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Effect of Combined β-Lactam / Macrolide Therapy on Mortality According to the Microbial Aetiology and Inflammatory Status of Patients with Community - Acquired Pneumonia.

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Running head: Antimicrobial Treatment of CAP.

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ABREVIATION LIST

β-lactam plus macrolide (BL+M)

Community-acquired pneumonia (CAP).

C-reactive protein (CRP)

Fluoroquinolone alone with or without a β-lactam (FQ±BL)

Intensive care unit (ICU)

Interquartile range (IQR)

Pneumonia Severity Index (PSI)

Randomised clinical trials (RCT)

Sepsis-related Organ Failure Assessment (SOFA)

ABSTRACT

Background: Antibiotic combinations that include macrolides have shown lower mortality rates than β-lactams in monotherapy or combined with fluoroquinolones in patients with community-acquired pneumonia (CAP). However, this effect has not been studied according to the levels of C-reactive protein (CRP) in CAP with identified microbial cause.

Objectives: In patients with CAP and known microbial cause we aimed to evaluate 30 day mortality of a β-lactam plus macrolide (BL+M) compared to a fluoroquinolone alone with or without a β-lactam (FQ±BL)

Methods: We analysed a prospective observational cohort of patients with CAP admitted to Hospital Clinic of Barcelona between 1996 to 2016. We only included patients with known microbial cause.

Results: Of 1,715(29%) patients with known aetiology, a total of 932 patients (54%) received BL+M. Despite a lower crude mortality in the BL+M group in the overall population (BL+M 5% vs. FQ±BL 8% p=0.015), after adjusted by a propensity score and baseline characteristics, the combination of BL+M had a protective effect on mortality only in patients with high inflammatory response (C-reactive protein >15 mg/dL) and pneumococcal CAP, (adjOR 0.28, 95%CI 0.09 to 0.93). No benefits on mortality were observed for the population without high inflammatory response and pneumococcal CAP or with other etiologies.

Conclusions: The combination of a β-lactam with a macrolide was associated with a decreased mortality in patients with pneumococcal CAP and, in patients with high systemic inflammatory response. When both factors occurred together, BL+M were protective for mortality in the multivariate analysis.

Keywords: Community-acquired Pneumonia, Sepsis, Inflammatory response, Macrolide, *Streptococcus pneumoniae.*

BACKGROUND

Community-acquired pneumonia (CAP) is a major cause of death worldwide [1]. The mortality attributed to CAP is high, despite adequate and early empiric antimicrobial treatment [2]. Empiric antibiotics must cover the main pathogens that cause pneumonia. Guidelines suggest the use of a β-lactam plus a macrolide (BL+M), or a β-lactam plus a fluoroquinolone or a fluoroquinolone alone (FQ±BL) as empiric treatment for hospitalized patients, but with fluoroquinolone monotherapy restricted to non-ICU patients [3–5].

Few randomised clinical trials (RCT) have compared these antibiotic regimens, and the data available are the result of retrospective observational analyses [6–17]. In many of these studies, combinations of a BL+M showed better results than β-lactam monotherapy, even in patients with higher severity or when the responsible pathogen is resistant to macrolides. These benefits have been attributed to the immunomodulatory effect of macrolides in addition to their antimicrobial effect [18,19]. However, fluoroquinolones also have an immunomodulatory effect and a similar antimicrobial spectrum for usual etiologic pathogens of CAP [20]. Pneumococcal pneumonia usually has a higher inflammatory response than pneumonia caused by other organisms, with some exceptions such as *Legionella pneumophila* [21] and toxin-producing *Staphylococcus aureus*. Therefore, we might expect a greater beneficial effect of including a macrolide in pneumococcal CAP compared with other etiologic groups. Indeed, several studies have shown the benefits of including macrolides in the treatment of pneumococcal CAP compared to monotherapy, particularly in the presence of bacteraemia [13,22–24].

The hypothesis of this study was that combining a β-lactam with a macrolide in patients with CAP resulted in decreased 30-day mortality, when compared to a quinolone-based regimen. We also aimed to test whether stratifying patients according to microbial aetiology of CAP and the level of systemic inflammation was related to this benefit in mortality.

METHODS

Study design and patients

We performed an observational study on a prospective cohort of consecutive CAP patients who were admitted to the Hospital Clinic of Barcelona (January 1996 to December 2016).

Inclusion criteria were: a) adults ≥18 years-old at diagnosis; b) CAP confirmed by chest radiograph and consistent clinical manifestations (e.g., fever, cough, sputum production, pleuritic chest pain); c) patients with known aetiology; and d) patients who received a BL+M or FQ±BL as empiric treatment.

Exclusion criteria were: a) previous hospital admission for ≥48 hours in the preceding 14 days; b) absence of complete clinical follow up for 4–6 weeks; c) severe immunosuppression, as in transplantation, HIV co-infection, or in patients receiving chemotherapy or other immunosuppressive drugs (>20 mg prednisone-equivalent per day for 2 weeks or more); and d) empiric treatment with combinations other than those described above.

Ethics statement

The Ethics Committee of the Hospital Clinic of Barcelona approved the study for the purpose of publication (Register: 2009/5451). The need for written informed consent was waived because of the non-interventional design. Patients' identity remained anonymous.

Data collection

The co-morbidities were recorded from the medical records. Clinical, laboratory and radiographic characteristics were recorded on admission (described in detail in the Online Supplement Material). During hospitalization, the following data were recorded: length of stay, admission to the intensive care unit (ICU), need for mechanical ventilation, invasive or non-invasive, and 30-day mortality.

Severe CAP was defined according to ATS/IDSA guidelines [3]. Pneumonia Severity Index (PSI) [25], Sepsis-related Organ Failure Assessment (SOFA) [26], and CURB-65 [27] scores were used to stratify cases according to severity.

Microbiological evaluation

Microbiological examination is described in detail in the online Supplement Material.

Definitions

We separated the patients according to initial antimicrobial treatment into two groups: patients who received a BL+M, and patients who received a FQ±BL.

