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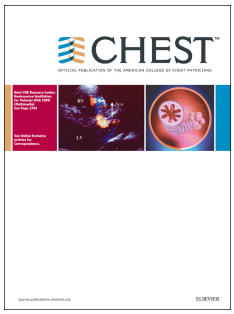

Community-Acquired Pneumococcal Pneumonia in Virologically Suppressed HIV-Infected Adult Patients: A Matched Case-Control Study

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Community-Acquired Pneumococcal Pneumonia in Virologically Suppressed HIV-Infected Adult Patients: A Matched Case-Control Study

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Abbreviations list

Community-acquired pneumonia (CAP)

Human Immunodeficiency Virus (HIV)

Antiretroviral therapy (ART)

White blood cell (WBC) count

C-reactive protein (C-RP)

Acute respiratory distress syndrome (ARDS)

Tracheobronchial aspirates (TBAS)

Bronchoalveolar lavage (BAL)

Interquartile range (IQR)

Standard deviation (SD)

Mean (SD)

Confidence interval (CI)

Receiver operating characteristic (ROC)

Minimal inhibitory concentration (MIC)

Hepatitis C virus (HCV)

Lactate deshydrogensase (LDH)

Pneumonia Severe Index (PSI)

Consciousness, Urea, Respiratory rate, Blood pressure, 65 years old (CURB-65)

Chronic obstructive pulmonary disease (COPD)

Intensive Care Unit (ICU)

Length of stay (LOS)

ABSTRACT

Background: The study aimed to investigate whether the clinical presentations and outcomes (length-of-stay (LOS), intensive care unit (ICU) admission and 30-day mortality) of pneumococcal pneumonia in virologically suppressed HIV-infected patients on ART with a CD4+ T cell count >350 cells/mm^3 are comparable to those seen in non-HIV-infected patients, using a case-control design.

Methods: A case-control study was carried out in Hospital Clinic, Barcelona, Spain (2001-2016). Controls were matched by age (±10 years), gender, co-morbidities and pneumonia diagnosis in the same calendar period. Clinical presentation and outcomes of pneumococcal pneumonia in HIV-infected patients and non-HIV-infected patients were compared.

Results: Pneumococcal pneumonia was studied in 50 cases (HIV-infection) and 100 controls (non-HIV-infection). Compared with the control patients, case patients had higher rates of influenza (14% *vs.* 2%, p=0·007) and pneumococcal vaccination (10% *vs.* 1%, p=0·016). The group of cases also presented a higher rate of co-infection with HBV (6% *vs.* 0%, p=0·036). Both groups presented similar ICU admission (18% *vs.* 27%, p=0·22), need for mechanical ventilation (12% *vs.* 8%; p=0·43), length of stay (7 days *vs.* 7 days, p<0·76) and 0% of 30-day mortality. No evidence was found of a more severe presentation or a worse clinical outcome in cases than in controls.

Conclusions: Pneumococcal pneumonia episodes requiring hospitalization in virologically suppressed HIV-infected patients with >350 CD4+ T cell count/mm^3 were neither more severe nor had worse prognosis compared with uninfected patients. These results support the fact that such patients do not need treatment, admission or care sites different to the general population.

Introduction

Community-acquired pneumonia (CAP) is still an important complication in HIV-infected patients, even in the era of combined antiretroviral therapy (ART)[1]. HIV-infected patients are generally known to be more susceptible to pneumococcal infections with a higher rate of bacteremia than non-HIV-infected patients[2]. Several studies have examined microbial etiology and prognostic factors of CAP in HIV-infected patients[3-6]. Despite the high rate of bacterial pneumonia in HIV-infected patients, mortality rates are not higher than in non-HIV-infected patients.

The data on clinical presentation and outcomes of pneumococcal CAP in HIV-infected patients are limited and conflicting, because these variables in HIV-infected patients are difficult to compare with those of non-HIV-infected patients, as bacterial pneumonia in non-HIV-infected patients often occurs in older subjects than in the HIV population [7]. It is known that the incidence of bacterial pneumonia is related to immunological status in HIV-infected patients; despite the introduction of ART, however, the risk of invasive pneumococcal disease remains 35 times greater in HIV-infected patients than in similarly aged non-HIV-infected adults[8]. Nevertheless, there is no data on whether clinical presentation and outcomes of pneumococcal CAP in HIV-infected patients with effective ART are similar to those of non-HIV-infected patients. The hypothesis was that both clinical presentation and outcomes are similar. The aim of this study, therefore, was to investigate whether the clinical presentations and outcomes (LOS, ICU admission and 30-day mortality) of pneumococcal pneumonia in virologically suppressed HIV-infected patients on ART with a CD4+ T cell count >350 cells/mm^3 are comparable to those seen in non-HIV-infected patients, using a case-control design.

