International Journal of Infectious Diseases 15 (2011) e822–e827

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

CD4+ cell counts and HIV-RNA levels do not predict outcomes of community-acquired pneumonia in hospitalized HIV-infected patients

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ARTICLE INFO

Article history:
Received 14 February 2011
Received in revised form 26 April 2011
Accepted 30 May 2011

Corresponding Editor: Mark Holodniy, California, USA

Keywords:
Community-acquired pneumonia
Clinical outcomes
CD4+ cell counts
HIV-RNA level

SUMMARY

Background: Outcomes of community-acquired pneumonia (CAP) in relation to CD4+ cell counts have not been established. We examined the correlation of CD4+ cell count and HIV-RNA level with the clinical outcomes of CAP in hospitalized HIV-infected patients.

Methods: This was a retrospective study of 127 adult hospitalized patients with HIV infection enrolled with the CAP Organization (CAPO), examining the time to clinical stability (TCS), length of hospital stay (LOS), and all-cause mortality.

Results: Mortality data were available for 117 HIV-infected patients with CAP. Death within 28 days was reported in 28 patients. The risk of mortality at 28 days was not significant when adjusted for CD4+ cell count ($p = 0.123$), HIV-RNA <400–1000 copies/ml ($p = 0.093$), HIV-RNA ≥1000–10 000 copies/ml ($p = 0.543$), and HIV-RNA ≥10 000–100 000 copies/ml ($p = 0.383$). The propensity-adjusted Cox proportional hazards regression models did not show any statistically significant differences in LOS or TCS for CD4+ cell counts ($p = 0.590$ and $p = 0.420$, respectively) or HIV-RNA levels ($p = 0.470$ and $p = 0.080$, respectively). Multivariable Cox proportional hazards models did not reveal any statistically significant relationships between CD4+ cell counts or HIV-RNA levels with LOS or TCS.

Conclusions: Our study shows that clinical outcomes of HIV-infected patients with CAP are not predicted by CD4+ cell counts or HIV-RNA levels after adjusting for confounders. The management of CAP in patients with HIV infection should not be based on CD4+ cell counts or HIV-RNA levels of the HIV infection.

1. Introduction

HIV infection is a major risk factor for the development of community-acquired pneumonia (CAP).[1–3] *Streptococcus pneumoniae* is the most common pathogen of bacterial pneumonia in HIV patients.[4] An association has been established between a high risk of CAP in HIV-infected patients and low CD4+ cell counts;[4–7] however CAP outcomes in relation to CD4+ cell counts in these patients remain controversial.[8–10] Some reports have indicated the increased morbidity and mortality of HIV-infected patients with CAP,[11,12] therefore physicians may consider that it is safer to hospitalize these patients.[13,14] A nationwide Danish cohort study from 1995 to 2007 showed that HIV infection remains a major indication for the need of hospitalization in patients with pneumonia.[15] First-time hospitalization for pneumonia was six-fold greater among HIV-infected patients compared with the general population until 2007.[15] Because the clinical outcomes of HIV-infected patients with CAP remain unknown, the need for and benefits of hospitalization in these patients are contentious.

Effective antiretroviral therapy (ART) has been shown to prevent CAP among HIV-infected patients.[15,16] However, bacterial pneumonia was reported to be a major source of morbidity in HIV-infected patients regardless of ART in a cohort of patients with CD4+ cell counts of >350/mm^3.[16] Poorer outcomes among HIV-infected patients with CAP are likely due to limited healthcare resources for patients with advanced HIV disease and severity of illness.[11,12]

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doi:10.1016/j.ijid.2011.05.021

Determining any correlations of CD4+ cell count and HIV-RNA levels with clinical outcomes of hospitalized HIV-infected patients with CAP may guide clinicians to optimize management and the use of resources. The clinical outcomes of CAP in relation to CD4+ cell count, HIV-RNA level, and type of ART have not been fully examined. This study examined the correlation of CD4+ cell count, HIV-RNA level, and type of ART on the clinical outcomes of CAP among hospitalized HIV-infected patients.