We also grouped them according to aetiology into three groups: patients with pneumococcal aetiology, patients with atypical pathogen aetiology (*Chlamydophila*

pneumoniae, Chlamydia psittaci, Coxiella burnetii, Mycoplasma pneumoniae and *Legionella pneumophila)* and patients with other aetiology (organisms not included in previous groups, or polymicrobial aetiology).

We defined patients with a high inflammatory response as those with a C-reactive protein (CRP) greater than 15 mg/dL at admission, based on the results of a previous study [28].

Appropriateness of empiric antimicrobial treatment in patients was defined when the isolated pathogens were susceptible in vitro to ≥1 of the antimicrobials administered.

Outcomes

The main outcome was 30-day all-cause mortality.

Statistical analysis

We report the number and percentage of patients for categorical variables, the median and interquartile range (IQR) for continuous variables with a non-normal distribution, and the mean and standard deviation for those with a normal distribution. Categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the t-test or the non-parametric Mann-Whitney test.

Logistic regression analyses [29] were used to examine the associations between 30-day mortality and risk factors. In the first step, each risk factor was tested individually. In the second step, all risk factors that showed an association in the univariate model ($p<0.10$) were added into the multivariable model. Finally, a backward stepwise selection ($pin<0.05$, $pout>0.10$) was used to determine factors associated with 30-day mortality. If two independent variables were highly correlated ($r > |\pm 0.30|$), the variable with the largest variance was excluded from the multivariable analyses [30]. The odds ratio (OR) and 95% confidence interval (CI) were calculated.

A propensity score for patients receiving antimicrobial treatment was developed [31] because the antimicrobial treatment was not randomly administered to these patients, resulting in a potential confounding factor and selection bias. The propensity score was determined, irrespective of the outcome, through a multinomial logistic regression to predict the influence of 18 predetermined variables on the use of antimicrobial treatment. Variables were chosen for inclusion in the propensity score calculation according to the methods of Brookhart et al [32] and included variables associated with antimicrobial use and

outcome. The score was finally entered as a continuous variable in the multivariable logistic regression analysis for 30-day mortality, together with the antimicrobial treatment, the microbial aetiology, the year of occurrence of pneumonia, and admission to the ICU. As sensitivity analyses, the same analyses were performed on the subset of pneumococcal CAP patients, and for patients with CRP >15 mg/dL.

We used the multiple imputation method [33] for missing data in the multivariable analyses. The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS Statistics version 23.0 (Armonk, New York, USA).

RESULTS

Patients' characteristics

Of the 6,442 patients with CAP admitted during the study period, 1,715 (28%) were included in the present study; the main exclusion criteria was unknown aetiology in 3840 (60%) patients (Fig. 1) Nine hundred and thirty-two patients (54%) received empiric antibiotic treatment with a BL+M and 783 patients (46%) with a FQ±BL.

The baseline characteristics of the two groups are summarized in Table 1. Patients who received a BL+M had more frequent chronic pulmonary disease and were more often former or current smokers; they had less frequent neurological disease, previous influenza vaccination, nursing home residence or previous antibiotic therapy.

The main causal organism was *Streptococcus pneumoniae* in both groups (Fig. 1). Detailed information on microbial aetiology is shown in Table 2. High inflammatory response (CRP >15 mg/dL) at admission was present in 534 (70%) patients with pneumococcal CAP, 117 (55%) patients with atypical aetiology, and 341 (46%) patients with another aetiology.

We found no differences in severity scores such as CURB-65, PSI or SOFA; however, patients who received a FQ±BL were more frequently admitted to the ICU**,** and more often required non-invasive ventilation, or presented with severe CAP, particularly septic shock. No differences were observed in the requirement for invasive mechanical ventilation (Table 3).

Antibiotic treatment

Among 1,715 patients, 1387 (81%) were treated with a β-lactam; of these, 1,209 (87%) received ceftriaxone. Patients treated with BL+M received azithromycin in 758 (81%) cases, erythromycin in 111 (12%) and clarithromycin in 63 (7%).

In patients treated with FQ±BL, 455 (58%) received a fluoroquinolone in combination with a β-lactam. In this group 767 (98%) patients received levofloxacin, 12 (1.5%) ciprofloxacin, and 4 (0.5%) moxifloxacin; all patients treated with ciprofloxacin were in combination with a β-lactam.

Outcomes

Patients receiving BL+M had lower crude 30-day mortality compared to patients who received a FQ±BL (5% vs. 8%, p=0.015; Table 4). Similar results were observed in patients with a high inflammatory response (BL+M 3% vs. FQ±BL 8% p<0.001) and for patients with pneumococcal CAP (BL+M 4% vs. FQ±BL 9% p=0.004). The greatest difference in mortality was observed in patients with both a high inflammatory response and pneumococcal CAP (BL+M 2% vs. FQ±BL 10% p= <0.001). No differences in 30-day mortality between both groups were observed in patients with atypical or other aetiologies. Moreover, we grouped all patients without pneumococcal CAP and without a high inflammatory response and again no significant differences were observed.

In the overall population and specifically in patients with pneumococcal pneumonia, the propensity-adjusted multivariable analysis did not show any significant association between the antibiotic treatment and 30-day mortality (eTables 1 and 2, and eFigure 1), however for the population with a high inflammatory response we observed a significant interaction between antimicrobial treatment and aetiology, specifically for patients with pneumococcal CAP, who also received antibiotic treatment with BL+M (adjOR: 0.28 95% CI: 0.09 to 0.92, p=0.036) (Table 5). The multivariable analysis adjusted by propensity score for 30-day mortality also showed that, PSI risk class IV–V, acute respiratory distress syndrome, septic shock, and inappropriate treatment were independent risk factors for death. The area under the ROC curve was 0.85 (95% CI: 0.80 to 0.89) (eFigure 1) for the model of 30-day mortality.

Internal validation of logistic regression model for patients with high inflammatory response was conducted using bootstrapping with 1,000 samples (eTable 3). All variables

included in the model demonstrated robust results, with low 95% CIs around the original coefficients.

DISCUSSION

In this well characterized cohort of patients with CAP we compared the effect of two types of empiric antibiotic treatments, BL+M and FQ±BL, on 30-day mortality. After adjusting for confounders, BL+M did not protect for mortality in the overall population, however, our analyses revealed that the combination of a BL+M compared with FQ±BL had an independent association with less 30-day mortality only in patients with pneumococcal CAP and in those with a high inflammatory response (CRP >15 mg/L), with the greatest benefit in those with both factors present. No differences in mortality were observed between groups in patients with other microbial aetiologies and high inflammatory response.

