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Atrial Fibrillation and Mortality in Outpatients with Heart Failure in Tanzania: A prospective cohort study

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Abstract

Objective: In recent years, the prevalence and mortality of heart failure (HF) and other associated cardiovascular diseases have doubled in Sub-Saharan Africa (SSA). Studies in high-income countries indicate that HF with concurrent atrial fibrillation (AF) is linked to increased mortality. Our objective was to determine the incidence and clinical outcomes of AF among heart failure patients in SSA.

Design: A prospective cohort study using data collected between October 2018-May 2020

Setting: Outpatient clinic at a tertiary hospital in Mwanza, Tanzania

Participants: 303 adult participants (aged ≥ 18 years) with HF as defined by the ESC guidelines (2016) and 100 adults with HF as defined by clinical criteria alone were enrolled into the study. Patients with comorbid medical condition that had prognosis of <3 months (i.e. advance solid tumors, advance hematological malignancies) were excluded.

Methods: Participants were screened for atrial fibrillation, and their medical history, physical exams, and sociodemographic information were obtained. Multivariable logistic regression models were used to examine factors associated with AF incidence. Cox regression models were used to analyze 3-month mortality and its associated risk factors.

Results: We enrolled 403 participants with HF (mean age 60±19 years, 234 (58%) female). The AF prevalence was 17%. In multivariable models, factors associated with AF were low income, alcohol consumption and longer duration of heart failure. At the end of the three-month follow-up, 120/403 (30%) participants died, including 44% (31/70) of those with AF. Higher heart rate on ECG, more severe New York Heart Association HF class, rural residence and anemia were significantly correlated with mortality.

Conclusion: Atrial fibrillation is common, underdiagnosed and associated with significant mortality among outpatients with HF in Tanzania (HR:1.749, 95% CI:1.162-2.633, p=0.007). Our findings additionally identify tachycardia (>110 bpm, HR:1.879, 95% CI:1.508-2.340, p<0.001) as an easily measurable, high-impact physical exam finding for adverse outcomes in HF patients.

Strengths and limitations of this study

- This study is one of the few to examine the prevalence and mortality of atrial fibrillation among outpatients with heart failure in Sub-Saharan Africa.
- This study focuses on readily accessible physical exam measures, demographics, socioeconomic and lifestyle attributes. They are inexpensive to acquire and are well adapted for risk stratification in resource limited settings.
- As a cohort study, no causal relationships can be established between the risk factors and mortality. Questionnaire data on social and personal history are contingent on patient report accuracy. Given the limitations in medical equipment, concurrent coronary artery disease, the order in which atrial fibrillation and heart failure developed, and whether heart failure was due to non-ischemic or ischemic causes were not established.
- All participants were recruited from a single healthcare facility, which may qualify the generalizability of the findings.

Introduction

As global life expectancy increases, the incidence of heart failure (HF) has risen substantially [1]. Approximately 26 million people live with heart failure worldwide [2], with low- and middle-income countries bearing the greatest burden [1,3]. From 1990 to 2013, cardiovascular disease-related deaths in Africa increased two-fold, and accounted for roughly 38% of all non-communicable disease mortalities [1,4]. Within Sub-Saharan Africa (SSA), previous studies have indicated an "epidemiological transition," whereby chronic, non-communicable diseases are gradually overtaking infectious diseases in prevalence [1,3]. In particular, heart failure constitutes roughly 9.4–42.5% of all hospital admissions and 25.6–30.0% of the cardiology clinic visits at institutions across Africa [5]. HF has a higher one-year post-hospital discharge mortality than all other diagnoses [6]. In addition to patient-level burden, HF poses significant economic strain secondary to recurrent hospitalizations, lost productivity, and pharmacologic costs [5,7].

Atrial fibrillation (AF) incidence is also escalating rapidly among new cardiovascular diagnoses [8]. Between 1990-2010, the annual deaths caused by AF grew by 2 and 1.9 fold in men and women, respectively [9]. While AF and HF are known to share common cardiometabolic risk factors, growing evidence suggests that the presence of one may precipitate the severity of the other. Compared to sinus-rhythm, comorbid AF is associated with higher all-cause mortality and hospitalization rates in patients with heart failure [10]. Furthermore, AF-related atrial remodeling, altered ventricular hemodynamics and arrhythmia-induced myopathy are linked to further heart failure progression [11].

