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Death after cure: Mortality among pulmonary tuberculosis survivors in rural Uganda

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Authors' contribution

JBB – Conceptualization, methodology, data accrual, formal analysis, interpretation of results, drafting manuscript, review and editing manuscript, and final approval.

BN, SN, DKR, GM, CN, BT, IN – methodology, data accrual, interpretation of results, drafting manuscript, review and editing manuscript, and final approval.

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JS – Methodology, formal analysis, drafting manuscript, review and editing of manuscript, and final approval.

SK – Methodology, funding acquisition, interpretation of results, review and editing of manuscript, and final approval.

Use of generative AI

During the preparation of this work the authors used *Google Bard AI* in order to improve the grammar and sentence construction. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare no conflict of interests.

Ethical approval

The study was approved by the Mildmay Uganda Research Ethics Committee (Protocol number MUREC-2023-187) and the Uganda National Council of Science and Technology (HS2947ES). TB survivors or their next of kin provided verbal consent for using their retrospective data. Waiver of written consent for adults and assent for minors was provided by the Mildmay Uganda Research Ethics Committee.

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Abstract

Objectives: To determine the incidence of mortality and its predictors among pulmonary tuberculosis (PTB) survivors treated at a rural Ugandan tertiary hospital.

Methods: We conducted a retrospective chart review of data between 2013 and 2023. We included all people that met the World Health Organisation's definition of tuberculosis cure and traced them or their next of kin to determine vital status (alive/deceased). We estimated the cumulative incidence of mortality per 1000 population, crude all-cause mortality rate per 1000 person-years, and median years of potential life lost for deceased individuals. Using Cox proportional hazard models, we investigated predictors of mortality.

Results: Of 334 PTB survivors enrolled, 38 (11.4%) had died. The cumulative incidence of all-cause mortality was 113.7 per 1000 population, and the crude all-cause mortality rate was 28.5 per 1000 person-years. The median years of potential life lost for deceased individuals was 23.8 years (IQR: 9.6-32.8). Hospitalization (adjusted hazard ratio (aHR): 4.3, 95% CI: 1.1-16.6) and unemployment (aHR: 7.04, 95% CI: 1.5-31.6) at TB treatment initiation predicted mortality.

Conclusion: PTB survivors experience post high mortality rates after TB cure. Survivors who were hospitalized and unemployed at treatment initiation were more likely to die after cure. Social protection measures and long-term follow-up of previously hospitalized patients could improve the long-term survival of TB survivors.

Keywords

TB; Cure; Treatment completion; Survivors; Unemployment; Hospitalization; Years of potential life lost

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There were an estimated 155 million tuberculosis (TB) survivors globally as of 2020 [1]. However, the risk of mortality among TB survivors is thrice that of people who have never suffered TB [2]. Early identification of risk factors for long-term mortality in people with TB, especially in rural areas where studies have found a four-fold increase in mortality, could significantly improve their long-term survival [3]. This study aimed to determine the incidence and predictors of mortality among TB survivors at a rural tertiary hospital in Uganda. The absence of a long-term follow-up policy for drug-susceptible TB survivors in Uganda leaves a critical knowledge gap regarding rural TB survivor outcomes. This study highlights the need to address this gap.

We conducted a cross-sectional study that used retrospective data from TB survivors at Masaka Regional Referral Hospital (MRRH) in Southern Uganda. First, we reviewed data for a retrospective cohort of TB survivors who were cured of TB at MRRH from 2013 to 2023. These individuals (or their next of kin) were contacted by telephone or physically traced by the district TB and Leprosy supervisors and village health team members to establish their vital status (alive or dead). The study population was all people cured of bacteriologically confirmed pulmonary TB from 2013 to 2023 at MRRH [4]. Participants were excluded if they were missing telephone contacts and could not be physically traced. Data were abstracted from the unit TB registers and treatment files. The data extracted pertained to the characteristics of survivors at the time of TB treatment initiation. Data were

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analyzed in SPSS (version 29.0.1). The cumulative incidence was estimated as a proportion of TB survivors who were dead to the total eligible survivors per 1000 population. The crude mortality rate was the proportion of those who died to the total person-years. For an individual TB survivor who died, the years of potential life lost (YPLL) were calculated by subtracting the age at death from 63.3 years (the life expectancy of Ugandans) [5]. This was limited to the 32 individuals who died before the life expectancy age. We performed survival analysis using Cox proportional hazard models to determine predictors of mortality. In constructing a multivariable Cox proportional hazards model, we included all factors that had $P < .1$ at bivariate analysis in addition to other known predictors of mortality among TB survivors (sex, time from TB diagnosis to treatment initiation, and residence type [rural vs urban]). Statistical significance has been set at $P < .05$.