2. Materials and methods

2.1. Study design

This was a retrospective study of adult patients with HIV infection hospitalized with CAP enrolled in the Community-Acquired Pneumonia Organization (CAPO) database. This study examined the outcomes: mortality at 28 days, the length of hospital stay (LOS), and the time to clinical stability (TCS) in relation to CD4+ cell count and HIV-RNA level. The CAPO study protocol has been approved by each local institutional review board of the CAPO centers. Patients were enrolled from six centers: Louisville, KY, USA; Washington, DC, USA; Orlando, FL, USA; Vigo, Spain; Tarragona, Spain; and Barcelona, Spain. CAPO is an international, retrospective, observational study of adult patients hospitalized with CAP. Random medical records of hospitalized patients with the diagnosis of CAP were reviewed at each participating center. Confirmation of HIV infection was obtained from the medical history. Each investigator filled out a case report form that was transferred via the internet to the CAPO study center at the University of Louisville. A sample of the data collection form is available at the study website (http://www.caposite.com). Validation of data quality was performed at the study center before the case was entered into the CAPO database. These CAPO study cases were enrolled from June 6, 2001 to January 5, 2010. These study cases were from centers in the USA and Spain; they received medical management according to national guidelines and were expected to receive similar antibiotic treatment and overall medical management.

2.2. Inclusion criteria

The diagnosis of CAP was according to the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria.[17] CD4+ cell counts and HIV-RNA levels were obtained: CD4+ cell counts available at least once at 12, 6, or 3 months before hospitalization and at the time of hospitalization for CAP; HIV-RNA levels if available within the 12 months before hospitalization and at the time of hospitalization for CAP.

ART was defined as a combination of antiretrovirals including two nucleoside drugs plus either one non-nucleoside drug or one protease inhibitor. Salvage ART was not considered an exclusion criterion. Information on antimicrobial therapy prior to hospitalization for *Pneumocystis jirovecii* pneumonia (PCP) and *Mycobacterium avium* complex was obtained.

2.3. Exclusion criteria

Patients with a presumptive or definitive diagnosis of PCP, mycobacterial, or fungal pneumonia were excluded from this study. Patients were excluded if they were treated for a suspected PCP, mycobacterial, or fungal etiology.

2.4. Study outcomes

The study outcomes were: (1) TCS: a patient was defined as clinically stable and ready to be switched to an oral antibiotic the day that the following four criteria were met: (a) improved cough and shortness of breath, (b) lack of fever for at least 8 h, (c) improving leukocytosis (decreased at least 10% from the previous day), and (d) tolerating oral intake with adequate gastrointestinal absorption.[18] Patients were evaluated daily within the first 7 days of hospitalization to determine the day when clinical stability was reached. (2) LOS: defined in days and calculated for each patient as the day of discharge minus the day of admission. Patients hospitalized for more than 14 days were censored at 15 days in an effort to capture LOS data related only to CAP. (3) All-cause mortality: patients were categorized as 'survivor' or 'non-survivor' and patients who were still hospitalized at day 28 were considered as survivors.

2.5. Confounding variables

The following 28 variables were obtained from each study participant: demographics: age, gender, and nursing home residency; coexisting conditions: neoplastic disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, renal disease, liver disease, use of alcohol and/or illegal drugs, cerebrovascular accident (CVA), and congestive heart failure (CHF); physical examination: temperature, respiratory rate, heart rate, blood pressure, and altered mental status; laboratory tests: sodium, arterial partial pressure of O_2, hematocrit, blood urea nitrogen (BUN), glucose, and arterial pH; chest X-ray: multilobar involvement, presence of cavity, and presence of pleural effusion; severity of CAP: need for intensive care unit (ICU) admission, risk class according to the pneumonia severity index (PSI), and CRB-65 score.[19] Arterial partial pressure of O_2 and arterial pH were done only if patients were admitted to the ICU.

2.6. Statistical methods

The predictor variables in this study were CD4+ cell count and HIV-RNA level. The CD4+ cell count and the HIV-RNA level were utilized as both continuous variables and categorical variables. The categorical CD4+ cell count was expressed using the following cutoffs: <50 cells/mm^3, 51–200 cells/mm^3, 201–350 cells/mm^3, and >350 cells/mm^3. The categorical HIV-RNA level was expressed using the following cutoffs: <400 copies/ml, 401–10 000 copies/ml, and $>10\,000$ copies/ml. The primary outcome variable was mortality at 28 days, and the secondary outcome variables were LOS and TCS.

Baseline patient characteristics were compared between those who survived until 28 days and those who had died within 28 days. Categorical variables were compared using the Chi-square test or Fisher's exact test, and continuous variables were compared using Mann–Whitney *U*-tests.

