

# Definition and epidemiology of acute respiratory distress syndrome

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**Abstract:** Fifty years ago, Ashbaugh and colleagues defined for the first time the acute respiratory distress syndrome (ARDS), one among the most challenging clinical condition of the critical care medicine. The scientific community worked over the years to generate a unified definition of ARDS, which saw its revisited version in the Berlin definition, in 2014. Epidemiologic information about ARDS is limited in the era of the new Berlin definition, and wide differences are reported among countries all over the world. Despite decades of study in the field of lung injury, ARDS is still so far under-recognized, with 2 out of 5 cases missed by clinicians. Furthermore, although advances of ventilator strategies in the management of ARDS associated with outcome improvements—such as protective mechanical ventilation, lower driving pressure, higher PEEP levels and prone positioning—ARDS appears to be undertreated and mortality remains elevated up to 40%. In this review, we cover the history that led to the current worldwide accepted Berlin definition of ARDS and we summarize the recent data regarding ARDS epidemiology.

**Keywords:** Acute respiratory distress syndrome (ARDS); definition; epidemiology

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## Introduction

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung process, which leads to protein-rich non-hydrostatic pulmonary edema, causes refractory hypoxemia, increases lung “stiffness” and impairs the ability of the lung to eliminate carbon dioxide.

At a macroscopical level, computed-tomography (CT) studies gave birth to the fascinating concept of “baby lung”, suggesting a change of perspective from a “stiff” to a “small” lung (1). Furthermore, the CT study of the gravity effect on the lungs, using the prone position, helped to better understand how the “baby lung” was not an anatomical and static concept, but a functional one, visualized in a “sponge”

model (2). High dead space fraction was discovered to be correlated to increased mortality in ARDS patients (3). In other words, the higher was the amount of lungs that did not participate to gas exchanges, the higher was the proportion of ARDS mortality. The continuous efforts aimed to improve the ARDS definition, together with the advanced diagnostic tools and therapeutic strategies, had an impact on the ability to recognize the onset of ARDS and to change the clinical history of ARDS. In this review, we will provide the readers the essential information to understand the process leading to the new Berlin definition and the change of ARDS epidemiology over 50 years since original Ashbaugh’s definition of ARDS.

## History of ARDS: the long path to define a syndrome—new acquisitions and limitations

The first description of ARDS probably belongs to Laennec, who defined it as “idiopathic pulmonary edema” in 1821 (4). The following century saw a number of traumatic injuries during the “big wars” period that eventually earned the definition of “wet lung” or “shock lung” to the unexplained lung edema (5,6). However, it was only in 1967 that Ashbaugh and colleagues termed, for the first time, “ARDS” a syndrome characterized by “acute onset of tachypnoea, hypoxaemia, and loss of compliance after a variety of stimuli” (7).

Ashbaugh *et al.* reported the presence of a specific clinical presentation seen in 12 adult patients and characterized by severe dyspnea and tachypnea, cyanosis not responsive to oxygen therapy, loss of lung compliance and presence of diffuse alveolar infiltration at chest X-ray evaluation, with a high mortality rate.

Since then, ARDS paradigm included the presence of a known risk factor for ARDS, severe hypoxemia despite high FiO<sub>2</sub> delivery, bilateral pulmonary infiltrates and the exclusion of cardiogenic edema as a cause.

From the first ARDS definition, 50 years ago, different efforts have been dedicated to clarify the pathophysiology and the severity of this multifaceted syndrome.

In 1988, Murray and colleagues proposed a definition known as “expanded definition of ARDS”. The authors took into account four different variables to which they assigned a score [0–4]: (I) the chest roentgenogram score, that describes the amount of pulmonary consolidation of the four quadrants; (II) the hypoxaemia stratified according to PaO<sub>2</sub>/FiO<sub>2</sub> classes; (III) the PEEP level; and (IV) the compliance of the respiratory system. The final score, called “the Murray Lung Injury Score”, is calculated as the sum of the single components score divided by the number of the accounted variables, and defines three categories: absence of lung injury (0), mild to moderate lung injury (1–2.5), and severe lung injury (>2.5) (8).

