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RESEARCH ARTICLE

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Prepandemic viral community-acquired pneumonia: Diagnostic sensitivity and specificity of nasopharyngeal swabs and performance of clinical severity scores

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Abstract

The objectives of this work were to assess the diagnostic sensitivity and specificity of nasopharyngeal (NP) swabs for viral community-acquired pneumonia (CAP) and the performance of pneumonia severity index (PSI) and CURB-65 severity scores in the viral CAP in adults. A prospective observational cohort study of consecutive 341 hospitalized adults with CAP was performed between January 2018 and March 2020. Demographics, comorbidities, symptoms/signs, analytical data, severity scores, antimicrobials, and outcomes were recorded. Blood, NP swabs, sputum, and urine samples were collected at admission and assayed by multiplex real time-PCR, bacterial cultures, and *Streptococcus pneumoniae* and *Legionella pneumophila* antigens detection, to determine the etiologies and quantify the viral load. The etiology was identified in 174 (51.0%) patients, and in 85 (24.9%) it was viral, the most frequent rhinovirus and influenza virus. The sensitivity of viral detection in sputum (50.7%) was higher than in NP swabs (20.9%). Compared with sputum, the positive predictive value and specificity of NP swabs for viral diagnosis were 95.8% and 96.9%, respectively. Performance of PSI and CURB-65 scores in all CAP with etiologic diagnosis were as expected, with mortality associated with higher values, but they were not associated with mortality in patients with viral pneumonia. NP swabs have lower sensitivity but high specificity for the diagnosis of viral CAP in adults compared with sputum, reinforcing the use NP swabs for the diagnostic etiology work-up. The PSI and CURB-65 scores did not predict mortality in the viral CAP, suggesting that they need to be updated scores based on the identification of the etiological agent.

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KEYWORDS
clinical severity scores, endemic infection, infection, nasopharyngeal swabs sensitivity and specificity, respiratory tract, viral community-acquired pneumonia

1 | INTRODUCTION

The last Global Burden of Disease Study (GBD, WHO, 2019) placed lower respiratory tract infections (LRTI), including community-acquired pneumonia (CAP) and bronchiolitis, as the primary infective cause of death globally, accounting for 6.1% of deaths, and affecting 489 million people globally, especially children and elderly.[1,2] Approximately, 50% of CAP remain without etiologic diagnosis despite an intensive diagnostic work-up.[3] Bacteria, mainly represented by *Streptococcus pneumoniae*, have been identified as the primary cause of CAP, however, the improvement and introduction in the clinical practice of molecular tools based on the real-time PCR for the detection of the respiratory virus has broadened the etiologic diagnosis. Thus, rhinovirus (RV), influenza (IV) and parainfluenza viruses (PIV), respiratory syncytial virus (RSV), metapneumovirus (MPV), adenovirus (AdV), and endemic coronavirus, have increasingly been recognized as causative agents of LRTI and hospitalization.[4–7]

Although widely used in the clinical practice, the specificity of viruses detected in the upper respiratory airways for the etiologic diagnosis of CAP remains a challenge, mostly because about 7.1% healthy people are asymptomatic carriers.[8–10] In addition, diagnostic samples with high specificity from lower respiratory tract (LRT) are difficult to obtain or need invasive procedures.[9]

The pneumonia severity index (PSI) and the CURB-65 scores are the most common indexes used to help clinicians to predict the outcomes of patients with CAP at the first hospital evaluation and to guide the clinical decisions.[11] The PSI is a score based on 20 prognostic variables independently associated with mortality.[12] These variables include demographics, chronic underlying diseases, symptoms, signs, and laboratory findings, to stratify patients into five classes depending on their mortality risk. The CURB-65 score,[13] developed by the British Thoracic Society, includes five criteria (confusion, urea, respiratory rate, blood pressure, and age ≥65 years) to stratify patients in three mortality risk groups. Since these scores were originally developed for the general adult population with CAP, independently of the etiology, there is currently no evidence that they are appropriate when considering the specific CAP etiologies, despite the prognosis of CAP is well-known to be influenced by the causative agent. Thus, the severity and mortality of the viral CAP have not been validated for these two indexes. Some authors' claim that patients with a negative identification of viral pathogens had lower PSI scores than patients with viral or mixed pneumonia, while others did not find differences in the PSI or the CURB-65 scores among the different etiologic groups.[14–16]

The main objective of our study was to evaluate the sensitivity and specificity of nasopharyngeal (NP) swabs for the diagnosis of viral CAP, other than SARS-CoV-2, compared with sputum samples and to assess the performance of PSI and CURB-65 severity scores to predict the clinical outcome in the CAP of viral etiology.

2 | PATIENTS AND METHODS

2.1 | Study population and clinical diagnosis criteria

We conducted a prospective observational cohort study at the Virgen del Rocío University Hospital of consecutive cases of CAP, identified through daily review of hospital admitted adult patients (≥18 years old), in the general wards and in the intensive care units (ICUs), except during the weekends from Friday 14:00 h to Sunday 14:00 h. Patients were enrolled over a 27-month period, between January 2018 and March 2020, when the COVID-19 pandemic begun in the hospital area; patients diagnosed of COVID-19 were excluded. CAP was defined by respiratory symptoms (cough, expectoration, and/or dyspnea), axillary temperature over 37.5°C, and new X-ray infiltrate, according to the Guidelines for Diagnosis and Treatment of Infectious Diseases, Institutional Programme for the Optimization of Antimicrobial Treatment (PRIOAM), Virgen del Rocío University Hospital, Seville, Spain (https://www.guiaprioam.com/). Exclusion criteria were: (i) patients with chronic pulmonary diseases that may condition the etiology, such as bronchiectasis, cystic fibrosis or lung cancer; and (ii) patients with criteria of aspiration pneumonia.[17] The study protocol was approved by the Ethics Committee of Virgen Macarena and Virgen del Rocío University Hospitals (C.I. 1549-N-17) and complied the Declaration of Helsinki. An informed consent was established as a mandatory requirement before the enrollment of patients. The design and analysis of this cohort followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (Supporting Information Material).

2.2 | Data collection

Before study initiation, the physicians of the multidisciplinary team (Infectious Diseases, Microbiology, Respiratory Diseases, Internal Medicine, Emergency, and ICU) were properly informed of the study protocol. Staff members from each service interviewed patients (or their caregivers) at admission and collected demographics, comorbidities, symptoms, signs, hematologic and biochemistry analytical data, microbiology data, including sputum samples, blood cultures, and urinary antigen detection of *L. pneumophila* serogroup 1 or *S. pneumoniae*, complications, and outcomes using a standardized case report form. Pneumonia severity was assessed by PSI and

CURB-65 at admission.[12,13] The empirical antimicrobial therapy for the CAP was recorded. The treatment followed the "Guidelines for Diagnosis and Treatment of Infectious Diseases, Institutional Programme for the Optimisation of Antimicrobial Treatment" (PRIOAM), Virgen del Rocío University Hospital, Seville, Spain (https://www.guiaprioam.com/), which recommend to initiate empirical antimicrobial treatment within 4 h of hospital admission and preferably before leaving the Emergency Services and, if presenting with sepsis/septic shock, to initiate antimicrobial treatment within 1 h. In patients with an etiological diagnosis, the empirical antimicrobial therapy was considered appropriate if it included an in vitro active drug for the identified bacterial etiologies, or oseltamivir in the influenza cases; for the rest of the virus there is no appropriate therapy available. Patients were followed up to 30 days, until discharge, or death, whichever occurred first. All data were validated by the study coordinators.

2.3 | Specimen collection and testing

In the first 24 h after hospital admission, NP swabs were obtained from patients using nylon flocked swabs (FLOQSwabs; COPAN) with viral stored medium. Blood samples were collected in ethylenediaminetetraacetic acid tubes (4 ml) and representative sputum samples were obtained by spontaneous expectoration in plastic bottles and processed according to the dunk and swirl method previously reported.[18] All samples were coded, recorded in a database, and processed before being properly stored at −80°C.

2.4 | Bacterial identification

Bacterial or atypical respiratory pathogens were identified by the Clinical Microbiology laboratory according to their standard protocols. Samples were considered positive if one of the following criteria was met: (1) positive bacterial culture from blood, representative and purulent sputum (<10 epithelial cells and >25 neutrophils per field, at ×10 magnification, respectively)[19] (≥10^6 cfu/ml), bronchial aspirate (≥10^6 cfu/ml), bronchoalveolar lavage (BAL) (≥10^3 cfu/ml), or pleural fluid; (2) urinary antigen detection of *L. pneumophila* serogroup 1 or *S. pneumoniae* (Binax Inc.); and (3) detection of *M. pneumoniae*, *C. pneumoniae*, *S. pneumoniae*, *or H. influenzae* in blood, NP swabs, and representative sputum by RT-PCR (Allplex Respiratory Panel Assay 4, Seegene).