For the time-to-event outcomes of LOS and TCS, Kaplan–Meier survival curves were created to compare the above-mentioned cutoffs of CD4+ cell count and HIV-RNA level. Log-rank tests were used to compare statistically significant differences between the survival curves.

Considering the relatively small sample size of this study, traditional statistical methodology for adjustment of confounding variables would have limited the ability to adjust for multiple confounding variables in multivariate analyses. To overcome this statistical limitation, a propensity score was created from all demographic and clinical variables with *p*-values of ≤ 0.05. This propensity score was then used to adjust for the possibility of confounding effects in a series of regression models.

For the primary outcome of mortality at 28 days, propensity-adjusted logistic regression models were used to evaluate the risk of mortality for a given CD4+ cell count or HIV-RNA level, as well as for the patient's PSI. Predicted probabilities from each regression model were used to create line charts to examine the trends in risk of mortality.

To evaluate the secondary time-to-event outcomes of LOS and TCS, propensity-adjusted Cox proportional hazards regression models were used. Hazard ratios and 95% confidence intervals were calculated to express the relative likelihood of the outcome for the categorized values of CD4+ cell count and HIV-RNA level. p-Values of ≤ 0.05 were considered statistically significant in all analyses. SAS v9.2 (SAS Inc., Cary, NC, USA) and MedCalc v11 (MedCalc Software, Mariakerke, Belgium) were used for all analyses.

Table 1
Baseline characteristics of HIV-infected patients with CAP according to survival status at 28 days of hospitalization[a]

Variable	Dead at 28 days ($n=28$), n (%)	Alive at 28 days ($n=89$), n (%)	p-Value
Demographics			
Age (years), mean (SD)	42.9 (7.9)	43.8 (9.1)	0.643
Male gender	24 (85.7)	56 (62.9)	0.083
Nursing home residence	2 (7.1)	0 (0)	0.014
Comorbidities and other risk factors			
Altered mental status	3 (10.7)	14 (15.7)	0.451
Aspiration pneumonia	2 (7.1)	3 (3.4)	0.437
BMI (kg/m^2), mean (SD)	23.1 (4.5)	27.9 (40.6)	0.297
Obesity (BMI >30)	0 (0)	11 (12.4)	0.269
COPD	6 (21.4)	11 (12.4)	0.291
CHF	0 (0)	4 (4.5)	0.238
Cerebrovascular accident	0 (0)	3 (3.4)	0.309
Diabetes mellitus	6 (21.4)	7 (7.9)	0.066
Liver disease	2 (7.1)	30 (33.7)	0.004
Neurological disease	3 (10.7)	11 (12.4)	0.730
Neoplastic disease	2 (7.1)	2 (2.2)	0.246
Previous CAP	7 (25)	10 (11.2)	0.955
Previous PCP	6 (21.4)	3 (3.4)	0.159
Renal disease	6 (21.4)	4 (4.5)	0.008
Substance use			
Cocaine	0 (0)	10 (11.2)	0.057
Crack	1 (3.6)	9 (10.1)	0.253
Heroin	1 (3.6)	3 (3.4)	1.000
Marijuana	3 (10.7)	8 (9.0)	0.855
Methadone	0 (0)	2 (2.2)	0.410
Alcohol	4 (14.3)	3 (3.4)	0.043
Bacteremia	4 (14.3)	10 (11.2)	0.740
Severity of disease			
ICU admission	7 (25)	8 (9.0)	0.039
PSI class IV or V	3 (10.7)	13 (14.6)	0.759
CRB-65 class II, III or IV	3 (10.7)	25 (28.1)	0.060
HIV-specific variables			
AIDS-defining illness	10 (35.7)	6 (6.7)	0.252
CD4+ (cells/mm^3)			
<200	19 (67.9)	49 (55.1)	0.320
200–350	2 (7.1)	17 (19.1)	
351–500	2 (7.1)	12 (13.5)	
>500	5 (17.9)	11 (12.4)	
CD4+ cell %, mean (SD)	2.7 (1.5)	12.8 (8.7)	0.053
CD4+ cell absolute, mean (SD)	164.8 (213.6)	239.2 (250.6)	0.315
CD4+ cells at CAP, mean (SD)	239.6 (286.4)	230.1 (207.6)	0.406
CD4+ cells at 3 months before CAP, mean (SD)	246 (290.5)	280 (196.5)	0.688
CD4+ cells at 6 months before CAP, mean (SD)	377 (396.6)	291.9 (173.7)	0.443
CD4+ cells at 12 months before CAP, mean (SD)	338.1 (390.2)	250.6 (208.8)	0.348
CD4+ cells <200 at 3 months before CAP	4/10 (40)	6/12 (50)	0.639
CD4+ cells <200 at 12 months before CAP	8/24 (33.3)	37/85 (43.5)	0.370
Detectable HIV-RNA level at CAP	23/25 (92)	44/61 (72.1)	0.044
HIV-RNA level at CAP (copies/ml), mean (SD)	173 438.8 (229 706.2)	159 420.6 (440 566.3)	0.848
HIV-RNA level >100 000 copies/ml at CAP	8/25 (32)	16/60 (26.7)	0.619
HIV-RNA level 12 months after CAP (copies/ml), mean (SD)	200 985 (275 648.1)	212186.5 (722 485.3)	0.931
HIV treatment			
ART	21 (75)	61 (68.5)	0.494
Protease inhibitor-based ART	10 (35.7)	41 (46.1)	0.196
ART duration <2 months	2 (7.1)	3 (3.4)	0.429
ART duration <6 months	1 (3.6)	3 (3.4)	1.000
ART duration <12 months	13 (46.4)	28 (31.5)	0.225
Prophylaxis			
PCP prophylaxis	15 (53.6)	37 (41.6)	0.275
PCP prophylaxis <3 months	16 (57.1)	37 (41.6)	0.249
PCP prophylaxis <6 months	14 (50)	55 (61.8)	0.175
Atovaquone	0 (0)	1 (1.1)	0.562
Dapsone	2 (7.1)	4 (4.5)	0.629
Trimethoprim/sulfamethoxazole	9 (32.1)	28 (31.5)	0.910
MAC prophylaxis	5 (17.9)	11 (12.4)	0.240
Azithromycin	7 (25)	11 (12.4)	0.141

