TITLE: Impact of viral detection in patients with community-acquired pneumonia: an observational cohort study

RUNNING TITLE: Viral detection in CAP

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ABSTRACT:

Purpose: The presence of a respiratory virus in patients with community-acquired pneumonia (CAP) may have an impact on the bacterial etiology and clinical presentation. In this study we aimed to assess the role of viral infection in the bacterial etiology and outcomes of patients with CAP.

Methods: We performed a retrospective study of all adults hospitalized with CAP between November 2017 and October 2018. Patients were classified according to the presence of viral infection. An unvaried and a multivaried analysis were performed to identify variables associated with viral infection and clinical outcomes.

Results: Overall 590 patients were included. A microorganism was documented in 375 cases (63.5%). A viral infection was demonstrated in 118 (20%). The main pathogens were *S. pneumoniae* (35.8%), *S. aureus* (2.9%) and influenza virus (10.8%). A trend to a higher rate of *S. aureus* (p=0.06) in patients with viral infection was observed. Patients with viral infection had more often bilateral consolidation patterns (17.8% vs 10.8%, p=0.04), respiratory failure (59.3% vs 42.8%, p=0.001), ICU admission (17.8% vs 7%, p=0.001) and invasive mechanical ventilation (9.3% vs 2.8%, p=0.003). Risk factors for respiratory failure were chronic lung disease, age > 65 years, positive blood cultures and viral infection. Influenza, virus but no other respiratory viruses, was associated with respiratory failure (OR, 3.72; 95%CI, 2.06-6.73).

Conclusions: Our study reinforces the idea that co-viral infection has an impact in the clinical presentation of CAP causing a more severe clinical picture. This impact seems to be mainly due to influenza virus infection.

KEYWORDS: Pneumonia; influenza, human; virology; *Staphylococcus aureus*, respiratory failure

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the main challenges in infectious diseases, as it represents an important cause of morbidity and mortality, and it is a frequent cause of hospitalization worldwide [1–3]. CAP can be caused by various pathogens, being the bacteria, and specifically *Streptococcus pneumoniae* the microorganism most frequently identified. However, through the development of new diagnostic methods such as molecular testing, there has been an increase in the identification of respiratory viruses [4,5]. In recent years, the rate of viral detection in patients with CAP has raised, reaching up to 24,5-30% of all cases, according to a recent systematic review and meta-analysis[6,7]. This is important since some bacteria, such as *Staphylococcus aureus,* have traditionally been related to viral co-infection. Furthermore, recent studies have warned about a possible correlation between bacterial-viral co-infection and the severity of CAP, with a greater risk of respiratory failure [8,9]. However, data on the etiological and clinical impact of viral co-infection in patients with CAP are scarce, since most studies focus in immunocompromised hosts, pediatric patients or in critically ill patients [10–12].

In order to improve the knowledge of the impact of respiratory viruses in the etiology and clinical presentation of patients with CAP, we designed this study. The objectives were: 1) to assess the role of viral infection in the bacterial etiology, clinical features, and outcomes of patients with CAP, 2) to investigate factors associated with poor outcomes, focusing specially on respiratory failure and 3) to describe the clinical response to current empirical treatments for CAP.

MATERIALS AND METHODS

Study design and inclusion criteria

This is an observational retrospective study of all consecutive adult patients (age ≥18 years) hospitalized with CAP at Vall d'Hebron Universitary Hospital, a 1100 beds-tertiary teaching Hospital in Barcelona, between November 2017 and October 2018. Patients with nosocomial pneumonia and those with evidence of aspiration pneumonia (dysphagia, altered gag reflex, low level of consciousness) were excluded.

