or pulmonary nodule; 3) cardiogenic edema ruled out as an etiology of pulmonary edema; and 4) S/F ratio of at most 315 in adults. The S/F ratio has been validated as a surrogate for P/F ratio, and is commonly used in research studies of ARDS in high and low resource settings [45].

1.6. Evaluation of ARDS

In addition to the application of diagnostic criteria, clinicians often make several other considerations in the evaluation of ARDS (Table 3). A physical exam is generally non-specific, but the expected findings include evidence of respiratory distress, hypoxemia, and presence of coarse or diminished breath sounds bilaterally. Notably, a physical exam should also be used to help exclude alternative diagnoses to ARDS. For example, peripheral edema, presence of a third heart sound (S3), and jugular venous reflux would provide evidence in support of a cardiogenic cause of the patient's respiratory process.

ARDS can result from a number of different clinical insults. These are typically categorized as either resulting from direct lung

Table 3
History and exam findings consistent with ARDS.

History	Exam	Other Considerations
• Cough, shortness of breath, and/or difficulty breathing • Respiratory symptoms tend to worsen after several day history of feeling ill • May be preceded by symptoms of infection (such as fever or chills), or less commonly by abdominal pain, nausea, and/or vomiting	• Tachypnea • Increased work of breathing • Hypoxemia • Abnormal lung sounds bilaterally (such as coarse or decreased breath sounds) • Absence of gallop rhythm, jugular venous distention, or other signs suggestive of primary cardiogenic process	• Symptoms are not due to new or worsening heart failure • Symptoms are not due to pre-existing conditions (such as chronic lung disease)

Table 4
Examples of Clinical Insults Associated with ARDS.

Direct lung injury	Indirect lung injury
More Common • Pneumonia [45,46] • Bacterial: *Streptococcus pneumoniae* (A and b), *S. aureus*, *H. influenzae*, *Chlamydia pneumoniae*, Mycobacteria (M. tuberculosis, M. avium), Neisseria sp., *Enterococcus* sp. • Viral: Influenza A and B, parainfluenza 1–3, RSV, Coronavirus, SARS-CoV-1, SARS-CoV-2 and MERS, adenovirus, hMPV, measles, varicella • Fungal: Aspergillus, blastomyces, cryptococcus, *Pneumocystis jiroveci* • Parasites: Malaria	**More Common** • Sepsis • Severe trauma with shock and multiple transfusions
Less Common • Pulmonary contusion • Pneumonia • Viral: SARS-CoV-1,MERS, Measles • Fungal: Aspergillus • Mycobacteria: M. avium • Near-drowning • Fat emboli • Aspiration of gastric contents • Inhalational injury • Burn injury • Reperfusion pulmonary edema after procedure	**Less Common** • Cardiopulmonary bypass • Drug overdose • Acute Pancreatitis • Transfusion of blood products

injury (such as pneumonia) or indirect lung injury (such as sepsis). Table 4 shows a variety of more common and less common clinical insults of each type. Further, while a patient may meet imaging and oxygenation criteria for ARDS as a result of a pre-existing condition (e.g., cyanotic heart disease) at baseline, this does not exclude the patient from being diagnosed with ARDS. However, the clinical status must represent an acute change from baseline, such as new imaging findings and worsening hypoxemia.

While the PaO_2 measurement is the only laboratory value included by the Berlin and PALICC Definitions, clinicians may find several other laboratory tests useful during the evaluation of ARDS to investigate alternative and additional diagnoses, underlying etiologies, and sequelae. For example, studies to evaluate cardiac disease or pulmonary embolism may be useful depending on the clinical context. Laboratory tests may help identify an etiology for ARDS, such as a white blood cell count and microbiologic studies to assess for infection, and lipase to evaluate for pancreatitis.

As noted in the imaging component of ARDS consensus definitions, the presence of bilateral infiltrates on chest radiograph or CT scan are required for the diagnosis of ARDS in adults, whereas any infiltrate on chest radiograph is sufficient for the diagnosis in pediatric patients. In the absence of these imaging modalities, lung ultrasound can be considered, and per the Kigali modification of the Berlin Definition, imaging criteria would be met in the presence of B-lines without evidence of effusion in at least one field on each side of the chest in adults [24]. Ultrasound has been an increasingly used imaging modality in the evaluation of patients with respiratory disease and has been found to be sensitive and specific in ARDS [47]. An additional imaging modality that may be employed in the evaluation of acute respiratory illness is the transthoracic echocardiogram (TTE) to evaluate cardiogenic causes of edema and left ventricular function.