2.5 | Viral identification and viral loads (VL) quantification

A viral etiology was identified by detection of respiratory virus in blood, representative sputum (<10 epithelial cells per field, at ×10 magnification), or NP swabs by multiplex real-time PCR panel (Allplex Respiratory Panel Assays 1, 2, and 3; Seegene Inc.), which included IV A (H1, H1pdm09, H3), IV B, RSV A and B, AdV, enterovirus, MPV, coronavirus OC43, NL63 and 229E, RV and PIV 1, 2, 3 and 4. VL for AdV, coronaviruses OC43/NL63/229E, IV A/B, enterovirus (EV), RV, and RSV B in blood were calculated using standard curves generated with the PCR standards Amplirun® DNA/RNA (Vircell).

2.6 | Definitions

Bacterial pneumonia: If in absence of viral identification, a bacterium causing CAP was isolated in one of the following samples: blood, representative and purulent sputum (<10 epithelial cells and >25 neutrophils per field, at ×10 magnification; ≥10^6 cfu/ml), bronchial aspirate (≥10^6 cfu/ml), BAL (≥10^3 cfu/ml), and pleural fluid, or if *S. pneumoniae* or *L. pneumophila* antigenuria was detected. **Viral pneumonia**: When only viruses were identified by RT-PCR in one of the following samples: NP swab, blood, representative sputum (<10 epithelial cells, at ×10 magnification), bronchial aspirate, BAL, and pleural fluid. **Mixed bacterial-viral pneumonia**: When a bacterium plus a virus were isolated or identified following the previous detailed criteria.

2.7 | Statistical analyses

Data of continuous variables are expressed as medians (interquartile ranges [IQR]) and categorical variables as frequencies (percentages). Comparison of VLs between respiratory samples was assessed by Mann–Whitney *U* test. The small number of missing data (Table S3) and the fact that they were missing completely at random, has enabled the implementation of a so-called complete-case analysis, without affecting the validity of the results.

CAP patients were classified into four groups depending of the etiology: bacterial, viral, mixed bacterial and viral, and nondefined etiologies. To compare multiple groups, analysis of variance or Kruskal–Wallis tests were run, and Bonferroni or HSD Tukey post hoc analyses were developed when a significance between groups was found. Categorical variables were compared using χ^2 test or Fisher exact test. To estimate the significance of categorical variables for etiological groups a post hoc analyses for odds ratio and 95% confidence intervals were developed when a significance between groups was found. Additionally, a univariate Cox regression analysis was used to identify variables associated with 30-day all-cause mortality; next, significant variables, in which interaction, confusion, and collinearity were thoroughly explored, were introduced in a multivariate Cox regression analysis. Analysis of survival curves by the Kaplan–Meier method, and its significance using the log-rank test was performed, to compare the different etiological groups in each PSI and CURB-65 score values. All data were analyzed using the IBM SPSS Statistics version 22.0 (IBM Corp.) package and two-sided $p < 0.05$ was considered statistically significant.

To evaluate the sensitivity and specificity of the NP swabs for the viral etiology identification, we compared the NP swabs and the

representative sputum results in those patients with both samples available. Taking the sputum sample as reference, NP swabs results were considered true positive (TP) and true negative (TN) when their results agreed with those obtained with the sputum. When the results from NP swabs and representative sputum were the same these were considered concordant results. On the other hand, discordant results were indicated when the results were different between both samples. The positive (PPV) and the negative (NPV) predictive values of NP swabs were calculated as follows: PPV = TP/(TP + FP) and NPV = TN/(FN + TN), where FP is false positive, and FN is false negative.

3 | RESULTS

3.1 | Demographics, clinical characteristics, etiologies, and outcomes

A total of 341 hospitalized adult patients with CAP were included in the study whose demographics and clinical characteristics are detailed in Table 1. Data regarding CAP cases classified by etiological identification are in the Supporting Information Material (Table S1). An etiological diagnosis was achieved in 174 (51.0%) patients. Bacterial, viral, and mixed bacterial/viral etiologies were confirmed in 89 (26.1%), 36 (10.6%), and 49 (14.4%) patients, respectively (Figure 1A). The most frequent bacterial etiologies were *S. pneumoniae* in 105 (30.8%) and *H. influenzae* in 30 (8.8%) patients (Figure 1B). Eleven (10.4%) of *S. pneumoniae* and 1 (3.2%) of *H. influenzae* cases had secondary bloodstream infection (BSI).

As for the viral etiologies, the most frequents were RV in 34 (9.9%) and IV in 20 (5.9%) patients (Figure 1B). Blood samples at admission were available in 322 (94.4%) patients and only five patients had positive identification of viral nucleic acids (DNAemia or RNAemia), two patients by IV B, and three each by RV, AdV, and coronavirus 229E (Figure 2A). NP swabs were available in 340 patients, and up to 8 different viruses were identified by multiplex RT-PCR in 71 (20.9%) patients, being the most frequent RV in 32 (9.4%) patients, IV A/B in 16 (4.71%) patients, RSV A/B in 7 (2.06%) patients, and endemic coronavirus (NL63/OC43) in 7 (2.06%) patients (Figure 2B). As for the sputum, representative samples were available in 67 (19.6%) patients, with viral identification

TABLE 1 Demographics, chronic underlying diseases, clinical and analytical characteristics, and therapy of all 341 patients with CAP

Variables	Median [IQR]/N (%)
Demographics	
Age, years	71 [57–81]
Age group >75 years old	141 (41.3%)
Male sex	187 (54.8%)
Underlying conditions	
Smoking (last 5 years)	97 (28.4%)
Excessive alcohol consumption	50 (14.7%)
Chronic underlying diseases	
Charlson comorbidity index ≥3	246 (72.1%)
Diabetes	101 (29.7%)
Chronic pulmonary disease	92 (27.0%)
Chronic cardiovascular disease	99 (29.0%)
Cerebrovascular disease	33 (9.7%)
Chronic kidney disease	35 (10.3%)
Chronic liver disease	18 (5.3%)
Connective tissue disease	2 (0.6%)
Neoplasia	34 (10.0%)
Solid organ transplantation	15 (4.4%)
Previous treatments	
Statins	68 (19.9%)
Corticosteroids	42 (12.3%)
Antibiotics	108 (31.7%)
Symptoms at admission	
Odynophagia	5 (1.5%)
Cough	244 (71.6%)
Arthro-myalgia	34 (10.0%)
Dyspnea	196 (57.5%)
Diarrhea	25 (7.3%)
Vomiting	20 (5.9%)
Headache	6 (1.8%)
Pleuritic chest pain	83 (24.3%)
Disturbance of consciousness	33 (9.7%)
Signs at admission	
Temperature, °C	37.5 [36.3–38.5]
Temperature ≥37.5°C	150 (44.0%)
$SatO_2$	95 [92–97]
SatO2 < 95%	165 (48.4%)
SBP < 90 mmHg	28 (8.2%)
DBP < 60 mmHg	65 (19.1%)
HR ≥ 100 bpm	72 (21.1%)
Shock at admission	14 (4.1%)
Laboratory data at admission	
Leucocytes ($\times 10^9$/L)	12.9 [9.0–19.0]
Leucocytes <4.0 × 109/L	17 (5.0%)

TABLE 1 (Continued)

Variables	Median [IQR]/N (%)
Neutrophils (×10^9/L)	10.8 [7.1–15.7]
Neutrophils >7.5 × 109/L	240 (70.4%)
Lymphocytes (×10^9/L)	1.1 [0.7–1.6]
Lymphocytes <1.0 × 109/L	148 (43.4%)
Platelets (×10^9/L)	236 [176–321]
Platelets <130 × 109/L	34 (10.0%)
Sodium (mEq/L)	138 [135–141]
Sodium <135 mEq/L	84 (24.6%)
Potassium (mEq/L)	4.2 [3.8–4.7]
Potassium >5 mEq/L	51 (15.0%)
Creatinine (mg/dl)	1.01 [0.77–1.50]
Creatinine >1.3 mg/dl	105 (30.8%)
CRP (mg/L)	155.8 [71.7–277.5]
CRP ≥ 100 mg/L	187 (54.8%)
Glucose (mg/dl)	124 [97–167]
Urea (mg/dl)	48 [32–75]
Severity scores	
CURB-65	2 [1, 2]
PSI	92 [70–117]
CAP therapy	
Empirical antiviral therapy	58 (17.0%)
Empirical antibiotic therapy	322 (94.4%)
Appropriated antimicrobial therapy[a]	117 (67.2%)
Bacterial etiologies[b]	110 (79.7%)
Viral etiologies[c]	7 (46.7%)
Outcome	
IMV	8 (2.3%)
ARDS	3 (0.9%)
ICU admission	20 (5.9%)
Length of stay (days)	5 [3–8]
Unfavorable outcome[d]	34 (10.0%)
Mortality	21 (6.2%)

Note: Represented data are *N* (%) or median [IQR]. Excessive alcohol consumption is defined as more than three drink units/day.

