Acute respiratory distress syndrome in mechanically ventilated patients with community-acquired pneumonia

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In mechanically ventilated patients with community-acquired pneumonia, ARDS based on the Berlin criteria was not related to aetiology or mortality http://ow.ly/BDMm30izoCN

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ABSTRACT Our aim was to assess the incidence, characteristics, aetiology, risk factors and mortality of acute respiratory distress syndrome (ARDS) in intensive care unit (ICU) patients with community-acquired pneumonia (CAP) using the Berlin definition.

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

Among 5334 patients hospitalised 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 hospitalised patients and 13% of ICU patients. Based on the baseline arterial oxygen tension/inspiratory oxygen fraction ratio, 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 were independently associated with a lower risk. The 30-day mortality was similar between patients with and without ARDS (25% *versus* 30%, p=0.25), confirmed by propensity-adjusted multivariate analysis.

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

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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 aetiological agent in 22% of patients requiring ICU admission [7], and ∼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 ∼3% of patients hospitalised with pneumococcal CAP [9]. This condition is characterised 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 hospitalised 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 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 >1 year [13, 14]. In addition, ARDS may be underrecognised and undertreated [14].

We hypothesised 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

Refer to the online supplementary 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 h of hospital admission, between November 1996 and December 2016. The inclusion criteria were as follows. Patients 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 noninvasive mechanical ventilation (NIMV) during the first 24 h 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, comorbidities, antibiotic treatment in the 30 days before admission, treatment with oral and inhaled corticosteroids, clinical symptoms and signs, arterial blood gas measurements and chest radiography findings. All chest radiographs were reviewed by at least two co-authors, and consensus was required to define cases as ARDS or non-ARDS; in addition, we 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 hospitalisation and mortality were noted. Finally, we calculated pneumonia severity index (PSI) [16] and the sepsis-related organ failure assessment (SOFA) [17] scores at hospital and ICU admission.

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 h 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 aetiological diagnosis can be found in a previous report [18].

Definitions

Pneumonia was defined as a new pulmonary infiltrate on chest radiography 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 h 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 an arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio ⩽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 ($200<P_{aO_2}/F_{IO_2}\leqslant 300$ mmHg), moderate ($100<P_{aO_2}/F_{IO_2}\leqslant 200$ mmHg) and severe ($P_{aO_2}/F_{IO_2}<100$ mmHg) [12]. We chose the initial 24 h to differentiate 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 Global Initiative for Chronic Obstructive Lung Disease strategy [21].

Clinical outcomes

The primary outcome was 30-day mortality. Other outcomes were length of hospitalisation and 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 (Hospital Clinic of Barcelona, Barcelona, Spain; no. 2009/5451). The need for written informed consent was waived due to the noninterventional design of the study.

Statistical analysis

Categorical variables are reported as n (%), whereas continuous variables are reported as median (interquartile range) for non-normal distributions or as mean±SD for normal distributions. Categorical variables were compared using the Chi-squared test or the Fisher exact test, and continuous variables were compared using the t-test or the nonparametric Mann–Whitney U-test, as appropriate. The significance level was $p<0.05$ (two-tailed), unless otherwise specified. All analyses were performed using IBM SPSS Statistics (version 23.0; IBM, 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 ($r>|\pm 0.30|$), the variable with the largest variance was excluded from multivariate analysis [24]. The odds ratios (ORs) and 95% confidence intervals 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 1000 bootstrap samples and bias-corrected, accelerated 95% confidence intervals [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

Patient characteristics

Among 5334 patients hospitalised 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 hospitalised with CAP and in 13% of those admitted to the ICU. According to the severity classification based on the baseline P_{aO_2}/F_{IO_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 often received treatment with inhaled corticosteroids; had less chronic respiratory comorbidity, particularly COPD; had poorer baseline oxygenation, higher organ dysfunction, and lower PSI risk; and had more multilobar involvement. Trends only were seen in less pneumococcal vaccination, fewer males and more frequent prior antibiotic treatment.

