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MAJOR ARTICLE

Hyperglycemia and Risk of All-cause Mortality Among People Living With HIV With and Without Tuberculosis Disease in Myanmar (2011–2017)

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Background. There is limited empirical evidence on the relationship between hyperglycemia, tuberculosis (TB) comorbidity, and mortality in the context of HIV. We assessed whether hyperglycemia at enrollment in HIV care was associated with increased risk of all-cause mortality and whether this relationship was different among patients with and without TB disease.

Methods. We conducted a retrospective analysis of adult (≥15 years) HIV-positive patients enrolled into HIV care between 2011 and 2016 who had random blood glucose (RBG) measurements at enrollment. We used hazards regression to estimate associations between RBG and rate of all-cause mortality.

Results. Of 25 851 patients, 43% were female, and the median age was 36 years. At registration, the median CD4 count (interquartile range [IQR]) was 162 (68–310) cell/mm^3, the median RBG level (IQR) was 88 (75–106) mg/dL, and 6.2% (95% confidence interval [CI], 6.0%–6.5%) had hyperglycemia (RBG ≥140 mg/dL). Overall 29% of patients had TB disease, and 15% died during the study period. The adjusted hazard of death among patients with hyperglycemia was significantly higher (adjusted hazard ratio [aHR], 1.2; 95% CI, 1.1–1.4) than among those with normoglycemia without TB disease, but not among patients with TB disease (aHR, 1.0; 95% CI, 0.8–1.2). Using 4 categories of RBG and restricted cubic spline regression, aHRs for death were significantly increased in patients with RBG of 110–140 mg/dL (categorical model: aHR, 1.3; 95% CI, 1.2–1.4; restricted spline: aHR, 1.1; 95% CI, 1.0–1.1) compared with those with RBG <110 mg/dL.

Conclusions. Our findings highlight an urgent need to evaluate hyperglycemia screening and diagnostic algorithms and to ultimately establish glycemic targets for PLHIV with and without TB disease.

Keywords. diabetes mellitus; loss to follow-up; noncommunicable disease; restricted cubic spline; sensitivity analysis.

Hyperglycemia during infectious disease is a predictor of increased morbidity and mortality. Previous studies have reported that hyperglycemia with or without diabetes mellitus (DM) is associated with poor outcomes in sepsis, dengue, pneumonia, and tuberculosis (TB) [1–4]. However, whether hyperglycemia in people living with HIV infection (PLHIV) is associated with higher mortality or morbidity is not clear.

There are biological mechanisms by which hyperglycemia likely increases the risk of mortality in hospitalized critical care patients [1, 5]. However, in patients with HIV/TB, the extent to which hyperglycemia impacts mortality risk is poorly understood. Both type 1 and 2 DM immunopathy increase the risk of TB [6–9], and hyperglycemia or poor glycemic control is associated with adverse TB treatment outcomes [10–12]. In addition, TB enhances HIV disease progression via the inflammatory response to TB disease, and globally TB remains one of the most important causes of mortality among PLHIV [13–15]. Concomitantly, HIV may increase the risk of DM due to chronic inflammation, adverse effects of antiretroviral therapy, and accelerated epigenetic aging among PLHIV [16–20]. Early evidence indicates that DM is also associated with an increased risk of mortality in PLHIV [21], but whether hyperglycemia increases the risk of mortality in PLHIV due to its effect on TB or whether there is a direct association is unknown.

There is a lack of empirical evidence regarding the relationship between hyperglycemia, TB comorbidity, and all-cause mortality in the context of HIV to guide the clinical management of dysglycemia and TB in PLHIV [22]. Therefore, in this

Received 5 October 2018; editorial decision 18 December 2018; accepted 26 December 2018; published online December 28, 2018

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Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofy355

observational study, we assessed whether hyperglycemia at the time of enrollment to HIV care was associated with increased risk of all-cause mortality in PLHIV during 5 years of follow-up. We also examined whether the hyperglycemia and mortality relationship was different among patients with and without TB disease.

METHODS

Design and Setting

We conducted a retrospective cohort study using routinely collected data from PLHIV registered in the Integrated HIV Care Program in Myanmar between January 2011 and December 2016 among those who had random blood glucose (RBG) measured at enrollment to HIV care.

Standard of care at 33 HIV clinics throughout Myanmar included clinical and laboratory evaluation, including blood glucose measurement and TB disease screening at enrollment, TB disease screening during quarterly follow-up visits, treatment and prophylaxis for opportunistic infections, and providing antiretroviral therapy (ART) according to World Health Organization (WHO) and national HIV treatment guidelines. Patients with abnormal RBG levels were referred to diabetes clinics for diagnosis and management. Although cut-points for abnormal RBG were not indicated in clinical guidelines, patients with an RBG level >110 mg/dL were typically evaluated for diabetes diagnosis and management.

Study Participants

Eligible patients included adult (≥15 years) PLHIV who were registered at HIV clinics between January 2011 and December 2016 and were screened for TB disease and received a random blood glucose test at the time of registration to the HIV clinic. Patients were followed up from the time of registration until June 30, 2017. Patients who received isoniazid preventive therapy and second-line anti-TB treatment for drug-resistant TB were excluded.

