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EDITORIAL

Global definition of acute respiratory distress syndrome: An epidemiology perspective

Definición global del síndrome de distrés respiratorio agudo: una visión epidemiológica

Acute Respiratory Distress Syndrome (ARDS) is one of the major challenges most intensivists face on a daily basis. Its clinical definition has evolved over time, leading to the recent "global definition of ARDS".[1] However, the conceptual framework of the syndrome ("acute, diffuse and inflammatory lung injury triggered by at least one risk factor and resulting in increased epithelial and vascular permeability leading to lung edema and respiratory failure") has remained relatively stable.[1,2] From the histological perspective, diffuse alveolar damage (DAD) is commonly regarded as the most characteristic feature of ARDS. Although present in only 50% of patients, the recent demonstration of its impact on the evolution and prognosis of ARDS provides strong evidence to consider DAD as the gold standard of ARDS.[3,4]

From the epidemiological perspective, a definition is a set of criteria considered by a group of experts to be necessary to characterize a condition or disease. Usually, there are at least two levels of decision – one clinical and one definitive – usually referred to as the "gold standard". In the case of ARDS, there is no general agreement on the gold standard, with histology (DAD) and/or the conceptual framework of the disease being proposed. The relationship between the clinical definition and the gold standard can be assessed in terms of sensitivity, specificity, precision and validity (Fig. 1). Sensitivity is the proportion of patients who have a positive gold standard and meet the clinical definition. As sensitivity increases, the proportion of individuals with a positive gold standard but who do not meet the definition (false-negative cases) decreases. Specificity is the proportion of patients with a negative gold standard who do not meet the definition. As specificity increases, the proportion of individuals with a negative gold standard who meet the definition (false-positive cases) decreases. Precision refers to how reproducible the result is under similar conditions. For example, two people evaluating the same patient at the same time should reach the same conclusion. Validity refers to the ability of a test to correctly measure what it is intended to measure, i.e. "how close the clinical definition is to the gold standard".

The recent global definition of ARDS incorporates clinical modifications that make it much more sensitive. For example, it includes lung ultrasound, which is more sensitive than conventional radiography and tomography. Two new categories are included: non-intubated patients with ARDS and ARDS in resource-constrained settings. The non-intubated category includes patients on high-flow nasal cannula (HFNC) oxygen therapy, which is characterized by a more indolent course of the disease. For ARDS in resource-constrained settings, the Kigali modification is used, which employs the $Sp0_2/Fi0_2$ ratio.[5] This parameter shows good correlation with $Pa0_2/Fi0_2$ but is influenced by several factors (e.g., hemoglobin concentration, skin color, tissue hypoperfusion), which inevitably leads to increased measurement error.

Regarding the precision and validity of the global definition, given the increase in sensitivity and the consequent decrease in specificity, it can be expected that precision will increase and validity will decrease, i.e., there will be more interobserver agreement and more patients will be diagnosed with ARDS, but the proportion of them presenting the gold standard will decrease. This aspect is not a simple academic issue, because for a therapeutic intervention to be effective, it must have a therapeutic target. The changes introduced by the global definition will facilitate the identification of patients with ARDS and, consequently, their enrollment in clinical trials[6]; however, the inclusion of heterogeneous patient groups will make it more difficult to demonstrate beneficial results.[7] In line with these

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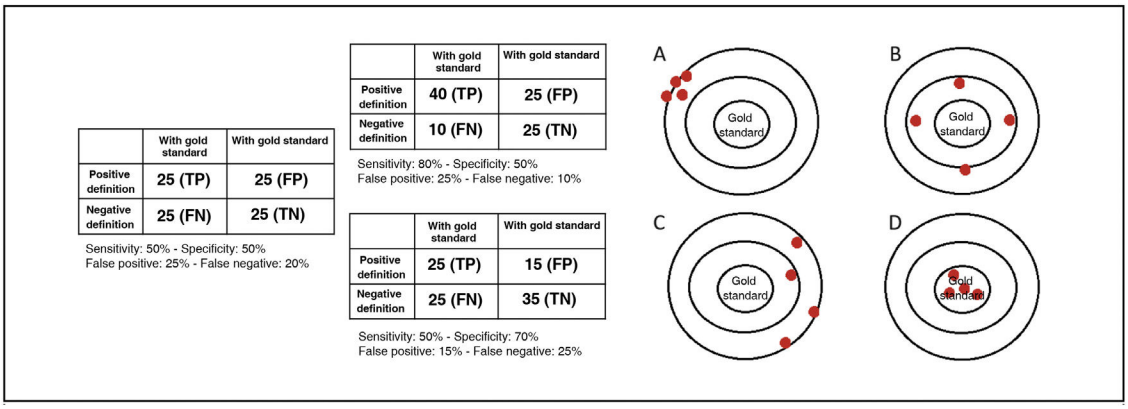

Figure 1 Sensitivity, specificity, validity and precision.
Panel at right: Example of a hypothetical ''clinical'' definition and its relationship to its gold standard. TP: true positive; TN: true negative; FP: false positive; FN: false negative.
Panel at left: The gold standard is located at the center of the bull's eye; each red dot represents the result of applying the definition by different observers. **A**: The definition is precise, as evidenced by the fact that all the observers reached the same conclusion. However, it is also scantly valid, as it is ''far'' from the gold standard; **B**: The definition is valid, as it is consistently close to the gold standard. However, it is also scantly precise, as the results between observers are not similar; **C**: scantly precise and scantly valid (worst situation); **D**: precise and valid (ideal situation).

assertions, the term "therapeutic paradox" was introduced 10 years ago to refer to the success of interventions in preclinical research (where diagnoses are usually made on the basis of the gold standard) and their failure when transferred to clinical practice (where diagnoses are made on the basis of surrogate biomarkers or syndromes).[8] Incorporating the new definition could exacerbate this phenomenon and slow down the transfer of basic research to the clinical setting.

Finally, it is clear that intensive care medicine is moving towards personalization of treatment, seeking to identify homogeneous groups of patients who will benefit from specific therapies. The identification of sub-phenotypes is an attractive, feasible and effective strategy in this regard, as it can pinpoint groups of patients with common clinical, laboratory test, prognostic and interventional response characteristics.[9] Such strategies are based on the use of mathematical techniques and algorithms to identify groupings in observable variables that may reflect the presence of one or more latent (i.e., unobservable) variables. Several studies have shown the existence of different subphenotypes within the same syndrome, which may reflect the existence of different latent variables, the fact that different samples were involved in the analysis of different observable variables, the effect of different environmental stimuli (e.g., treatments applied), variations in the statistical techniques used, or – most likely – the effect of the combination of all these factors. The new global definition is in clear contradiction with the concept of personalized medicine since it simplifies several of the diagnostic criteria – most of which were already arbitrary and questionable[10] – and practically eliminates all traces of pathophysiological variables, tending to generate a definition where "one size fits all".[11]

In summary, the new global definition increases the sensitivity of the definition, allowing for the diagnosis to be made in virtually any setting. However, this comes at the cost of sacrificing specificity. As a result, a global increase in the incidence of the syndrome can be expected. All this will make clinical investigators very happy and those trying to develop specific treatments very sad. It seems that the goal of providing personalized medicine has receded a bit. Only time will tell whether this definition will be universally accepted or whether it will be just another bold initiative that fails to pass the filter of clinical practice.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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