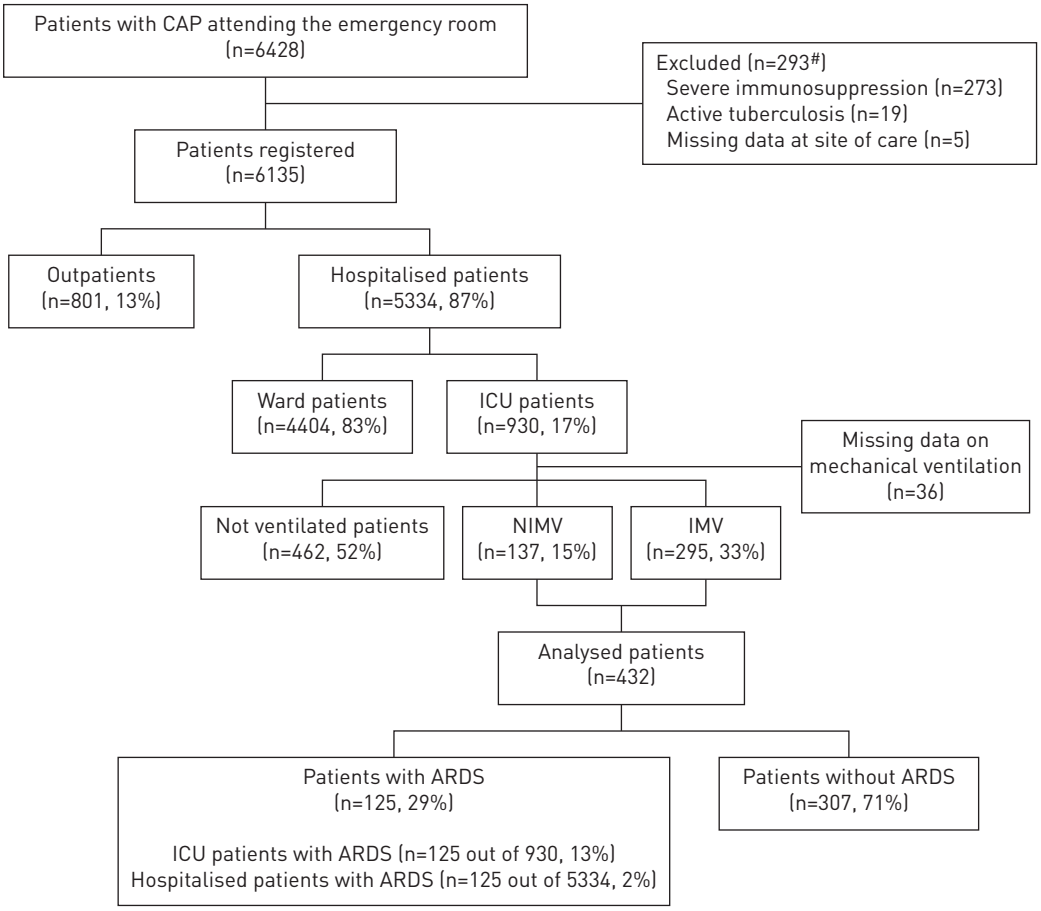

FIGURE 1 Flow diagram of the study population. CAP: community-acquired pneumonia; ICU: intensive care unit; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; ARDS: acute respiratory distress syndrome. #: four patients had two exclusion criteria.

Microbiological diagnosis

An aetiological diagnosis was obtained in 228 (53%) patients (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 (96%) patients (online supplementary table S1). The most frequent regimens were β-lactam plus either a respiratory fluoroquinolone (42%) or a macrolide (31%). ARDS patients more often received a β-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 supplementary figure S1). Internal validation of the logistic regression model by bootstrapping demonstrated robust results for all the variables in the model, with small 95% confidence intervals around the original coefficients (online supplementary table S2).

Mortality and length of stay

We did not find significant differences between groups regarding mortality or length of hospitalisation (table 5). However, in cases with pneumococcal CAP, mortality in the ICU was higher among those with

TABLE 1 Patient characteristics at baseline

	Non-ARDS patients	ARDS patients	p-value
Subjects	307	125	
Age years	65.8±14.4	63.1±17.3	0.26
Male	212 (69)	75 (60)	0.071
Current smoker	93 (31)	34/122 (28)	0.53
Current alcohol abuse	66 (22)	34 (28)	0.21
Previous antibiotics[#]	46 (17)	29 (25)	0.052
Influenza vaccine	66 (38)	26 (34)	0.62
Pneumococcal vaccine	33 (18)	7 (9)	0.054
Inhaled corticosteroids	80 (27)	18 (15)	0.008
Systemic corticosteroids	13 (6)	8 (8)	0.41
Previous episode of pneumonia	29 (11)	7 (6)	0.18
Nursing home resident	16 (5)	5 (4)	0.62
Comorbidity[¶]	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[+]	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