Data collection

We collected epidemiologic information (age, sex, residency in nursing home, smoking, alcohol consumption, vaccination status), medical history (hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic renal failure, neurological disorders, and neoplasms) and immunosuppressive factors (solid organ transplantation, hematopoietic transplantation, chemotherapy, long-term use of corticosteroids, and HIV infection). We also registered clinical information, laboratory results, radiological findings, microbiological information and severity data (shock septic, respiratory failure). Empirical treatment was recorded, and we evaluated if it was suitable for the microorganisms causing the CAP. Evolutive variables, such as admission at the Intensive Care Unit (ICU) and in-hospital mortality were collected. CURB-65 score and Pneumonia Severity Index (PSI) were calculated.

Microbiologic procedures

Microbiologic diagnostic procedures were performed according to the hospital protocol and included (1) two sets of blood cultures, (2) when available, qualitative and semi-quantitative culture of a good quality sputum sample as previously defined [13], (3) in patients who required orotracheal intubation, an endotracheal aspirate or bronco-alveolar-lavage samples (4), urinary antigen for *Streptococcus pneumoniae* in all patients, (5) urinary antigen for *Legionella pneumophila* if there was clinical or epidemiological suspicion and in all cases of severe CAP and (6) multiplex real-time PCR determination of respiratory virus (Influenza A and B, including Flu A-H1pdm09, Respiratory Syncytial Virus A and B, Adenovirus, Enterovirus, Metapneumovirus, Parainfluenza 1-4 Virus, Rhinovirus, Bocavirus 1-4, and Coronavirus NL63, OC43 and 229E) in a nasopharyngeal swab if requested by the attending physician in case of clinical or epidemiological suspicion (Allplex™ Respiratory Panels 1, 2 and 3, Seegene Inc., Korea). During the flu season (from November 2017 to March 2018) a rapid narrow-range real-time PCR for influenza virus was also performed (Xpert Flu/RSV→. Cepheid, Sunnyvale, CA, USA). Other microbiological techniques such as PCR for *S. pneumoniae* in pleural fluid or serologic

determinations for antibodies against atypical pathogens were performed according to clinical or epidemiological suspicion.

We considered a positive sputum culture when the semi-quantitative culture yielded > 1.000.000 colony-forming units (CFU) or when the microorganism was found to be predominant in qualitative cultures.

Definitions

Pneumonia was defined as the presence of signs or symptoms of respiratory-tract infection (cough, fever, purulent sputum, pleuritic chest pain or pulmonary semiology compatible with lung consolidation) associated with the presence of a newly visualized infiltrate in the chest radiography.

Bacterial pneumonia was diagnosed in patients with pneumonia when 1) a microorganism likely to cause bacterial pneumonia was isolated in blood, pleural fluid, acceptable-quality sputum, endotracheal aspirate or bronco-alveolar-lavage samples, 2) a PCR for *S. pneumoniae* was positive in pleural fluid, 3) an urinary antigen test for *S. pneumoniae* or *L. pneumophila* was positive, 4) seroconversion of *L. pneumophila*, *M. pneumoniae*, *C. pneumoniae*, *C. psittaci* and *C. burnetii* antibody titers was documented.

Viral infection was considered in all patients presenting a positive real PCR test for respiratory virus, regardless of the detection of a bacterial microorganism.

Respiratory failure was defined as pO2 in arterial blood lower or equal to 60 mmHg or peripheral pulse oximetry lower than 90%. Septic shock was defined as the need of vasoactive drugs to maintain medium blood pressure over 65 mmHg.

Treatment

Patients received antibiotic treatment according to current local protocols. Hospitalized patients

with non-severe CAP receive amoxicillin-clavulanic acid and in those with severe CAP, a third-generation cephalosporin (ceftriaxone or cefotaxime) associated with a macrolide (azithromycin) is prescribed. Fluoroquinolones are recommended in cases of penicillin allergy or as an alternative treatment at the attending physician discretion when there is a clinical suspicion for atypical pneumonia. A five-day course of oseltamivir is recommended for inpatients with confirmed influenza infection.