Data Source and Management

Patients' data were recorded using standardized forms at each clinic visit by medical officers and entered into an electronic database by data entry operators. Data for this retrospective study were extracted from the electronic database in December 2017.

Measures and Definitions

The primary exposure of interest was RBG measurement at enrollment into HIV care. We used RBG levels as continuous and categorical variables. We categorized RBG dichotomously; ≥140 mg/dL was defined as hyperglycemia according to previous studies and WHO 2-hour postprandial blood glucose classification for diagnosis of prediabetes [23–25]. Additionally, RBG was defined with a 4-level categorical variable: <110 mg/dL, 110–140 mg/dL, 141–199 mg/dL, and >199mg/dL.

The study's primary outcome was all-cause mortality, which was determined using patients' medical records. Patients' death status was reported by family members, caretakers, or peer volunteers when the patient died at home or in the hospital. Date of death was recorded from hospital records if patients died at the hospital or as reported by families if the patient died at home.

Patients' TB disease status was a key covariate determined by firstline anti-TB treatment use for any duration for either pulmonary or extrapulmonary TB disease. TB disease status was categorized as prevalent (at the time or within 1 month of clinic registration), incident (any time during follow-up but >1 month after registration), and any TB disease (either prevalent or incident). Firstline anti-TB treatment in this setting included isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin.

Additional key covariates included age, gender, body mass index (BMI), CD4 cell count, WHO clinical disease staging [26], anemia, hepatitis B surface antigen, and hepatitis C antibody at the time of registration to HIV care. BMI and anemia were defined by WHO guidelines for Asian populations [27, 28].

Data Analyses

We used logistic regression to assess unadjusted associations between patients' clinical characteristics and hyperglycemia. We calculated incidence rate (IR) per 100 person-years (PYs) by dividing the number of deaths by the person-time in years and 95% confidence intervals (CI) using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. We used cumulative incidence curves to estimate the unadjusted association between RBG and time to all-cause mortality and Cox proportional models to estimate hazard ratios (HRs) and 95% CIs to compare hyperglycemia at registration and hazard of mortality among all PLHIV. Survival time was defined as the number of days between the date of registration and date of death or censorship. Patients were right-censored if they were lost to follow-up, transferred to other health care facilities, or alive at the end of the study (June 30, 2017). Proportional assumptions were assessed using the log-log survival curves, and goodness of fit was assessed using Schoenfeld residuals [29]. We used a priori criteria to identify potential confounding covariates based on directed acyclic graph theory and observed bivariate associations [30]. Statistical interaction between TB disease and RBG with mortality was assessed using likelihood ratio tests, and HRs were stratified by TB disease status. We also tested whether the relationship between RBG and mortality was linear. We then estimated HRs with nonlinear categories of RBG, including (1) estimation of adjusted hazard ratios (aHRs) with 4 categories of RBG (<110, 110–140, 141–199, >199 mg/dL) and (2) restricted cubic spline regression using 4 equal knots and 3 reference points of RBG at 110, 140, 199, and 260 mg/dL [31, 32]. We performed sensitivity analyses to assess potential systematic error due to competing risks using

cumulative incidence functions and subdistribution hazard functions according to Fine and Gray [33] and to quantify systematic error due to loss to follow-up and nonindependence of censorship [34]. A 2-sided *P* value <.05 was considered statistically significant in all analyses. Analyses were performed using STATA, version 14.0 (StataCorp, College Station, TX).

Ethical Approval

Ethical approval was obtained from the Ethical Review Committee, Department of Medical Research, Myanmar, and the Ethics Advisory Group, International Union Against Tuberculosis and Lung Disease, Paris, France.

RESULTS

Patient Factors Associated With Hyperglycemia

During the study, 25 851 patients (Figure 1) provided 64 755 person-years of follow-up time. The median age of study participants (interquartile range [IQR]) was 36 (30–42) years, 43% were female, and the median CD4 count at registration (IQR) was 162 (68–310) cell/mm^3. At registration, the median RBG (IQR) was 88 (75–106) mg/dL, and 6.2% (95% CI, 6.0%–6.5%) had hyperglycemia. Overall, 91% (n = 23 490) of patients received ART, 29% (n = 7495) of patients had TB disease, and 15% (n = 3985) died during the study period. Patients aged 25–45 years (odds ratio [OR], 1.7; 95% CI, 1.3–2.2) or ≥46 years old (OR, 3.1; 95% CI, 2.4–4.0), male patients (OR, 1.3; 95% CI, 1.2–1.4), patients who were overweight (OR, 1.4; 95% CI, 1.2–1.6) or obese (OR, 1.4; 95% CI, 1.1–1.7), and those who had hepatitis C co-infection (OR, 1.5; 95% CI, 1.3–1.8) were associated with hyperglycemia at the time of registration (Table 1).

