Supplementary Material

Acute Respiratory Distress Syndrome in Hospitalized Patients with Community-Acquired Pneumonia

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Extended methods

Study design and patients

We performed a prospective observational cohort study of consecutive adult patients with community-acquired pneumonia (CAP) who were transferred to our intensive care unit (ICU) within 24 hours of hospital admission. The study was conducted between November 1996 and December 2016 at the Hospital Clinic, Barcelona, which is a 700-bed tertiary care university hospital. The inclusion criteria were as follows: 1) patients meeting the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) criteria for severe CAP [1] who were admitted to the ICU, including associated intermediate care units; and 2) patients who received either invasive mechanical ventilation (IMV) or non-invasive mechanical ventilation (NIMV) during the first 24 hours of hospital admission. Patients were excluded if they had active tuberculosis or severe immunosuppression. The latter included the following: neutropenia after chemotherapy or hematopoietic transplantation; drug-induced immunosuppression because of solid-organ transplantation, long-term corticosteroid treatment (>10 mg/day), or cytotoxic therapy; and all patients infected with HIV.

Data collection and evaluation

The following parameters were recorded at admission: age, sex, smoking, alcohol and drug consumption, co-morbidities, antibiotic treatment in the 30 days before hospital admission, treatment with oral and inhaled corticosteroids, clinical signs and symptoms, arterial blood gas measurements, chest radiograph findings. Co-morbidities included chronic respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], asthma, and bronchiectasis), diabetes mellitus, and chronic cardiovascular, neurological, renal, or liver disease. Clinical symptoms of interest were fever, cough, pleuritic chest pain, dyspnea, mental confusion, and aspiration, while signs of interest were blood pressure, body temperature, respiratory rate, and heart rate.

All chest x-rays were reviewed by at least two co-authors, either as part of the medical team of the ICU (MF, GLB, AT) or as attending physicians (AC, OR, CGV). For chest x-rays, we recorded the number of lobes affected, and the presence or absence of pleural effusion and atelectasis. Agreement by at least two co-authors was required to define a case as acute respiratory distress syndrome (ARDS) or non-ARDS.

We also assessed laboratory parameters (e.g., hemoglobin level, white blood cell count, platelet count, serum creatinine, and C-reactive protein), diagnostic procedures, empiric antibiotic therapy, ventilatory support (IMV and NIMV), pulmonary complications (e.g., empyema, pleural effusion, and surgical pleural draining), other clinical events (e.g., cardiac arrhythmias, septic shock, and acute renal failure). The duration of treatment, length of hospitalization, and mortality were also noted. Finally, we calculated the Pneumonia Severity Index (PSI) [2] and the Sepsis-related Organ Failure Assessment (SOFA) [3] scores at hospital and ICU admissions.

Microbiological evaluation and diagnostic criteria

Microbiological examination was performed in sputum, urine, nasopharyngeal swabs and two blood samples. Pleural puncture, tracheobronchial aspirates and bronchoalveolar lavage fluid, when available, were collected for Gram and Ziehl–Neelsen stains, and for bacterial, fungal, and mycobacterial cultures.

Lower respiratory tract samples and blood samples were obtained in the emergency department for bacterial culture before the start of antibiotic therapy. Nasopharyngeal swabs for respiratory virus detection and urine samples for *S. pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 hours of hospital admission. Blood samples for atypical pathogen and respiratory virus serology were taken at admission and in the third and sixth weeks thereafter. The criteria used for etiological diagnosis have been reported previously [4].

Definitions

Pneumonia was defined as a new pulmonary infiltrate on chest x-ray at hospital admission, with symptoms and signs compatible with a lower respiratory tract infection. A prior episode of pneumonia was defined as a case of pneumonia within the past 12 months. Severe CAP was defined according to when at least one major or three minor criteria of the IDSA/ATS guidelines were present [1] or if the patient was admitted to the ICU.

ARDS was identified by applying the Berlin definition in the first 24 hours after hospital admission [5]: new or worsening respiratory symptoms, bilateral pulmonary radiologic opacities not fully explained by effusions, lobar/lung collapse or nodules and not fully explained by cardiac failure or fluid overload, and a PaO_2/FiO_2 (i.e., partial pressure of oxygen in arterial blood/fraction of inspired oxygen) ≤300 mmHg with a positive end-expiratory pressure or continuous positive airway pressure >5 cmH_2O [5,6]. The severity of ARDS was divided into three categories: mild (200 < PaO_2/FiO_2 ≤300 mmHg), moderate (100 < PaO_2/FiO_2 ≤ 200 mmHg) and severe (PaO_2/FiO_2 < 100 mmHg) [5]. We chose the initial 24 hours to differentiate as ARDS and non-ARDS patients because this period of time is considered the limit to differentiate between clinical features at admission and worsening evolution in the hospital [7]. COPD was defined according to the criteria of the 2017 GOLD strategy [8].