Statistical analysis

We performed a descriptive analysis of basal characteristic and clinical and microbiological information of the study population. Categorical variables are expressed as percentages, and numerical data are expressed in cases of normal distribution as mean and standard deviation (SD) or as median and interquartile range (IQR) for non-normally distributed data. We carried out an unvaried analysis to identify the variables associated with viral infection using the Chi-square test for qualitative variables and T-student test for quantitative variables. To determine variables associated with respiratory failure and with ICU admission, we performed a multivariate analysis (forward onwards) by binary logistic regression. We included in the model those variables with significant differences in the unvaried analysis and those with clinical relevance. To assess the role of influenza virus, a second analysis including influenza separately from other respiratory viruses in a multivariate model was performed. Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY; IBM Corp. Released 2011.

Ethics statement

The study was approved by the Ethics Committee of Vall d'Hebron Research Institute (registration code PR(AG)345/2018). Need for informed consent was waived, as data were analyzed retrospectively, and the study was non-interventional in nature.

RESULTS

Etiology of CAP

During the study period, 590 patients were diagnosed with CAP. Three hundred and fifty-nine (60.8%) were men and the median age was 70 (IQR: 53-81 years). There were no differences in basal characteristics between patients with and without viral infection. In Table 1 we show the demographic characteristics and comorbidities of the study population.

Regarding the microbiological tests performed, all the patients included had a *S. pneumoniae* urinary antigen, blood cultures were performed in 490 subjects (83.1%), sputum culture in 293 (49.6%), and PCR for respiratory viruses in 256 (43.4%). Table 2 shows the proportion of each microbiologic test that performed, according to flu season or not.

A microorganism was documented in 375 cases (63.5%): 321 (54.4%) were bacteria and 118 (20%) were viruses. *S. pneumoniae* (211, 35.8%), *S. aureus* (17, 2.9%), *Haemophilus influenzae* (15, 2.5%) and *L. pneumophila* (16, 2.7%) were the main bacteria documented. No outbreaks of Legionella were reported during the study period. Regarding virus, influenza A and B predominated (31, 5.2% and 33, 5.6% respectively) followed by rhinovirus (20, 3.4%) and syncytial respiratory virus (16, 2.7%).

In 64 patients (10.8%) a viral-bacterial coinfection was diagnosed (see Table 3). *S pneumoniae* was the bacteria most frequently associated to any respiratory virus, and simultaneous presence of *S. pneumoniae* with an influenza virus (18 cases, 28.1%) or with rhinovirus (11 cases, 17.2%) were the commonest associations. Table 4 shows detailed information on the co-infections.

We did not find significant differences in the bacteria documented in patients with and without viral infection, although patients with confirmed viral infection had a trend to a higher rate of *S. aureus* pneumonia (7 (5.9%) vs 10 (2.1%), p=0.06). We performed the same analysis in patients with and without influenza virus infection with similar results (4 (6.3%) vs10 (2.1%), p=0.074).

Severity outcomes associated with viral infection

Regarding clinical features, 272 (46.1%) patients had respiratory failure, 37 (6.3%) had septic shock and 54 (9.2%) were admitted to the ICU. Overall, 42 (7.1%) patients died during hospitalization. Table 5 provides an overview of clinical information and severity outcomes in patients with and without viral infection.

Patients with viral infection presented higher rates of bilateral consolidation patterns in the chest radiography (p=0.04), respiratory failure (p=0.001), and required more often ICU admission (p=0.001) and invasive mechanical ventilation (p=0.003). Even though patients with viral infection had respiratory failure more frequently, neither early (within 48 h) or late (within 30 days) mortality were higher than in non-viral CAP cases (p=1.0).

In the multivariate model, the only risk factor associated with ICU admission was viral infection. On the other hand, variables independently associated with respiratory failure were chronic lung disease, age > 65 years, positive blood cultures and-viral infection (Table 6). When we analyzed influenza virus separately from other respiratory viruses in a multivariate model, interestingly, influenza virus but no other viruses, was independently associated to respiratory failure (OR, 3.72; 95%CI, 2.06-6.73 and 1.26; 95% CI; 0.69-2.29, for influenza virus and other virus, respectively).