Of 469 pulmonary TB survivors who met the World Health Organisation (WHO) definition of cure, 334 (71.2%) were included in the study. Of these, 317 (94.9%) were contacted by telephone. Among the 135 excluded survivors, 62 (45.9%) had no contact details (both telephone number and residence details), while 73 (54.1%) had invalid telephone numbers and could not be traced by the study team.

Of 334 TB survivors, the median age was 32.0 (IQR: 25.0-47.0) years, 209 (62.6%) were male, 98 (29.3%) were coinfected with Human Immunodeficiency Virus (HIV), and 77 (28.4%) were unemployed at the time of TB treatment initiation. Further, 108 (34.1%) were hospitalized at the time of TB treatment initiation. Demographic and clinical characteristics of TB survivors at the time of TB treatment initiation are shown in Table 1.

The total observation time was 1333.8 person-years, and the duration from cure to the study follow-up was a median of 46.7 (interquartile range (IQR): 27.2-63.7) months. Of 334 TB survivors enrolled, 38 (11.4%) had died. The median survival from TB cure to death was 8.8 (IQR: 1.1-34.5) months. The cumulative incidence of mortality was 113.7 (95% confidence interval (CI): 81.4-147.3) per 1000 population, and the crude all-cause mortality rate was 28.5 per 1000 person-years. The total YPLL were 708 years. The median YPLL for deceased individuals was 23.8 (IQR: 9.6-32.8) years. Hospitalization (adjusted hazard ratio (aHR): 4.3, 95% CI: 1.1-16.6, $P = .034$) and unemployment (aHR: 7.04, 95% CI: 1.5-31.6, $P = .012$) at TB treatment initiation were significantly associated with increased mortality risk at multivariable analysis (Table 2).

The mortality rate in our study (25 per 1000 person-years) is comparable to that reported in rural Ethiopia among TB survivors [3]. This rate is 5-9.5 times higher than the mortality rate reported in the general rural population in Uganda [6,7]. The high incidence of mortality is of concern since the majority of those who died were in their productive years (20-60 years of age). This translates to significant losses to families and the national economy, suggesting current TB mortality estimates likely underestimate overall TB-related mortality [8]. The findings advocate for long-term follow-up of previously hospitalized patients to address lingering health issues and potential complications. Additionally, the median survival of deceased individuals suggests a follow-up period of at least 1 year might be necessary. Unemployment's association with mortality aligns with observations in India and underscores the detrimental role of socio-economic factors [9]. Social protection

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measures like cash transfers, education, and unemployment insurance could improve TB survivors' prospects [10]. In our study setting, we have previously demonstrated that a 1-dollar incentive improved TB treatment success and reduced rates of lost-to-follow-up [11]. Unfortunately, participation in existing social protection programs is low in Uganda, necessitating the design of specific and accessible programs tailored to TB survivors [12].

Study limitations include missing data on known mortality predictors like alcohol use, smoking, and nutrition, highlighting the need for improved data collection in TB registers. Additionally, almost 29% of potential participants were excluded because they had no contacts and could not be traced physically. This implies that we might have underestimated the mortality rate among TB survivors in this setting. While the individuals we failed to trace could have been matched to mortality registries, such registries are not readily available in Uganda. Addressing these challenges through robust registries, long-term studies, and support groups for TB survivors is crucial to gain a deeper understanding of their experiences and improve their outcomes. These also would be important in surveilling for TB reinfection and relapse rates, which were data points missed in our study.

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Availability of data

Datasets used in this analysis are available from the corresponding author upon reasonable request.

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Table 1

Characteristics of TB survivors compared by crude mortality rates.

		Alive		Deceased		*P*-value[a]
Characteristic	**Total 334**	***N* 296**	**% 88.6**	***N* 38**	**% 11.4**	
Age group (*n* = 333)						.006
<20 years	32	30	10.2	2	5.3	
20-60 years	277	249	84.4	28	73.7	
60+ years	24	16	5.4	8	21.1	
Sex						.056
Male	209	180	60.8	29	76.3	
Female	125	116	39.2	9	23.7	
Residence (*n* = 331)						.806
Rural	186	165	56.1	21	56.8	
Urban	145	129	43.9	16	43.2	
Education level (*n* = 215)						.045
Educated	200	190	92.7	10	100.0	
Not educated	15	15	7.3	0	0.0	
Employment status (*n* = 271)						.076
Employed	194	184	72.7	10	55.6	
Unemployed	77	69	27.3	8	44.4	
TB Resistance type						.954
Drug susceptible TB	268	237	88.4	31	11.6	
Drug resistance TB	66	59	89.4	7	10.6	
Hospitalization status (*n* = 317)						.072
Inpatient	125	108	37.8	17	54.8	
Outpatient	192	178	62.2	14	45.2	
TB symptoms (*n* = 267)						.016
Yes	208	81.4	16	51.6		
No	59	18.6	15	48.4		
Cough (*n* = 210)						.857
Yes	199	94.8	15	93.8		