Abbreviations: ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; CRP: C-reactive protein; DBP, diastolic blood pressure; HR, heart rate; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; PSI, pneumonia severity index; SBP, systolic blood pressure.

[a]In the 174 patients with etiological diagnosis.

[b]In the 138 patients with bacterial etiology.

[c]In the 15 patients with influenza virus etiology.

[d]Defined by ICU admission and/or mortality.

in 34 (50.7%), which showed a similar viral diversity (Figure 2C) as the NP swabs, being the most frequents RV and IV A/B.

While bacteria/bacteria co-infections occurred in 22 (6.4%) cases, only 2 (0.6%) patients had virus/virus co-infections. *S. pneumoniae* and *H. influenzae* were the most common agents in bacterial co-infections while in both cases of viral co-infections RV was identified together with an endemic coronavirus (229E or NL63).

As for the empirical antimicrobial therapy at hospital admission, 58 (17.0%) patients received oseltamivir and 323 (94.7%) received antibiotics (ceftriaxone/cefotaxime alone [41.6%], levofloxacin/moxifloxacin alone [10.0%], 3rd generation cephalosporin plus fluoroquinolone [16.1%], and amoxicillin-clavulanic acid [9.4%]). In 117 (67.2%) out of 174 patients with final etiological diagnosis, the empirical antimicrobial therapy was appropriated (Table 1).

The variables associated with 30-day all-cause mortality in the univariate analysis are detailed in the Table S4. The multivariate Cox regression analyses identified as independently associated with mortality the Charlson Comorbidity Index ≥3, systolic blood pressure <90 mmHg, and the acute respiratory distress syndrome (Table S5).

3.2 | VLs in NP swabs, sputum, and blood

VL was variable depending on the etiological agent identified and the sample used for quantification (Table S2). In NP swabs, the lower median VL was found for RSV (4.40 $\log_{10}$ copies/ml), while for AdV, CoV-OC43, and IV A/B the medians were between 4.89 and 5.25 $\log_{10}$ copies/ml. RV infections presented the highest NP VL, with a median of 7.05 $\log_{10}$ copies/ml. RV and IV A/B virus showed similar VL in sputum samples and NP swabs while the VL in sputum for AdV, CoV-OC43, and RSV was between 1 and 2 $\log_{10}$ copies/ml higher than in NP swabs. CoV-NL63 showed the higher VL in sputum (7.31 $\log_{10}$ copies/ml). Influenza B virus showed the highest values of VL in blood with 6.97 $\log_{10}$ copies/ml (IQR: 6.81–7.12). The VL in blood of AdV, CoV-229E, and RV were among 4.49 and 4.92 $\log_{10}$ copies/ml. Table S2). The VL in blood was not related to higher VL in NP swabs or sputum. Only two patients with DNAemia by AdV and RNAemia by IV B, had underlying chronic diseases, and there were not associated with unfavorable outcome in any case.

3.3 | Etiology and clinical outcome

Two different approaches were used to analyze the clinical outcomes according to etiological groups; First, patients were grouped based on the existence of a definite etiological identification ($N = 174$), independently of the specific etiologies, and compared with patients without an etiological identification ($N = 167$) (Table 2). The need of invasive mechanical ventilation (IMV) and ICU admission were higher for patients with a definite etiology, which had also higher frequency of unfavorable outcome, defined as ICU admission and/or mortality (14.45% vs. 5.5%, $p = 0.008$), although there was not

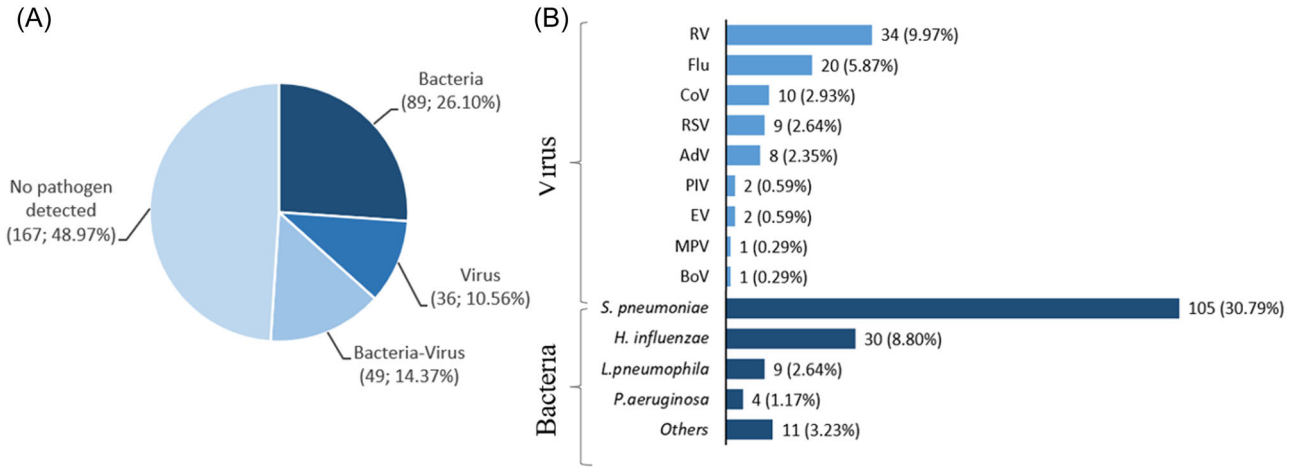

FIGURE 1 Frequency of etiologies in all 341 patients with community-acquired pneumonia. *S. pneumoniae*: *Streptococcus pneumoniae*; *H. influenzae*: *Haemophilus influenzae*; *L. pneumophila*: *Legionella pneumophila*; *P. aeruginosa*: *Pseudomonas aeruginosa*. *Others: Fusobacterium necrophorum*, *F. nucleatum*, *Klebsiella pneumoniae*, *M. avium*, *Prevotella sp.*, *P. intermedia*, *Staphylococcus aureus*, *Stenotrophomonas sp.*, *Streptococcus pyogenes*, *Parvimonas micra*. (A) Etiological agents identified in blood, NP swabs, and sputum samples. (B) Diversity detected of bacterial and viral agents in the same collected samples. AdV, Adenovirus; BoV, Bocavirus; CoV, Coronavirus; EV, Enterovirus; Flu, Influenza virus; MPV, Metapneumovirus; PIV, Parainfluenza virus; RSV, respiratory syncytial virus; RV, Rhinovirus

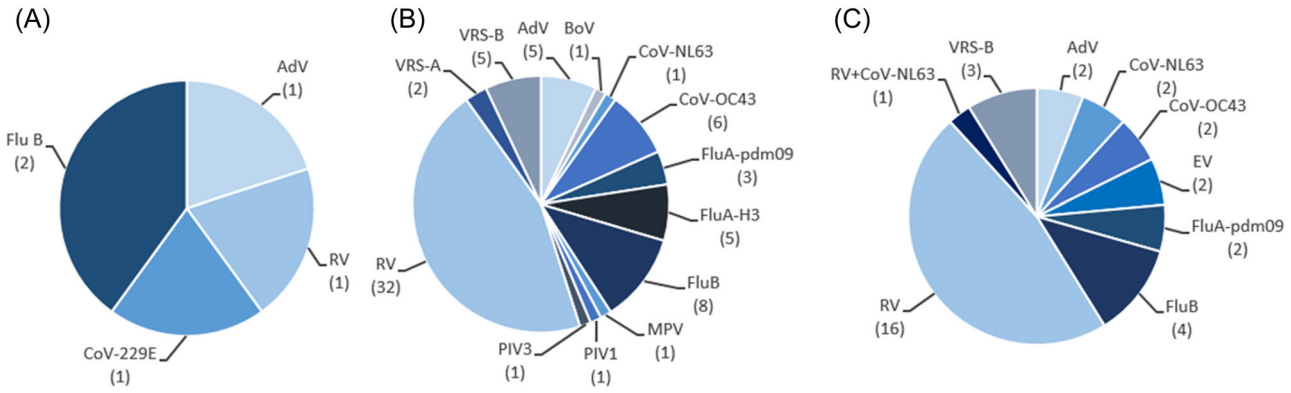

FIGURE 2 Viral diversity identified in the different samples: (A) blood ($N = 322$, positive 5), (N) NP swabs ($N = 340$, positive 71), and (C) sputum ($N = 67$, positive 34). AdV, Adenovirus; BoV, Bocavirus; CoV, Coronavirus; EV, Enterovirus; Flu, Influenza virus; MPV, Metapneumovirus; PIV, Parainfluenza virus; RSV, respiratory syncytial virus; RV, Rhinovirus

difference in the 30-day mortality between both groups (Table 2). In a second step, the 174 patients with a definite etiological identification were grouped into three different etiological groups: bacterial, viral, and mixed (bacterial and viral). When clinical outcomes were compared among these three etiological groups there were not differences (Table 3).