Despite the synergistic comorbidity of AF and HF, little is known about the prevalence of atrial fibrillation among outpatients with heart failure within Sub-Saharan Africa, or its impact

on clinical outcomes. Therefore, we conducted a prospective cohort study to elucidate the prevalence, correlates and mortality associated with this patient population in Tanzania.

Methods

Overview

This clinic-based prospective cohort study involved 403 patients who were enrolled in a registry of HF. This registry was created as part of a more extensive hospital quality improvement program for heart failure patients. Data collection and follow-up spanned from October 2018 to May 2020.

Setting and Participants

The study was conducted at the outpatient clinic of Bugando Medical Center (BMC), a zonal hospital for the Lake Victoria Zone in northwest Tanzania. BMC serves a population of over 14 million with a 950-bed capacity. In each month, BMC provides care for approximately 400 patients with HF, with an average of 100 patients seen weekly. BMC is similar to other facilities that provide care for heart failure in Tanzania and Uganda [12,13].

All patients attending the outpatient clinic with a diagnosis of heart failure were screened between October and December of 2019. Patients ≥ 18 years of age and seeking heart failure care were recruited serially until the target sample size was attained (n ≥ 331). Patients with comorbid medical conditions with a prognosis of <3 months (i.e. advanced malignancy) were excluded from the study. Of the 403 enrolled patients, 303 had the diagnosis of HF objectively confirmed according to the European Society of Cardiology (ESC) 2016 guidelines [14], where 133 had heart failure with reduced ejection fraction (HFrEF) and 170 had heart failure with preserved ejection fraction (HFpEF). For the remaining 100 patients, the diagnosis of HF was

made according to the Framingham criteria, and in the absence of another primary diagnosis responsible for volume overload [15].

Study Procedures

Consented participants were interviewed using a standard questionnaire that collected clinical and demographic information such as age, sex, residence, duration of heart failure, and New York Heart Association (NYHA) functional classification. Participants were also evaluated for palpitations, shortness of breath, syncope or presyncope, exercise intolerance, chest pain and fatigue. Physical examination was performed on every participant. Blood pressure measurements were taken from the right arm using an automated blood pressure monitor after subjects had rested for at least 5 minutes. Pulse rate was determined, and noted for irregularity, regularity and amplitude, then compared to the heart rate for pulse deficit.

Height was measured using a rigid ruler attached to a wall and rounded to the nearest 0.5cm. Weight was measured without shoes, with patients wearing light clothing and recorded to the nearest 500g using the DETECTO scale. Body Mass Index (BMI) was calculated using the Quetelet equation [16] and categorized using the WHO Classification Scale, with underweight BMI classified as <18.5 kg/m^2, normal BMI as 18.5-24.9 kg/m^2, overweight BMI as 25-29.9 kg/m^2, and obese BMI as $\geq$ 30kg/m^2. Additionally, electronic medical records were reviewed to extract blood hemoglobin and serum creatinine values.

Study participants were then subjected to a resting 12-lead electrocardiography. The heart rate on ECG was recorded for all subjects. Tracings with irregular QRS Complexes and absent discrete P waves were categorized as AF, in accordance with the ESC 2016 criteria [17]. All diagnoses of atrial fibrillation were confirmed by a staff cardiologist. Patients with AF had their results communicated to the attending physician and were treated according to protocol.

Follow Up and Outcome Determination

At least three contact phone numbers were obtained at the time of enrollment, including one from the patient and two from friends and relatives. All participants were followed for a period of three months, with none lost to follow up. The research team interviewed the participants during their regularly scheduled visits on a monthly basis. Phone calls were made to those not presenting to clinic. During these interviews, information about their recent medical updates or hospitalizations were collected. If the participant could not be reached, the designated alternate contact was called to determine the patient's vital status. Mortality was ascertained via phone call to each individual family. The families confirmed the death was cardiac in origin or related to their cardiac diagnosis (HF/cardio-embolic stroke/cardio-renal syndrome). Additionally, for those who died during hospitalization, care was taken to confirm with the family member that the original admission was due to cardiac etiologies.

