CHEST

The Presence of Diffuse Alveolar Damage on Open Lung Biopsy Is Associated With Mortality in Patients With Acute Respiratory Distress Syndrome

A Systematic Review and Meta-Analysis

Pablo Cardinal-Fernández, MD, PhD; Ednan K. Bajwa, MD; Andrea Dominguez-Calvo, MD; Justo M. Menéndez, MD, PhD; Laurent Papazian, MD; and B. Taylor Thompson, MD

OBJECTIVE: Diffuse alveolar damage (DAD) is considered the histologic hallmark of ARDS although DAD is absent in approximately half of patients with ARDS. The clinical implications of having the syndrome of ARDS with DAD vs other histologic patterns is unknown. To address this question, we conducted a meta-analysis of lung biopsy series for patients with ARDS.

METHODS: Studies were identified using MEDLINE, EMBASE, Cochrane Register of Controlled Trials, LILACS, and citation review from January 1, 1967, to September 1, 2015. Studies were included if they included all of the following: open lung biopsies (OLB) performed after ARDS diagnosis; a clear definition of ARDS and DAD; histologic results of the OLB indicated the presence or absence of DAD; and mortality reported for the DAD and non-DAD groups. We excluded studies conducted solely on a specific histology subgroup (eg, DAD) and studies with fewer than 5 patients. Two authors independently selected studies for inclusion, and there were no language restrictions.

RESULTS: Of 8 included studies, 4 were high-quality (n = 227) and 4 were middle-quality trials (n = 123). The meta proportion of DAD between all the groups was 0.48 (95% CI, 0.42-0.53; Q test, 31.6; I^2, 77.9%; $P \leq .01$). The pooled OR for mortality in ARDS with DAD compared with ARDS without DAD was 1.81 (95% CI, 1.14-2.86; Q test, 8.95; I^2, 21.8%; $P = .256$). Age and days elapsed between ARDS diagnosis and OLB as well as sequential organ failure assessment score and Pa_{O_2}/F_{IO_2} ratio on the day of OLB did not differ between DAD and non-DAD groups.

CONCLUSIONS: This meta-analysis demonstrated that ARDS with DAD is associated with higher mortality than ARDS without DAD. CHEST 2016; 149(5):1155-1164

KEY WORDS: ARDS; diffuse alveolar damage; meta-analysis; open lung biopsy

ABBREVIATIONS: DAD = diffuse alveolar damage; EMBASE = Excerpta Medica dataBASE; LILACS = Literatura Latinoamericana y del Caribe en Ciencias de la Salud; MEDLINE = Medical Literature Analysis and Retrieval System Online; OLB = open lung biopsy; PEEP = positive end expiratory pressure; SOFA = sequential organ failure assessment

AFFILIATIONS: From the Emergency Department (Drs Cardinal-Fernández and Menéndez) and the Internal Medicine Department (Drs Dominguez-Calvo and Menéndez), Hospital Universitario HM Sanchinarro, and the Universidad CEU San Pablo (Dr Menéndez), Madrid, Spain; the Division of Pulmonary and Critical Care (Drs Bajwa and Thompson), Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, MA; and the Assistance Publique, Hôpitaux de Marseille, Hôpital Nord, Réanimation des Détresses Respiratoires et des Infections Sévères, Chemin des Bourrely, and the Faculté de Médecine, Aix-Marseille Université, Marseille, France (Dr Papazian).

Dr Cardinal-Fernández is currently at Department of Genetic Medicine, Weill Cornell Medical College (New York, NY).

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ARDS is a common indication for ICU admission. It is estimated that 4% of patients receiving mechanical ventilation have ARDS, with an associated mortality rate of greater than 40%.[1-3]

ARDS was described in 1967 in a series of 12 patients who presented with acute and severe hypoxemia and diffuse alveolar infiltrates evident on chest radiograph.[4] Histologic findings at autopsy included hyperemia, alveolar atelectasis, interstitial and intraalveolar hemorrhage or edema, numerous alveolar macrophages, and the presence of hyaline membranes. The American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias[5] requires all these histologic findings for the diagnosis of diffuse alveolar damage (DAD). The finding of DAD supports the clinical diagnosis of acute interstitial pneumonia if the clinical presentation is not consistent with ARDS.

