REVIEW

Missed or delayed diagnosis of ARDS: a common and serious problem

Giacomo Bellani[1,2], Tài Pham[3] and John G. Laffey[4,5*]

Abstract

Clinical recognition of acute respiratory distress syndrome (ARDS) is delayed or missed entirely in a substantial propor-tion of patients. In the LUNG SAFE study, the largest international cohort of patients with ARDS, investigators were able to determine if ARDS was present, and at what stage the clinician made the diagnosis of ARDS. The diagnosis of ARDS was delayed or missed in two-thirds of patients, with the diagnosis missed entirely in 40% of patients, while ARDS recognition ranged from 51% in mild ARDS to 79% in severe cases. Failure to recognize ARDS in a timely fashion leads to failure to use strategies that improve survival in ARDS. Early diagnosis of ARDS may facilitate measures to abrogate progression of the lung injury, including protective mechanical ventilation, fluid restriction, and adjunc-tive measures proven to improve survival such as prone positioning. Information overload and a complex 'syndrome' diagnosis likely play key roles in ARDS under-recognition. Clinical under-recognition has important consequences particularly in terms of therapeutic options not considered. The development of approaches to enable more timely recognition has the potential to save lives.

Keywords: Acute respiratory distress syndrome, Diagnosis, Recognition, Therapy, Outcome

Introduction

Early recognition of acute respiratory distress syndrome (ARDS) may be important to facilitate measures to abro-gate progression of the lung injury, including protective mechanical ventilation, fluid restriction, and adjunctive measures proven to improve survival such as prone posi-tioning. ARDS diagnosis is delayed or missed entirely in a substantial proportion of patients. In the LUNG SAFE study, the largest existing international cohort of patients with ARDS, investigators were able to deter-mine if ARDS was present, and at what stage the clinician made the diagnosis of ARDS [1]. The diagnosis of ARDS was delayed or missed in two-thirds of patients, with the diagnosis missed entirely in 40% of patients, while ARDS

recognition ranged from 51% in mild ARDS to 79% in severe cases [1].

Does ARDS under-recognition matter?

Yes, several lines of evidence suggest that recognition of ARDS influences patient management. Failure of clini-cians to recognize ARDS is a barrier to the use of pro-tective lung ventilation strategies [2, 3]. The importance of early recognition and management is underscored by the finding that patients receiving higher tidal vol-umes shortly after the onset of ARDS onset have a higher mortality, suggesting that high tidal volume is *more* injurious if used *earlier* [4]. While in the LUNG SAFE study, patients that clinicians recognized as ARDS received only marginally lower tidal volumes, this may be more a reflection of the penetration of lower tidal volume ventilation into clinical practice. Clinician rec-ognition of ARDS was associated with the use of higher PEEP levels and with greater use of prone positioning,

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neuromuscular blockade and extracorporeal membrane oxygenation, suggesting that failure to recognize ARDS in a timely fashion leads to failure to use strategies that improve survival in ARDS. Furthermore, failure of clinicians to recognise ARDS may impair broader (research funders, policy makers, general public) awareness of the impact of ARDS.

Why is ARDS under-recognized?

In the absence of a diagnostic test, patients must fulfil a set of clinical criteria within a specific time frame that have relatively high sensitivity but low specificity for ARDS (Table 1) [5]. The inter-observer reliability of the Berlin ARDS definition is moderate, mainly due to variability in chest X-ray (CXR) interpretation [6]. The oxygenation criterion, namely the ratio of arterial PO_2 to inspired oxygen fraction, is not measured at standardized ventilator settings, and can vary substantially in a single patient as different FiO_2 [7]. In fact, it is often not calculated at the bedside, possibly because clinicians may incorrectly assume that these patients cannot have ARDS if they receive a "safe" FiO_2. The anteroposterior CXR criterion is central to the diagnosis of ARDS—yet this is a poorly reliable test with high inter-observer variability in interpretation [8] while training programs in CXR interpretation have limited efficacy [9]. Other aspects of the definition, such as the timing criterion are relatively arbitrary. These concerns may erode clinician confidence in the utility of making the diagnosis of ARDS. The Berlin definition of ARDS presents an ambiguity in how the patients non-invasively ventilated with CPAP, with a PaO_2/FiO_2 ratio lower that 200 mmHg should be classified as these do not, technically, fit in any of the categories [5]. The inability to proper apply the Berlin definition in these patients may contribute to ARDS under-diagnosis.