Statistical Analysis

By the difference in proportions calculation, a minimum sample size of 331 patients was needed to provide at least 80% power to detect the difference in mortality rates between patients with AF and those without (two-sided test with a 5% level of significance) [18]. Our pre-test estimation of AF prevalence was 16% [19,20]. For the secondary analyses, this sample size was expected to provide at least 10 observations (i.e., number of patients with AF or death events) per predictor in the final models to allow good estimates [21,22]. Stata 16.1 was the statistical analysis software used in this study. Unknowns were recorded as null prior to analysis. For tabulation purposes, we reported count for discrete variables, and mean/standard deviation or median/interquartile range for continuous variables. Logistic regression was used to determine which baseline features were most strongly correlated with atrial fibrillation, and Cox

Proportional Hazard Analysis was used to evaluate their associations with mortality. The primary outcome of interest was death within 3 months of the index visit. A p-value < 0.05 was considered statistically significant.

Patient and Public Involvement Statement

No patients involved in the design of this study.

Results

Baseline Characteristics

Baseline characteristics of the patients are described in **Table 1**. The cohort included 234 females (58.1%) and 169 males (41.9%), with a mean age of 60±19 years. Nearly one-half (186, 46.2%) were overweight or obese (≥ 25kg/m^2). Among the participants, 202 (50.1%) had health insurance. One hundred and fifty-four (154, 38.2%) self-identified as low income (less than 500,000 TZS/month). Two hundred and thirty-four participants lived in rural settings (234, 58.1%) and 169 (41.9%) lived in urban environments. One hundred and nine participants (109, 27.1%) did not receive formal education, 214 (53.1%) completed primary school, and 80 (19.9%) obtained secondary or higher degrees. The median heart failure duration in this cohort was four years (IQR 3-9), and 180 (44.7%) noted a family history of heart failure. The majority, 320 (79.4%), were diagnosed with advanced HF (III/IV NYHA class). The most predominant comorbidity was hypertension, with 323 cases (80.2%). Ninety-seven (97, 24.1%) had concurrent diabetes mellitus. Nearly half of the participants (189, 46.9%) reported a social history positive for alcohol consumption, and 77 (19.1%) had a smoking history.

Table 1. Social, Demographic, and Past Medical History of Enrolled Patients

Patient Data (n=403)	Subclass	Number (n=403)

Sex	Female	234 (58.1%)
Age	Mean (SD)	60.2 (18.8)
Education	Informal	109 (27.1%)
	Primary	214 (53.1%)
	Secondary or Higher	80 (19.9%)
Reside	Urban	169 (41.9%)
	Rural	234 (58.1%)
Health Insurance	Yes	202 (50.1%)
Income Level	Low	154 (38.2%)
	Medium/High	249 (61.8%)
BMI Categories	Underweight	26 (6.5%)
	Normal	191 (47.4%)
	Overweight	120 (29.8%)
	Obese/Severely Obese	66 (16.4%)
History of Hypertension	Yes	323 (80.2%)
Duration of Heart Failure (Years) - Median (IQR)		4 (3-9)
Family History of Heart Failure	Yes	180 (44.7%)
NYHA Function Class	II	83 (20.6%)
	III	317 (78.7%)
	IV	3 (0.7%)
Diabetes Mellitus	Yes	97 (24.1%)
HIV	Positive	21 (5.2%)
Atrial Fibrillation	Present (ECG confirmed AF)	70 (17.4%)
Alcohol	Yes	189 (46.9%)
(Average Units of Alcohol/Day)	Median (IQR)	0 (0-10)
	Range	0-60
Cigarette Smoking	Yes	77 (19.1%)
Echo LV EF (%)	<40	133 (33.0%)
	>=40	170 (42.2%)
	Unknown	100 (24.8%)
Hemoglobin	Normal (>12g/dl)	175 (43.4%)
	Mild Anemia (10-11.9g/dl)	188 (46.7%)
	Moderate/Severe Anemia (<=9.9g/dl)	38 (9.9%)
Rheumatic Heart Disease	Positive History & AF	6 (1.5%)
	Positive History & No AF	18 (4.5%)
	Negative History & AF	64 (15.8%)
	Negative History & No AF	315 (78.2%)
Creatinine Level - Median (IQR)		94 (77-169)
Systolic Blood Pressure - Median (IQR)		122 (106-142)

