Long-term Mortality after Histoplasma Infection in People Living with HIV

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ABSTRACT #923

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ABSTRACT

Background: Histoplasmosis is a common opportunistic infection afflicting people living with HIV (PLWH) globally. There are no data on long term survival of PLWH with histoplasmosis

Methods: A single-center retrospective cohort study of PLWH diagnosed with histoplasmosis between 2002 and 2017. Data collected included demographics, clinical characteristics, treatment, and mortality. Patients were categorized into three groups based on length of survival after diagnosis: early mortality (death within 90 days), late mortality (death at or after 90 days), and survivors. Between group differences in demographic and clinical characteristics were assessed using Chi square for categorical variables and Mann-Whitney U non-parametric tests for continuous variables. Mortality was compared using Cox proportional hazards. Insurance type (i.e. private versus public option) served as a surrogate indicator of socioeconomic status (SES). Patients diagnosed with histoplasmosis in or after 2008 were considered a part of the modern ART era, regardless of treatment regimen.

Results: 54 PLWH infected with histoplasmosis from 2002-2017. Overall mortality was 37%, with 14.8% early mortality and 22.2% late mortality. Median survival time in the early mortality group was 13.5 days (IQR 2.5-41 days), and 338 days (IQR 180.5-803.3) in the late mortality group. Compared to the late mortality group, survivors were over 6 times more likely to have suppressed HIV viral load at last observation (HR 6.19, p=0.013). Median HIV viral load at last observation was lower among the survivors (2 log copies/ml, IQR 0, 4.5) compared to the late mortality group (4.1 log copies/ml, IQR 2.6,5.5) (p=0.010). Survivors were twice as likely to have private insurance, but this did not reach statistical significance (HR 2.19, p=0.14). There was no statistically significant difference in survival based on the availability of modern ART (p=0.85). The year of diagnosis made no difference with regards to survival (p=0.914).

Conclusion: Histoplasmosis continues to be associated with high mortality among PLWH. Improved long-term survival is seen in patients with suppressed HIV viral loads.

BACKGROUND

- Histoplasma is the most prevalent endemic mycosis in the United States with highest rates in the Midwest—5.1 cases per 100,000 population [1,2]

- Histoplasmosis carries high 90 day mortality at 16%, with increased mortality among immunocompromised individuals up to 24%

- Few studies have assessed factors associated with long term mortality of histoplasmosis among people living with HIV/AIDS (PLWH)

METHODS

- **Design:** Retrospective cohort from Barnes Jewish Hospital, a 1,368 bed academic hospital in St. Louis, MO.

- **Study Period:** January 1st, 2002 to December 31st, 2017

- **Inclusion Criteria:** Positive Histoplasma antigen from urine, serum, CSF or other body fluid; isolation of Histoplasma from any source in culture; positive Histoplasma antibody; ICD code for Histoplasma

- **Exclusion Criteria:** positive antigen/antibody testing in the setting of another fungal infection confirmed by culture or histopathology; low antigen level with another fungal infection; determination of false positive on review; ocular histoplasmosis or fibrosing mediastinitis; ICD code with no other evidence of Histoplasma infection; or insufficient clinical data.

- Patients with HIV sub-selected if had positive 3rd or 4th generation HIV screening test with positive confirmatory HIV viral load test

RESULTS

Table 1 - Baseline characteristics and presentation of PLWH with histoplasmosis (n=54) among three groups (survivors, early-mortality, and late-mortality) 2002 – 2017

	Survived n=34 (%)	Early mortality n=8 (%)	Late mortality n=12 (%)	P value
Male	23 (67%)	6 (75%)	8 (67%)	0.911
Age (median, IQR)	43 (32, 51)	41 (36, 49)	36 (25, 40)	0.773
Race				0.105
African American	16 (47%)	7 (87%)	9 (75%)	
Non African American	17 (50%)	1 (13%)	2 (17%)	
Site of infection				
CNS	3 (9%)	0 (0%)	0 (0%)	0.393
Pulmonary	24 (71%)	6 (75%)	7 (58%)	0.670
Bloodstream	15 (44%)	3 (38%)	8 (67%)	0.327
Other				
Presenting symptoms				
Fever	26 (76%)	4 (50%)	10 (83%)	0.217
Cough	17 (50%)	4 (50%)	5 (42%)	0.878
Night sweats	10 (29%)	1 (13%)	5 (42%)	0.375
Dyspnea	13 (38%)	3 (38%)	6 (50%)	0.760
Chest pain	6 (18%)	0 (0%)	3 (25%)	0.329
Arthralgias	3 (9%)	0 (0%)	1 (8%)	0.686
Dysphagia	5 (15%)	2 (25%)	2 (17%)	0.781
Weight loss	22 (65%)	5 (63%)	5 (42%)	0.370
GI symptoms	23 (68%)	4 (50%)	8 (67%)	0.635
Disseminated disease	26 (76%)	5 (63%)	11 (92%)	0.293