Clinical outcomes

The primary outcome was 30-day mortality. Other outcomes were the hospitalization length, and the ICU and in-hospital mortality rates. Patients were followed for 30 days or until hospital discharge, whichever was the longest period.

Ethics statement

The study was approved by the ethics committee of our institution (no. 2009/5451). The need for written informed consent was waived due to the non-interventional design.

Statistical analysis

All analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). The level of significance was set at 0.05 (2-tailed), unless otherwise specified. We used a logistic regression model to identify factors associated with ARDS (1). Factors were included in the multivariate model when univariate comparisons yielded a level of significance of $p < 0.15$. We tested the following variables: age (years), gender (male vs female), influenza and pneumococcal vaccination status (no vs yes), systemic and inhaled corticosteroid use (no vs yes), prior antibiotic treatment (no vs yes), chronic pulmonary disease (no disease vs. COPD vs chronic bronchitis vs asthma vs bronchiectasis vs other), chronic cardiovascular disease (no vs yes), chronic renal disease (no vs yes), chronic liver disease (no vs yes), diabetes mellitus (no vs yes),

neurological disease (no vs yes), pneumonia in the past year (no vs yes), nursing home resident (no vs yes), C-reactive protein (mg/dL), and SOFA score (points). A backward stepwise selection ($p_{in} < 0.05$, $p_{out} < 0.10$) was used to identify factors predictive of ARDS.

The factors associated with the 30-day mortality were also assessed by univariate and multivariate analyses (using the same inclusion criterion, $p < 0.15$). Inadequate antibiotic therapy (no vs yes) was also tested for 30-day mortality. A propensity score for patients with ARDS was developed (2), irrespective of the outcome, through a multivariate logistic regression to predict the influence of the 14 predetermined variables on the presence of ARDS. We included variables in the propensity score calculation based on the methods of Brookhart et al. (3), plus any variables associated with ARDS and clinical outcomes. Finally, we performed a logistic regression analysis to predict 30-day mortality by incorporating the propensity score, the year of occurrence of pneumonia, the presence of ARDS, the microbial etiology, and the interaction between ARDS and microbial etiology. This included all risk factors with an association in the univariate analyses ($p < 0.15$), calculated in a stepwise backward elimination procedure ($p_{in} < 0.05$, $p_{out} < 0.10$). To identify collinearity, we calculated the r coefficient between two independent variables, and if they were highly correlated ($r >|\pm 0.30|$), the variable with the largest variance was excluded from multivariate analysis (4) The analyses were repeated for the subset of patients with pneumococcal CAP.

We investigated the missing data patterns for covariates and assumed missing at random condition for covariates (5). We then used multiple imputation (6) to generate five datasets to evaluate the prediction performance for ARDS and 30-day mortality. The model for multiple imputation included all covariates of the risk models, plus ARDS and 30-day mortality. To simplify the performance evaluation, we filled in missing values with the first set of imputed values from the multiple imputation.

Online **Table S1: Empiric antibiotic treatment in the study population**

Therapy	**Non-ARDS patients n = 307**	**ARDS patients n = 125**	**p-value**
Fluoroquinolones monotherapy	16 (5)	3 (2)	0.18
β-lactam monotherapy	15 (5)	3 (2)	0.22
Macrolide monotherapy	2 (1)	0 (0)	>0.99
Glycopeptide monotherapy	0 (0)	1 (1)	0.30
β-lactam plus fluoroquinolone	110 (38)	65 (53)	0.003
β-lactam plus macrolide	95 (33)	35 (29)	0.44
β-lactam plus aminoglycoside	17 (6)	3 (3)	0.15
Other combinations	37 (13)	12 (10)	0.42
Inappropriate empiric treatment [a]	21 (17)	4 (7)	0.070

Abbreviations: ARDS = acute respiratory distress syndrome. Percentages were calculated for non-missing data.

[a] Calculated among patients with defined aetiology only.

The percentages of therapies are related to the numbers of patients receiving empiric antibiotic treatment in each group (292 patients in the non-ARDS group and 122 patients in the ARDS group).