1.7. Severity evaluation of ARDS

Severity of ARDS is defined by the patient's oxygenation status. In the Berlin Definition, patients with PEEP or CPAP of $\geq$5 cm H_2O or greater can be categorized into three different severity groups based on arterial oxygenation. P/F ratio defines mild disease (>200 to $\leq$300 mmHg), moderate disease (>100 to $\leq$200 mmHg), and severe disease ($\leq$100 mmHg). Severity category in adults is associated with differential 90-day mortality: 27% for mild disease, 32% for moderate disease, and 45% for severe disease [5].

In contrast to adults, in children the severity of ARDS is first distinguished between those requiring mechanical ventilation and those receiving NIPPV. For patients who are intubated, severity is then classified by calculation of a patient's oxygen index (OI) or oxygen saturation index (OSI). This measurement is the mean airway pressure (MAP) multiplied by FiO_2, which is then divided by PaO_2 (OI) or SpO_2 (OSI). Comparable to adults, severity is defined as mild, moderate, or severe according to increasing OI or OSI. While these categories do not reliably stratify risk of mortality in between mild and moderate groups, the severe category has a significantly higher risk of in-hospital mortality (10–15% vs. 33%) [34,45,48].

Both P/F and OI/OSI have important limitations to consider. First, P/F and OI rely on measurement of PaO_2. This can be both resource-intensive and technically challenging, making it infeasible in some clinical settings. While OSI is an accepted substitution for OI in pediatrics, the Berlin Definition does not include considerations for use of S/F ratios to diagnose ARDS. However, other studies have addressed this challenge. Reported criteria for severity based on S/F ratios include mild disease >235 but $\leq$315, moderate disease as >144 but $\leq$235, and severe disease as $\leq$144 [45,49]. In addition, the Kigali modification of Berlin Definition defines describes any ARDS as having S/F ratio below 315 (with no PEEP or CPAP requirement), and authors have proposed a S/F ratio below 250 (also with no PEEP or CPAP requirement) to define moderate/-severe ARDS [50]. While WHO promotes the use of the Kigali modification of Berlin Definition for the diagnosis of ARDS in settings where either no chest imaging or blood gas analysis is possible, it does not provide guidance for severity assessment absent PaO_2 measurement [51].

1.8. ARDS after SARS-CoV-2 illness

Severe respiratory distress syndrome associated with SARS-CoV-2 infection deserves special consideration given the current pandemic. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) illness was first described in December 2019 in Wuhan, China, and has caused over 1,000,000 deaths worldwide as of October 2020. Clinical illness caused by SARS-CoV-2 infection is designated COVID-19 and can manifest in a range of respiratory illness, including ARDS.

An estimated 10–20% of patients with COVID-19 require admission to ICU [52,53]. ARDS is the most common complication of COVID-19 [54], and its incidence has ranged between 14 and 52% [53,55]. COVID-19 ARDS is a risk factor for mortality [56]. Obesity, chronic lung, cardiac and/or renal failure, immune deficiencies and active neoplasms, are risk factors for COVID-19 ARDS [25]. Similar to other causes of ARDS, patients with older age, diabetes, hypertension, obesity, cardiovascular disease and malignancies have a higher risk of developing severe COVID-19 and mortality [55–57].

In most cases, COVID-19 is milder in children than in adults. However, children with underlying complex medical conditions are at higher risk of ICU admission and developing severe COVID-19, than healthy children, with approximately 38% requiring mechanical ventilation [58] and a 30% incidence of ARDS [59]. Up to 71–74% of the pediatric patients developing COVID-19 ARDS had at least one co-morbidity, and up to almost 30% had two [58,59]. Obesity, pre-existing respiratory illness, hematologic, oncologic and/or immune disease and existing neurologic diseases were associated with the development of COVID-19 ARDS. Hispanic and African-American adolescents and adults of are at higher risk of COVID-19 ARDS [59].

