

Comparison of Clinical Criteria for the Acute Respiratory Distress Syndrome with Autopsy Findings

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Background: The American–European Consensus Conference definition for the acute respiratory distress syndrome (ARDS) has never been validated.

Objective: To compare clinical criteria for ARDS with autopsy findings.

Design: Independent comparison of autopsy findings with clinical characteristics retrospectively abstracted from medical records.

Setting: Tertiary medical–surgical intensive care unit.

Participants: 382 patients who underwent clinical autopsy.

Measurements: Sensitivity, specificity, and likelihood ratios for clinical criteria were calculated in 3 cohorts by using diffuse alveolar damage at autopsy as the reference standard. The 3 cohorts were 1) all patients, 2) patients with any risk factor for ARDS, and 3) patients who were separated according to their pulmonary or extrapulmonary risk factors.

Results: 127 patients (33%) met the clinical criteria, and 112 (29%) had diffuse alveolar damage. In all patients, the sensitivity

of the clinical definition was 75% (95% CI, 66% to 82%) and the specificity was 84% (CI, 79% to 88%). In 284 patients with risk factors, the sensitivity was 76% (CI, 67% to 83%) and the specificity was 75% (CI, 68% to 81%). Compared with patients with pulmonary risk factors, patients with extrapulmonary risk factors had significantly higher sensitivity (61% vs. 85%; $P = 0.009$) and the specificity did not statistically significantly differ (69% vs. 78%; $P > 0.2$).

Limitations: Only patients who died and underwent autopsy could be included in this study, so these results may not apply to less severe cases of ARDS.

Conclusions: In a series of autopsy patients, the accuracy of the American–European Consensus Conference definition of ARDS was only moderate. The definition was more accurate for patients with extrapulmonary risk factors than for patients with pulmonary risk factors.

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In 1967, Ashbaugh and colleagues (1) reported a syndrome characterized by the acute onset of tachypnea, hypoxemia, and loss of lung adherence that occurred after various stimuli. Over the subsequent 2 decades, the acute respiratory distress syndrome (ARDS) remained very loosely defined even in clinical trials. In a systematic overview of the incidence of and risk factors for ARDS, Garber and colleagues (2) found that 51% of 83 articles identified did not specifically define this syndrome. In 1992, however, the American–European Consensus Conference on ARDS was formed with the goal of “bringing clarity and uniformity to the definition of acute lung injury and acute respiratory distress syndrome” (3). The resultant American–European Consensus Conference definition of ARDS requires the acute onset of bilateral chest radiographic infiltrates with hypoxemia but without left atrial hypertension (3).

Diffuse alveolar damage is the histopathologic finding that corresponds to the clinical entity of ARDS. Katzenstein and colleagues (4) described diffuse alveolar damage in 1976, and their criteria remain in use today. We are unaware, however, of any study that has systematically analyzed the correlation between clinical criteria for ARDS and histologic findings. This may be important because several diseases with different histopathologic findings, such as bacterial pneumonia, pulmonary hemorrhage, and bronchiolitis obliterans–organizing pneumonia, may present with a clinical picture identical to that of ARDS. In addition, ARDS associated with pulmonary risk factors

may differ from that associated with extrapulmonary risk factors, a concept introduced by the American–European Consensus Conference (3). Several studies have documented differences in the radiologic pattern (5), the respiratory mechanics (6), and the response to prone position (7) between pulmonary and extrapulmonary cases of ARDS. These findings suggest that we are faced with 2 different clinical entities or that the American–European Consensus Conference definition operates differently depending on the origin of ARDS.

To interpret the results of both observational and interventional research in ARDS, we must be confident that these studies are truly examining patients with ARDS and diffuse alveolar damage. We therefore need a measure of the validity of the widely used American–European Consensus Conference definition. We evaluated the criterion validity of the definition of ARDS proposed by the American–European Consensus Conference (3) by using autopsy findings as the reference standard. Second, we analyzed whether the validity of this definition was modified according to the presence of pulmonary or extrapulmonary risk factors.

METHODS

Patients

We included all patients who died in the intensive care unit of the Hospital Universitario de Getafe, Madrid, Spain, between June 1991 and December 2002 and whose

relatives gave informed consent to perform a clinical autopsy. We approached the families of all patients who died except those who became organ donors (because donated organs were not available for autopsy) and those whose autopsies were legally mandated (because these autopsies were performed outside the hospital and we could not access their results). The institutional ethics committee approved the study.

