Acute Respiratory Distress Syndrome in Mechanically-Ventilated Patients with Community-Acquired Pneumonia

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Take-home message: In patients with community-acquired pneumonia, the incidence of acute respiratory distress syndrome based on the Berlin definition was 2% among all patients in hospital, 13% among patients in intensive care, and 29% among patients receiving mechanical ventilation. Acute respiratory distress syndrome was not related to the aetiology or mortality in this population.

Take-home message: In mechanically-ventilated patients with community-acquired pneumonia, ARDS based on the Berlin criteria was not related to the aetiology or mortality.

ABSTRACT

Question: To assess the incidence, characteristics, aetiology, risk factors and mortality of acute respiratory distress syndrome (ARDS) in ICU patients with community-acquired pneumonia (CAP) using the Berlin definition.

Methods: We prospectively enrolled consecutive mechanically-ventilated ICU adults with CAP over 20 years, compared with mechanically-ventilated patients without ARDS. The main outcome was 30-day mortality.

Results: Among 5,334 patients hospitalized with CAP, 930 (17%) were admitted to the ICU, and 432 required mechanical ventilation; 125 (29%) cases met the Berlin ARDS criteria. ARDS was present in 2% of hospitalized patients and 13% of ICU patients. Based on the baseline PaO_2/FiO_2, 60 (48%), 49 (40%), and 15 (12%) patients had mild, moderate, and severe ARDS, respectively. *Streptococcus pneumoniae* was the most frequent pathogen, with no significant differences in aetiology between groups. Higher organ system dysfunction and previous antibiotic use were independent risk factors for ARDS in the multivariate analysis, while previous inhaled corticosteroids was independently associated with a lower risk. The 30-day mortality was similar between patients with and without ARDS (25% vs. 30%, p=0.25), confirmed by propensity-adjusted multivariate analysis.

Conclusions: ARDS occurs as a complication of CAP in 29% of mechanically-ventilated patients, but is not related to the aetiology or mortality.

INTRODUCTION

Community-acquired pneumonia (CAP) is associated with increased morbidity, mortality, and health costs [1,2]. The incidence of severe CAP requiring intensive care unit (ICU) admission is increasing, both because of septic shock and the need for invasive mechanical ventilation (IMV) [3]. Despite global efforts to improve outcomes, mortality remains high in severe CAP [4-6]. *Streptococcus pneumoniae* is the leading cause of CAP; it is the underlying etiological agent in 22% of patients requiring ICU admission [7], and approximately 30% of these patients develop pulmonary complications during their clinical courses [8].

Acute respiratory distress syndrome (ARDS) is a potential complication of severe CAP that is reported in approximately 3% of patients hospitalized with pneumococcal CAP [9]. This condition is characterized by the rapid development of severe acute respiratory failure, and is associated with high morbidity and mortality despite advances in supportive care and ventilator management [10,11]. However, there is limited information regarding the incidence of ARDS, associated pathogens, risk factors, and specific outcomes in hospitalized patients with severe CAP, especially in the era of the current Berlin definition, according to which patients must be receiving positive-pressure ventilation [12]. Although the overall survival from ARDS is improving [12,13], mortality remains as high as 35%, and disabling complications persist among ICU survivors, with recovery sometimes continuing for more than one year [13,14]. In addition, ARDS may be under recognized and undertreated [14].

We hypothesized that patients with severe CAP and ARDS have a higher mortality than those patients who require mechanical ventilation without ARDS. The aim of the study was to assess the incidence, clinical characteristics, aetiology, risk factors and mortality of ICU patients with severe CAP and ARDS according to the new Berlin definition [12], compared with ventilated patients without ARDS.

METHODS

Study design and patients

Please refer to the online Supplemental Material for full details of the methods. This was a prospective observational cohort study of consecutive adult patients with CAP admitted to the ICU within 24 hours of hospital admission, between November-1996 and December-2016. The inclusion criteria were as follows: 1) met the criteria for severe CAP [15] and were admitted to the ICU, which included intermediate care units; and 2) received either IMV or non-invasive mechanical ventilation (NIMV) during the first 24 hours of hospital admission. Patients were excluded if they had severe immunosuppression or active tuberculosis.

Data collection and evaluation

The following were recorded at admission: age, sex, smoking history, alcohol and drug consumption, co-morbidities, antibiotic treatment in the 30 days before admission, treatment with oral and inhaled corticosteroids, clinical symptoms and signs, arterial blood gas measurements, and chest x-ray findings. All chest x-rays were reviewed by at least two co-authors, and consensus was required to define cases as ARDS or non-ARDS; we also assessed laboratory parameters, diagnostic procedures, empiric antibiotic therapy, ventilator support (IMV and NIMV), pulmonary complications, and other clinical events (cardiac arrhythmias, septic shock, and acute renal failure). Duration of treatment, length of hospitalization, and mortality were noted. Finally, we calculated the Pneumonia Severity Index (PSI) [16] and the Sepsis-related Organ Failure Assessment (SOFA) [17] scores

at hospital and ICU admissions.

