

Mortality Predictors for Disseminated Histoplasmosis in Colombian HIV-infected Patients

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Abstract

Introduction: In Central and South American countries mortality rates in HIV-infected patients for progressive disseminated histoplasmosis (PDH) vary from 18% to 48%. Our aim was to identify clinical and laboratory factors associated with mortality in patients with HIV and PDH.

Methods: Retrospective descriptive study in patients with HIV and PDH from 2002 to 2013 in a hospital in Medellín, Colombia. The diagnosis of histoplasmosis was made based on the recommendations of the EORTC/MSG. Demographic, laboratory, and clinical information was collected to identify factors associated with mortality using logistic regression.

Results: 124 HIV-infected patients with PDH were identified. 84% were males. The median age was 37 years (standard deviation [SD] 11 years) and the mean CD4 count was 56 CD4 cells/μl (SD 87). 73 patients (59%) had other co-infections; of these, 73% had an additional opportunistic infection and 27% had 2 or more. The most frequent co-infections were: tuberculosis (47%), candidiasis (14%), pneumocystosis and cryptococcosis (12% each), *Herpes simplex* virus and cytomegalovirus infection (11% each). Symptoms included fever (91%), weight loss (89%), anorexia (85%), pulmonary (77%), gastrointestinal manifestations (82%) and hematological abnormalities (95%). The mortality for the entire cohort was 23%. Non-survivors were more likely to have thrombocytopenia (OR 2.75), rales (OR 3.04) and vomiting (OR 3.96). Antifungal treatment (96% vs. 79%, OR 0.16, p <0.01) and highly active antiretroviral therapy (HAART) (77% vs. 17%, OR 0.06, p <0.01) were more frequent in patients that survived. On multivariable analysis, rales (OR 15.27, CI 95% 1.63-143.0, p=0.017) and vomiting (OR 12.58, CI 95% 1.28-123.3, p=0.030) were associated with an increased mortality risk, whereas treatment with itraconazole (OR 0.008, CI 95% 0.00-0.27, p=0.008) and HAART (OR 0.043, CI 95% 0.00-0.30, p=0.002) were associated with a decreased mortality risk.

Conclusions: Mortality for PDH in HIV-infected patients remains high in Colombia. Prompt antifungal and antiretroviral treatment, especially in acutely-ill patients, should help mitigate this risk. Our data suggest the risk of death due to treatment delays could supersede the risk of IRIS-associated death with early treatment.

Introduction

In the United States, histoplasmosis has an incidence rate of 2 to 5% in persons with AIDS, figures that may rise up to 27% in highly endemic regions. In Colombia, the incidence of histoplasmosis in HIV infected patients is 22%. Despite advances in the treatment of persons with HIV/AIDS, the incidence and mortality associated with PDH remains high, especially in developing countries. In Central and South America, mortality rates vary from 18% to 48%. Disease caused by *H. capsulatum* is thus an important public health problem in this susceptible population. Consequently, identifying clinical and laboratory factors associated with mortality in patients with HIV/AIDS and PDH is of critical importance. Such findings could allow for earlier diagnosis and treatment, potentially reducing the high mortality rates observed.

Methods

Retrospective descriptive study from 2002 to 2013 in patients with AIDS and PDH from one hospital in Medellín, Colombia. The diagnosis of histoplasmosis was made based on the recommendations of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG). Patients with a previous diagnosis of histoplasmosis were excluded. Demographic, laboratory and clinical information was collected. Variables with biological plausibility and those with a p value less than 0.25 on bivariate analyses were used in a logistic regression model to identify independent factors associated with mortality. All analyses were performed using EPIDAT 3.1 and STATA 8.0 software.