Figure 1 – Mortality among individuals with (red) and without (blue) HIV viral suppression at last observation
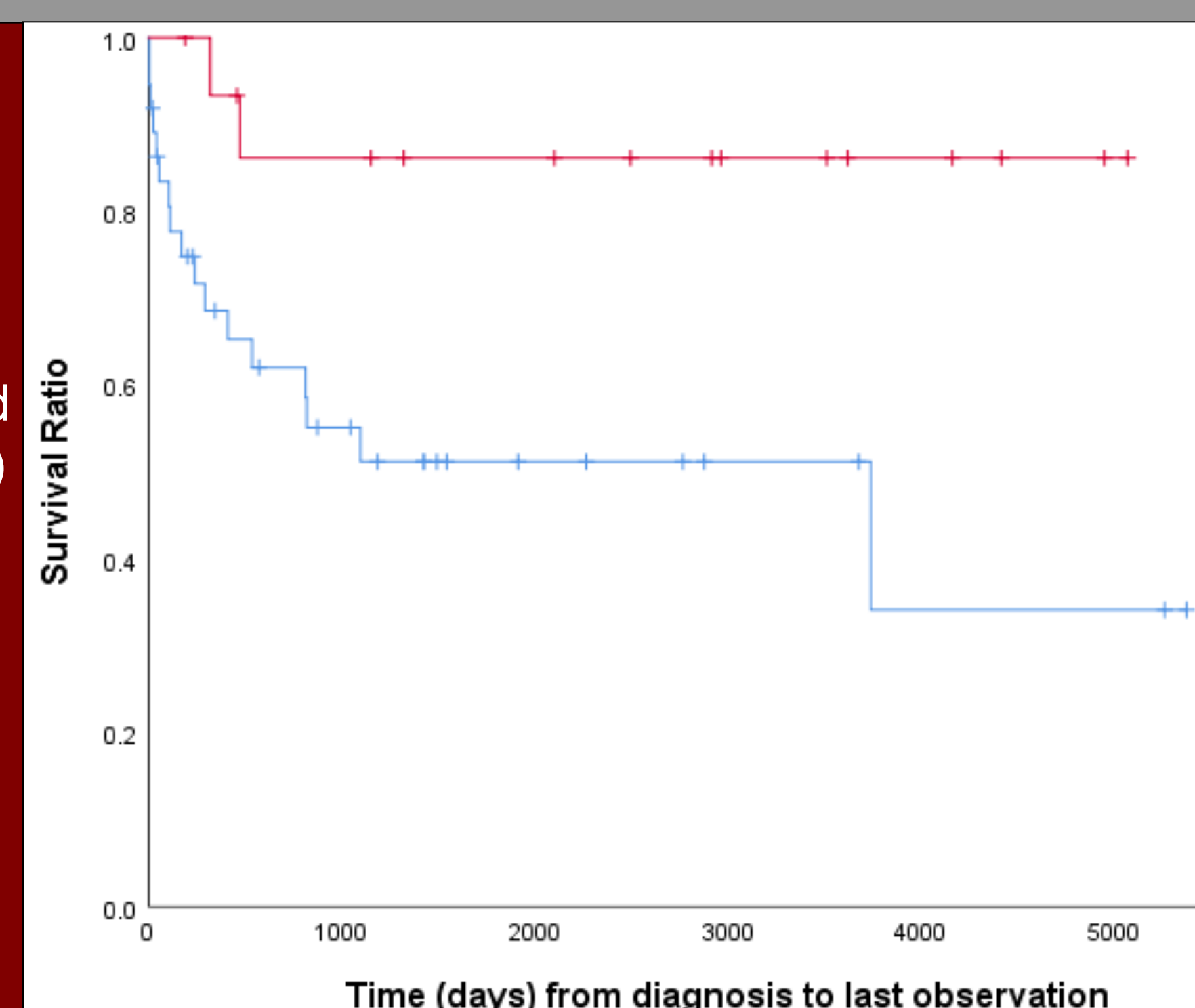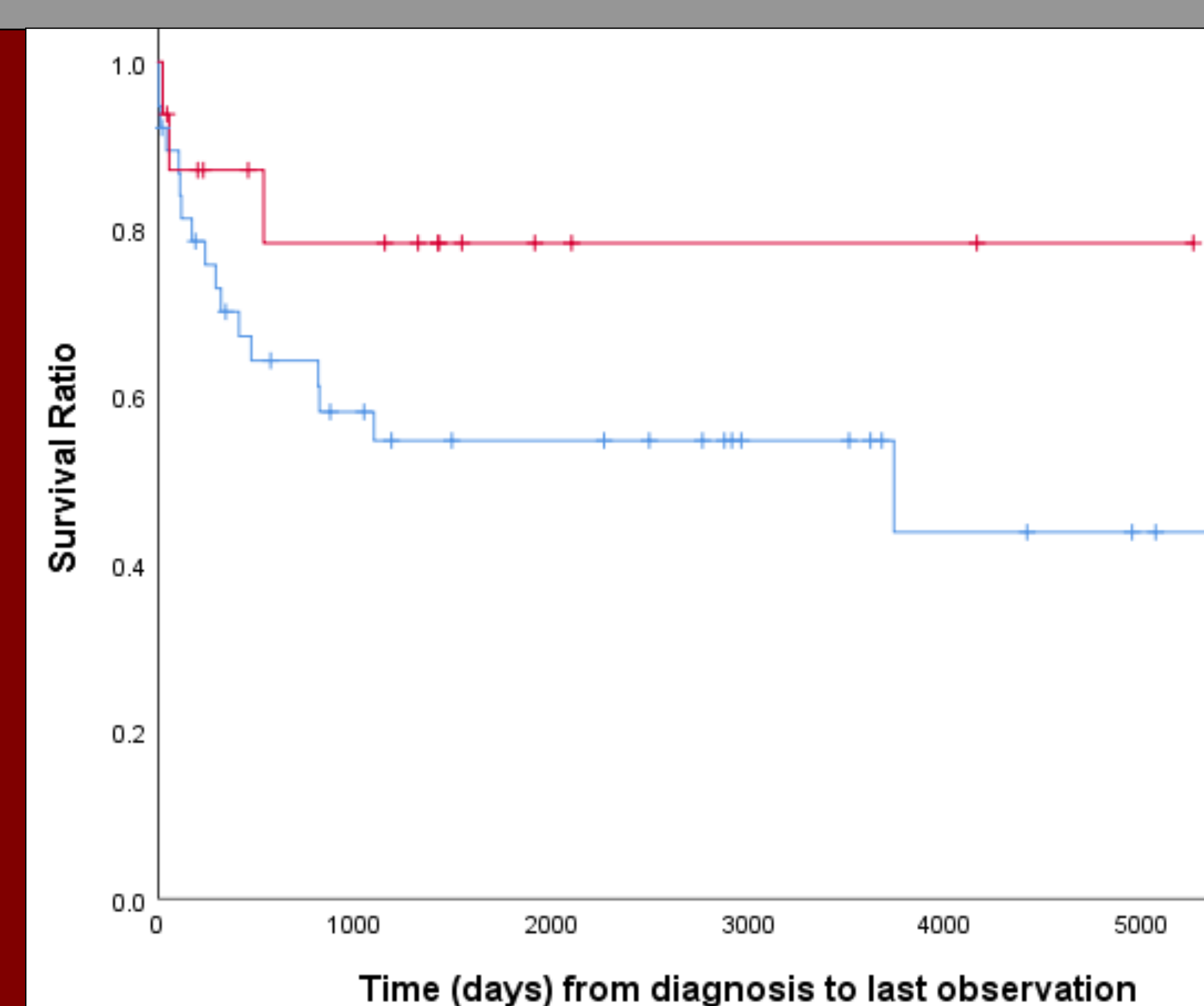
HR 6.19
p=0.01