Overall Risk of All-cause Mortality

Among all PLHIV, the IR of all-cause mortality was 6 deaths per 100 person-years (Table 2), and the median time to death from enrollment among patients who died (IQR) was 140 (63–387) days. The IR of all-cause mortality among patients with hyperglycemia was significantly higher than among patients with normoglycemia (IR, 7.3; 95% CI, 6.5–8.2; vs IR, 6.1; 95% CI, 5.9–6.3 per 100 person-years; $P < .05$). The unadjusted hazard of death among patients with hyperglycemia was 1.1 (95% CI, 1.0–1.3) times the hazard of normoglycemic patients (Table 2 and Figure 2A). Other patient factors associated with increased hazard of death included having TB disease (HR, 1.4; 95% CI, 1.3–1.5), being underweight (HR, 2.1; 95% CI, 1.9–2.3), having a lower CD4 count (patients with CD4 count 200–350: HR, 1.6; 95% CI, 1.4–1.9; patients with CD4 <200: HR, 4.2; 95% CI, 3.7–4.7), not being on ART (HR, 5.3; 95% CI, 4.9–5.8), being anemic (patients with mild to moderate anemia: HR, 2.8; 95% CI, 2.5–3.1; patients with severe anemia: HR, 6.4; 95% CI, 5.8–7.2), and having hepatitis B co-infection (HR, 1.2; 95% CI, 1.1–1.4).

Hyperglycemia and Mortality Among HIV-Positive Patients With and Without TB Disease

After adjusting for age, gender, BMI, and hepatitis C co-infection, the hazard of all-cause mortality was higher among hyperglycemic patients compared with patients with normoglycemia (aHR, 1.1; 95% CI, 1.0–1.3) (Table 3). A significant interaction between hyperglycemia and TB disease was observed ($P < .001$). Among patients without TB disease, the IR of all-cause mortality among patients with normoglycemia was 5.5 per 100 PYs (95% CI, 5.3–5.7), and among hyperglycemic patients, it was 7.3 per 100 PYs (95% CI, 6.3–8.5) (Figure

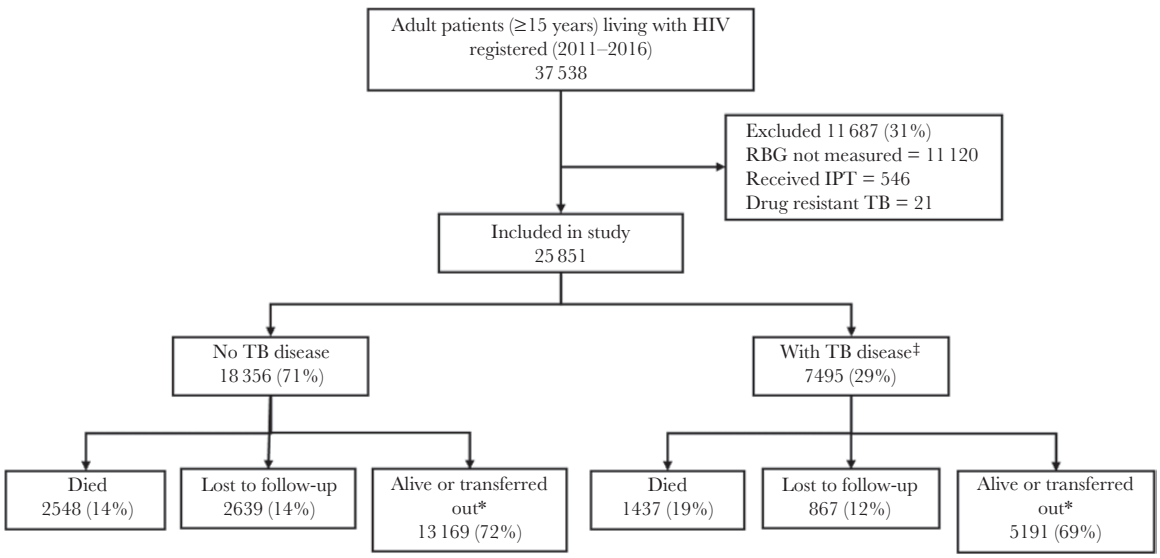

Figure 1. Flow diagram of patients included in the study stratified by their comorbidity with tuberculosis (TB) status and outcomes among people living with HIV registered in HIV clinics in Myanmar between 2011 and 2016. [a]Patients with TB disease include both prevalent TB at the time of registration to the program and incident TB developed during follow-up. [b]Transferred out to other programs to continue care. Abbreviations: IPT, isoniazid preventive therapy; RBG, random blood glucose.

Table 1. Demographic and Clinical Characteristics of Patients Stratified by Hyperglycemia and Factors Associated With Hyperglycemia Among PLHIV (≥15 Years) Registered in HIV Clinics in Myanmar Between January 2011 and December 2016