Clinical Criteria for ARDS

After a patient's death, 2 intensivists, who were blinded to the autopsy findings, reviewed clinical charts together. They recorded the following data for each patient: age, sex, date of admission to intensive care unit, date of initiation of mechanical ventilation, principal diagnosis, risk factor for ARDS (pulmonary [pneumonia, aspiration, near-drowning, inhalational injury, or lung contusion] or extrapulmonary [sepsis syndrome, multiple trauma, several blood transfusions, shock, or pancreatitis]), date when all American-European Consensus Conference criteria were first met, date of death, and clinical condition at the time of the death. If a patient had 2 or more risk factors for ARDS, we recorded the risk factor that presented first. The clinical condition at the time of death was considered to be shock with hypoxemia, shock without hypoxemia, or hypoxemia without shock. Shock was defined as a systolic blood pressure persistently below 90 mm Hg during the 6 hours before death, and hypoxemia was defined as arterial oxygenation saturation persistently below 85% during the final 6 hours. We used a case report form that was specifically designed to define and uniformly capture the variables of interest.

A diagnosis of ARDS was established when all criteria defined by the American-European Consensus Conference were met: acute onset, evidence on chest radiographs of airspace changes in all 4 quadrants, ratio of PO_2 to inspired fraction of oxygen of less than 200, and pulmonary artery wedge pressure less than 18 mm Hg or no clinical evidence of left atrial hypertension (3).

Pathologic Criteria for Diffuse Alveolar Damage

We used a predefined protocol, described previously (8), for the pathologic examination and clinical-pathologic correlation. Postmortem study was performed within 12 hours of death. After removal from the thorax, the lungs were inflated with 10% formalin to a pressure of 35 cm of H_2O and were fixed in block with 10% formalin. After 48 hours, the lungs were cut into slices 3 cm thick. We took samples for microscopic analysis from each pulmonary lobe and additional samples from areas with macroscopic injuries. Two pathologists independently analyzed each sample, and a third pathologist resolved any discrepancies.

Criteria for diffuse alveolar damage were hyaline membranes plus at least 1 of the following: alveolar cell type I or endothelial cell necrosis, edema, organizing interstitial fibrosis, or prominent alveolar cell type II proliferation (4, 9).

Histologic criteria for the diagnosis of acute pneumo-

Context

Do all patients who meet clinical criteria for the acute respiratory distress syndrome (ARDS) have diffuse alveolar damage?

Contribution

Of 382 patients who had autopsies after dying in an intensive care unit, 127 met clinical criteria for ARDS. The sensitivity and specificity of clinical criteria for identifying patients with diffuse alveolar damage at autopsy were 75% and 84%, respectively. People with extrapulmonary risk factors, such as sepsis syndrome, more often had findings of diffuse alveolar damage than did those with only pulmonary risk factors, such as pneumonia.

Implications

In severely ill patients, clinical criteria and pathologic findings for ARDS are not closely linked.

—The Editors

nia included the presence of intense neutrophilic infiltration in the interstitium and intra-alveolar spaces, particularly around terminal bronchioles. Alveoli had to be at least partially full with neutrophils, fibrinous exudates, and cellular debris to establish a histologic diagnosis of acute pneumonia. Alveolar hemorrhage was diagnosed when acute hemorrhage was observed in alveoli and airways, along with the presence of macrophages staining positive for hemosiderin.

Statistical Analysis

Data are expressed as means (\pm SD), medians (interquartile ranges), or proportions (95% CIs), as appropriate. All *P* values are 2-sided.

We performed 3 analyses to evaluate the validity of the clinical criteria of ARDS: including all patients, including patients with any risk factor for ARDS, and separating patients with risk factors according to pulmonary or extrapulmonary origin. We calculated operative indexes, including sensitivity, specificity, and likelihood ratios, according to standard criteria (10). We used chi-square tests to compare sensitivity and specificity (11) and the Cochran *Q*-test to compare likelihood ratios between the cohort with pulmonary risk factors and the cohort with extrapulmonary risk factors (12). We used SPSS 11.5 (SPSS Inc., Chicago, Illinois) and Meta-Disc for Windows (Ramón y Cajal Hospital, Madrid, Spain [13]) for statistical analysis.

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The funding source had no role in the design, conduct, or analysis of the data or in the decision to submit the manuscript for publication.

