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Risk factors for mortality among tuberculosis patients on treatment at Bugando Medical Centre in north-western Tanzania: a retrospective cross-sectional study

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Abstract

Background: Tuberculosis (TB) is still an important cause of morbidity and mortality worldwide. Though it can effectively be treated, still a significant proportion of patients die on the course of their treatment. The objective of this study was to determine the outcome and risk factors of mortality among patients diagnosed with TB in a tertiary hospital in north-western Tanzania.

Methods: A retrospective cross sectional study was done among all patients diagnosed with TB between January and December 2015 at Bugando Medical Centre. Information of demographic characteristics, smear positivity, haemoglobin concentration, HIV status, CD4 counts for HIV positive patients and treatment outcomes were collected and analysed. TB treatment outcomes as dead or alive were calculated and logistic regression was done to determine the factors associated with increased risk of death of patients on anti-TB treatment.

Results: In total 701 patients were diagnosed with TB during the study period. Of these, 361 (51.5%) were males with a median age of 38 (IQR 27- 47) and 421 (60.06%) were younger than 40 years. Majority of the participants 409 (58.35%) had smear positive pulmonary tuberculosis and about half of patients (51.07%) tested positive for HIV. Of the enrolled patients 610 (87.02%) were alive at the end of TB treatment while 91 (12.98%) died in the course of treatment. The odds of deaths of patients on anti-TB treatment were strongly associated with male sex, HIV co infection and severe anaemia.

Conclusion: The proportion of patients who die from TB treatment at BMC is high, with an increased risk of death among HIV co-infected, older than 40 years and severely anaemic patients. Improvement of strategies for early diagnosis and prompt treatment of TB patients will potentially improve treatment outcome.

Keywords: Tuberculosis, treatment, mortality, old age, anaemia, Tanzania

Introduction

Tuberculosis (TB) is one of the oldest infectious diseases caused by an airoborne bacterium, *Mycobacterium tuberculosis* with the lungs being the commonest site of infection (Smith 2003; Sakamoto, 2012). About one third of the worlds' population is estimated to be infected with *M. tuberculosis* whereas about 33% develop active TB (Lonnroth & Raviglione, 2008), making a global prevalence of active TB of more than 13 million people with African region bearing more than 70% of the global burden (WHO, 2015). Patients infected with TB frequently present with cough with sputum smear being the most common mode of diagnosis (Sia & Wieland, 2011; Seni *et al.*, 2012). Smear positive patients are the most infectious ones capable of infecting up to 15 people a year (Sepkowitz, 1996).

Early diagnosis and treatment of smear positive patients is a corner stone for TB control. But even with the availability of potent anti-tuberculous agents, TB still remains as a leading cause of high morbidity and mortality after HIV/AIDS (WHO, 2013). In 2012 about 8.6 million people were newly diagnosed to have TB and 1.3 million died of the disease (WHO 2013), while the 2015 WHO report indicate that 9.6 million people were newly diagnosed with TB globally with mortality of 1.5

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million people (WHO, 2015). Of a note here is that though this increment of TB cases could be because of improved diagnostic abilities but then this means also that more TB cases still remain undiagnosed in the community. The undiagnosed cases in this view are important that they are potential foci of ongoing new transmission and are likely to be diagnosed late at which point they are likely to have poor outcome on their treatment.

The mortality rate due to TB varies widely across the globe with some regions reporting higher rates (Kantipong *et al.*, 2012; WHO, 2015). At Bugando Medical Centre in north-western Tanzania, TB has been reported previously as a cause of morbidity in more than 30% of the admissions among febrile patients (Meremo *et al*., 2012). Several factors have been studied previously and reported to be associated with increased likelihood of early TB mortality together with Late diagnosis of TB due to poor health seeking behaviour (Storla *et al*., 2008; Virenfeldt *et al.*, 2014), advanced age (Amnuaiphon *et al*., 2009; Horne *et al.*, 2010), HIV co infection (Vijay *et al*., 2011) and several co morbidities including severe anaemia, liver failure and diabetes mellitus (Alavi-Naini *et al.*, 2013). In Tanzania, the information regarding the magnitude and risk factors of this problem is still inadequate. This study was therefore carried out to determine the outcome and risk factors of mortality among patients diagnosed with TB in a tertiary hospital in north-western Tanzania.

