EPIDEMIOLOGY

Pneumocystis Carinii Pneumonia Versus Wasting Syndrome Among AIDS Cases in Puerto Rico: A Survival Analysis

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Objective. **To compare mortality of wasting syndrome (WS) versus *Pneumocystis carinii* pneumonia (PCP) in AIDS patients reported in Puerto Rico after controlling for gender, age, and CD4 levels.**
Methods. **AIDS patients for which a diagnosis of WS (n=1,180) or PCP (n=765), who were reported to the AIDS Surveillance System of Puerto Rico between 1989 and 1992, were used to analyze the mortality risk among these diagnoses using a Cox's proportional hazard regression model.**
Results. **Cox model showed that WS patients had a 14% to 33% reduction in mortality risk compared with PCP patients after adjusting for gender and age (95% confidence level). Mortality risks for males were 18% (95%CI: 1%, 39%) higher than females risk after adjusting for AIDS defining condition and age. It was shown that a decrease in 100 CD4 cells increased the mortality by 37% (95%CI: 16%, 62%) after adjusting for AIDS defining conditions, gender, and age.** *Key words: AIDS, Survival analysis, Wasting syndrome, Pneumocystis carinii pneumonia, CD4, Cox proportional hazard regression model, Puerto Rico.*

The acquired immunodeficiency syndrome (AIDS) is an unprecedented health problem with serious social, political, medical and economic implications (1). Several investigations have analyzed the survival time following AIDS diagnosis. Their findings have had a great impact in the prognosis and treatment of AIDS patients and in the planning of specific AIDS health-care programs. The survival studies have been geared to gain insight into AIDS pathophysiology and to devise different interventions at different stages of the disease. Previous studies have reported variations in the AIDS survival times when gender, age, AIDS defining conditions, CD4 cell counts, risk behavior, and the type of therapy (antiretroviral, nutritional) are controlled (2,3,4,5,6).

The initial diagnosis of *Pneumocystis carinii* pneumonia (PCP) and Kaposi's sarcoma as an AIDS defining condition were related with an increase in the survival time when they were compared with other AIDS defining conditions (2,3). On the other hand, younger patients (4) and high levels of CD4 cells (2,5) were associated with longer survival times.

Disease progression in patients infected with the human immunodeficiency virus (HIV) is strongly associated with depletion of CD4 lymphocytes (7). Gender differences have also been associated with variations in survival; females tend to live longer than males (5).

To evaluate the effects of AIDS survival predictors, we decided to statistically compare the survival of the two most frequent AIDS defining conditions in Puerto Rico: Wasting syndrome (WS) and *Pneumocystis carinii* pneumonia (8,9). The data for this research was provided by the AIDS Surveillance Program of the Puerto Rico Health Department.

Materials and Methods

The AIDS Surveillance Program in Puerto Rico, in coordination with the Centers for Disease Control and Prevention (CDC) in Atlanta, receive and store the information of all medically confirmed AIDS cases.

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Since September 1987, this program has included wasting syndrome (WS) and *Pneumocystis carinii* pneumonia (PCP) as AIDS defining conditions (9). Because of the changes in the AIDS definition in 1993 and the availability of AZT for AIDS patients, it was selected all patients diagnosed with WS and PCP between January 1989 and December 1992 (accrual period). Patients who had a diagnosis of both WS and PCP were excluded from analysis. To determine the survival time after diagnosis, patients were followed-up through May 1993; therefore, the study period comprised the period from January 1989 through May 1993. For patients who died during the study period the survival time was calculated as the time between date of AIDS diagnosis and the date of death. For patients who remained alive at the end of the study period, the survival time was calculated as the time between date of AIDS diagnosis and May 1993 and were defined as censored or patients with incomplete information.

The distribution of the two AIDS defining conditions by gender, age, CD4 cells count, and number of censored observation was described. A Cox proportional hazard regression model (12,13, 14,15) was then used to estimate the hazard ratio (relative comparison of instantaneous death after specific time) between WS and PCP after adjusting for gender and age. There were 1,945 subjects available for this model. Because of the reduced number of AIDS patients with reported CD4 levels (n=354), a second Cox model was run to estimate the hazard ratio between different levels of CD4 adjusted by gender, age and AIDS defining condition. To determine significant predictors in the Cox models, an analysis of deviance was performed using the Chi-square distribution (13). In order to determine the appropriateness of the Cox model , the assumption that the predictor variables were time invariant in the hazard ratio was tested and validated (p>0.05). Data were analyzed using the procedure PHREG in SAS (16)

Results

During the accrual period, there were 765 AIDS cases with diagnosis of PCP without WS, 1,180 cases with WS without PCP. The distribution of the AIDS defining conditions by gender was similar. The male to female ratio was 4:1 for both conditions. Most of the study patients were younger than 40 years old; 74% in WS and 70.2% in PCP. Three hundred and fifty-four (18.2%) in the study group reported CD4 cell counts at time of diagnosis. When CD4 cell counts were analyzed, 59% of the patients with WS had levels over 100cells/:L compared with 35.2% of patients with PCP. Only 1,043 (67.2%) of the 1,552 male cases reported homosexual behavior. Homosexual contact was reported by 45.7% of the PCP patients and 37.8% of the WS patients (Table 1).

