Original Article

Accuracy of clinical diagnosis of acute respiratory distress syndrome in comparison with autopsy findings*

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Abstract

Objective: To compare the American-European Consensus Conference (AECC) definition of acute respiratory distress syndrome (ARDS) to autopsy findings. **Methods:** All patients who died in the intensive care unit of the University Hospital of the Juiz de Fora Federal University between 1995 and 2003 and were submitted to autopsy were included in the study. Patient clinical charts were reviewed to establish whether cases met the AECC criteria for a diagnosis of ARDS, histologically defined as the presence of diffuse alveolar damage (DAD). **Results:** During the study period, 592 patients died, and 22 were submitted to autopsy. Of those 22 patients, 10 (45%) met the AECC criteria, and 7 (32%) met the histopathological criteria for DAD. The AECC clinical criteria presented a sensitivity of 71% (95%CI: 36-92%) and a specificity of 67% (95%CI: 42-85%). The positive and negative predictive values were, respectively, 50 and 83%, whereas the positive and negative likelihood ratios were, respectively, 2.33 and 0.47. The histopathological findings in the 5 patients who met AECC criteria but did not present DAD were pneumonia (n = 2), pulmonary embolism (n = 1), tuberculosis (n = 1), and cryptococcosis (n = 1). **Conclusion:** The accuracy of the AECC definition of ARDS was less than satisfactory. Due to the low positive predictive value and the low positive likelihood ratio, other hypotheses must be considered when ARDS is suspected.

Keywords: Respiratory distress syndrome, adult; Diagnostic Techniques and Procedures; Autopsy.

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Introduction

Acute respiratory distress syndrome (ARDS) is a clinical condition of severe acute respiratory failure, resulting from disruption of the alveolar-capillary barrier membrane and subsequent influx of protein-rich edema into the alveolar spaces. Simultaneously, the alveolar epithelium injury reduces the production of surfactant, and the edema contributes to inactivate part of this lipoprotein that is still synthesized. The reduction of surfactant favors alveolar collapse, which, in conjunction with the edema, significantly impairs gas exchange and lung mechanics.[1] Histopathological findings include the accumulation of neutrophils, macrophages and erythrocytes, the presence of protein-rich edema in the alveolar spaces and the formation of hyaline membranes, establishing diffuse alveolar damage (DAD). Although the injury is spontaneously resolved after the acute phase in some patients, in others it evolves to a second stage, known as the fibroproliferative phase, marked by the presence of chronic inflammation, fibrosis and neovascularization.[2]

Although the microscopic characteristics of the syndrome are very well defined, histopathological confirmation is rarely possible, and the diagnosis is therefore usually obtained from clinical criteria. In 1994, during the American-European Consensus Conference (AECC), the criteria that are currently used to define this entity were proposed: the acute onset of bilateral alveolar images on the chest X-ray, with hypoxemia, but without left atrial hypertension.[3] Without a doubt, the lack of specificity of the criteria adopted enables the diagnosis of acute pulmonary conditions that do not necessarily course with ARDS. The objective of this study was to evaluate the accuracy of the ARDS diagnosis criteria proposed at the AECC, in comparison with histopathological data obtained from autopsies.

Methods

Retrospective study conducted using the data related to all of the patients who were admitted to the intensive care unit (ICU) of the University Hospital of the Juiz de Fora Federal University, died and were submitted to autopsies between 1995 and 2003. The study was approved by the Ethics Committee of the University Hospital.

Patient medical charts were evaluated by two pulmonologists, and the following information was obtained: age, gender, ICU admission date, date when mechanical ventilation was started, date of death and primary diagnosis. The clinical diagnosis of ARDS was defined as the presence of all criteria established at the AECC: acute onset of respiratory failure, evidence of alveolar opacity in the four quadrants of the pleuropulmonary fields on the chest X-ray, a arterial oxygen tension to fraction of inspired oxygen ratio of less than 200 mmHg and a pulmonary artery occlusion pressure of less than 18 mmHg or the absence of clinical evidence of left atrial hypertension.[3] These data were obtained with no knowledge of the histopathological analysis results.

