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HIV-Associated Community– Acquired Pneumonia: Assessment of Risk Factors for Poor Patient Outcomes from a Single Center Experience

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ABSTRACT

Assessment of risk factors which may predict poor outcomes for patients with community-acquired pneumonia (CAP) in individuals with HIV is important for further evaluation of possibility their modification and through that the reduction mortality rate and improved patient outcomes. We aimed to investigate the risk factors for CAP in patients with HIV infection in term on their modification and through that reduction associated poor outcomes in such patients. We conducted a retrospective cohort study involving patients with diagnosed CAP who were admitted to the pulmonary and critical care medicine unit at medical university hospital, Baku city, Azerbaijan, between January of 2018 and December of 2022. One hundred ninety three adults (>18 years) patients with CAP were enrolled to the study. Pneumonia was diagnosed as CAP when it occurs before 48 h of hospital admission, 59 of 193 patients with CAP pneumonia was developed in individuals with HIV infection, and 16 of them the HIV infection was diagnosed accidently in our hospital. We have found five major and independent risk factors predicting in-hospital mortality in such patients: severe malnutrition; CD4 count <100 cells/mm^3; radiographic progression of the disease with P/F<250; bacteremia; and severe sepsis/septic shock. In our study the presence of HIV infection in CAP patients is associated with an increased risk of ICU admission with an increased risk of in-hospital mortality (2.5[0.94-5.6]; p<.02). We found a several risk factors in our sample, related to development of bacterial pneumonia in individuals with HIV infection. We found a high burden of comorbidities commonly related to chronic kidney failure and severe malnutrition as well as considerable high in-hospital mortality in such patients. We identified factors associated with an increased risk of ICU admission and fatal outcomes which could help identify patients who might benefit from anti-pneumococcal vaccination, adequate nutrition and antiretroviral therapy, as well as determine prognosis. Our findings should be validated by studies with larger samples of patients.

Keywords

HIV infection, Community -acquired pneumonia, Risk factors, ICU admission, Poor outcomes, Mortality.

Introduction

Community-acquired pneumonia CAP in individuals with HIV results from multiple risk factors, particularly immune defects ACD4 count decrease, especially when below < 100 cells\mm^3 continues to be a risk factor for pneumonia due to routine bacterial pathogens [1,2].

Other immune defects include quantitative and qualitative B-cell abnormalities that result in impaired pathogen specific antibody production, abnormalities in neutrophil function and members, and abnormalities in alveolar macrophage function. Lack of anti-retroviral therapy CART or intermittent use of ART increases the risk of pneumonia, likely due to uncontrolled HIV viremia [3].

Additional risk factors that contribute to the continued risk for bacterial pneumonia in individuals with HIV include chronic viral hepatitis, tobacco, alcohol, injection drug use and prescribed opioid

use, particularly higher doses and opioids with immunosuppressive properties [4-6]. Chronic obstructive pulmonary disease [COPD], malignancy, renal replacement therapy, and congestive heart failure (CHF) are risk factors for pneumonia, particularly in the population of older adults with HIV.

In individuals with HIV the incidence of bacteremia accompanying pneumonia is greater than in individuals without HIV, especially when infection is due to *S.* pneumonia [7]. With the introduction of ART and pneumococcal conjugate vaccines for both the general pediatric population and individuals living with HIV, this disparity in incidence rates of bacteremia between people without HIV has narrowed but has not been eliminated [8-12]. In one recent study of invasive pneumococcal disease (IPD), which includes bacteremia, IPD was more common in people with HIV who had CD4 counts <500 cells/mm^3, but even those with counts >500 cells/mm^3, had a higher incidence than in the general population [13].

Assessment of risk factor which may predict poor outcomes for patients with CAP in individuals with HIV is important for further evaluation of possibility they modification and through that reduction mortality rate and improved patient outcomes we aimed to investigate the risk factors for CAP in patients with HIV infection and poor outcomes in such patients.

Methods

We conducted a retrospective cohort study involving patients with diagnosed CAP who were admitted to the pulmonary and critical care medicine unit at Medical University hospital, Baku City, Azerbaijan, between January of 2018 and December of 2022. One hundred ninety three adults (>18 years) patients with CAP were enrolled to the study.