Treatment

All patients with confirmed influenza infection received oseltamivir. In 15 (4.7%) out of 322 patients in whom a bacterial isolate was detected, empirical treatment was not adequate. Treatment was considered appropriate for the bacteria isolated in 95.7% patients with viral infection and in 93.7% patients without it (p=0.510). We did not find differences between patients who received adequate or inadequate empirical treatment regarding mortality (8.3% vs 13.3%, p=0.373), ICU admission (10.6% vs 6.7%, p=1) and need for respiratory support (15% vs 20% p=0.71).

DISCUSSION:

In the last decade different studies have assessed the prevalence of viral infection in patients diagnosed with CAP [5,14,15]. In fact, when routine PCRs to detect viruses are performed, viral detection reaches 24,5-30% [6,7]. In our study we have detected a virus in 20% of all cases. With these newly detected microorganisms it seems logical to wonder if the presence of respiratory viruses has an impact on the bacterial etiology or in patients' outcomes. Despite this, how bacterial agents vary when CAP is associated with viral infection and what is the impact in clinical outcomes, have been barely reported.

In textbooks, *S. aureus* is referred as a frequent cause of CAP during the influenza season. Some studies performed in ICU patients report rates of *S. aureus* coinfection as high as 11-36.5%[12]. Moreover, in an observational study of 1392 inpatients with CAP and influenza infection, the proportion of *S. aureus* coinfection reached 46%. Nevertheless, such proportion may be overestimated, since bacterial etiology was based only in sterile-fluid cultures [16].

In our study we have not found significant differences in the bacteria documented in patients with viral coinfection. However, a slightly higher proportion of *S. aureus* pneumonia in patients with viral infection (5.9%) as well as in patients with influenza (6.3%), compared to the proportion in patients without viral infection (2.1%) was observed. Although the low number of patients with a staphylococcal infection precludes drawing robust conclusions, these rates are consistent with other studies. In a prospective study performed in the USA that included 2259 patients with CAP, *S. aureus* was documented in 1.6% cases, 8.1% of which had also an influenza infection [17]. In another study performed in Spain among 1123 episodes of adults with CAP admitted to conventional wards, the prevalence of *S. aureus* pneumonia was 7% and 2.2% in patients with and without viral coinfection respectively [8]. So, although the proportion of *S. aureus* and viral co-infection in hospitalized non-critically ill patients with CAP seems to be higher than in those without viral infection, it should be around 5-8%.

Regarding the clinical outcomes of patients with CAP, only few studies have compared the severity of pneumonia according to the presence or not of viral co-infection, and the findings have been inconsistent. A small study that included 235 patients with CAP, found bacterial-viral co-infection as a risk factor of mortality [15]. In a prospective study performed in Japan that included 2617 patients with CAP, influenza virus was associated with a three-fold higher mortality in

patients with chronic respiratory disease but not with other comorbidities [4]. In contrast, another recent study performed in Spain found that patients with viral-bacterial co-infection presented more respiratory failure and more often required ICU admission, but did not found higher mortality rates [8]. In the present study, we also find that patients with viral infection have higher rates of respiratory failure and ICU admission, and despite this, there are no differences in mortality.

In the multivariate analysis we found that viral infection was the only risk factor for ICU admission. This result should be interpreted with caution since it could be due to a selection bias resulting from greater diagnostic efforts in critically ill patients. Moreover, we believe that UCI admission is not an adequate variable to assess severity, since some patients may not be admitted due to their age or comorbidities regardless of severity. Respiratory failure, in contrast, does not have this limitation. Variables associated to respiratory failure were viral infection, chronic lung disease, age > 65 years and positive blood cultures. This is concordant with other studies [18]. Remarkably only influenza virus and no other respiratory viruses was associated with respiratory failure, which highlights the role of influenza as a cause of respiratory distress.

