

# Associated Factors for In-Hospital Mortality in Patients with Meningeal Cryptococcosis and HIV Infection at a Local Hospital in Lima, Peru

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## ABSTRACT

**Objective:** To determine the associated factors for in-hospital mortality in patients with meningeal cryptococcosis and HIV infection at a local hospital in Lima, Peru. **Materials and methods:** We carried out a case-control study by reviewing the medical histories available at a local hospital in Lima, Peru. We determined the factors associated with mortality using a logistic regression model. **Results:** The information of 90 patients was analyzed, 37 dead and 53 alive. In the multivariate analysis we found two variables associated with mortality: Glasgow at admission ( $OR = 4.55$  ( $1.61 - 12.20$ ),  $p = 0.01$ ) and serum antigen titer greater than 1024 ( $OR = 20.48$  ( $1.6 - 261.04$ ,  $p = 0.02$ )). The protective factor found was a longer hospitalization stay ( $OR = 0.80$  ( $0.69 - 0.93$ ,  $p = 0.005$ )). **Conclusions:** A low Glasgow score and serum antigen titer greater than 1024 are associated factors with mortality, whereas hospitalization length is a protective factor.

**Keywords:** Meningeal Cryptococcosis, Cryptococcus, HIV, Mortality, Death, Cryptococcal Meningitis

## 1. Introduction

Cryptococcosis is an opportunistic disease [1] which is potentially mortal [2,3], caused by the encapsulated cosmopolitan fungus *Cryptococcus neoformans* [4,5], of which three variants exist: *neoformans*, *grubii* (most prevalent worldwide) [4,6,7] and *gatti* [8,9]. Its pathogenicity is related to patients with altered T-cell immunity [8,10], particularly those affected with the Human Immunodeficiency Virus (HIV) and with CD4 blood counts below  $100/\text{mm}^3$  [5,8]. Cryptococcosis defines AIDS in up to 25% of cases [11,12].

This pathogen is found in pigeon droppings [4,5] and in the heartwood of eucalyptus trees in tropical and subtropical areas [5,7,13]. It most often enters the host through inhalation [7,8], forming a primary infection in immunocompetent patients [8]. In those immunocompromised, it travels hematogenously with a predilection for the central nervous system [8], causing an acute or subacute meningoencephalitis [14]. The probability of acquiring cryptococcosis in HIV-infected patients who are not under HAART (Highly Active Anti-Retroviral Therapy) is around 10-30% [12,15], with an annual incidence in Latin-American series of 1.1-3.7 per million inhabitants

per year [12].

The most common signs and symptoms are: headache, fever [7,10,16], vomiting [15,16], cranial nerve palsy [7,8], altered consciousness [10], convulsions [8], visual alterations [7,15,17], dermatological lesions [10], but only one third of patients will present classic meningeal signs [16]. The natural history of the disease shows a 35% survival at day 14 and 0% survival at day 42 [3].

Factors that have been associated to mortality at admission are: cryptococemia [1,18], absence of treatment with HAART [19], abnormal mental status [8,11,19], CD4 values below  $50/\text{mm}^3$  [20], intracranial hypertension [10,11], malnutrition [19], hyponatremia [21], lumbar puncture's opening pressure greater than  $25\text{cmH}_2\text{O}$  [7,22,23], high antigen titer [7,10,23], low cerebrospinal fluid (CSF) inflammatory response [7,21,23], and an abnormal cerebral image (magnetic resonance or computed tomography) [10].

Mortality since the extended use of HAART has decreased [25-29], although the mortality in the acute phase is still around 10-20% [30,31]. In countries in South America, Africa and Asia, the use of HAART is still low [12,25,32,33]. On the other hand, prognosis is still poor in patients receiving antifungal monotherapy, with a 60-65%

failure at week ten [10,34]. Besides, because of its high toxicity the treatment itself has been related to death, especially in the absence of an adequate concomitant fluid therapy [19]. It is important to mention that in some African countries, meningeal cryptococcosis mortality is even higher than that caused by tuberculosis [28].

The aim of this study is to determine the associated factors for in-hospital mortality in patients with meningeal cryptococcosis and HIV-infection at a hospital in Lima-Peru because of the nonexistence of previous studies of this sort in our country.