Microbiological evaluation and diagnostic criteria

We collected sputum samples, and when available, pleural fluid, tracheobronchial aspirates, and bronchoalveolar lavage fluid. Sputum and blood samples were obtained for bacterial culture in the emergency department, before antibiotic therapy. Respiratory samples were processed for Gram and Ziehl–Neelsen stains and for bacterial, fungal, and mycobacterial cultures. 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 serology of atypical pathogens and respiratory viruses were taken at admission and in the third and sixth weeks thereafter. The criteria for etiological diagnosis can be found in a previous report [18].

Definitions

Pneumonia was defined as a new pulmonary infiltrate on chest x-ray at hospital admission with symptoms and signs of lower respiratory tract infection. A prior episode of pneumonia was defined as a case within the past 12 months.

ARDS was identified within the first 24 hours of hospital admission based on the Berlin definition [12]: new or worsening respiratory symptoms; bilateral pulmonary radiologic opacities, not fully explained by effusions; lobar/lung collapse or nodules, 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 [12,19]. 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) [12]. 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 [20]. Chronic obstructive pulmonary disease (COPD) was defined according to the 2017 GOLD strategy [21].

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.

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

Categorical variables are reported as number of patients (%), whereas continuous variables are reported as median (interquartile range [IQR]) for non-normal distributions or as mean (standard deviation [SD]) for normal distributions. Categorical variables were compared using the χ^2 test or the Fisher exact test, and continuous variables were compared using the *t*-test or the nonparametric Mann–Whitney test, as appropriate. The significance level was $p < 0.05$ (2-tailed), unless otherwise specified. All analyses were performed using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

Logistic regression analyses [22] were used to examine the associations between ARDS and risk factors. First, each risk factor was tested individually. Second, all risk factors with an association in the univariate model (p < 0.15) were added to the multivariate model. Finally, a backward stepwise selection (p_{in} < 0.05, p_{out} < 0.10) was used to determine factors associated with ARDS. The association with 30-day mortality was tested by univariate and multivariate analyses with the same inclusion criterion (p < 0.15).

A propensity score was developed for patients with ARDS [23]. Together with the year of occurrence of pneumonia, the presence of ARDS, the microbial aetiology, and the interaction between ARDS and the microbial aetiology, this was incorporated into the multivariate logistic regression analysis to predict 30-day mortality. If two independent variables were highly correlated (r > |±0.30|), the variable with the largest variance was excluded from multivariate analysis [24]. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the models. The areas under the receiver operating characteristic curves (AUCs) of the multivariate models were calculated to predict ARDS and 30-day mortality. Internal validation of the prediction models was conducted by ordinary nonparametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% CIs [25]. The same analyses were performed on the subset of patients with pneumococcal CAP. Finally, we used multiple imputation [26] to handle missing data.

RESULTS

Patients' characteristics

Among 5,334 patients hospitalized with CAP during the observation period, 930 (17%) were admitted to the ICU, of whom 462 (52%) were not ventilated, 137 (15%) received NIMV, and 295 (33%) received IMV (Figure 1).

The study population comprised 432 patients treated in ICU with either IMV or NIMV: 125 cases (29%) met the Berlin ARDS criteria, and 307 cases (71%) did not. ARDS was present in 2% of all patients hospitalized with CAP and in 13% of those admitted to the ICU. According to the severity classification based on the baseline PaO_2/FiO_2 ratio, 60 (48%), 49 (40%), and 15 (12%) patients had mild, moderate, and severe ARDS, respectively. Two patients had been ventilated in the prone position. None of them had received extracorporeal membrane oxygenation.

The patients' characteristics are shown in Tables 1 and 2. Compared to patients without ARDS, those with ARDS had less frequently received treatment with inhaled corticosteroids; had less chronic respiratory co-morbidity, particularly COPD; had poorer baseline oxygenation, higher organ dysfunction, and lower PSI risk; and had more multilobar involvement. However, there was only a trend to have less frequently received pneumococcal vaccination, for less frequent male gender, and more frequent prior antibiotic treatment.

Microbiological diagnosis

An etiologic diagnosis was obtained in 228 patients (53%; Table 3). The most frequent pathogen in both groups was *S. pneumoniae*, with no significant differences in aetiology between the groups. Among the 100 cases of pneumococcal CAP, 29 met the ARDS criteria, the same proportion as in the overall population.

Empiric antibiotic therapy

Data on empiric antibiotic treatment were available in 414 patients (96%; Online Table 1). The most frequent regimens were ß-lactam plus either a respiratory fluoroquinolone (42%) or a macrolide (31%). ARDS patients more often received a ß-lactam plus a respiratory fluoroquinolone compared with non-ARDS patients (p=0.003).

Predictors of ARDS

Among the variables associated with ARDS in the univariate analysis (Table 4), a higher SOFA score and previous antibiotic treatment remained significant independent risk factors for ARDS in the multivariate analysis. Interestingly, prior treatment with inhaled corticosteroids was independently associated with a lower risk for ARDS. The AUC was 0.66 (95% CI, 0.60–0.71) for the model predictive of ARDS (Online Figure 1). Internal validation of the logistic regression model by bootstrapping demonstrated robust results for all the variables in the model, with small 95% CIs around the original coefficients (Online Table 2).