Results

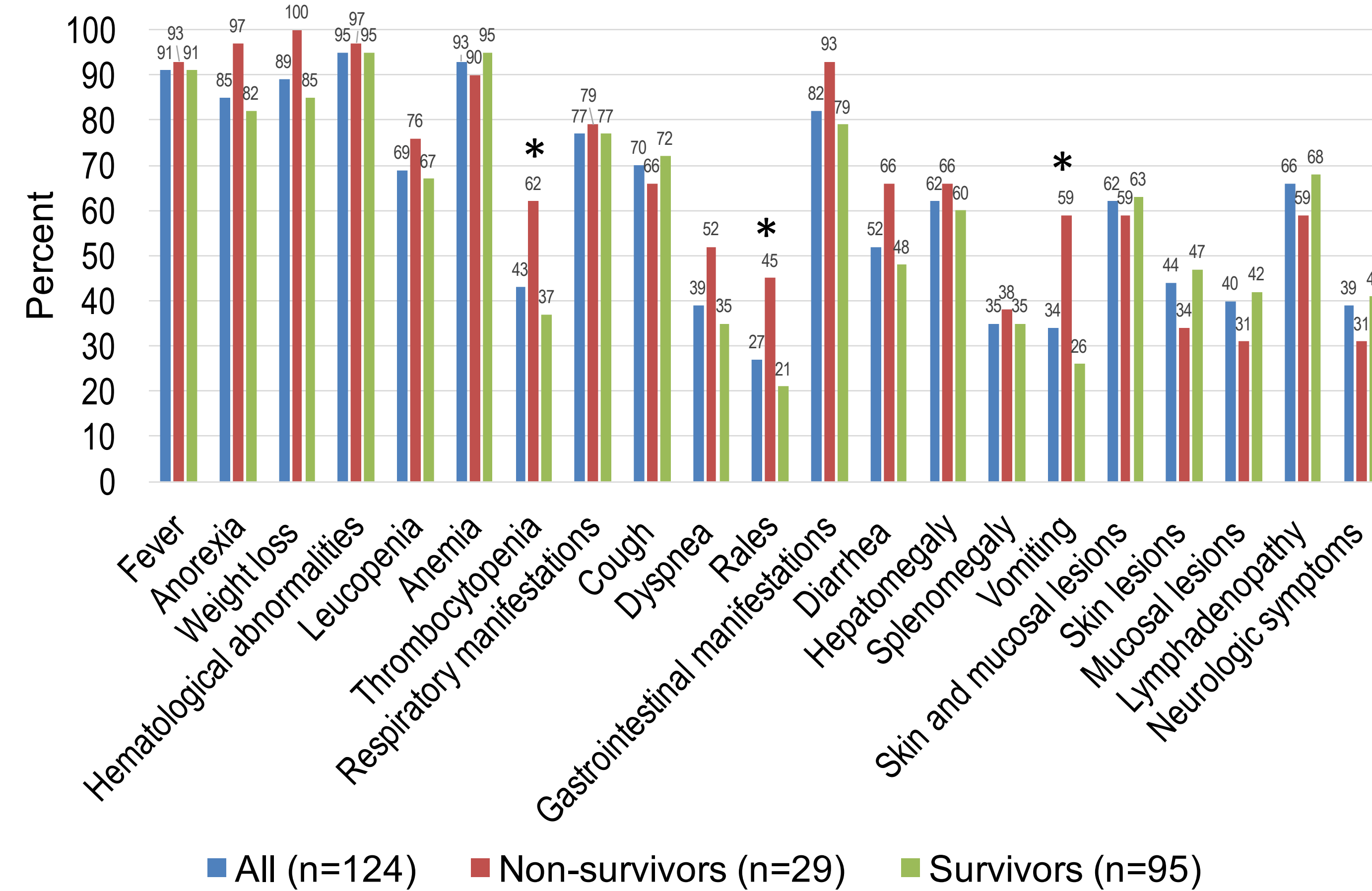
Descriptive and bivariate analysis

Demographic and treatment characteristics of HIV+ patients with PDH (n=124): Comparison between survivors and non-survivors

Variable	All (n=124)	Non-survivors (n=29)	Survivors (n=95)	p
Age [‡]	37 (11)	39 (51)	36 (66)	0.47
Sex (male) [‡]	104 (84)	22 (76)	82 (86)	0.29
CD4 cell count [‡]	56 (87)	26 (21)	62 (94)	0.17
HIV viral load [‡]	726,723 (1.496,417)	799,063 (4.518,535)	186,977 (9.999,960)	0.86
Other OI [†]	73 (59)	18 (62)	55 (58)	0.82
Antifungal [†]	114 (92)	23 (79)	91 (96)	<0.01*
AMBD	87 (70)	20 (69)	67 (70)	0.87
Itraconazole [†]	105 (85)	15 (52)	90 (95)	<0.01*
HAART [†]	78 (63)	5 (17)	73 (77)	<0.01*

[‡] mean (standard deviation); [†] Number (%). Opportunistic infection (OI), Highly active antiretroviral therapy (HAART), (*) statistically significant differences (p< 0.05), AMBD: Amphotericin B Deoxycolate.