		Total	Normoglycemia ≤140 mg/dL		Hyperglycemia >140 mg/dL		OR	95% CI
		No.	No.	%	No.	%		
Total		25 851	24 237	93.8	1614	6.2		
Age at enrollment, y	15–24	1889	1823	96.5	66	3.5	Ref	
	25–45	19 878	18 740	94.3	1138	5.7	**1.7**	**(1.3 to 2.2)**
	≥46	4084	3674	90.0	410	10.0	**3.1**	**(2.4 to 4.0)**
Gender	Female	11 054	10 460	94.6	594	5.4	Ref	
	Male	14 797	13 777	93.1	1020	6.9	**1.3**	**(1.2 to 1.4)**
BMI at enrollment, kg/m^2	Underweight (<18.5)	8079	7599	94.1	480	5.9	1.1	(1.0 to 1.2)
	Normal (18.5–22.9)	8508	8043	94.5	465	5.5	Ref	
	Overweight (23–27.5)	3041	2817	92.6	224	7.4	**1.4**	**(1.2 to 1.6)**
	Obese (>27.5)	1809	1675	92.6	134	7.4	**1.4**	**(1.1 to 1.7)**
	Unknown	4418	4103	93.0	311	7.0	**1.3**	**(1.1 to 1.5)**
CD4 at enrollment, cell/mm^3	>350	5172	4864	94.0	308	6.0	Ref	
	200–350	5748	5396	93.9	352	6.1	1.0	(0.9 to 1.2)
	<200	14 590	13 666	93.7	924	6.3	1.1	(0.9 to 1.2)
	Not recorded	341	311	91.2	30	8.8	**1.5**	**(1.0 to 2.3)**
WHO staging at enrollment	1 and 2	11 179	10 510	94.0	669	6.0	Ref	
	3 and 4	14 590	13 650	93.6	940	6.4	1.1	(1.0 to 1.2)
	Not recorded	82	77	93.9	5	6.1	1.0	(0.4 to 2.5)
ART at enrollment	On ART	4	456	93.8	30	6.2	Ref	
	Not on ART	25 365	23 781	93.8	1584	6.2	1.0	(0.7 to 1.5)
Anemia at enrollment	No anemia	8096	7581	93.6	515	6.4	Ref	
	Mild to moderate	15 105	14 192	94.0	913	6.0	1.0	(0.8 to 1.1)
	Severe	2221	2056	92.6	165	7.4	1.2	(1.0 to 1.4)
	Not recorded	429	408	95.1	21	4.9	0.8	(0.5 to 1.2)
Hepatitis B co-infection at enrollment	Negative	21 036	19 694	93.6	1342	6.4	Ref	
	Positive	2049	1900	92.7	149	7.3	1.2	(1.0 to 1.4)
	Unknown	2766	2643	95.6	123	4.4	**0.7**	**(0.6 to 0.8)**
Hepatitis C co-infection at enrollment	Negative	20 631	19 363	93.9	1268	6.1	Ref	
	Positive	2438	2215	90.9	223	9.1	**1.5**	**(1.3 to 1.8)**
	Unknown	2782	2659	95.6	123	4.4	**0.7**	**(0.6 to 0.9)**
TB disease comorbidity	Without TB disease	18 356	17 283	94.2	1073	5.6	Ref	
	With TB disease	7495	6954	92.8	541	7.2	**1.3**	**(1.1 to 1.4)**

Bolded text indicates a *P* value <.05. Some lower limits of CIs were >1 or <1, but due to the rounding to 2 decimal places, they became 1.00.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; OR, odds ratio; PLHIV, people living with HIV; TB, tuberculosis; WHO, World Health Organization.

2B). Similarly, the cumulative incidence of all-cause mortality was higher, and the adjusted hazard of death was significantly higher (aHR, 1.2; 95% CI, 1.0–1.4) among patients with hyperglycemia compared with patients with normoglycemia (Table 3).

Among patients with TB disease, the IR of all-cause mortality was 7.4 per 100 PYs (95% CI, 7.0–7.8) among normoglycemic patients and was 7.3 per 100 PYs (95% CI, 5.9–8.8) among those with hyperglycemia (Figure 2C). In patients with TB disease, the adjusted hazard of mortality was similar in those with and without hyperglycemia (aHR, 1.0; 95% CI, 0.8–1.2). The adjusted hazard of mortality was not significantly different by hyperglycemia status when TB disease was categorized separately as prevalent TB (aHR, 1.0; 95% CI, 0.8–1.2) and incident TB (aHR, 1.2; 95% CI, 0.6–2.3) (Table 3).

Categorical and Restricted Cubic Spline Models

We found that the adjusted HRs of mortality across different glycemic levels were nonlinear ($P < .0001$). Using 4 categories of RBG, the adjusted hazard for all-cause mortality was increased in the group of patients with glycemic levels between 110 and 140 mg/dL compared with those with RBG <110 mg/dL (HR, 1.2; 95% CI, 1.1–1.3). Among patients without TB disease, those with RBG 110–140 mg/dL and RBG 141–199 mg/dL had a significantly increased hazard of death (aHR, 1.3; 95% CI, 1.2–1.4; aHR, 1.2; 95% CI, 1.1–1.5) (Table 3). In restricted cubic spline regression, the aHRs were significantly increased among patients with a glycemic level between 110 and 140 mg/dL but not among patients with an RBG of 141–190 mg/dL or >199 mg/dL (aHR, 1.1; 95% CI, 1.0–1.1; vs aHR, 1.1; 95% CI, 0.9–1.2; or aHR, 1.1; 95% CI, 0.8–1.3) (Table 3; Supplementary Figure 1).