The pathogenic mechanisms explaining the association of viral co-infection and respiratory failure in patients with CAP is not completely elucidated. It has been suggested that influenza-mediated damage results from the combination of intrinsic viral pathogenicity, attributable to viral tropism for host airway and alveolar epithelial cells, with aberrant local host response, consisting of dysregulated inflammatory response, which contributes to the development of lung edema and respiratory failure. This local action explains why respiratory failure is the main clinical complication observed over other systemic complications, such as septic shock. Finally, influenza infection contributes to an indirect lung damage, favoring bacterial superinfection [19–21].

Ceftriaxone or cefotaxime plus a macrolide are among the preferred treatment options for inpatients with severe CAP according to the european and IDSA guidelines [22,23]. Whereas this holds true for the most prevalent bacterial causes of CAP, concern arises regarding its suitability for the treatment of staphylococcal infections [24], which could be higher in patients with viral co-infection. The limited number of patients with *S. aureus* infection in our study precludes further analysis about the suitability of empirical treatment in cases of CAP with viral co-infection.

One of the limitations of our study is that a nasopharyngeal swab to investigate respiratory viruses was not performed to all patients. However, this procedure was performed to most of the patients during the flu season, so we think that the role of influenza virus is accurately analyzed. Moreover, the rate of viral co-infection was similar than those observed in studies in which virus detection were systematically performed [2,5,25]. Finally, our study was performed before the emergence of the SARS-CoV-2 pandemic, so we have not addressed the interaction between bacterial pneumonia and SARS-CoV-2 infection. However, in contrast to what occurs in patients with severe influenza in which bacterial co-pathogens are commonly identified, the overall proportion of bacterial coinfection among patients with COVID-19 seems to be low. In a recent meta-analysis, the proportion of COVID-19 patients with bacterial infection was 6.9% [26]. Moreover, the most common microorganisms reported in patients with COVID-19 are quite different from bacterial co-pathogens most associated to influenza infection. Thus, the observations of our study cannot be applicable in the context of SARS-CoV-2.

CONCLUSIONS:

In summary, our study reports a trend towards a slight increase in *S. aureus* infections associated to viral infection in patients with CAP. Moreover, influenza infection, but not other respiratory virus, is associated with respiratory failure. Additional studies should be conducted to gain better insight into the etiology and clinical role of bacterial and viral coinfections, and as well as the need to adjust empirical treatment.

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TABLE 1: Baseline and microbiological characteristics of the study population and differences in patients with and without viral infection

Characteristics	Total n=590 (%)	No viral infection n= 472 (%)	Viral infection n= 118 (%)	p
Gender				
Male	359 (60.8)	282 (59.7)	77 (65.3)	0.29
Nursing home	35 (5.9)	27 (5.7)	8 (6.8)	0.66
Median (IQR) age (years)	70 (53-81)	70 (53-81)	69 (53-80)	0.64
Underlying conditions				
Arterial hypertension	319 (54.1)	252 (42.7)	67 (56.8)	0.54
Diabetes	132 (22.4)	106 (22.5)	26 (22)	1
Heart disease[1]	177 (30)	140 (29.7)	37 (31.4)	0.74
Chronic lung disease[2]	174 (29.5)	143 (30.3)	31 (26.3)	0.43
Chronic renal disease[3]	112 (19)	85 (18)	27 (22.9)	0.24
Neurologic chronic disease[4]	67 (11.4)	14 (11.9)	53 (11.2)	0.87
Immunosuppressive conditions				
HIV infection	18 (3.1)	14 (3.0)	4 (3.4)	0.77
Solid organ transplant	18 (3.1)	15 (3.2)	3 (2.5)	1.0
Bone marrow transplant	3 (0.5)	1 (0.2)	2 (1.7)	0.10
Use of chronic corticosteroids[5]	30 (5.1)	23 (4.9)	7 (5.9)	0.64
Hematologic malignancies	35 (5.9)	24 (4.1)	11 (9.3)	0.09
Solid organ neoplasm	22 (3.7)	21 (4.4)	1 (0.8)	0.10