In 1994, the American-European Consensus Conference (AECC) defined acute lung injury (ALI) and ARDS as respiratory failure with: (I) acute onset; (II) presence of bilateral infiltrates at the chest X-ray; (III) pulmonary wedge pressure ≤18 mmHg or no clinical evidence of high left atrial pressure (to rule out a cardiogenic cause of lung edema); and (IV) hypoxemia, independently of the PEEP level. The severity of hypoxia, defined the class of lung injury as ALI (PaO<sub>2</sub>/FiO<sub>2</sub> ≤300) or ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> ≤200) (9).

Compared to the Murray Score, AECC definition of ARDS was characterized by the exclusion of a cardiogenic cause of edema, but it did not include the respiratory system compliance calculation at the diagnosis, and did not mention the PEEP level set.

Since respiratory failure due to ARDS is not just typical of the adult population but it is represented also in infants, AECC definition was clinically used either in adult or in pediatric critical care (10–12) to contextualize the grade of lung injury. However, oxygenation index (OI), proposed for the first time by Dr. Bartlett studying indications for ECMO in neonates with respiratory failure (13,14), is a commonly accepted indicator to describe lung injury in the pediatric population. OI is calculated as the product of mean airway pressure (in mmHg) × FiO<sub>2</sub> (in percent)/arterial partial pressure of oxygen (in mmHg).

In 2005, a group of experts from the University of Toronto proposed a formal consensus method to improve the AECC ARDS definition, using the Delphi technique (15). The Delphi technique consists in an individual survey of the participating panelists who anonymously receive group comments between iterations. The novelty of this approach included a clear definition of the acuity of the respiratory failure (<72 hours), the standardization of hypoxemia (PaO<sub>2</sub>/FiO<sub>2</sub> ≤200 setting a threshold of PEEP level ≥10 cmH<sub>2</sub>O), the inclusion of the static respiratory system compliance (calculated with a tidal volume of 8 mL/kg of ideal body weight in a sedated patient with a PEEP level ≥10 cmH<sub>2</sub>O), and the presence of an ARDS predisposing factor (pulmonary versus extrapulmonary ARDS). Radiographic abnormalities introduced the concept of airspace disease involving ≥2 quadrants on frontal chest X-ray, and the role of echocardiography was mentioned to exclude a possible cardiogenic origin of the lung edema, under clinical indication.

In 2013, Villar and colleagues, proposed a refinement of the classification of severity of ARDS, aimed at assessing the ICU mortality risk, according to the PaO<sub>2</sub>/FiO<sub>2</sub> ratio. The authors measured PaO<sub>2</sub>/FiO<sub>2</sub> ratio at ARDS onset and 24 hours later, testing two different combinations of PEEP (≥5 and ≥10 cmH<sub>2</sub>O) and FiO<sub>2</sub> (≥0.5 and 1.0). The better ARDS risk stratification was obtained setting PEEP ≥10 cmH<sub>2</sub>O and FiO<sub>2</sub> ≥0.5 at 24 hours after ARDS diagnosis, with mortality rates increasing from 17%, to 40.9%, to 58.1%, in mild, moderate and severe ARDS, respectively (16).

After 18 years of AECC definition, the need of a new definition of ARDS with more specific and generalizable

criteria emerged.

Hence, the most recent revisited definition of ARDS was proposed by a “task force” endorsed by the European Society of Intensive Care Medicine, and it is now known as the “Berlin definition” of ARDS (17).

Compared to the AECC definition, the ARDS Berlin definition clarified: (I) the acute onset, established within one week; (II) the characteristics of the bilateral lung infiltrates, on chest X-ray or CT scan; (III) the source of lung edema, without including a pulmonary capillary wedge pressure cut-off; (IV) the standardization of the hypoxemia, calculated with a PEEP level  $\geq 5$  cmH<sub>2</sub>O, and the categorization of the lung injury into three grades of severity according to the PaO<sub>2</sub>/FiO<sub>2</sub> ratio; furthermore, (V) if no predisposing condition was identified, as specified also in the Delphi consensus, an “objective” evaluation is mandated to rule out the cardiogenic origin of the lung edema. Berlin definition does not separate anymore, as the AECC definition of ARDS did, ALI and ARDS, unifying ARDS definition in a single entity graded into three classes of severity, according to the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and with a necessary minimum amount of PEEP (5 cmH<sub>2</sub>O). This important step led not to overestimate patient hypoxemia just caused by lung atelectasis and then easily reversible with minimal PEEP (18). Consequently, ARDS definition could be applied to a less heterogeneous population, excluding patients with compromised oxygenation only in the absence of PEEP. The classification of ARDS into three increasing stages of severity—mild, moderate, and severe—according to the level of hypoxemia, significantly reflected an increased mortality rate (respectively: 27%, 95% CI, 24–30%; 32%, 95% CI, 29–34%; and 45%, 95% CI, 42–48%). Compared to AECC definition, predictive validity for mortality was significantly improved in the Berlin definition of ARDS (area under the ROC, 0.577, 95% CI, 0.561–0.593 vs. 0.536, 95% CI, 0.520–0.553).