CAP, community-acquired pneumonia; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; PCP, *Pneumocystis jirovecii* pneumonia; ICU, intensive care unit; PSI, pneumonia severity index; ART, antiretroviral therapy; MAC, *Mycobacterium avium* complex.

[a] From a total of 127 patients enrolled in this study, 10 patients were excluded from the analysis of outcome mortality because mortality data were not available.

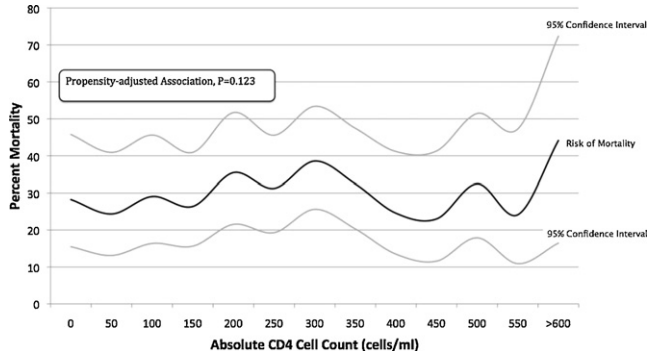

Figure 1. Propensity-adjusted risk of mortality at 28 days with 95% confidence intervals by CD4+ cell count for patients hospitalized with community-acquired pneumonia.

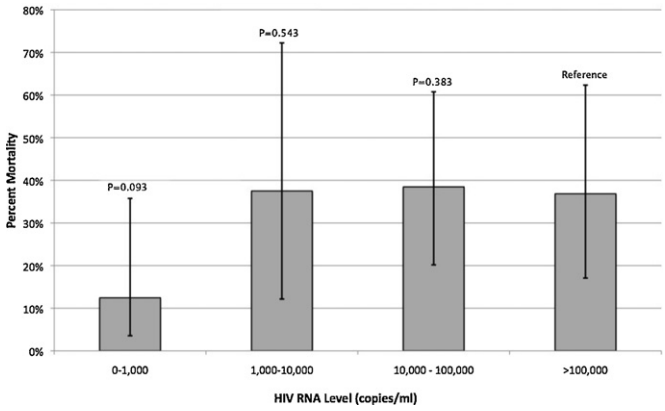

Figure 2. Propensity-adjusted risk of mortality at 28 days with 95% confidence intervals by HIV-RNA level for patients hospitalized with community-acquired pneumonia.