The pulmonary tissue fragments obtained from the autopsies were analyzed separately by two pathologists. Discrepancies between the two, in relation to the presence or absence of the diagnostic criteria, were resolved by joint analysis of the material. The histopathological diagnosis of ARDS was defined as the presence of DAD, which, as proposed by some authors, is defined as the presence of hyaline membranes and at least one of the following findings: necrosis of type I pneumocytes or endothelial cells, edema, organizing interstitial fibrosis and prominent proliferation of type II pneumocytes.[4] The pathologists had no knowledge of the respective clinical data when they conducted the analysis.

Statistical analysis

The validity of the clinical ARDS diagnosis in comparison with the histopathological diagnosis (gold standard) was evaluated using sensitivity, specificity, positive and negative predictive values and likelihood ratio calculations. The intervals were calculated using confidence intervals for binominal proportions based on the Wilson test score method.[5] Calculations were performed using the Hmisc package of the R statistical program (R Development Core Team, 2004).

Results

During the study period, 592 patients died in the ICU. However, only 22 (3.7%) were submitted to autopsies. The clinical and demographic characteristics, clinical diagnoses, the presence or absence of the AECC criteria for ARDS, the presence or absence of DAD during the autopsy, ICU admission duration

and duration of mechanical ventilation before death are shown in Table 1.

Of the 22 study patients, 10 (45%) met the AECC clinical criteria for ARDS, however, only 5 presented DAD as a histopathological finding. Nevertheless, of the 12 patients (55%) without a clinical diagnosis for ARDS, 2 presented DAD. Based of these data, the clinical diagnosis of ARDS as per the AECC criteria, in comparison with the histopathological diagnosis, presented a sensitivity of 71%, a specificity of 67%, a positive predictive value of 50%, a negative predictive value of 83%, a positive likelihood ratio of 2.33 and a negative likelihood ratio of 0.47 (Table 2).

The histopathological findings in the 5 patients meeting the clinical criteria for ARDS, but without DAD, were as follows: pneumonia in 2, tuberculosis in 1, cryptococcosis in 1 and pulmonary embolism in 1.

Discussion

The syndrome now know as ARDS was first described in 1967 in 12 patients with acute respiratory failure, hypoxemia refractory to oxygenation, decreased lung compliance and alveolar opacities on the chest X-ray.[6] The authors reported that, although all of the patients presented these common findings, there was a significant variety of insults that caused the syndrome. Since its description, there has been a great deal of controversy in regard to the incidence of ARDS, partially due to the lack of standardized diagnostic criteria but also due to the shortage of large, population-based prospective studies addressing this issue. Using the AECC criteria, and consequently the accuracy limitations, other authors conducted a regional study in the USA and found that the incidence of acute lung injury (including ARDS and less serious levels of hypoxemia, but with the other findings of the syndrome)

Table 1 - Characteristics of the patients admitted to the intensive care unit and submitted to autopsies during the study.

Patient	Age	Gender	Diagnosis	ARDS - AECC	DAD	Days on MV	Days in ICU
1	44	M	Cerebral hemorrhage	No	No	3	3
2	58	M	Sepsis (nonpulmonary)	Yes	No	1	1
3	40	M	Sepsis (nonpulmonary)	No	No	1	1
4	29	M	Chagasic cardiomyopathy	No	No	5	5
5	52	F	Pneumonia	Yes	Yes	8	9
6	37	M	Miliary tuberculosis	Yes	No	3	7
7	44	M	Sepsis (nonpulmonary)	Yes	Yes	13	13
8	16	F	Sepsis (nonpulmonary)	No	No	0	2
9	38	M	Acute pancreatitis +	No	No	1	1
10	52	F	pneumonia	Yes	No	1	2
11	46	F	Pneumonia	No	No	1	1
12	72	F	Epilepsy	No	No	1	1
13	50	M	Sepsis (nonpulmonary)	No	No	1	1
14	31	F	Sepsis (nonpulmonary)	No	Yes	4	7
15	30	M	Sepsis (nonpulmonary)[a]	No	No	1	1
16	30	M	Sepsis (nonpulmonary)	No	Yes	1	1
17	35	M	Acute pancreatitis	No	No	1	2
18	39	M	Miliary tuberculosis	Yes	Yes	5	5
19	51	M	Pneumonia[a]	Yes	Yes	4	4
20	41	F	Pneumonia[a]	Yes	No	2	2
21	16	F	Pneumonia[a]	Yes	Yes	2	2
22	68	M	Sepsis (nonpulmonary)	Yes	No	1	2
Mean	41.77		Sepsis (nonpulmonary)			2.73	3.32