## 2. Materials and Methods

### 2.1. Study Design

We carried out an observational, longitudinal case-control study, in patients with meningeal cryptococcosis and HIV-infection treated at a local hospital in Lima, Peru between January 1<sup>st</sup> 2000 and December 31<sup>st</sup> 2009. We included as cases, patients who died during hospitalization, with a confirmed diagnosis of HIV-infection [8,26], and of meningeal cryptococcosis by either CSF cultures, positive serum antigen titers or a positive CSF Indian Ink, and symptoms compatible with meningoencephalitis [8,13]. In the controls, we included patients who survived the hospitalization, and who had an equally confirmed diagnosis of both HIV-infection and meningeal cryptococcosis. We excluded from both branches of the study patients without a confirmed diagnosis of meningeal cryptococcosis, those immunocompromised by others causes rather than HIV, those who received antifungal treatment within one week previous to admission, or those with contraindications to a lumbar puncture. In recurrent patients, only the first hospitalization was taken into account.

### 2.2. Gathering of Information

We revised both medical records and epicrisis, to obtain the following information: past medical history [24,35], clinical, laboratory and mycological findings [26] and CSF characteristics (initial opening pressure, cellularity, cytochemical analysis, Indian Ink and fungal culture [2,26]. Finally, we registered total hospitalization duration and the outcome.

### 2.3. Statistical Analysis

Sample size was calculated using EpiInfo v6.1, with a 1:2 ratio (cases:controls), a statistic significance of 95% and a statistical power of 80% [18]. Considering exposure percentages among an opening pressure greater than 25cmH<sub>2</sub>O, we obtained a required sample size of 10:20 (OR = 20.4) [23], while in the case of serum antigen titer

greater than 1/1024, we obtained a sample size of 27:54 (OR = 3.17) [36]. Qualitative variables were analyzed using chi-squared and Fisher, while quantitative variables used t-student distribution and U-Mann-Whitney, all of them with a significance level of 0.05. Afterwards, we carried out a multiple logistic regression. We obtained the consent of the ethical department of both Cayetano Heredia University and Cayetano Heredia Hospital.

## 3. Results

A total of 90 patients were included in the study (33 cases and 57 controls). The range of age varied between 20 and 74 years, with a mean value of 35 (sd 10.31) years in those who died and 34.7 (sd 10.04) in those who survived. 76.67% of patients were male. As past medical history, 16.25% received HAART before admission (12 of which survived, while only 1 who died). We found a mean time between HIV diagnosis and hospital admission of 6 months in the cases versus 14 months in the controls ( $p = 0.025$ ).

Hospitalization stay was of 7 days on average in patients who died, compared to 21 days in those who did not die ( $p = 0.0001$ ). Mean arterial pressure was of 111.77/70.34 mmHg, with differences between cases and controls of 119.72/75.84 and 107.8/67.6 respectively ( $p = 0.0007$  in the systolic and  $p = 0.0005$  in the diastolic). Furthermore, the body mass index (BMI) was on average 20.62 kg/m<sup>2</sup>. In the neurological examination, the mean Glasgow score was 14.4, with values of 13.29 in those who died, contrasted with 14.84 in those who did not ( $p < 0.001$ ). The presence of focalization in the cases was 37% ( $n = 10$ ) while in the controls it was 3.7% ( $n = 2$ ).

In laboratory studies, we observe that the mean value for CD4 in patients who died was 14/mm<sup>3</sup>, compared to a value of 36/mm<sup>3</sup> in those who survived ( $p = 0.04$ ), while in the case of albumin, the mean in this study was of 3.14 g/dL (2.7 g/dL in the former group and 3.52 g/dL in the latter,  $p = 0.039$ ).

Finally, median serum antigen titer was 1/4096 in the cases, while in the controls it was 1/256 ( $p = 0.0001$ ).

Referring to CSF characteristics, we found a mean initial opening pressure of 30.94 cmH<sub>2</sub>O (35.91 in the dead versus 26.67 in those who survived,  $p = 0.12$ ), white blood cell count was on average 38.62, while glucose and proteins scored 36.63 and 76.9 mg/dL, respectively. The remaining results can be consulted in **Table 1**.