Patients and Methods

Study Design and Patients

A case-control study was carried out in Hospital Clinic, Barcelona, Spain. All consecutive cases of adult patients with CAP diagnosed between January 2001 and January 2016 were included. CAP was defined as the presence of a new infiltrate on chest x-ray, together with clinical signs and symptoms suggestive of lower respiratory tract infection. Mycobacterial and fungal infections (other than *Pneumocystis jiroveci*) were also recorded but not included in the analysis. The diagnosis of pneumococcal CAP was performed according to the following criteria. Definite diagnosis: positive blood culture or positive pleural fluid culture or positive urinary antigen test for pneumococcus; and presumptive diagnosis: positive culture of respiratory samples (sputum, bronchoalveolar aspirate and bronchoalveolar lavage) in patients with pulmonary infiltrates.

Case Patients, Control Subjects and Matched Criteria

Case patients were identified from our database of CAP patients. Case patients were defined as HIV-infected adults (age, ≥18 years and ≤50 years) with a diagnosis of pneumococcal pneumonia between 2001 and 2016, with a CD4 lymphocyte count of ≥350 cells/mm^3 and undetectable levels of HIV-RNA (copies/mL) on ART.

Two control cases of pneumococcal pneumonia patients without HIV-infection were selected for each case patient and matched for the following variables: age (age of the case patients at the time of pneumococcal CAP ±10 years), sex, co-morbidities (chronic respiratory disease, diabetes mellitus, neurological disease, chronic cardiovascular disease, chronic liver disease, chronic renal disease) and CAP diagnosis in the same calendar period.

This study was approved by the local Institutional Review Board (Register #2009/5451). Patients remained anonymous and informed consent was waived due to the observational nature of the study.

Study Variables

After case patients and control subjects were identified, the following data were collected at the time of hospital admission: age, gender, HIV infection, AIDS-defining criteria, CD4+ cell count, plasma HIV viral load within the previous three months of admission, previous or current intravenous drug use, current smoking habits (>10 pack-years), alcohol habits (ingestion of an estimated amount of >80 g alcohol per day for at least one year before presentation), co-morbidities (chronic respiratory disease, diabetes mellitus, neurological disease, chronic cardiovascular disease, chronic liver disease, chronic renal disease), antimicrobial treatment prior to hospital admission, ART, duration of symptoms before the diagnosis of pneumonia, physical examination clinical signs and symptoms (fever, cough, pleuritic pain, dyspnea, mental confusion, and aspiration, blood pressure, body temperature, respiratory rate, and heart rate), chest X-ray pattern (number of lobes affected, pleural effusion, and atelectasis), blood analysis (hemoglobin level, white blood cell (WBC) count, platelet count, serum creatinine levels, C-reactive protein (C-RP) levels, and other biochemical parameters), pulmonary complications (empyema, acute respiratory distress syndrome (ARDS) criteria, pleural effusion, surgical pleural draining), clinical events (cardiac arrhythmia, septic shock, acute renal failure) and antimicrobial treatment at admission. Pneumonia severity index (PSI) and CURB-65[9] scores were determined in all patients[10]. All surviving patients were visited or contacted by telephone within 30 days after discharge.

Microbiological Evaluation

Microbiological investigation was performed on sputum, urine, two blood samples and nasopharyngeal swabs (see Supplementary Material). Pleural puncture, tracheobronchial aspirates (TBAS) and bronchoalveolar lavage (BAL) fluid, where available, were collected for Gram, Ziehl-Nielsen, May-Grünwald Giemsa and Gomori methenamine silver stains and for cultures for bacterial, fungal and mycobacterial pathogens.

Sputum and blood samples were obtained for bacterial culture before the start of antibiotic therapy in the emergency department. Nasopharyngeal swabs for respiratory virus detection and urine samples for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection were obtained within 24 hours of admission to hospital. Blood samples for serology of atypical pathogens and respiratory virus were performed at admission and at 4-6 weeks thereafter (see Supplementary Material).