Mortality and length of stay

We did not find significant differences between groups regarding mortality or length of hospitalization (Table 5). However, in cases with pneumococcal CAP, mortality in ICU was higher among those with ARDS (p=0.026; Online Table 3), but neither the in-hospital mortality (p=0.070) nor the 30-day mortality (p=0.088) reached statistical significance.

According to ARDS severity, the 30-day mortality rate was 32%, 33%, and 60% for patients with mild, moderate and severe ARDS, respectively.

Predictors of 30-day mortality

Among the different variables associated with 30-day mortality in the univariate analysis (Table 6), the following were independent predictors of 30-day mortality in the propensity-adjusted multivariate analysis: older age, previous antibiotic treatment, other chronic pulmonary diseases (including only the *sequelae* of pulmonary tuberculosis, pulmonary hypertension, and interstitial lung disease), chronic cardiovascular and liver disease, higher SOFA score, and inadequate empiric antibiotic treatment. It was notable that having a previous episode of pneumonia and having received the pneumococcal vaccination were independently associated to a reduced 30-day mortality rates.

Overall, ARDS was not associated with 30-day mortality, even after adjustment for potential confounders. The AUC was 0.79 (95% CI, 0.75–0.84) for the model predictive of 30-day mortality (Online Figure 2). Internal validation of the logistic regression model by bootstrapping with demonstrated robust results for all variables included in the model, with small 95% CIs around the original coefficients. Finally, the same analysis in the subset of patients with pneumococcal CAP confirmed that ARDS was not independently associated with 30-day mortality after adjustment for potential confounders (adjusted OR, 1.77; 95% CI, 0.70–4.50; p=0.23).

DISCUSSION

The main findings of this study are as follows. First, based on the Berlin definition, ARDS was present in 2% of all hospitalized patients with CAP, 13% of those admitted to the ICU, and 29% of those ICU patients requiring mechanical ventilatory support. Second, higher SOFA scores and previous antibiotic use were independent predictors for ARDS among ventilated patients with CAP,

while previous inhaled corticosteroid treatment was protective. Third, ARDS had no different aetiologies or mortality in patients requiring mechanical ventilation for CAP.

ARDS is recognized globally as a major clinical problem [13], with pneumonia and extrapulmonary sepsis being the main risk factors in 75% of cases [14]. However, there has been a lack of information about the incidence of ARDS in CAP after the Berlin definition was proposed. Our data are consistent with those of the LUNG SAFE study [14], which evaluated the incidence of ARDS in 459 ICUs in 50 countries. They reported that ARDS occurred in 10% of all ICU admissions and in 23% patients who required mechanical ventilation. According to the Berlin criteria, 30%, 47%, and 23% of their patients had mild, moderate, and severe ARDS, respectively. By contrast, there was a higher proportion of mild ARDS and a lower proportion of severe ARDS in our cohort.

Over the past century only a few small case series of ARDS in pneumococcal CAP have been reported [27-29]. A recent French multicenter study [30] concerning pneumococcal CAP in the ICU indicated that the incidence of ARDS was 45%, which was substantially higher than that reported in this study. However, those authors used the prior American–European consensus definition of ARDS [31] and not the current Berlin definition, and included non-ventilated patients (16%).

To our knowledge, this is the first study to provide data on the incidence of ARDS using the Berlin definition among patients hospitalized with CAP. We studied a cohort with severe CAP requiring mechanical ventilation, and compared those with and without ARDS. Regarding the independent predictors for ARDS, the association of higher organ system dysfunction to ARDS was to be expected because these patients had worse baseline oxygenation, an important component of the score.

We previously reported that inhaled corticosteroid use before admission in patients hospitalized because of CAP can reduce the systemic inflammatory response [32], possibly with a selective modulation of the mechanisms of defences to infection [33], with reduced serum levels of tumour necrosis factor (TNF)-alpha, among others. This biomarker has been involved in the pathophysiology of ARDS [34].

We have no clear explanation for the independent association between previous antibiotic use and increased risk of ARDS. To our knowledge, this association has not previously been reported. We have shown that previous antibiotic use can be associated with antibiotic-resistant bacteraemia in patients with CAP [35], resulting in more inappropriate therapy. Whether this could predispose patients to ARDS remains to be assessed. However, this association requires confirmation in future studies.

Mortality among ARDS patients was no different to that among ventilated non-ARDS patients. Indeed, even the propensity-adjusted multivariate analysis did not show an association between ARDS and patients' mortality. According to our results, we think that the expected association of ARDS with mortality seems more related to the need for mechanical ventilation in these patients with CAP rather than ARDS itself, as we have recently reported that invasive mechanical ventilation in patients with severe CAP independently predicts mortality [36]. However, we cannot exclude that specific populations of patients with CAP and ARDS may have different mortality, since sub-phenotypes of ARDS patients with different outcomes related to inflammation [37] or fluid responsiveness [38] have recently been proposed.

Independent predictors of mortality have previously been reported for CAP and other pulmonary infections in critically-ill patients, including older age, chronic liver disease [39], chronic cardiovascular disease [39-41], increased organ system dysfunction [42-44], and inadequate empiric

treatment [45]. It is not clear the reason for the association of previous pneumonia with lower mortality; possibly these patients might have developed a more effective immune response to infection. This is also consistent with pneumococcal vaccination being independently associated with reduced mortality. Given that ARDS was related to mortality in patients with pneumococcal pneumonia, previous vaccination might reduce disease severity in these patients.