3. Results

A total of 127 HIV-infected patients with CAP were enrolled in this study. Ten patients did not have mortality data and were excluded from the analysis of mortality outcome. Death within 28 days was reported for 28 patients. The main characteristics of survivors and non-survivors are shown in Table 1. The presence of AIDS was not statistically different between non-survivors (35.7%) and survivors (6.7%). More than half of the patients in both groups had CD4+ cell counts of $<200\ mm^3$. There was no significant difference between the groups in CD4+ cell counts regardless of cutoffs, means, and counts in the 12 months preceding CAP; however the CD4+ cell percent was lower for non-survivors ($p = 0.053$). Both groups had similar mean CD4+ cell counts at the time of CAP: 239.6 ± 286.4 for non-survivors and 230.1 ± 207.6 for survivors. At the time of diagnosis of CAP, 92% of non-survivors had a detectable HIV-RNA level versus 72.1% of survivors ($p = 0.044$). The mean HIV-RNA load at CAP was 173 438 copies/ml for non-survivors and 159 420 copies/ml for survivors ($p = 0.848$).

The etiology of CAP was identified in 36 (28.3%) of 127 study cases. The pathogens identified were *S. pneumoniae* ($n = 22$), methicillin-resistant *Staphylococcus aureus* ($n = 5$), methicillin-susceptible *S. aureus* ($n = 1$), coagulase-negative Staphylococcus ($n = 1$), *Pseudomonas aeruginosa* ($n = 4$), *Legionella spp* ($n = 1$), influenza A 2009 H1N1 ($n = 1$), and adenovirus ($n = 1$).

The propensity-adjusted logistic regression models did not show any statistically significant difference in the risk of mortality at 28 days for the cohort of HIV-infected patients with CAP according to CD4+ cell count ($p = 0.123$) (Figure 1). The risk of mortality at 28 days was not significant when adjusted for HIV-RNA levels at three different ranges: HIV-RNA <400–1000 copies/ml ($p = 0.093$), HIV-RNA ≥ 1000–10 000 copies/ml ($p = 0.543$), and HIV-RNA $\geq 10\,000$–100 000 copies/ml ($p = 0.383$) (Figure 2). The propensity-adjusted Cox proportional hazards regression models did not reveal any statistically significant difference in LOS for CD4+ cell counts ($p = 0.590$) or HIV-RNA levels ($p = 0.470$) (Figure 3). There was no significant difference in the likelihood of TCS in relation to CD4+ cell count ($p = 0.420$) or HIV-RNA level ($p = 0.080$) (Figure 4). Multivariable Cox proportional hazards models did not reveal any statistically significant relationships between CD4+ cell counts or HIV-RNA levels with LOS or TCS (Tables 2 and 3).