Data are expressed as numbers and percentages unless otherwise indicated
Abbreviations: SD: Standard deviation, IQR: interquartile range, HIV: human immunodeficiency virus
[1]Heart disease: heart failure, moderate valvulopathy or atrial fibrillation.
[2]Chronic lung disease: Chronic Obstructive Pulmonary Disease (COPD) or bronchiectasis
[3]Chronic renal disease: Glomerular Filtration rate < 60 ml/min.
[4]Neurologic chronic disease: vascular or degenerative neurologic disease
[5]Use of corticosteroids: for more than 3 months

TABLE 2: Microbiological procedures performed according to the time of the year

Microbiological test	Total n=590 (%)	Flu Season [a] n=363 (%)	Between seasons [b] n=131 (%)	Summer season [c] n=96 (%)
Blood cultures	490 (83.1)	289 (79.6)	116(88.5)	85 (88.5)
Sputum cultures	293 (49.6)	185 (51.0)	53 (40.5)	55 (57.3)
PCR for respiratory virus	256 (43.4)	228 (62.8)	22 (16.8)	6 (6.2)
Legionella urinary Antigen	415 (70.3)	255 (70.2)	90 (68.7)	70 (72.9)
S. pneumoniae urinary antigen	590 (100)	363 (100)	131 (100)	96 (100)

Data are expressed as numbers and percentages unless otherwise indicated
[a] Flu season: from November 2017 to March 2018, both included
[b] Between seasons: April, March, September and October 2018
[c] Summer season: From June to August 2018, both included

TABLE-3: Bacterial pathogens documented in patients with and without viral infection

Bacteria documented	Total n=590 (%)	No viral infection n= 472 (%)	Viral infection n= 118 (%)	p
Total bacterial pathogens	321 (54.4)	257 (54.4)	64 (54.2)	1.0
S. pneumoniae	211 (35.8)	168 (35.6)	43 (36.4)	0.92
S. aureus	17 (2.9)	10 (2.1)	7 (5.9)	0.06
Legionella pneumophila	16 (2.7)	15 (3.2)	1 (0.8)	0.22
Other atypical pneumonia	8 (1.4)	8 (1.7)	0	0.37
Haemophilus influenzae	15 (2.5)	9 (1.9)	6 (5.1)	0.09
Other bacteria	25 (4.2)	21 (4.4)	4 (3.4)	0.80
Mixed bacterial pneumonia	29 (4.9)	26 (5.5)	3 (2.5)	0.24
No bacteria detected	269 (45.6)	215 (45.6)	54 (45.8)	1.0

TABLE ~~3~~ 4: Detailed microbiological information

			Virus detected								
		No virus	Influenza A	influenza B	RSV[1]	rhinovirus	adenovirus	coronavirus	metapneu-movirus	parainflu-enza	Total
No bacteria detected		215 (36.4%)	19	16	7	4	3	3	1	1	269
Bacteria detected	***S. pneumoniae***	168	6	12	8	11	0	5	1	0	211 (35.8%)
	S. aureus	10	2	2	0	1	0	1	1	0	17 (2.9%)
	Other streptococci	5	2	0	1	0	0	0	0	0	8 (1.4%)
	Legionella pneumophila	15	0	1	0	0	0	0	0	0	16 (2.7%)
	Haemophilus influenzae	9	1	1	0	2	0	0	2	0	15 (2.5%)
	Other atypical microorganisms	8	0	0	0	0	0	0	0	0	8 (1.4%)
	P. aeruginosa	6	0	0	0	0	0	0	0	0	6 (1.0%)
	S. pneumoniae + H. influenzae	13	0	0	0	1	0	0	0	0	14 (2.4%)
	B. catarrhalis + H. influenzae	2	0	1	0	0	0	0	0	0	3 (0.5%)
	S. aureus + H. influenzae	3	0	0	0	0	0	0	0	0	3 (0.5%)
	Other bacteria	10	0	0	0	1	0	0	0	0	11 (1.9%)
	Mix: 2 or more bacteria (not mentioned above)	8	1	0	0	0	0	0	0	0	9 (1.5%)
	Total	472	31 (5.3%)	33 (5.6%)	16 (2.7%)	20 (3.4%)	3 (0.5%)	9 (1.5%)	5 (0.8%)	1 (0.2%)	590 (100%)