Several observational studies have shown that the combination of a β-lactam with a macrolide is better than a β-lactam alone. Therefore, clinical guidelines suggest the use of a combination of a β-lactam with a macrolide or a fluoroquinolone, or a fluoroquinolone alone for patients with CAP (but fluoroquinolone monotherapy only for non-severe CAP patients). The beneficial effect of a BL+M over a combination of a β-lactam with a fluoroquinolone or a fluoroquinolone alone is less clear. In this study we compared these combinations in different subgroups and found differences in favour of the macrolide combination in a specific group of patients. Benefits in pneumococcal bacteraemic CAP were previously reported for a BL+M combination; even though when compared with fluoroquinolone-based therapies, no benefits were observed [13], however this study did not look at the inflammatory status. A recent study has shown better outcomes in patients who received macrolide therapy and presented with bacteraemic pneumonia[34]. Moreover, the most common cause of bacteraemic pneumonia was pneumococcus in 74% of patients, and although the authors did not look at CRP levels, patients with invasive pneumococcal CAP usually presented greater levels of CRP [35]. A recent meta-analysis that compared the combination of a β-lactam with a macrolide versus a β-lactam with a fluoroquinolone showed no significant differences in short-term mortality (adjusted risk ratio 1.26, 95% CI 0.95–1.67, I^2 43%) [36]; and another meta-analysis showed that ceftriaxone combination therapy was similar in terms of treatment success compared to fluoroquinolone monotherapy in patients with CAP [37]. The study by Postma *et al* was a cluster-randomized clinical trial that showed that a β-lactam was

not inferior to a combination of a beta-lactam with a macrolide or a fluoroquinolone alone for patients with non-severe CAP [6], however this study had several methodology limitations that made the conclusions not generalized. A recent post-hoc analysis of a multicentre cohort in Japan evaluated the role of CRP in patients treated with a β-lactam compared with a combination β-lactam plus macrolide, showing mortality benefit regardless of whether the CRP level was above or below 15 mg/dL [38]. CRP is an inflammatory marker that can predict poor outcomes and treatment failure in patients with CAP or sepsis for other causes, and could be used for evaluate response to treatment [39–41]. As in previous studies on adjuvant treatments in CAP [28,42], we looked at specific populations in whom a BL+M could have a beneficial effect. Furthermore, a recent report by the US National Heart, Lung, and Blood Institute [43] recognized severe pneumonia with high inflammatory response as an endotype, and proposed that its presence might be used to guide therapy.

Macrolides and fluoroquinolones have immunomodulatory activity. Both act reducing the levels of pro-inflammatory cytokines and increasing the levels of anti-inflammatory cytokinesin *in-vitro* and *in-vivo* models [20,44,45]. The fluoroquinolones have effects on intracellular cyclic AMP and phosphodiesterases, and on transcription factors such as NF-kappa B, activator protein 1 [44]. Macrolides have effects on structural cells of the respiratory tract such as endothelial and epithelial cells, mainly on the expression of adhesion molecules, reducing the adherence of pneumococci to the respiratory epithelium [18,19,46,47]. A potential explanation of the impact on pneumococcal CAP with a high inflammatory response is the fact that macrolides not only inhibit bacterial protein synthesis but are also potent inhibitors of the production of pneumolysin, even at sub-inhibitory concentrations [48,49]. The combined impact on bacteria and on the host response may explain our findings [22–24].

The main limitation of this study is that it was performed at a single centre, and so the results should be confirmed in other databases or in prospective RCTs. Another limitation is that we observed that patients who received fluoroquinolones alone or in combinations had more severe disease and were admitted to ICU more frequently; this may represent a bias in our study, given that physicians including the ICU team more often used fluoroquinolones in patients with more severe disease. We tried to address this issue by adjusting all the multivariable analyses by ICU admission. In addition, the aetiology of CAP

identified in our study showed a high frequency of pneumococcal infection, a finding that is at variance with the data in a recent large study from the USA [50]. Our results suggest the need for a new RCT in a population with *S. pneumoniae* and high inflammatory response to evaluate the mortality benefit of adding a macrolide to a β-lactam. The strengths of our study are that we analysed a large database with a well characterized population with microbiologic data. In addition, we compared combinations of a β-lactam with either a macrolide or a fluoroquinolone; both regimens are active against the most common pathogens causing CAP, and both macrolides and fluoroquinolones have immunomodulatory activity.

In conclusion, the combination of a β-lactam with a macrolide was associated with a decreased mortality in patients with pneumococcal CAP and, in patients with high systemic inflammatory response. When both factors occurred together, BL+M were protective for mortality in the multivariate analysis.

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Author contributions: Study concept and design: AC, AT; data collection: AC, CC, LB, CGV, MF; statistical analysis: AG, analysis and interpretation of data: AC, IML, OR, CGV, MF, MN, AT; drafting of the manuscript: AC; critical revision of the manuscript for important intellectual content: IML, OR, CGV, MF, MN and AT; and study supervision: AT. AT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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468 **Table 1: Baseline characteristics of patients**