ARDS can be caused by a variety of different insults, some with direct impact to the lungs and others via a secondary mechanism. Early reports of ARDS in COVID-19 described an inconsistency between the severity of hypoxia and the findings in lung imaging [60]. When compared to ARDS by other viruses they found certain differences, such as lung compliance and laboratory markers, timing of onset of illness, and preliminary histopathology data, questioning the similarities with classic ARDS, its definition, and therefore, the approach to medical treatment. Recent studies, however, suggest that the physiological differences between COVID-19 patients and ARDS from other etiologies are clinically negligible, and some report up to 85% of the ICU patients meeting Berlin Definition criteria, and responding to standardized therapies such as: low tidal volumes ventilation; conservative fluid management, and in some instances, prone ventilation [61,62].

The presence of ARDS is associated with high mortality risk in adults, and lower probability of hospital discharge in children [59].

1.9. ARDS after vaccination

We conducted a PubMed search on August 20, 2020, to identify reports of ARDS after any vaccination. The terms used in the search were: (“Vaccines”[Mesh] OR “vaccine”[tiab] OR “vaccines”[tiab] OR “vaccination”[Mesh] OR “vaccination”[tiab] OR “vaccinations”[tiab] OR “vaccinate”[tiab] OR “vaccinated”[tiab] OR “immunization”[mesh] OR “immunization”[tiab] OR “immunizations”[tiab] OR “immunisation”[tiab]

OR "immunisations"[tiab] OR "immunize"[tiab] OR "immunized"[tiab] OR "immunise"[tiab] OR "immunised"[tiab]) AND ("Respiratory Distress Syndrome, Adult"[Mesh] OR "Respiratory Distress Syndrome"[tiab] OR "ARDS"[tiab]).

We found 324 articles. A review of the abstracts of these articles revealed that while various infectious diseases are associated with the development of ARDS, there are no reports suggesting a temporal association of ARDS after vaccination with currently licensed vaccines. Actually, a reduction in ARDS has been reported in vaccinated individuals for certain respiratory pathogens, such as influenza [63]. The exception is one case report from 1981, where a case of fatal ARDS occurred in a 15-month-old who had suffered minor scalding after immunization with the live attenuated measles, mumps, and rubella (MMR) vaccine. The report suggests that the scalding suppressed the normal immune response to the measles viremia, which caused the lung damage which, in turn, led to ARDS. According to the report, the lung had fibroblastic nodules, vessel wall inflammation and other signs consistent with ARDS [64]. In the US VAERS reporting system, 124 events of ARDS have been reported following various immunizations, with no data regarding association (https://vaers.hhs.gov/ accessed 14 Dec 2020).

The occurrence of possible vaccine associated enhanced disease (VAED), a phenomenon that may present clinically like ARDS but which is distinct in its pathogenesis, was described after administration of formalin-inactivated vaccines against respiratory syncytial virus (RSV) in the 1960s, and some measles, pandemic influenza, and other respiratory virus vaccines [65].

In a recent summary of key findings in non-human primates and phase I/II studies of the most advanced SARS-CoV-2 vaccine candidates [66], there was no evidence for COVID-19 enhanced disease either based on antibody dependent enhancement or on enhanced infiltration of eosinophils into the lung upon infection post-immunization. Clinical data have shown acceptable safety and reactogenicity profiles across different vaccine candidate platforms, production of varying neutralizing antibody titers, and some vaccine candidates also elicited T-cell responses. However, additional long-term monitoring of persons exposed to SARS-CoV-2 vaccines is required in pre- and post-licensure stages to determine the risk of vaccine associated disease enhancement, particularly once neutralizing antibody titers start to wane [67].

2. Case definition of ARDS

The Working Group evaluated existing definitions of ARDS and developed a case definition for the assessment of ARDS as a potential adverse event following any immunization. Within this definition, a level of diagnostic certainty is ascribed based on the quality of evidence to support the criteria used to make the diagnosis. The Level 1 definition is highly specific for ARDS. As maximum specificity normally implies a loss of sensitivity, we included two additional diagnostic levels in the definition, offering a stepwise increase in sensitivity from Level 1 down to Level 3, while retaining an acceptable specificity at all levels. In addition, the case definition also allows for characterization of severity as mild, moderate, or severe based on the degree of hypoxemia. This was included to

Table 5
Case definition of ARDS as an Adverse Event Following Immunization.

