The Prevalence of Disseminated Tuberculosis Among Tuberculosis Patients in Uganda

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Abstract

Background: The incidence of disseminated tuberculosis (DTB) is increasing worldwide yet its epidemiological characteristics in Uganda are not known. The purpose of this study was to determine the prevalence, associated factors, and treatment outcomes of DTB among patients at a national tuberculosis (TB) treatment center in Uganda.

Methodology: The study took place at the TB unit of Mulago National Referral Hospital in Kampala, Uganda. We conducted a retrospective chart review of TB patients who were enrolled in care between January 2015 and December 2019. Eligible charts were for patients with pulmonary bacteriologically confirmed TB enrolled into care in the period under study. DTB was defined as TB at two or more non-contiguous sites.

Results: Overall, 400 patient charts were eligible, of whom 240(60.0%) were aged 15 – 34 years and 205 (51.3%) were female. The prevalence of DTB was 8.5% (34/400) (95% CI: 6.0% – 11.7%). Patients with DTB were more likely to be casual laborers (44.1% vs 21.3%, p = 0.023), from Bantu ethnic group (67.7% vs. 40.5%, p = 0.0021), and had at least one comorbidity (82.4% vs 37.2%, p <0.001), of which HIV was the most frequent. Further, patients with DTB (n = 20) were more likely to have empyema (15% vs 2.6%, p = 028) but less likely to have bronchopneumonic opacification (0.0% vs 15.3%, p = 0.043) on chest x-ray imaging. Patients with DTB had higher mortality (26.5% vs 6.37%) and a lower cure rate (41.2% vs 64.8%), p = 0.002.

Conclusion: Our findings highlight the need for early detection of TB before dissemination and greater use of TB preventive therapies in HIV-infected individuals to counter the observed high mortality of DTB.

Background

Tuberculosis (TB), which is caused by the bacterium *Mycobacterium tuberculosis* (*Mtb*), is a major public health problem [1]. It remains a major threat to humanity despite improvements in health-care systems and the widespread implementation of TB control programs. According to World Health Organisation, TB is one of the top ten causes of death worldwide with an estimated 10 million new cases in 2019, of which majority were in South-East Asia and Sub-Saharan Africa [2]. In Uganda alone, there is an estimated 87,000 new TB cases annually and a prevalence of 253 per 100,000 persons [3]. TB typically affects the lung parenchyma (pulmonary TB) but can also affect other sites (extrapulmonary TB) [2].

Disseminated TB (DTB) is defined as TB infection involving 2 or more non-contiguous sites and involves several organs, or can present as TB bacteraemia (miliary TB) [4], [5],[6]. According to the US Centre for Disease Control, the incidence of DTB cases seems to be increasing worldwide, and this increases the risk of TB-related morbidity and mortality [7]. The prevalence of DTB varies among low- and high-income countries. A study in Portugal [8], a high income country, found that 19.5% of TB cases had DTB while the prevalence of DTB in a study in Oman, another high income country, was 10% [9]. In comparison, a study in Ghana, a middle-income country, showed that 32.8% of patients with extrapulmonary TB (EPTB) had DTB [10], while in Tanzania, 5.7% of febrile inpatients had bacteraemic disseminated TB [11]. In South Africa, an HIV/TB high-burdened country, 31% of hospitalised HIV positive patients had DTB [12].

There is still scarcity of data on the characteristics of patients with DTB and host risk factors for DTB. Studies suggests that HIV infection and cigarette smoking are potential risk factors as reported in Tanzania [11], Oman [9], and Portugal [8]. Liver disease and low CD4 count have also been associated with DTB [8, 12]. DTB has been observed to be infrequent in immunocompetent patients [10]. Although a miliary pattern is common on chest radiographs in patients with military-type of DTB, 10–15% of chest radiographs of DTB patients are found to be normal [5]. The TB diagnosis in such patients may be missed yet patients with DTB have been found to have higher mortality rates than those without [9, 12].

The burden, associated factors, and treatment outcomes of patients with DTB in Uganda is not well established. The purpose of this study, therefore, was to determine the prevalence, associated factors and treatment outcomes of patients with DTB at the tuberculosis unit of Mulago National Referral hospital in Kampala, Uganda.

Materials And Methods

Study Setting

This study took place at the TB unit of Mulago National Referral Hospital from December 2019 September 2020.This is the largest TB Treatment Center in Uganda and manages over 200 referred patients per quarter. The facility is located in Kampala, the capital city of Uganda. It is a center of excellence for drug sensitive and drug resistant TB, offering both outpatient and inpatient services.