Variables	**β-lactam plus a macrolide (n= 932)**	**β-lactam plus a fluoroquinolone or a fluoroquinolone alone (n= 783)**	***p*-value**
Age, median (IQR), years	72 (57; 80)	71 (55; 80)	0.512
Elderly (>65 years old), n (%)	607 (65)	475 (61)	0.057
Male sex, n (%)	602 (65)	475 (61)	0.094
Pneumococcal vaccine, n (%)	94 (16)	133 (19)	0.195
Influenza vaccine, n (%)	225 (38)	316 (45)	**0.016**
Chronic pulmonary disease, n (%)	469 (51)	322 (42)	**<0.001**
Heart failure, n (%)	122 (13)	107 (14)	0.722
Chronic renal failure, n (%)	65 (7)	48 (6)	0.486
Hepatic disease, n (%)	67 (7)	41 (5)	0.102
Diabetes mellitus, n (%)	178 (19)	164 (21)	0.301
Neurological disease, n (%)	104 (11)	110 (15)	**0.045**
Former or current smoker, n (%)	591 (63)	458 (58)	**0.043**
Alcohol consumption, n (%)	160 (17)	125 (16)	0.474
Nursing home, n (%)	21 (3)	51 (7)	**<0.001**
Previous antibiotic therapy n (%)	164 (18)	176 (24)	**0.004**
Systemic steroids, n (%)	27 (4)	48 (6)	0.088
Inappropriate treatment, n (%)	23 (5)	19 (5)	0.697
Creatinine, median (IQR), mg/dL	1.1 (0.9; 1.5)	1.1 (0.9; 1.6)	0.285
C-reactive protein, median (IQR), mg/dL	22 (11; 29)	22 (12; 30)	0.169
White blood cell count, median (IQR), $\times 10^9$/L	13.8 (8,9; 18.6)	13.1 (9; 18.3)	0.581
PaO_2/FiO_2, median (IQR), mmHg	281 (238; 314)	271 (229; 314)	0.072

469 Abbreviations: IQR, interquartile range. Percentages calculated on non-missing data.

Boldface entries indicate statistical significance.

472 **Table 2: Microbial aetiology of pneumonia**

Pathogen	**β-lactam plus a macrolide (n= 932) (%)**	**β-lactam plus a fluoroquinolone or a fluoroquinolone alone (n= 783) (%)**
Pneumococcal Pneumonia	415 (45)	346 (44)
Invasive pneumococcal pneumonia	185 (20)	145 (19)
Atypical bacteria	121 (13)	91 (12)
Legionella pneumophila	68 (7)	51 (7)
Chlamydophila pneumoniae	21 (2)	12 (2)
Mycoplasma pneumoniae	21 (2)	20 (3)
Other etiologies	396 (43)	316 (44)
Haemophilus influenzae	50 (5)	22 (3)
Klebsiella pneumoniae	3 (0.5)	9 (1)
Escherichia Coli	11 (1.5)	6 (1)
Pseudomonas aeruginosa	34 (4)	17 (2)
Staphylococcus aureus	19 (3)	15 (2)
Respiratory virus	102 (11)	152 (19)
Moraxella catarrhalis	0 (0)	5 (1)
Polymicrobial	148 (16)	91 (12)

473 Percentages calculated on non-missing data.

474

475 **Table 3. Severity scores, site of care and main complications**

Variables	**β-lactam plus a macrolide (n= 932)**	**β-lactam plus a fluoroquinolone or a fluoroquinolone (n= 783)**	***p*-value**
CURB-65 risk classes 3-5, n (%)	174 (20)	157 (22)	0.390
PSI score, median (IQR)	98 (76; 121)	101 (77; 124)	0.245
PSI risk classes IV-V, n (%)	428 (57)	340 (60)	0.365
SOFA score, median (IQR)	2 (2; 3)	2 (1; 3)	0.762
Site of care, n (%)			**<0.001**
General Ward	759 (82)	561 (72)	
ICU	171 (18)	221 (28)	
Length of hospital stay, median (IQR), days	7 (5; 11)	8 (6; 13)	**<0.001**
Severe CAP, n (%)	187 (27)	227 (35)	**0.001**
Non-invasive mechanical ventilation, n (%)	17 (2)	47 (7)	**<0.001**
Invasive mechanical ventilation[a], n (%)	63 (7)	65 (9)	0.176
Septic shock, n (%)	69 (7)	96 (12)	**0.001**
Severe CAP non admitted to ICU			
Mayor criteria, n (%)	3 (9)	4 (11)	0.72
≥3 minor criteria, n (%)	70 (58)	78 (73)	**0.021**
Mayor criteria & ≥3 minor criteria, n (%)	7 (10)	4 (9)	0.91

476 Abbreviations: CURB-65, confusion, blood-urea nitrogen, respiratory rate, blood pressure,
477 age >65; ICU, intensive care unit; PSI, pneumonia severity index; SOFA, Sequential Organ
478 Failure Assessment.

479 Percentages calculated on non-missing data. Boldface entries indicate statistical significance.

480 Severe CAP was considered according to ATS/IDSA criteria[3].

481 [a] Patients who initially received non-invasive ventilation but subsequently needed intubation
482 were included in the invasive mechanical ventilation group.

483

484 **Table 4: Crude 30-day mortality in overall population and subpopulations**

	β-lactam plus a macrolide	**β-lactam plus a fluoroquinolone or a fluoroquinolone alone**	***p*-value**
Overall population	(n= 932)	(n= 783)	
30-day mortality, n (%)	45 (5)	60 (8)	**0.015**
Pneumococcal pneumonia	(n= 415)	(n= 345)	
30-day mortality, n (%)	17 (4)	32 (9)	**0.004**
High inflammatory response (CRP>15 mg/dL)	(n= 398)	(n= 481)	
30-day mortality, n (%)	11 (3)	40 (8)	**<0.001**
Pneumococcal pneumonia and high inflammatory response	(n= 178)	(n= 239)	
30-day mortality, n (%)	3 (2)	25 (10)	**<0.001**
Pneumococcal pneumonia without high inflammatory response	(n= 94)	(n= 78)	
30-day mortality, n (%)	7 (7)	6 (8)	0.95
Patients without Pneumococcal pneumonia and high inflammatory response	(n= 220)	(n= 242)	
30-day mortality, n (%)	8 (4)	15 (6)	0.21
Atypical pathogens and without high inflammatory response	(n= 25)	(n= 14)	
30-day mortality, n (%)	0 (0)	0 (0)	-
Atypical pathogens and high inflammatory response	(n= 55)	(n= 63)	
30-day mortality, n (%)	0 (0)	1 (2)	>0.999
Other pathogens and without high inflammatory response	(n= 97)	(n= 125)	
30-day mortality, n (%)	6 (6)	9 (7)	0.77
Other pathogens and high inflammatory response	(n= 165)	(n= 179)	
30-day mortality, n (%)	8 (5)	14 (8)	0.26

485 Abbreviations: CRP: C-reactive protein.

High inflammatory response was defined as CRP>15 mg/dL**.** Boldface entries indicate statistical significance.