Due to the association of ARDS with higher mortality in pneumococcal pneumonia, there is a need to develop effective preventive measures for this complication. A recent randomized clinical trial [46] and a meta-analysis [47] found that short-term treatment with corticosteroids can prevent radiographic progression and ARDS development in CAP. However, these studies investigated CAP in general, not pneumococcal pneumonia specifically. Studies focusing on the acute treatment of pneumococcal pneumonia with corticosteroids or other immunomodulators [48] are therefore needed. Unfortunately, we have no systematic data on the number of patients who received pneumococcal conjugate vaccine-13 or pneumococcal polysaccharide vaccine-23.

In our opinion, the strengths of this study are the large sample, the prospective and consecutive data collection, the use of the current Berlin definition for ARDS, and the statistical analysis by propensity scoring to account for bias due to observed confounders. We think this study provides reliable data on the incidence of ARDS in patients with severe CAP, and that these data can be used for future studies in this important population. In addition, we assessed the association of ARDS with mortality in mechanically-ventilated patients to avoid potential bias due to worse outcomes associated with the need for ventilatory support.

Some limitations need to be addressed. First, the long period of recruitment (20 years) has undoubtedly been associated with major advances in patient care. Although we did incorporate advances in ventilatory management [10] and other support measures [13] over this time, our management protocol for CAP did not change substantially. We also allowed for this by including the period of admission when adjusting mortality outcomes. Second, this study was conducted at a single centre, which necessitates cautious extrapolation of the findings to other settings. Third, the Berlin definition requires the use of positive airway pressure, which is only applied to patients receiving ventilatory support. Fourth, the rate of respiratory viruses identified in our population may be underestimated since the diagnostic techniques employed were routinely implemented over the recruitment period.

In conclusion, ARDS complicating severe CAP occurs in 29% of ventilated patients, but is unrelated to either the aetiology or mortality. ARDS criteria should not be considered in the choice of the empiric antibiotic treatment in these patients.

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Figure 1
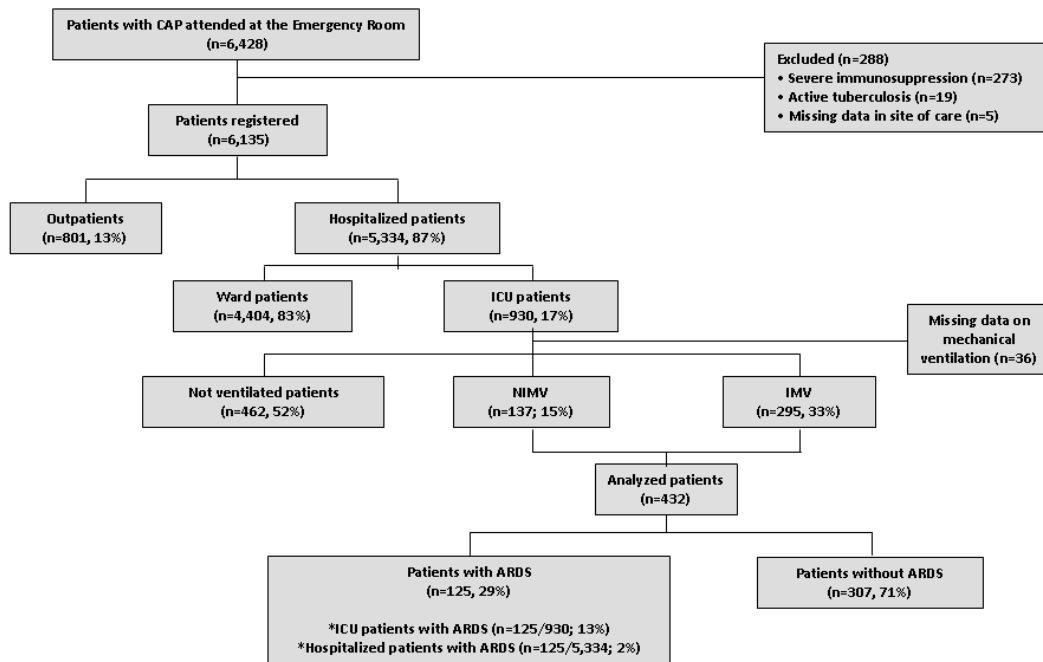
Table 1: Characteristics of patients at baseline

