A Challenges of Acute Respiratory Distress Syndrome Definition

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Abstract

For a long time, the ARDS had taken the name of the causative injury (insults) like, for instance, Da Nang lung, shock lung, post-traumatic lung, etc. It until 1967 when an article published in *The Lancet Journal*, that Ashbaugh, Bigelow, Petty, and Levine were first describing the clinical entity they called (Acute Respiratory Distress in adults). Since that time many researchers, investigators, as well as intensivists, were trying to put a definition for this complicated syndrome, which may fulfill the precise diagnosis.

Keywords: Acute Lung Injury; Acute Respiratory Syndrome; Definitions

Introduction

Acute respiratory distress syndrome seems to presents an important worldwide public health problem but with some geographic variation in incidence and with a very high mortality rate which may reach about 40%. A major finding was the under-recognition of ARDS by most clinicians, the low use of conservative ventilatory strategy and adjuncts, and the limited effect of physician diagnosis of ARDS on treatment decisions. Generally, these findings indicate the potential for improvements in the management of ARDS patients. It was suggested that ARDS continues to be under-recognized by many clinicians in the time of Berlin's definition, like previous findings using the American-European consensus definition (AECC). It was revealed that the rate of intensivists' recognition of ARDS was low with about 40% of all cases was not being diagnosed. An intensivists' recognition rate increased with increasing syndrome severity but was still less than 80% in severe cases of ARDS.

Definition of ALI/ARDS

The first description of a condition (disorder) like ARDS has belonged to a scientist Laennec, who at 1821 termed it as 'idiopathic pulmonary edema' [1]. In the 20th century, many traumatic injuries had occurred during the global war period, which makes the disorder to be termed as a 'wet lung or shock lung' trying to explain the occurrence of lung edema after trauma. However, it had been only in 1967 that Ashbaugh and colleagues who for the first time termed the disorder as an acute respiratory distress syndrome (ARDS). The syndrome is characterized by an acute onset of tachypnea, hypoxemia, and loss of chest compliance usually after a variety of stimuli (risk factor).

Interestingly, Ashbaugh and colleagues reported the occurrence of particular clinical presentations was observed in 12 patients which characterized by severe dyspnea, tachypnea, and cyanosis which not respond to a high percentage of oxygen therapy, also there was a loss of lung compliance and the presence of diffuse alveolar infiltration revealed at plain chest X-ray evaluation, with a high rate of mortality. Since then the ARDS pattern includes the presence of certain risk factors for ARDS, severe hypoxemia despite high FiO_2, chest X-ray bilateral pulmonary infiltration, and exclusion of cardiogenic edema as a cause [2-4].

Since the first definition of ARDS, more than 50 years ago, a variety of efforts had been laid down to make the pathophysiology and severity of the syndrome clear. In 1988, Murray and colleagues had proposed a definition called an expanded definition of ARDS. In 1994, the American-European Consensus Conference (AECC) was defining the acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) as a "respiratory failure" and differentiated the ALI from ARDS depending on the PaO_2/FiO_2 ratio [5,6]. Since the respiratory failure due to ARDS is not typical for the adult patients but it is may also affecting the children, AECC definition was, therefore, also used in an adult or in pediatrics critical care to decide the grade of lung injury.

However, the oxygenation index (OI) proposed by Bartlett who studies the indications of extracorporeal membrane oxygenation (ECMO) in children with respiratory failure was accepted as an indicator to clarifying the lung injury in the pediatric population. Anyhow, in 2005 a team of investigators from the University of Toronto decides a type of consensus to improve the AECC definition of ARDS by using the Delphi technique [7]. In 2013, Villar and colleagues proposed a classification of ARDS severity intending to assess the ICU mortality according to the ratio of PaO_2/FiO_2. Nonetheless, after 18 years passed since AECC definition, a new definition of ARDS is required, with more generalized criteria and more specificity appeared. So, the most recent definition of ARDS was needed. This definition was proposed by the European Society of Intensive Care Medicine, which is now known as the Berlin ARDS definition [8].

Sometimes the disease and specifically the syndrome have many limits which making difficult to diagnose, for instance in the case of ARDS. However, the mortality of ARDS still high even with recent advances in treatment and monitoring, specifically in severe cases. In accordance, it must continually improve diagnostic criteria to some extent reaching an acceptable and practicable definition that meets a greater applicable in a clinical setting. Additionally, the review of the definition is so important for research and daily clinical practice in ICU [9]. It has been about 50 years passed since Ashbaugh and colleagues when firstly create the term ARDS as a syndrome that is characterized by "acute onset tachypnea, hypoxemia and reduced chest compliance due to different stimuli". Anyhow, since that period a long journey of time had elapsed to reach a satisfied ARDS definition.

There was so much controversy and challenges regarding the ARDS definition from the Murray Lung Injury Score extended to the AECC definition reaching finally to Berlin's definition. Commonly, patients are defined as having ALI/ARDS when they meet specific predetermined diagnostic criteria. The aim of the diagnostic criteria is to diagnosing the patients with a specific clinical entity for epidemiological target, and also to select patients who will mostly respond to syndrome standard therapy. Nonetheless, the diagnostic criteria used to define ALI/ARDS have progressed over time. The abbreviation (PaO_2/FiO_2 ratio) will frequently be mentioned and commonly used in the texts of ALI/ARDS, so this abbreviation must be clarified (Table 1). Based on the available data with various studies it was recommended that the new definition should be standardized as follows:

1. Determined the risk factors if direct (pulmonary) or indirect (extrapulmonary) as the two entities have a different pathogenic mechanism.
2. Calculation of PaO_2/FiO_2 ratios with specifying the standard ventilator setting.
3. Exclude cardiogenic edema (Echocardiography).
4. The patient included are only those with a PaO_2/FiO_2 ratio of about 200 mmHg with a standard ventilator setting.