Data are presented as n, mean±SD or n (%), unless otherwise stated. ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease. Percentages were calculated for nonmissing data. [#]: information on previous antibiotics was obtained in 67 (89%) cases without any significant differences in the type of antibiotics each group had received: β-lactams (n=38), fluoroquinolones (n=12), macrolides (n=9) and other (n=8); [¶]: some patients may have more than one comorbid condition; [+]: other respiratory diseases included the sequelae of pulmonary tuberculosis, pulmonary hypertension and interstitial lung disease.

ARDS (p=0.026; online supplementary table S3), 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 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 supplementary figure S2). Internal validation of the logistic regression model by bootstrapping demonstrated robust results for all variables included in the model, with small 95% confidence intervals 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 hospitalised 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

TABLE 2 Patient characteristics at admission

	Non-ARDS patients	ARDS patients	p-value
Subjects	307	125	
Mechanical ventilation			0.55
Noninvasive	100 (33)	37 (30)	
Invasive	207 (67)	88 (70)	
Laboratory findings			
Creatinine mg·dL^{-1}	1.3 (1–1.8)	1.3 (0.9–2)	0.52
C-reactive protein mg·dL^{-1}	20.7 (9.5–30)	22.3 (14.8–30.2)	0.15
Pa_{O_2}/F_{IO_2}	233 (176–296)	195 (151–241)	<0.001
SOFA score[#]	4 (3–6)	5 (3–6)	0.026
PSI score	123 (101–143)	116 (81–139)	0.017
PSI risk class[¶]			0.020
I–III	42 (19)	29 (31)	
IV–V	180 (81)	65 (69)	
Bacteraemia	46 (19)	20 (19)	0.98
Pleural effusion	65 (22)	22 (18)	0.37
Multilobar disease	97 (32)	125 (100)	<0.001
Septic shock	106 (36)	45 (37)	0.87
Acute renal failure	140 (47)	61 (50)	0.63

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. ARDS: acute respiratory distress syndrome; Pa_{O_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; SOFA: sepsis-related organ failure assessment; PSI: pneumonia severity index. Percentages were calculated on nonmissing data. [#]: higher SOFA score in ARDS patients was due to a higher scoring in the respiratory component; [¶]: 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

	Non-ARDS patients	ARDS patients	p-value
Subjects	307	125	
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 cases[#]	30 (19)	13 (18)	0.89

Data are presented as n or n (%), unless otherwise stated. ARDS: acute respiratory distress syndrome; GNEB: Gram-negative enteric bacilli. Percentages calculated on nonmissing data. The percentages of pathogens are related to the number of patients with aetiological diagnoses in each group. [#]: 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 acute respiratory distress syndrome (ARDS) predictors

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

Data are presented as estimated odds ratios (ORs) (95% CI) of the explanatory variables in the ARDS group, unless otherwise stated. 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). COPD: chronic obstructive pulmonary disease; SOFA: sepsis-related organ failure assessment. [#]: the variables analysed in the univariate analyses were age, sex, 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; [¶]: adjusted for the propensity score, the year of occurrence of pneumonia, and the microbial aetiology; [+]: Hosmer–Lemeshow goodness-of-fit test, p=0.35; [§]: p-value corresponds to differences between the five groups (nonchronic respiratory disease, COPD/chronic bronchitis, asthma, bronchiectasis or other chronic respiratory diseases); [f]: other chronic respiratory diseases include sequelae of pulmonary tuberculosis, pulmonary hypertension and interstitial lung disease; [##]: p-value corresponds to differences between the three groups (unknown aetiology, *S. pneumoniae* or other aetiologies).

were independent predictors for ARDS among ventilated patients with CAP, while previous inhaled corticosteroid treatment was protective. Third, ARDS had no difference in aetiologies or mortality in patients requiring mechanical ventilation for CAP.