Variables	Non-ARDS patients n = 307	ARDS patients n = 125	p-value
Age, mean (SD), years	65.8 (14.4)	63.1 (17.3)	0.26
Male sex, n (%)	212 (69)	75 (60)	0.071
Current smoker, n (%)	93 (31)	34/122 (28)	0.53
Current alcohol abuse, n (%)	66 (22)	34 (28)	0.21
Previous antibiotic, n (%) [a]	46 (17)	29 (25)	0.052
Influenza vaccine, n (%)	66 (38)	26 (34)	0.62
Pneumococcal vaccine, n (%)	33 (18)	7 (9)	0.054
Inhaled corticosteroids, n (%)	80 (27)	18 (15)	0.008
Systemic corticosteroids, n (%)	13 (6)	8 (8)	0.41
Previous episode of pneumonia, n (%)	29 (11)	7 (6)	0.18
Nursing home resident, n (%)	16 (5%)	5 (4%)	0.62
Co-morbidity, n (%) [b]	244 (81)	83 (66)	0.002
Chronic respiratory disease	152 (51)	45 (37)	0.009
COPD	105 (36)	26 (22)	0.005
Asthma	9 (3)	4 (3)	0.89
Bronchiectasis	8 (3)	2 (2)	0.73
Other [c]	30 (10)	13 (11)	0.85
Chronic cardiovascular disease	52 (17)	20 (16)	0.76
Diabetes mellitus	75 (25)	26 (21)	0.38
Neurological disease	46 (16)	20 (17)	0.84
Chronic renal disease	27 (9)	8 (6)	0.37
Chronic liver disease	26 (9)	12 (10)	0.74

Abbreviations: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease. Percentages were calculated for non-missing data. [a] Information on previous antibiotics was obtained in 67 (89%) cases without any significant differences in the type of antibiotics each group had received: beta-lactams (38 cases), Fluoroquinolons (12 cases), Macrolides (9 cases), and other (8 cases). [b] Some patients may have more than 1 co-morbid condition. [c] Other respiratory diseases included the *sequelae* of pulmonary tuberculosis, pulmonary hypertension, and interstitial lung disease.

Table 2: Characteristics of patients at admission

Variables	Non-ARDS patients n = 307	ARDS patients n = 125	p-value
Mechanical ventilation, n (%)			0.55
Non-invasive	100 (33)	37 (30)	
Invasive	207 (67)	88 (70)	
Laboratory findings, median (IQR)			
Creatinine, mg/dL	1.3 (1; 1.8)	1.3 (0.9; 2)	0.52
C-reactive protein, mg/dL	20.7 (9.5; 30)	22.3 (14.8; 30.2)	0.15
PaO_2/FiO_2	233 (176; 296)	195 (151; 241)	<0.001
SOFA score, median (IQR)[a]	4 (3; 6)	5 (3; 6)	0.026
PSI score, median (IQR)	123 (101; 143)	116 (81; 139)	0.017
PSI risk class, n (%)[b]			0.020
I-III	42 (19)	29 (31)	
IV-V	180 (81)	65 (69)	
Bacteremia, n (%)	46 (19)	20 (19)	0.98
Pleural effusion, n (%)	65 (22)	22 (18)	0.37
Multilobar, n (%)	97 (32)	125 (100)	<0.001
Septic shock, n (%)	106 (36)	45 (37)	0.87
Acute renal failure, n (%)	140 (47)	61 (50)	0.63

Abbreviations: ARDS = acute respiratory distress syndrome; IQR = interquartile range; PaO_2/FiO_2 = arterial oxygen tension to inspired oxygen fraction ratio; PSI = pneumonia severity index; SOFA = sepsis-related organ failure assessment. Percentages were calculated on non-missing data. [a] Higher SOFA in ARDS patients was due to a higher scoring in the respiratory component. [b] Stratified according to 30-day risk mortality for community-acquired pneumonia: risk classes I-III (≤90 points) have low predicted mortality (range, 0%-10%), and risk classes IV-V (>90 points) have the highest predicted mortality (range, 10%-35%).

Table 3: Microbial aetiology in the study population

Pathogen	Non-ARDS patients n = 307	ARDS patients n = 125	p-value
Patients with defined aetiology	157 (51)	71 (57)	0.29
Streptococcus pneumoniae	71 (45)	29 (41)	0.54
Respiratory viruses	12 (8)	8 (11)	0.37
Atypical	10 (6)	5 (7)	>0.99
Mycoplasma pneumoniae	5 (3)	4 (6)	0.47
Coxiella burnetii	1 (1)	1 (1)	0.53
Chlamydophila pneumoniae	4 (3)	0 (0)	0.31
Pseudomonas aeruginosa	10 (6)	3 (4)	0.76
Staphylococcus aureus	8 (5)	4 (6)	>0.99
GNEB	5 (3)	3 (4)	0.71
Escherichia coli	3 (2)	3 (4)	0.38
Klebsiella pneumoniae	2 (1)	0 (0)	>0.99
Haemophilus influenzae	5 (3)	2 (3)	>0.99
Legionella pneumophila	2 (1)	4 (6)	0.077
Streptococcus constellatus	1 (1)	0 (0)	>0.99
Moraxella catarrhalis	1 (1)	0 (0)	>0.99
Others	2 (1)	0 (0)	>0.99
Polymicrobial[a]	30 (19)	13 (18)	0.89

Abbreviations: ARDS = acute respiratory distress syndrome; GNEB = Gram-negative enteric bacilli.

Percentages calculated on non-missing data.

The percentages of pathogens are related to the number of patients with etiologic diagnosis in each group.