Pneumonia was diagnosed as CAP when it occurs before 48h of hospital admission 59 of 193 patients with CAP pneumonia was developed in individuals with HIV infection, and 16 of them the HIV infection was diagnosed in our hospital .The criteria of diagnosis are new persistent pulmonary infiltrates appearing on chest radiographs and a least two of following: (1) Fever of >38*C; (2) leukocytosis of>12.000/mm^3 or <4.000/mm^3; and (3) purulent sputum. In case of clinically suspected pneumonia sputum and blood culture (in case of fever>38*C) was sent for microbiology and positive quantitative culture (cut of point > 10 ^{6} CFU/ml) was assessed. To analyze the predisposing factors and patients outcomes the following variables were evaluated: age, gender, comorbidities, the presence of HIV infection at the time of hospitalization, length of hospital stay, ICU admission rate, and mechanical ventilation rate, development of complications and in hospital mortality.

All comorbidities were defined as previously described [14,15]. Diagnosis of malnutrition was assessed based on the presence of one or more of the following criteria: body mass index less than <21kg /m^2; serum albumin concentrations <3.5g/L. Septic shock was defined as bacteremia and hypotension requiring use of vasopressors with presence of multi-organ dysfunction [16]. The severe pneumonia requiring ICV admission was defined with septic shock required use of vasoactive drugs and need to mechanical ventilation. Multi-drug resistant (MDR) pathogens was defined as isolation of bacterial strain non-susceptible to at one agent in three one more antimicrobial categories.

The study end points were the assessment risk factors for ICV admission and in hospital mortality. To identify risk factors associated with ICV admission and in hospital mortality were performed univariable and multivariable analysis to defect significant differences between groups we used the chi square test or fishers exact test for categorical variables and the two tailed test or Mam-Whitney test for continuous variables when appropriate continuous variables were reported as medians with interquartile ranges (IQR): members and percentages were reported for categorical variables. Baseline variables (recorded at pneumonia onset and hospital admission) were analyzed in the univariable analysis to identify ICV admission and in-hospital mortality. Statistical significance was established of <.05.

Result

In total, 193 patients with CAP were analyzed. The number of patients with CAP in individuals with HIV infection was 59 (30.9% of all CAP incidence) and 16 of them HIV infection was identified in our hospital. Table 1 describes baseline characteristics of our study population.

There was significant differences between age of patients recording HIV infection. The patients with CAP in individuals with HIV was younger compared to patients with CAP without HIV (44[32-56]) vs 58[42-76]; p<.01). Prior use of antibiotics (last 90 days) was common in patients with CAP in individuals with HIV (15.7% vs 66.1%; p<.001) and commonly it was related to the presence of persistent high fever in individuals with HIV before development of CAP. Hemodialysis also was common event in patients with CAP in individuals with HIV (p<.01) and chronic use of renal replacement therapy (RRT) in such patients was related to catheter -driven blood stream infection (bacteremia) and development of MDR-pathogen associated pneumonia (p<.01). Bronchiectasis as comorbidity was common in HIV-associated CAP patients (p<.05) and it was also predict the prevalence of MDR-Pathogen associated pneumonia in such patients. Malnutrition was common demonstrated in HIV-associated CAP patients (p<.003), and more severe malnutrition was associated with increased incidence of ICV admission of patients.

Unilateral and lobar consolidation frequently was found in patients with CAP (p<.002), whereas bilateral and focal, segmental consolidation commonly was presented in patients with HIV -associated CAP (<.004). Cavitation as radiographic feature of pneumonia has commonly found in HIV-associated pneumonia related to *S.aureus* and *P.aeruginosa* infections which were frequently presented in such patients (p<.01).

Table 1: Baseline characteristics of patients with CAP with-without HIV infection.