The Murray lung injury score: Over two decades, there was no satisfying definition to make the syndrome understanding easy. So, investigators act to use various criteria to enroll patients in clinical studies leading to difficulty across the trials. In 1988 Murray., *et al*. proposed an expanded definition of ARDS, aiming to explain if the syndrome is acute or chronic, the physiological severity of the pulmonary injury, and the primary clinical insult which leads to the development of lung injury (Table 2) [10,11]. Murray lung injury score actually cannot consider strictly the definition; however, the definition can analyze as:

The PaO_2/FiO_2 ratio [(P/F ratio) or (PFR)] is an index to characterize the ALI/ARDS, which involves severe hypoxemia. PaO_2 is the partial pressure of oxygen in arterial blood. It is usually measured in millimeters of mercury (mmHg or Torr). PaO_2 of 75 to 100 mmHg is considered normal. FiO_2 is the fraction of inspired oxygen or simply a percentage of oxygen in a gas mixture atmospheric or given by medical gas equipment. For example, the atmospheric air has a FiO_2 of 21% (0.21). If a patient needs mechanical ventilation, FiO_2 is usually in the 30% to 40% range. Therefore, the normal ratios in the condition of patient inhaling spontaneous [atmospheric air] without incremental oxygen will be:

PaO_2/FiO_2 = 75/0.21 = 357 mmHg [lower acceptable ratio]

85/0.21 = 404 mmHg

95/0.21 = 452 mmHg

100/0.21 = 476 mmHg [upper ratio]

Table 1: *The PaO_2/FiO_2 ratio.*

1. The first part explains the clinical course of the syndrome as an acute or chronic. Patients with the chronic state likely to develop pulmonary fibrosis and leading subsequently to a poor outcome.

2. The lung injury score (LIS) quantified the severity of lung injury from the degree of arterial hypoxemia, the level of PEEP, respiratory compliance, and the radiological abnormality.

3. The association of medical conditions (comorbidity) must be specified.

Part 1	Acute or chronic, depending on course.
Part 2	The severity of physiological lung injury as decided by the lung injury score (Table 1-3).
Part 3	Lung injury is caused by or associated with a known risk factor for ARDS such as sepsis, pneumonia, aspiration, or major trauma.

Table 2: *Three-part expanded definition of clinical acute lung injury and the acute respiratory distress syndrome proposed by Murray and colleagues.*

There are some advantages of Murray lung injury score, by regarding whether the patent in the acute state mostly may go to rapid resolution or chronic state with a very bad prognosis. The LIS (Table 3) usually quantifying the severity of lung injury so differentiating patients with severe lung injury (LIS > 2.5) from patients with mild lung injury (LIS < 2.5 > 0.1). Of importance that identification of the cause or associated medical condition (comorbidity) usually addressed the etiology of lung injury. As the authors claimed, "grouping all cases of ARDS under an umbrella classification potentially prevented the discovery of beneficial treatment aimed at a cause" [12-14].

Despite the Murray lung injury score still used [even not wildly], but it has not proved if the patient with scores of the same value corresponds to the same level of lung injury and so have the same prognosis. The LIS has many drawbacks such as:

1. It doesn't consider the effect of time on injury severity.

2. It has low specificity for ARDS as patients with cardiogenic edema and patients with fluid volume overload can be diagnosed as ARDS because the pulmonary capillary pressure is not estimated.

The American-European Consensus Conference [AECC] definition: The AECC definition of ARDS indeed facing the major goal of creating uniformity to the definition. The diagnostic criteria for ARDS of AECC definition were PaO_2/FiO_2 ≤ 200 or 150 mmHg, bilateral chest

Clinical data		Score
Chest radiography	No consolidation	0
	Consolidation confined to 1 quadrant	1
	Consolidation confined to 2 quadrants	2
	Consolidation confined to 3 quadrants	3
	Consolidation confined to 4 quadrants	4
Hypoxemia score	$PaO_2/FiO_2 \geq 300$ mmHg	0
	PaO_2/FiO_2 225-299 mmHg	1
	PaO_2/FiO_2 175-224 mmHg	2
	PaO_2/FiO_2 100-174 mmHg	3
	$PaO_2/FiO_2 < 100$ mmHg	4
PEEP score (when mechanically vent.)	≤ 5 cmH$_2$O	0
	6-8 cmH$_2$O	1
	9-11 cmH$_2$O	2
	12-14 cmH$_2$O	3
	≥ 15 cmH$_2$O	4
Chest compliance score (when available)	≥ 80 ml/cmH$_2$O	0
	60-70 ml/cmH$_2$O	1
	40-59 ml/cmH$_2$O	2
	20-39 ml/cmH$_2$O	3
	≤ 19 ml/cmH$_2$O	4
The score calculated by adding the sum of each part and dividing by the number of components used		
No lung injury = 0		
Mild to moderate lung injury = 0.1 - 2.5		
Severe lung injury (ARDS) = > 2.5		

***Table 3:** Calculation of the lung injury score.*

X-ray infiltration (not essentially diffuse), and pulmonary artery occlusion pressure ≤ 18 mmHg or no evidence of left atrial hypertension (if pulmonary artery catheter not available). Besides the disease severity is also expanded to include ARDS patients with mild hypoxemia. The AECC ARDS definition also includes what is called acute lung injury (ALI) with diagnostic criteria similar to ARDS except that the PaO_2/FiO_2 ratio is ≤ 300 mmHg (Table 4).