The first Cox proportional hazard model revealed that the hazard risk was statistically associated ($p < .05$) with the AIDS defining conditions, gender and age. Based on these results, the adjusted hazard ratios were estimated as follows (Table 2):

Table 1. Characteristics of Adult and Adolescent AIDS Patients with Wasting Syndrome (WS) and *Pneumocystis carinii* pneumonia (PCP), Puerto Rico, 1989-1992.

	WS		PCP	
Characteristics	**Cases**	**%**	**Cases**	**%**
Gender (n=1,945)				
Male	943	80.0	609	80.0
Female	237	20.0	156	20.0
Age (n=1,945)				
< 30 Years	326	27.6	218	28.5
30-40 Years	548	46.4	319	41.7
> 40 Years	306	26.0	228	29.8
CD4 cells count (n=354)				
< 50 cell / µL	68	30.1	57	44.5
51-100 cell / µL	24	10.6	26	20.3
101-200 cell / µL	57	25.2	22	17.2
> 200 cell / µL	77	34.1	23	18.0
Censored cases (n=1,945)				
Death	634	54.0	450	59.0
Alive (censored)	546	46.0	315	41.0

* AIDS Surveillance Program, Puerto Rico Department of Health

Table 2. Hazard Ratio (HR) between WS and PCP adjusted by gender and age, Puerto Rico, 1989-1992 (n=1,945)

Variables	**Hazard ratio**	**95% C.I.**	**p value**
AIDS defining condition†			
P. carinii pneumonia	1.00	_	0.0001
Wasting syndrome	0.759	(0.67,0.86)	
Age‡			
20 Years	1.00	_	0.0001
21 Years	1.014	(1.008,1.02)	
40 Years	1.315	(1.17,1.48)	
60 Years	1.729	(1.37,2.19)	
70 Years	1.987	(1.48,2.66)	
Sex**			
Female	1.00	_	0.036
Male	1.184	(1.01,1.39)	

p-value for ^{2} test
* AIDS Surveillance Program, Puerto Rico Department of Health.
† Adjusted by gender and age.
‡ Adjusted by AIDS defining condition and gender.
**Adjusted by AIDS defining condition and age.

- WS patients had 14% to 33% lesser mortality risk compared with PCP patients
  (HR = 0.759, 95% CI: 0.67, 0.86).
- Males had 1% to 39% higher mortality risk than females
  (HR=1.18, 95% CI: 1.01,1.39)
- One year increase in age at diagnosis increased the mortality risk from 0.8% to
  2.0% (HR = 1.014, 95% CI: 1.01, 1.02)

The second Cox model (Table 3), using only patients with reported CD4 levels (n=354), showed that a decrease of 100 CD4 lymphocyte cells increased the mortality risk by 37% (HR= 1.37, 95% CI: 1.16, 1.62) after adjusting by AIDS defining condition, gender and age.

Table 3. Hazard Ratio (HR) between CD4 levels adjusted for AIDS defining condition, gender and age, Puerto Rico, 1989-1992, (n=354)

Variables	Hazard ratio	95% C.I.	p value
CD4 levels†			
500 cells / μL	1.00	–	0.0001
400 cells / μL	1.369	(1.16,1.62)	
300 cells / μL	1.873	(1.35,4.20)	
200 cells / μL	2.563	(1.56,4.20)	
100 cells / μL	3.507	(1.82,6.78)	
50 cells / μL	4.103	(1.96,8.61)	

p-value for ^{2} test
* The AIDS Surveillance Program, Puerto Rico Department of Health
† Adjusted by AIDS defining condition, sex and age.

Source: The AIDS Surveillance Program, Puerto Rico Department of Health.

Discussion

The Cox's proportional hazard regression model model was useful in describing the mortality risks considering the specific time involved in each person studied, in addition to making statistical adjustments for confounding variables .

The results of this model showed a higher mortality in PCP patients compared with WS patients, after adjusting by gender and age. The results might be explained by the fact that some diagnostic procedures such as bronchoscopy, sputum examination, and biopsy are performed with a lower frequency in Puerto Rico compared with the United States. As a consequence, PCP may be diagnosed at a later stage of the disease. Another plausible explanation could be the variation in medical treatments and CD4 levels. Unfortunately, those variables were not available for all the patients in the surveillance system.

Despite of the reduced number of AIDS patients that had information on CD4 levels, it was possible to confirm the association of depletion of lymphocyte cells counts in AIDS progression (1,4). Therefore, it is recommended that the epidemiologic surveillance system of AIDS keeps a periodical record of the CD4 levels. This information will provide a clearer description of the real panorama of AIDS in Puerto Rico.

Resumen

Objetivo. Comparar mortalidad específica del síndrome de adelgazamiento (WS) contra neumonía por Pneumocistis carinii (PCP) en pacientes de SIDA.

Método. Los pacientes de SIDA con WS (n=1,180) y PCP (n=765) reportados en PR entre 1989 y 1992, fueron utilizados para analizar la mortalidad en un modelo de Cox.

Resultados. El modelo de Cox demostró con un 95% de confianza que las personas con WS tengan entre 14% y 33% reducción en los riesgos de mortalidad comparado con las personas de PCP, después de ajustar por género y edad. Este modelo demostró que la mortalidad para masculinos fue 18% (IC 95%: 1%, 39%) mayor que en las féminas cuando ajustamos por la enfermedad indicativa de SIDA y edad. Se observó que una disminución de 100 células de CD4 aumentó los riesgos de fallecer por un 37% (IC 95%: 16%,62%) luego de ajustar por la enfermedad indicativa de SIDA, sexo y edad.

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