Clinical and laboratory findings in 124 HIV+ patients with PDH: comparison between survivors and non-survivors



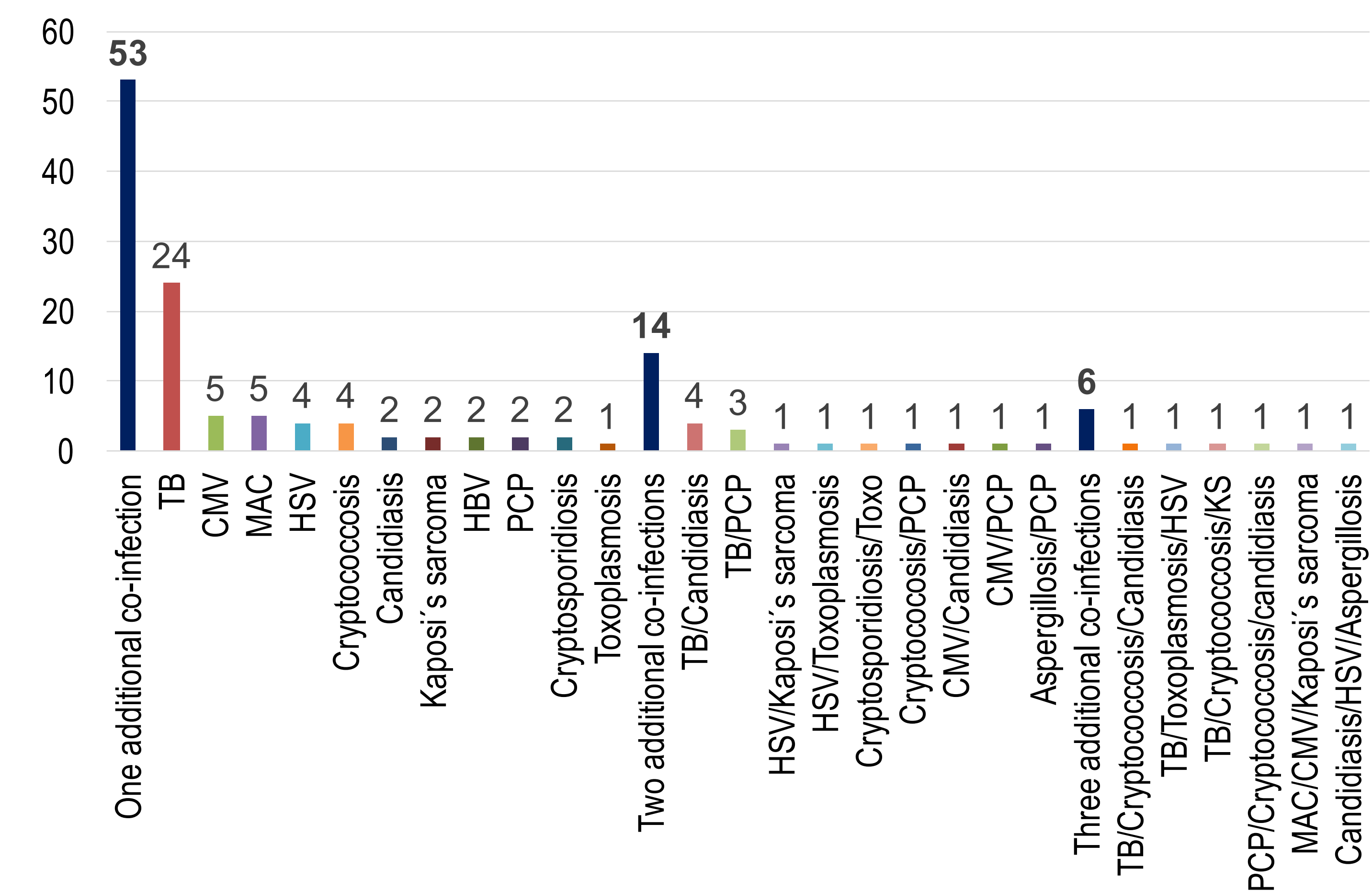
(*) Statistically significant differences between survivors and non-survivors (p< 0.05)

Multivariate analysis

Variable	p	OR	CI 95%
Rales on physical exam	0.017	15.27	1.63-143.0
Presence of vomiting	0.030	12.58	1.28-123.3
Itraconazole treatment	0.008	0.008	0.00-0.27
HAART	0.002	0.043	0.00-0.30