HIV-1 viral load was determined by Versant HIV-1 RNA 1·0 kPCR Siemens Diagnostics (Lower Limit of Quantification: 37 copies/mL; Upper Limit of Quantification: 11,000,000 copies/mL) (Lower limit of quantification in the period 2007-09 <50 copies/mL and in the period 2010-12 lower limit <37 copies/mL).

Statistical Analysis

A total sample size of 150 patients (50 patients in the case group and 100 patients in the control group, according to 1:2 allocation ratio) was estimated to provide at least a 80% power and a two-sided alpha value of 0.05 to detect as statistically significant a difference of 25% in the percentage of patients admitted to ICU between groups (39% cases *vs*. 14% controls[11].Data are shown as number of patients (%) for categorical

variables and either median (interquartile range [IQR]) for continuous variables with non-normal distribution or mean (standard deviation [SD]) for those with normal distribution. Categorical variables were compared using the X^2 test or the Fisher exact test. Continuous variables were compared using the *t* test or the nonparametric Mann-Whitney test. Unconditional logistic regression analyses[12] were used to examine the associations between outcomes (ICU admission and prolonged length of hospital stay [LOS >7 days; cut-off value the median value of LOS]) and risk factors (see the full list of variables in the Supplemental Material). First, each risk factor was tested individually, second, all risk factors which showed an association in the univariate model ($p<0{\cdot}10$) were added into the multivariate model, and finally, a backward stepwise selection ($p_{in}<0{\cdot}05$, $p_{out}<0{\cdot}10$) was used to determine factors associated with ICU admission and prolonged LOS, with adjustment for one predefined covariate (i.e., the case-control). 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[13]. Internal validation of the prediction models was conducted using ordinary nonparametric bootstrapping with 1,000 bootstrap samples and bias-corrected, accelerated 95% CIs[14]. Receiver operating characteristic (ROC) curves were constructed for the ability to predict ICU admission and prolonged LOS, using variables derived from the multivariate logistic regression models. Simple imputations of random effects were used, where necessary, for variables with missing values. The level of significance was set at 0·05 (2-tailed). All analyses were performed using IBM SPSS Statistics version 22·0 (Armonk, New York, USA).

Results

General Patient Characteristics

During the study period (January 2001 to January 2016), a total of 2,300 consecutive patients with CAP were admitted to our hospital. Of them, 525 (23%) were HIV-infected patients. Matching was successful in 50 cases and 100 control subjects with CAP caused by *Streptococcus pneumoniae*.

Cases Characteristics

Of the 50 cases included, 35 (70%) were males, with a mean (SD) age of 46·5 (12·2) years. All cases were on ART, with the three most frequent ART regimens being: two nucleoside analogue reverse transcriptase inhibitors (NRTI) + one integrase strand transfer inhibitor (INSTI) (18 cases [38%]), 2 NRTI + 1 protease inhibitor (PI) (16 cases [33%]), and 2 NRTI + 1 non-nucleoside reverse transcriptase inhibitors (NNRTI) (13 cases [27%]). The median CD4+ cell count was 517·5 (403; 700) /mm^3 and the proportion of patients with undetectable viral load was 100%. Nadir CD4+ cell count <200 cells/µl was 19 (39%). AIDS-defining illness was present in 23 (47%) of cases. The majority of patients (76%) were classified as low risk class (PSI risk class I-III). Seventeen patients (34%) presented co-infection with HCV, HBV or both viruses. The most frequent complications were multilobar pneumonia (16 patients [32%]) and bacteremia (24 patients [51%]). Nine patients (18%) were admitted to the ICU and six of these (12%) required mechanical ventilation. The median (IQR) LOS was 7·0 (5·0; 11·0) days. The overall 30-day mortality was 0%.

Comparison of Characteristics of Pneumonia Cases and Controls

Baseline characteristics comparing cases and controls appear in Table 1. Cases and controls did not differ significantly in terms of baseline characteristics. Compared with

the control cases, the case patients had higher rates of influenza and pneumococcal vaccination. The group of cases also presented a higher rate of co-infection with HBV. Also, the co-infection with HCV seemed to be higher in the case group than the control group (Table 1) but no statistically significant difference was found (p=0·059). The control group more frequently presented pleural pain as a symptom and pleural effusion as a complication when compared with case patients.