Category	Adult	Pediatric
Level 1 Confirmed ARDS	Berlin Definition To make diagnosis, must meet ALL of the following criteria: 1) Hypoxemia - P/F Ratio $\leq$ 300 2) Positive Pressure Requirement: 3) - PEEP/CPAP $\geq$ 5 cmH20 4) Imaging: Chest imaging with bilateral chest opacities not explained by other process 5) Origin of edema: not related to fluid overload or cardiogenic edema 6) Timing: within 1 week of known clinical insult*	PALICC Definition To make diagnosis, must meet ALL of the following criteria: 1) Hypoxemia - P/F $\leq$ 300 or S/F $\leq$ 264 for non-intubated patients - OI $\geq$ 4 or OSI $\geq$ 5 for intubated patients 2) Positive Pressure Requirement: 3) - PEEP/CPAP $\geq$ 5 cm H20 4) Imaging: Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease 5) Origin of edema: new infiltrate not related to fluid overload or cardiogenic edema 6) Timing: within 1 week of known clinical insult*
Level 2 Probable ARDS	Meet Berlin Definition excluding PPV requirement (#2) -AND- If PaO2 unavailable, then can classify as Level 2a using S/F criteria^ -OR- If CXR/CT unavailable, then can classify as Level 2b using chest US.	Meet PALICC Definition excluding PPV requirement (#2) -AND- If PaO2 unavailable, then can classify as Level 2a using S/F criteria^ -OR- If CXR/CT unavailable, then can classify as Level 2b using chest US.
Level 3 Suspected ARDS	Strong clinical concern+ but CXR, CT, or US not available to meet Berlin Definition - Diagnosis based on clinical exam and assessment	Strong clinical suspicion+ but CXR, CT, or US not available to meet all PALICC Definition - Diagnosis based on clinical exam and assessment
Level 4 Clinical suspicion for ARDS	Clinical suspicion but insufficient data to classify as Level 1–3	Clinical suspicion but insufficient data to classify as Level 1–3
Level 5 Not a case of ARDS	Patients that do not meet above criteria for ARDS but may have hypoxemia and/or chest imaging findings due to other pathologic process	Patients that do not meet above criteria for ARDS but may have hypoxemia and/or chest imaging findings due to other pathologic process

Abbreviations:
P/F ratio – PaO_2 to FiO_2 ratio (arterial oxygen pressure to inspired fraction of oxygen ratio); S/F ratio – Saturation by pulse oximeter to FiO_2 ratio; PEEP – positive end expiratory pressure; CPAP – continuous positive airway pressure; CXR – chest x-ray; CT = chest tomography; US = ultrasound; OI = oxygenation index; OSI = oxygen saturation index.

* Timing criteria for ARDS, may vary after vaccination.

^ Severity as defined by S/F: For adults, mild $\leq$ *315 but > 235, moderate* $\leq$ *235 but > 144, severe S/F* $\leq$ *144.* For pediatrics, mild $\leq$ *264 but > 221, moderate* $\leq$ *221 but > 150, severe S/F* $\leq$ *150.*

+ Strong clinical concern as defined in Table 3.

align the case definition with existing definitions for ARDS. However, the three levels of certainty must not be misunderstood as reflecting different groups grades of clinical severity.

While standard definitions of ARDS include consideration for timing between insult and the onset of respiratory findings, our definition does not prescribe a specified time between vaccination and the onset of ARDS, as long as all other criteria for diagnosis are fulfilled. However, a temporal association consistent with the expected clinical course of ARDS would be suggested by a typical interval of one to two weeks between the insult and ARDS. Therefore, when considering the possibility of ARDS as an adverse event following immunization it is unlikely that ARDS would occur months after the exposure. Therefore, in application of this definition, special consideration must be given to how details of this interval are collected and reported.

Similarly, the Working Group decided against using "treatment" or "treatment response" towards fulfillment of the ARDS case definition. A treatment response or its failure is not in itself diagnostic and may depend on variables like clinical status, time to treatment, and other clinical parameters. The case definition is not meant to determine causality, and, therefore, known causes of ARDS should be evaluated (see Table 4).

The case definition is accompanied by guidelines which are structured according to the steps of conducting a clinical trial, i.e., data collection, analysis and presentation (Appendix A). Neither case definition nor guidelines are intended to be used for management of ill infants, children, or adults. Review of the definition with its guidelines is planned on a regular basis and as needed.