Diastolic Blood Pressure - Median (IQR)		70 (66-82)
Pulse Rhythm	Regular	300 (74.4%)
	Irregular (diagnosed by clinical exam)	103 (25.6%)
Heart Rate (bpm) - Median (IQR)		79 (71-91)
Pulse Deficit (bpm) - Median (IQR)		6 (3-11)
ECG Heart Rate (bpm) - Median (IQR)		79 (67-94)
ECG Rhythm	Regular	304 (75.4%)
	Irregular	99 (24.6%)
Goal Directed Therapy	Beta-Blocker	254 (63.0%)
	ACE-inhibitor	188 (46.7%)
	Diuretic	300 (74.4%)
	Nitrates	39 (9.6%)
	Digitalis	58 (14.4%)
	ARB	156 (38.7%)
	Calcium Channel Blocker	48
	Vasodilator	35

Prevalence of Atrial Fibrillation

Of the 403 study participants with heart failure, 70 (17.4%) participants had atrial fibrillation detected on screening electrocardiogram. Of these, 29/70 (41.4%) had previously been diagnosed with atrial fibrillation and 41/70 (58.6%) were new diagnoses. Twenty-five percent (6/24) of participants with a history RHD had atrial fibrillation (**Table 1**).

Sociodemographic Correlates of Atrial Fibrillation

In a univariable logistic regression model (**Table 2**), advanced age, low income, informal education, alcohol consumption, and longer heart failure duration were significantly associated with atrial fibrillation. In the multivariable model (**Table 3**), lower income (high income aOR 0.5, 95% CI 0.3-0.9), duration of heart failure (aOR 1.05, 95% CI 1.0-1.1), and alcohol consumption (aOR 2.1, 95% CI 1.2-3.8) were associated with atrial fibrillation.

Table 2. Univariate logistic regression for sociodemographic, clinical history and anthropomorphic correlates associated with atrial fibrillation

Screening Characteristics	Subclass	AF (%)	No AF (%)	OR (95% CI)	p-value
Sex	Male	31 (18.3)	138 (81.7)	1.000	
	Female	39 (16.7)	195 (83.3)	0.890 (0.530-1.497)	0.661
Age	Mean±Std. Dev.	66.4±19.0	58.8±18.5	1.025 (1.009-1.041)	**0.002**
Education	Informal	27 (24.8)	82 (75.2)	1.000	
	Formal	43 (14.6)	251 (85.4)	0.520 (0.303-0.895)	**0.018**
Income	Low	34 (22.1)	120 (77.9)	1.000	
	Medium/High	36 (14.5)	213 (85.5)	0.597 (0.355-1.003)	**0.051**
Reside	Urban	26 (15.4)	143 (84.6)	1.000	
	Rural	44 (18.8)	190 (81.2)	1.274 (0.749-2.166)	0.372
Health Insurance	Yes	31 (15.4)	171 (84.7)	1.000	
	No	39 (19.4)	162 (80.6)	0.753 (0.448-1.264)	0.283
BMI (kg/m^2)	Underweight	4 (15.4)	22 (84.6)	1.000	
	Normal	43 (22.5)	148 (77.5)	1.598 (0.522-4.889)	0.411
	Overweight	15 (12.5)	105 (87.5)	0.786 (0.238-2.595)	0.692
	Obese	8 (12.1)	58 (87.9)	0.759 (0.207-2.774)	0.676
Duration of Heart Failure (Years) - Median (IQR)		6.5 [3-13]	4 [2-7]	1.076 (1.034-1.076)	**<0.001**
NYHA Function Class	I/II	9 (10.8)	74 (89.2)	1.000	
	III/IV	61 (19.1)	259 (80.9)	1.937 (0.918-4.083)	**0.083**
Diabetes Mellitus	No	55 (18.0)	251 (82.0)	1.000	
	Yes	15 (15.5)	82 (84.5)	0.835 (0.448-1.556)	0.57
Alcohol	No	26 (12.2)	188 (87.8)	1.000	
	Yes	44 (23.3)	145 (76.7)	2.194 (1.290-3.732)	**0.004**
Cigarette Smoking	No	53 (16.3)	273 (83.7)	1.000	
	Yes	17 (22.1)	60 (77.9)	1.459 (0.790-2.696)	0.227