Variables	Overall n=193 (%)	CAP without HIV n=134 (%)	CAP with HIV n=59 (%)	P value
Males	117 (60.0)	81 (60.4)	36 (61.0)	0.41
Females	76 (40.0)	53 (39.5)	23 (39.0)	0.42
Age, median years	51{32-76}	58{42-76}	44{32-56}	<.01
Prior antibiotic therapy (last 90 days)	60 (31.0)	21 (15.7)	39 (66.1)	<.001
Chronic heart failure	45 (23.3)	32 (23.1)	13 (22.0)	0.28
Renal replacement therapy	36 (18.6)	11 (8.2)	25 (42.4)	<.01
COPD	38 (19.6)	25 (18.6)	13 (22.0)	<.11
Bronchiectasis	29 (15.0)	8 (6.0)	21 (35.0)	<.05
Malnutrition	44 (22.8)	10 (5.2)	34 (57.6)	<.003
Diabetes	52 (26.9)	39 (29.1)	13 (22.0)	0.9
Pleural effusion	59 (30.5)	28 (20.8)	31 (52.5)	<.01
Bilateral pneumonia	49 (25.3)	21 (15.6)	28 (47.4)	<.004
Unilateral pneumonia	144 (74.7)	113 (84.3)	31 (52.6)	<.002
Lobar consolidation	82 (42.5)	69 (51.4)	13 (22.0)	<.002
Focal segmental consolidation	111 (57.5)	65 (48.5)	46 (77.9)	<.004
Cavitation	42 (21.7)	19 (14.1)	23 (39.0)	<.005
Bacteremia	51 (26.4)	26 (19.4)	25 (42.4)	<.01
CD4<500cells/mm3	48 (24.9)	9 (6.7)	39 (66.1)	<.0001
Recurrent pneumonia	42 (21.8)	8 (5.8)	34 (57.6)	<.001
Lack of pneumococcal vaccination	144 (74.6)	92 (68.6)	52 (88.9)	<.01
MDR pathogens	40 (20.7)	19 (14.2)	21 (35.5)	<.01
Severe sepsis/septic shock	55 (28.5)	23 (17.1)	22 (39.0)	<.01
ICV admission	60 (31.0)	26 (19.4)	34 (57.6)	<.002
In hospital mortality	39 (20.2)	18 (13.4)	21 (35.5)	<.003

Table 2: Pathogens isolated among 106 patients with culture-positive CAP.

Etiologies	Over all n=106 (%)	CAP without HIV n=64 (%)	CAP with HIV n=42 (%)	P value
Streptococcus pneumoniae	3030 (28.3)	18 (21.1)	12 (28.6)	44
Haemophilus influenza	18 (11.3)	8 (12.5)	4 (9.5)	19
Mycoplasma Pneumoniae	10 (11.3)	9 (14.1)	1 (2.3)	<.05
Chlamydia pneumoniae	8	8 (12.5)	--	NA
Klebsiella pneumoniae	2 (1.9)	1 (1.6)	1 (2.3)	NA
MSSA	4 (3.9)	2 (3.3)	2 (4.5)	NA
Eserichia coli MDR pathogens				
Pseudomonas aeruginosa	18 (16.9)	8 (6.7)	10 (23.8)	<.01
MRSA	13 (19.2)	4 (6.3)	9 (11.4)	<.01
Esherichia coli	4 (3.7)	1 (1.6)	3 (7.1)	NA
Klebsiella pneumoniae	5 (4.7)	2 (3.3)	NA	NA

We have found several risk factors which were predictable for developing bacteremia in our study and bacteremia as sign of invasive pneumonia was found frequently in HIV -associated CAP patients (42.4% vs 19.4%; p<.01). Lymphopenia (CD4<500 cells/mm^3) was common finding in HIV- associated CAP patients (p<.0001) and predict the severity of CAP.

More severe lymphopenia was associated with higher incidence of ICU admission and in hospital mortality of patients (p<.001). Lack of pneumococcal vaccination leads to clinically and radiographic more severe pneumonia and the number of patients vaccinated against pneumococcal disease was significantly lesser in patients with HIV -associated CAP (88.1% vs 68.6%; p<.01). Pathogens were identified in 65 of 193 patients (54.4%), *Streptococcus pneumoniae* and *Haemophilus influenza* species were most common frequently identified causes of CAP, and were the same in individuals with and without HIV (Table 2).