Berlin definition was proved to be adaptable also for pediatrics (19). De Luca *et al.*, on behalf of the Respiratory Section of the European Society for Pediatric and Neonatal Intensive Care, in a retrospective, international, multicenter study of infants and early children with ALI or ARDS—according to the AECC definition—reported that the predictive validity for ARDS mortality using the Berlin definition was confirmed and comparable to the results showed in adult population (17). This finding was mainly correlated to the introduction of the new category of “severe ARDS”, which demonstrated a higher mortality among the Berlin definition classes of ARDS. These results have been

further recently confirmed by Barreira *et al.* (20).

Still, despite the contributions of several scientists, an entirely satisfactory definition of ARDS proved to be an elusive goal.

The principal hindrance is due to the intrinsic nature of ARDS which is not a disease, with a univocal and straightforward trajectory of treatment and recovery, but a syndrome, composed of a multifaceted means of diagnosis and determined by different causes, with as many different clinical histories. Moreover, the pathological hallmark of ARDS (i.e., noncardiogenic pulmonary edema) cannot be easily identified by current clinical tool, and any clinical definition must rely on accessible proxies (e.g., hypoxaemia, chest X-ray).

The reliability of hypoxia definition is still controversial. Measurements of PaO<sub>2</sub> varies on time, PEEP level, and FiO<sub>2</sub> (16,21–24).

The chest X-ray, used to classify ARDS based on the presence of bilateral infiltrates, is not completely accurate, either for a relevant interobserver variability (25,26) or if compared to other diagnostic imaging tests, such as ultrasonography (27) and computed tomography (28). Promising diagnostic advances have been recently proposed, using ultrasound to rule out a cardiogenic source of lung edema and to predict ARDS in blunt trauma patients (29–31), and using low-dose chest CT to monitor and redirect the treatment strategy of the ventilator setting (32,33). Along with measurements of SpO<sub>2</sub>/FiO<sub>2</sub> by pulse-oximetry, in lack of PaO<sub>2</sub>/FiO<sub>2</sub> measurements (34), lung ultrasound (35) can be extremely appealing in settings with limited ICU resources, as lately proposed by the Kigali modification of the Berlin definition (36).

### **Etiology of ARDS and ARDS phenotypes**

ARDS is the result of a wide spectrum of different risk factors, which can be either local or systemic (37).

ARDS can be classified according to the origin of the inflammatory insult as direct lung insult or indirect lung injury.

The first one leads to the commonly known “pulmonary ARDS” (ARDS<sub>p</sub>), the second one to the “extrapulmonary ARDS” (ARDS<sub>exp</sub>) (38,39) (Table 1).

While pneumonia, extrapulmonary sepsis, and aspiration are the most frequent clinical risk factors for ARDS (40,41), chronic diseases such as obesity (42,43) and diabetes (44,45) have been associated to a lower occurrence of ARDS. The “obesity paradox”, as called in a recent meta-analysis of

**Table 1** Main determinants of pulmonary and extrapulmonary ARDS

Pulmonary ARDS
Pneumonia
Bacteria
Virus
Fungi
Parasites
Aspiration
Toxic gases inhalation
Smoking
Non-protective ventilation (i.e., VILI)
Lung contusion/trauma
Thoracic surgery
Drowning
Pulmonary vasculitis
Fat embolism
Extrapulmonary ARDS
Non-pulmonary sepsis
Blood transfusions (i.e., TRALI)
Trauma
Pancreatitis
Drug reaction
Burns
Cardio-pulmonary bypass
Non-cardiogenic shock