Materials and methods

Study design and population

This was a retrospective cross-sectional study, involving all patients diagnosed with pulmonary TB and put on standard anti tuberculous treatment Bugando Medical Centre (BMC) between January and December 2015. BMC is a tertiary and teaching hospital in Mwanza, north-western Tanzania. It has a catchment population of more than 16 million people from 8 regions of Tanzania, namely Mara, Mwanza, Geita, Shinyanga, Simiyu, Tabora, Katavi and Kigoma. It has a bed capacity of about 1000, running both in-patient and out-patient services. Patients diagnosed to have TB either in the inpatient or outpatient department are all registered with the TB clinic for treatment and follow up. About 600-1000 patients are diagnosed with TB every year.

The diagnosis of TB is made according to Tanzanian TB diagnosis algorithm (MoHSW, 2006). All TB suspects undergo sputum examination and on diagnosis HIV testing and counselling is additionally offered and patients get initiated on Anti-TB. Patients who as well test positive for HIV get linked to HIV care and treatment services for treatment and follow up. This study included all patients diagnosed to have TB and started on a 6-month course of anti-tuberculosis treatment at BMC between January 2015 and December 2015.

Sample size, sampling procedure and data collection

A minimum sample size of 553 was estimated from Leslie Kish formula for cross sectional studies assuming 10% mortality will occur in TB patients in the course of their treatment (Walpola *et al*., 2003; Lin *et al*., 2014). All patients diagnosed with TB during the study period whose data were available in the TB record were included in the study. A TB registry was used to identify patients diagnosed with TB. The patients' identifiers were then used to trace the files at Medical Records Department and at HIV Care and treatment Centre (CTC). The information extracted included age, sex, occupation, past history of TB treatment, smoking, HIV status, outcome of patients on treatment (either dead or alive) and TB treatment duration before death.

Data analysis

The data were cleaned and entered using Epi info software and analysis was done using STATA 12. All continuous variables were summarized as medians with interquartile range while categorical data were recorded as proportions with percentages. In this study any death occurring during TB treatment was regarded as TB related death as defined by WHO (WHO 2010). The proportion of TB

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patients who died was calculated and the Odds ratios of different factors with 95% confidence interval were determined using logistic regression model to find out the degree of association between different potential risk factors and the outcome of interest.

Ethical clearance

The permission to conduct this study and publish the findings was obtained from Bugando Medical Centre/Catholic University of Health and Allied Sciences research and ethical committee. Patients' identifiers like names and file number were not included in the analysis of this study to further maintain confidentiality.

Results

Baseline characteristics of study participants

A total of 701 patients were diagnosed to have TB between January and December 2015. Most of the patients 361 (51.5%) were males with a median age of 38 (IQR 27-47) years. About 60% (n= 421) were younger than 40 years. The majority of the study participants 409 (58.35%) had smear positive pulmonary tuberculosis and most patients 358 (51.07%) tested positive for HIV. The HIV positive participants had a median CD4 count of 315 [IQR 223-459] cells/µl and 66 (18.4%) of them had baseline CD4 counts <200 cells/µl. (Table 1).

Table 1: The basic demographic, clinical and laboratory characteristics of study participants

Factor/variable	Response	Frequency	Percent or Median (IQR)
Sex	Male	361	51.50
	Female	340	48.50
Age (years)	All	701	37.5 [27-47]
	≥40	280	39.94
	<40	421	60.06
Smoking	Yes	32	4.56
	No	669	95.44
TB recurrence	Yes	12	1.71
	No	689	98.29
Smear results	Positive	409	58.35
	Negative	292	41.65
HIV testing	Positive	358	51.07
	Negative	343	48.93
CD4 counts	All		315 [223-459]
	<200 Cells/µl	66	18.4
	>200 Cells/µl	292	81.6
WBC (*10^3/µl)	All	701	4.7 [3.7-5.4]
	<3.5	123	17.55
	>3.5	578	82.45
HB (g/dl)	All	701	11.7[10.2-13.4]
	Normal HB (>12/13)	343	48.93
	Mild anaemia(10-12/13)	202	28.82
	Moderate anaemia(8-10)	98	13.98
	Severe anaemia(<8)	58	08.27
Platelet (*10^3/µl)	<150	44	6.28
	>150	657	93.72
TB outcome on treatment	Died on TB treatment	91	12.98
	HIV positive	61	71.43
	HIV negative	30	28.57
	Alive	610	87.02
	Months on anti-TB	701	2 [1-3]