Study design and sample size estimation.

We used a cross sectional study design and retrospectively reviewed charts of TB cases managed at this unit from January 2015 to December 2019. Using OpenEpi [13]we estimated the sample size to be 406, assuming a prevalence of 50%, a 10% incomplete data rate, a confidence level of 95% and a known population of TB cases (7,460) in the period under study.

Study Participants

We included patients' charts for whom TB was bacteriologically confirmed using either sputum Ziehl Neelsen (ZN) stain, Xpert MTB/RIF, and/or mycobacterium culture as evidenced by laboratory results from the patients' charts. Patient files were selected by systematic sampling of every 19th patient file in the unit TB register and those with missing files were replaced by the next file. We excluded charts with missing information on age and sex.

Data collection and study measurements

Using a data abstraction form, data on HIV status, occupation, history of alcohol use, cigarette smoking, other substance abuse and other potential risk factors for DTB such as comorbidities (diabetes mellitus, HIV/AIDS, and cancer) and history of TB treatment were extracted from the charts by health workers. The treatment outcome data were extracted from the unit TB register for each patient. Baseline chest x-rays films were evaluated by a radiologist for hilar/ mediastinal lymphadenopathy, bronchopneumonic opacification, segmental/lobar consolidation, cavities, miliary opacification, pleural effusion, empyema, bronchiectasis, atelectasis, fibrotic bands, pneumothorax, and bullae. The location of the lesion was described by side and zone of the lung. TB outside the lung parenchyma was diagnosed by abdominal ultrasound scan, lymph node biopsy and spinal imaging. We considered any of the following as features of abdominal TB on abdominal ultrasound Scan: ascites with fibrous stranding, splenic hypoechoic lesions, organomegaly of spleen and liver and lymphadenopathy. Features of spine TB on spine imagining were: intraosseous and para spinal abscess, vertebral body destruction and collapse, and loss of trabecular pattern. For lymph node TB, histology features from lymph node biopsy showing caseous necrosis or granulomas were considered.

Study Outcomes

DTB was defined as having pulmonary TB (all patients had bacteriologically confirmed TB on sputum samples) and features of TB at any another noncontiguous site(s) TB. The prevalence of DTB was computed as the proportion of patients with DTB to the entire study population. Treatment outcomes were cure, death, treatment failure, loss to follow up, and transferred out as defined by the World Health Organisation [14]. Factors associated with TB were those variables for which the frequencies were significantly different among patients with and without DTB.

Statistical Analysis.

Raw data were entered in EpiData 3.0. Normality was assessed using the Shapiro-Wilk test. Means were compared using the Student's t-test whereas percentages for categorical data were compared using $\chi 2$ test and Fisher's exact test. The statistical significance was determined using a p- value of 0.05 and a 95% confidence interval. The data was analyzed using SAS Version 9.4 [15].

Ethical approval

Approval for the study was obtained from Mulago Hospital Research and Ethics Committee (reference Number; MHREC#1808). The study was conducted after a consent waiver was obtained from the ethics committee.

Findings

Sociodemographic and clinical characteristics of patients with and without DTB

A total of 476 TB cases were reviewed, of which 400 met the eligibility criteria (figure 1). Of all cases, 240 (60.0%) were aged 15 – 34 years and 205 (51.3%) were female. Further, 170 (42.82%) belonged to the bantu ethnic group, 93(23.25%) were casual laborers and comorbidities were found in 164 (41%) of cases. HIV co-infection was observed among 159 (39.8%) cases. Table 1 summarizes sociodemographic characteristics while table 2 shows clinical characteristics of the study participants with and without DTB.

Prevalence of DTB

Of the 400 TB cases reviewed, 34 (8.5%) (95% CI: 5.96%– 11.68%) had DTB. The most common sites of dissemination were the abdomen (52.94%), larynx (2.94%) and other sites (pericardium, brain, spine) (17.66%). Miliary TB was present in 8 (23.53%) DTB cases.

Treatment outcomes of patients with disseminated TB

Overall, treatment success (cure and treatment completion) was observed among 317 (80.25%). Patients with DTB (n = 34) had higher mortality (26.5% vs 6.37%) and a lower cure rate (41.2% vs 64.8%), p = 0.002, than patients without DTB as shown in table 2.

Factors associated with DTB

As shown in table 1 and 2, patients with DTB were more likely to be casual laborers (44.1% vs 21.3%, p = 0.023), from Bantu ethnic group (67.7% vs. 40.5%, p = 0.0021), and had at least one comorbidity (82.4% vs 37.2%, p <0.001), of which HIV was the most frequent. Notably 34 (100%) cases with DTB had HIV co-infection.