Despite postmortem studies demonstrating that only half of patients with ARDS have DAD,[4,6-9] DAD is considered the pathological hallmark of ARDS.[10] The histologic findings in patients with ARDS without DAD at autopsy are quite heterogeneous and include pulmonary embolism, lung cancer, and pneumonia, or no lung histologic abnormalities at all.[4,6,10-13] This histologic heterogeneity confounds attempts at identifying biomarkers and specific pharmacologic treatments for patients with ARDS, as many such efforts are targeted toward the biological processes specifically leading to DAD.[14-18] Because there is no biomarker for DAD, the only way to confirm the presence of DAD is the examination of lung tissue obtained from open lung biopsies (OLB) or autopsies.

Recently, Kao et al[19] found that DAD is an independent risk factor for ARDS mortality. Given these data, further study of the association between the presence of DAD and outcome is of utmost importance. We hypothesized that in patients with a clinical diagnosis of ARDS, the presence of DAD on lung biopsy is associated with a different mortality rate than the absence of DAD.

Methods

Data Sources

Studies were identified using MEDLINE, EMBASE, Cochrane Register of Controlled Trials, LILACS, and citation review from January 1, 1967, to September 1, 2015.

Study Selection

Two authors independently selected studies for inclusion (A. D.-C. and P. C.-F.). Studies were considered eligible if they fulfilled the following criteria: (1) included patients with OLB performed after ARDS diagnosis, (2) included a clear definition of ARDS and DAD, (3) included the histologic results of the OLB (presence or absence of DAD), and (4) included mortality from DAD and non-DAD groups. Studies were excluded if they (1) were conducted solely on a specific histology subgroup (eg, DAD) and (2) included fewer than 5 patients. If the same group of patients was used in different publications, we analyzed the manuscript that included more patients. No language restrictions were applied. The outcome of interest was in-hospital mortality. We required that studies define ARDS according to the definitions found in one of the following articles: Ashbaugh et al,[4] Murray et al,[11] Bernard et al,[20] Ferguson et al,[12] or Ranieri et al.[10]

Data Extraction

Two authors independently extracted data on participants (A. D.-C. and P. C,-F.), intervention, ARDS and DAD definitions, and mortality for each study using a standardized form. We contacted authors if we required clarification of data for the primary outcome (e-Appendix 1). Disagreements in all phases were resolved by consensus in consultation with a senior author (B. T. T., E. B., J. M., and L. P.).

Quality Assessment

The primary investigator (P. C.-F.) independently appraised the quality of included studies using a 14-point quality assessment tool based on the QUADAS criteria.[21] Studies that scored greater than 9 were deemed to be of higher quality, 6 to 9 of middle quality, and the rest of lower quality.

Data Synthesis

The outcome of the meta-analysis was OR for mortality in hospitalized patients with ARDS and OLB findings of DAD, compared with patients without DAD. All OLBs were performed after ARDS diagnosis.

Analysis

We decided a priori to calculate weighted-pooled summary estimates of ORs (meta-OR) using fixed effects models because 1) we consider all the studies to be functionally similar (the diagnosis of ARDS and DAD was well defined, the main outcome [hospital mortality] was objective, and the effect of DAD is likely to be the same in patients with ARDS) and 2) the number of studies expected to be included was low. To detect the risk of publication bias and the small-study effect, we performed a funnel plot analysis by plotting the ORs of individual studies against their variance. The asymmetric inverted funnel shape suggested an association between pooled estimate and study size (publication or small study bias). An Egger's test to objectively assess the funnel plot asymmetry was also performed.[22] All analyses were done using the "meta" package of R program. Probability values of less than .05 were considered statistically significant.

Results

Our literature search and review of reference lists initially identified 609 articles; 601 articles were

CORRESPONDENCE TO: Pablo Cardinal-Fernández, MD, PhD, Hospital Universitario HM Sanchinarro, Emergency Department, Calle Oña, 10, 28050 Madrid, Spain; e-mail: pablocardinal@hotmail.com

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