Criteria	Timing	Oxygenation	Chest X-ray	Pulmonary artery wedge pressure
ALI criteria	Acute onset	$PaO_2/FiO_2 \leq 300$ (regardless of PEEP level)	Bilateral infiltrates	≤ 18 mmHg or no clinical evidence of left atrial hypertension
ARDS criteria	Acute onset	$PaO_2/FiO_2 \leq 200$ (regardless of PEEP level)	Bilateral infiltrates	≤ 18 mmHg or no clinical evidence of left atrial hypertension

***Table 4:** Recommended criteria for acute lung injury and acute respiratory distress syndrome.*

To clarifying the accuracy of the Murray lung injury score and the AECC definition, the diagnostic criteria for both definitions were compared with the early definition of ARDS which needed the four diagnostic criteria. Both definitions getting a high degree of accuracy for ICU patients with a defined at-risk diagnosis of the development of ARDS. consequently, it is likely they both definitions show a patients population like in the older definitions of ARDS for patients with defined at-risk diagnoses [15]. The AECC definition experts decided to clarify some problems concerning the diagnostic criteria for ARDS. It was clamming that the theoretical definition of ARDS for ALI based on the severity of hypoxemia had not proved the 2 separate entities with different clinical associations and outcomes. Regarding the chest X-ray criteria, the AECC claims that the bilateral infiltration should be consistent with pulmonary edema whatever if it is mid-infiltrate or patchy form. The AECC also claiming that there is a difficulty in excluding hydrostatic or cardiogenic causes as the only cause of pulmonary edema. Indeed, there is a lack of a perfect cutoff value of the pulmonary artery occlusion pressure which determines the hydrostatic pulmonary edema from permeability edema. The AECC definition didn't put a time limit for acuteness of syndrome, but ARDS mostly differentiate from interstitial lung disease which developed over a long time (weeks). The definition was showed that all patients when developing ARDS mostly by 7 days of the time of the at-risk diagnosis, so the length of time for the development of ARDS is defined as being < 7 days from time of onset of critical illness [6].

In some patients (for instance) with chest X-ray bilateral infiltration PaO_2/FiO_2 < 200 mmHg while they received artificial (mechanical) ventilation with 0-low level PEEP the PaO_2/FiO_2 then increased more than 200 mmHg or even to 300 mmHg when low or moderate PEEP level if applied [16-18]. In these patients, it was found that atelectasis could be the cause of hypoxemia rather than shunt from consolidation and pulmonary edema. It was found that the mortality of these patients was mostly lower than those whose PaO_2/FiO_2 stay less than 200 mmHg after increasing PEEP to a high level [19]. Besides in many patients with chest bilateral infiltration PaO_2/FiO_2 increased when FiO_2 is raising from moderate to high levels. This phenomenon is suggesting that between patients with similar PaO_2/FiO_2 levels, oxygenation failure is worse and there may a high risk of death in patients receiving higher FiO_2. This without standardized PEEP and FiO_2 the AECC criteria may show a heterogeneous group of patients, some are mostly at minimal risk of outcome such as death. In accordance, the use of AECC criteria to recognize patients for ALI/ARDS trials without PEEP and FiO_2 could reduce the power of trials due to the potential effects of new interventions that may be smaller in patients with mild ARDS. So, some investigators had suggested that the results of trials which enrolled ALI/ARDS patients applying the AECC criteria without the low-level PEEP were in confounding by the imbalance between the study groups in patients with mild and severe lung injury who could not detected without increasing the PEEP [17,20]. Since 1996 the National Institute of Health ARDS Network was using the AECC criteria the inclusion criteria for most of their trials. The exclusion criteria act to reducing the heterogeneity of the studied population, but patients were not excluded if they put on 0 or low-level PEEP or low FiO_2 [21-24]. However, it was found that the baseline PEEP alone may predict outcome or mortality, but after controlling for baseline PEEP and PaO_2/FiO_2 then cannot predict mortality (Table 5) [25].

In conclusion, the AECC definition differs from Murray lung injury score in 4 aspects:

1. The AECC definition didn't depend on the principle of 4 areas of chest X-ray scoring. But instead, depending on the appearance of bilateral infiltration.

2. Some investigators or intensivists exclude PEEP measurement to reduce variability when PEEP is applied.

3. A variety of degrees of hypoxemias was required for oxygenation criteria.

4. Mostly including either measurement of pulmonary artery occlusion pressure or instead predicting the absence of clinical evidence of left atrial increased pressure by either clinical assessment or by using echocardiography.