Chest X-ray findings

Of all cases, 156(39.0%) had normal chest x-rays. Patients with DTB (n = 20) were more likely to have empyema (15% vs 2.6%, p = 028) but less likely to have bilateral bronchopneumonic opacification (0.0% vs 15.3%, p = 0.043) on chest x-ray imaging as shown in table 2.

Table 1: Sociodemographic Characteristics of TB Patients Stratified by DTB

Characteristic	Total (N=400) n(%)	With DTB (n =34) n(%)	Without DTB (n =366) n(%)	p-value
Age (years)				0.6773
<15	7(1.75)	1 (2.94)	6(1.64)	
15-34	240(60.0)	23(67.65)	217(59.29)	
35-60	142(35.5)	9(26.47)	133(36.34)	
>60	11(2.75)	1(2.94)	10(2.73)	
Sex				0.6093
Male	195(48.75)	18(52.94)	177(48.36)	
Female	205(51.25)	16(47.06)	189(51.64)	
Occupation				**0.0225**
Formal Work	10(2.5)	1(2.94)	9(2.46)	
Causal Work	93(23.5)	15(44.12)	78(21.31)	
Unemployed	35(8.75)	3(8.82)	32(8.74)	
Unknown	262(65.5)	15(44.12)	247(67.49)	
Marital status				0.1846
Married	48(12)	8(23.53)	40(10.93)	
Divorced	1(0.25)	0(0)	1(0.27)	
Single	18(4.5)	1(2.94)	17(4.64)	
Unknown	333(83.25)	25(73.53)	308(84.15)	
Education status				0.053
Tertiary	6(1.5)	0(0)	6(1.64)	
Secondary	8(2)	0(0)	8(2.19)	
Primary	5(1.25)	2(5.88)	3(0.82)	
Unknown	381(95.5)	32(94.12)	349(95.36)	
Ethnic group				**0.0021**
Bantu	170 (42.82)	23 (67.65)	147 (40.50)	
Nilotics	7 (1.76)	2 (5.88)	10 (2.75)	
Nilo-hamites	7 (1.76)	1 (2.94)	6 (1.65)	
Non-Ugandan	12 (3.02)	1 (2.94)	6 (1.65)	
Unknown	201 (50.63)	7 (20.59)	194 (53.44)	

Table 2: clinical characteristics of TB patients stratified by DTB

Characteristic	Total (N=400) n(%)	With DTB (n =34) n(%)	Without DTB (n =366) n(%)	p-value
Year of treatment initiation				0.6239
Missing	5(1.5)	0(0)	5(1.37)	
2015	120(30.25)	14(41.18)	106(28.96)	
2016	101(25.5)	7(20.59)	94(25.68)	
2017	89(20.75)	5(14.71)	84(22.95)	
2018	44(12)	5(14.71)	39(10.66)	
2019	41(10)	3(8.82)	38(10.38)	
PTB dETAILS				
Type of TB				0.4863
New case	355(88.75)	32(94.12)	323(88.25)	
Relapse	34(8.5)	2(5.88)	32(8.74)	
Return after loss to follow-up	11(2.75)	0(0)	11(3.01)	
Patients with comorbidities				**<0.0001**
No	236(59.0)	6(17.65)	230(62.84)	
Yes	164(41.0)	28(82.35)	136(37.16)	
Comorbidities present				1.0000
HIV/AIDS	159 (96.95)	28 (100.00)	131 (96.32)	
Cancer	1 (0.61)	0 (0.00)	1 (0.74)	
Diabetes mellitus	4 (2.44)	0 (0.00)	4 (2.94)	
Substances abused				0.2641
Tobacco	1(1.76)	0(0)	7(1.93)	
Alcohol	12(3.02)	3(8.82)	9(2.48)	
Marijuana	1(0.25)	0(0)	1(0.28)	
Others	7(1.76)	1(2.94)	6(1.65)	
None	33(8.31)	5(14.71)	28(7.71)	
Unknown	319(80.35)	24(70.59)	295(81.27)	
Both alcohol and tobacco	18(4.53)	1(2.94)	17(4.68)	
Treatment Outcome				**0.0024**
Cured	248(62.78)	14(41.18)	234(64.82)	
Treatment failure	6(1.52)	1(2.94)	5(1.39)	
Lost to follow-up	16(4.05)	1(2.94)	15(4.16)	
Completed Treatment	69(17.47)	8(23.53)	61(16.9)	
Transferred	4(1.01)	0(0)	4(1.11)	
Died	32(8.1)	9(26.47)	23(6.37)	
Unknown	20(5.06)	1(2.94)	19(5.26)	
Chest Xray findings				
Normal X-ray findings				0.7856
Yes	156(39.00)	14(41.18)	142(38.80)	

