**High prevalence of tuberculosis among adults with fever admitted at a tertiary hospital in North-Western Tanzania**

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**ABSTRACT**

Tuberculosis is a leading cause of death in developing countries where HIV is endemic. This hospital based study was done to estimate the magnitude of pulmonary and extra-pulmonary tuberculosis and to determine predictors of tuberculosis among febrile adults admitted at Bugando Medical Centre, Mwanza, Tanzania. A total of 346 adults febrile patients admitted in medical wards were studied. Sputum for AFB microscopy and chest–x rays were used to diagnose tuberculosis. Clinical features were collected using standardized data collection tool. HIV testing and CD4 were determined. Data were analyzed using STATA version 11 software. Of 346 febrile adults patients 116 (33.5%) were diagnosed to have tuberculosis; of which 79 (68.1%) and 37 (31.9%) had pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis respectively. Smear negative PTB were more common in HIV positive than in HIV negative patients (50% vs. 18.5%, p=0.007). Extra-pulmonary tuberculosis were more common in HIV positive patients than pulmonary tuberculosis (86.4% vs. 13.6%), p=0.0001). On multivariate logistic regression analysis the predictors of tuberculosis were; age above 35 years (OR =2.38, p=0.007), cardinal symptoms (OR=37, p=<0.0001), pleural effusion (OR=24, p=0.0001), and HIV status (OR =3.2, p=0.0001). Of 79 patients with PTB, 48 (60.7%) were AFB smear positive and 31 (39.3%) were AFB smear negative. HIV patients with smear negative tuberculosis had significantly lower CD4 count than HIV patients with smear positive tuberculosis (63.5 cells/µl versus 111.5 cells/µl) [Mann-Whitney test p=0.0431]]. No different in mortality was observed between patients with TB and those without TB admitted in BMC medical wards (28.5% vs. 23.0%, p= 0.1318). Tuberculosis is the commonest cause of fever among adults patients admitted at BMC and is predicted by age above 35 years, positive HIV status, cardinal PTB symptoms, and pleural effusion. Routinely TB screening is highly recommended among adults with fever, cough, night sweating and wasting in sub-Saharan countries where HIV is endemic.

**Background**

More than 11 million adults living with HIV/AIDS are also infected with tuberculosis (WHO 2007). In some sub-Saharan countries, one-third of patients with tuberculosis have HIV (WHO 2007). TB affects more than half of those infected with HIV (WHO 2007). The overlapping between tuberculosis and HIV epidemics has had a devastating impact on morbidity, mortality, and control, rendering tuberculosis the leading killer of HIV-positive people. More than 29% of global burden of TB is in Africa with 34% related deaths (WHO 2007). TB in adults causes fever, often lasting weeks, retrosternal discomfort or pain due to mediastinal lymph node enlargement and pleuritic pain (Bruchfeld *et al* 2003). Symptoms vary from a gradual insidious onset with anorexia, weight loss, fatigue and low-grade fever to acute onset with fever, night sweats, productive cough and dyspnea (Nyirenda *et al* 2006). In Malawi among adults patient admitted with fever mycobacterium was the commonest isolate from the blood affecting 57 of 344 patients (17%) (Lewis *et al* 2003). Other study in Malawi found the prevalence of *Mycobacterium tuberculosis* (MTB) blood stream infection in HIV endemic areas to range from 9-12% (Archibald *et al* 2000). In Tanzania 57/282 of HIV adult patients were found to be infected with TB compared to 3/235 of HIV negative (Lennox *et al* 1998). Diagnosis of TB in developing countries where HIV is endemic brings more challenges (Shea *et al* 2009).

Little is known about the magnitude of TB among febrile adults admitted in many hospitals in developing countries. This cross-sectional prospective study was conducted to determine the magnitude, predictors and case fatality rate of tuberculosis among febrile adults admitted at tertiary hospital in Northern-Western Tanzania.

**Methods**

**Study design**

A prospective cross-sectional hospital based study was conducted at Bugando Medical Center (BMC) in Mwanza region between June 2011-December 2011. BMC is a tertiary hospital and University teaching hospital serving approximately 13 million people in the North-Western zone of Tanzania.

**Sample size**

Sample size was estimated using Kish and Leslie formula, the proportion of 20% (Lennox *et al* 1998) was used in the formular, this is the prevalence of TB among HIV patients in Tanzania.