Limitations of the AECC definition: Although the AECC definition had the perfect formulation regarding diagnostic criteria for ARDS and is simple for used in daily practice, it has discussed over the years considering the increased knowledge of ARDS [18]. However, the limitation of the AECC definition can be grouped as follow:

Parameters	PEEP ≤ 5	5 < PEEP ≤ 10	11 ≥ PEEP	Total**
$PaO_2/FiO_2 > 175$	23.1 ± 5%	22.0 ± 6%	25.9 ± 18%	23.1 ± 2%
$110 < PaO_2/FiO_2 ≤ 175$	31.4 ± 9%	25.4 ± 5%	28.1 ± 13%	27.8 ± 3%
$PaO_2/FiO_2 ≤ 115$	35.7 ± 2%	35.2 ± 7%	38.2 ± 7%	36.5 ± 3%
Total*	27.8 ± 3%	27.8 ± 2%	33.3 ± 4%	
Note: Overall mortality was 29.2% ± values are standard errors. Data analyzed using the Cochran-Armitage trend test. * Within each PEEP range there is a highly significant increase in mortality with lower PaO_2/FiO_2 levels (p < 0.0001). ** Within each PaO_2/FiO_2, tertile there is no significant difference in mortality with increasing PEEP level.				

Table 5: *Mortality rates according to PaO_2/FiO_2 tertile and PEEP levels.*

- **Heterogeneity:** The AECC definition mostly considering a variety of physiological changes and different patients in a single syndrome. The triggers of lung injury, the stages of syndrome, and the time of onset of mechanical ventilation are contributing to the heterogeneity [26-28]. The practical implication of these problems is obvious, as the management of some patients with positive results may be not the same effect as other ones [9,29].

- **Time of onset:** The AECC definition does not clarify the acute from a chronic state of the syndrome.

- **Hypoxemia assessment:** The AECC definition commonly using the PaO_2/FiO_2 ratio for evaluation of the degree of hypoxemia. But, indeed there is inconsistency in the usage of this ratio, because of PEEP and FiO_2 variables [17,19,25,30]. Despite the ratio values to diagnose ALI is ≤ 300 mmHg and that for ARDS is ≤ 200 mmHg are explicit, it is mandatory to take into account that the index values are varying according to the FiO2 used [particularly with $FiO_2 < 0.5$ and $PaO_2 > 100$ mmHg], or when the fraction of intrapulmonary shunt is low. Besides many patients who initially meet the criterion of AECC may show an increase in the PaO_2/FiO_2 ratio to > 200 mmHg after a short time of applying PEEP or an increase in FiO_2 [30]. Also, hypoxemia may be due to other pathological changes like atelectasis, low cardiac output, and/or shunting through foramen ovale [31,32].

- **The problem of ALI:** In the AECC definition, all patients with PaO_2/FiO_2 ratio < 300 mmHg was diagnosed as ALI. There is a problem in the classification of patients whose ratio is of 201 - 300 as to whether they would be classified as ALI or ARDS [33].

- **Risk factors:** They are not included in the AECC definition.

The Delphi consensus definition: As there were no agreements between definitions that developed till now, Ferguson and colleagues developed a new clinical definition of ARDS in 2005. This definition utilizing the Delphi technique to improve the accuracy of the AECC definition [7,34]. This definition was incorporating other variables such as:

1. The level of PEEP.

2.   A precise definition of acute onset (within 72 hours).

3.   A subjective assessment of cardiac involvement.

4.   An objective assessment of cardiac involvement (pulmonary capillary pressure ≤ 18 mmHg or ejection fraction ≥ 40%).

5.   Assessment of pulmonary compliance (static compliance < 50 cmH$_2$O, with a tidal volume of 8 ml/kg).

6.   Quantification of radiological criteria for the syndrome in 2 or more quadrants (Table 6).

	Defining criteria	Operational definition
1	Hypoxemia	PaO$_2$/FiO$_2$ < 200 with PEEP ≥ 10.
2	Acute onset	Rapid onset within < 72 hours.
3	Radiological abnormalities	Bilateral airspace disease involving ≥ 2 quadrants on frontal chest X-ray.
4	Noncardiogenic in origin	No clinical evidence of congestive heart failure (including the use of pulmonary artery catheter and/or echocardiography).
5	Decreased lung compliance	Static respiratory system compliance < 50 ml/cmH$_2$O (with the patient sedated, tidal volume of 8 ml/kg, ideal body weight, PEEP ≥ 10).
6	Predisposition	Direct and/or indirect factors associated with lung injury.
The presence of 1 of criteria 1-4 and 1 of 5 or 6 indicates ARDS.		

Table 6: *The Delphi definition of ARDS.*

Although it - to some extent - solved the problems of the earlier definitions, the same researchers reported that, although the Delphi definition is more specific than the AECC definition it was less sensitive when autopsy findings of diffuse alveolar damage were choosing as a standard for diagnosis of ARDS [35].

Oxygenation index (OI) and PaO$_2$/FiO$_2$ ratio: Oxygenation Index (OI) is the most widely used system to quantify the degree of lung injury and hypoxemia in pediatric critical care. OI specifically takes into account mean airway pressure (MAP), an important determinant of oxygenation. OI is defined as the product of:

Mean airway pressure (MAP) × FiO$_2$ × 100/PaO$_2$.

The OI has been associated with outcome in both adults and children with ALI/ARDS. The original study in 2005 reported on the ability of OI to predict the duration of mechanical ventilation but not survival. Since then many adult studies have examined the efficacy of OI as a predictor of both duration of mechanical ventilation and mortality. In comparison, the measurement of PaO$_2$/FiO$_2$ as a predictor of mortality in ALI/ARDS is uncertain. Although there are little differences in outcome based on the PaO$_2$/FiO$_2$ ratio early in the course of ARDS, it is likely that persistently lower PaO$_2$/FiO$_2$ ratios are associated with higher mortality.