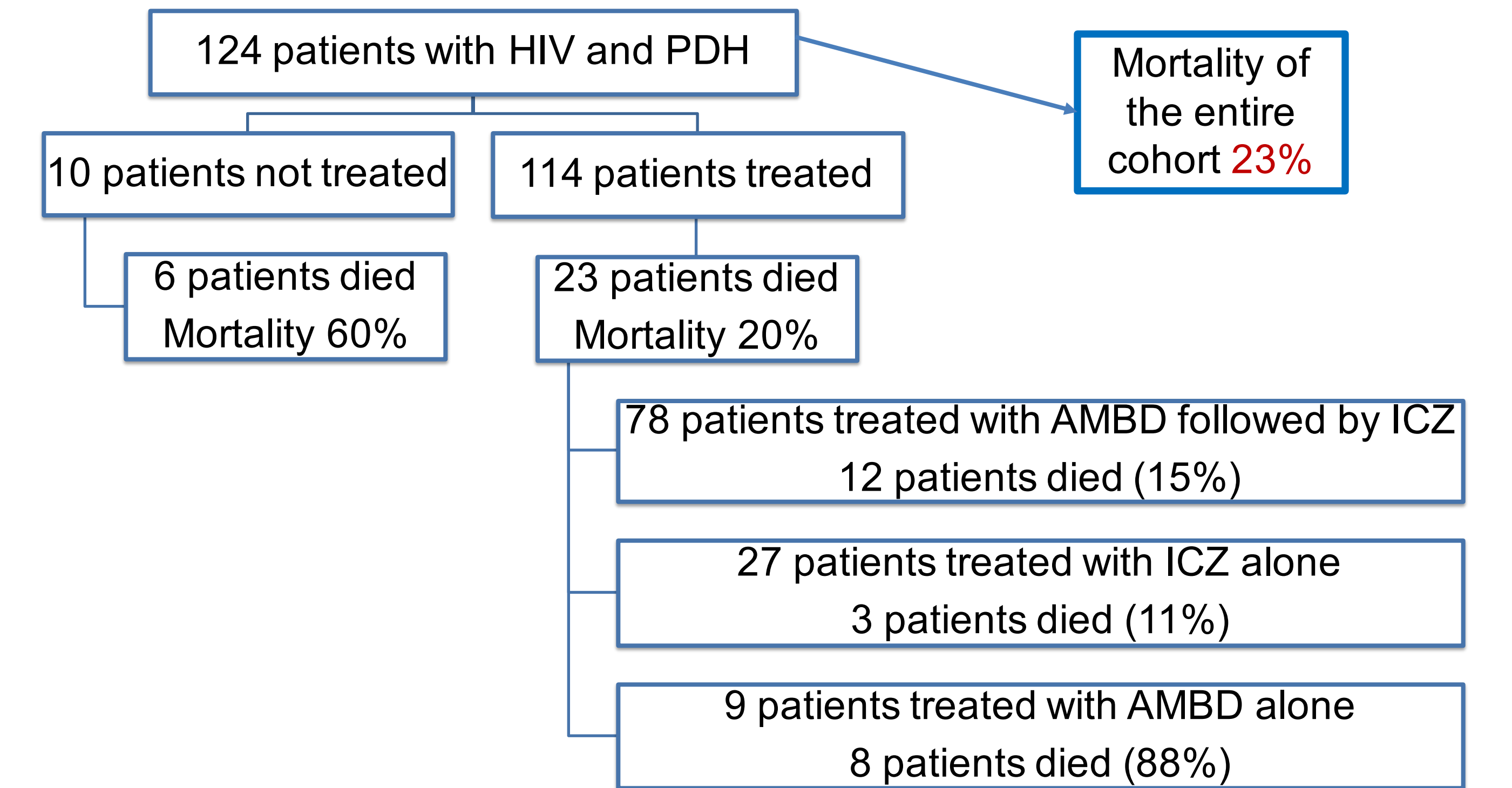
Highly active antiretroviral therapy (HAART), OR: Odds ratio, CI: 95% confidence interval

Number of co-infections in 73 patients with AIDS and PDH



(+) additional; (TB) Tuberculosis; (CMV) Cytomegalovirus; (HSV) Herpes Simplex Virus; (MAC) Mycobacterium avium complex; (HBV) hepatitis B virus; (PCP) Pneumocystis jirovecii pneumonia; (Toxo) Toxoplasmosis; (KS) Kaposi's sarcoma

Description of antifungal therapy in patients with HIV and PDH, differences between treated and untreated patients



AMBD: Amphotericin B deoxycolate; ICZ: Itraconazole

Conclusions

Mortality for PDH in HIV-infected patients remains high in Colombia. Symptoms associated to higher mortality probably reflect multi-organ involvement and are indirect markers of disease severity. The survival benefits observed with HAART and antifungal treatment are expected; however, the reason why Itraconazole specifically ameliorated this risk is likely due to the high mortality rates observed in severely-ill patients that did not survive beyond initial treatment with Amphotericin B. Prompt antifungal and antiretroviral treatment should help lower the high mortality rates observed. Our data suggest the risk of death due to delays in treatment could supersede the risk of IRIS-associated death with early treatment.