3. Rationale for selected decisions about the case definition of ARDS as an adverse event following immunization

3.1. Levels of certainty in the diagnosis of ARDS

Because ARDS is a heterogeneous disease process, diagnostic accuracy under typical circumstances is imperfect [68]. Furthermore, case definitions that require positive pressure or mechanical ventilation, chest imaging, and blood gas analyses pose barriers to diagnosis in resource-limited settings [69]. To address these concerns, the working group developed diagnostic criteria that are stratified according to level of certainty as summarized in Table 5 and Fig. 1. These levels reflect the accuracy of the evidence to support the diagnosis. Levels of certainty include confirmed ARDS (Level 1), probable ARDS (Level 2), and suspected ARDS (Level 3). In addition, Level 4 defines cases with insufficient data to make the diagnosis, and Level 5, cases for which there is sufficient data to attribute ARDS to another cause (i.e., not a case of ARDS).

3.2. Specific levels of certainty

Confirmed cases of ARDS (Level 1) are reserved for patients that meet the criteria set forth by the Berlin Definition for adults and PALICC Definition for pediatrics. These criteria represent the most widely accepted clinical criteria used to diagnose ARDS in adults and children, respectively. While the working group gave consideration to a single set of criteria, evidence supports that this would lead to missed cases [33], and therefore, we developed separate adult and pediatric criteria. Consistent with the standard ARDS definitions which were derived from heterogenous data sets that used variable age cutoffs, we do not provide guidance on age cutoffs for each.

While the Berlin and PALICC Definitions are the most widely used criteria, there are limitations to each that result in potential missed cases of ARDS [49]. To address this, alternative criteria were reviewed and included to define probable (Level 2) and suspected (Level 3) cases of ARDS. The relevant clinical scenarios are those without access to blood gas analysis, settings without radiographs or computed tomography scans, or patients not supported with positive pressure ventilation (PPV).

For Level 2, or probable ARDS, the relevant considerations are access to arterial blood gas analysis and chest imaging, which are used to subdivide the group into levels 2a and 2b. Level 2a is applicable in settings without access to arterial blood gases and uses an S/F rather than P/F ratio. While the discriminatory power of S/F to predict mortality with mild/moderate cases is inferior to P/F, it is comparable in severe cases [49,70]. Furthermore, it accurately predicts increasing mortality with worsening hypoxemia.