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Characteristic	Total 334	Alive *N* 296	% 88.6	Deceased *N* 38	% 11.4	*P*-value[a]
No	11	5.2	1	6.3		
Dyspnoea (*n* = 208)						.915
Yes	69	33.3	5	31.3		
No	139	66.7	11	68.8		
Chest pain (*n* = 208)						.669
Yes	104	51.0	6	37.5		
No	104	49.0	10	62.5		
Haemoptysis (*n* = 206)						.241
Yes	32	16.3	1	6.3		
No	174	83.7	15	93.8		
Night sweats (*n* =207)						.088
Yes	122	61.3	5	31.3		
No	85	38.7	11	68.8		
Bacillary load (*n* = 122)						.980
Low or 1 +	31	25.7	3	23.1		
Medium or 2+	43	34.9	5	38.5		
High or 3+	48	39.4	5	38.5		
HIV status						.333
Negative	236	71.3	25	65.8		
Positive	98	28.7	13	34.2		
Cotrimoxazole prophylaxis (*n* = 93)[c]						.461
Yes	89	96.3	11	91.7		
No	4	3.7	1	8.3		
ART (*n* = 95)[c]						.010
Yes	86	92.7	10	76.9		
No	9	7.3	3	23.1		
History of ART default (*n* = 60)						.626
Yes	4	5.4	1	25.0		
No	56	94.6	3	75.0		
Comorbidities						.013

Characteristic	Total 334	Alive *N* 296	Alive % 88.6	Deceased *N* 38	Deceased % 11.4	*P*-value[a]
Yes	47	12.2	11	28.9		
No	287	87.8	27	71.1		
Cardiometabolic disease[b]						.008
Yes	30	7.8	7	18.4		
No	304	92.2	31	81.6		
Diabetes (*n* = 64)						.393
Yes	13	19.6	2	25.0		
No	51	80.4	6	75.0		
Hypertension (*n* = 79)						.003
Yes	11	10.0	4	44.4		
No	68	90.0	5	55.6		
Renal disease (*n* = 73)						.007
Yes	11	10.9	4	44.4		
No	62	89.1	5	55.6		
Allergies (*n* = 18)						.383
Yes	6	40.0	0	0.0		
No	12	60.0	3	100.0		
Other comorbidities (*n* = 25)						.226
No	11	55.6	1	14.3		
Yes	14	44.4	6	85.7		

[a] Indicated *P*-values generated from cox regression bivariate analysis.

[b] Cardiometabolic disease constituted clients who had a diagnosis of either Diabetes, Hypertension, or Renal Disease.

[c] A subset of people with HIV.

TB: tuberculosis, ART: Antiretroviral therapy.

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Table 2:

Predictors of mortality among TB survivors ($N = 196$).

Characteristic	cHR	95% CI	*P*-value	aHR	95% CI	*P*-value
Age (every additional year)	1.038	(1.018, 1.059)	<.001	1.029	(0.989, 1.07)	.158
Sex						
Female	Ref			Ref		
Male	2.083	(0.918, 4.424)	.056	3.512	(0.715, 17.249)	.122
Residence						
Urban	Ref			Ref		
Rural	1.085	(0.565, 2.085)	.806	0.419	(0.111, 1.583)	.199
Employment status						
Employed	Ref			Ref		
Unemployed	2.347	(0.916, 6.018)	.076	6.957	(1.531, 31.612)	.012
Hospitalization status						
Outpatient	Ref			Ref		
Inpatient	1.944	(0.942, 4.014)	.072	4.314	(1.118, 16.638)	.034
Night sweats						
No	Ref			Ref		
Yes	0.396	(0.137, 1.147)	.088	0.433	(0.124, 1.511)	.189
HIV status						
Negative	Ref			Ref		
Positive	0.716	(0.365, 1.407)	.333	2.985	(0.713, 12.493)	.134
Cardiometabolic disease						
No	Ref			Ref		
Yes	3.110	(1.347, 7.181)	.008	4.956	(0.467, 52.588)	.184
Time from diagnosis to treatment (every additional day)	0.999	(0.992, 1.007)	.867	1.02	(0.852, 1.222)	.83

aHR: Adjusted Hazard ratio; cHR: Crude Hazard ratio; CI: confidence interval.

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