3.4 | Sensitivity, specificity, and predictive values of NP swabs for the viral etiology diagnosis

Viral detection in NP swabs was compared with that from representative sputum samples. In our cohort, the same viruses were detected in patients with positive NP swabs and sputum. Only one patient had a dual virus etiology detected in sputum (RV plus CoV-NL63) meanwhile in the NP swab only RV was identified (Table 4). NP swabs were positive for viral detection in 23 out of 34 patients with virus identification in sputum, i.e., sensitivity of 67.6%, and NP swabs were negative in 32 out of 33 patients with negative results for viral identification in sputum, i.e. specificity of 96.9% (Table 4). The positive (PPV) and negative (NPV) predictive values of NP swabs were 95.8% and 74.4%, respectively.

3.5 | PSI and CURB-65 scores performance severity indexes as a function of etiology

As for the severity indexes, the median score for the CURB-65 was 2 (IQR: 1–2) and 92 (IQR: 70–117) for the PSI index. The distribution in the different risk classes according to the PSI and CURB-65 values were evaluated based on the same groups used to evaluate the

clinical outcomes (Tables 5 and 6). As shown in Table 5, mortality rates increased in the IV and V PSI risk classes for the whole cohort and in both groups, with and without definite etiological diagnosis. However, in the case of the CURB-65 this increase was only observed with the score ≥3, for the whole cohort and the group of patients with definite etiological diagnosis (Table 5). Next, the PSI and CURB-65 scores were compared among the three definite etiological groups (bacterial, viral, and mixed etiologies). In case of the PSI, high mortality rates were only observed for the bacterial etiology in the IV and V risk classes, and for the mixed etiologies for the V risk class. In the CURB-65 the mortality increase was only observed with the score ≥3 for the groups of bacterial and mixed etiologies. Regarding the viral CAP, the values of the PSI and CURB-65 scores were not associated with different mortality rates (Table 6). The survival analysis did not find differences, except for the CURB-65 ≥ 3, but it relies on a unique dead event in the viral CAP group (Figures S1 and S2).

TABLE 2 Clinical outcomes based in community-acquired pneumonia groups with and without etiologic identification

	Any etiological agent (*N* = 174)	No etiological agent (*N* = 167)	*p* value
Outcome			
ARDS	2 (1.1%)	1 (0.6%)	1.000
IMV	8 (4.6%)	0 (0.0%)	**0.007**
ICU admission	17 (9.8%)	3 (1.8%)	**0.002**
Mortality	13 (7.5%)	8 (4.8%)	0.303
Unfavorable outcome[a]	25 (14.4%)	9 (5.4%)	**0.006**
Length of stay (days)	5 [3–8]	4 [3–8]	0.314

Note: Represented data are *N* (%) or median [IQR]. All *p* values (two-tailed test) were calculated by Chi-squared test χ^2 or Fisher's test for qualitative data and the Student *t* test for quantitative data, as appropriate. Bold values indicates statistically significant $p < 0.05$.

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range.

[a]ICU admission and/or death.

4 | DISCUSSION

The results of the present study show that the virus etiology of the CAP in adults can be identified in half of the patients with available representative sputum, while the NP swabs identify the viral etiology in one out of five samples. Compared with sputum, the positive predictive value and specificity of NP swabs for viral diagnosis are higher than 96%. In addition, the performance of PSI and CURB-65 scores in all CAP with etiologic diagnosis were as expected, with mortality associated with higher values. However, the values of both scores were not associated with mortality in patients with viral pneumonia.

We found a high diversity of pathogens as causative agent of CAP in adults. Bacterial etiology was the most common, followed by mixed and viral etiologies, as it had previously been reported.[20] However, our results show that the frequency of CAP of viral

TABLE 4 Data for concordant and discordant results between NP and sputum samples in 67 patients

	Representative sputum		
	Positive	Negative	Total
NP swabs			
Positive	23 (34.3)	1 (1.5)	24 (35.8)
Negative	11 (16.4)	32 (47.7)	43 (64.2)
Total	34 (50.7)	33 (49.3)	67 (100)

Note: Represented data are *N* (%).

Abbreviation: NP, nasopharyngeal.

TABLE 3 Clinical outcomes in all community-acquired pneumonia cohort and in different etiological groups

	All CAP cases (*N* = 341)	Bacterial etiology (*N* = 89)	Viral etiology (*N* = 36)	Mixed etiology (*N* = 49)	*p* value
Outcome					
ARDS	3 (0.9%)	0 (0.0)	0 (0.0)	2 (4.1)	0.076
IMV	8 (2.3%)	3 (3.4)	1 (2.8)	4 (8.2)	0.368
ICU admission	20 (5.9%)	7 (7.9)	3 (8.3)	7 (14.3)	0.453
Mortality	21 (6.2%)	8 (9.0)	1 (2.8)	4 (8.2)	0.478
Unfavorable outcome[a]	34 (10.0%)	13 (14.6)	4 (11.1)	8 (16.3)	0.792
Length of stay (days)	5 [3–8]	5 [3–8]	5 [4–7]	5 [3–7]	0.318

Note: Represented data are *N* (%) or median [IQR]. All *p* values (two-tailed test) were calculated by ANOVA or Kruskal–Wallis test, as appropriate.

Abbreviations: ANOVA, analysis of variance; ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range.

[a]ICU admission and/or death.

TABLE 5 Analysis of CURB-65 and PSI scores between community-acquired pneumonia groups with and without etiological identification

Prognostic indexes	All CAP cases (*N* = 341)		Any etiological agent (*N* = 174)		No etiological agent (*N* = 167)		*p* value for etiological groups
	N	Mortality[a]	*N*	Mortality[a]	*N*	Mortality[a]	
CURB-65 (median [IQR])	341	2 [1, 2]	174	2 [1, 2]	167	2 [1, 2]	0.205
CURB-65 ≤ 1	142	4 (2.8%)	7	1 (1.4%)	70	3 (4.3%)	0.363
CURB-65 = 2	141	7 (5.0%)	65	2 (3.1%)	76	5 (6.6%)	0.452
CURB-65 ≥ 3	58	10 (17.2%)	37	10 (27.0%)	21	0 (0.0%)	**0.009**
PSI (median [IQR])	341	92 [70–117]	177	90 [70–117]	167	94 [66–117]	0.968
I	42	1 (2.4%)	14	0 (0.0%)	28	1 (3.6%)	0.483
II	47	0 (0.0%)	32	0 (0.0%)	15	0 (0.0%)	(..)
III	72	2 (2.8%)	41	1 (2.4%)	31	1 (3.2%)	1.000
IV	133	10 (7.5%)	65	7 (10.8%)	68	3 (4.4%)	0.200
V	47	8 (17.0%)	22	5 (22.7%)	25	3 (12.0%)	0.446

Note: CURB-65: confusion, urea >64 mg/dl, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg (systolic) or <60 mmHg (diastolic), age ≥65 years; all *p* values (two-tailed test) were calculated by Chi-squared test (χ^2) or Fisher's test for qualitative data and the Student *t* or Mann–Whitney *U* test for quantitative data, as appropriate. Bold values indicates statistically significant $p < 0.05$.

Abbreviations: IQR, interquartile range; PSI, pneumonia severity index; (..), undefined.

[a]Data are median [IQR] or *N* (%).

TABLE 6 Analysis of CURB-65 and PSI scores among on the three etiological groups of community-acquired pneumonia

Prognostic indexes	Bacterial etiology (*N* = 89)		Viral etiology (*N* = 36)		Bacterial/viral etiology (*N* = 49)		*p* value	Log rank
	N	Mortality[a]	*N*	Mortality[a]	*N*	Mortality[a]		
CURB-65 (median [IQR])	92	2 [1, 2]	35	2 [0 – 2]	50	2 [1–3]	0.087	N/A
CURB-65 ≤ 1	38	1 (2.6%)	15	0 (0.0%)	19	0 (0.0%)	0.635	0.484
CURB-65 = 2	29	1 (3.4%)	20	0 (0.0%)	16	1 (6.3%)	0.552	0.144
CURB-65 ≥ 3	22	6 (27.3%)	1	1 (100.0%)	14	3 (21.4%)	0.232	**<0.001**
PSI (median [IQR])	92	89 [70–112]	35	79 [67–108]	50	104 [76–128]	**0.017**	N/A
I	7	0 (0.0%)	4	0 (0.0%)	3	0 (0.0%)	(..)	(..)
II	17	0 (0.0%)	7	0 (0.0%)	8	0 (0.0%)	(..)	(..)
III	21	1 (4.8%)	13	0 (0.0%)	7	0 (0.0%)	0.614	0.529
IV	35	6 (17.1%)	10	1 (10.0%)	20	0 (0.0%)	0.142	0.061
V	9	1 (11.1%)	2	0 (0.0%)	11	4 (36.4%)	0.295	0.484

Note: CURB-65: confusion, urea >64 mg/dl, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg (systolic) or <60 mmHg (diastolic), age ≥65 years; all *p* values (two-tailed test) were calculated by ANOVA or Kruskal–Wallis test, as appropriate, and HSD Tukey post hoc analyses were developed when a significance between groups was found. Chi-squared test (χ^2) or Fisher's test were also used to estimate the significance of categorical variables. Log rank test to compare Kaplan–Meier curves for each etiology group. Bold values indicates statistically significant $p < 0.05$.