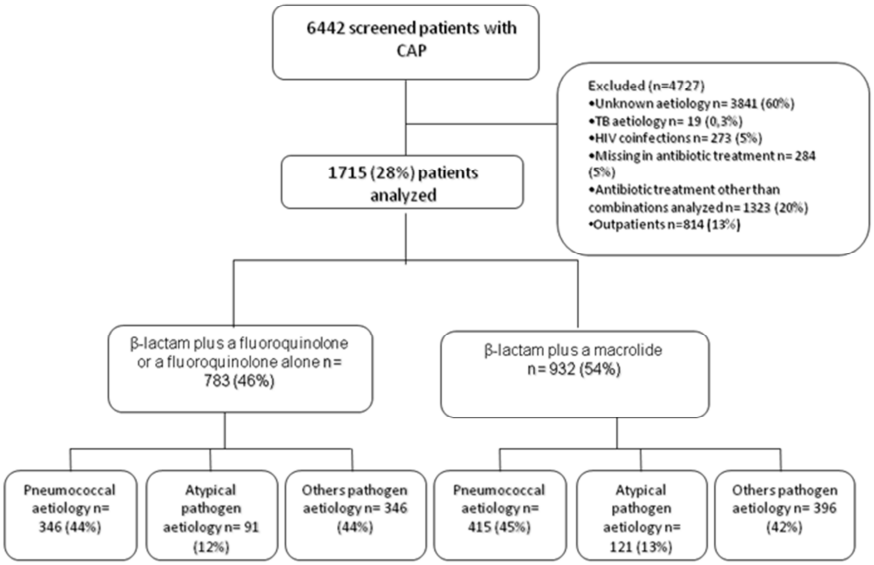
Table 5. Significant Univariate and Multivariable Logistic Regression Analyses for 30-day Mortality. Patients with high inflammatory response.

Variable	Univariate			Multivariable [a, b]		
	OR	CI 95%	p-value	OR	CI 95%	p-value
Interaction Treatment and aetiology			0.062			0.11
β-lactam plus a macrolide and *Streptococcus pneumoniae*	0.27	0.09 to 0.80	**0.019**	0.28	0.09 to 0.92	**0.036**
β-lactam plus a macrolide and Atypical bacterial	0.44	0.04 to 5.53	0.52	0.59	0.04 to 7.83	0.69
β-lactam plus macrolide treatment	0.97	0.46 to 2.03	0.93	1.32	0.58 to 3.00	0.50
Aetiology			0.11			0.27
Streptococcus pneumoniae	1.52	0.77 to 2.98	0.23	1.36	0.64 to 2.88	0.42
Atypical bacterial aetiology	0.36	0.08 to 1.64	0.19	0.41	0.09 to 1.98	0.27
Other aetiology	1	-	-	1	-	-
Admission after 2007 year	1.47	0.90 to 2.42	0.13	1.06	0.45 to 2.48	0.89
ICU admission	6.65	3.93 to 11.23	**<0.001**	1.93	0.89 to 4.20	0.096
Elderly (>65 years old)	2.32	1.29 a 4.18	**0.005**	-	-	-
PSI IV-V	5.96	2.82 to 12.60	**<0.001**	3.97	1.81 to 8.71	**0.001**
ARDS	6.80	3.61 to 12.80	**<0.001**	2.63	1.24 to 5.61	**0.012**
Acute renal failure	5.99	3.46 to 10.35	**<0.001**	-	-	**-**
Septic shock	10.75	6.31 to 18.30	**<0.001**	4.17	2.05 to 8.45	**<0.001**
Adequate antibiotic treatment	0.17	0.07 to 0.42	**<0.001**	0.34	0.12 to 0.95	**0.040**

Abbreviations: CI, confidence interval; OR: odds ratio. [a] Adjusted by propensity score. [b] Hosmer Lemeshow goodness-of-fit test p=0.88

Boldface entries indicate statistical significance.

Figure 1. Flowchart



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e-Appendix 1.

METHODS

Definitions

Pneumonia Severity Index (PSI) [1] score was used to stratify patients based on severity. PSI score stratified according to 30-day mortality risk for community-acquired pneumonia (CAP): risk classes I-III (≤90 points) have low mortality (range, 0%-10%) and risk class IV (91-130 points) and risk class V (>130 points) have the highest mortality (range, 10%-35%).

Severe pneumonia was defined as patients with one of the 2 major severity criteria (invasive mechanical ventilation or septic shock) or the presence of the least 3 minor criteria (respiratory rate ≥30 /min, PO_2/FiO_2 <250, multi-lobar, altered mental status, leukocytes <4,000 x 10^9/L, platelets <100 x 10^9/L, temperature <36.0 °C, systolic blood pressure <90 mmHg and creatinine ≥1.5 mg/dL) according to ATS/IDSA guidelines [2].

The following co-morbidities were registered according to medical records: chronic pulmonary disease (asthma, bronchiectasis, chronic bronchitis, interstitial pulmonary disease, COPD [medical history and spirometry], pulmonary tuberculosis sequelae, pulmonary hypertension, pneumothorax), cardiac and renal failure, chronic hepatic and neurological disease, diabetes mellitus, HIV infection, and previous neoplasia.

Microbiological evaluation and diagnostic criteria

Microbiological examination was performed on sputum, urine, two samples of blood and nasopharyngeal swabs. Pleural puncture, tracheobronchial aspirates and bronchoalveolar lavage (BAL) fluid, when available, were collected. Conventional tests were used to evaluate the presence of bacterial, parasitic and fungal agents, and of respiratory viruses. Sputum, Bronchial aspirate sample (BAS) and BAL specimens were stained using the Gram and Ziehl-Neelsen methods for bacterial and mycobacteria detection, respectively. In BAL samples, the following additional stains were used: May-Grünwald Giemsa for fungal detection and cellular differential count, and Gomori methenamine silver for *Pneumocystis jirovecii*. Sputum and pleural fluid samples were qualitatively cultured for bacterial pathogens, fungi and mycobacteria. Bronchial aspirate sample (BAS) and BAL samples were homogenized and processed for quantitative culture by serial dilutions for bacterial pathogens; undiluted cultures for *Legionella* spp., fungi and mycobacteria were also carried out.