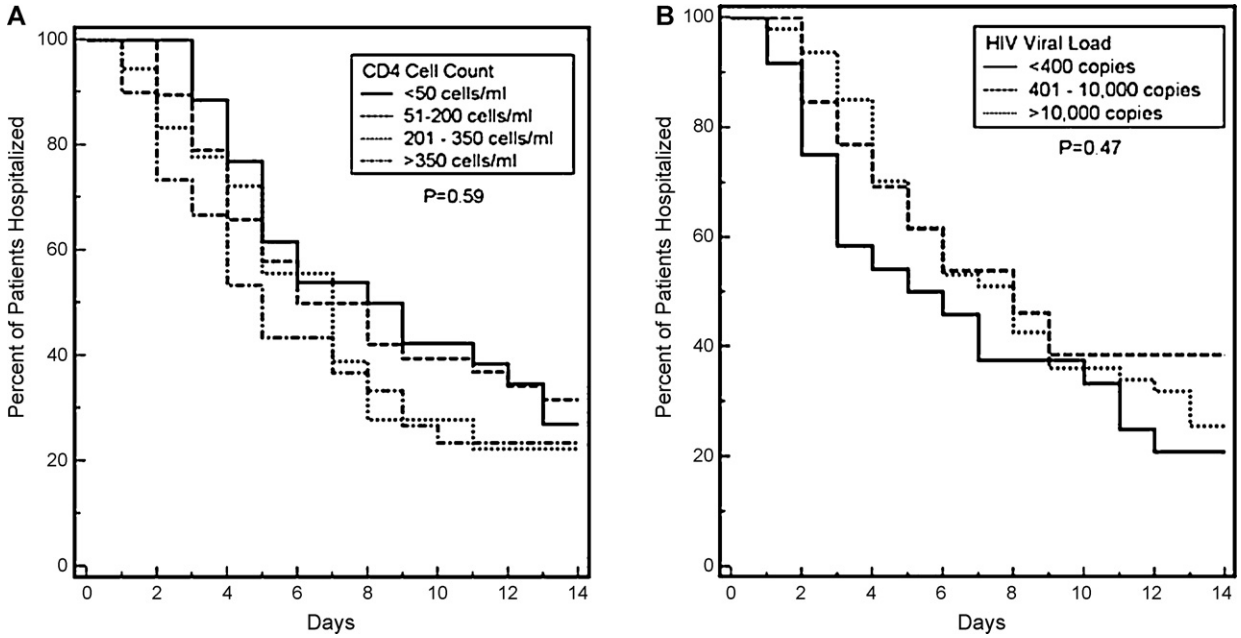

Figure 3. Kaplan–Meier survival curves indicating length of hospital stay (LOS) by (A) CD4+ cell count and (B) HIV-RNA level, for patients hospitalized with community-acquired pneumonia.

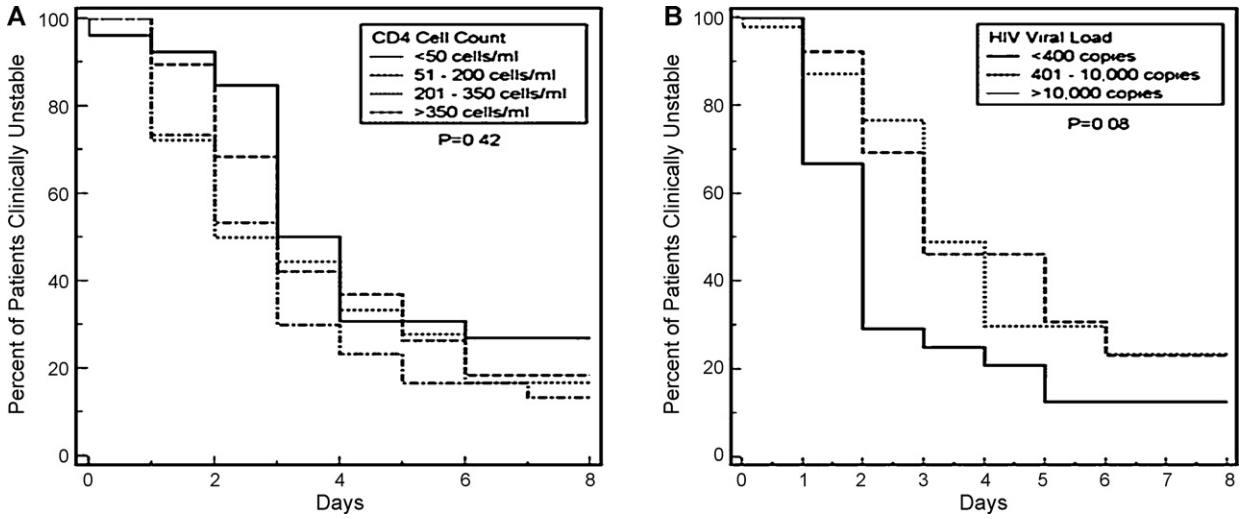

Figure 4. Kaplan–Meier survival curves indicating time to clinical stability (TCS) by (A) CD4+ cell count and (B) HIV-RNA level, for patients hospitalized with community-acquired pneumonia.

Table 2
Length of stay (LOS), propensity-adjusted Cox proportional hazards models

Predictor variable	Measurement	Hazard ratio	95% CI	*p*-Value
CD4+ cells/mm^3	<50	0.673	0.26–1.742	0.414
	50–200	0.791	0.354–1.766	0.566
	201–350	0.506	0.176–1.454	0.206
	>350	Reference	Reference	Reference
HIV-RNA copies/ml	0–400	1.421	0.757–2.666	0.274
	401–10 000	0.851	0.392–1.846	0.683
	>10 000	Reference	Reference	Reference

CI, confidence interval.