Abbreviations: ANOVA, analysis of variance; IQR, interquartile range; N/A, not applicable; PSI, pneumonia severity index; (..), undefined.

[a]Data are median [IQR] or *N* (%).

etiology seem to be higher than previously reported.[20] Bacterial etiology in CAP is widely described, with *S. pneumoniae*, *H. influenzae*, and *M. pneumoniae* being among the most common agents detected, due to the availability of quick and sensitive tests, such as urine antigen detection tests and blood and sputum cultures, with high sensitivity and specificity in hospitalized CAP patients.[21,22] In the recent years, some studies have highlighted the etiological importance of endemic respiratory viruses (ERV) in the setting of the CAP.[23,24] RV, IV, RSV, and CoV are the viruses most frequently reported as causative agents of CAP,[5,23,24] while the rest of viruses were supposed to be anecdotal,[20,25] among these, AdV, MPV, PIV, or bocavirus are detected only in 1%–2.5% of patients.[24,26] Our results

support this viral abundance and diversity, with viruses being the etiology of CAP, alone or in a mixed bacterial/viral etiology, in 1 out of 4 CAP cases, and in 1 out of 2 cases in CAP episodes with definite etiological diagnosis.

We proved the high performance of NP swabs for the viral diagnosis of CAP, with high specificity and PPV. Although representative sputum showed higher sensitivity than NP swabs in detecting viruses (51% vs. 21%, respectively) in CAP episodes, the greatest availability of the later (67 vs. 340 recovered samples), together with its accuracy for the etiological diagnosis, supports its wide use in the clinical practice, regardless the upper airways symptoms. The idea that the diagnostics supported by NP swabs reduce the chances to identify viral pathogens[7,23] is highlighted in different studies that collected both NP swabs and LRT samples.[27,28] In one of these studies, 21 viruses were detected in the LRT samples and only 7 were detected in NP swabs.[27] In other work, samples from both, NP swabs and BAL samples were collected and 5 out of 23 patients showed a positive PCR for virus in the BAL samples while any of the NP swabs samples were positive.[28] In the present study, we show that the NP sample is not better than the reference sputum to detect viral pathogens. However, when the PCR of the NP swab is positive, it has almost the same PPV of representative sputum and a high specificity, supporting that a positive detection of viral pathogens in NP swabs can be considered as truly identified. Thus, NP swabs and sputum samples are complementary for the etiological diagnosis of CAP. This is in agreement with the results of Azadeh et al.[29] showing that the performance of the identification of pathogens in BAL samples after a negative NP swab may contribute with useful additional microbiologic information while if a pathogen was already detected and identified in a NP swab, the evaluation of the LRT specimens is unlikely to provide additional information.

We have analyzed the impact of the etiological agents of the CAP on the mortality and clinical outcome in adult patients. Thus, a worse clinical outcome or a higher mortality rate were independent of the etiological agent identified, which is in agreement with results reported by Kim et al.[15] Our results suggest that the identification of an etiological agent, whether viral or bacterial, is associated with an increased need of IMV, and a higher rate of ICU admission and unfavorable outcome. This conclusion also agrees with Quah, J. et al.[30] who found higher in-hospital mortality when the etiology of CAP had been identified, particularly in mixed viral-bacterial etiology. Additionally, Nair and Niederman[31] also observed a significant difference in 28-day mortality for people with bacterial etiology but it was attributed to delayed antibiotic administration or antimicrobial therapy no consistent with the IDSA CAP guidelines.

The mortality prediction of the PSI score, when patients with or without any etiological agent were considered, was consistent with the IV and V risk classes.[12] However, regarding the CURB-65 score we observed a clear different pattern in the mortality prediction depending on the etiology identification. Thus, CURB-65 score ≥3 showed increased mortality rates in CAP with etiological identification but not in cases without defined etiology. Muñoz et al.[32] found consistent results according to PSI I–II risk classes and CURB-65 0–1 scores and mortality in CAP by bacterial, viral, mixed and without defined etiologies groups, but they did not analyze the performance in cases with higher scores. Gadsby et al.[24] analyzed the etiologies of CAP in a cohort of 323 hospitalized adults, using sputum cultures and molecular methods, selecting the cases from the sputum samples sent for diagnosis to the Microbiology laboratory, without providing information on their representativeness of lower respiratory tract. Regarding the performance of predictive scores, it was only analyzed in *S. pneumoniae* cases using a composed outcome of mortality and/or ICU admission, with results consistent with the CURB-65 values of the score.

Our work casts serious doubts on the usefulness of the PSI and CURB-65 severity scores when considering CAP caused by endemic viruses. Thus, only one patient died among 36 cases of viral CAP, despite 21 cases with CURB-65 score value ≥2 or PSI score value ≥IV in 12 patients. Several studies argued that CURB-65 had a worse predictive value in influenza A virus cases due to the age factor of the score,[33,34] which was not observed in our results, where the viral etiology group did not show differences in age with the rest of the etiological groups. Regarding the PSI, our results do not confirm the data from Kim et al.,[15] who observed no differences in this score, between viral and bacterial CAP, nor in mortality between these two groups (15% and 16%, respectively). However, our results agree with those from other authors who evaluated disease severity in the setting of viral versus bacterial CAP.[35] Their results showed that bacterial CAP more frequently had PSI ≥ class IV, despite the fact that viral CAP significantly showed higher frequencies of ICU admission, intubation, and in hospital mortality, concluding that PSI scores cannot be used to accurately predict the outcome in viral CAP.[35]

The low number of deaths and patients per PSI and CURB-65 scores risk classes, especially in the viral CAP group, are limitations of this study to confirm our findings regarding the usefulness of the severity scores, especially in the viral etiology. In addition, comparison of NP and sputum results with BAL samples was not possible because the latter were only obtained in three patients in whom this invasive technique was clinically indicated. In one of these three cases, the only one for which a representative sputum sample was also available, Stenotrophomonas sp. was identified in both cases. Finally, in only 67 patients was possible to obtain NP swabs and sputum samples, due to the already well-known low availability of representative and purulent sputum samples.[36,37]

5 | CONCLUSIONS

In summary, and always with the necessary caution given that this is a small size cohort, our work suggests the need to update the severity scores and adjust them based on the CAP etiological agent, particularly for viral CAP by ERV. In addition, our results support the clinical use of molecular methods for the accurate identification of the viral etiology of CAP in NP swabs, due to the high predictive positive value and specificity, and the higher feasibility of sampling. The implementation of these improvements in the diagnosis of CAP will allow a better management of these patients and the

optimization of the antimicrobial therapy. These results will need to be confirmed, ideally in a multicenter cohort study using a larger sample size, to substantiate these observations with adequate power and representativeness.

AUTHOR CONTRIBUTIONS

Javier Sánchez-Céspedes, Rocío Álvarez-Marín, Manuela Aguilar-Guisado, and Jerónimo Pachón: conceived and designed the study; obtained public funding from the Spanish Ministry of Economy, Industry, and Competitiveness; and take responsibility for the integrity of the data and the accuracy of its analysis. **Jerónimo Pachón, Javier Sánchez-Céspedes, and Judith Berastegui-Cabrera**: did the scientific literature search. **Juan Carlos Crespo-Rivas, Macarena López-Verdugo, Laura Merino, Ana Escoresca-Ortega, Carmen Calero-Acuña, Laura Carrasco-Hernández, Javier Ignacio Toral-Marín, María Abad-Arranz, Nieves Ramírez-Duque, and Bosco Barón-Franco**: provided the data. **Judith Berastegui-Cabrera**: processed the data, did the statistical analysis, and together with **Javier Sánchez-Céspedes and Jerónimo Pachón** wrote the draft of the manuscript. **Rocío Álvarez-Marín and Manuela Aguilar-Guisado**: critically revised the manuscript for important intellectual content. All the authors gave final approval for the current version.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SUPPLEMENTARY MATERIAL

Prepandemic viral community-acquired pneumonia: diagnostic sensitivity and specificity of nasopharyngeal swabs and performance of clinical severity scores.

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STROBE Statement—Checklist

	Item No	Recommendation	Manuscript location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction, last paragraph
Methods			
Study design	4	Present key elements of study design early in the paper	Patients and Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Patient and Methods
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Patients and Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Nor applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Patients and Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Patients and Methods
Bias	9	Describe any efforts to address potential sources of bias	Patients and Methods, and Results
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Patients and Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Patients and Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Patients and Methods
		(*c*) Explain how missing data were addressed	Supplementary Table S3
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Patients and Methods, and Results

		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Figures 1 and 2, Tables S1 and S4
		(b) Indicate number of participants with missing data for each variable of interest	Supplementary Table S3
		(c) Summarize follow-up time (eg, average and total amount)	Patients and Methods
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 1, 2, 3, and S4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Patients and Methods Results Tables S5 and S6
		(*b*) Report category boundaries when continuous variables were categorized	Table 1 Tables S1, S5, and S6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results Tables 4, 5, 6
Discussion			
Key results	18	Summarize key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgments

*Give information separately for exposed and unexposed groups.