Key: HB: Haemoglobin; HIV: Human immunodeficiency virus; IQR: Interquartile range; TB: Tuberculosis WBC: White blood cell

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The majority (87.02%; n= 610) of the study participants were alive at the end of their TB treatment while 91(12.98%) of them died during the course of their anti-TB treatment; 61(71.43%) of these being HIV co infected patients. Three quarters (75%) of all TB deaths occurred within the first three months of anti-TB treatment with a median time of 2 months on anti-TB drugs before deaths (Figure 1).

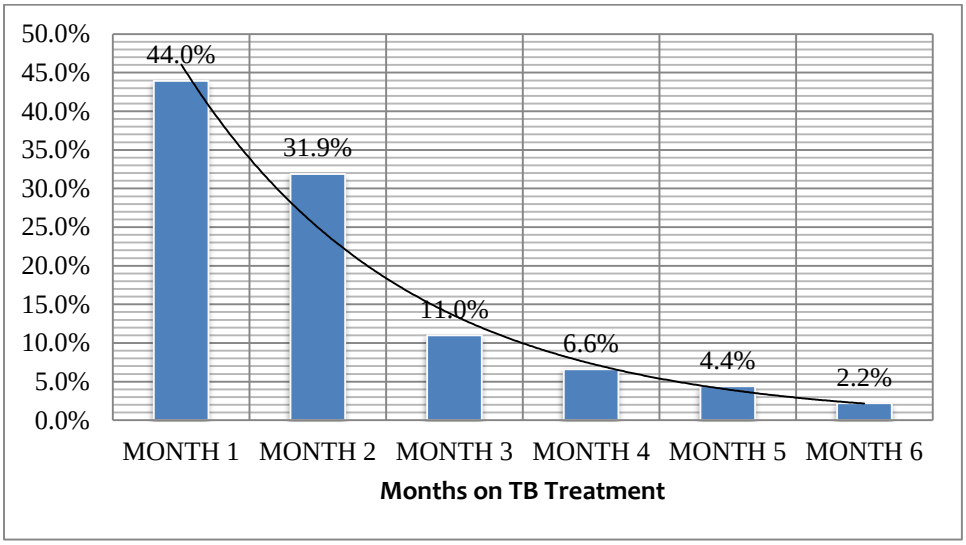

Figure 1: Distribution of death by month on treatment

Factors associated with mortality

The odds of TB related deaths on univariate analysis were strongly correlated to a male sex (OR=2.1, p=0.002), age older than 40 years (OR=1.6, p=0.048), Smear positive TB (OR=3.6, p<0.001), HIV co infection (OR=2.7, p<0.001), and severe anaemia (OR=3.2, p<0.001). However, on a multivariate analysis only male sex (OR=2.2, p=0.001), HIV co infection (OR=2.6, p<0.001) and severe anaemia (OR=2.9, p=0.001) remained independently associated with deaths from TB treatment (Table 2). The difference in the distribution of other factors was not statistically significant.

Table 2: Univariate and multivariate analysis for factors related to mortality among TB patients