Microbiological Findings, Antimicrobial Resistance and Pneumococcal Serotypes

With regard to microbiological diagnosis, 46 patients (92%) in the case group had a definitive diagnosis of pneumococcal pneumonia and 4 patients (8%) were diagnosed with presumptive diagnosis. In the control group, 90 patients (90%) had a definitive diagnosis of pneumococcal pneumonia and 10 patients (10%) were diagnosed with presumptive diagnosis. The percentages of patients with positive microbiological test results are shown in Table 2.

We did not observe any association between pneumococcal vaccination and the incidence of bacteremia in either HIV (23 [55%] vs. 1 [20%]; p=0.19) or non-HIV (37 [43%] vs. 1 [100%]; p=0.43) patients.

Minimal inhibitory concentration (MIC) testing was performed in 82 out of 121 of the *S. pneumoniae* isolates (68%). A total of 11 pneumococcal isolates showed some degree of penicillin non-sensitivity. In addition, 13 pneumococcal isolates were non-susceptible to erythromycin and there was a significant difference in regard to the erythromycin resistance between groups (9 cases [31%] *vs.* 4 controls [8%]; p=0·005).

Thirty-four out of 69 invasive isolates (49%) were available for serotyping. The most frequent serotypes in the whole population were 1 (n=10, 29%), 7F (n=7, 21%), 9N (n=3, 9%), 3 (n=3, 9%), 19A (n=2, 6%), 14 (n=2, 6%), 13 (n=2, 6%), and 4 (n=4, 6%), as

summarized in e-Table 1. Serotypes covered by the PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) vaccine represented 79% of all serotypes, and 21% were not included in this vaccine. No significant differences were observed in the distribution of serotypes covered by the PCV13 between cases and controls (7 cases [70%] *vs.* 20 controls [83%]; p=0·38). In 20 patients (83%) from the control group, however, serotypes (1, 19A, 3, 14, and 7F) that are described in the literature as being associated with complicated pneumococcal pneumonia were found[15]. Significant differences were observed in the distribution of this group of serotypes between cases and controls (4 cases [40%] *vs.* 20 controls [83%]; p=0·034) (e-Table 2). A further analysis was performed comparing this group of serotypes (1, 19A, 3, 14 and 7F) in patients with and without empyema; however, the numbers are smaller and differences were not statistically significant (0 empyema cases in the case group *vs.* 7 cases in the control group; p=0·15) (data not shown).

Empirical Antibiotic Therapy

The most frequent regimens were ß-lactam plus macrolide (28 cases [56%] *vs.* 45 controls [45%]; p=0·23), ß-lactam plus fluoroquinolones (10 cases [20%] *vs.* 19 controls [19%]; p>0·99), fluoroquinolone monotherapy (5 cases [10%] *vs.* 21 controls [21%]; p=0·093), and ß-lactam monotherapy (4 cases [8%] *vs.* 7 controls [7%]; p>0·99). All regimens were administered similarly in case and control patients.

Outcomes

Rate of ICU admission was similar in case and control groups (18% *vs.* 27%; p=0·22). Furthermore, the need for mechanical ventilation was similar for case and controls (12% *vs.* 8%; p=0·43). The LOS was also similar between case and controls (7 [5; 11]

277 days *vs.* 7 [4; 161] days; p=0·76). None of the patients included in either group died
278 (Table 3).

279 **Prognostic Factors**

280 We performed univariate and multivariate analyses for ICU admission and prolonged
281 LOS. In the first multivariate logistic regression analysis, the following factors were
282 independently associated with ICU admission: PSI risk class IV-V, levels of LDH
283 <498 U/L and the presence of multilobar involvement (Table 4). The area under the
284 ROC curve was 0·81 (95% CI 0·72-0·89) for the model predictive of ICU admission.
285 In the second multivariate logistic regression analysis for prolonged LOS (>7 days), the
286 following factors were independently associated: chronic lung disease, LDH ≥498 U/L,
287 multilobar involvement, pleural effusion and invasive mechanical ventilation (Table 5).
288 The area under the ROC curve was 0·84 (95% CI 0·78 to 0·91) for the model predictive
289 of prolonged LOS (>7 days). HIV-infection was not associated with ICU admission or
290 increased LOS in the multivariate analysis, even after adjustments for case patient and
291 potential confounding factors.
292 Internal validation of the two logistic regression models was conducted using
293 bootstrapping with 1,000 samples. All the variables included in the models for ICU
294 admission and prolonged LOS demonstrated robust results, with small 95% CIs around
295 the original coefficients, except for invasive mechanical ventilation in the model for
296 prolonged LOS, which appeared to be less reliable with wider 95% CIs around the
297 original coefficients (e-Table 3 and e-Table 4).