The Berlin definition: The suggestion about an update of the AECC definition of ARDS has been published in recent times by a task force panel of experts by using the same terminology as had reported previously (ARDS definition task 2012). However, by using the teleconference, expert discussion, and retrospective data, it is proposed that a classification of ARDS with 3 categories of severity as a mild, moderate, and sever for empirical evaluation:

1.   The term mild ARDS was taken for defining the patients who considered as ALI (in the AECC definition), their PaO$_2$/FiO$_2$ is from ≥ 300 - > 200.

2. The term moderate is using for patients whose $PaO_2/FiO_2 > 100$ and < 200.

3. The term server is used for patients with $PaO_2/FiO_2 \leq 100$.

The panel had found that the hospital mortality increased per every stage of severity [that mean progression from one category to another] is mostly associated with increased mortality (mild about 27%, moderate about 23%, sever about 45%) (Table 7) [36].

Acute respiratory distress syndrome		
Timing	Within 1 week of a known clinical insult or new worsening respiratory symptoms.	
Chest image*	Bilateral opacities - not fully explained by effusion, lobar/lung collapse, or nodules.	
Origin of edema	Respiratory failure is not fully explained by cardiac failure or fluid overload so need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor presents.	
Oxygenation**	Mild	$200 < PaO_2/FiO_2 \leq 300$ with PEEP or CPAP ≥ 5 cmH$_2$O.***
	Moderate	$100 < PaO_2/FiO_2 \leq 200$ with PEEP ≥ 5 cmH$_2$O.
	Severe	$PaO_2/FiO_2 \leq 100$ with PEEP ≥ 5 cmH$_2$O.
*Chest radiograph or CT scan.		
**If altitude is higher than 1000 m, the correction factor should be calculated as follow: $[PaO_2/FiO_2 \times$ (barometric pressure/760)].		
***This may deliver non-invasively in the mild acute respiratory distress syndrome group.		

Table 7: The Berlin definition of ARDS (the ARDS definition task force: The Draft Berlin Definition, ESICM 24 the Annual Congress Berlin, October 2011).

In 2010 a study was initiated by members of the European Society of Intensive Care Medicine and chose other professionals from Europe and the United States acting to review the definition of ARDS [37]. The discussion panel confirms the applicability, reliability, validity, and predictive capacity of a new definition. It was determined that any reviews of the definition must be comparable with the definition of AECC definition to facilitate the interpretation of practice and studies. Then a pre-definition was established and evaluated by using the meta-analysis of data from 4188 ARDS patients from 4 different centers as well as physiological data of 269 ARDS patients from 3 centers [30]. Interestingly, the pre-definition proposed 3 exclusive categories of ARDS based on the degree of hypoxemia as mentioned above. Anyhow, the final definition was submitted to discussion and refinement until its applicated clinically.

However, the definition was reviewed to identify studies for meeting the following criteria:

1. Extensive studies involving many centers to clarify the radiological or physiological data of patients with ALI/ARDS according to the criteria of the AECC definition.

2. Other studies collecting data revealed to apply both the plan of the Berlin as well as AECC definitions.

3. Then a decision is taken to the authors of studies that were involved to participate and share data.

The following variables were used in the analysis:

1. The mortality at 90 days, and survival days of free from mechanical ventilation at 28 days after the diagnosis.

2. Duration of mechanical ventilation in survivors used as an indirect marker of lung injury severity and progression of ARDS severity at 7 days.

3. Radiological assessment: patients with more extensive involvement (3 - 4 quadrants) were differentiated from patients with a mild lesion (1 - 2 quadrants).

4. Static respiratory compliance is calculated as tidal volume divided by plateau pressure subtracted from PEEP.

5. The corrected expired volume per minute is calculated by the product of minute ventilation for $PaCO_2$ divided by 40 mmHg.

6. Calculating the total weight of the lung by computed tomography images and the intrapulmonary shunt fraction.

Interestingly, (Table 8) shows the main limitations of AECC and the usage of the corresponding measure adapted by Berlin's definition to overcome the difficulties [33,38,39].

Parameter	Limitations of the AECC definition	Proposal of the Berlin definition
Time	The time of disease was not defined.	The time corresponding to acute was specified.
Acute lung injury category	Erroneously interpreted when the PaO_2/FiO_2 ratio is between 201 and 300 mmHg, resulting in misperception.	• Three ARDS subgroups were included, according to the severity, which is mutually exclusive. • The term acute lung injury is removed.
Oxygenation	Inconsistency in the PaO_2/FiO_2 ratio due to the effects of PEEP and/or FiO_2.	• A minimum level of PEEP was added to each subgroup. • FiO_2 effects are less important in the most severe subgroup.
Chest X-ray	Poor reliability of chest X-ray interpretation.	• The radiographic criteria were clarified. • An example of an X-ray was created.
Pulmonary capillary pressure (PCP)	• High PCP and ARDS can coexist. • Poor interobserver reliability in PCP measurement and the clinical assessment of left atrial hypertension.	• Need to measure PCP was removed. • Hydrostatic edema is not the primary cause of respiratory failure. • Clinical elements were created to help rule out hydrostatic edema.
Risk factors	Was not formally included.	• Included. • When there are no risk factors, it is necessary to objectively rule out hydrostatic edema.