[a] Polymicrobial cases: *S. pneumoniae* + respiratory viruses; *S. pneumoniae* + H. *influenzae*; *S. pneumoniae* +atypical bacteria; *S. pneumoniae* + *E. coli*; *S. pneumoniae* + *S. aureus, S. pneumoniae*+ *Acinetobacter* spp*.; S. pneumoniae* +others, Respiratory viruses + *H. influenzae*; Respiratory viruses + *S. aureus*; Respiratory viruses + *P. aeruginosa*; Respiratory viruses + other; *P. aeruginosa* + *L. pneumophila*; *P. aeruginosa* + *K. pneumoniae*; *P. aeruginosa* + other; *S. aureus*+ *M. Catarrhalis*; *S. aureus* + atypical: *S. aureus* + *P. aeruginosa*.

Table 4: Significant univariate and multivariate logistic regression analyses of ARDS predictors

Variable	Univariate[a]			Multivariate[bc]		
	OR	95% CI	p-value	OR	95% CI	p-value
Year of occurrence of pneumonia ≥2007	0.96	0.64 to 1.46	0.86	0.99	0.64 to 1.54	0.98
Age (+1 year)	0.99	0.98 to 1.00	0.12	-	-	-
Female sex	1.49	0.97 to 2.29	0.071	1.52	0.97 to 2.39	0.067
Pneumococcal vaccination	0.62	0.34 to 1.12	0.11	-	-	-
Inhaled corticosteroids	0.45	0.26 to 0.77	0.004	0.48	0.27 to 0.85	0.012
Previous antibiotic	1.60	0.99 to 2.61	0.057	1.80	1.08 to 2.98	0.024
Previous episode of pneumonia	0.57	0.26 to 1.21	0.14	-	-	-
Chronic respiratory disease[d]			0.076	-	-	-
Non-chronic respiratory disease	1	-	-	-	-	-
COPD	0.47	0.28 to 0.79	0.004	-	-	-
Asthma	0.72	0.27 to 1.92	0.51	-	-	-
Bronchiectasis	0.96	0.28 to 3.29	0.95	-	-	-
Other[e]	0.81	0.40 to 1.63	0.55	-	-	-
SOFA score (+1 point)[f]	1.12	1.03 to 1.22	0.007	1.13	1.03 to 1.23	0.009
Microbial etiology			0.36			0.37
Unknown	1	-	-	-	-	-
Streptococcus pneumoniae	1.10	0.67 to 1.82	0.70	1.17	0.69 to 1.97	0.56
Other	1.45	0.87 to 2.41	0.15	1.46	0.86 to 2.47	0.16

Abbreviations: ARDS = acute respiratory distress syndrome; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio; SOFA = sepsis-related organ failure assessment. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the ARDS group. The OR is defined as the probability of having ARDS divided by the probability of not having ARDS. The p-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect).

[a] The variables analyzed in the univariate analyses were as follows: age, gender, influenza and pneumococcal vaccination, systemic and inhaled corticosteroids, prior antibiotic treatment, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, pneumonia in the past year, nursing home resident, C-reactive protein, and SOFA score.

[b] Adjusted for the propensity score, the year of occurrence of pneumonia, and the microbial etiology.

[c] Hosmer–Lemeshow goodness-of-fit test, p = 0.35.

[d] The p-value corresponds to differences between the five groups (non-chronic respiratory disease, COPD/chronic bronchitis, asthma, bronchiectasis, or other chronic respiratory diseases).

[e] Other chronic respiratory diseases include sequelae of pulmonary tuberculosis, pulmonary hypertension, and interstitial lung disease.

[f] The p-value corresponds to differences between the three groups (unknown etiology, *Streptococcus pneumoniae*, or other etiologies).

Table 5: Clinical Outcomes

Variables	Non-ARDS patients n = 307	ARDS patients n = 125	p-value
Length of hospital stay, median (IQR), days	15 (10; 27)	16 (9; 30)	0.96
ICU mortality, n (%)	70 (23)	37 (30)	0.14
In-hospital mortality, n (%)	81 (26)	41 (33)	0.18
30-day mortality, n (%)	90 (30)	44 (35)	0.25

Abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range. Percentages were calculated for non-missing data.

Table 6: Significant univariate and multivariate logistic regression analyses for predictors of 30-day mortality

Variable	Univariate[a]			Multivariate[bc]		
	OR	95% CI	p-value	OR	95% CI	p-value
Year of occurrence of pneumonia ≥2007	0.56	0.37 to 0.84	0.005	0.69	0.42 to 1.14	0.15
Age (+1 year)	1.02	1.01 to 1.04	0.002	1.03	1.01 to 1.05	0.002
Pneumococcal vaccination	0.50	0.27 to 0.92	0.025	0.38	0.18 to 0.82	0.013
Previous antibiotic	1.50	0.92 to 2.42	0.10	2.09	1.17 to 3.72	0.012
Previous episode of pneumonia	0.43	0.20 to 0.96	0.039	0.33	0.14 to 0.81	0.016
Chronic respiratory disease[d]			0.017			0.040
Non-chronic respiratory disease	1	-	-	-	-	-
COPD	0.94	0.58 to 1.50	0.78	0.85	0.46 to 1.59	0.62
Asthma	0.37	0.11 to 1.28	0.12	0.28	0.06 to 1.26	0.096
Bronchiectasis	0.77	0.20 to 2.92	0.70	0.77	0.17 to 3.46	0.74
Other[e]	2.53	1.31 to 4.89	0.006	2.42	1.09 to 5.35	0.029
Chronic cardiovascular disease	2.11	1.26 to 3.53	0.005	1.97	1.07 to 3.61	0.029
Chronic liver disease	2.58	1.33 to 5.01	0.005	2.35	1.09 to 5.06	0.029
Diabetes mellitus	1.42	0.89 to 2.26	0.14	-	-	-
SOFA score (+1 point)	1.28	1.17 to 1.40	<0.001	1.25	1.09 to 1.43	0.001
Inadequate antibiotic therapy	2.72	1.59 to 4.65	<0.001	2.55	1.30 to 4.99	0.006
Microbial aetiology [f]			0.15			0.30
Unknown	1	-	-	1	-	-