ARDS, acute respiratory distress syndrome; VILI, ventilator induced lung injury; TRALI, transfusion related acute lung injury.

the literature (42), is still hard to understand, due to the lack of a clear pathophysiologic mechanism behind these findings (46), and with some conflicting preclinical data (47). On the other side, instead, diabetes might be protective by means of a depressed immune response of the organism against an inflammatory insult (44). Among the modifiable risk factors for ARDS, alcohol abuse emerges (48,49) and impaired immune response involving alveolar macrophages is reported (50,51). Since the observation that positive cumulative fluid balance is independently associated to higher mortality rate in patients with lung injury (52), a number of study raised in order to assess the impact of

conservative fluid management or active fluid removal on mortality in ARDS patients, but results are yet not conclusive (53,54).

High occurrence of ARDS has been linked also to demographic and environmental risk factors. These include older age (55), non-Caucasian race (56), defined genetic variants (57) and ozone exposure (58).

Some authors, studying patients with a number of predisposing conditions of ARDS and with associated risk factors for the development of ARDS, conceived and validated the acute lung injury prediction score (LIPS). However, the best LIPS score cut-off was able to predict ARDS with sub-optimal sensitivity (69%) and specificity (78%) (59).

Recently, thanks to an analysis of clinical and laboratory data from two large randomized clinical trials (RCTs)—the ARMA (60-62) and the ALVEOLI trials (63)—the ARDS Network identified two different phenotypes of ARDS. Phenotype 2—named hyperinflammatory subphenotype—is characterized by higher prevalence of inflammation, shock, sepsis and metabolic acidosis than phenotype 1.

The relevance of the ARDS subphenotypes classification showed not just a difference about clinical and laboratory data between the two clinical conditions, but more important, that subphenotype 2 recognizes a cohort of patients with worse clinical outcome, and with higher mortality, than phenotype 1 (64). A further analysis by the same group of the Fluid and Catheter Treatment Trial (FACTT) simplified the 2 phenotypes using a three-variable model (IL-8, bicarbonate and tumor necrosis factor receptor-1) that had a different answer in terms of fluid management strategy. In other words, ARDS subphenotypes can predict the severity of the disease and can direct the treatment choice (65).

### Pathology of ARDS

As stated, diffuse alveolar damage (DAD) leading to high permeability pulmonary edema is considered the histopathologic hallmark of ARDS (66-69). For this reason, while a “perfect” bedside definition of ARDS should capture all patients with DAD, without false positives, this is not always the case. This was evident since the first description by Ashbaugh and colleagues, later proved by the group of Vincent JL (70). More recently, these findings were further confirmed by Guerin and colleagues, studying patients with non-resolving ARDS (71).

The authors reported that DAD was markedly



represented in non-resolving ARDS with no difference among the increasing level of ARDS severity, according to the Berlin definition. The presence of DAD, at the pathology examination, has also a relevant role to identify the clinical history of the disease.

In a recent meta-analysis of lung biopsy series for patients with ARDS, the presence of a pathologic pattern of DAD was associated with higher mortality compared to ARDS with no DAD (72).

ARDS is pathologically categorized into acute, subacute and chronic phase (73,74). The acute phase—exudative—(within 6 days) see the presence of either interstitial or alveolar edema, with acute inflammatory cells and red blood cells into the alveoli. Both endothelial and epithelial layers are damaged, and hyaline membranes develop in the alveoli. The subacute phase—proliferative—(between 7–14 days) shows the reabsorption of the edema, the proliferation of the alveolar epithelial type II cells and the fibroblastic infiltration with deposition of collagen fibers. The chronic stage—fibrotic—(following 14 days) presents the clearance of the neutrophils, the abundance of alveolar mononuclear cells and macrophages into the alveoli and marked fibrosis, with a repairing process involving the alveolar epithelium.

ARDS<sub>sp</sub> and ARDS<sub>sexp</sub> are two different features of ARDS, not just in terms of etiology, but also regarding the characteristics of the lung lesions. Of note, ARDS<sub>sp</sub> is characterized by the more pronounced alveolar collapse, fibrinous exudative material and edema of the alveolar walls, compared to ARDS<sub>sexp</sub> (75). Furthermore, ARDS<sub>sp</sub> has an increased collagen content, with a prevalence of the extracellular matrix remodeling (76).