RESULTS

During the study period, 8157 patients were admitted to the intensive care unit and 1399 (17%) died. We sub-

Table 1. Characteristics of the Patients Who Died in the Intensive Care Unit during the Study*

Characteristic	Patients with Clinical Autopsy (n = 382)†	Patients without Clinical Autopsy		
		Autopsy Declined (n = 704)‡	Organ Donors (n = 94)§	Legally Mandated Autopsy (n = 86)
Mean age ± SD, y	67 ± 13	66 ± 15	48 ± 18	46 ± 21
Women, n (%)	138 (36)	282 (40)	39 (41)	23 (27)
Main reason for admission to ICU, n (%)				
Medical problem				
Cardiovascular	103 (27)	211 (30)	7 (7)	7 (8)
Infectious	81 (21)	106 (15)	1 (1)	–
Digestive	44 (11)	49 (7)	–	–
Respiratory	39 (10)	63 (9)	1 (1)	1 (1)
Neurologic	17 (4)	60 (8.5)	49 (52)	4 (5)
Other	17 (4)	7 (1)	–	7 (8)
Surgical problem				
Digestive	57 (15)	106 (15)	–	–
Cardiovascular	17 (4)	49 (7)	–	–
Neurosurgical	3 (1)	28 (4)	8 (9)	–
Thoracic	2 (0.5)	11 (1.5)	–	–
Trauma	2 (0.5)	14 (2)	28 (30)	67 (78)
Patients with risk factors for ARDS, n (%)	284 (74)	450 (64)	17 (18)	61 (71)
Pulmonary				
Infection	91 (32)	138 (31)	3 (18)	11 (18)
Aspiration	12 (4)	9 (2)	–	2 (3)
Pulmonary contusion	2 (1)	–	6 (35)	23 (38)
Inhalation injury	1 (0.3)	–	–	2 (3)
Extrapulmonary				
Sepsis syndrome	125 (44)	194 (43)	1 (6)	2 (3)
Shock	18 (6)	77 (17)	6 (35)	20 (33)
Pancreatitis	18 (6)	9 (2)	–	–
Several transfusions of blood products	10 (3)	14 (3)	1 (6)	1 (2)
Other	7 (2)	9 (2)	–	–

* ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

† Twenty-four of 406 (6%) eligible patients with clinical autopsy had unavailable clinical information.

‡ Ninety-five of 799 (12%) eligible patients in whom autopsy was declined had unavailable clinical information.

§ Ten of 104 (10%) eligible patients who were organ donors had unavailable clinical information.

|| Four of 90 (4%) eligible patients in whom legally mandated autopsy was performed had unavailable clinical information.

sequently excluded 104 organ donors and 90 patients with legally mandated autopsies. We obtained consent and performed a clinical autopsy in 406 (34%) of the remaining patients. Twenty-four (6%) of these patients were excluded from the analysis because the hospital clinical records were lost and the information needed to determine both risk factor and clinical definition status was therefore unavailable. Table 1 shows the patient demographic and clinical characteristics. Organ donors and patients who required legally mandated autopsy were younger than other patients, and more of them had trauma as a risk factor for ARDS. Organ donors were more likely to be admitted to the intensive care unit with a neurologic problem, and patients with legally mandated autopsy were more likely to be men. Patients whose relatives declined autopsy were similar to the patients included in the study. Study patients had a median duration of mechanical ventilation of 4 days (interquartile range, 1 to 11 days) and a median length of stay in the intensive care unit of 5 days (interquartile range, 1 to 12 days).

A total of 127 patients (33%) met the American–European Consensus Conference criteria. After first meeting these criteria, they had a median time to death of 3 days (interquartile range, 1 to 6 days). Meanwhile, 112

patients (29%) met the pathologic criteria for diffuse alveolar damage. Table 2 shows the agreement between the clinical and pathologic diagnoses of ARDS and the operative indexes calculated by using these data. In all patients, the sensitivity of the American–European Consensus Conference criteria was 75% (95% CI, 66% to 82%) and the specificity was 84% (CI, 79% to 88%). When only patients with risk factors for ARDS (n = 284) were analyzed, the specificity decreased to 75% (CI, 68% to 81%) with a similar sensitivity. Compared with patients with pulmonary risk factors, patients with extrapulmonary risk factors had significantly higher sensitivity (61% vs. 85%; P = 0.009), while the specificity was higher but not significantly different (69% vs. 78%; P > 0.2). Patients with extrapulmonary risk factors had significantly better likelihood ratios (P = 0.02 for positive likelihood ratio; P = 0.001 for negative likelihood ratio) (Table 2).

The pathologic findings in the 43 patients who met American–European Consensus Conference criteria but who did not have diffuse alveolar damage were pneumonia (n = 32), pulmonary hemorrhage (n = 4), pulmonary edema (n = 3), pulmonary embolism (n = 3), and interstitial fibrosis secondary to chemotherapy (n = 1). Conversely, the clinical diagnoses of the 27 patients with dif-

fuse alveolar damage at autopsy who did not have a clinical diagnosis of ARDS were pneumonia ($n = 12$), pulmonary edema ($n = 12$), and no pulmonary diagnosis ($n = 3$).