Table 8: Limitations of the AECC ARDS definition and proposals of the Berlin definition to overcome these limitations.

Limitations of the Berlin definition [36]:

1. Children were not included in the definition criteria.

2. The auxiliary is not shown the subgroup of ARDS patients at higher risk due to many unmeasured variables like the number of quadrants in chest X-ray cannot reliably be measured, the PEEP was manipulated as a predictor, and respiratory compliance (Crs) and corrected expired volume/minute were not accurately measured. In Berlin's definition, both PEEP and Crs were evaluated in clinical practice and not as pre-specific elements.

3. The definition is not including criteria indicating the prognosis of ARDS.

Technical investigations may assist the diagnosis of ARDS by Berlin definition: It was found that some investigations may be used for more accurate the diagnosing ARDS by Berlin definition: It was found that extravascular lung water (EVLW) is an independent prognostic

factor for ARDS patients. The EVLW and mean cumulative fluid balance are mostly associated. It was found that EVLW is an exclusive marker of lung injury, and not related to a liberal fluid strategy which leading to fluid overload. Indeed, in so many cases of ARDS. The EVLW could be normal. The EVLW is underestimated if indexed to the actual body weight and should be indexed to predictive body weight [40,41]. It is also that EVLW is underestimated in the presence of an inhomogeneous form of ARDS. Besides pulmonary microemboli and/or vascular damage due to ARDS also may lead to an inhomogeneous distribution of the cold marker [42,43]. The increase of PEEP and tidal volume during mechanical ventilation mostly induces a decrease in pulmonary blood volume (PBV) and changes in dimensions of heart ventricles, so the ratio between heart and PBV could change in those conditions. The pulmonary vascular permeability index (PVPI) is the ratio between EVLW and PBV or more accurately is the ratio between EVLW and intra-thoracic blood volume (ITBV), so this index reflects the pulmonary microvascular permeability. An increase in pulmonary vascular permeability is considered as an important pathological feature of ARDS. However, the PVPI > 3 confirms the diagnosis of ARDS with 100% specificity, while the PVPI < 1 - 7 excludes the diagnosis of ARDS [42,44-46].

Indeed, the PVPI has the same limitation as that of EVLW. The global end-diastolic volume (GEDV) is the volume of all 4 cardiac chambers at the end-diastolic. The GEDV is including the cardiac volume as well as a part of the superior vena cava volume and the aortic volume which is between the bolus injection site and the thermistor [45,47,48]. There is a controversy in a lot of studies about the volume markers of cardiac preload measured by the transpulmonary thermodilution (TPTD) that are best than pressure markers. The GEDV is better correlated than pulmonary artery occlusion pressure (PAOP) with stroke volume. It was found that if the ventricular compliance is low a small volume change will inducing large changes in pressure, therefore, changes in volume will be underestimated the change in cardiac preload. The limitation of GEDV is that it doesn't distinguish between the left and right champers, for instance, the right dilatation may be misinterpreting as an elevation of left ventricular preload [39,45].

The TPTD is an interesting tool for the assessment of pulmonary edema, however, the interpretation must be cautious. Some investigators trying to including the thermodilution in the Berlin definition but it is unacceptable due to its cost, invasiveness of method, and unavailability of it in many countries [42,49]. It is of importance to notice that the thermodilution didn't distinguish between hydrostatic and inflammatory edema. In the past (before the Berlin definition), the definition of ARDS commonly includes the PAOP value measured by pulmonary artery catheterization (Swan-Ganz catheter). This method is even more invasive, expensive, and methodologically limited than transpulmonary thermodilution. At now inflammatory pulmonary edema may include cardiogenic edema. Nowadays, cardiac ultrasound (echocardiography) is essential to detecting the mixed situation with combined pulmonary edema, especially it is proving that about 30% of patients with ARDS are presented with left heart failure [49,50].

The use of echocardiography is essential for complete diagnosis in patients with valvulopathology or the condition of heart failure without an elevation of the volume of cardiac champers. A complete pulmonary edema assessment is mostly requiring thermodilution and echocardiography together. Anyhow, the pressures are as important as volumes for identifying both components (ARDS and hydrostatic lung edema) for guiding an accurate therapy of ARDS. In condition, with Berlin's definition of ARDS and for adequate diagnosis of ARDS, it used 2 technical investigations, the thermodilution, and echocardiography together, as the thermodilution alone may miss the diagnosis in about 30% of ARDS patients [51].

The Berlin and Kigali definitions of ARDS

Due to low-income countries, an objection regarding the validity of the Berlin definition comes from Kigali [Kigali is the largest city in Rwanda]. Riviello and colleagues estimated the incidence of ARDS at the university teaching hospital at Kigali [52]. The teamwork was screened for all patients in the hospital for about 6 weeks and acting to collecting the data on ARDS risk factors by lung sonography. The first results were that the Berlin definition could not be applying in most ARDS patients due to the inaccessibility of mechanical ventilation, arterial blood analysis, and chest radiography.

So that, the teamwork obligated to change the ARDS definition to a what known the Kigali version of definition: the requirement of PEEP was removed and the most changes are replacing the PaO_2/FiO_2 ratio with the SpO_2/FiO_2 ratio by using the pulse oximetry which is commonly available (hypoxemia cut-off is ≤ 315) [53]. Cardiac function was assessed by echocardiography. The results were that about 42 patients of 1046 hospital admissions (4%) was met the Kigali criteria for ARDS, 39% of ARDS patients were admitted to ICU, and the mortality was about 50%. Therefore, the results of this important scientific contribution are that the Berlin definition is inapplicable or is underestimated the incidence of ARDS in low-income countries that are a large part of the world and so may results in estimating only - treated incidence - in high-income countries [54].