## Epidemiology

### *ARDS incidence—an underestimated syndrome*

Since the beginning of the recognition of ARDS as defined entity, several studies tried to provide essential information about ARDS epidemiology. Most of them were constructed following the AECC definitions.

It is surprising the huge variability of ARDS incidence, including all ARDS categories, in various population-based studies (77) between different continents such as South America (10.1 per 100,000 person-years) (78), Europe, (17.9 per 100,000 person-years) (79), Australia (34 per 100,000 person-years) (80) and USA (78.9 per 100,000 person-years) (81) with a relevant geographic diversity. Furthermore, in countries of the same continent

such as Europe, ARDS occurrence varies consistently, ranging from 10.6 per 100,000 person-years in Finland (82), to 17.9 per 100,000 person-years in Scandinavia (79), to 25.5 per 100,000 person-years in Spain (55). This is the case also for hospitalization based studies (77), which showed a ARDS proportion ranging from 7.1% (83) to 12.5% (84) of incidence proportion of all ICU admissions in Europe to 19% in 14 ICUs of Ireland (85), among the admitted patients (Table 2).

Data incidence of ARDS in pediatric population shows less variability between different continents such as Europe [2.2 per 100,000 person-years in the Netherlands (90) and 3.9 per 100,000 person-years in Spain (91)] and Australia [2.6 per 100,000 person-years (92)], with the highest ARDS incidence in USA with 9.5 ARDS cases per 100,000 person-years (93). However, the less relevant geographic difference of ARDS incidence in children has to be interpreted considering the lower ARDS incidence in pediatrics compared to adult population.

Differences in availability of diagnostic methodologies, health resources, hospital admission practices and emergency medicine networks clearly impact on the recognition of critical diseases. In a careful overview on the global burden of critical illness in adults, Rubinfeld and coworkers observe how the availability of ICU beds differs between high-income countries and less advantaged countries. This disproportion might lead, therefore, to different filtering of acute critical diseases—such as ALI—due to different levels of care, and to a wide discrepancy in incidence estimation (94).

Recent insights about the epidemiology of ARDS, according to the current Berlin definition, came from the LUNG SAFE study, an International, multicenter, prospective cohort study conducted in Intensive Care Units in 50 countries (41). Due to its design, the LUNG SAFE study cannot provide “population-based” estimates of ARDS incidence, or prevalence, but only ICU. ARDS occurrence was estimated to be 10.4% in all ICU admissions and in more than double (23.4%) among the mechanically ventilated patients. In a further analysis by country, the incidence of ARDS was the highest in Oceania, with 0.57 cases/ICU bed/year, followed by Europe, North America, Africa, South America and Asia, with the lowest ARDS occurrence of 0.27 cases/ICU bed/year. These findings are in line with previous epidemiologic studies (80,81,88,89,95,96) and might be interpreted in the light of the different distribution of ICU resources.

One of the most striking finding of the LUNG SAFE

**Table 2** Main epidemiologic studies on ARDS incidence after AECC definition

Authors, year of publication (reference)	Study period	Incidence of all ARDS categories (per 100,000 person-years- population-based studies) or percentage (%), hospitalization based studies)	Incidence of moderate and severe ARDS categories (per 100,000 person-years-population-based studies) or percentage (%), hospitalization based studies)
Sigurdsson <i>et al.</i> , 2013 (86)	1988–2010		3.65–9.63
Nolan <i>et al.</i> , 1997 (87)	1990–1994		7.3–9.3
Luhr <i>et al.</i> , 1999 (79)	1997	17.9	13.5
Bersten <i>et al.</i> , 2002 (80)	1999	34	28
Brun-Buisson <i>et al.</i> , 2004 (83)	1999	7.1% (of all ICU admissions)	6.1% (of all ICU admissions)
Rubinfeld <i>et al.</i> , 2005 (81)	1999–2000	78.9	58.7
Manzano <i>et al.</i> , 2005 (55)	2001	25.5	23
Sakr <i>et al.</i> , 2005 (84)	2002	12.5% (of all mechanically ventilated patients)	10.6% (of all ICU admissions), 16.5% (of all mechanically ventilated patients)
Li <i>et al.</i> , 2011 (88)	2001–2008		81 (in 2001), 38.3 (in 2008)
The Irish Critical Care Trials Group, 2008 (85)	2006	19%	
Caser <i>et al.</i> , 2014 (78)	2006–2007	10.1	6.3
Linko <i>et al.</i> , 2009 (82)	2007	10.6	5
Villar <i>et al.</i> , 2011 (89)	2008–2009		7.2
Bellani <i>et al.</i> , 2016 (41)	2014	10.4% of all ICU admissions, 5.5 cases per ICU bed per year	