Figure 2 – Mortality among individuals with private insurance (red) vs. government or no insurance (blue).

HR 2.19
p= 0.14

Table 2- Baseline HIV related characteristics of PLWH with histoplasmosis (n=48) among two groups (survivors and late-mortality) 2002 – 2017

	Survived (n=34)	Late mortality (n=12)	P value
Median CD4 count (median, IQR)	12 (6, 46)	26 (8, 52)	0.515
Median HIV viral load at diagnosis (median, IQR)	5.5 (4.4, 6.2)	5.2 (3.8, 5.5)	0.250
Median HIV viral load at last observation (median, IQR)	2.0 (0, 4.5)	4.1 (2.6, 5.5)	0.010
New HIV diagnosis at diagnosis	18 (53%)	3 (25%)	0.095
Median time for HIV diagnosis to histoplasma diagnosis, years (median, IQR)	0.2 (0, 13.6)	3.5 (0.1, 5.3)	0.871
ART-experienced	14 (41%)	7 (58%)	0.194
Modern ART	12 (35%)	4 (33%)	0.902
HIV viral load suppressed at last observation	14 (41%)	2 (17%)	0.125
HIV viral load suppressed at diagnosis	1 (3%)	2 (17%)	0.098
History of previous OIs	17 (50%)	9 (75%)	0.133
Pneumocystis pneumonia	10 (29%)	2 (17%)	
Disseminated MAC	2 (6%)	0 (0%)	
Tuberculosis	0 (0%)	1 (8%)	
Oral Candidiasis	4 (12%)	2 (17%)	
Cryptosporidium	0 (0%)	1 (8%)	
CMV	2 (6%)	2 (17%)	
Kaposi Sarcoma	1 (3%)	0 (0%)	
Toxoplasmosis	1 (3%)	1 (8%)	
Private insurance	13 (38%)	1 (8%)	0.053
History of substance abuse	13 (38%)	2 (17%)	0.171
History of psychiatric illness	4 (12%)	0 (0%)	0.214

STATISTICAL ANALYSIS

- Categorical variables compared using a Pearson Chi-square test for independence or Fisher's exact test as appropriate

- Continuous variables analyzed using Mann-Whitney U test

- Kaplan-Meier survival models used to evaluate mortality

Analysis

- Overall mortality for the cohort was 37%
  - 14.8% mortality within 90 days of histoplasmosis diagnosis with median length of survival 13.5 days (IQR 2.5-41)
  - 22.2% mortality after 90 days with median length of survival 338 days (IQR 180.5-803.3)
- Disseminated histoplasmosis most common disease presentation in all groups, p=0.293
  - 75% in survivors
  - 63% early mortality
  - 92% late mortality
- Median HIV viral load at last observation significantly lower in survivors (2 log copies/ml, IQR 0-4.5) compared to late mortality individuals (4.1 log copies/ml, IQR 2.6-5.5) (p=0.01)
- Higher viral load suppression among survivors (41%) compared to late mortality individuals (17%) but not statistically significant (p=0.125)
- Median HIV viral load at time of Histoplasma diagnosis did not vary significantly between groups (p= 0.250)
  - Survivors: 5.5 median log copies/ml (IQR 4.4-6.2)
  - Individuals with late mortality: 5.2 median log copies/ml (IQR 3.8-5.5)
- ART experience made no difference with respect to survival (n=14, 41% of survival group versus n=7, 58% of late mortality group, p=0.305),
- Diagnosis within the era of modern ART had no effect on survival (35% of survivors vs. 33% of late mortality group, p=0.848)
- Prior infection with an opportunistic pathogen did not have statistically significant effect between survival groups (50% of survivors vs. 75% of late mortality individuals, p=0.133)
- Survivors more than twice as likely to have private insurance compared to no or government insurance but not statistically signficiant (hazard ratio 2.19, p=0.14)
- No significant difference between survivors and late mortality individuals with respect to history of substance abuse or psychiatric illness

CONCLUSIONS

- Histoplasmosis is associated with high mortality among people living with HIV
- For two-thirds of patients, death occurred after 90 days
- Improved mortality with viral load suppression.
- Diagnosis in the era of modern ART had no effect on survival
- Having private insurance showed a trend towards imparting a survival benefit. Though this finding was not statistically significant in our cohort, it correlates with other studies showing similar findings.

Sources

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2. Baddley, J.W., et al., *Geographic distribution of endemic fungal infections among older persons, United States.* Emerg Infect Dis, 2011. **17**(9): p. 1664-9.