Another issue is the complexity of making a diagnosis that relies on recognition of specific criteria combining

clinical, biological and radiological features (Fig. 1) in critically ill patients with multiple comorbidities and ongoing critical clinical issues. The presence of chronic underlying lung disorders may affect the ARDS radiologic or oxygenation criteria. It should not be that surprising that clinicians fail—sometimes frequently—to recognize these clinical patterns in a timely fashion. ICU clinicians are exposed to information overload from many sources, including clinical reports, flowcharts, bedside monitors, and laboratory results [10]. The ability of even experienced clinicians to consistently integrate multiple clinical variables is limited to perhaps 3–5 information chunks [11]. In LUNG SAFE, higher nurse (or physician)-to-patient ratio increased the likelihood of recognition, suggesting that clinician workload and its related information overload may promote under-recognition. Indeed, the more 'stereotypical' the presentation, i.e. the younger the patient, the greater the severity of hypoxemia, and the presence of pneumonia the greater the clinician recognition.

How can we improve ARDS recognition?

Clearly understanding the importance of early diagnosis of ARDS, and the reasons underlying delayed or failed recognition is a key first step. Determining whether the clinical criteria for ARDS at standardized ventilator settings in all patients receiving mechanical ventilation with a PaO_2/FiO_2 ratio ≤ 300 mmHg on a standardized FiO_2 (e.g. 1.0) is a reasonable option given that we know that > 20% of all ventilated patients will meet current criteria [1]. In resource constrained situations, pulse
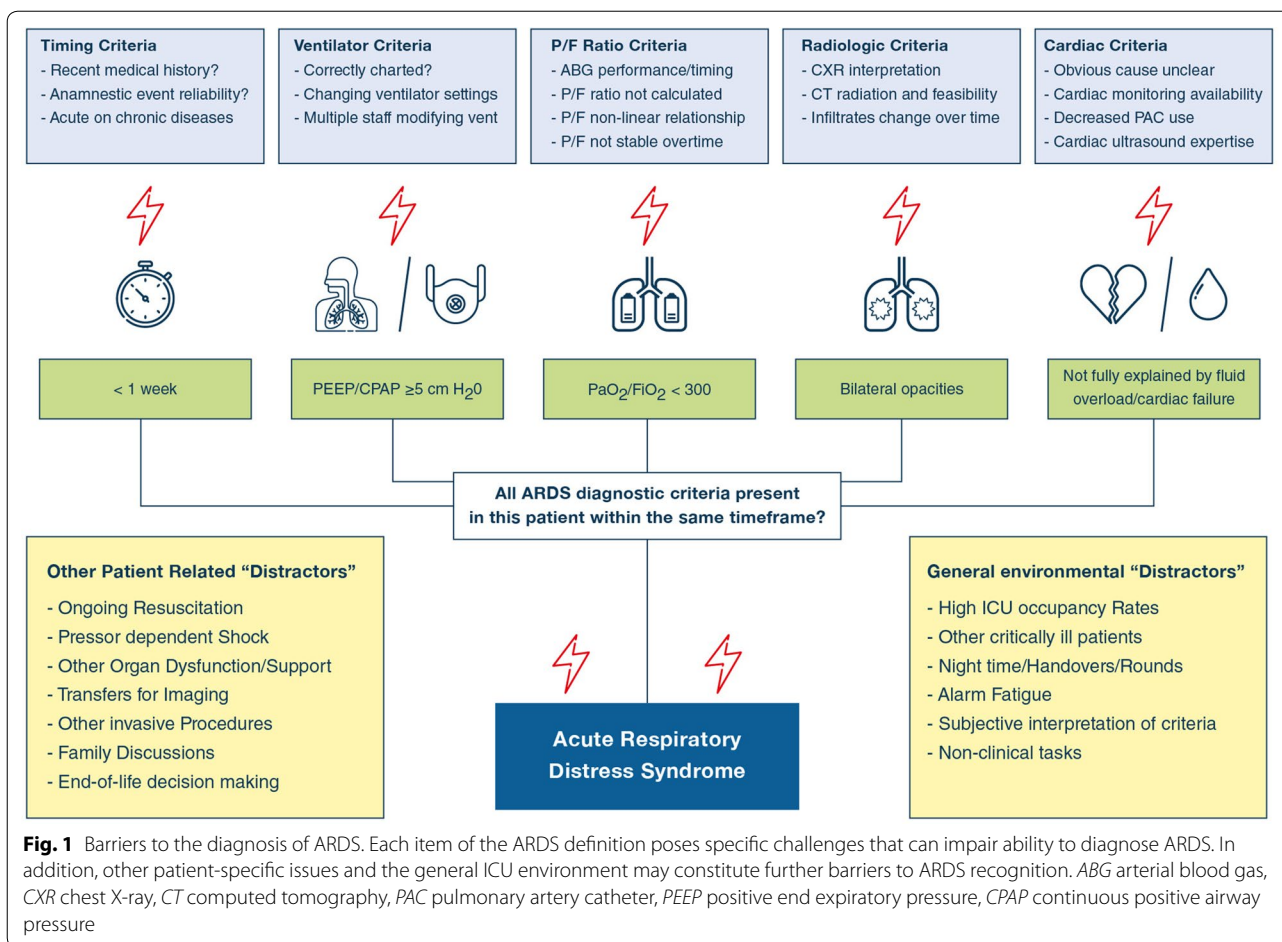
Table 1 The Berlin definition of acute respiratory distress syndrome *Note*: Reproduced from ARDS Definition Taskforce et al. [5]