Among 127 patients with clinical criteria for ARDS, 89 (70%) had shock without hypoxemia, 20 (16%) had shock and hypoxemia, and 11 (9%) had hypoxemia without shock. Other causes of death (sudden cardiac arrest or withdrawal of life support) were observed in 7 patients (5.5%); a similar proportion was observed in patients with clinical criteria for ARDS and diffuse alveolar damage at autopsy.

DISCUSSION

The main finding of our study is that the sensitivity and specificity of the American–European Conference Consensus criteria for ARDS are both moderate. The positive and negative likelihood ratios produce only a mild change in the pretest probability (10). These operating characteristics were modified when patients were grouped according to type of risk factor for ARDS; the definition was more accurate in patients with extrapulmonary risk factors.

The reported incidence of ARDS varies from 1.5 to 70 cases per 100 000 persons, and the mortality rate seen in observational studies continues to exceed 50% (14–19). This combination of a relatively common incidence and a high mortality rate makes ARDS an important clinical entity to both clinicians and researchers. A valid clinical definition of ARDS is of vital importance in clinical research because a gold standard test to confirm the diagnosis is not available in most cases. The American–European Consensus Conference criteria for ARDS (3) is currently widely used, but concerns about the definition have been raised, including the fact that it has never been formally validated (20–26).

We believe that our study is the first to compare the American–European Conference Consensus definition for

ARDS with the reference standard of diffuse alveolar damage (4) at autopsy. Other studies have used autopsy to look for diagnostic errors (27–32), but none have systematically evaluated definitions of ARDS. The relatively higher specificity we saw when all patients were included may be misleading, because including patients without clinical suspicion of ARDS may inflate the specificity, along with the negative predictive value (10). When we limited our analysis to patients with a known risk factor for ARDS, we found only moderate accuracy, with a sensitivity and specificity of approximately 0.75 and a positive likelihood ratio of 3.0. This accuracy, however, is slightly better than that reported for the clinical criteria of ventilator-associated pneumonia compared with histologic findings on postmortem biopsies (33, 34).

Of interest, the operating characteristics of the American–European Consensus Conference criteria differed when we separated patients into those with pulmonary versus extrapulmonary risk factors. We observed a large and significant difference in sensitivity and a smaller, nonsignificant difference in specificity, both favoring the extrapulmonary group. Several authors have reported differences between ARDS originating from pulmonary disease and that originating from extrapulmonary disease. Gattinoni and colleagues (6) found different respiratory mechanics and responses to positive end-expiratory pressure in 12 patients with ARDS of pulmonary origin and 9 patients with ARDS of extrapulmonary origin. They postulated that these differences were consistent with a predominance of consolidation in pulmonary ARDS as opposed to a predominance of edema and alveolar collapse in extrapulmonary ARDS. Goodman and colleagues (5) assessed the differences in computed tomography results between pulmonary and extrapulmonary ARDS. They found that pulmonary ARDS tended to be asymmetric with a mix of consolidation and ground-glass opacification, whereas extrapulmonary ARDS had predominantly symmetrical

Table 2. American–European Consensus Conference Definition and Sensitivity, Specificity, and Likelihood Ratios Assessed in Patients Who Died in the Intensive Care Unit*

Patients	Clinical Criteria for ARDS		No Clinical Criteria for ARDS		Sensitivity (95% CI), %†	Specificity (95% CI), %‡	Positive Likelihood Ratio (95% CI)§	Negative Likelihood Ratio (95% CI)
	Diffuse Alveolar Damage, <i>n</i>	No Diffuse Alveolar Damage, <i>n</i>	Diffuse Alveolar Damage, <i>n</i>	No Diffuse Alveolar Damage, <i>n</i>				
All patients ($n = 382$)	84	43	28	227	75 (66–82)	84 (79–88)	4.7 (3.5–6.3)	0.3 (0.2–0.4)
Patients with risk factors for ARDS ($n = 284$)	84	43	27	130	76 (67–83)	75 (68–81)	3.0 (2.3–4.0)	0.3 (0.2–0.5)
Patients with pulmonary risk factors ($n = 106$)	27	19	17	43	61 (47–74)	69 (57–79)	2.0 (1.3–3.1)	0.6 (0.4–0.8)
Patients with extrapulmonary risk factors ($n = 178$)	57	24	10	87	85 (75–92)	78 (70–85)	3.9 (2.7–5.7)	0.2 (0.1–0.3)

* ARDS = acute respiratory distress syndrome.