M: male; F: female; Days in ICU: number of days spent in the intensive care unit before death; Days on MV: number of days on mechanical ventilation before death; ARDS-AECC: clinical diagnosis of acute respiratory distress syndrome as per the criteria of the American-European Consensus Conference; and DAD: diffuse alveolar damage (diagnosed during the autopsy). [a]Three patients with pneumonia and one with nonpulmonary sepsis presented acquired immunodeficiency syndrome.

Table 2 - Sensitivity, specificity, positive and negative likelihood ratios of the American-European Consensus Conference clinical diagnostic criteria for acute respiratory distress syndrome in comparison with histopathological results.

Clinical diagnosis (+)		Clinical diagnosis (–)		Sensitivity	Specificity	PLR	NLR
DAD (+)	DAD (–)	DAD (+)	DAD (–)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
5	5	2	10	71% (36-92%)	67% (42-85%)	2.33 (0.69-7.94)	0.47 (0.20-1.10)

DAD: diffuse alveolar damage; PLR: positive likelihood ratio; NLR: negative likelihood ratio; and 95% CI: 95% confidence interval.

was 78.9 for every 100,000 inhabitants.[7] Mortality data are also limited. Most studies are conducted in specific patient groups with strict inclusion and exclusion criteria, with the objective of assessing treatment strategies rather than mortality. Among these, two more recent studies reported mortality rates of 35% and 40%.[8,9] The epidemiologic trials conducted by these two groups of authors produced similar outcomes, both reporting an ARDS mortality rate of 41.1% (95% CI: 36.7-45.4%).[7]

These numbers demonstrate the importance of recognizing ARDS, and the need for a reliable clinical definition, since an accurate diagnosis, obtained from histopathological findings, is not possible in most cases. The principal finding of this study was that the sensitivity and specificity of the AECC criteria to diagnose ARDS, which are widely used in everyday practice and to conduct clinical trials, are not appropriate. Consequently, the positive and negative likelihood ratios obtained cannot safely confirm or rule out, respectively, a diagnosis of ARDS.

In a study that also evaluated the efficiency of the AECC criteria based on autopsy results, another group of authors found similar values. Of 127 patients with clinical ARDS criteria, 43 did not present histopathological findings of DAD. The principal findings for these patients were: pneumonia (n = 32), alveolar hemorrhage (n = 4), cardiogenic pulmonary edema (n = 3), pulmonary embolism (n = 3), and pulmonary interstitial disease secondary to chemotherapy (n = 1). In contrast, the autopsy confirmed the presence of DAD in the 27 patients that did not present clinical criteria for the ARDS diagnosis. Of those 27, 12 had been diagnosed with pneumonia, 12 had been diagnosed with cardiogenic pulmonary edema, and 3 had not been diagnosed with any respiratory disorder. These discrepancies between clinical and histopathological findings in relation to ARDS reveal the limited accuracy of the AECC criteria, which were found to have a sensitivity of 75%, a specificity of 84%, a positive likelihood ratio of 4.7 and a negative likelihood ratio of 0.3, results very similar to those obtained in the present study.

The reason for this low accuracy is that, although ARDS is a complex inflammatory condition that attacks the alveolar-capillary barrier, involving various mediators and the development of edema and alveolar collapse, the AECC diagnostic criteria only reflect the consequences of these alterations on the chest X-ray and gas exchange, as well as attempting to ignore the cardiogenic nature of the process. With such great discrepancies, and in view of the fact that the lungs suffer diverse types of injuries related to various etiologies, it is not surprising that the lung injury diagnosis criteria are not accurate. However, there is no simple solution for this problem, and this could explain the fact that the AECC criteria have continued to be used since their implementation in 1994, despite the known limitations, to clinically diagnose ARDS. For example, adding inflammatory markers to the diagnosis in an attempt to include pathogenic data would not necessarily increase the accuracy, since there are many mediators involved and none are specific to the syndrome. In addition, invasive procedures such as bronchoalveolar lavage, which is not always easy to perform in critical patients, would be required to measure the markers involved in the lung injury.