In the logistic regression, the protective factor was hospitalization duration, with an odds ratio of 0.80 ( $p = 0.005$ ) in the multivariate analysis. On the other hand, the associated factors to in-hospital mortality in the univariate analysis were: blood pressure (OR = 1.07,  $p = 0.004$  and OR = 1.10,  $p = 0.003$ ) in the case of systolic and diastolic

**Table 1. Statistical tests of the variables.**

Patients with HIV and meningeal cryptococcosis					
	Variable	Died	Survived	Test	p-value
Previous medical history	Time of HIV diagnosis (in months)	6 (1 - 24)	14 (3 - 60)	U-Mann-Whitney	0.025
	HAART treatment			Fisher	0.095
	Yes	1	12	Chi-squared	0.055
	No	23	44		
	Previous episode of meningeal cryptococcosis			Chi-squared	0.11
	Yes	5	6		
	No	13	44		
	Oportunistic diseases			Chi-squared	0.14
	Yes	24	37		
	No	6	20		
Clinical characteristics	Age (in years)	35 sd 10.31	34.7 sd 10.04	t-student	0.89
	Gender			Chi-squared	0.23
	Female	10	11		
	Male	23	46		
	Hospitalization duration (in days)	7 (5 - 13)	21 (17.5 - 33.5)	U-Mann-Whitney	0.0001
	Weight (in kilograms)	54.87 sd 8.36	57.13 sd 9.25	t-student	0.44
	Height (in meters)	1.56 sd 0.02	1.63 sd 0.07	t-student	0.07
	BMI (kg/m <sup>2</sup> )	19.55 sd 3.26	20.95 sd 3.84	t-student	0.47
	Blood pressure (mmHg)				
	Systolic	119.72 sd 20.27	107.8 sd 9.04	t-student	0.0007
	Diastolic	75.84 sd 12.08	67.6 sd 7.43	t-student	0.0005
	Pulse (per minute)	82.36 sd 14.56	84.26 sd 12.86	t-student	0.56
	Respiratory frequency (per minute)	22 sd 6.1	20.36 sd 3.04	t-student	0.12
	Temperature (in °C)	37.03 sd 0.35	37.24 sd 0.70	t-student	0.25
	Glasgow scale	13.29 sd 1.78	14.84 sd 0.66	t-student	<0.001
	Focalization			Chi-squared	<0.001
	Yes	10	2	Fisher	<0.001
No	17	52			
Laboratory study	WBC count (/microL)	7222.48 sd 4816.4	5601.37 sd 3156.8	t-student	0.09
	Hemoglobin (g/dL)	13.84 sd 8.99	10.76 sd 1.79	t-student	0.35
	Serum electrolytes (in mEq/dL)				
	Sodium (Na <sup>+</sup> )	133.61 sd 5.61	136.29 sd 4.38	t-student	0.048
	Potasium (K <sup>+</sup> )	3.98 sd 0.43	3.96 sd 0.63	t-student	0.65
	Chloride (Cl <sup>-</sup> )	101.27 sd 6.35	103.57 sd 5.65	t-student	0.17
	CD4 (/mm <sup>3</sup> )	14 (2 - 18)	36 (23 - 105)	U-Mann-Whitney	0.04
	Albumin (g/dL)	2.7 sd 0.24	3.52 sd 0.67	t-student	0.039
	Serum antigen titer	1/4096 (1/2048 - 1/4096)	1/256 (1/32 - 1/1024)	U-Mann-Whitney	0.0001
	Culture			Chi-squared	0.24
Micologic study	Positive	6	4		
	Negative	13	3		
CSF characteristics	Opening pressure (cmH <sub>2</sub> O)	35.91 sd 16.87	26.67 sd 12.39	t-student	0.12
	Leukocytes (/microL)	10 (3 - 20.5)	4 (0 - 17)	U-Mann-Whitney	0.33
	Proteins (mg/dL)	87 sd 53.81	73.08 sd 51.87	t-student	0.4
	Glucose (mg/dL)	30.93 sd 20.16	38.94 sd 14.87	t-student	0.11

This table depicts the complete set of variables analyzed in this study, showing the statistical difference between patients who died and those who survived during hospitalization.

respectively, Glasgow score (OR = 3.13,  $p < 0.001$ ), serum antigen titer (OR = 23.13,  $p = 0.003$ ) and focalization (OR = 15.29,  $p = 0.001$ ). In the multivariate analysis, the factors that remained associated to a negative outcome were serum antigen titers (OR = 4.55,  $p = 0.01$ ) and Glasgow score (OR = 20.48,  $p = 0.02$ ). The complete data for the logistic regression model can be reviewed in **Table 2**.

#### 4. Discussion

This is the first investigation carried out in Peru aiming to find the mortality-associated factors in patients with meningeal cryptococcosis and HIV infection, despite the high mortality among them. The significant clinical patterns were: blood pressure, serum albumin level and deprived mental status. Blood pressure was higher in those patients who died, probably reflecting intracranial hypertension [29], concurring with previous studies in New Guinea [36] and Thailand [37]. Similarly, it was found that patients presented with lower serum albumin levels in

the case group, as an indirect indication of malnutrition and implying that these patients had a worse previous state at admission. Referring to the neurological findings, the scores in the Glasgow scale were lower in those who died, and that same patients group had focalization more often, matching the findings of other studies [8,11,19,22] and possibly signaling that these patients at admission were in a poorer mental state, either because of a longer disease evolution or because of factors inherent to the subject.