Discussion

To the best of our knowledge, this is the first case-control study addressing the issue of hospitalized pneumococcal CAP in virologically suppressed HIV-Infected patients with >350 CD4+ T cells/mm^3. The most important finding of this study is that hospitalized HIV-infected patients with pneumococcal CAP did not have a more severe presentation or worse clinical outcome than uninfected patients. Also, in multivariate analysis we found no evidence that HIV-infection was a risk factor for ICU admission or longer LOS (>7 days).

There is conflicting information regarding clinical presentation and outcomes of hospitalized HIV-infected patients with CAP [4;16-18]. Some studies have shown that mortality or LOS is unaffected by HIV infection whereas others have shown the opposite. Feldman et al[19] reported significant differences in the clinical presentation and outcome of bacteremic pneumococcal pneumonia when comparing HIV and non-HIV patients. In this study, HIV-infected patients had more clinical symptoms, especially among those with lower CD4 cell counts. In our study, case patients presented with rates of bacteremia of nearly 50%. In a larger series from our group, on HIV and CAP (331 patients), published in 2014, 100 patients had pneumococcal CAP and 50% of them also had bacteremia[6]. Other series have reported rates of bacteremia ranging from 23% to 75% [16;20;21]. In the same way, Mayaud et al[7] reported differences in presentation of CAP between HIV-infected and uninfected patients, high rates of bacteremia and pleural effusion are presented in HIV-infected patients. Nevertheless, the study by Bordon et al[18] showed that clinical outcomes of HIV-infected patients with CAP are not predicted by CD4+ T cell count or HIV-RNA levels; they comment that management of CAP in patients with HIV infection should

not be based on CD4+ T cell count or HIV-RNA levels of the HIV infection. Also, a secondary analysis of this data showed that the presence of HIV infection did not influence the clinical outcomes of CAP[22]. According to this study, there was no evidence that HIV-infected patients with pneumococcal pneumonia have a more severe presentation or worse clinical outcomes than HIV-uninfected patients. Our results are also in line with these findings. We found that clinical presentations and outcomes are similar between virologically suppressed HIV-infected patients and uninfected patients with pneumococcal pneumonia.

The patients in this study were young, with mainly low severity scores. The mortality rate is not surprising and is low according to the PSI score, although this could be due to the specific population analyzed. Differences were found in the presence of chest pain and pleural effusion between case and controls. Controls presented higher frequencies of chest pain and pleural fluid with statistical differences compared with the case group. Also, we found that the serotypes (1, 19A, 3, 14 and 7F) described in the literature as associated with complicated pneumococcal pneumonia[15] were more frequently observed in the control group (40% *vs.* 83%; p=0·034). These results explain the higher rate of chest pain, pleural effusion and the higher percentages of empyema in the case group. Because the physician in charge of patients takes the thoracentesis decision directly, we do not have a clear explanation as to the low rate of thoracentesis in case patients. One possibility is the higher amount of radiographic pleural fluid observed in cases compared to controls being probably due to the concern of an alternative diagnosis in HIV-infected patients.

There are currently no specific guidelines or recommendations for virologically suppressed HIV-infected patients on ART with >350 CD4 cells/mm^3, and these results

support the approach whereby these patients do not need specific treatments, hospital admission or sites of care that are different to the general population.

Despite a higher rate of vaccination in the case group, only 10% and 14% of HIV-infected patients were vaccinated against pneumococcus and influenza, respectively. We did not find any association between pneumococcal vaccination and the rate of bacteremia in our study. This result highlights the importance of improving these vaccinations in the HIV-population (as recommended by all international guidelines), in particular because most of the pneumococcus serotypes in the case group were included among those present in 13V pneumococcal vaccine.

Our study has a number of limitations. First, the defined sample size is too small to make a robust analysis of all related questions. The sample-size calculation was based on the percentage of patients admitted to ICU, where a total sample size of 150 patients (50 patients in the case group and 100 patients in the control group, according to 1:2 allocation ratio) is large enough if the expected difference is 25%. However, when comparing several characteristics between the two groups of patients, i.e. outcomes, the current study was underpowered. Second, as the data were collected from a single academic teaching hospital in Spain, the results might not generalize to other patients admitted to other types of hospitals in other countries. Third, the study took place over a long period; the protocols and microbiologic procedures have not, however, substantially changed during those years. Finally, the low mortality ratio in our study limits the generalization of our results. However, there are no data in the literature showing that virologically suppressed HIV-infected patients on ART should be treated in the same way as non-HIV infected patients.