Table 3. Multivariate logistic regression of demographic factors associated with atrial fibrillation

Variable	aOR (95% CI)	p-value
Age	1.006 (0.987-1.025)	0.564
Education (Formal)	0.659 (0.354-1.223)	0.186
Income (Med/High)	0.531 (0.306-0.920)	**0.024**
Duration of Heart Failure (Years)	1.049 (1.000-1.100)	**0.050**
NYHA (III/IV)	1.347 (0.612-2.962)	0.459

Alcohol Consumption	2.083 (1.150-3.771)	**0.015**

Clinical and Physical Exam Correlates of Atrial Fibrillation

By univariate logistic regression (**Table 4**), irregular pulse rhythm, higher baseline heart rate, and greater pulse deficit were linked to AF prevalence. Conversely, higher systolic blood pressure at baseline was associated with a decreased risk of having atrial fibrillation. With respect to physical exam findings, in the multivariate analysis (**Table 5**), irregular pulse rhythm (OR 38.0, 95% CI 15.3-94.4) and pulse deficit (OR 1.1, 95% CI 1.0-1.2) are strongly suggestive of AF presence.

Table 4: Univariate logistic regression for physical exam correlates of atrial fibrillation

Screening Characteristics	Subclass	AF (%)	No AF (%)	OR (95% CI)	p-value
Systolic Blood Pressure - Median (IQR)		117 [97-134]	124 [107-145]	0.985 (0.974-0.996)	**0.009**
Diastolic Blood Pressure - Median (IQR)		69 [64-82]	70 [67-82]	0.996 (0.977-1.016)	0.699
Pulse Rhythm	Regular	7 (2.3)	293 (97.7)	1.000	
	Irregular	63 (61.2)	40 (38.8)	**65.925 (**28.237-153.915**)**	**<0.001**
Heart Rate (bpm) - Median (IQR)		85 [74-102]	78 [70-89]	1.026 (1.013-1.040)	**<0.001**
Pulse Deficit (bpm) - Median (IQR)		11 [10-13]	5 [3-8]	1.328 (1.233-1.431)	**<0.001**

Table 5. Multivariate logistic regression for screening factors associated with atrial fibrillation

Variable	OR (95% CI)	p-value
SBP	0.987 (0.967-1.007)	0.186
DBP	1.019 (0.988-1.051)	0.240
Pulse Rhythm (Irregular)	38.001 (15.292-94.436)	**<0.001**

Heart Rate	1.003 (0.984-1.022)	0.778
Pulse Deficit	1.110 (1.018-1.211)	**0.018**

Three Month Mortality

At the end of the three-month follow-up, 120 (29.8%) participants died, including 44.3% and 26.7% of those with and without AF, respectively. Among the clinical variables (**Table 6**), the factor most significantly associated with three-month mortality was higher heart rate on ECG (Hazard Ratio (HR) 1.88, 95% CI 1.508-2.340). Other noteworthy risk factors for death include atrial fibrillation (HR 1.75, 95% CI 1.162-2.633), worse heart function (III/IV) on the NYHA scale (HR 1.64, 95% CI 0.981-2.738), rural residence (HR 1.47, 95% CI 1.006-2.150), and anemia (HR 1.33, 95% CI 1.012-1.738). Conversely, higher education, higher ejection fraction (≥40%) and baseline systolic blood pressure within the normal range were associated with decreased hazard ratio. By multivariate analysis (**Table 7**), increased ECG heart rate remained significantly associated with mortality. Collinearity was noted between AF and other measures of heart failure, and the singular inclusion of AF displayed statistically significant mortality hazards when other diluting factors were omitted (**Table 8**). On stratified analysis, death rate increased significantly with each increment in ECG heart rate, with a three-month mortality of 21.5% for those with HR below 90 bpm, 38.6% for those between 90-110 bpm and 64.4% for patients with >110 bpm at baseline (**Figure 1&2**). Additional analyses comparing the AF prevalence and three-month mortality data for participants with echocardiograph confirmed heart failure (according to the ESC criteria) against those participants diagnosed based on clinical criteria alone was conducted. In the HFrEF cohort, death rate at 3-months was similar for those with AF and those without. For both HFpEF and clinical criteria diagnosis, there was a marked increase in the 3-month mortality in those with AF (**Table 9**).