ARDS is recognised 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 since the Berlin definition was proposed. Our data are consistent with those of LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) [14], which evaluated the incidence of ARDS in 459 ICUs in 50 countries. They reported that

TABLE 5 Clinical outcomes

	Non-ARDS patients	ARDS patients	p-value
Subjects	307	125	
Length of hospital stay days	15 (10–27)	16 (9–30)	0.96
ICU mortality	70 (23)	37 (30)	0.14
In-hospital mortality	81 (26)	41 (33)	0.18
30-day mortality	90 (30)	44 (35)	0.25

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. ARDS: acute respiratory distress syndrome; ICU: intensive care unit. Percentages were calculated for nonmissing data.

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

	Univariate[#]		Multivariate[¶,+]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Year of occurrence of pneumonia ⩾2007	0.56 (0.37–0.84)	0.005	0.69 (0.42–1.14)	0.15
Age +1 year	1.02 (1.01–1.04)	0.002	1.03 (1.01–1.05)	0.002
Pneumococcal vaccination	0.50 (0.27–0.92)	0.025	0.38 (0.18–0.82)	0.013
Previous antibiotic	1.50 (0.92–2.42)	0.10	2.09 (1.17–3.72)	0.012
Previous episode of pneumonia	0.43 (0.20–0.96)	0.039	0.33 (0.14–0.81)	0.016
Chronic respiratory disease[§]		0.017		0.040
Nonchronic respiratory disease	1			
COPD	0.94 (0.58–1.50)	0.78	0.85 (0.46–1.59)	0.62
Asthma	0.37 (0.11–1.28)	0.12	0.28 (0.06–1.26)	0.096
Bronchiectasis	0.77 (0.20–2.92)	0.70	0.77 (0.17–3.46)	0.74
Other[f]	2.53 (1.31–4.89)	0.006	2.42 (1.09–5.35)	0.029
Chronic cardiovascular disease	2.11 (1.26–3.53)	0.005	1.97 (1.07–3.61)	0.029
Chronic liver disease	2.58 (1.33–5.01)	0.005	2.35 (1.09–5.06)	0.029
Diabetes mellitus	1.42 (0.89–2.26)	0.14		
SOFA score +1 point	1.28 (1.17–1.40)	<0.001	1.25 (1.09–1.43)	0.001
Inadequate antibiotic therapy	2.72 (1.59–4.65)	<0.001	2.55 (1.30–4.99)	0.006
Microbial aetiology[##]		0.15		0.30
Unknown	1		1	
Streptococcus pneumoniae	1.44 (0.89–2.34)	0.14	1.57 (0.78–3.16)	0.20
Others	1.58 (0.95–2.61)	0.078	1.60 (0.78–3.28)	0.20
ARDS	1.31 (0.84–2.04)	0.23	1.06 (0.49–2.32)	0.88
Interaction microbial aetiology × ARDS[¶¶]		0.33		0.65
Streptococcus pneumoniae × ARDS	1.62 (0.56–4.69)	0.38	1.64 (0.48–5.53)	0.43
Other × ARDS	0.67 (0.22–1.99)	0.47	0.93 (0.27–3.21)	0.90

Data are shown as estimated odds ratios (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). COPD: chronic obstructive pulmonary disease; SOFA: sepsis-related organ failure assessment; ARDS: acute respiratory distress syndrome. [#]: the variables analysed in the univariate analyses were age, sex, 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; [¶]: adjusted for propensity score, year of occurrence of pneumonia, ARDS, microbial aetiology and the interaction between ARDS and microbial aetiology; [+]: Hosmer–Lemeshow goodness-of-fit test, p=0.27; [§]: p-value corresponds to differences between the five groups (nonchronic respiratory disease, COPD/chronic bronchitis, asthma, bronchiectasis or other chronic respiratory diseases); [f]: other chronic respiratory diseases include sequelae of pulmonary tuberculosis, pulmonary hypertension and interstitial lung disease; [##]: p-value corresponds to differences between the three groups (unknown aetiology, *S. pneumoniae* or other aetiologies); [¶¶]: p-value corresponds to the interaction between microbial aetiology and ARDS.

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. In 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 multicentre 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 nonventilated patients (16%).

To our knowledge, this is the first study to provide data on the incidence of ARDS using the Berlin definition among patients hospitalised 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 hospitalised 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-α, 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 further 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 patient 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 subphenotypes of ARDS patients with different outcomes related to inflammation [37] or fluid responsiveness [38] have 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]. The reason for the association of previous pneumonia with lower mortality is unclear; possibly these patients might have developed a more effective immune response to infection. This is 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 randomised 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 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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