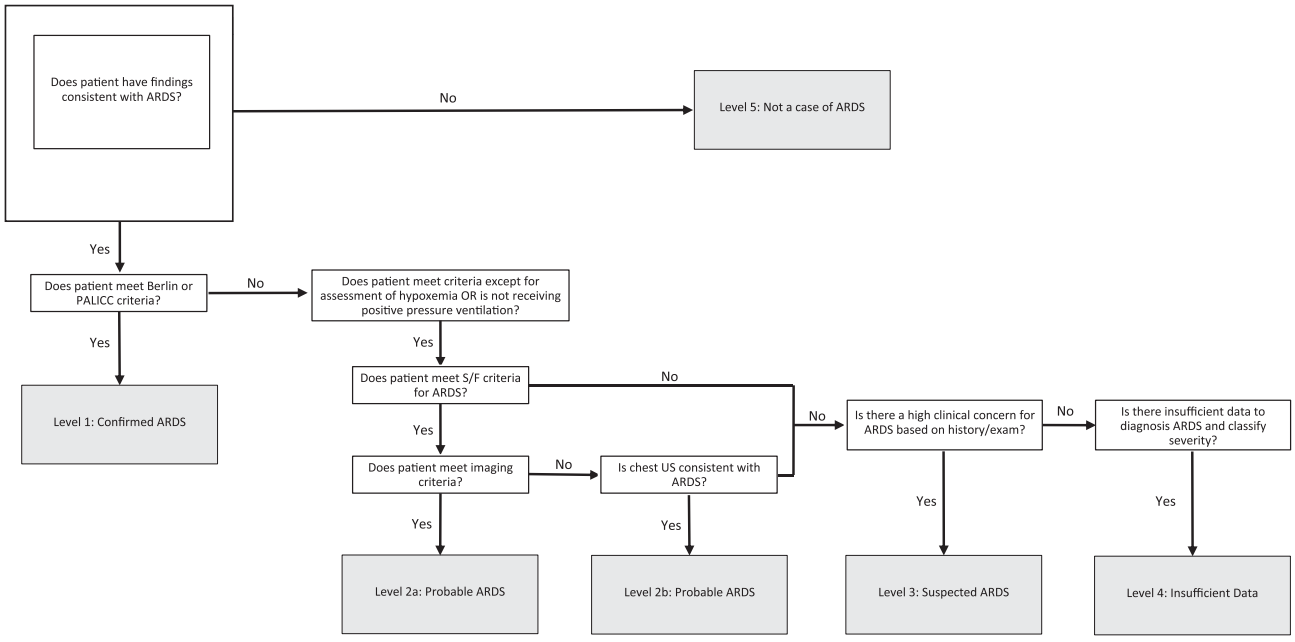

Fig. 1. Algorithm for the assessment of ARDS using the Brighton Collaboration Case Definition.

In comparison, Level 2b definition is applicable to clinical settings where chest radiograph or CT scans are unavailable. While typically thought of as an adjunct to routine imaging, chest ultrasound is becoming increasingly common, and has been shown to accurately identify ARDS in both adult and pediatric populations [8,71]. Although data are inconclusive regarding chest ultrasound equivalence to routine imaging, there are sufficient data to merit its inclusion as an alternative imaging modality [72].

Note that for Level 2 cases and below, PPV is not a requirement to meet the case definition for ARDS. Given that high-flow nasal cannula support is becoming increasingly common, especially as an alternative form of non-invasive support for patients with ARDS [73], the working group determined that inclusion of PPV would lead to too many missed cases. This would be especially true in resource-limited settings where access to PPV may be limited.

Lastly, because ARDS is a clinical diagnosis, special designation was given to include suspected ARDS (Level 3). In this category, a clinician would make the diagnosis based on a thorough history, physical examination, and characterization of hypoxemia, and then the clinician would make the assessment on a clinical basis alone (Table 3). This is most relevant in the setting where chest radiograph, CT scan, and ultrasound are unavailable. While it is difficult to estimate the performance of diagnosis based on clinical criteria alone, the working group believes that it is important to include this category while acknowledging the decreased diagnostic certainty, so clinical expertise in limited resource settings is also considered.

3.3. Special clinical scenarios

The diagnosis of ARDS is challenging, especially in patients with pre-existing conditions. For example, patients with cyanotic heart disease or chronic lung disease may meet several criteria for ARDS at baseline. To account for this, the case definition specifies that a patient's clinical presentation must represent an acute change from baseline, which aligns with other criteria for ARDS.

Disclaimer

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant's organization (e.g., government, university, or corporation).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.01.053.