Some challenges for global studies in the future can be postulated that: on one hand, different definitions of syndrome or their severity around the world will be counteracted the globalization of science which is continuous and necessary [55]. On the other hand, it seems to be impossible to work with definitions not applicable in some parts of the world or when applied may producing invalid results. Therefore, when is the compromise and how can to continue. In the results the Kigali definition is a landmark study for a global approach to pulmonology and intensive care medicine:

1. The Kigali definition confirms and focuses on daily life circumstances in a resource-constrained country with typical for diagnosis and therapy, which are far-away from the standard of developed countries.

2. The definition is considered as a crucial step for the improvement of systematic health trials which are important to understand and may improve the pathways of health care in countries with a limited health-care ability [29].

3. Despite the Kigali definition of ARDS required a validation before widespread use, indeed there is no doubt that the scientists and intensivists invited to starting a project for stimulating further cooperative work to refine an ARDS definition that can be applicable in high-income as well as low-income countries.

In support of Kigali's definition, since the protective ventilatory strategy significantly improving the outcome of ARDS patients, early identification of ARDS and early application of ventilatory strategy, therefore, is crucial. Levitt and colleagues were defining the clinical diagnosis of early ALI at hospital admission if there were bilateral opacity in chest X-ray and an oxygen requirement of > 2 L/minute [56]. This approach indeed showed high sensitivity and specificity for progression to ALI. Also, Festic., *et al.* had shown that the SpO_2/FiO_2 ratio measured within the first 6 hours after hospital admission is an independent indicator of the development of ARDS among high-risk patients. Anyhow, the use of the SpO_2/FiO_2 ratio for diagnosis of ARDS rather than the PaO_2/FiO_2 ratio may found patients with a similar outcome. In conclusion, since the SpO_2/FiO_2 ratio is highly available in every department of the hospital, then its use may help earlier diagnosis and an early application of the protective ventilatory strategy [57]. Using pulse oximetry for watching the SpO_2/FiO_2 ratio for evaluating the degree of hypoxemia in critically ill patients has several advantages over the PaO_2 monitoring:

1. The pulse oximetry avoiding the arterial blood drawing and so avoiding the complications like hemorrhage and vascular injury.

2. Pulse oximetry enables continuous monitoring of the O_2 saturation which acts to increase the possibility of early detection of ARDS and doesn't obligate to waiting for a time-consuming of repeated arterial sampling [58].

Anyhow, these theoretical advantages, go on with data from many studies suggesting that ARDS which was diagnosed by using SpO_2/FiO_2 is not clinically too different from ARDS diagnosed by the PaO_2/FiO_2 ratio. Although there has been some controversy about the accuracy of pulse oximetry in dark-skin patients, the reports were showing that the arterial oxygen saturation was slightly different (3.56% ± 2.45%) from SpO_2 only at very low oxygen saturation (60% - 70%).

It was found that more patients who developed ARDS after the second day of enrollment among those who received a diagnosis of ARDS by SpO_2/FiO_2 ratio. This finding explains that the SpO_2/FiO_2 ratio is particularly most suited for the diagnosis of delayed cases of ARDS after ICU admission, since the frequency of arterial blood gas measurement may sometimes diminish after the first ICU day. Despite

the difference did not reach a significant degree, but a higher percentage of patients in the SpO_2/FiO_2 diagnosed group received noninvasive ventilation on the day of ARDS diagnosis. This finding is suggesting that the SpO_2/FiO_2 ratio is useful in the diagnosis of ARDS, as the ARDS patients receiving noninvasive ventilation, this group of patients may be less likely to have an arterial access catheter placed or to undergo arterial blood gas sampling [53].

Correcting the PaO_2 to FiO_2 at altitude

In the Berlin definition of ARDS there is a recommendation of adjustment of PaO_2/FiO_2 at altitude, but without a reference as to how it derived. However, at the same shunt state, the PaO_2/FiO_2 is decreasing with altitude and therefore impairing the proper comparison of patients with similar lung damage if they exist at different stages of altitudes and if the shunt is not directly measured as in the case in most patients [59]. Therefore, it is very important in studies to correct the PaO_2/FiO_2 by altitude or barometric pressure (i.e. raise the value of PaO_2/FiO_2 obtained at altitudes), but unfortunately, the adjustment is not so simple a function of altitude or barometric pressure. It was found that the correction suggested by working groups dose the opposite of what is needed, due to it is requesting a multiplication by a fraction [Barometric pressure (Pbar)/760]. If instead of multiplying by Pbar/760, it is divided by the ratio [to set, for instance, varying limits for the severity of ARDS at different altitudes]. The resulting PaO_2/FiO_2 then is closer to that expected at sea level for lower shunt (and high PaO_2/FiO_2) but overcorrects at higher shunts and of course, doesn't consider the changes in PaO_2/FiO_2 due to modifications of FiO_2 [60].