Online Table S2: Internal validation of the prediction model for ARDS, using the nonparametric bootstrap technique

Variable	Original	Bias	SE	95% BCa CI
Year of occurrence of pneumonia ≥2007	-0.007	0.004	0.238	-0.457 to 0.482
Male sex	0.421	0.008	0.241	-0.050 to 0.924
Inhaled corticosteroids	-0.726	-0.037	0.307	-1.356 to -0.236
Previous antibiotic	0.585	0.010	0.280	0.040 to 1.168
SOFA score	0.118	0.001	0.047	0.027 to 0.214
Microbial aetiology				
Streptococcus pneumoniae	0.156	-0.012	0.280	-0.395 to 0.687
Other	0.377	0.001	0.271	-0.137 to 0.877

Abbreviations: ARDS = acute respiratory distress syndrome; BCa = adjusted bootstrap; CI = confidence interval; SE = standard error; SOFA, sepsis-related organ failure assessment.

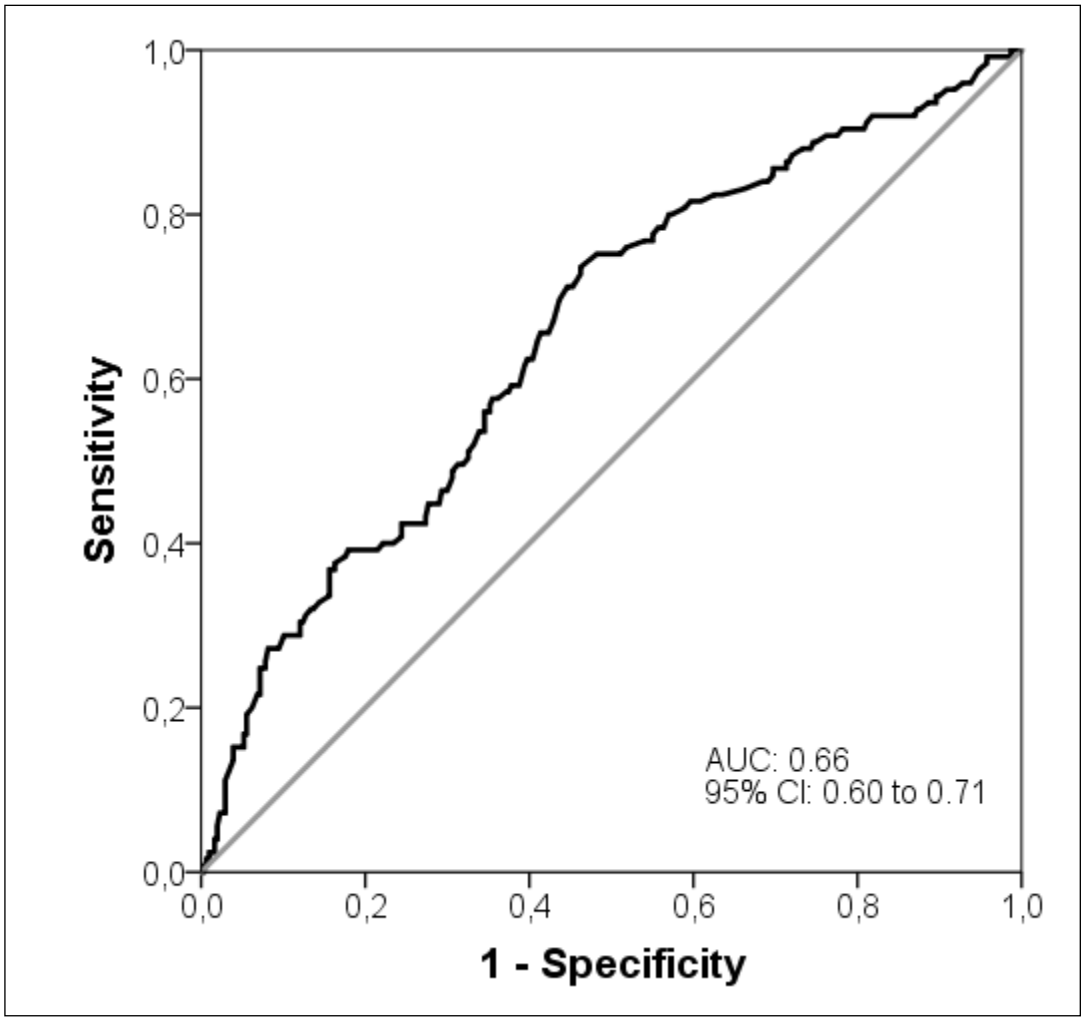
Online Table S3. Clinical outcomes of pneumococcal CAP

Variables	Patients with non-ARDS n = 88	Patients with ARDS n = 35	p-value
Length of hospital stay, median (IQR), days	15.5 (11; 31.5)	15 (9; 31)	0.46
ICU mortality, n (%)	18 (20)	14 (40)	0.026
In-hospital mortality, n (%)	23 (26)	15 (43)	0.070
30-day mortality, n (%)	26 (30)	16 (46)	0.088

Abbreviations: ARDS = acute respiratory distress syndrome; CAP = community-acquired pneumonia; ICU = intensive care unit; IQR = interquartile range.