However, atypical bacterial pathogens such as *Mycoplasma pneumoniae* and *Chladmidophilia pneumoniae* were common in patients with CAP without HIV infection (p<.05). The frequency of MDR-pathogens such as *Pseudomonas aeruginosa* and *Staphilococcus aureus* caused CAP was higher in patients with HIV infection and as usual in such patients were several risk factors for MDR-pathogens associated CAP including poorly controlled HIV related to lack of ART and frequently use of antibiotics before admission to hospital for CAP. In our study there was played role previously structural lung disease such as bronchiectasis in patients with CAP developed in individuals with HIV (p<.05). As known exacerbations of bronchiectasis required frequently use of antibiotics which is associated with development of MDR pathogens. In our study gravity of MDR pathogens was higher compared to pathogens with CAP without HIV (21 (35.5) vs 19 (14.2); p<.01). Bacteremia and severe sepsis/septic shock were common among patients with CAP in individuals HIV (Table 3).

Table 3: Multivariate analysis of in bacteremia and severe sepsis/septic shock in patients with CAP associated with HIV infection.

Variables	OR	95%CL	P value
CD<100cells/mm^3	20.9	10.4-30.8	<.0001
Lack of ART	7.2	2.4-13.6	<.001
Lack of pneumococcal vaccination	3.4	1.2-7.6	<.01
MDR pathogens	2.7	1.0-5.7	<.02
Severe malnutrition	3.1	2.9-5.6	<.001
Hemodialysis	2.6	0.9-5.2	<.01

Low CD4 level was associated with an increased risk of bacteremia and severe sepsis with ICU admission and it was strongly independent risk factor for severe pneumonia in patients with ICU admission (20.9 [10.4-30.8]); p <0.001). Lack of ART in HIV infected patients as usual is associated with poorly controlled infection and viremia. However, it is also was associated with increased risk of severe sepsis and bacteremia (7.2 [2.4-13.6]; p<0.01).

In our study bacteremia and severe sepsis together with severe respiratory failure (PaO_2/FiO_2< 250) were associated with high incidence of ICU admission of patients (p<.002). Mortality was higher in patients with CAP associated with HIV infection, and multivariable analysis showed that severe malnutrition (serum albumin level <2.5 g/l, 31[0.8-5.8]; p<.05), CD4<100 cells/mm^3 (10.4[2.8-19.6]; p<.001); radiographic progression of disease (3.2[0.99-6.7]; p<.01); severe respiratory failure (PaO_2/FiO_2<250; 3.5[1.1-6.9]; p<.01); and bacteremia and severe sepsis/septic shock (8.4[2.8-18.9; p<.001) were associated an increased risk of in hospital mortality of patients (Table 4).

Table 4: Multivariate analysis of in hospital mortality in CAP patients associated with HIV infection.

Variables	OR	95%CL	P valve
Severe malnutrition	3.1	0.8-5.8	<.05
CD4<100 cells/mm^3	10.4	2.8-19.6	<.001
Radiographic progression of disease	3.2	0.94-6.7	<.01
PaO2/FiO2<250	3.5	1.1-6.9	<.001
Bacteremia and severe sepsis	8.4	2.8-18.9	<.001

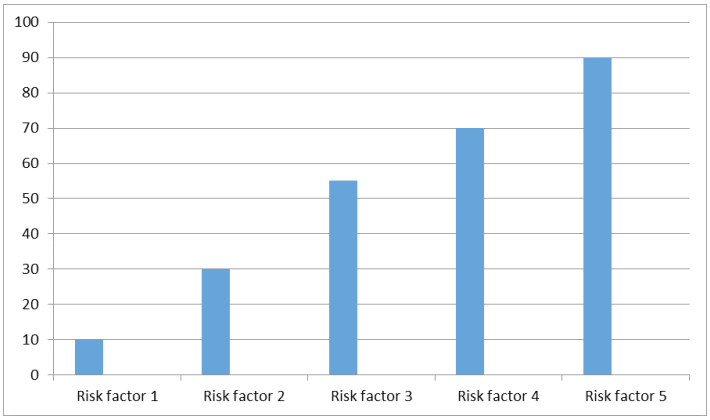

Figure 1: Combination of risk factors and mortality rate among patients with CAP associated HIV infection.

Combination of risk factors significantly an increased death rate among HIV infection associated CAP patients (Figure 1).

The presence of all five risk factors in one patients was associated with highly incidence of in hospital death and decreased the number of risk factors predicted mortality was associated with an increased survival of patients and single risk factor was associated with less mortality late.

Discussion

Bacterial pneumonia is a common cause of HİV-associated morbidity. Recurrent pneumonia, considered two or more episodes within all year period, is an AIDS defining condition. The incidence of bacterial pneumonia in individuals with HIV has decreased progressively with the accent of combination antiretroviral therapy (ART) [17-19].