Table S1. Demographics, chronic underlying diseases, clinical and analytical characteristics, and therapy of patients with CAP by etiology groups.

	Without etiological diagnosis (N = 167)	With etiological diagnosis * (N = 174)	Bacterial etiology (N = 89)	Viral etiology (N = 36)	Mixed etiology ** (N=49)
Demographics					
Age, years	74 [56 – 81]	70 [58 – 80]	70 [61 – 79]	68 [48 – 81]	72 [60 – 84]
Age group >75 years old	78 (46.7%)	63 (36.2%)	29 (32.6%)	11 (30.6%)	23 (46.9%)
Male sex	85 (50.9%)	102 (58.6%)	51 (57.3%)	24 (66.7%)	27 (55.1%)
Underlying conditions					
Smoking (Last 5 years)	36 (21.6%)	61 (35.1%)	28 (31.5%)	18 (50.0%)	15 (30.6%)
Excessive alcohol consumption	16 (9.6%)	34 (19.5%)	17 (19.1%)	8 (22.2%)	9 (18.4%)
Chronic underlying diseases					
Charlson Comorbidity Index ≥3	122 (73.1%)	124 (71.3%)	62 (69.7%)	24 (66.7%)	38 (77.6%)
Diabetes	54 (32.3%)	47 (27.0%)	21 (23.6%)	10 (27.8%)	16 (32.7%)
Chronic pulmonary disease	38 (22.8%)	54 (31.0%)	28 (31.5%)	9 (25.0%)	17 (34.7%)
Chronic cardiovascular disease	57 (34.1%)	42 (24.1%)	18 (20.2%)	7 (19.4%)	17 (34.7%)
Cerebrovascular disease	15 (9.0%)	18 (10.3%)	12 (13.5%)	2 (5.6%)	4 (8.2%)
Chronic kidney disease	20 (12.0%)	15 (8.6%)	5 (5.6%)	4 (11.1%)	6 (12.2%)
Chronic liver disease	7 (4.2%)	11 (6.3%)	6 (6.7%)	2 (5.6%)	3 (6.1%)
Connective tissue disease	2 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neoplasia	22 (13.2%)	12 (6.9%)	8 (9.0%)	1 (2.8%)	3 (6.1%)
Solid organ transplantation	9 (5.4%)	6 (3.4%)	2 (2.2%)	2 (5.6%)	2 (4.1%)
Previous therapies					
Statins	36 (21.6%)	32 (18.4%)	14 (15.7%)	8 (22.2%)	10 (20.4%)
Corticosteroids	17 (10.2%)	25 (14.3%)	8 (9.0%)	8 (22.2%)	9 (18.4%)
Antibiotics	58 (34.7%)	50 (28.7%)	18 (20.2%)	15 (41.7%)	17 (34.7%)

Symptoms at admission					
Odynophagia	2 (1.2%)	3 (1.7%)	1 (1.1%)	1 (2.8%)	1 (2.0%)
Cough	113 (67.7%)	131 (75.3%)	65 (73.0%)	24 (66.7%)	42 (85.7%)
Arthro-myalgia	11 (6.6%)	23 (13.2%)	15 (16.9%)	2 (5.6%)	6 (12.2%)
Dyspnea	89 (53.3%)	107 (61.5%)	49 (55.1%)	25 (69.4%)	33 (67.3%)
Diarrhea	13 (7.8%)	12 (6.9%)	3 (3.4%)	4 (11.1%)	5 (10.2%)
Vomiting	11 (6.6%)	9 (5.2%)	5 (5.6%)	3 (8.3%)	1 (2.0%)
Headache	3 (1.8%)	3 (1.7%)	1 (1.1%)	2 (5.6%)	0 (0%)
Pleuritic chest pain	26 (15.6%)	57 (32.8%)	33 (37.1%)	10 (27.8%)	14 (28.6%)
Disturbance of consciousness	15 (9.0%)	18 (10.3%)	7 (7.9%)	2 (5.6%)	9 (18.4%)
Signs at admission					
Temperature, ^{o}C	37.1 [36.1 – 38.2]	37.7 [36.5 – 38.5]	37.8 [36.5 – 38.6]	37.4 [36.5 – 38.1]	37.7 [36.5 – 38.4]
Temperature ≥37.5^{o}C	66 (39.5%)	84 (48.3%)	45 (50.6%)	14 (38.9%)	25 (51.0%)
$SatO_2$	95 [91 – 97]	94 [92 – 96]	95 [92 – 96]	95 [92 – 97]	94 [92 – 97]
SatO2 <95%	77 (46.1%)	88 (50.6%)	44 (49.4%)	18 (50.0%)	26 (53.1%)
SBP <90 mmHg	13 (7.8%)	15 (8.6%)	7 (7.9%)	2 (5.6%)	6 (12.2%)
DBP <60 mmHg	31 (18.6%)	34 (19.5%)	16 (18.0%)	4 (11.1%)	14 (28.6%)
HR ≥100 bpm	28 (16.8%)	44 (25.3%)	24 (27.0%)	7 (19.4%)	13 (26.5%)
Shock at admission	2 (1.2%)	12 (6.9%)	3 (3.4%)	2 (5.6%)	7 (14.3%)
Laboratory data at admission					
Leucocytes (x10^9/L)	11.9 [8.0 – 16.7]	14.3 [9.9 – 20.6]	16.3 [10.8 – 22.4]	12.6 [7.3 – 16.2]	14.0 [8.7 – 19.4]
Leucocytes <4.0 x 10^9/L	11 (6.6%)	6 (3.4%)	0 (0%)	3 (8.3%)	3 (6.1%)
Neutrophils (x10^9/L)	9.2 [5.9 – 13.6]	12.5 [8.3 – 18.9]	14.1 [9.2 – 19.6]	10.4 [5.5 – 14.7]	11.9 [7.3 – 15.7]
Neutrophils >7.5 x 10^9/L	105 (62.9%)	135 (77.6%)	79 (88.8%)	23 (63.9%)	33 (67.3%)
Lymphocytes (x10^9/L)	1.1 [0.8 – 1.6]	1 [0.6 – 1.6]	1.0 [0.7 – 1.4]	1.2 [0.7 – 1.9]	0.9 [0.5 – 1.7]
Lymphocytes <1.0 x 10^9/L	72 (43.1%)	76 (43.7%)	38 (42.7%)	13 (36.1%)	25 (51.0%)
Platelets (x10^9/L)	245 [175 – 316]	227 [176 – 324]	227 [186 – 321]	268 [176 – 359]	212 [160 – 303]
Platelets <130 x 10^9/L	18 (10.8%)	16 (9.2%)	5 (5.6%)	4 (11.1%)	7 (14.3%)
Sodium (mEq/L)	138 [135 – 141]	138 [134 – 141]	138 [134 – 141]	139 [135 – 141]	138 [134 – 141]

Sodium <135 mEq/L	37 (22.2%)	47 (27.0%)	26 (29.2%)	8 (22.2%)	13 (26.5%)
Potassium (mEq/L)	4.2 [3.9 – 4.8]	4.1 [3.7 – 4.6]	4.1 [3.6 – 4.6]	4.1 [3.9 – 4.6]	4.1 [3.8 – 4.5]
Potassium >5 mEq/L	30 (18.0%)	21 (12.1%)	12 (13.5%)	4 (11.1%)	5 (10.2%)
Creatinine (mg/dl)	0.99 [0.73 – 1.40]	1.01 [0.80 – 1.53]	1.00 [0.83 – 1.53]	0.98 [0.75 – 1.38]	1.06 [0.78 – 1.61]
Creatinine >1.3 mg/dl	47 (28.1%)	58 (33.3%)	30 (33.7%)	9 (25.0%)	19 (38.8%)
CRP (mg/L)	124.1 [62.4 – 252.8]	185.8 [93.4 – 318.0]	217.8 [112.5 – 338.2]	115.6 [63.4 – 249.2]	172.4 [102.0 – 270.2]
CRP ≥100 mg/L	75 (44.9%)	112 (64.4%)	64 (71.9%)	16 (44.4%)	32 (65.3%)
Glucose (mg/dl)	126 [96 – 173]	123 [98 – 163.5]	122 [99 – 158]	119 [96 – 193]	143 [102 – 216]
Urea (mg/dl)	43 [30 – 70]	51 [34 – 77]	53 [33 – 78]	48 [27 – 65]	52 [36 – 86]
CAP Therapies					
Empirical antiviral therapy	19 (11.6%)	39 (22.4%)	15 (16.9%)	12 (33.3%)	12 (24.5%)
Empirical antibiotic therapy	153 (91.6%)	169 (97.1%)	86 (96.6%)	35 (97.2%)	48 (98%)
Appropriated antimicrobial therapy ***	0 (0%)	117 (67.2%)	72 (80.9%)	7 (19.4%)	38 (77.6%)

Represented data are N (%) or median [IQR]. Excessive alcohol consumption is defined as more than three drink units/day. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; PSI: Pneumonia Severity Index; CRP: C-reactive protein. * Etiological diagnosis included bacterial, viral and mixed etiologies. ** Mixed etiology included cases with bacterial and viral etiologies. *** In the 174 patients with etiological diagnosis.