274 **Table 6. Univariate Cox Hazard Model with death as outcome**

Patient Data (n=403)	Subclass	No Death (%)	Death (%)	HR (95% CI)	P>|z|
Sex	Female	157 (67.1)	77 (32.9)	1.304 (0.898-1.894)	0.163
	Male	126 (74.6)	43 (25.4)		
Age				1.000	0.998
Reside	Urban	129 (76.3)	40 (23.7)	1.471 (1.006-2.150)	**0.046**
	Rural	154 (65.8)	80 (34.2)		
Education	Informal	68 (62.4)	41 (37.6)	0.689 (0.472-1.004)	**0.053**
	Formal	215 (73.1)	79 (26.9)		
Income Level	Low	103 (66.9)	51 (33.1)	0.827 (0.576-1.188)	0.303
	Medium/High	180 (72.3)	69 (27.7)		
Health Insurance	Yes	147 (72.8)	55 (27.2)	1.183 (0.826-1.694)	0.359
	No	136 (67.7)	65 (32.3)		
BMI Categories	Underweight/Normal	148 (68.2)	69 (31.8)	0.876 (0.610-1.258)	0.474
	Overweight/Obese	135 (72.6)	51 (27.4)		
Hypertension	Yes	227 (70.3)	96 (29.7)	0.982 (0.628-1.536)	0.936
	No	56 (70.0)	24 (30.0)		
HF Duration (Years)				1.282 (0.767-2.141)	0.343
NYHA	I/II	66 (79.5)	17 (20.5)	1.639 (0.981-2.738)	**0.059**
	III/IV	217 (67.8)	103 (32.2)		
Diabetes	Yes	70 (72.2)	27 (27.8)	0.903 (0.588-1.386)	0.641
	No	213 (69.6)	93 (30.4)		
AF	Absent	244 (73.3)	89 (26.7)	1.749 (1.162-2.633)	**0.007**
	Present	39 (55.7)	31 (44.3)		
Alcohol	Yes	132 (69.8)	57 (30.2)	1.051 (0.735-1.504)	0.785
	No	151 (70.6)	63 (29.4)		
Smoking	Yes	53 (71.6)	21 (28.4)	0.964 (0.602-1.544)	0.879
	No	230 (69.9)	99 (30.1)		
Echo LV EF (%)	<40	86 (64.7)	47 (35.3)	0.736 (0.488-1.111)	0.144
	>=40	126 (74.1)	44 (25.9)		
	Unknown	71 (71)	29 (29)		
Hb	Normal (>12g/dl)	131 (74.9)	44 (25.1)	1.326 (1.012-1.738)	**0.041**
	Mild (10-11.9g/dl)	129 (68.6)	59 (31.4)		
	Moderate/Severe Anemia (<=9.9g/dl)	23 (57.5)	17 (42.5)		
Creatinine Level				0.996 (0.990-1.002)	0.200
SBP				0.992 (0.985-1.000)	**0.051**

DBP				0.991 (0.977-1.005)	0.195
ECG Heart Rate				1.017 (1.012-1.023)	**<0.001**
ECG HR Category (bpm)	<90	216 (78.6)	59 (21.5)	1.879 (1.508-2.340)	**<0.001**
	90-110	51 (61.5)	32 (38.6)		
	>110	16 (35.6)	29 (64.4)		