Variable	Univariate[a]			Multivariate[bc]		
	OR	95% CI	p-value	OR	95% CI	p-value
Streptococcus pneumoniae	1.44	0.89 to 2.34	0.14	1.57	0.78 to 3.16	0.20
Others	1.58	0.95 to 2.61	0.078	1.60	0.78 to 3.28	0.20
ARDS	1.31	0.84 to 2.04	0.23	1.06	0.49 to 2.32	0.88
Interaction microbial etiology × ARDS[g]			0.33			0.65
Streptococcus pneumoniae × ARDS	1.62	0.56 to 4.69	0.38	1.64	0.48 to 5.53	0.43
Other × ARDS	0.67	0.22 to 1.99	0.47	0.93	0.27 to 3.21	0.90

Abbreviations: ARDS = acute respiratory distress syndrome; CI = confidence interval; OR = odds ratio; PSI = pneumonia severity index; SOFA = sepsis-related organ failure assessment. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the 30-day mortality group. The OR is defined as the probability of 30-day mortality divided by the probability of no 30-day mortality. The p-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect).

[a] The variables analyzed in the univariate analyses were: age, gender, influenza and pneumococcal vaccination, systemic and inhaled corticosteroids, prior antibiotic treatment, chronic pulmonary disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, pneumonia in the past year, nursing home resident, creatinine, C-reactive protein, SOFA score, and inadequate antibiotic therapy.

[b] Adjusted for the propensity score, the year of occurrence of pneumonia, the ARDS, the microbial etiology, and the interaction between ARDS and microbial etiology.

[c] Hosmer-Lemeshow goodness-of-fit test, p = 0.27.

[d] The p-value corresponds to differences between the five groups (non-chronic respiratory disease, COPD/chronic bronchitis, asthma, bronchiectasis, or other chronic respiratory diseases).

[e] Other chronic respiratory diseases include *sequelae* of pulmonary tuberculosis, pulmonary hypertension, and interstitial lung disease.

[f] The p-value corresponds to differences between the three groups (unknown etiology, *Streptococcus pneumoniae*, or other etiologies).

[g] The p-value corresponds to the interaction between microbial etiology and ARDS.

Supplementary Material

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

Catia Cilloniz[1], Miquel Ferrer[1], Adamantia Liapikou[2], Carolina Garcia-Vidal[4], Albert Gabarrus[1], Adrian Ceccato[1] ,Jorge Puig de La Bella Casa[3] ,Francesco Blasi[4] ,Antoni Torres[1] MD

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$_2$O [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 1: 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 2: 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 3. 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 1: ROC curve analysis of significant variables derived from the logistic regression model to predict ARDS
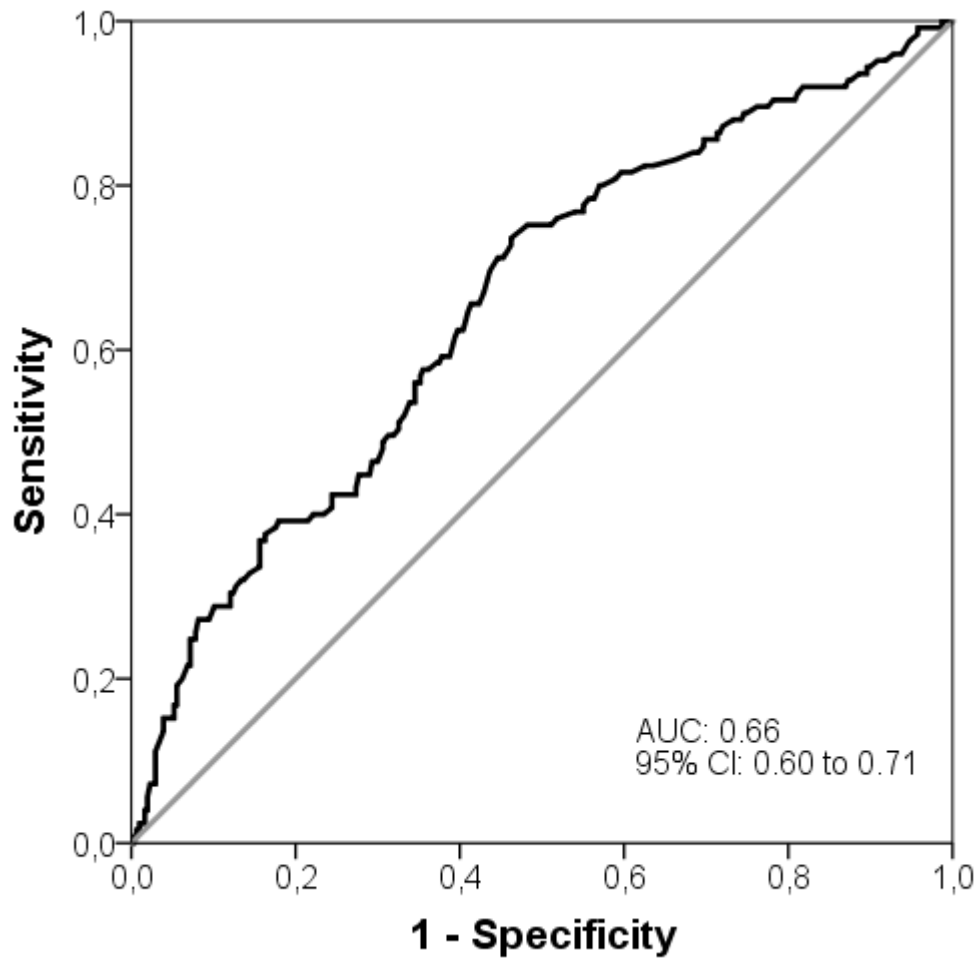
Abbreviations: AUC indicates area under the curve; ARDS = acute respiratory distress syndrome; CI, confidence interval; ROC, receiver operating characteristic.