These suggested adjustments appropriately are rasing the PaO_2/FiO_2 which is measured at altitude, so that the same sea level at-point limits to classifying ARDS severity then can be used when comparing patients who living at different altitudes above sea level. The empirical testing of estimation is necessary although complicated because so many factors that are kept constant in the computer simulation regularly have variations in critical patients. However, it is important to do adjustments as shown by the shift in severity classification of a group of patients with ARDS, displaced towards mild stages - as expected - because part of the decreased PaO_2/FiO_2 is observed in Mexico City was due to altitude and not to lung damage. Anyhow, it was found that the classification by saturation of O_2 (SaO_2/FiO_2) had a similar tendency (Table 9) [61].

> Using altitude in meters to estimate PaO_2/FiO_2 at sea level (PaO_2/FiO_2 SL):
> PaO_2/FiO_2 SL = (PaO_2/FiO_2 × 1.245) + (FiO_2 × 51.51) + (0.0307 × altitude) – 88
> Using mean Pbar in mmHg:
> PaO_2/FiO_2 SL = 224.46 + (PaO_2/FiO_2 × 1.245) – (Pbar × 0.413389) + (FiO_2 × 51.55)

Table 9: Shows the severity of ARDS with the original classification and after the proposed adjustment, duplicating the percentage of patients with mild ARDS.

ARDS mimickers

The approach to the deferential diagnosis in ARDS patients should include the mimickers of ARDS. Despite that, the definitions of ARDS including parameters that reduce the possibility of misclassification but other disorders may also be presented in an acute form with symptoms and signs of hypoxemia, chest X-ray bilateral infiltration, and without shreds of evidence of cardiogenic dysfunction [6,36]. The diagnosis of such as diffuse alveolar hemorrhage, pulmonary alveolar proteinosis, acute interstitial pneumonia, acute eosinophilic pneumonia, and acute exacerbation of idiopathic pulmonary fibrosis may meet the diagnostic criteria of ARDS (Table 10).

However, these diseases are not resulting from the same inflammatory mechanisms of ARDS and the treatment may vary dramatically based on the diagnosis. Conclusionally, carful attention must played to the possibility of an alternative diagnosis in ARDS patients, espe-

Disease	Chest imaging characteristics	Diagnostic tests	Potential changes in therapy
Diffuse alveolar hemorrhage	Bilateral alveolar and ground-glass infiltration	Bronchoscopy with bronchoalveolar lavage	Glucocorticoids, transfusion, immunosuppressive therapy
Pulmonary alveolar proteinosis	Central and lower lung zone alveolar infiltrates, batwing appearance, crazy paving on CT	High-resolution CT, bronchoscopy with bronchoalveolar lavage	Whole lung lavage, granulocyte macrophage-colony simulating factor
Acute interstitial pneumonia	Bilateral alveolar and ground-glass infiltrates, septal thickening, traction bronchiectasis	No alternative cause of ARDS found, open or thoracoscopic lung biopsy	Glucocorticoids
Cryptogenic organizing pneumonia	Peripheral distribution of alveolar infiltrates, migratory infiltrates	Bronchoscopy with transbronchial lung biopsy	Glucocorticoids
Acute exacerbation of idiopathic pulmonary fibrosis	Ground-glass opacities superimposed on peripheral, basilar fibrotic changes	CT	Glucocorticoids
Acute eosinophilic pneumonia	Bilateral alveolar and ground-glass infiltrates	Bronchoscopy with bronchoalveolar lavage	Glucocorticoids

Table 10: *The mimickers of ARDS.*

cially when no clear underlying cause of ARDS is readily found [62]. The definition of ARDS was updated recently as mentioned above, with new categories of ARDS severity giving a better prognostic accuracy [36]. However, the diagnostic criteria don't distinguish between different etiologies of respiratory failure. The respiratory failure with both physiological and radiological changes compatible with ARDS, but where no [Common Risk Factors (CRF) can be found (ARDSCRF-)] is a category covering the different pathological conditions that should be characterizing and may be managed separately [38]. The important aspect of this differential diagnosis is highly potential with the following implications:

1. Inflammatory changes may be predominant in ARDSCRF-diseases, as apposing to diffuse alveolar damage (DAD), which is characterized by the presence of hyaline membranes.

2. Widespread inflammation makes the lung more affected by ventilatory-related lung injury but also potentially responding to using steroids.

3. Some of the ARDS mimickers like the lung carcinomatosis and alveolar hemorrhage may have poor prognostic value.

It was found that there were 4 etiological categories of ARDSCRF-diseases which are:

- Immune-associated connective tissue disorders

- The drug-induced disorders

- The malignancy and

- The idiopathic disorders.

  In general, ARDSCRF-patients commonly had a longer course of the complaint before ICU admission and a lower incidence of shock in the 1st 48 hours of admission. The steroids were mostly prescribed in ARDSCRF-patients and all ARDSCRF-survivors had steroid treat-

ment. Anyhow, ARDSCRF- was associated with about a two-fold increase in the ICU death. Among the ARDSCRF- a hemorrhagic or lymphocytic bronchoalveolar lavage and absence of chest X-ray signs of fibrosis were associated with increased potential reversibility and increasing of ICU survival. Nonetheless, ARDSCRF- may be more often be met than expected and is associated with increased ICU mortality if associated with other pathological changes [63].

Conclusion

Even with all the above-mentioned efforts to create a satisfactory definition that completely involving all categories of the syndrome and aid the researchers and intensivists to depends on it as an acceptable and perfect definition covering all aspects of ARDS was continue. However, at now the Berlin definition may take a priority, but even so, we need a new definition that may be more equivalent than it.

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