ARDS severity	Mild	Moderate	Severe
Timing	Acute onset within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules		
Oxygenation[b]	PaO_2/FiO_2 201–300 mmHg with PEEP/ CPAP ≥ 5 cm H_2O[c]	PaO_2/FiO_2 101–200 mmHg with PEEP/ CPAP ≥ 5 cm H_2O	$PaO_2/FiO_2 \leq 100$ mmHg with PEEP/ CPAP ≥ 5 cm H_2O
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload (objective assessment required if no ARDS risk factor present)		

[a] Chest radiograph or computed tomography scan

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

[c] This may be delivered non-invasively in the mild acute respiratory distress syndrome group

Fig. 1 Barriers to the diagnosis of ARDS. Each item of the ARDS definition poses specific challenges that can impair ability to diagnose ARDS. In addition, other patient-specific issues and the general ICU environment may constitute further barriers to ARDS recognition. *ABG* arterial blood gas, *CXR* chest X-ray, *CT* computed tomography, *PAC* pulmonary artery catheter, *PEEP* positive end expiratory pressure, *CPAP* continuous positive airway pressure

peripheral oxygen saturation to FiO_2 ratio (SpO_2/FiO_2) might usefully replace PaO_2/FiO_2 ratio.

More controversially, it is time to reconsider the role of the chest radiograph in ARDS diagnosis. Low-dose computed tomography may be preferable for ARDS diagnosis [12], although it does require patient transport to the scanner, a limitation in severely ill patients. Lung ultrasound, now becoming widely available even in limited resources settings, appears to be sensitive and reproducible [13], and may have a role in ARDS diagnosis at the bedside [14]. Biomarker panels may help, but given the high sensitivity of the consensus criteria, additional markers may be superfluous for detection—but be of great use in confirmation (i.e. to reduce 'false positives') or to identify biologically homogenous subgroups within the ARDS population. Identifying ARDS sub-phenotype, using latent class analysis [15] or transcriptomic approaches [16] show significant promise.

Additional criteria might be applied for entry into ARDS clinical trials, particularly trials assessing biologic agents that affect specific pathways. For example, if

a pathway blocker is to be tested in ARDS patients (e.g. Tocilizumab for COVID-19 ARDS), then it would be important to first demonstrate that this pathway is active (e.g. by measuring IL-6) in that patient. Such criteria would differ depending on the study, and would supplement rather than replace the clinical definition of ARDS.

ARDS recognition might be further enhanced by computer-aided pattern recognition, bypassing information overload [17]. Artificial Intelligence approaches such as machine learning may assist in identification of patients at risk of or fulfilling diagnostic criteria for ARDS, although this technology is not yet ready for clinical implementation [18].

Conclusion

ARDS continues to be under-recognized in the era of the Berlin definition. Information overload and a complex 'syndrome' diagnosis likely play key roles in ARDS under-recognition. Clinician under-recognition has important consequences particularly in terms of therapeutic options

not considered. The development of approaches to enable more timely recognition has the potential to save lives.

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Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflict of interests.

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