ARDS was defined using the Berlin definition nomenclature: all ARDS categories include mild, moderate and severe ARDS. AECC, American-European Consensus Conference; ARDS, acute respiratory distress syndrome.

study was that of all ARDS patients, clinicians missed almost 40% of ARDS diagnosis, despite a specific online training on ARDS diagnosis, which was offered to all investigators. Even among severe ARDS, diagnosis was missed in at least one patient out of 5. These results are in line with another study that estimated ARDS under-recognition by clinicians in up to 50% of cases, despite the accepted use of AECC definition and staff training (55). In LUNG SAFE, organizational and patient factors were reported to be associated with higher clinician recognition of ARDS in invasively ventilated patients. Among the first ones, the authors observed higher nurse-to-patient and physician-to-patient ratios. Patient variables associated with a lower ARDS under-diagnosis were younger patient age, lower predicted body weight, higher non-pulmonary SOFA score, a lower PaO<sub>2</sub>/FIO<sub>2</sub> ratio, and the presence of pneumonia, pancreatitis, neoplastic or immune or hematological disease, trauma at admission, absence of ARDS risk factors and concomitant presence heart failure.

### ***ARDS clinical management***

A second relevant finding of LUNG safe regards the therapeutic management of ARDS. Mechanical ventilation and therapeutic adjunctive measures to target ARDS are still not yet optimized, with significant potential future improvement. About 4 out of 5 patients were treated with a PEEP level below 12 cmH<sub>2</sub>O. Plateau pressure, a well-known parameter of respiratory mechanics associated with mortality in ARDS patients (60), was measured in only 40.1% of the ARDS population. Among patients with ARDS, about 1 out of 3 patients with ARDS did not receive protective mechanical ventilation, with either a plateau pressure above 30 cmH<sub>2</sub>O or a tidal volume above 8 mL/kg of predicted body weight. Large tidal volumes are far from a diffuse and accepted clinical practice, but they mirror the results showed in two recent RCTs (97,98). Furthermore, data suggest that clinicians seem more incline to adjust FiO<sub>2</sub> than to increase PEEP to treat hypoxemia. Finally, adjunctive measures such as recruitment maneuvers and prone positioning were used in a minority of ARDS patients (20.9% and 7.9%, respectively) (41).

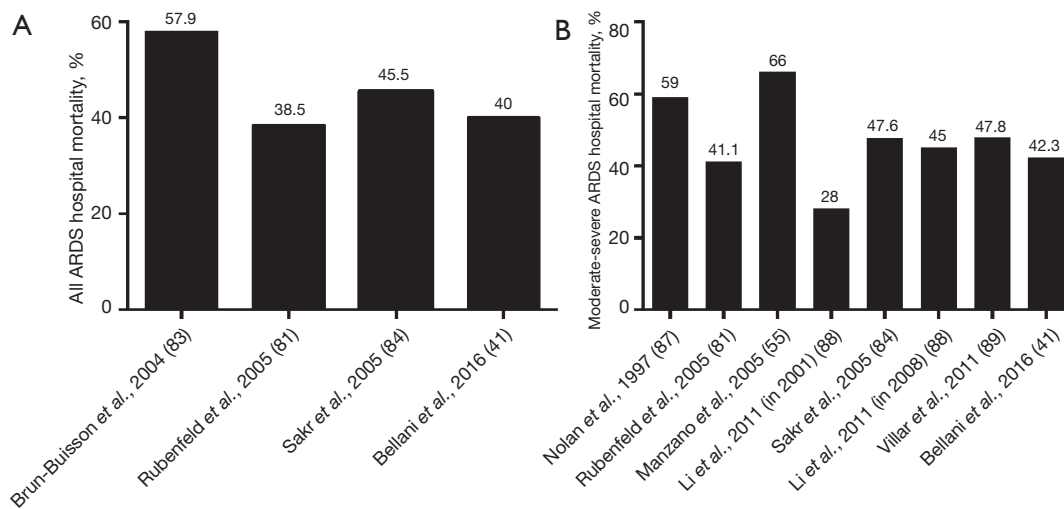
### ***ARDS mortality—still a critical challenge***