Table S2. Frequency of positive results and viral loads in nasopharyngeal (NP) swabs, representative sputum, and blood in viral community-acquired pneumonia.

	Patients with positive detection	Positive NP swabs N (%)	Median (IQR) virus load (Log_{10} copies/ml)	Positive sputum N (%)	Median (IQR) virus load (Log_{10} copies/ml)	RNA/DNAemia N (%)	Median (IQR) virus load (Log_{10} copies/ml)	*P* value [a]
Virus identification								
Adenovirus	8	5 (62.5)	4.92 (4.92 – 4.93)	2 (25)	6.22 (5.68 – 6.75)	1 (12.5)	4.92	**0.048**
Coronavirus	10	8 (80)	5.78 (5.02 – 7.29)	5 (50)	7.00 (6.74 – 7.31)	1 (10)	4.49	0.315
Coronavirus (OC43)	6	6 (100)	5.25 (4.95 – 5.70)	2 (33.33)	6.14 (5.84 – 6.44)	0 (0)	[..]	0.429
Coronavirus (NL63)	3	1 (33.33)	8.67	3 (100)	7.31 (7.16 – 8.49)	0 (0)	[..]	0.700
Coronavirus (229E)	1	1 (100)	6.61	0 (0)	[..]	1 (100)	4.49	[..]
Influenza virus	20	16 (80)	4.89 (4.57 – 6.12)	7 (35)	5.32 (4.74 – 6.15)	2 (13.33)	6.97 (6.81 – 7.12)	0.802
Influenza A (H1-pdm09)	4	3 (75)	5.39 (5.08 – 6.69)	2 (50)	5.69 (5.51 – 5.86)	0 (0)	[..]	1.000
Influenza A H3	5	5 (100)	4.93 (4.72 – 5.74)	0 (0)	[..]	0 (0)	[..]	[..]
Influenza B	11	8 (72.73)	4.70 (4.38 – 5.59)	4 (36.36)	4.76 (4.70 – 5.12)	2 (18.18)	6.97 (6.81 – 7.12)	0.808
Enterovirus	2	0 (0)	[..]	2 (100)	5.55 (4.98 – 6.11)	0 (0)	[..]	[..]
Rhinovirus	34	32 (94.12)	7.05 (6.63 – 7.27)	17 (50)	7.29 (7.26 – 7.30)	1 (2.94)	4.75	**0.025**
Respiratory syncytial virus (RSV)	7	5 (71.43)	4.40 (4.27 – 7.29)	3 (42.86)	6.35 (5.23 – 6.66)	0 (0)	[..]	0.786
RSV B	7	5 (71.43)	4.40 (4.27 – 7.29)	3 (42.86)	6.35 (5.23 – 6.66)	0 (0)	[..]	0.786

[a] Two-tailed, Mann-Whitney U test for comparing viral load between NP swabs and sputum samples.

Figure S1. Kaplan-Meier's plot in CAP patients with bacterial, viral, and mixed etiologies, and categorized by PSI III, IV, and V risk classes. Plots for PSI I and II were not created because of the absence of mortality in these categories.

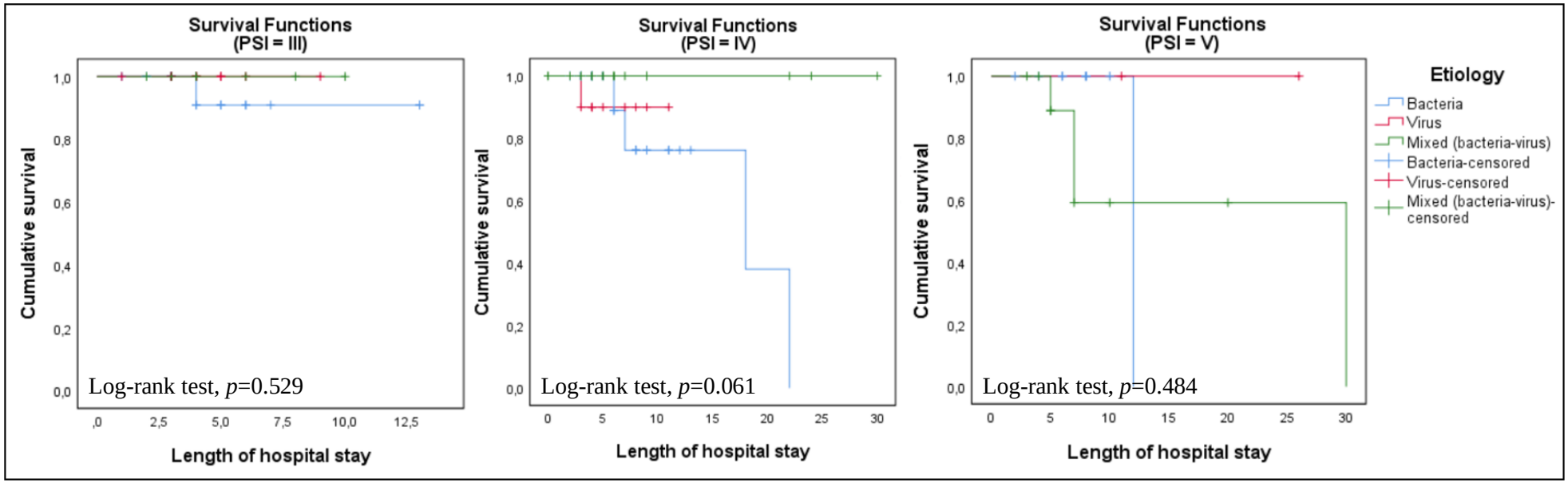

Figure S2. Kaplan-Meier's plot in CAP patients with bacterial, viral, and mixed etiologies, and categorized by CURB-65.

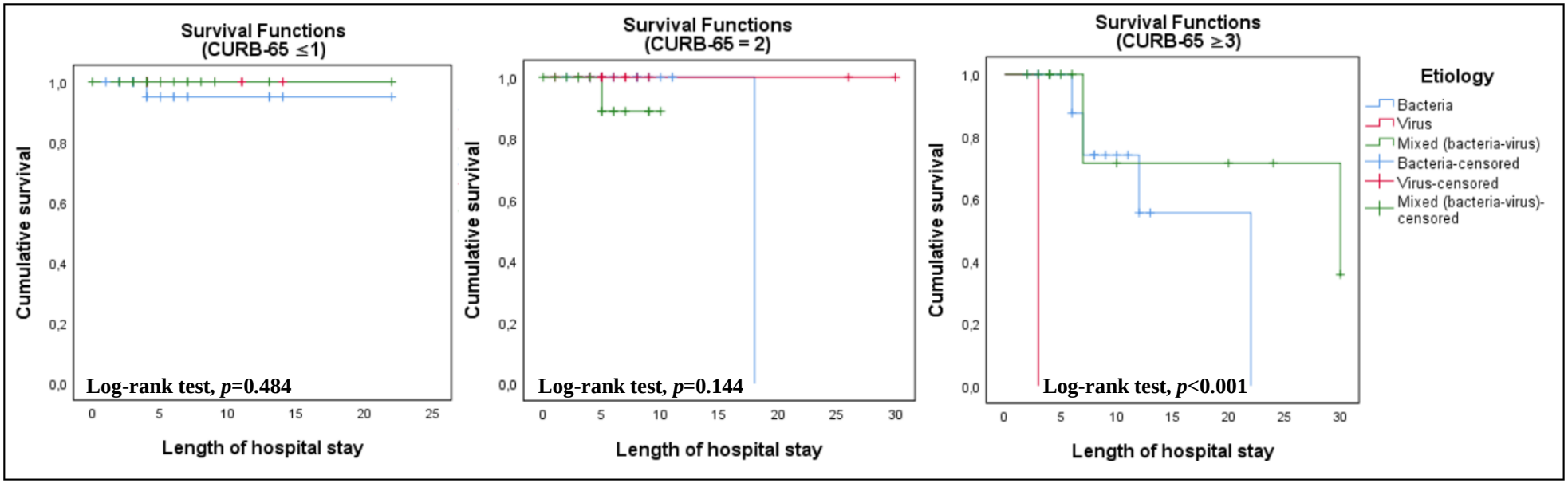

Table S3. Missing data for the variables collected in the cohort.