**Patients’ recruitment and laboratory procedures**

All adults patients above 18 years with fever admitted in medical wards were enrolled into the study. Patients were asked to sign informed consent and were counseled for HIV testing. Sputum for acid fast bacilli (AFB) and blood for HIV testing and CD4 estimation were obtained as previously described (Bakari *et al* 2008, WHO 1998, Enarson *et al*., 2000, IUATLD 2000).

Patient clinical history and physical examination findings were collected using standardized data collection tool. Chest X ray was done in all patients suspected to have tuberculosis. HIV testing was done as per Tanzania National algorithm and CD4+ counts determined using FACS Calibur (BD UK).

**TB Diagnosis**

Smear positive tuberculosis was diagnosed if a patient had positive spot and early morning AFB smear or one positive smear with positive chest-x-ray findings (Bakari *et al* 2008). Smear negative tuberculosis were diagnosed if a patient had three negative smear (spot, early morning, spot), and failed to respond on 14 days antibiotic treatment, but improved when anti-TB is started. Extra pulmonary tuberculosis was defined as previously described (<http://www.stoptb.org/wg/gli/assets/documents/TBcasedefinitions_20110506b.pdf>).

**Quality control**

Adequate mucoid or mucopurulent sputum specimens were collected from TB suspects. The sputum specimens were transported immediately to the BMC laboratory and examined for the presence of AFB by experienced laboratory technician based on the standard procedure (Kubi & Kent 1985). All the slides were checked again by the three investigators who are expert in the subject and no discrepancy was observed. All chest –x-ray were read by experienced radiologist in the hospital. All patients were seen after 2 weeks and assessed for clinical improvement.

**Data Analysis**

Data collected were entered into a computer using Epidata version 3.1 (CDC, Atlanta, USA) and analyzed using STATA version 11 (College Station, Texas, USA). Data were summarized in form of proportions and frequent tables for categorical variables and to assess the significance of their distribution chi-square test was used. For non parametric continuous variables, we used medians to summarize them and Mann-Whitney test to test for the significance of the difference of the medians between two groups. To determine predictors of tuberculosis, logistic regression analysis was performed, starting with univariate then followed by multivariate logistic regression analysis with the dichotomous outcome being tuberculosis or no tuberculosis. Odds ratio with 95% confidence interval was calculated to test for strength of association between predictor variables and tuberculosis. Predictors with p-value less than 0.05on univariate analysis were then fitted into the multivariate regression analysis and predictors with a p-value of less than 0.05 were considered to have significant strength of association. In present study cough, night sweating and wasting were considered as cardinal symptoms of tuberculosis and were combined together and tested if they independently predict tuberculosis in multivariate analysis. We further analyzed the strength of HIV on predicting the two types of tuberculosis here we used multinomial logistic regression with the outcome being no tuberculosis, pulmonary tuberculosis and extra pulmonary tuberculosis. Based on patients with no tuberculosis as the reference group, relative risk ratio with 95% confidence interval was calculated to test for strength of association between HIV and tuberculosis type.

**Ethical clearance**

Ethical clearance and approval was obtained from a joint Catholic University of Health and Allied Sciences (CUHAS) and Bugando Medical Centre (BMC) research and publications ethics review board. Written informed consent was obtained from each patient. If patient was unable to provide consent, written consent was obtained from their legal guardians.

**Limitations**

Failure to perform mycobacterium culture bacterial blood culture and results of other causes of fever were routinely performed and were not included in the analysis.

**Results**

**Demographic and other characteristics**

Over the study period 1,552 patients were admitted to the medical wards at BMC and were screened for eligibility. A total of 417 (26.9%) met inclusion criteria of whom 346 (83%) were enrolled into the study. The median age was 35 (inter quartile range [IQR] 25-48) years and 179 (51.7%) were male. The median temperature was 38.5 with IQR of 38-39 oC. A total of 156 (45.1%) of the participants had HIV infection; of these 112 (71.8%) had WHO stage four. The median CD4 count among patients with HIV infection was 78 cells/µl.

**Magnitude of Tuberculosis**

Of 346 adult febrile patients 116 (33.5%) were confirmed to have tuberculosis; of which 79 (68.1%) and 37 (31.9%) had pulmonary tuberculosis and extra-pulmonary tuberculosis respectively. Of 79 patients with PTB, 48 (60.7%) were AFB smear positive and 31 (39.3%) were AFB smear negative. All 37 patients with extra-pulmonary tuberculosis had pleural effusion.