No	244 (61.00)	20(58.82)	224(61.20)	
Bilateral bronchopneumonic opacification				**0.0432**
Yes	30(13.89)	0(0)	30(15.31)	
No	186(86.11)	20(100)	166(84.69)	
Consolidation				0.7992
Yes	54(24.88)	6(30.00)	48(24.37)	
No	163(75.12)	14(70.00)	149(75.63)	
Cavitations				0.1611
Yes	18(8.33)	0(0)	18(9.18)	
No	198(91.67)	20(100)	178(90.82)	
Atelectasis				0.9024
Yes	6(2.78)	1(5)	5(2.55)	
No	210(97.22)	19(95)	191(97.45)	
Fibrotic bands				0.2952
Yes	49(22.58)	3(15.00)	46(23.35)	
No	168(77.42)	17(85.00)	195(76.65)	
Bullae				0.9074
Yes	1(0.46)	0(0)	1(1.51)	
No	215(99.54)	20(100)	195(100)	
Lymphadenopathy				0.0602
Yes	97(44.91)	5(25)	92(46.94)	
No	119(55.09)	15(75)	104(53.06)	
Pleural Effusion				0.8682
Yes	72(33.33)	7(35)	65(33.16)	
No	144(66.67)	13(65)	131(66.84)	
Empyema				**0.0283**
Yes	8(3.7)	3(15)	5(2.55)	
No	208(96.3)	17(85)	191(97.45)	

Discussion

Disseminated TB (DTB) is a potentially lethal form of TB that affects other organs, other than the lung parenchyma, through lymphohematogenous spread with typical extrapulmonary disease locations including lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum and pericardium. DTB has been increasingly observed in immunocompromised hosts, especially in developing countries, where DTB is the principal cause of morbidity and mortality due to higher rates of TB-HIV co-infection [16]. However, little is known about the burden, risk factors and treatment outcome of this condition in Uganda.

In both the DTB and non-DTB cases in our study, the modal age was 15-34 years, which is consistent with the most frequent age group affected by TB[17] . The prevalence of DTB was found to be 9%, which is similar to that found in Oman (10%) [9] but lower than that in Portugal (20%) [8], Ghana (33%) [10] and South Africa (31%) [12]. Further, our prevalence is higher than that found in Tanzania (5.7%) [11]. These differences can be explained by variations in the study populations and definition of DTB used. The study populations consisted of EPTB patients in Ghana, hospitalised HIV patients in South Africa, and febrile inpatients in Tanzania. It is often difficult to establish the diagnosis of DTB as there is no standardised diagnostic criteria and the clinical presentation of DTB is commonly non-specific, with symptoms varying according to the affected organs [5]. In our study, the commonest site of dissemination was the abdomen. In contrast, Leeds *et al* [18] in their retrospective review of EPTB cases in the United

States found the most common site of dissemination to be lymphatic. Ultrasound scan services are more readily available in Uganda than other advanced diagnostic methods such as lymph node biopsy and histology. This may have influenced the frequency of abdominal TB that we observed due to higher diagnostic capability for abdominal TB than other sites. It is possible that some sites of TB dissemination are not confirmed due to lack of readily available diagnostic resources.

Casual laborers were more likely to have DTB in our study. Casual labor as a source of income is a proxy for low socio-economic status and low education level. Low socio-economic status is associated with increased TB susceptibility, TB infection, TB progression to active TB, severe forms of TB (such as DTB) and poor TB treatment outcomes due to poor living and working conditions, undernutrition and poor health seeking behavior [19].

There were more Bantu-speaking individuals with DTB than without. While the reason is not apparent from our study results, genetic differences (as is expected in different ethnic backgrounds) are widely recognized to influence immune responses against *Mycobacterium tuberculosis(Mtb)*[20] and TB dissemination[21]. The Bantu-speaking individuals in our study may have had a low frequency of HLA sub-types that are important in mycobacterial epitope recognition as has been suggested by a study among a South African Colored population [22]. It is noteworthy that ethnic background was unknown for >50% of the study population. There is, therefore, a risk for misclassification bias. The association between Bantu ethnicity and DTB deserves further investigation.