Variables	% Missing data
Demographics	
Age group >75 years old	0
Male sex	0
Underlying conditions	
Smoking (Last 5 years)	0
Excessive alcohol consumption	0
Chronic underlying diseases	0
Charlson Comorbidity Index ≥3	0
Diabetes	0
Chronic pulmonary disease	0
Chronic cardiovascular disease	0
Cerebrovascular disease	0
Chronic kidney disease	0
Chronic liver disease	0
Connective tissue disease	5.87
Neoplasia	0
Solid organ transplantation	0
Previous treatments	
Statins	0
Corticosteroids	0
Antibiotics	0
Symptoms at admission	
Odynophagia	0
Cough	0
Arthro-myalgia	0
Dyspnea	0
Diarrhea	0
Vomiting	0
Headache	0
Pleuritic chest pain	0
Disturbance of consciousness	0
Signs at admission	
Temperature ≥37.5 ºC	12.32
$SatO_2$ <95%	0
SBP <90 mmHg	2.64
DBP <60 mmHg	2.64
HR ≥100 bpm	9.97
Shock at admission	2.64
Laboratory data at admission	
Leucocytes <4.0 x 109/L	0.29
Neutrophils >7.5 x 109/L	0.29
Lymphocytes <1.0 x 109/L	0.29
Platelets <130 x 109/L	0.29
Sodium <135 mEq/L	0.29
Potassium >5 mEq/L	0.29

Creatinine >1.3 mg/dl	0.29
CRP ≥100 mg/L	0.29
Etiology data (with or without defined etiology)	0
Severity scores	
CURB-65 ≥2	0
PSI ≥3	0
PSI ≥4	0
CAP Therapy	
Empirical antiviral therapy	6.45
Empirical antibiotic therapy	0.29
Outcome	
IMV	0
ARDS	0
ICU admission	0

Table S4. Univariate Cox regression analysis of the association of different variables with 30-day all-cause mortality in the CAP cohort (n = 341).

Variable	Mortality			
	Yes (n = 21)	No (n = 320)	*P* value	Crude HR (95% CI)
Demographics				
Age group >75 years old	11 (52.4)	130 (40.6)	**0.050**	2.58 (1.01-6.67)
Male sex	12 (57.1)	175 (54.7)	0.980	1.00 (0.64-1.57)
Underlying conditions				
Smoking (last 5 years)	3 (14.3)	94 (29.4)	0.158	2.43 (0.71-8.37)
Excessive alcohol consumption	2 (9.5)	48 (15.0)	0.571	0.65 (0.15-2.84)
Chronic underlying diseases				
Charlson Comorbidity Index ≥3	19 (90.5)	227 (70.9)	0.066	3.95 (0.91-17.12)
Diabetes	9 (42.9)	92 (28.7)	0.394	1.48 (0.59-5.67)
Chronic pulmonary disease	7 (33.3)	85 (26.6)	0.239	1.75 (0.69-4.47)
Chronic cardiovascular disease	7 (33.3)	92 (28.7)	0.616	1.28 (0.49-3.36)
Cerebrovascular disease	3 (14.3)	30 (9.4)	0.270	2.02 (0.58-7.07)
Chronic kidney disease	3 (14.0)	32 (10.0)	0.532	1.49 (0.42-5.24)
Chronic liver disease	3 (14.3)	15 (4.7)	0.235	2.13 (0.61-7.44)
Connective tissue disease	1 (5.0)	1 (0.3)	**0.019**	11.7 (1.49-91.61)
Neoplasia	4 (19.0)	30 (9.4)	0.332	1.73 (0.57-5.28)
Solid organ transplantation	1 (4.8)	14 (4.4)	0.499	0.48 (0.06-3.98)
Previous treatments				
Statins	6 (28.6)	62 (19.4)	0.716	1.19 (0.45-3.15)
Corticosteroids	5 (23.8)	37 (11.6)	0.214	1.93 (0.68-5.47)
Antibiotics	5 (23.8)	104 (32.5)	0.497	0.70 (0.25-1.95)
Symptoms at admission				
Odynophagia	0 (0.0)	5 (1.6)	0.657	0.047 (0.00-32649.71)
Cough	10 (47.6)	234 (73.1)	0.154	0.53 (0.22-1.27)
Dyspnea	14 (66.7)	182 (56.9)	0.965	0.98 (0.39-2.47)
Diarrhea	1 (4.8)	24 (7.5)	0.391	0.41 (0.05-3.11)
Vomiting	1 (4.8)	19 (5.9)	0.605	0.59 (0.08-4.42)
Headache	0 (0.0)	6 (1.9)	0.695	0.048 (0.00-188283.4)
Pleuritic chest pain	1 (4.8)	82 (25.6)	0.104	0.19 (0.02-1.41)
Disturbance of consciousness	5 (23.8)	28 (8.8)	0.494	1.44 (0.50-4.11)
Signs at admission				
Temperature ≥37.5 ºC	7 (33.3)	143 (44.7)	0.181	0.53 (0.21-1.34)
SpO2 <95%	14 (66.7)	151 (47.2)	0.148	1.98 (0.78-5.01)
SBP <90 mmHg	6 (28.6)	22 (7.1)	**0.028**	3.20 (1.13-9.05)
DBP <60 mmHg	8 (38.1)	57 (18.3)	0.155	1.96 (0.78-4.96)
Hr ≥100 bpm	8 (44.4)	64 (22.1)	0.357	1.58 (0.59-4.22)
Shock at admission	5 (25.0)	9 (3.0)	0.328	1.75 (0.57-5.36)
Laboratory data at admission				
Leucocytes <4.0 x 10^9/L	2 (9.5)	15 (4.7)	0.772	0.80 (0.18-3.56)
Neutrophils >7.5 x 10^9/L	16 (76.2)	224 (70.2)	0.451	1.43 (0.56-3.64)

Lymphocytes <1.0 x 10^9/L	13 (61.9)	135 (42.3)	0.510	1.35 (0.55-3.34)
Platelets <130 x 10^9/L	4 (19.0)	30 (9.4)	0.392	1.62 (0.54-4.91)
Sodium <135 mEq/L	5 (23.8)	79 (24.8)	0.629	0.78 (0.28-2.17)
Potassium >5 mEq/L	3 (14.3)	48 (15.0)	0.599	1.40 (0.39-4.94)
Creatinine >1.3 mg/dl	8 (38.1)	97 (30.4)	0.642	1.24 (0.50-3.04)
CRP ≥100 mg/L	15 (83.3)	172 (64.7)	0.172	2.37 (0.68-8.23)
Severity scores				
CURB-65 ≥2	17 (81.0)	182 (56.9)	0.155	2.21 (0.74-6.65)
PSI ≥3	20 (95.2)	232 (75.5)	0.063	6.73 (0.89-50.46)
PSI ≥4	18 (85.7)	162 (50.6)	**0.019**	4.38 (1.28-15.03)
Etiology				
Bacterial etiology	8 (38.1)	81 (25.3)	0.117	2.08 (0.83-5.22)
Viral etiology	1 (4.8)	35 (10.9)	0.377	0.403 (0.054-3.03)
Mixed etiology	4 (19.0)	45 (14.1)	0.958	1.03 (0.33-3.18)
No etiological agent	8 (38.1)	159 (49.7)	0.406	1.47 (0.58-3.72)
CAP Therapy				
Empirical antiviral therapy	6 (31.6)	52 (17.3)	0.553	1.36 (0.49-3.79)
Empirical antibiotic therapy	21 (100.0)	301 (94.4)	0.532	22.01 (0.001-358034.36)
Outcome				
IMV	4 (19.0)	4 (1.3)	0.235	2.08 (0.62-6.97)
ARDS	2 (9.5)	1 (0.3)	0.055	4.36 (0.97-19.64)
ICU admission	7 (33.3)	13 (4.1)	0.109	2.28 (0.83-6.24)

Data are presented as No. (%) and HR (95% CI).

Abbreviations (in order of appearance): HR, hazard ratio; CI, confidence interval; SpO_2, peripheral capillary oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hr, heart rate; CRP, C reactive protein; CURB-65, Severity Score for Community-Acquired Pneumonia; PSI, pneumoniae severity index; CAP, community acquired pneumonia; IMV, invasive mechanical ventilation; ARDS, acute respiratory distress syndrome.

Table S5. Multivariate Cox regression analyses of risk factors associated with 30-day all-cause mortality in the CAP cohort (n = 341).

Model 1

Variable	Adjusted analysis		
	P value	**HR**	**95% CI**
Charlson Comorbidity Index ≥3	**0.032**	5.37	1.16-24.87
SBP<90 mmHg	**0.015**	3.73	1.29-10.74
ARDS	**0.005**	9.41	1.97-44.87

Abbreviations (in order of appearance): HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; ARDS, acute respiratory distress syndrome.

Model 2

Variable	Adjusted analysis		
	P value	**HR**	**95% CI**
Age group >75 years old	0.080	2.33	0.90-6.04
SBP<90 mmHg	**0.036**	3.12	1.07-9.07
ARDS	**0.033**	5.32	1.14-24.68

Abbreviations (in order of appearance): HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; ARDS, acute respiratory distress syndrome.