Diabetes Mellitus as a Risk Factor for Cryptococcosis: A Multicenter Research Network Study

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Background

- Cryptococcosis is one of the most common life-threatening opportunistic fungal infections worldwide. Its diagnosis can be delayed or missed, when providers do not recognize risk factors for infection.[1,2]
- Relatively established risk factors for cryptococcosis are AIDS, glucocorticoid use, transplantation, malignancy, cirrhosis, sarcoidosis, and autoimmune diseases.[2-4]
- Diabetes mellitus (DM) is prevalent, and known to increase the risk of certain bacterial and fungal infections. The role of DM as an independent risk factor for cryptococcosis is unclear.[4-7]
- We aim to better characterize the natural history of cryptococcosis in patients with DM, without other established immunocompromising conditions.

Methods

- We used TriNetX, a global federated research network that captures anonymized data from the electronic medical records of 59 healthcare organizations, to identify immunocompetent adults with cryptococcosis.
- Cryptococcosis was identified by ICD-10-CM (ICD) code B45, or by labs detecting Cryptococcus antigen or DNA. DM was identified by ICD codes E08-E13. Patients with known immunocompromising conditions were identified and excluded by ICD codes: HIV by B20, Z21; long-term steroid use by Z79.5; organ transplant by Z48.2; malignant neoplasm by Z85; fibrosis/cirrhosis by K74; sarcoidosis by D86; systemic connective tissue disorders (including vasculitides, SLE, dermatopolymyositis, systemic sclerosis, Sjogren syndrome, polymyalgia rheumatica) by M30-M35, RA by M05-06, psoriasis by L40, ankylosing spondylitis by M45, IBD by K50-K51; and other immune disorders by D80-D89.
- DM was considered a comorbidity, if it was diagnosed at or anytime prior to index diagnosis of cryptococcosis.
- Demographic characteristics, underlying comorbidities, symptoms, and laboratory data were compared between patients with DM and those without DM.
- Clinical outcomes were compared, with propensity score matching for age and sex.
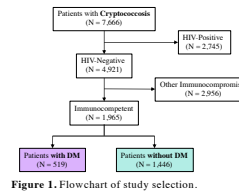
Results

Figure 1. Flowchart of study selection.

- Among immunocompetent patients with cryptococcosis, 519 had DM, and 1,446 did not have DM (**Figure 1**).

Table 1. Baseline characteristics of immunocompetent patients diagnosed with cryptococcosis, stratified by DM status.

	Cryptococcosis patients with DM (N = 519)	Cryptococcosis patients without DM (N = 1,446)	p-value
Mean Age (years)	59.8 ± 13.5	52.1 ± 16.6	< 0.0001
Male Sex	310 (64%)	853 (67%)	0.3983
Race			
White	291 (60%)	732 (57%)	0.2034
Black / African-American	81 (17%)	219 (17%)	0.8986
Asian	14 (3%)	21 (2%)	0.0884
American Indian / Alaska Native	10 (2%)	10 (1%)	0.0219
Native Hawaiian / Pacific Islander	0 (0%)	10 (1%)	0.0520
Unknown	93 (19%)	301 (23%)	0.0617
Ethnicity			
Hispanic / Latino	63 (13%)	96 (7%)	0.0003
Socioeconomic / Psychosocial Hazards	11 (2%)	12 (1%)	0.0261
Selected Comorbidities			
Mean BMI	28.5 ± 6.3	27.7 ± 6.18	0.3253
Lipidemia	147 (31%)	108 (8%)	< 0.0001
Hypertension	193 (40%)	176 (14%)	< 0.0001
Heart Failure	54 (11%)	20 (2%)	< 0.0001
Chronic Ischemic Heart Disease	70 (15%)	42 (3%)	< 0.0001
Cerebrovascular Disease	34 (7%)	46 (4%)	0.0018
Chronic Kidney Disease	89 (19%)	55 (4%)	< 0.0001
Dependence on Renal Dialysis	13 (3%)	10 (1%)	0.0015
Chronic Lower Respiratory Diseases	67 (14%)	73 (6%)	< 0.0001
Gastro-Esophageal Reflux Disease	77 (16%)	92 (7%)	< 0.0001
Nicotine Dependence	34 (7%)	56 (4%)	0.0220

- Patients with DM were older (59.8 years vs. 52.1 years), and more likely to belong to racial/ethnic minority groups (**Table 1**).
- DM patients more frequently had been on long-term antibiotics (2% vs. 1%, p = 0.0219).
- Patients with DM had higher mean hemoglobin A1c (7.4 vs. 6.0, p < 0.0001), creatinine (1.5 vs. 1.2, p = 0.0057), and BUN (24 vs. 18, p < 0.0001) values.