Table 7. Multivariate Cox Hazard Ratio

Patient Data	HR (95% CI)	p-value
Reside	1.288 (0.821-2.021)	0.271
Education	0.841 (0.535-1.322)	0.453
Income Level	0.964 (0.631-1.471)	0.863
NYHA Function Class	1.275 (0.701-2.318)	0.426
AF	1.030 (0.629-1.687)	0.907
Echo LV EF (%)	0.910 (0.578-1.431)	0.682
ECG Heart Rate	1.015 (1.009-1.021)	**<0.001**
Hemoglobin	1.062 (0.760-1.485)	0.723
SBP	0.996 (0.987-1.005)	0.377

Table 8. Multivariate Cox Hazard Ratio (without collinear measures of heart failure)

Patient Data	HR (95% CI)	p-value
Reside	1.343 (0.912-1.979)	0.136
Education	0.813 (0.551-1.200)	0.297
Income Level	0.931 (0.645-1.345)	0.704
AF	1.541 (1.012-2.345)	**0.044**
Hemoglobin	1.217 (0.925-1.602)	0.161
SBP	0.995 (0.987-1.003)	0.23

Table 9. Stratified Analysis of HFpEF, HFrEF, Clinical Criteria Diagnosis and AF

Heart Failure Condition	**AF/History of AF**	**N**	**3-Month Mortality (% of Subgroup N)**
HFrEF – Echo Diagnosis	Yes	35	12 (34.3%)
	No	98	35 (35.7%)
HFpEF – Echo Diagnosis	Yes	27	13 (48.1%)
	No	143	29 (20.3%)
Clinical Criteria Alone	Yes	8	7 (87.5%)
	No	92	18 (19.6%)

Discussion

In this study, we sought to elucidate the prevalence and correlations of atrial fibrillation, as well as the significant 3-month mortality risk factors for heart failure patients in Tanzania. Atrial fibrillation was common among our cohort: nearly one out of six (17.4%) ambulatory adults had AF that was evident on a screening electrocardiogram. This high prevalence is similar to other reports from East Africa [19], and is likely a result of poor post-diagnosis linkage to care [23]. Of note, patients were more likely to be symptomatic if they were alcohol consumers, more elderly, or had longer heart failure duration. These are common risk factors for disruptions in cardiac electrophysiology, and in particular, heavy drinking is linked to sudden-onset supraventricular arrhythmias [24]. Unlike age and HF duration, decreasing alcohol consumption is a lifestyle adjustment that patients can readily make to reduce their risk of developing AF. In addition, we found that socioeconomic factors associated with poverty, such as less education and lower monthly income, were correlated with atrial fibrillation. Previous studies [19,25] cited these attributes as major barriers to outpatient care access, and potential contributors to poorer outcomes.

At the end of the three-month follow-up, almost half of the patients with atrial fibrillation died (44.3%). Participants with heart failure and concurrent AF experienced a 75% higher risk of dying in the first three months after enrollment compared to those with heart failure alone. This finding aligns with data from the Framingham Heart Study, which indicated a 1.5–1.9-fold increased mortality risk for patients with atrial fibrillation, further highlighting the need for early detection and treatment [26]. Anemia, a common condition in lower-income countries, was significantly linked to mortality in our study participants, a finding corroborated by other reports from Tanzania [19]. Lower systolic blood pressure was also associated with reduced survival,

which was possibly a consequence of severely diminished left ventricular function [27]. Finally, rural residence emerged as one of the significant predictors of mortality for HF outpatients. In developing regions, wealthier populations often congregate in urban areas, leading to significant disparities in healthcare access and physician-shortages in rural communities [28]. These barriers contribute to delayed diagnosis of existing conditions as well as severely limited treatment options, thus further exacerbating the disease burden.

In both univariate and multivariate models of mortality, elevated heart rate on ECG was the strongest independent predictor of death within three months [29–31]. Above the bounds of normal resting heart rate (>110 bpm), an increase of 20 beats per minute was associated with >65% increased risk of death; a finding which remained significant even after adjusting for the presence of atrial fibrillation and other possible confounders. Furthermore, nearly 40% of people with ECG heart rates between 90-110 (i.e. controlled by current guidelines) are dead at the end of the three-month study period. It is likely that higher heart rate signals heart failure exacerbation. Our data identify a heart rate of >125 beats per minute as extraordinarily high risk; therefore, this cutoff could help risk-stratify patients to appropriate care (i.e., admission vs. outpatient).