In conclusion, this study describes a subpopulation of hospitalized virologically suppressed HIV-infected patients on ART with >350 CD4 cells/mm^3 and pneumococcal pneumonia in whom clinical presentation and outcomes did not differ from uninfected patients. The management of these HIV-infected patients should be the same as for HIV-uninfected individuals and should be included in the CAP management guidelines.

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Table 1. Baseline Characteristics of the Whole Population

Variables	Case Patients (HIV-infection) (n = 50)	Control Patients (non-HIV-infection) (n = 100)	P value
Age, mean (SD), years	46·5 (12·2)	47·5 (11·5)	0·64
Male sex, n (%)	35 (70)	70 (70)	>0·99
Current smoker, n (%)	34 (68)	56 (56)	0·16
Current alcohol abuse, n (%)	13 (26)	24 (24)	0·79
Previous antibiotic, n (%)	3 (6)	10 (10)	0·55
Influenza vaccine, n (%)	7 (14)	2 (2)	**0·007**
Pneumococcal vaccine, n (%)	5 (10)	1 (1)	**0·016**
Length of symptoms, median (IQR), days	3·0 (2·0; 5·0)	3·0 (2·0; 5·0)	0·91
Comorbidity, n (%)[a]	13 (26)	26 (26)	>0·99
Chronic respiratory disease	7 (14)	13 (13)	>0·99
Diabetes mellitus	2 (4)	4 (4)	>0·99
Chronic renal disease	1 (2)	2 (2)	>0·99
Chronic liver disease	3 (6)	7 (7)	>0·99
Co-infection with HCV, n (%)	12 (24)	12 (12)	0·059
Co-infection with HBV, n (%)	3 (6)	0	**0·036**
Co-infection with HCV/HBV, n (%)	2 (4)	2 (2)	0·60
Calendar year diagnosis, n (%)			>0·99
2001-2008	13 (26)	26 (26)	
2009-2016	37 (74)	74 (74)	
Symptoms, n (%)			
Fever	42 (84)	89 (89)	0·43
Cough	38 (76)	78 (78)	0·83
Purulent sputum	28 (56)	51 (51)	0·60
Pleuritic pain	23 (46)	69 (69)	**0·008**
Laboratory findings, median (IQR)			
Creatinine, mg/dL	1·0 (0·9; 1·4)	1·1 (0·9; 1·4)	0·52
C-reactive protein, mg/dL	25·1 (13·8; 29·4)	25·0 (17·5; 29·7)	0·78

Variables	Case Patients (HIV-infection) (n = 50)	Control Patients (non-HIV-infection) (n = 100)	P value
White blood cell count, $x10^9$ cell/L	11·9 (8·9; 16·6)	13·3 (9·2-19·6)	0·54
LDH, UI/L	387 (306; 500)	450 (350; 618)	0·16
Sat 0_2, %	92·7 (89·9; 95·2)	93·2 (89·3; 95·0)	0·98
PaO_2/FIO_2	276·2 (228·6; 342·9)	279·5 (242·9; 314·3)	0·91
Pneumonia Severity Index risk class, n (%)[b]			0·57
I-III	38 (76)	80 (80)	
IV-V	12 (24)	20 (20)	
CURB-65 score, n (%)[c]			0·61
0-2	45 (94)	91 (94)	
3-5	3 (6)	6 (6)	
Multilobar involvement, n (%)	16 (32)	32 (32)	>0·99
Pleural effusion, n (%)	6 (12)	28 (28)	**0·027**
Respiratory distress, n (%)	6 (6)	4 (8)	0·73
Septic shock, n (%)	3 (6)	3 (3)	0·40
Acute renal failure, n (%)	21 (21)	12 (24)	0·68

Abbreviations: CURB-65 indicates consciousness, urea, respiratory rate, blood pressure, 65; HAART, highly active antiretroviral therapy; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; Sat O_2, oxygen saturation; SD, standard deviation.

[a] Could have more than 1 comorbid condition.

[b] Stratified according to 30-day risk mortality for community-acquired pneumonia: risk classes I-III (≤90 points) have low mortality and risk classes IV-V (>90 points) have the highest mortality.

[c] Stratified according to 30-day risk mortality for community-acquired pneumonia: risk scores 0-2 have low mortality and risk scores 3-5 have the highest mortality.