In our study recurrent pneumonia episodes, especially in patients with CD4<500cells/mm^3 was higher and the severity of immunodeficiency has predicted the frequency recurrent pneumonia (9.5[2.8-18.7]; p<0.01). Our study has not shown the decreased incidence of CAP in individuals with HIV because lack of ART was common in our patients and it was associated with an increased incidence of viremia and poorly controlled HIV infection which was predicted higher incidence of CAP (7.2 [2.4-13.6]; p<.001).

However despite ART, bacterial pneumonia remains more common in people with HIV than in those who do not have HIV [1-3]. Bacterial pneumonia may be the first manifestation of underlying infection and can occur at any stage of HIV disease and at any CD4 count. In our study, the CD4< 500cells/mm^3 level was major risk factor for bacterial pneumonia, however the CD4<100 cells/mm^3 level was major risk factor predicting ICU admission and bacteremia with sepsis /septic shock (20.9 [10.4-30.8]; p<.0001).

The clinical and radiographic presentation in individuals with HIV, particularly in those with higher CD4 count and HIV viral supression is similar to that in individuals without HIV [15]. In contrast in our study there were significantly differences between clinical and radiographic features of bacterial pneumonia with an without HIV infection. Lack of auscultative signs, such as egophony and fine crackles and bilateral focal segmental consolidation was common in HIV associated CAP patients. Compared to CAP patients in HIV associated CAP patients pleural effusion and cavitation were common and was caused by increased incidence of MDR *S.aureus* and *P.aeruginosa* infections. In patients with CAP unilateral and lobar consolidation was common findings (p<0.02).

Although some studies suggest that bacterial pneumonia is associated with increased mortality in individuals with HIV [9,16], others do not [12,15]. Independent predictors of increased mortality in a prospective multicenter study of individuals with HIV community acquired bacterial pneumonia were CD4<100cells/

mm^3, radiographic progression of disease and presence of shock [20]. In our study the presence of HIV infection in CAP patients with associated with an increased risk of ICU admission was associated with an increased risk of in hospital mortality (2.5[0.94-5.6]); p<.002). We have found five major and independent risk factor predicting in hospital mortality in such patients; severe malnutrition; CD4 <100cells/mm^3; radiographic progression of disease P/F<250; and bacteremia with severe sepsis/sepsis shock. In our study the presence of HIV-infection in CAP patients with associated with an increased risk of ICV-admission and ICV-admission was associated with an increased risk of in-hospital mortality (2.5[0.94-5.6]; p<.002). We have found five major and independent risk factor predicting in-hospital mortality in such patients: severe malnutrition; CD4<100cells/mm^3; radiographic progression of disease; P/F<250; and bacteremia with severe sepsis/septic shock. Comparison to reference analysis data we have found two additional risk factors which highly associated with an increased in hospital mortality in HIV-associated CAP patients (3.1[0.8-50.8]; p< .05 and 3.5 [1.1-6.9]; p< .01; respectively).

The present study has several limitations. First, it is a study carried out in a single center. Second, some variables and co-founders may not have been taken into account given the difficulty of including them in a retrospective study. Third, for microbiological identification we used sputum, blood, pleural effusion and in some intubated patients we use endobronchial aspirate which are characterized with low accuracy for definition of bacterial pathogens in mechanical ventilated patients the use of bronchoalveolar lavage (BAL) fluid and protected bronchial brush from affected area of lung would associated with an increased incidence of causative pathogen identification. Fourth, the sample size was somewhat small, so external validity might have been compromised and the results might not be fully generalizable for some of the findings. This highlights need to for multicenter studies that address the particular aspects of CAP patients in individuals with HIV- infection.

In conclusion, we found a several risk factors in our sample, related to development of bacterial pneumonia in individuals with HIV-infection. We found a high burden of comorbidities mostly related to chronic kidney failure and severe malnutrition as well as considerably high in-hospital mortality in such patients. We identified factors associated with increased risk of ICU admission and fatal outcomes which could help identify patients who might benefit from anti-pneumococcal vaccination, adequate nutrition and antiretroviral therapy as well as determine prognosis. These findings should be validated by studies with larger samples of patients.

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