Table 2. Crude Estimate of Association Between Patients' Demographic and Clinical Characteristics and Death Among People Living With HIV Registered in HIV Clinics in Myanmar Between 2011 and 2016 Who Were Followed up Until June 2017

		Total		Died	IR (95% CI)		cHR	(95% CI)
		No.	PYs	No.				
		25 851	64 755	3985	6.2	(6.0 to 6.4)		
Glycemic status at enrollment	Normoglycemia	24 237	61 078	3717	6.1	(5.9 to 6.3)	Ref	
	Hyperglycemia	1614	3676	268	7.3	(6.5 to 8.2)	**1.1**	**(1.0 to 1.3)**
TB disease status	Without TB disease	18 356	45 363	2548	5.6	(5.4 to 5.8)		
	With TB disease	7495	19 391	1437	7.4	(7.0 to 7.8)	**1.4**	**(1.3 to 1.5)**
Age at enrollment, y	15–24	1889	4464	156	3.5	(3.0 to 4.1)	Ref	
	25–45	19 878	50 897	3003	5.9	(5.7 to 6.1)	**1.8**	**(1.5 to 2.1)**
	≥46	4084	9393	826	8.8	(8.2 to 9.4)	**2.6**	**(2.2 to 3.1)**
Gender	Female	11 054	29 805	1259	4.2	(3.9 to 4.5)	Ref	
	Male	14 797	34 949	2726	7.8	(7.5 to 8.1)	**1.7**	**(1.6 to 1.9)**
BMI at enrollment, mg/kg^2	Underweight (<18.5)	8079	20 845	1691	1.1	(7.7 to 8.5)	**2.1**	**(1.9 to 2.3)**
	Normal (18.5–22.9)	8508	22 963	903	3.9	(3.6 to 4.2)	Ref	
	Overweight (23–27.5)	3041	8101	197	2.4	(2.1 to 2.8)	**0.6**	**(0.5 to 0.7)**
	Obese (>27.5)	1809	4486	109	2.4	(2.0 to 2.9)	**0.6**	**(0.5 to 0.7)**
	Unknown	4418	8354	1085	12.9	(12.2 to 13.8)	**2.9**	**(2.6 to 3.1)**
CD4 at enrollment, cell/mm^3	>350	5172	12 216	253	2.1	(1.8 to 2.3)	Ref	
	200–350	5748	15 180	469	3.1	(2.8 to 3.4)	**1.6**	**(1.4 to 1.9)**
	<200	14 590	37 218	3100	8.3	(8.0 to 8.6)	**4.2**	**(3.7 to 4.7)**
	Unknown	341	139	163	116.6	(100.0 to 135.9)	**29.1**	**(23.9 to 35.5)**
WHO staging at enrollment	1 and 2	11 179	28 847	844	2.9	(2.7 to 3.1)	Ref	
	3 and 4	14 590	35 745	3122	8.7	(8.4 to 9.1)	**3.0**	**(2.8 to 3.3)**
	Not recorded	82	161	19	11.7	(7.5 to 18.4)	**3.6**	**(2.3 to 5.6)**
ART during follow-up	Received	23 490	63 254	3293	5.2	(5.0 to 5.4)	Ref	
	Not received	2361	1500	692	46.1	(42.8 to 49.7)	**5.3**	**(4.9 to 5.8)**
Anemia at enrollment	No anemia	8096	20 820	526	2.5	(2.3 to 2.8)	Ref	
	Mild to moderate	15 105	38 895	2632	6.7	(6.5 to 7.0)	**2.8**	**(2.5 to 3.1)**
	Severe	2221	4377	747	17.1	(15.8 to 18.3)	**6.5**	**(5.8 to 7.2)**
	Not recorded	429	661	80	12.1	(9.7 to 15.1)	**4.0**	**(3.1 to 4.9)**
Hepatitis B co-infection at enrollment	Negative	21 036	55 643	2553	4.6	(4.4 to 4.8)	Ref	
	Positive	2049	5202	299	5.7	(5.1 to 6.4)	**1.2**	**(1.1 to 1.4)**
	Unknown	2766	3908	1133	28.9	(27.3 to 30.7)	**4.9**	**(4.5 to 5.2)**
Hepatitis C co-infection at enrollment	Negative	20 631	55 549	2544	4.5	(4.4 to 4.7)	Ref	
	Positive	2438	5282	302	5.7	(5.1 to 6.4)	1.1	(1.0 to 1.3)
	Unknown	2782	3922	1139	29.0	(27.4 to 30.77)	**4.8**	**(4.5 to 5.2)**

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cHR, crude hazard ratio; CI, confidence interval; IR, incidence rate per 100 person-years of follow-up; PYs, person-years of follow-up; TB, tuberculosis; WHO, World Health Organization.

Bolded text indicates a *P* value <.05. Some lower limits of CIs were >1 or <1, but due to the rounding to 2 decimal places, they became 1.00.

Sensitivity Analyses

In competing risk analyses, both the cause-specific analysis (aHR, 1.2; 95% CI, 1.1–1.4) and subdistribution analysis (aHR, 1.2; 95% CI, 1.0–1.4) indicated an increased hazard of mortality due to hyperglycemia among patients without TB disease, but the association was not significant in the subdistribution analysis. Among patients with TB disease, the association between RBG and mortality was not significant in both models (cause-specific aHR, 1.0; 95% CI, 0.8–1.2; subdistribution aHR, 1.0; 95% CI, 0.9–1.2) (Supplementary Table 1).

During the study, there were 3506 (13.6%) patients lost to follow-up; of these, 2639 (75.3%) had a normoglycemic level and 867 (24.7%) had hyperglycemia. In sensitivity analyses that randomly assigned a death outcome to records that were lost to follow-up, the aHRs among all patients ranged from 0.6 to 2.7; among patients without TB disease, the aHR ranged from 0.6 to 2.6, and among patients with TB disease, the aHR ranged from 0.6 to 1.5 (Supplementary Table 2).