Table 2. Microbial Diagnosis of Pneumococcal Pneumonia

Microbiological Test	Case Patients (HIV-infection)	Control Patients (non-HIV-infection)	P value
Blood culture	24 / 47 (51)	38 / 88 (43)	0·38
Pleural fluid	0 / 3 (0)	7 / 18 (39)	0·52
Urine pneumococcal antigen	38 / 43 (88)	72 / 85 (85)	0·57
Sputum	16 / 31 (52)	32 / 63 (51)	0·94
Bronchoalveolar lavage	1 / 5 (20)	3 / 7 (43)	0·58

Data are expressed as no. of patients with positive result / no. of patients tested (%).

Table 3. Clinical Outcomes

Variables	Case Patients (HIV-infection) (n = 50)	Control Patients (non-HIV-infection) (n = 100)	P value
ICU admission, n (%)	9 (18)	27 (27)	0·22
Mechanical ventilation, n (%)	6 (12)	8 (8)	0·43
Length of hospital stay, median (IQR), days	7·0 (5·0; 11·0)	7·0 (4·0; 11·0)	0·76
30-day mortality, n (%)	0 (0)	0 (0)	-

Abbreviations: IQR indicates interquartile range.

Table 4. Significant Univariate and Multivariate Logistic Regression Analyses for ICU Admission

Variable	Univariate			Multivariate[a]		
	OR	95% CI	P value	OR	95% CI	P value
Case Patients (HIV-infection)	0·59	0·25 to 1·38	0·23	0·60	0·23 to 1·59	0·30
C-reactive protein level ≥14·75 mg/dL[b]	6·63	1·50 to 29·24	0·012	-	-	-
LDH <498 U/L[b]	2·10	1·01 to 4·38	0·047	2·68	1·11 to 6·48	0·028
Pneumonia Severity Index risk class IV-V	4·90	2·11 to 11·39	<0·001	5·68	2·15 to 14·95	<0·001
Multilobar involvement	4·51	2·05 to 9·95	<0·001	5·32	2·18 to 13·00	<0·001
Pleural effusion	2·50	1·09 to 5·73	0·030	-	-	-
Acute renal failure	4·56	1·98 to 10·52	<0·001	-	-	-

Abbreviations: CI indicates confidence interval; ICU, intensive care unit; LDH, lactate dehydrogenase; OR, odds ratio. [a] Hosmer-Lemeshow goodness-of-fit test, p=0·39. [b] Optimal cut-off value of cases and controls using ROC curves.

Table 5. Significant Univariate and Multivariate Logistic Regression Analyses for Prolonged LOS (>7 days)

Variable	Univariate			Multivariate[a]		
	OR	95% CI	P value	OR	95% CI	P value
Case Patients (HIV-infection)	1·08	0·55 to 2·14	0·82	2·14	0·88 to 5·21	0·093
Chronic lung disease	3·39	1·22 to 9·39	0·019	6·88	2·06 to 22·94	0·002
LDH ≥498 U/L[b]	2·13	1·09 to 4·14	0·026	3·06	1·26 to 7·43	0·014
Pneumonia Severity Index risk class IV-V	2·13	0·96 to 4·72	0·062	-	-	-
Multilobar involvement	4·40	2·11 to 9·19	<0·001	3·59	1·46 to 8·85	0·005
Pleural effusion	9·21	3·52 to 24·12	<0·001	17·76	5·60 to 56·32	<0·001
Acute renal failure	2·29	1·04 to 5·05	0·040	-	-	-
Invasive mechanical ventilation	11·12	1·35 to 91·31	0·025	12·81	1·41 to 116·57	0·024

Abbreviations: CI indicates confidence interval; LDH, lactate dehydrogenase; LOS, length of hospital stay; OR, odds ratio. [a] Hosmer-Lemeshow goodness-of-fit test, p=0·94. [b] Optimal cut-off value of cases and controls using ROC curves

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e-Appendix 1.