Online Figure 2. ROC curve analysis of significant variables derived from the logistic regression model to predict 30-day mortality
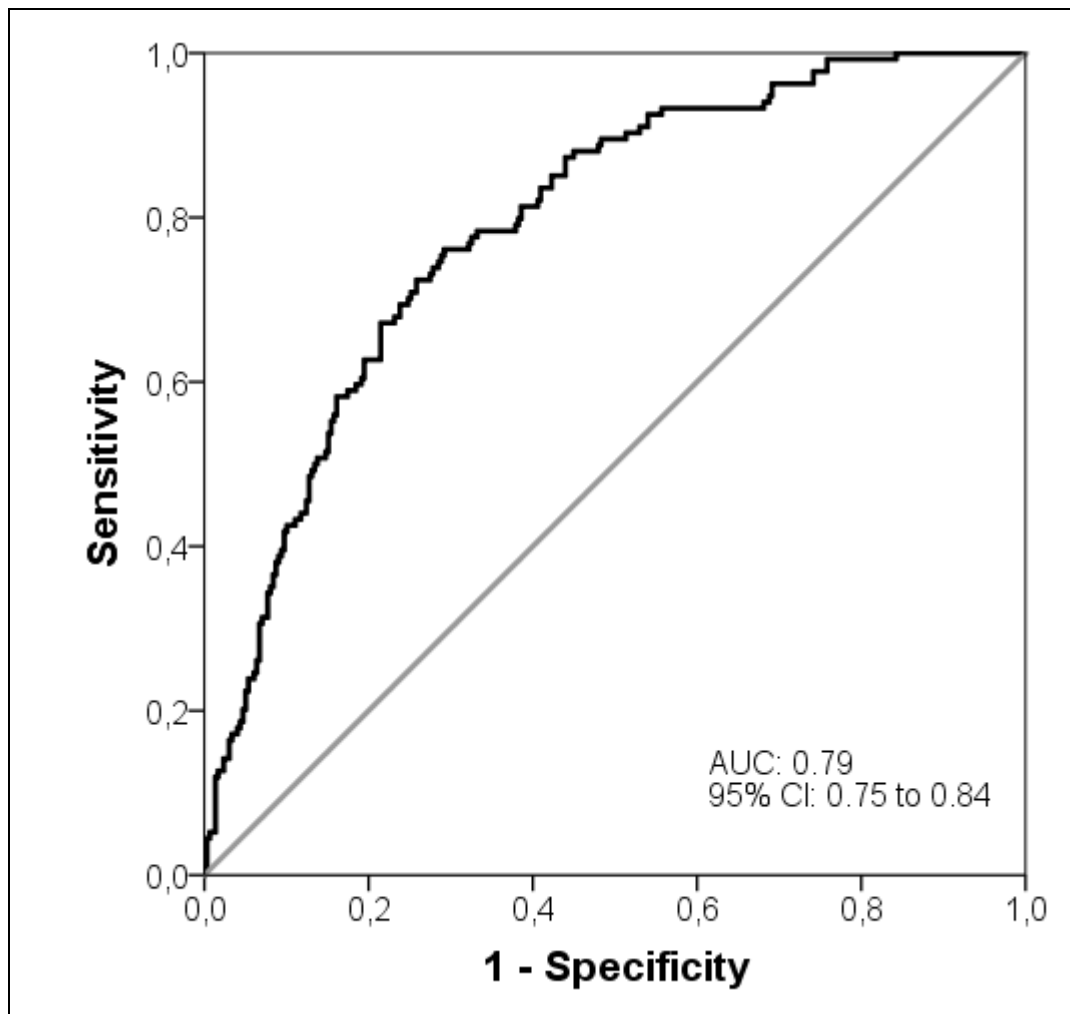
Abbreviations: AUC indicates area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

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