Nasopharyngeal swabs and BAL specimens were processed for antigen detection by immunofluorescence assay and for isolation of viruses in cell culture (influenza virus A, influenza virus B, human parainfluenza viruses 1 to 3, adenovirus and respiratory syncytial

virus). In addition, two independent multiplex-nested RT-PCR assays able to detect from 1 to 10 copies of viral genomes were performed for the diagnostics of respiratory viruses. One RT-PCR assay detected influenza virus types A, B and C, respiratory syncytial viruses A and B, and adenovirus (available since 2009). Another RT-PCR assay available since 2002 studied parainfluenza viruses 1, 2, 3 and 4, coronaviruses 229E and OC43, rhinoviruses and enteroviruses. All positive results were subsequently confirmed by a second independent assay. Sputum and blood samples were obtained for bacterial culture before the start of antibiotic therapy in the emergency department. Nasopharyngeal swab for respiratory virus detection and urine samples for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 hours after hospital admission (both urinary antigen detection available since 1997). Blood samples for serology of atypical pathogens and respiratory virus were taken at admission and within the third and sixth week thereafter.

Criteria for aetiological diagnosis

The aetiology was considered definite if one of the following criteria was met: blood culture positive (in the absence of an apparent extrapulmonary focus); positive bacterial culture of pleural fluid or transthoracic needle aspiration samples; elevated serum levels of IgM against *Chlamydophila pneumoniae* (≥ 1:64), *Coxiella burnetii* (≥ 1:80) and *Mycoplasma pneumoniae* (any positive titre); seroconversion (that is, a fourfold increase in IgG titres) for *C. pneumoniae* and *L. pneumophila* > 1:128, *C. burnetii* > 1:80 and respiratory viruses (influenza viruses A and B, parainfluenza viruses 1 to 3, respiratory syncytial virus and adenovirus); positive urinary antigen for *L. pneumophila* (Binax Now *L. pneumophila* urinary Antigen Test; Trinity Biotech, Bray, Ireland); positive urinary antigen for *S. pneumoniae* (Binax Now *S. pneumoniae* urinary Antigen Test; Emergo Europe, The Hague, The Netherlands); bacterial growth in cultures of tracheobronchial aspirates (≥ 10^5 cfu/ml), in a protected specimen brush (≥ 10^3 cfu/ml) and in BAL (≥ 10^4cfu/ml); and detection of antigens by immunofluorescence assay plus virus isolation or detection by RT-PCR testing for respiratory virus (influenza viruses A and B, parainfluenza viruses 1 to 3, respiratory syncytial virus, rhinovirus and adenovirus). The aetiology of pneumonia was classified as presumptive when a predominant microorganism was isolated from a purulent sample (leukocytes > 25 per high-power microscopic field and few epithelial cells < 10 per high-power microscopic field) and the findings of Gram staining were compatible. For the purpose of the present study, presumptive and definitive diagnostics were analyzed together.

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Empiric antibiotic treatment.

Initial empiric antibiotic therapy was administered according to the attending physician's discretion. The local policy and practice were based mainly on a local adaptation of the ATS/IDSA guidelines [2,3]. The antibiotics dose were based on recommendation of guidelines and manufacturers, and adjusted when were necessary. The usual dose for main antibiotics treatments used were: Ceftriaxone 1 gr. BID, Amoxiciline – clavulanate 1.2 gr TID, azithromycin 500 mg QD, erythromycin 500 mg QID, clarithromycin 500 mg BID, levofloxacin 500 mg BID, moxifloxacin 400 mg QD, ciprofloxacin 400 mg BID.

Statistical analysis

Propensity Score

The following variables were used to calculate propensity scores: year of admission, age, gender, tobacco use, alcohol consumption, influenza and pneumococcal vaccination, systemic and inhaled corticosteroids, prior antibiotic treatment, chronic pulmonary disease, heart failure, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, PSI risk class (IV-V), and ICU admission.

Univariate analysis

The following variables were tested in univariate analysis for 30 day mortality: age (<65 vs. ≥65 years), gender, chronic pulmonary disease, heart failure, chronic renal disease, chronic liver disease, diabetes mellitus, neurological disease, PSI risk class (IV-V), pleural effusion, ARDS, acute renal failure, septic shock and adequacy treatment.

Multivariate analysis

Logistic regression analyses [4] were used to examine the associations between 30-day mortality and risk factors. In the first step, each risk factor was tested individually. In the second step, all risk factors that showed an association in the univariate model ($p<0.10$) were added into the multivariable model. Finally, a backward stepwise selection ($pin<0.05$, $pout>0.10$) was used to determine factors associated with 30-day mortality. If two independent variables were highly correlated ($r > |\pm 0.30|$), the variable with the largest variance was excluded from the multivariable analyses [5]. The odds ratio (OR) and 95% confidence interval (CI) were calculated. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the models. The area under the receiver operating characteristic (ROC) curve of the multivariable models used to analyze 30-day mortality was calculated. To evaluate possible overfitting and instability of selection variables in our final model, we performed an internal validation using ordinary nonparametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% CIs [6].

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ADDITIONAL RESULTS

Multivariable analysis adjusted by propensity score for 30-day mortality in patients with Severe CAP

For the population with SCAP, the following mortality risk factors were found: neurological disease, ARDS, acute renal failure and septic shock. Appropriate treatment was the only protective factor for mortality (eTable 4). The area under the ROC curve was 0.74 (95% CI: 0.67 to 0.80) (eFigure , panel D) for the model of 30-day mortality.