**Predictors of tuberculosis**

On univariate logistic regression analysis night sweat, cough, wasting, positive HIV status, pleural effusion and anemia were found to predict tuberculosis (table 1). On multivariate logistic regression analysis the predictors of tuberculosis were; age above 35 years (OR =2.38, p=0.007), cardinal symptoms (OR=37, p=<0.0001), pleural effusion (OR=24, p=0.0001), and HIV status (OR =3.2, p=0.0001) table 2.

**HIV status and tuberculosis**

Of 48 patients with smear positive TB, 22 (45.8%) were HIV positive and 26 (54.2%) were HIV negative. Smear negative PTB were more common in HIV positive than in HIV negative patients (83.9% vs. 16.1%, p=0.007) table 3. When compared to patients without tuberculosis as a reference group, HIV patients were much more likely to have extra pulmonary tuberculosis (RRR 14.0 [95% CI 5.3 - 37.5], p<0.001) than having pulmonary tuberculosis (RRR 4.2 [95% CI 2.5 - 7.3], p<0.001). Figure 1. Though HIV predicts tuberculosis, HIV positive serostatus predicts more extra-pulmonary tuberculosis than it does for pulmonary tuberculosis.

The median CD4 of HIV patients with smear positive tuberculosis was 111.5 cells/µl compared to 63.5cells/ µl of HIV patients with smear negative tuberculosis (Mann-Whitney test p=0.0431). HIV patients with smear negative tuberculosis had significantly lower CD4 count than HIV patients with smear positive tuberculosis.

**Table 1: Predictors of tuberculosis among febrile adult patients admitted at BMC: Univariate analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable (N)** | **Positive tuberculosis N =116** | **Odd ratio** | **95% CI** | **P value** |
| ***Age*** |  |  |  |  |
| ≤35 year (179) | 45 (25.1 %) | 1 |  |  |
| >35 years (167) | 71 (42.5%) | 2.2 | 1.395-3.475 | 0.001 |
| ***Sex*** |  |  |  |  |
| Male ( 179) | 59 (32.9%) | 1 |  |  |
| Female (167) | 57 (34.1%) | 1.05 | 0.674-1.64 | 0.818 |
| ***Chronic Cough*** |  |  |  |  |
| Absent (154) | 1 (0.65%) | 1 |  |  |
| Present (192) | 115(59.9%) | 228 | 31.3-1667 | <0.0001 |
| ***Night sweat*** |  |  |  |  |
| Absent (299) | 81 (27.0%) | 1 |  |  |
| Present (47) | 35 (74.5%) | 7.8 | 3.88-15.86 | <0.0001 |
| ***Wasting*** |  |  |  |  |
| Absent(254) | 56 (22.0%) | 1 |  |  |
| Present(92) | 60 (65.2%) | 6.6 | 3.93-11.16 | <0.0001 |
| ***Pleural effusion*** |  |  |  |  |
| Absent (289) | 65 (22.5%) | 1 |  |  |
| Present (57) | 51 (89.5%) | 29.3 | 12-71.31 | <0.0001 |
| ***HIV status*** |  |  |  |  |
| Negative(190) | 32 (16.8%) | 1 |  |  |
| Positive(156) | 84 (53.9%) | 5.8 | 3.5-9.43 | <0.0001 |
| ***WBC*** |  |  |  |  |
| 4000-11000 (123) | 42 (34.2%) | 1 |  |  |
| ≤4000/µl (74 | 39 (52.7%) | 2.14 | 1.19-3.87 | 0.011 |
| >4000/µl (149) | 35 (23.5%) | 0.59 | 0.34-1.00 | 0.053 |
| ***Anemia*** |  |  |  |  |
| ≥10g/dl (109) | 24 (22.0%) | 1 |  |  |
| <10g/dl (237) | 92 (38.8%) | 2.24 | 1.33-3.79 | 0.002 |

**Table 2: Multivariate logistic regression analysis of predictors of tuberculosis among febrile adults**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Odd ratio** | **95% CI** | **P value** |
| Age >35 years | 2.38377 | 1.2658-4.489 | 0.007 |
| Sex | 1.49688 | 0.8011-2.796 | 0.206 |
| Cardinal symptoms  | 37.3454 | 7.695-181.243 | <0.0001 |
| Pleural effusion | 24.35281 | 9.297-63.789 | <0.0001 |
| HIV status | 3.2313 | 1.676-6.2289 | <0.0001 |
| Anemia | 0.9612 | 0.4692-1.9693 | 0.914 |