Factor	Response/ Results	Outcome of TB on treatment		Unadjusted		Adjusted	
		Alive	Dead	OR(95%CI)	P- value	OR(95%CI)	P-Value
Sex	Male	300 (49.18)	61 (67.03)				
	Female	310 (50.82	30 (32.97)	2.1 (1.3-3.3)	0.002	2.2 (1.4-3.4)	0.001
Age (years)	≥40	235 (38.52)	45 (49.45)				
	<40	375 (61.48)	46 (50.55)	1.6 (1-2.4)	0.048	1.3 (0.8-2.1)	0.222
Smoking	Yes	088 (96.70)	03 (03.30)				
	No	581 (95.25)	29 (04.75)	0.7 (0.2-2.2)	0.537		
TB recurrence	Yes	089 (97.80)	02 (02.20)				
	No	600 (98.36)	10 (01.64)	1.3 (0.3-6.2)	0.703		
Smear results	AFB +ve	355 (58.20)	54 (59.34)				
	AFB -ve	255 (41.80)	37 (40.66)	3.6 (2-6.2)	0.000	1.0 (0.6-1.6)	0.973
HIV status	Positive	293 (48.03	61 (71.43)				
	Negative	317 (51.97	26 (28.57)	2.7 (1.8-4.4)	0.000	2.6 (1.6-4.3)	0.000
Leukopenia	Yes	080 (87.91)	011 (12.09)				
	No	498 (81.64)	112 (18.36)	0.6 (0.3-1.2)	0.146		
Anaemia	Severe	041 (6.72)	17 (18.68)	3.2 (1.7-5.9)	0.000	2.9 (1.5-5.6)	0.001
	Moderate	088 (14.4)	10 (10.99)	0.7 (0.4-1.5)	0.379		
	Mild	186 (30.49	16 (17.58)	0.5 (0.3-0.9)	0.013		
Thrombopenia	Yes	086 (94.51)	05 (05.49)				
	No	571 (93.61)	39 (39.00)	0.9 (0.3-2.2)	0.742		

Key: AFB: Acid fast bacilli; CI: Confidence interval; HIV: Human immunodeficiency virus; OR: Odds ratio; TB: Tuberculosis

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Discussion

Of the TB patients diagnosed during the study period, about 13% died in the course of their TB treatment. The risk factors associated with their deaths were male sex, HIV co infection and severe anaemia. The TB related deaths in our current study are similar to findings of a study in South Africa (Mabunda *et al.*, 2014). However, this rate is higher than that reported previously in a study in Australia (Walpola *et al*., 2003). This low death rate in Australia is probably attributed to overall low prevalence of TB and HIV. In Australia the national annual TB notification rate is at 4.6 cases per 100,000 population (Lumb *et al.*, 2014). This lower burden of TB infection could as well be accompanied by lower mortality rate from the disease. On the other hand, the rate reported in the index study is much lower than the rates reported from several other studies Taiwan(Lo *et al*., 2015) and China (Lin *et al*., 2014).

In Tanzania, a TB related mortality rate of 26.9% was previously reported among HIV/TB co-infected patients admitted to Muhimbili National Hospital in Dar es Salaam (Kamenju & Aboud 2011). This higher rate could be due to the reason that this study involved only those TB patients who were admitted to the hospital which represents a sub-group of seriously ill patients. In a recent systematic review determining the cause of death among HIV patients, TB was responsible for more than one-third of all deaths among adult patients (Gupta *et al*., 2015), where the death rates varied regionally with the highest rate of 63.2% reported in Asia and the lowest rate of 27.1% in America while in sub Saharan Africa the death rate was 43.2%. Additionally, in this study it was found that TB was diagnosed at autopsy in one-third to over half of the patients. This suggests that the lower rates in other reports could partly be due to some percentages of un-diagnosed TB especially in resource limited settings.

Even with these differences one other crucial finding is the similarity in the timing of these deaths. The first two months of anti-TB treatment match with the maximum rate of deaths. More than three-quarters of the deaths occurred within this period in the current study. Similarly, in between 41% and 46% of death among TB patients occurred within the first month of treatment in Thailand and Malawi (Harries *et al.*, 2001; Moolphate *et al*., 2011). On clinical grounds these findings are important that to reduce the rate of mortality among TB patients on treatment probable intervention strategies could be planed around this point of highest rate of mortality. While these high rates of deaths during the first phase of TB treatment could partly be related to advanced stage of TB on diagnosis and a poor tolerance to TB drugs, a number of factors comparable to our findings have been found to increase the risk of deaths including a male sex (Amnuaiphon *et al.* 2009; Low *et al*., 2009; Horne *et al*., 2010; Djouma *et al.*, 2015), older age than 40 years (Amnuaiphon *et al*., 2009; Low *et al*., 2009; Horne *et al*., 2010; Pepper *et al*., 2015), smear positive PTB (Waitt & Squire, 2011; Alavi-Naini *et al*., 2013), HIV co-infection (Horne *et al.*, 2010; Waitt & Squire, 2011; Djouma *et al.*, 2015; Pepper *et al*., 2015) and severe anaemia (Alavi-Naini *et al*., 2013). A female sex (Pepper *et al*., 2015), smear negative TB and extra pulmonary TB (Djouma *et al*., 2015), history of smoking, drug hepatitis, diabetes mellitus and history of previous TB (Alavi-Naini *et al.*, 2013) are additional risk factors reported in other studies. The presence of any of these factors could be useful in identifying the at risk patients and plan them on a potential intervention to improve their outcome on treatment.