In the laboratory study, patients who died presented hyponatremia more often, exhibiting an internal imbalance and a greater systemic compromise. Subramian *et al.* in 2005 reported similar findings [21], but it is still not possible to propose a cut point below which it can be considered hazardous. In what concerns CD4 levels, those in the cases were substantially lower than those in the controls. In other studies it has been reported a global mean CD4 value of  $45/\text{mm}^3$  in meningeal cryptococcosis patients [12,15,24], without differentiating between those

**Table 2. Univariate and multivariate logistic regression.**

Category	Variable	OR 95% (IC) a	p-value	OR 95% (IC) b	p-value
	Time of HIV diagnosis (in months)	0.98 (0.95 - 1.004)	0.11		
Previous medical history	HAART treatment		0.087		
	Yes	0.15 (0.019 - 1.3)			
	No	1			
	Oportunistic diseases		0.14		
	Yes	2.16 (0.75 - 6.16)			
	No	1			
	Hospitalization duration (in days)	0.87 (0.81 - 0.93)	>0.001	0.80 (0.69 - 0.93)	0.005
Clinical characteristics	Blood pressure (in mmHg)				
	Systolic	1.07 (1.02 - 1.12)	0.004		
	Diastolic	1.10 (1.03 - 1.17)	0.003		
	Glasgow scale	3.13 (1.67 - 5.88)	>0.001	4.55 (1.61 - 12.20)	0.01
	Focalization		0.001		
	Yes	15.29 (3.04 - 76.81)			
	No	1			
Laboratory study	WBC count (/microL)	1.00 (0.99 - 1.00)	0.09		
	Serum sodium (mEq/dL)	1.14 (1.00 - 1.30)	0.055		
	CD4 count	1.12 (0.97 - 1.32)	0.14		
	Serum albumin	125 (0.37 - 10000)	0.1		
Micologic study	Serum antigen titer	23.13 (2.87-186.1)	0.003	20.48 (1.6 - 261.04)	0.02

This table presents the univariate (ICa) and multivariate (ICb) analysis for those variables that resulted significant in the statistical test shown in table 1.

who die and those who survive. In this study, we obtained a much lower mean in patients who died.

Some publications state that up to 60% of patients with meningeal cryptococcosis present with a serum antigen titer of 1/1024 [35] or 1/2048 (CSF) [6,19,23], with a 90% sensibility [8,20,38]. In our study, the cut point in the case of the initial serum antigen was also located at 1/1024, because above that dilution the proportion of deaths increased importantly. However, the follow-up dilutions of antigen titer do not predict the final outcome [39,40].

In what concerns the CSF, a previous study in our country showed that 57.9% of the initial opening pressures in the lumbar puncture were abnormally high [15]. In our case, the mean opening pressure was higher in those who died, but without finding significant differences between both groups. Opening pressures above 25 cmH<sub>2</sub>O have been associated to higher short-term mortality [7,23,35] and with a requirement for daily decompression [19,29,41]. The fact that we did not find this association is probably due to the fact that some of the records did not contain data for this specific variable, even though the procedure was executed. Having said that, it is described that as many as 25% of patients with cryptococcosis can have a normal CSF study [16,24].

In the multivariate analysis, we found as a protective factor the duration of hospitalization, resulting that each additional day reduced in 29% the probability of dying. In studies in other countries, it has been reported that the mean time of death is around 10 to 14 days [7,11,19], while in our case it was much shorter (7 days) [23]. This could be explained because patients in our country take longer to seek for professional help, presenting at the emergency department in a more debilitated neurologic and systemic state, and dying sooner because of complications such as intracranial hypertension.

Mortality-associated factors included a low score in the Glasgow scale and elevated serum antigen titers. In the former, it was found that the decrease in one point in the scale meant 4.55 times more probability of dying. In the case of the serum antigen titers, the variable was dichotomized with a cut point at 1/1024. This concurs to Dromer *et al.* prospective study where a 1/512 cut point was proposed as a predictor of therapeutic failure at day 14 [10]. On another level, neurologic focalization is associated to death in the univariate regression model, but was diluted in the multivariate study, probably because of a lack of power of the study. This contrasts to publications by Cachay *et al.* who were able to link focalization with complications including death [22].

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