4. Discussion

Our study indicates that the mortality of hospitalized HIV-infected patients with CAP is not predicted by the CD4+ cell counts or HIV-RNA levels after adjusting for confounders. Jordano et al. reported similar mortality in patients with invasive pneumococcal disease with CD4+ cell counts of >200 vs. ≤200 cells/μl without adjusting for confounders.[8] Others have reported a significantly greater mortality in HIV-infected patients with CAP in relation to CD4+ cell counts of <200 cells/μl.[11] In a study reported by Feldman et al. that included 83% of patients from South Africa, a high mortality of patients was associated with HIV infection and CAP.[12] The higher mortality in relation to the low CD4+ cell count could be related to the fact that this study examined only bacteremic pneumococcal pneumonia and that there were likely other unknown factors.[12] Our study was largely represented by middle-aged individuals with advanced HIV infection, as reflected by the fact that more than half of the patients in both the survivor and non-survivor groups had CD4+ cell counts of ≤200/μl. HIV-infection is primarily driven by abnormalities in CD4+ cells and to a lesser extent by abnormalities in humoral and innate immunity including neutrophils.[20–22] In contrast to eosinophils,[23] neutrophils play a major role in the lung inflammatory changes of pneumonia;[24] therefore CAP outcomes are not expected to be affected among HIV-infected patients. The lack of correlation of CD4+ cell counts with mortality found in our study suggests that factors other than CD4+ cells contribute to the host response in CAP and mortality. Our results may help clinicians to consider that the mortality of HIV-infected patients with CAP cannot be anticipated by CD4+ cell counts.

In a multivariable analysis, Malinis et al. reported a similar TCS in patients with CAP regardless of their HIV status.[10] In this study, a CD4+ cell count was present for 57% of patients.[10] Similarly, our propensity-adjusted Cox proportional regression models did not show any significant difference in TCS in relation to CD4+ cell count or HIV-RNA level (Figure 4). Differences in LOS have been reported among patients with CAP in relation to the CD4+ cell count.[8,11] In underdeveloped countries, LOS is expected to be affected by the presence of advanced HIV diseases associated with malnourishment and limited healthcare resources that would stabilize the

Table 3
Time to clinical stability (TCS), propensity-adjusted Cox proportional hazards models

Predictor variable	Measurement	Hazard ratio	95% CI	*p*-Value
CD4+ cells/mm^3	<50	0.786	0.307–2.009	0.614
	50–200	0.981	0.447–2.154	0.961
	201–350	0.803	0.292–2.209	0.670
	>350	Reference	Reference	Reference
HIV-RNA copies/ml	0–400	1.78	0.952–3.331	0.071
	401–10 000	1.002	0.493–2.034	0.997
	>10 000	Reference	Reference	Reference

CI, confidence interval.

patient in a timely manner. In the USA and Europe, LOS is likely affected by evolving medical management to decrease the LOS. Our study failed to predict the LOS of patients with CAP adjusted by CD4+ cell count or HIV-RNA level. Our results suggest that TCS and LOS are driven by factors other than CD4+ cell count and HIV-RNA levels.

Our study has important limitations. This was a retrospective non-longitudinal study of cases randomly selected from CAPO centers. Therefore, our results need to be validated in a prospective study. A major strength of our study is the utilization of multivariate techniques and a propensity score to adjust potential confounders to more precisely measure the impact of CD4+ cell count and HIV-RNA level on clinical outcomes. PSI and CRB-65 have been validated for the outcomes of CAP in HIV-uninfected individuals but not for HIV-infected individuals with CAP, therefore our data measuring the severity of CAP in HIV-infected individuals may not be optimal. Because many of our study cases were not admitted to the ICU, it was not possible to obtain APACHE II scores. Finally, our study does not report tobacco smoking given the difficulty in obtaining optimal data on tobacco smoking.

In conclusion, our study shows that the clinical outcomes of HIV-infected patients hospitalized with CAP are not predicted by the CD4+ cell counts or HIV-RNA levels after adjusting for confounders. Clinicians should be aware that the clinical outcomes and management of CAP in patients with HIV infection should not be based on CD4+ cell counts or HIV-RNA levels.

Acknowledgments

We thank Mrs RoseMarie Leone for her editing support. Funding: Partially funded by CIBERES and AGAUR 09SGR1256.

Conflict of interest: No conflict of interest to declare.

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