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e-Table 1: Significant univariate and multivariate logistic regression analyses for the prediction of 30-day mortality. Overall population

Variable	Univariate			Multivariate [a,b]		
	OR	CI 95%	p-value	OR	CI 95%	p-value
β-lactam plus a macrolide treatment	0.61	0.41 to 0.91	0.016	0.81	0.52 to 1.26	0.35
Aetiology			0.034			0.14
Streptococcus pneumoniae	0.91	0.61 to 1.37	0.66	0.84	0.54 to 1.32	0.44
Atypical bacterial aetiolgy	0.26	0.09 to 0.71	0.009	0.35	0.12 to 1.00	0.050
Other aetiology	1	-	-	1	-	-
Admission after 2007 year.	1.36	0.92 to 2.02	0.13	1.36	0.70 to 2.64	0.36
ICU admission	5.13	3.42 to 7.70	<0.001	2.19	1.20 to 4.01	0.011
Elderly (>65 years old)	2.78	1.67 to 4.61	<0.001	-	-	-
Chronic renal failure	2.32	1.28 to 4.22	0.006	2.09	1.07 to 4.08	0.030
Liver disease	1.83	0.95 to 3.52	0.073	-	-	-
Neurologic disease	2.00	1.23 to 3.25	0.005	1.95	1.13 to 3.36	0.017
PSI IV-V	4.58	2.67 to 7.87	<0.001	2.69	1.51 to 4.81	0.001
ARDS	5.05	2.97 to 8.58	<0.001	2.19	1.17 to 4.10	0.014
Acute renal failure	5.37	3.53 to 8.17	<0.001	-	-	-
Septic shock	8.39	5.45 to 12.89	<0.001	3.78	2.14 to 6.69	<0.001
Adequate antibiotic treatment	0.19	0.10 to 0.35	<0.001	0.30	0.15 to 0.63	0.001

Abbreviations: CI, confidence interval; OR: odds ratio. [a] adjusted by propensity score. [b] Hosmer - Lemeshow goodness-of-fit test p=0.50

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e-Table 2: Significant univariate and multivariate logistic regression analyses for the prediction of 30-day mortality. Patients with pneumococcal pneumonia

Variable	Univariate			Multivariate [a, b]		
	OR	CI 95%	p-value	OR	CI 95%	p-value
β-lactam plus a macrolide treatment	0.42	0.23 to 0.77	0.005	0.65	0.33 to 1.31	0.23
Admission after 2007 year	1.54	0.86 to 2.77	0.15	2.20	0.81 to 5.99	0.13
ICU admission	5.23	2.87 to 9.54	<0.001	3.08	1.40 to 6.75	0.005
Elderly (>65 years old)	5.64	2.21 to 14.39	<0.001	-	-	-
Chronic renal failure	3.04	1.34 to 6.88	0.008	-	-	-
Liver disease	2.41	1.03 to 5.67	0.043	-	-	-
PSI IV-V	6.75	2.64 to 17.22	<0.001	3.18	1.14 to 8.7	0.027
ARDS	6.78	3.31 to 13.89	<0.001	2.41	1.05 to 5.53	0.038
Acute renal failure	7.93	3.98 to 15.81	<0.001	4.25	1.99 to 9.09	<0.001
Septic shock	6.98	3.74 to 13.04	<0.001	-	-	-
Adequate antibiotic treatment	0.10	0.03 to 0.35	<0.001	0.20	0.04 to 0.98	0.047

Abbreviations: CI, confidence interval; OR: odds ratio. [a] adjusted by propensity score. [b] Hosmer y Lemeshow goodness-of-fit test p=0.55

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e-Table 3: Internal validation of the multivariate logistic regression model using Bootstrap method. Model for patients with high inflammatory response

Variable	Original	Bias	Standard Error	*P* value	95% Confidence Interval	
					Lower	Upper
PS	-,794	-,075	1,698	,621	-4,134	2,186
β-lactam plus a macrolide and *Streptococcus pneumoniae*	-1,271	-,102	,676	,036	-2,493	-,239
β-lactam plus a macrolide and Atypical bacterial	-,533	-3,681	10,202	,330	-18,216	17,707
β-lactam plus a macrolide treatment	,280	,017	,450	,494	-,726	1,323
Streptococcus pneumoniae	,308	,032	,425	,466	-,544	1,223
Atypical bacterial aetiolgy	-,883	-2,372	6,020	,163	-18,504	,178
Admission after 2007 year	,059	,009	,472	,893	-,834	1,010
ICU admission	,660	-,036	,392	,076	-,087	1,309
PSI IV-V	1,378	,114	,687	,001	,613	3,227
ARDS	,967	,018	,444	,022	-,014	1,927
Septic shock	1,427	,071	,390	,001	,676	2,453
Adequate antibiotic treatment	-1,091	-,012	,567	,041	-2,115	-,029
Constant	-3,044	-,148	1,400	,009	-5,825	-,990

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e-Table 4: Significant univariate and multivariate logistic regression analyses for the prediction of 30-day mortality. Patients with severe CAP

Variable	Univariate			Multivariate [a, b]		
	OR	CI 95%	p-value	OR	CI 95%	p-value
β-lactam plus a macrolide treatment	0.85	0.50 to 1.44	0.54	1.04	0.57 to 1.91	0.90
Aetiology			0.33			0.47
Streptococcus pneumoniae	0.92	0.54 to 1.58	0.77	0.85	0.47 to 1.54	0.59
Atypical bacterial aetiolgy	0.39	0.11 to 1.34	0.13	0.45	0.12 to 1.65	0.23
Other aetiology	1	-	-	1	-	-
Admission after 2007 year.	0.97	0.57 to 1.66	0.92	1.03	0.44 to 2.40	0.95
ICU admission	1.86	1.05 to 3.29	0.034	1.19	0.58 to 2.54	0.65
Neurologic disease	2.12	1.13 to 3.97	0.019	2.96	1.45 to 6.04	0.003
Acute renal failure	2.51	1.38 to 4.58	0.003	2.68	1.40 to 5.14	0.003
Septic shock	2.79	1.63 to 4.75	<0.001	2.95	1.56 to 5.58	0.001
Adequate antibiotic treatment	0.25	0.11 to 0.56	0.001	0.28	0.11 to 0.70	0.006

Abbreviations: CI, confidence interval; OR: odds ratio. [a] adjusted by propensity score. [b] Hosmer y Lemeshow goodness-of-fit test p=0.17

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e-Table 5. Crude 30-Day Mortality in Overall and Subpopulations in Patients with Septic Shock