DISCUSSION

This large observational cohort of PLHIV from Myanmar found an important effect of hyperglycemia on all-cause mortality during 5 years of follow-up. More than 6% of PLHIV had hyperglycemia at the time of registration into HIV care, and 1 out of every 6 patients with hyperglycemia died during follow-up. Importantly, we also demonstrated that the relationship between hyperglycemia and all-cause mortality is different by

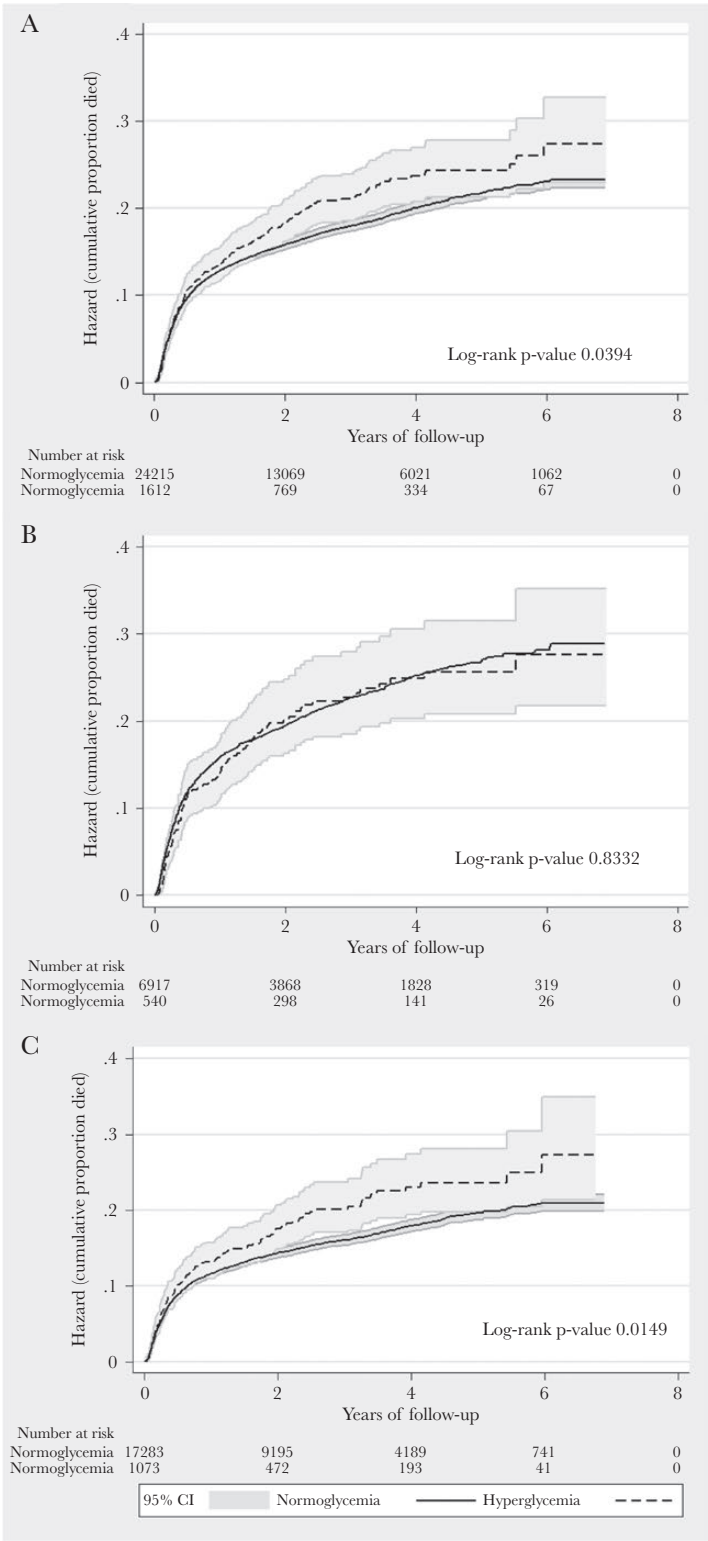

Figure 2. Nelson-Aalen plots of cumulative mortality stratified by hyperglycemia status (A) among all people living with HIV (PLHIV), (B) among PLHIV with tuberculosis (TB) disease, and (C) among PLHIV without TB disease enrolled in the Integrated HIV Care program in Myanmar between 2011 and 2017. Abbreviation: CI, confidence interval.

TB disease status and the risk of mortality is nonlinear across glycemic levels. In analyses stratified by TB disease status, we reported that the rate of mortality in PLHIV with hyperglycemia but no TB disease (7 deaths per 100 PYs) was similar to the rate of mortality in patients with TB regardless of hyperglycemia status.