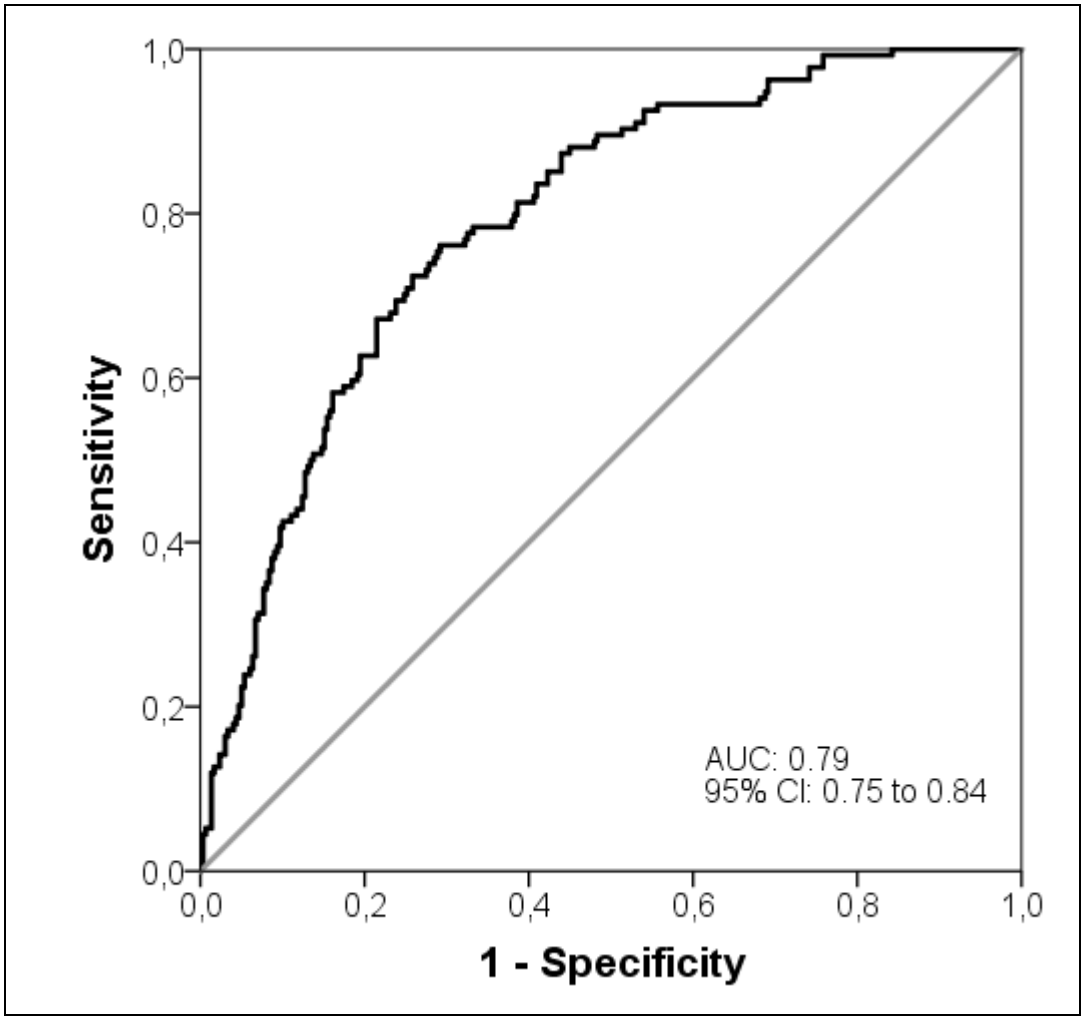
Percentages calculated on non-missing data.

Online Figure S1: ROC curve analysis of significant variables derived from the logistic regression model to predict ARDS



Abbreviations: AUC indicates area under the curve; ARDS = acute respiratory distress syndrome; CI, confidence interval; ROC, receiver operating characteristic.

Online Figure S2. ROC curve analysis of significant variables derived from the logistic regression model to predict 30-day mortality



Abbreviations: AUC indicates area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

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