Similar to previous reports by Meira et al, [23] and Wang et al [16], we found DTB to be associated with comorbidities of which HIV was the most predominant (100% of patients with DTB had HIV co-infection). This should be expected because HIV globally impairs immune responses against *Mtb* resulting in TB dissemination [24].

Typical chest radiographic findings in DTB are not well established. In our study, only 35% of DTB cases had military pattern. In contrast, Khan *et al* [5] estimate that the classic miliary pattern occurs in 85% - 90% cases of DTB. It is unclear whether this is among patients with any form of DTB per se or among patients with bacteremia DTB (miliary TB). Interestingly, we found that DTB patients were more likely to have empyema but less likely to have bronchopneumonic opacities. More studies are needed to characterize chest x-ray findings among patients with DTB with or without bacteremic DTB.

Our findings about the treatment outcomes are consistent with other studies that found DTB to be highly fatal [11]. We found that DTB patients had a fourfold mortality rate as compared to those without DTB. In Portugal, Meira *et al.* [23] found a mortality rate of 36% among patients with DTB but was not significantly higher than that among patients without DTB (21%). However, many patients in their study had other comorbidities and HIV was prevalent in only 47% (cf. 100% in our study) of patients with DTB. The rate of cure was lower in the DTB than in non-DTB cases in our study. This is expected since patients with predominantly extrapulmonary forms of TB may be unable to produce sputum during treatment follow up to enable confirmation of TB cure [25]. From our results, it is evident that patients with DTB were more likely to be assigned “treatment completion” as opposed to cure.

Our study had limitations. We had a small number of cases with DTB which limited our ability to construct a robust model for predictors of DTB. We also did not evaluate some biomedical differences such as anemia, organ dysfunction, and clinical symptoms. These were not consistently documented in the charts. Our discussion of the relevance of ethnicity in DTB was limited by not knowing the ethnicity of 201 study participants and being a retrospective study, we could not obtain this information . Lastly, our study was at a national referral center and our estimate of the prevalence may be an over-estimate due to referral bias.

Conclusion

DTB is prevalent in Uganda especially among TB/HIV co-infected individuals. DTB was more common among casual laborers, individuals from the Bantu ethnic groups and those with chest radiological findings of empyema and bilateral bronchopenumonic opacities. A higher mortality was observed in DTB. Our findings highlight the need for early detection of TB before dissemination in individuals with comorbidities and low socioeconomic status. More studies are needed to determine the diagnostic accuracy of chest imaging in DTB and the role of ethnicity as a risk factor for DTB.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

Approval for the study was obtained from Mulago Hospital Research and Ethics Committee (reference Number; MHREC#1808). The study was conducted after a consent waiver was obtained from the ethics committee.

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Author Contribution

EK – Conceptualisation, data accrual, data analysis and interpretation, drafting manuscript, manuscript revision and final approval

JM- Conceptualisation, data accrual, drafting manuscript, manuscript revision and final approval

BN- Conceptualisation, data accrual, drafting manuscript, manuscript revision and final approval.

SN- Data accrual, drafting manuscript, manuscript revision and final approval.

JT- Data accrual, drafting manuscript, manuscript revision and final approval.

AO- Conceptualisation, data accrual, manuscript revision and final approval.

DM- Data analysis and interpretation, drafting manuscript, manuscript revision and final approval.

MK- Data analysis and interpretation, drafting manuscript, manuscript revision and final approval.

JBB- Conceptualisation, data accrual, data analysis and interpretation, drafting manuscript, manuscript revision and final approval.

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Figures

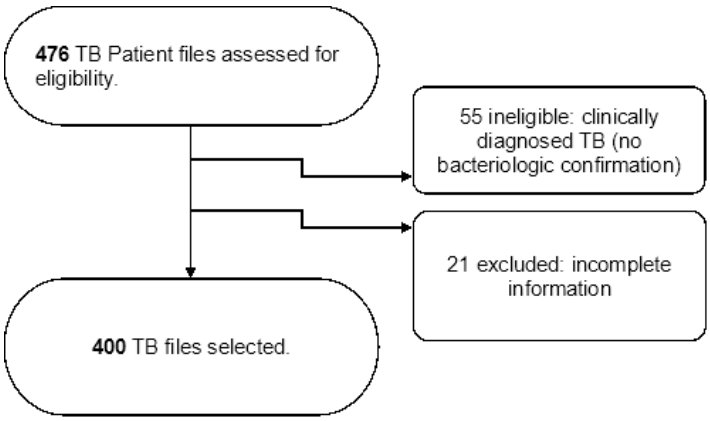

Figure 1

STUDY FLOW DIAGRAM