References

[1] Laennec R. A treatise on the diseases of the chest and on mediate auscultation. New York; Philadelphia: Samuel Wood & Sons; Desilver, Thomas & Co.; 1835.
[2] Ashbaugh DG, Bigelow DB, Petty TL, Levine BE, et al. Acute respiratory distress in adults. The Lancet, Saturday 12 August 1967. Crit Care Resusc, 2005;7(1):60–1.
[3] Murray JF et al. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988;138(3):720–3.
[4] Bernard GR et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med, 199149(3 Pt 1):818-24.
[5] Ranieri VM et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526–33.
[6] Ferguson ND et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38(10):1573–82.
[7] Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16(5):428-39.
[8] Riviello ED, Buregeya E, Twagirumugabe T. Diagnosing acute respiratory distress syndrome in resource limited settings: the Kigali modification of the Berlin definition. Curr Opin Crit Care 2017;23(1):18–23.
[9] Rubenfeld GD et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353(16):1685–93.
[10] Li G et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. Am J Respir Crit Care Med 2011;183(1):59–66.
[11] Pfeifer R et al. Incidence of adult respiratory distress syndrome in trauma patients: A systematic review and meta-analysis over a period of three decades. J Trauma Acute Care Surg 2017;83(3):496–506.
[12] Caser EB et al. Impact of distinct definitions of acute lung injury on its incidence and outcomes in Brazilian ICUs: prospective evaluation of 7,133 patients*. Crit Care Med 2014;42(3):574–82.
[13] Linko R et al. Acute respiratory failure in intensive care units. FINNALI: a prospective cohort study. Intensive Care Med 2009;35(8):1352–61.
[14] Villar J et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med 2011;37(12):1932–41.
[15] Sigurdsson MI et al. Acute respiratory distress syndrome: nationwide changes in incidence, treatment and mortality over 23 years. Acta Anaesthesiol Scand 2013;57(1):37–45.
[16] Luhr OR et al. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. Am J Respir Crit Care Med 1999;159(6):1849–61.
[17] Acute lung injury and the acute respiratory distress syndrome in Ireland: a prospective audit of epidemiology and management. Crit Care, 2008;12(1):R30.
[18] Manzano F et al. Incidence of acute respiratory distress syndrome and its relation to age. J Crit Care 2005;20(3):274–80.
[19] Brun-Buisson C et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med 2004;30(1):51–61.
[20] Bersten AD et al. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med 2002;165(4):443–8.
[21] Chen W et al. Incidence and Outcomes of Acute Respiratory Distress Syndrome: A Nationwide Registry-Based Study in Taiwan, 1997 to 2011. Medicine (Baltimore) 2015;94(43):e1849.
[22] Siddiqui S et al. National survey of outcomes and practices in acute respiratory distress syndrome in Singapore. PLoS ONE 2017;12(6):e0179343.
[23] Huang X et al. Incidence and outcomes of acute respiratory distress syndrome in intensive care units of mainland China: a multicentre prospective longitudinal study. Crit Care 2020;24(1):515.
[24] Riviello ED et al. Hospital Incidence and Outcomes of the Acute Respiratory Distress Syndrome Using the Kigali Modification of the Berlin Definition. Am J Respir Crit Care Med 2016;193(1):52–9.
[25] Bellani G et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016;315(8):788–800.
[26] Zimmerman JJ et al. Incidence and outcomes of pediatric acute lung injury. Pediatrics 2009;124(1):87–95.
[27] Parvathaneni K et al. Evaluating the Performance of the Pediatric Acute Lung Injury Consensus Conference Definition of Acute Respiratory Distress Syndrome. Pediatr Crit Care Med 2017;18(1):17–25.
[28] Kneyber MC et al. Acute respiratory distress syndrome: is it underrecognized in the pediatric intensive care unit?. Intensive Care Med 2008;34(4):751–4.
[29] López-Fernández Y et al. Pediatric Acute Lung Injury Epidemiology and Natural History study: Incidence and outcome of the acute respiratory distress syndrome in children. Crit Care Med 2012;40(12):3238–45.
[30] Bindl L, Dresbach K, Lentze MJ. Incidence of acute respiratory distress syndrome in German children and adolescents: a population-based study. Crit Care Med 2005;33(1):209–312.
[31] Erickson S et al. Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study. Pediatr Crit Care Med 2007;8(4):317–23.
[32] Hu X et al. Incidence, management and mortality of acute hypoxemic respiratory failure and acute respiratory distress syndrome from a prospective study of Chinese paediatric intensive care network. Acta Paediatr 2010;99(5):715–21.
[33] Gupta S et al. Comparison of Prevalence and Outcomes of Pediatric Acute Respiratory Distress Syndrome Using Pediatric Acute Lung Injury Consensus Conference Criteria and Berlin Definition. Front Pediatr 2018;6:93.
[34] Khemani RG et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med 2019;7(2):115–28.
[35] Schouten LR et al. Incidence and Mortality of Acute Respiratory Distress Syndrome in Children: A Systematic Review and Meta-Analysis. Crit Care Med 2016;44(4):819–29.