Mortality in ARDS patients is still high. The LUNG SAFE study reports a hospital mortality of 40%, with a significant increase across the ARDS severity categories, in line with

Berlin definition (34.9%, in mild ARDS; 40.3% in moderate ARDS; 46.1% in severe ARDS). These results proof that the Berlin definition of ARDS is an excellent predictor of outcomes in the studied population. In this context, Laffey and colleagues examined the predictors associated with outcome in a secondary analysis of the LUNG SAFE study. In 2,377 ARDS patients, who received mechanical ventilation, the authors observed that lower ventilation pressure (peak, plateau and driving), higher PEEP level, and lower respiratory rate confirm their validity as predictors of improved survival from ARDS (99). These results are in line with data from previously observed clinical trials (60,63,100,101). ARDS mortality decreased over the years probably also thanks to the improved therapeutic management of the ventilatory settings (60,63,100-102). In the early 90s, Nolan and colleagues reported a hospital mortality of 59% in moderate and severe ARDS in a population based study conducted in Australia (87). Brun-Buisson *et al.* described similar findings in the late 90s, in a hospitalization based study conducted in 78 ICUs in Europe, with a proportion of 57.9% even including mild ARDS (83). Since then, ARDS hospital mortality decreased to a stable level of about 40%, including all ARDS categories (25,84), and of about 45% considering moderate-severe ARDS (84,88,89). These findings are corroborated by mortality data of the recent LUNG SAFE study (41) (*Figure 1A,B*). Moreover, data from two large population based study in northern European countries, analyzing patients with higher severity of ARDS (moderate and severe ARDS), reports a 90-day long term mortality among 38–41.2% (79,86), and when overall ARDS is analyzed, Linko *et al.* described a 90-day mortality of 47% (82). While in adult population ARDS has shown a clear trend of decrease in mortality over the last decades, these results are not univocally confirmed in pediatric population, as reported with conflicting results in two recent meta-analysis of the literature (103,104). Over the last few years, different RCTs have proposed promising results in terms of ARDS mortality improvement (53,105,106). Unfortunately, this enthusiasm has to be well weighted in sight of the study design (107,108). Enrolled subjects of RCTs are rigorously selected, and the generalization of the results from a RCT might be deceptive if applied to the entire population.

### **Conclusions**

After 50 years of study, ARDS still looks nowadays a threatening enemy to defeat. Definition of ARDS has



**Figure 1** Hospital mortality reported in the main epidemiological studies after AECC ARDS definition in all ARDS categories (mild, moderate and severe) (A) and in the subgroups of moderate-severe ARDS (B). On the X-axis, the studies are chronologically ordered based on the study period. In panel (B), moderate-severe ARDS hospital mortality in the study by Li *et al.* [2011] is reported in two different years of study, 2001 and 2008 (88). The studies are reported as first author *et al.*, year of publication (41,55,81,83,84,87-89). AECC, American-European Consensus Conference; ARDS, acute respiratory distress syndrome.

been improved over the years. Even so, the definition of hypoxemia in different settings and timing is debatable and the agreement about the optimal diagnostic imaging is yet to be reached. Studies on ARDS incidence consistently show that the disease is not rare, albeit often not recognized by clinicians. ARDS is undertreated and basic ventilator strategies are not yet standardly optimized, despite major advances in the management of mechanical ventilation and non-ventilatory strategies, aimed at preventing the VILI. Finally, ARDS mortality remains high. This suggests the need of a commonly accepted therapeutic strategy for ARDS, which should be prerogative of all the countries including the less developed ones.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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