**Table 3: HIV status in relation to smear positive and smear negative pulmonary tuberculosis**

|  |  |  |
| --- | --- | --- |
| **Variable**  | **Pulmonary tuberculosis** | **Total** |
| ***HIV status*** | ***Smear +Ve*** | ***Smear -Ve*** |  |
|  Negative  | 22 (81.5%) | 5 (18.5%) | 27 |
|  Positive  | 26 (50.0%) | 26 (50.0%) | 52 |
| **Total** | **48** | **31** | **79** |

**Chi square 7.3876, p=0.007**



***Figure 1: HIV status in relation to TB types;* HIV positive serostatus predicts more extra-pulmonary tuberculosis than it does for pulmonary tuberculosis. RRR 4.2 [95% CI 2.5 - 7.3] versus 14.0 [95% CI 5.3 - 37.5] *all differences observed were statistically significant p-value <0.001***

**Discussion**

In this study, we have confirmed the high prevalence of tuberculosis in North-western Tanzania among HIV febrile adults. Overall the prevalence of tuberculosis observed in this study agrees with that of other studies in Africa (Corbett *et al* 2003, Dagnara *et al* 2011). Among TB patients 72% were co-infected with HIV. There have been several studies of the prevalence of HIV in TB patients in different parts of Africa ranges from 6.1% in Nigeria to 57.1% in Ethiopia (Anteyi *et al* 1996, Bruchfeld *et al* 2002). The prevalence of HIV in TB patients observed in this study is higher than 57.1% reported previously in the same area (Range *et al* 2007); this could be explained by the fact that this was a tertiary hospital based study.

 Majority of HIV patients in our study were in WHO stage 3 and 4, this could be contributed by poor health seeking behavior in developing countries. As reported previously patients with smear positive tuberculosis had higher median CD4+ count than HIV patients with smear negative tuberculosis (Sameer *et al* 2011, Rawat *et al* 2008, Mbwana *et al* 2011). HIV infected smear positive patient tend to secrete significant fewer organisms per ml than HIV negative patient (Long *et al* 1991). Our study has confirmed that smear negativity increases as immunosuppression increases (Sameer et al 2011, Shea *et al* 2009).

Various risk factors have been assessed in relation to tuberculosis in present study. Patient`s risk factors associated with increased risk of tuberculosis includes chronic cough, wasting, advanced age, HIV status, Diabetes Mellitus, Malnutrition etc (Lewis *et al* 2003, David et al 2004]. In the present study as in others studies (Bruchfeld *et al* 2003, Mtei *et al* 2005) factors found to predict tuberculosis on univariate logistic regression analysis were age above 35 years, cough more than 2 weeks, night sweats, severe wasting, present of pleural effusion, positive HIV status and anemia. Independent risk factors found to predict tuberculosis on multivariate logistic regression analysis were cardinal symptoms of tuberculosis (chronic cough, night sweating and wasting); the risk of tuberculosis in patients with these three symptoms was more than 10 times compared to patient without these symptoms. Other factors found to predict tuberculosis on multivariate analysis were positive HIV status, presence of pleural effusion and age above 35 years. Clinicians should know these factors so that they can have high index of suspicion of tuberculosis diagnosis in patients presenting with these factors. In present study HIV has been a statistically significant predict extra-pulmonary tuberculosis than it does for pulmonary tuberculosis (RRR 14 vs. 4.2). Previous studies have reported this; extra-pulmonary disease is more common in HIV infected patients (Harries *et al* 1998).

The case fatality rate observed was 28.4%, this seems to be higher than previous reported in Tanzania (Range *et al* 2007, Matei *et al* 2005, van den Broek et al 1998); this could be explained by the fact that majority of our patients with tuberculosis were HIV infected and WHO stage 3 and 4 with the evidence of severe immunosuppression based on CD4+ (Kiertiburanakul *et al* 2012).

In conclusion; sputum smear is still important diagnostic tool among HIV patients with CD4 count more than 111cells/µl; other techniques like routine culture, GeneXpert are urgently needed in our setting so that TB control can be assured and sustained. Strategies such as creating public awareness and the involvement of the private health sector, traditional practitioners and religious institutions in HIV and TB control should be emphasized in order to improve health seeking behavior among HIV patients in developing countries.

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