Abstract 2713
Presentation 0748

Tuberculosis in HIV-Associated Cryptococcal Meningitis and its Impact on Mortality

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Abstract

Background: Tuberculosis (TB) and cryptococcal meningitis are leading causes of morbidity and mortality in advanced HIV disease. Data are limited on TB co-infection among individuals with cryptococcal meningitis.

Methods: We performed a retrospective analysis of HIV-infected participants with cryptococcal meningitis from 2010-2017. Baseline demographics were compared between three groups: 'prevalent TB' if TB treated >14 days prior to cryptococcal meningitis diagnosis, 'concurrent TB' if TB treated ±14 days from diagnosis, or 'No TB at baseline'. We used time-updated proportional-hazards regression models to assess TB diagnosis as a risk for death.

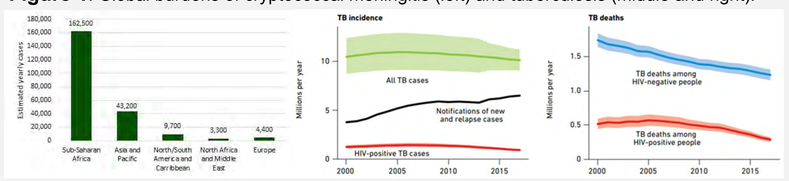
Results: Of 870 participants with cryptococcal meningitis, 50 (6%) had prevalent TB, 67 (8%) had concurrent TB, and 753 (86%) had no baseline TB. Among participants without baseline TB, 67 (9%) were diagnosed with incident TB (after >14 days), with a median time to TB incidence of 41 days (IQR, 22-69). The 18-week mortality was 50% (25/50) in prevalent TB, 46% (31/67) in concurrent TB, and 45% (341/753) in the no TB group. TB co-infection was associated with an increased hazard of death (HR=1.75; 95%CI, 1.33-2.32; p<0.001) in the time-updated model.

Conclusion: TB is a common co-infection in patients with cryptococcal meningitis. New TB diagnosis was associated with increased mortality in a time-updated model.

Introduction

- Tuberculosis and cryptococcal meningitis each continue to contribute greatly to AIDS-related mortality (**Figure 1**).
- The attributable mortality of TB is ~33% among HIV-infected persons followed by cryptococcosis at 15% of AIDS-related attributable mortality.
- Despite the overlapping epidemiology and large influence both infections have on HIV-related mortality, co-infection of TB and cryptococcosis is not well described
- We aimed to describe baseline characteristics and clinical outcomes of patients with HIV-associated cryptococcal meningitis and concurrent TB treatment.

Figure 1: Global burdens of cryptococcal meningitis (left) and tuberculosis (middle and right).



Methods

- Retrospective analysis of subjects enrolled in sequential cryptococcal meningitis research studies from Nov 2010 through June 2017.
- Baseline TB status was classified as:
  1. **Prevalent TB**: if TB diagnosed >14 days prior to cryptococcal diagnosis
  2. **Concurrent TB**: if diagnosed with TB +/-14 days from cryptococcal diagnosis
  3. **No baseline TB**
- Baseline demographics were compared between groups.
- Among those with no baseline TB, 'TB incident' was defined as occurrence of TB >14 days after cryptococcal diagnosis.
- Time-updated proportional hazards regression models were used to assess TB diagnosis as a risk factor for death.
- Models were adjusted for age, antiretroviral therapy (ART) status, Glasgow Coma Scale (GCS) <15, and cerebrospinal fluid (CSF) quantitative cryptococcal culture.

Study Population

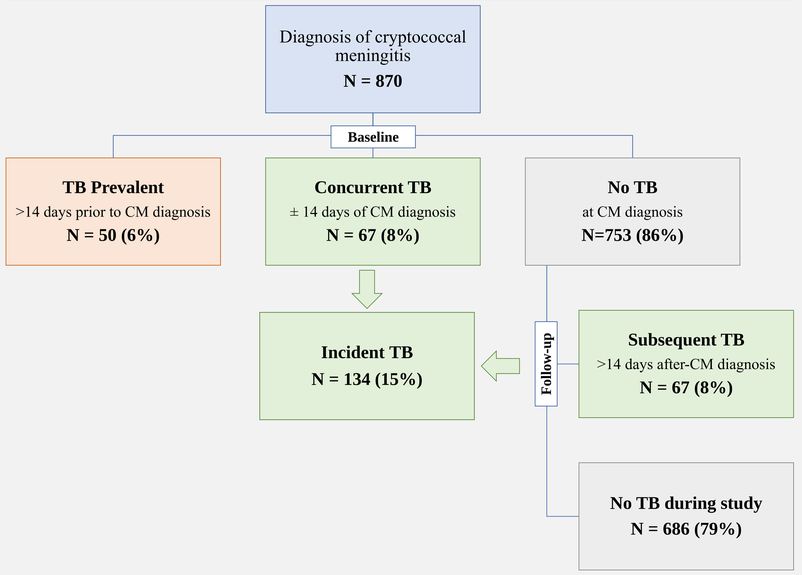


Figure 2: Classification of study participants. Patients with cryptococcal meningitis were classified at baseline (± 14 days of cryptococcal meningitis diagnosis) as 'TB prevalent', 'concurrent TB', or 'no TB'. Those developing TB during study follow-up period were classified as 'subsequent TB'. Incident TB included those with concurrent or subsequent TB.