[36] Acute Lung Injury (Monograph), ed. H. Wiedemann, M. Matthay, and R. Matthay. Vol. 2. 1986: Critical Care Clin.
[37] Li JT et al. Unexpected Role for Adaptive αβTh17 Cells in Acute Respiratory Distress Syndrome. J Immunol 2015;195(1):87–95.
[38] Millar FR et al. The pulmonary endothelium in acute respiratory distress syndrome: insights and therapeutic opportunities. Thorax 2016;71(5):462–73.
[39] Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. N Engl J Med 2017;377(6):562–72.
[40] Spadaro S et al. Biomarkers for Acute Respiratory Distress syndrome and prospects for personalised medicine. J Inflamm (Lond) 2019;16:1.
[41] Fanelli V et al. Acute respiratory distress syndrome: new definition, current and future therapeutic options. J Thorac Dis 2013;5(3):326–34.
[42] Schouten LR et al. Age-dependent differences in pulmonary host responses in ARDS: a prospective observational cohort study. Ann Intensive Care 2019;9(1):55.
[43] Khemani RG et al. Pulse oximetry vs. PaO2 metrics in mechanically ventilated children: Berlin definition of ARDS and mortality risk. Intensive Care Med 2015;41(1):94–102.
[44] Lazzeri C, Peris A. The Kigali modification of the berlin definition: a new epidemiological tool for ARDS?. J Thorac Dis 2016;8(6):E443–5.
[45] Rice TW et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007;132(2):410–7.
[46] Lee KY. Pneumonia, Acute Respiratory Distress Syndrome, and Early Immune-Modulator Therapy. Int J Mol Sci 2017;18(2).
[47] Baston C, West TE. Lung ultrasound in acute respiratory distress syndrome and beyond. J Thorac Dis 2016;8(12):E1763–6.
[48] Beltramo F, Khemani RG. Definition and global epidemiology of pediatric acute respiratory distress syndrome. Ann Transl Med 2019;7(19):502.
[49] Chen W et al. Clinical Characteristics and Outcomes Are Similar in ARDS Diagnosed by Oxygen Saturation/Fio2 Ratio Compared With Pao2/Fio2 Ratio. Chest 2015;148(6):1477–83.
[50] Vercesi V et al. External confirmation and exploration of the Kigali modification for diagnosing moderate or severe ARDS. Intensive Care Med 2018;44(4):523–4.
[51] World Health Organization. Clinical care of severe acute respiratory infections – Tool kit. 2020; (WHO/2019-nCoV/SARI_toolkit/2020.1). Licence: CC BY-NC-SA 3.0 IGO.]. Available from: https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit.
[52] Jain V, Yuan J-M. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health 2020;65(5):533–46.
[53] Zhang JJY et al. Risk Factors for Severe Disease and Efficacy of Treatment in Patients Infected With COVID-19: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. Clin Infect Dis 2020.
[54] Xie Y et al. Epidemiologic, clinical, and laboratory findings of the COVID-19 in the current pandemic: systematic review and meta-analysis. BMC Infect Dis 2020;20(1):640.
[55] Rodriguez-Morales AJ et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623.
[56] Qiu P et al. Clinical characteristics, laboratory outcome characteristics, comorbidities, and complications of related COVID-19 deceased: a systematic review and meta-analysis. Aging Clin Exp Res 2020.
[57] Hu Y et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Virol 2020;127:104371.
[58] Shekerdemian LS et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatrics 2020;174(9):868–73.
[59] Derespina KR et al. Clinical Manifestations and Outcomes of Critically Ill Children and Adolescents with Coronavirus Disease 2019 in New York City. J Pediatr 2020.
[60] Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS?. Crit Care 2020;24(1):198.
[61] Ziehr DR et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. Am J Respir Crit Care Med 2020;201(12):1560–4.
[62] Grieco DL et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. Crit Care 2020;24(1):529.
[63] Lobo SM et al. Excess mortality is associated with influenza A (H1N1) in patients with severe acute respiratory illness. J Clin Virol 2019;116:62–8.
[64] Pfenninger J, Zimmermann A. Fatal adult respiratory distress syndrome in a scalded child after immunization with attenuated virus (measles, mumps and rubella). Helv Paediatr Acta 1981;36(4):371–5.
[65] Graham BS. Rapid COVID-19 vaccine development. Science 2020;368(6494):945–6.
[66] Krammer F. SARS-CoV-2 vaccines in development. Nature 2020.
[67] Munoz FM et al. Vaccine-associated Enhanced Disease: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Vaccine; 2020.
[68] Bellani G, Pham T, Laffey JG. Missed or delayed diagnosis of ARDS: a common and serious problem. Intensive Care Med 2020;46(6):1180–3.
[69] Riviello ED, Pisani L, Schultz MJ. What's new in ARDS: ARDS also exists in resource-constrained settings. Intensive Care Med 2016;42(5):794–6.
[70] Chen WL et al. The Value of Oxygenation Saturation Index in Predicting the Outcomes of Patients with Acute Respiratory Distress Syndrome. J Clin Med 2018;7(8).
[71] De Luca D et al. The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity. Lancet Respir Med 2017;5(8):657–66.
[72] See KC et al. Chest radiography versus lung ultrasound for identification of acute respiratory distress syndrome: a retrospective observational study. Crit Care 2018;22(1):203.
[73] Ding L et al. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care 2020;24(1):28.