† Sensitivity = True positives/(true positives + false negatives). True positives were patients with clinical criteria for ARDS and with diffuse alveolar damage in autopsy. False negatives were patients without clinical criteria for ARDS and with diffuse alveolar damage at autopsy.

‡ Specificity = True negatives/(true negatives + false positives). True negatives were patients without clinical criteria for ARDS and without diffuse alveolar damage at autopsy. False positives were patients with clinical criteria for ARDS and without diffuse alveolar damage at autopsy.

§ Positive likelihood ratio = sensitivity/(1 – specificity).

|| Negative likelihood ratio = (1 – sensitivity)/specificity.

ground-glass opacification. Finally, Lim and colleagues (7) examined whether the response to the prone position differed between these risk factor types. They observed that pulmonary and extrapulmonary ARDS, in their early stages, responded differently to the prone position with regard to the time course of oxygenation changes, respiratory mechanics, and radiographic changes. They hypothesized that the early pathophysiology of ARDS might differ according to the type of lung injury. We found, however, that the American–European Consensus Conference definition is not as accurate in patients with pulmonary ARDS and that bacterial pneumonia is present in most patients who are clinically misclassified. These findings suggest that previously observed differences between pulmonary and extrapulmonary ARDS may be due in part to the erroneous inclusion of many patients with pneumonia but without ARDS in the pulmonary group.

We need to address the generalizability of our findings to other intensive care units and patients. We used autopsy as a reference standard, and therefore by design included only patients who died in the intensive care unit and whose family consented to an autopsy. This cohort represents 5% of all patients admitted to the intensive care unit and 27% of patients who died in the intensive care unit. We compared the cohort of included patients with those excluded, and we observed that the age and sex of the study patients were similar to those of patients whose relatives declined autopsy. Although these data are limited, they do not indicate systematic differences between these samples. Trauma patients were systematically excluded from our cohort because most either became organ donors or had legally mandated autopsies performed, making it impossible for us to examine their lungs pathologically.

The other major systematic selection bias in our cohort was that we could study only patients who died during their intensive care unit stays. To evaluate a diagnostic test or definition in an ideal study, researchers should enroll consecutive patients with a range of pretest probabilities for the diagnosis and subsequently perform both the test being evaluated and the gold standard in each patient. In ARDS, however, no gold standard other than histopathologic examination is available and performing an autopsy or even an open lung biopsy in all patients with suspected ARDS is clearly impossible. Patients with ARDS who die may have different pathophysiologic findings than those who survive. It is difficult to accurately predict how our findings might translate to patients with suspected ARDS who ultimately survive their intensive care unit stay. Plausible arguments can be made, on the basis of suspected severity of illness and presence of comorbid conditions, to support either improved or worsened operating sensitivity, specificity, and likelihood ratios in intensive care unit survivors compared with our autopsy patients. Nevertheless, because of the lack of other reference standards, our estimates in autopsy patients currently are the best available estimates for use in intensive care unit survivors.

Another possible limitation to consider when interpreting our results is the manner in which we determined the clinical diagnosis of ARDS. In our study, 2 critical care specialists retrospectively reviewed charts and chest radiographs. This allowed us to review the patients' clinical and radiologic progression over their full course in the intensive care unit before determining whether ARDS was present. This method allowed us to make the most accurate clinical determination possible. This method, however, is clearly not available to either the clinician or researcher evaluating patients in real time. The specificity may be lower than we have documented if the American–European Conference Consensus criteria are applied prospectively, especially in the context of a clinical trial with a narrow enrollment time window. For example, patients with transient hypoxemia and mild bilateral infiltrates could be enrolled in an ARDS trial. They would stay enrolled in the study even if these abnormalities resolved within 12 hours, which would certainly put the diagnosis of ARDS in doubt.

Because of the need for formal definitions, our study may have more implications for the design of future clinical trials of ARDS than for the clinical management of individual patients. However, some of our findings may have important clinical implications, particularly that it may be difficult to distinguish severe pneumonia from ARDS in patients with pulmonary risk factors by using the existing clinical definition. This might prompt clinicians to be more liberal in using invasive investigations and or empirical antibiotics in such patients. Therefore, we believe that the American–European Consensus Conference definition should be revised or new definitions should be developed particularly for research purposes to address the limitations that we have observed. We recommend that these new or revised definitions should undergo validity testing. Currently, we feel that pathologic findings are the best available reference standard.

In conclusion, the American–European Consensus Conference criteria for ARDS were only moderately accurate in our patients. Our results suggest that these criteria perform differently in patients with pulmonary versus extrapulmonary risk factors for ARDS. It may, therefore, be useful for clinicians and researchers to distinguish between patients with pulmonary and extrapulmonary risk factors for ARDS.

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