At older age than 40 years, vulnerability to TB and death is increased. This age group is known to have a disrupted immunity due to ageing process on top of co-morbidities like chronic obstructive pulmonary diseases (Negin *et al*., 2015). Based on this the TB presentation is often atypical (Dahmash *et al.*, 1995) usually confused with age related illnesses (Tan *et al*., 1991; Yoshikawa, 1992) and difficult to diagnose by conventional methods. The diagnosis is then most of the time delayed at stages that are more advanced with fatal outcome (Yoshikawa, 1992; Cantalice Finlo *et al*., 2007; Negin *et al*., 2015) and most elderly patients may therefore die undiagnosed (Yoshikawa, 1992). Use of constitutional symptoms like wasting and drenching nights (Cantalice

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Finlo *et al*., 2007) may be helpful in supporting early identification and prompt treatment of these potential elderly with TB to improve their outcome around these possible diagnostic challenges.

The anaemia in TB patient is often of low mean corpuscular volume (MCV)<80fl which is either iron deficiency or from a chronic inflammatory process (Isanaka *et al*., 2012; Oliveira *et al*., 2014). Both of these situations make iron un-available for most biological functions including its role in cell mediated immunity. Iron deficiency may decrease T-cell numbers by reducing the proliferative response and potentially dropping the macrophage activity (Dallman 1987; Oppenheimer, 2001) increasing morbidity and mortality from most infections. A previous study in Tanzania had indicated that iron deficiency anaemia was associated with 2-3 fold risk of death among TB patients (Isanaka *et al*., 2012), and a study from Korea had shown that up to one-third had anaemia on diagnosis (Lee *et al.*, 2006), which significantly improved with TB treatment. Some studies have indicated a haematological improvement with smear conversion (Morris *et al*., 1989; Das *et al*., 2003) suggesting that early diagnosis and prompt treatment of TB could potentially reduce the morbidity and mortality from anaemia.

TB+HIV co infection being the commonest co infections carry an increasingly high mortality (Akksilp *et al*., 2007; Vijay *et al*., 2011). On TB treatment the mortality is especially high among patients who are not on ART (Akksilp *et al*., 2007; Sileshi *et al*., 2013), those with low CD4 counts (Bhowmik *et al*., 2012; Sileshi *et al*., 2013) and not being on cotrimoxazole prophylaxis (Sileshi *et al*., 2013). This information supports a routine screening of HIV among all TB infected patients and early initiation of ART and cotrimoxazole prophylaxis could potentially reduce the mortality of TB patients on treatment.

This study had a number of limitations. The study was a single centre study; the results from this study may not necessarily be generalizable. The cause of death among this sub group of patients could not be established because autopsy was not done. Being a retrospective study, missing data for some patients was also a limitation. All in all, the findings of this study will add some knowledge on the magnitude of mortality and the factors associated with mortality due to TB. In conclusion, the proportion of patients who die at the early stage of TB treatment is still high in Tanzania with an increased risk of death among HIV co-infected, males and severely anaemic patients. Improvement of strategies for early diagnosis and prompt treatment of TB patients will potentially improve treatment outcome of TB patients.

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Authors' contribution

DWG SMB SBK designed the study and prepared the study protocol; SMB DWG collected the data; DWG SBK BCP analyzed and interpreted the data, DWG SMB did literature search and drafted the manuscript; SBK MCP ERS critically reviewed the manuscript for its intellectual content. All authors approved the last version before submission.

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Conflict of interest

The authors have no conflict of interest to declare.

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