METHODS

Statistical Analysis

Receiver operating characteristic (ROC) curves were constructed to determine the best cut-points for C-reactive protein and lactate dehydrogenase (LDH) in relation to case-control patients. Youden's index[1] was defined for all points along the ROC curve, and the maximum value of the index was used as a criterion for selecting the optimum cut-off point. To identify factors associated with outcomes (intensive care unit [ICU] admission and prolonged length of hospital stay [LOS; LOS >7 days; cut-off value the median value of LOS]) unconditional logistic regression models were used[2]. Variables were included in the multivariate model when univariate comparisons yielded a level of significance of $p<0{\cdot}10$. The following variables were tested: age (<65 *vs.* ≥65 years), gender, previous antibiotic, influenza vaccination, pneumococcal vaccination, inhaled corticosteroids, systemic corticosteroids, chronic pulmonary disease, chronic cardiovascular disease, diabetes mellitus, neurological disease, chronic renal disease, chronic liver disease, pleuritic pain, fever, altered mental status, dyspnea, C-reactive protein (<14·75 *vs.* ≥14·75 mg/dL), white blood cell count (<10 *vs.* ≥10 $x10^9$ cells/L), LDH (<498 *vs.* ≥498 U/L), Sat O_2 (<92% *vs.* ≥92%), PaO_2/FiO_2 (<250 *vs.* ≥250), multilobar affectation, pleural effusion, septic shock, and acute renal disease. To identify the problem of colinearity, the *r* coefficient of two variables were calculated. Where two independent variables were highly correlated ($r > |\pm 0{\cdot}30|$), the variable with the largest variance was excluded from the multivariate analysis[3].

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e-Table 1. Serotype Distribution

Pneumococcal Serotype	Case Patients (HIV-infection) (n = 10)	Control Patients (non-HIV-infection) (n = 24)	P value
1	0 (0)	10 (42)	**0·017**
3	0 (0)	3 (13)	0·54
4	2 (20)	0 (0)	0·080
5	1 (10)	0 (0)	0·29
7F	4 (40)	3 (13)	0·071
9N	1 (10)	2 (8)	>0·99
13	1 (10)	1 (4)	0·51
14	0 (0)	2 (8)	>0·99
19A	0 (0)	2 (8)	>0·99
22F	0 (0)	1 (4)	>0·99
29	1 (10)	0 (0)	0·29

Abbreviations: HIV indicates human immunodeficiency virus.

Data are expressed as no. of patients (%).

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e-Table 2. Serotype Associated with Complicated Pneumococcal Pneumonia (1, 3, 7F, 14, and 19A) Versus Not Associated (4, 5, 9N, 13, 22 and 29)

Pneumococcal Serotype	Case Patients (HIV-infection) (n = 10)	Control Patients (non-HIV-infection) (n = 24)	P value
Serotype associated with complicated pneumococcal pneumonia: 1, 3, 7F, 14, and 19A	4 (40)	20 (83)	**0·034**
Serotype not associated with complicated pneumococcal pneumonia: 4, 5, 9N, 13, 22 and 29	6 (60)	4 (17)	

Abbreviations: HIV indicates human immunodeficiency virus.

Data are expressed as no. of patients (%).

e-Table 3. Internal Validation of the Multivariate Logistic Regression Model for ICU Admission Using Nonparametric Bootstrap Technique

Variable	Original	Bias	SE	95% BCa CI
Case Patients (HIV-infection)	-0·509	-0·040	0·549	-1·758 to 0·407
LDH <498 U/L[a]	0·986	0·049	0·473	0·088 to 2·005
Pneumonia Severity Index risk class IV-V	1·736	0·089	0·569	0·728 to 3·055
Multilobar involvement	1·672	0·082	0·510	0·732 to 2·768

Abbreviations: BCa indicates adjusted bootstrap; CI, confidence interval; HIV, human immunodeficiency virus; ICU, intensive care unit; LDH, lactate dehydrogenase; SE, standard error.

[a] Optimal cut-off value of cases and controls using ROC curves.

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e-Table 4. Internal Validation of the Multivariate Logistic Regression Model for Prolonged LOS Using Nonparametric Bootstrap Technique

Variable	Original	Bias	SE	95% BCa CI
Case Patients (HIV-infection)	0·762	0·053	0·498	-0·188 to 1·804
Chronic lung disease	1·929	0·155	0·691	0·840 to 3·558
LDH ≥498 U/L[a]	1·118	0·086	0·530	0·147 to 2·341
Multilobar involvement	2·877	0·260	1·412	1·845 to 4·610
Pleural effusion	1·278	0·071	0·494	0·403 to 2·361
Invasive mechanical ventilation	2·550	6·644	9·466	0·380 to 22·329

Abbreviations: BCa indicates adjusted bootstrap; CI, confidence interval; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; LOS, length of hospital stay; SE, standard error.

[a] Optimal cut-off value of cases and controls using ROC curves.

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