	Overall population	β-lactam plus a fluoroquinolone or a fluoroquinolone alone	β-lactam plus a macrolide	*p*-value
Patients with septic shock	(n= 165)	(n= 96)	(n= 69)	
30-day mortality, n (%)	43 (26)	21 (22)	22 (32)	0.15
Pneumococcal pneumonia	(n= 84)	(n= 51)	(n= 33)	
30-day mortality, n (%)	20 (24)	12 (24)	8 (24)	0.94
High inflammatory response (CRP>15 mg/dL)	(n= 87)	(n= 62)	(n= 25)	
30-day mortality, n (%)	19 (22)	16 (26)	3 (12)	0.16
Pneumococcal pneumonia and high inflammatory response (CRP>15 mg/dL)	(n= 48)	(n= 34)	(n= 14)	
30-day mortality, n (%)	10 (21)	9 (26)	1 (7)	0.24
Pneumococcal pneumonia and low inflammatory response (CRP<15 mg/dL)	(n= 23)	(n= 14)	(n= 9)	
30-day mortality, n (%)	4 (17)	2 (14)	2 (22)	>0.999
Non-pneumococcal pneumonia and high inflammatory response (CRP>15 mg/dL)	(n= 39)	(n= 28)	(n= 11)	
30-day mortality, n (%)	9 (23)	7 (25)	2 (18)	>0.999
Atypical pathogens and low inflammatory response (CRP<15 mg/dL)	(n= 1)	(n= 1)	(n= 0)	
30-day mortality, n (%)	0 (0)	0 (0)	0 (0)	-
Atypical pathogens and high inflammatory response (CRP>15 mg/dL)	(n= 11)	(n= 9)	(n= 2)	
30-day mortality, n (%)	1 (9)	1 (11)	0 (0)	>0.999
Other pathogens and low inflammatory response (CRP<15 mg/dL)	(n= 13)	(n= 9)	(n= 4)	
30-day mortality, n (%)	1 (8)	0 (0)	1 (25)	0.31
Other pathogens and high inflammatory response (CRP>15 mg/dL)	(n= 28)	(n= 19)	(n= 9)	
30-day mortality, n (%)	8 (29)	6 (32)	2 (22)	>0.999

Abbreviations: CRP: C-reactive protein

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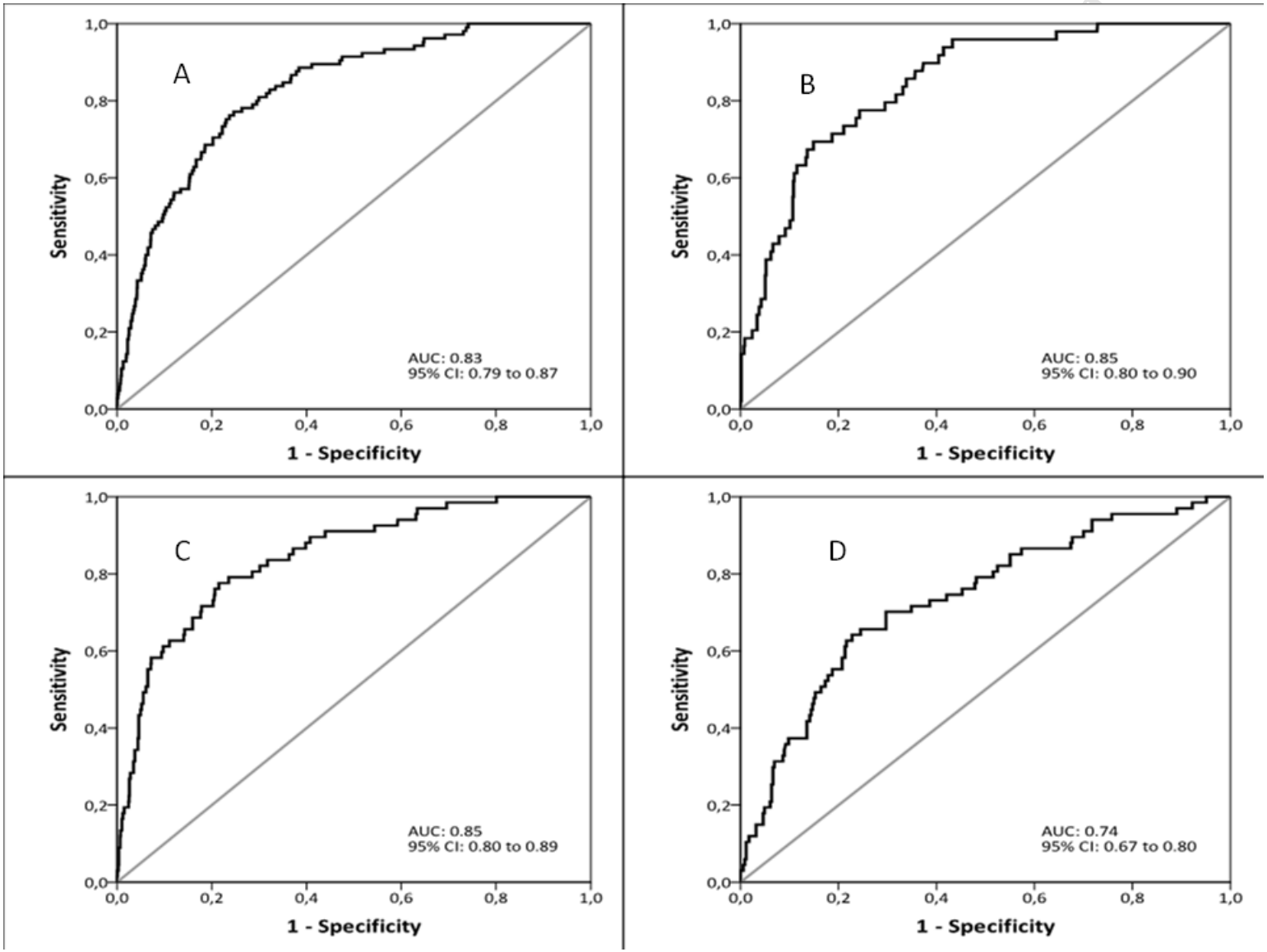
e-Figure 1: Receiver operating characteristic curve for multivariable logistic regression model to predict 30-day mortality.
Panel A: Overall population, B: Pneumococcal pneumonia, C: Patients with high inflammatory response, D: Severe CAP



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