Table 3. Adjusted Hazard Ratios of Mortality Across Blood Glucose Level at Registration Among People Living With HIV Registered in HIV Clinics in Myanmar Between 2011 and 2016 Who Were Followed up Until June 2017, Stratified by Their TB Comorbidity Using Different Models

Blood Glucose Level, mg/dL	All patients (n = 25 851)	Patients Without TB Disease (n = 18 356)	Patients With TB Disease[a] (n = 7495)	Patients With Prevalent TB Disease[b] (n = 6518)	Patients With Incident TB Disease[c] (n = 977)
Adjusted Hazard Ratio[d]					
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Glycemic status as dichotomous predictor					
Normoglycemia	Ref	Ref	Ref	Ref	Ref
Hyperglycemia	1.1 (1.0 to 1.3)	**1.2 (1.0 to 1.4)**	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	1.2 (0.6 to 2.3)
Categorical model					
<110	Ref	Ref	Ref	Ref	Ref
110–140	**1.2 (1.1 to 1.3)**	**1.3 (1.2 to 1.4)**	1.1 (0.8 to 1.2)	1.0 (0.9 to 1.2)	1.4 (0.9 to 2.2)
141–199	1.1 (1.0 to 1.3)	**1.2 (1.1 to 1.5)**	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.2)	1.3 (0.7 to 2.7)
>199	1.2 (0.9 to 1.7)	1.4 (0.9 to 2.1)	1.0 (0.6 to 1.7)	1.0 (0.5 to 1.7)	0.9 (0.1 to 6.3)
Restricted cubic spline[e]					
<110	Ref	Ref	Ref	Ref	Ref
110–140	**1.1 (1.0 to 1.1)**	**1.1 (1.0 to 1.1)**	1.0 (0.9 to 1.1)	1.0 (1.0 to 1.1)	1.0 (0.8 to 1.3)
141–199	1.1 (0.9 to 1.2)	1.1 (0.9 to 1.3)	1.0 (0.8 to 1.2)	1.0 (0.8 to 1.2)	1.0 (0.5 to 2.1)
>199	1.0 (0.8 to 1.3)	1.1 (0.8 to 1.6)	1.0 (0.6 to 1.4)	1.0 (0.6 to 1.5)	0.9 (0.2 to 3.6)
Incidence Rate[f]					
	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)	IR (95% CI)
Glycemic status as dichotomous predictor					
Normoglycemia	6.1 (5.9 to 6.3)	5.5 (5.3 to 5.7)	7.4 (7.0 to 7.8)	7.9 (7.4 to 8.3)	5.1 (4.4 to 6.0)
Hyperglycemia	7.3 (6.5 to 8.2)	7.3 (6.3 to 8.5)	7.3 (5.9 to 8.8)	7.4 (6.1 to 9.2)	5.9 (3.2 to 11.1)
IR difference (hyperglycemia vs normoglycemia)	**1.2 (0.3 to 2.1)**	**1.7 (0.6 to 2.8)**	–0.0 (–0.2 to 0.1)	–.0.4 (–0.2 to 0.2)	0.8 (–2.9 to 4.6)
Categorical model					
<110	5.8 (5.7 to 6.1)	5.2 (4.9 to 5.4)	7.3 (6.9 to 7.8)	7.7 (7.3 to 8.2)	4.6 (4.2 to 5.9)
110–140	7.4 (6.8 to 8.0)	6.9 (6.2 to 7.6)	8.0 (7.1 to 9.1)	8.2 (7.2 to 9.6)	6.3 (4.2 to 9.3)
141–199	7.4 (6.5 to 8.4)	7.3 (6.2 to 8.6)	7.4 (6.0 to 9.1)	7.6 (6.1 to 9.5)	6.0 (3.1 to 11.6)
>199	6.3 (4.5 to 8.8)	6.2 (4.0 to 9.4)	6.3 (3.7 to 11.0)	6.7 (3.8 to 11.7)	4.0 (0.6 to 28.6)

Bolded text indicates a *P* value <.05. Some lower limits of CIs were >1 or <1, but due to the rounding to 2 decimal places, they became 1.00.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; IR, incidence rate; TB, tuberculosis.

[a]Includes patients with any TB disease (either prevalent or incident TB).

[b]Refers to those with TB disease at the time of or within 1 month of registration to clinics.

[c]Refers to those with TB disease diagnosed any time during follow-up but later than 1 month after registration to clinics.

[d]Adjusted for age, gender, body mass index, and hepatis C co-infection.

[e]Blood glucose levels of 110, 140, 199 and 260 mg/dL were used as reference points for spline regression.

[f]Incidence rate per 100 person-years of follow-up.

In this study, hyperglycemia among PLHIV increased the hazard of mortality by 10% compared with patients with normoglycemia levels, even after adjustment of confounding demographic and clinical factors. The highest hazard of mortality was observed with RBG of 110–140 mg/dL, whereas the hazard was similar comparing those with RBG >199 mg/dL with patients with <110 mg/dL. We hypothesized that previous DM diagnosis and treatment may modulate the association between glycemic status and mortality [35]; therefore, the observed U-shaped relationship may be due to preexisting DM diagnosis among patients with higher glucose levels (RBG, 141–199 mg/dL or >199 mg/dL). It is also plausible that patients with moderate hyperglycemia (RBG, 110–140 mg/dL) had stress hyperglycemia, resulting in more adverse outcomes compared with those with DM hyperglycemia.