Baseline Characteristics

	TB Prevalent (>14 days Prior) (N=50)	Concurrent TB (Days -14 to +14) (N=67)	No TB (By day +14) (N=753)	P-value*
Demographics				
Age, years	35 [29, 40]	35 [30, 40]	35 [30, 41]	0.88
Women	22 (44%)	21 (31%)	312 (41%)	0.24
Clinical characteristics				
Weight, kg	50 [45, 55]	58 [50, 60]	52 [48, 60]	<0.001
Glasgow Coma Score < 15	14 (28%)	23 (34%)	303 (40%)	0.16
Receiving HIV therapy	30 (60%)	18 (27%)	298 (40%)	<0.01
Duration of HIV, months	3.0 [1.5, 22.3]	6.0 [0.4, 55.1]	4.1 [0.2, 37.0]	0.55
CD4 T cells/mm^3	26 [11, 54]	21 [6, 65]	17 [7, 51]	0.25
Confirmed TB	23 (46%)	12 (18%)		
Baseline CSF parameters				
Culture *Crypto* $\log_{10}$ CFU /mL	4.2 [2.4, 5.3]	4.4 [2.7, 5.5]	4.7 [3.3, 5.4]	0.17
Sterile CSF culture	3 (6%)	4 (6%)	51 (7%)	0.95
Opening pressure, mm H_2O	210 [155, 305]	260 [180, 360]	280 [180, 420]	<0.01
White cell ≥5 cells/mm^3	19 (42%)	28 (44%)	287 (40%)	0.71
Protein, mg/dL	54 [30, 110]	71.5 [24, 164]	60 [25, 120]	0.61

Data are median (IQR) or N (%). Abbreviations: TB, tuberculosis; CSF, cerebrospinal fluid; QCC, cryptococcal quantitative culture.

*P-value from Kruskall-Wallis test for medians, Chi-squared test for proportions.

Timing of TB in relation to Cryptococcal Diagnosis

Days on TB Medications	TB Prevalent (At least 14 days) N=50	Concurrent TB (Days -14 to 14) N=67	No TB (by day 14)[1] N=753
Prior to Cryptococcal Diagnosis			
Max	180	12	
Median [IQR]	41 [29, 72]	4 [0, 11]	
Min	17	0	
N	50	15	
After Cryptococcal Diagnosis [1]			
Max		15	126
Median [IQR]		7 [2, 11]	41 [22, 69]
Min		1	12
N		52	67

Abbreviations: TB, tuberculosis; CM, cryptococcal meningitis; IQR, interquartile range

[1]For those with no TB history at screening, this is N and time to TB incident.

Mortality Risk

	Unadjusted Model HR (95% CI)	P-value	Adjusted Model* HR (95% CI)	P-value
Including TB prevalent † (N=870)				
Death by day 30	1.33 (0.90, 1.97)	0.15	1.47 (1.00, 2.17)	0.05
Any death	1.62 (1.23, 2.14)	<0.001	1.75 (1.33, 2.32)	<0.001
Excluding TB prevalent (N=805)				
Death by day 30	1.30 (0.80, 2.11)	0.29	1.34 (0.83, 2.19)	0.23
Any death	1.72 (1.25, 2.36)	<0.001	1.77 (1.28, 2.43)	<0.001

*Adjusted for age, ART use, Glasgow coma scale score < 15 and CSF quantitative cryptococcal culture.

†Those with prevalent TB have the time-updated indicator for TB active on study day 1.

Conclusions

- Nearly 1 in 4 patients with cryptococcal meningitis are diagnosed with TB
- TB diagnosis has a higher risk death in patients with cryptococcal meningitis; however, the quality of diagnoses is variable (confirmed vs. empiric TB diagnoses)
- Additional studies are needed to validate our findings.
- Remaining questions around TB-*Cryptococcus* coinfection in HIV include:
  - The role of TB preventive therapy
  - The optimal timing of TB therapy with cryptococcal coinfections
  - Drug interactions and pharmacokinetics occurring in patients with TB, *Cryptococcus* and HIV co-infections

Acknowledgements

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