[1]RSV: respiratory syncytial virus

TABLE 5-: Clinical characteristics and outcomes of patients with and without viral infection

Characteristics	Total n=590 (%)	No viral infection n= 472 (%)	Viral infection n= 118 (%)	p
Bilateral consolidation	72 (12.2)	51 (10.8)	21 (17.8)	0.04
Pleural effusion	101 (17.1)			
Complicated[1]	21 (3.6)	19 (4.0)	2 (1.7)	0.28
Not complicated	80 (13.6)	453 (96)	116 (98.3)	
Severity scores				
PSI high mortality classes (IV or V)	325 (55.1)	253 (53.6)	72 (61.0)	0.18
CURB-65 high mortality risk group (≥ 3 points)	146 (24.7)	115 (24.4)	31 (26.3)	0.72
ICU admission	54 (9.2)	33 (7.0)	21 (17.8)	0.001
Septic shock[2]	37 (6.3)	27 (5.7)	10 (8.5)	0.29
Respiratory failure[3]	272 (46.1)	202 (42.8)	70 (59.3)	0.001
Conventional ward managment[4]	191 (32.4)	146 (30.9)	45 (38.1)	0.153
ICU managment[5]	81 (13.7)	56 (11.9)	25 (21.2)	0.011
Invasive mechanical ventilation	24 (4.1)	13 (2.8)	11 (9.3)	0.003
Mean of ICU hospitalization, days (SD)	14.5 (18.2)	16.0 (21.6)	12 (11.5)	0.479
Mean of hospitalization, days (SD)	8.7 (11.9)	8.4 (11.7)	10.2 (12.5)	0.144
Mortality				
Mortality during hospitalization	42 (7.1)	35(7.4)	7 (5.9)	0.69
48-hour mortality	15 (2.5)	12 (2.5)	3 (2.5)	1.0
30-days mortality	34 (5.8)	27 (5.7)	7 (5.9)	1.0

Data are expressed as numbers and percentages unless otherwise indicated
Abbreviations: ICU: Intensive Care Unit, SD: Standard deviation, PSI: pneumonia severity index
[1]Complicated pleural effusion: pH<7.2, low glucose levels or evidence of microorganism by culture or gram stain,
[2]Septic shock: need of vasoactive drugs,
[3]Respiratory failure: pO2 in arterial blood lower or equal to 60 mmHg or peripheral pulse-oximetry lower than 90%
[4]Conventional ward management: supplementary oxygen with nasal cannula or Venturi mask
[5]ICU management: respiratory support with high flow nasal cannula or mechanical ventilation (invasive or not)

TABLE 6: Risk factors for respiratory failure and ICU admission. Multivariate analysis.

	Respiratory failure		ICU admission	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Heart disease	1.50 (0.99-2.25)	0.056	0.94 (0.45-1.95)	0.863
History of chronic lung disease	2.16 (1.47-3.17)	<0.001	0.99 (0.85-1.16)	0.905
Age > 65 years	2.14 (1.45-3.17)	<0.001	0.57 (0.30-1.07)	0.08
Viral infection	2.23 (1.44-3.45)	<0.001	2.77 (1.52-5.02)	0.001
Positive blood cultures[1]	1.97 (1.07-3.65)	0.03	1.51 (0.63-3.62)	0.352
Isolation of any bacteria	1.21 (0.85-1.74)	0.296	1.26 (0.68-2.33)	0.464

[1]Positive blood cultures: growth of a pathogen concordant with a cause of CAP.

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