Although few previous studies on DM and mortality in patients with HIV exist, limited evidence suggests that there is increased mortality due to comorbidity between hyperglycemia and HIV. For example, a cohort study of HIV-positive patients from Brazil during 1999–2011 reported that DM was a significant risk factor for mortality [21]. In another Brazilian study, a significantly higher proportion of annual deaths were due to DM in HIV/AIDS patients compared with a non-HIV control group (4.1% vs 3.9%) [36]. Similarly, a Swiss HIV cohort study (n = 8444) reported that among PLHIV, the 3-year hazard of death among DM was 3.75 (95% CI, 1.80–7.85) times the hazard of death among patients without DM [37].

Among HIV/TB patients, the incidence rate of mortality was similar in those with and without hyperglycemia at enrollment in HIV care in this cohort. However, our results contradict those from a cohort study conducted by Moreira at el. in Brazil, which

reported that hyperglycemia was a risk factor for increased 1-year mortality among HIV/TB-co-infected patients (aHR, 3.72; 95% CI, 2.17–6.38) [38]. Our divergent findings may be due to different baseline characteristics of study patients and definitions of hyperglycemia. For example, the proportion of patients on ART in the Brazilian study was about 50%, whereas the ART coverage in our study was >90%. The protective effect of ART in our study might shift the hazard due to hyperglycemia on mortality in HIV/TB patients toward the null. Second, the study by Moreira et al. defined hyperglycemia using fasting blood glucose levels ≥126 mg/dL or glycated hemoglobin >6.5% (compared with our RBG of >140 mg/dL) and used multiple glucose measurements at different time points during anti-TB treatment. Patients with known DM were also excluded from the study by Moreira at el., whereas our study did not exclude patients with DM.

There are important clinical implications from this study. First, RBG levels >110 mg/dL may predict mortality among PLHIV. Because RBG is inexpensive and often standard of care, it could be readily used among PLHIV to augment risk profiles. However, where feasible, PLHIV with RBG >110 mg/dL should also be screened for DM using more accurate glycemic diagnostic tests at registration and during follow-up, and those diagnosed with DM should be referred for further treatment and management. Second, our study demonstrates the need for additional basic science and operational research to understand the immunopathology of how hyperglycemia may increase the risk of mortality among PLHIV and why there are differences between those with and without TB. Third, our results highlight the urgent need for clinical guidelines for blood glucose targets among PLHIV and suggest that these targets may be different based on baseline glucose levels and comorbidity with TB disease.

Our study has limitations. First, there was potential misclassification of hyperglycemia status, as we relied on the only standard of care measure of dysglycemia (RBG) at HIV clinics in Myanmar. Compared with hemoglobin A1c or oral glucose tolerance tests, RBG is a less definitive measure for dysglycemia, and there is no consensus for classification of hyperglycemia by RBG alone. Nonetheless, we used different cut-points of RBG to define hyperglycemia and consistently found that hyperglycemia increased the risk of mortality among PLHIV, especially those without TB disease. Second, misclassification of the outcome (mortality) could not be ruled out, as 14% of patients were lost from care during follow-up. However, we performed sensitivity analyses using different plausible proportions of mortality among patients lost to follow-up [32, 33].

We demonstrated that even with high proportions of death among patients lost during follow-up, the estimated effect of hyperglycemia on mortality did not significantly change. Third, our study measured RBG at 1 time point. Hence, we could not determine changes in glucose levels during HIV care. Similarly, we did not have information on DM diagnosis or DM treatment, and therefore we could not determine whether the effect of glycemic level on hazard of mortality differed by DM status. Fourth, unmeasured confounders such as patients' economic status, access to other health care, and presence of other chronic conditions such as hypertension and hyperlipidemia were not assessed. Therefore, we could not exclude the possibility of systematic error in our estimates due to residual confounding. Fifth, we excluded patients who did not have RBG at enrollment and patients who received isoniazid therapy from this study. Although these exclusions may have impacted the generalizability of our study results, the excluded patients' demographic characteristics did not differ significantly from those included in the study (data not shown).

Despite limitations, there are important strengths to this study. We studied a large cohort of PLHIV with more than 65 000 person-years of follow-up time. We used various methods to estimate the effect of hyperglycemia on mortality among PLHIV, including methods that accounted for competing risks and loss to follow-up. Our multiple model specifications, thorough evaluation of RBG categories, and sensitivity analyses extend additional credibility to the validity of our results.

CONCLUSIONS

We found that hyperglycemia was associated with increased risk of all-cause mortality among PLHIV. Pertinent to clinical care, we observed that the effect of hyperglycemia was different by TB disease status; much of the increased mortality risk due to hyperglycemia was among PLHIV without TB disease. Important gaps in knowledge remain regarding how to systematically screen and diagnose hyperglycemia among PLHIV. Further research is urgently needed to establish glycemic targets among PLHIV. When and how to achieve glycemic targets will likely be different among patients with and without TB disease.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

The authors are grateful to the clinical and administrative staff working with the National HIV/AIDS Program and The Union Mandalay office for their dedication in caring for patients and their attentiveness in accurately recording the patients' data. All patients included in this study are also gratefully acknowledged.

Financial support. This work was supported by the Department for International Development (DFD; UK), which funded the Global Operational Research Fellowship Program at the International Union Against Tuberculosis and Lung Disease (The Union; Paris, France), where the first author works as an operational research fellow.

Potential conflicts of interest. All authors report no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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