Table 2. Clinical presentation of immunocompetent patients at index diagnosis of cryptococcosis, stratified by DM status.

	Cryptococcosis patients with DM (N = 519)	Cryptococcosis patients without DM (N = 1,446)	p-value
Fever	32 (7%)	41 (3%)	0.0012
Hypotension	28 (6%)	17 (1%)	< 0.0001
Somnolence, Stupor, & Coma	11 (2%)	13 (1%)	0.0401
Convulsions	11 (2%)	27 (2%)	0.8176
Headache	32 (7%)	68 (5%)	0.2772
Dyspnea	73 (15%)	78 (6%)	< 0.0001
Cough	68 (14%)	84 (7%)	< 0.0001
Hemoptysis	10 (2%)	10 (1%)	0.0219
Abdominal Pain	44 (9%)	50 (4%)	< 0.0001
Nausea & Vomiting	47 (10%)	56 (4%)	< 0.0001
Ascites	13 (3%)	10 (1%)	0.0015
Enlarged Lymph Nodes	17 (4%)	26 (2%)	0.0682
Rash & Skin Eruption	26 (5%)	39 (3%)	0.0192

- Patients with DM were more likely to experience serious cryptococcosis symptoms and signs, such as hypotension and somnolence (**Table 2**).
- Patients with DM were more likely to have pulmonary (32% vs. 24%, p = 0.0013) or disseminated (24% vs. 17%, p = 0.0014) cryptococcosis, while rates of cerebral cryptococcosis were not significantly different (16% vs. 14%, p = 0.6297).

- Clinical outcomes of intubation (4% vs. 2%, p = 0.1264), transfer to ICU (12% vs. 7%, p = 0.0691), and death (12% vs. 10%, p = 0.5173) within 90 days of index cryptococcosis diagnosis, were not significantly different between patients with vs. without DM.
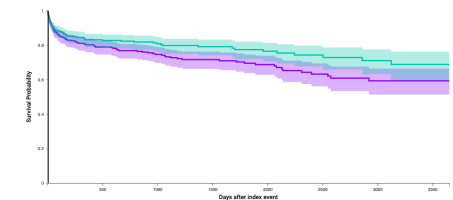

Figure 2. Kaplan-Meier survival curve, comparing immunocompetent cryptococcosis patients with DM (purple) and without DM (green).

Conclusions

- Cryptococcosis is rare in immunocompetent patients. Among these patients, having DM was associated with more severe cryptococcosis symptoms, and disseminated infection, but did not significantly affect mortality.
- Factors that may be associated with cryptococcosis among patients with DM include belonging to a racial/ethnic minority group, uncontrolled hyperglycemia, increased antibiotic usage, renal disease, and other comorbidities.
- Limitations of our study include its retrospective design and limitations of the TriNetX database.
- Future directions include subgroup analyses for uncontrolled DM, and multivariable analyses to parse out the contributions of other comorbidities to cryptococcosis risk in patients with DM.

Acknowledgements

References:
1. Liao C-H, Ho M-W, et al. J Microbiol Immunol Infect 2012, 45, 296.
2. Salazar AS, Spec A, et al. EClinicalMedicine 2020, 27, 100563.
3. Pyrgos V, Williamson PR, et al. PLoS ONE 2013, 8, e56269.
4. Lin Y-Y, Fang C-T, et al. PLoS ONE 2015, 10, e0119090.
5. Archuleta S, Henao-Martinez AF, et al. Ther Adv Infectious Dis 2021, 8, 1.
6. Nsenga L, Bongomin F, et al. Ther Adv Infectious Dis 2021, 8, 1.
7. Li Y, Chen M, Pan W, et al. Mycoses 2017, 60, 706.