The primary implication of these results is that when there is a clinical suspicion of ARDS, other diagnostic hypotheses should be considered, whether associated with the syndrome or not. There is a diverse group of pulmonary parenchymal diseases with noninfectious etiologies such as alveolar hemorrhage, pulmonary embolism, neoplasias, bronchiolitis obliterans organizing pneumonia, acute eosinophilic pneumonia and drug toxicity that could have acute onset and meet all the clinical, physiological and radiographic criteria for ARDS. Other diseases with infectious etiologies could

also simulate the syndrome. In 2004, one group of authors published a study with the objective of evaluating the role of the lung biopsy in ARDS. In that study, involving 57 patients, the most common alternative or concomitant diagnosis to ARDS were infection in 8 cases, alveolar hemorrhage in 5 cases and bronchiolitis obliterans organizing pneumonia in 5 cases, as well as drug reactions, lymphangitic carcinomatosis, chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis and cardiogenic pulmonary edema in 1 case each. Based on the results, the treatment for most of the patients was changed, with the addition of specific therapy in 60% and the discontinuation of unnecessary treatment in 37%.

Another significant implication of these results is that it is possible that not all of the patients involved in the studies investigating different ARDS treatment strategies, whether using ventilators or medication, really had the disease.[8,9,12,13] These studies typically use AECC criteria to define ARDS, which, as demonstrated by our results and those of other authors, have limited accuracy. Therefore, positive or negative evidence regarding different ARDS treatments could be determined based on unreliable criteria. This limitation could be minimized by establishing stricter inclusion criteria beyond the simple clinical diagnosis of ARDS. Some authors already limit inclusion in studies of ARDS ventilator strategies to patients that continue to present radiographic alterations and hypoxemia consistent with ARDS after a minimum positive end-expiratory pressure of, for example, 10 cmH_2O has been applied for at least 24 hours.[14] Even if this type of strategy does not improve diagnostic accuracy, it establishes a more restrictive level of lung injury severity, increasing the reproducibility of the results obtained.

Our study had significant limitations, chief among which was the small number of cases evaluated. Nevertheless, the results were very similar to those found in a study conducted by other authors with a larger population (n = 382), which underscores its pertinence. The retrospective nature of the collection of clinical data for the diagnosis of ARDS is another significant limitation. Although these data were few and objective, they were included in the complementary test (arterial blood gas analysis and chest X-ray) or in patient follow-up reports.

Another significant limitation was the very specific patient group that was evaluated, that is, those who died and were submitted to autopsies, which are not routine at our institution. To validate a diagnostic definition, the best option would be to compile a cohort of consecutive patients, who would be submitted to clinical evaluation (in this case the AECC criteria to diagnose ARDS), and the clinical evaluation would be compared to the gold standard. In this study, the autopsy findings were used as the gold standard, although they were applied to a specific population. Autopsies are not a routine procedure at our institution and are usually only performed when it is difficult to establish a clinical diagnosis. This explains, for example, the short periods of time that the patients studied spent in the ICU and on mechanical ventilation. In addition, the autopsies were conducted in order to determine the cause of death and not to specifically look for evidence of DAD which requires a detailed search for alterations consistent with the diagnosis in the various regions of both lungs. As a result, the gold standard used in our study also presented limitations.

In conclusion, the AECC criteria for the diagnosis of ARDS have limited accuracy, indicating a potential need to develop and validate other criteria that would provide better results. In view of these limitations, physicians should be aware of the possible differential or concomitant diagnoses when treating patients suspected of having ARDS, and these limitations should be borne in mind by those interpreting the results of studies that have employed these diagnostic criteria.

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