Atrial fibrillation is specifically associated with higher mortality in the participants with confirmed heart failure with preserved ejection fraction as well as those with heart failure diagnosed based on clinical criteria alone. In fact, participants with atrial fibrillation in these two groups had higher mortality than those participants with confirmed heart failure with reduced ejection fraction. One possible explanation may be that those with worsened heart function necessitate more physician visits. The greater contact with the healthcare system allows for more regular screenings, and any incidental findings to be noted and addressed in a timelier manner.

Despite the growing global burden of AF, electrocardiograms are not routinely conducted in many HF clinics in low-income communities (9). Barriers to AF screening include the relative paucity of medical devices such as electrocardiograms, supplies such as electrocardiogram paper, and available specialty physicians per capita (12,13,21). Encouragingly, our data imply that physical examination findings such as irregularly irregular pulse rate and pulse deficit are highly sensitive to detect patients with atrial fibrillation. Both measures can be ascertained with only palpation and a stethoscope and remain useful in clinical environments where electrocardiogram machines are not available.

There are limitations to this study. All participants were recruited from a single healthcare facility. Therefore, the heart failure patients included in this study may have different risk profiles than patients in other geographic locations and clinics. However, our study facility follows identical standards of care and the same protocols as other East African heart failure clinics, which promotes the generalizability of the results. Some aspects of the questionnaire, such as social history, rely on patient self-report, which may suffer from recall bias. Another study limitation is that we did not assess for rate-control medication adherence. This information could have helped differentiate deaths due to AF alone from those caused by poor drug adherence. While none of the subjects had a history of coronary artery disease, the diagnosis cannot be objectively ruled out from the existing clinical data. Additionally, because the focus of this study is the presence of atrial fibrillation and heart failure, the order in which the two conditions developed, and whether heart failure was due to non-ischemic or ischemic causes were not recorded.

Conclusions

Our data highlights the compounding morbidity and mortality of AF and HF in low- and middle-income countries. Atrial fibrillation is common, underdiagnosed and is associated with high mortality. In resource-limited settings, the presence of irregular heart rate and pulse deficit, along with affirmative responses to alcohol consumption and chronic heart failure should push atrial fibrillation forward on the differential. Heightened resting heart rate should alert physicians to possible HF-related mortality. Common predictors that emerged for both AF and death are associated with systemic impediments to healthcare access and disparities in fiscal and human resource distribution. Thus, in order to effectively alleviate cardiovascular disease burden in Tanzania and other medically underserved regions, in general, there needs to be wider availability of preventative care and targeted screening of atrial fibrillation, particularly among vulnerable populations in rural communities. Our findings also provide a reminder to clinicians in low-income countries that physical examination still matters, and that HF patients with high heart rate deserve more careful clinical scrutiny.

Figure Legends

Figure 1. Three-month mortality per categorical heart rate.

Figure 2. Kaplan-Meier Curve for three-month survival of adults with heart failure

List of Abbreviations

AF	Atrial Fibrillation
BP	Blood Pressure
DBP	Diastolic Blood Pressure

EF	Ejection Fraction
HF	Heart Failure
HIV	Human Immunodeficiency Virus
LV	Left Ventricle
SBP	Systolic Blood Pressure
SSA	Sub-Saharan Africa
TZS	Tanzanian Shilling

Declarations

Ethics approval and consent to participate

This study was approved by the CUHAS-BMC joint Ethics and Review Committee (CREC408/2019). All participants provided written informed consent before enrollment. Research was performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

The datasets and statistical code are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

EA & YC: study design, investigation, formal analysis, and original draft preparation, EM: investigation and review & editing, AM: study design and review & editing, GAK & JRK: review & editing, FK & RNP: study design, supervision, and review & editing. All authors read and approved the final manuscript.

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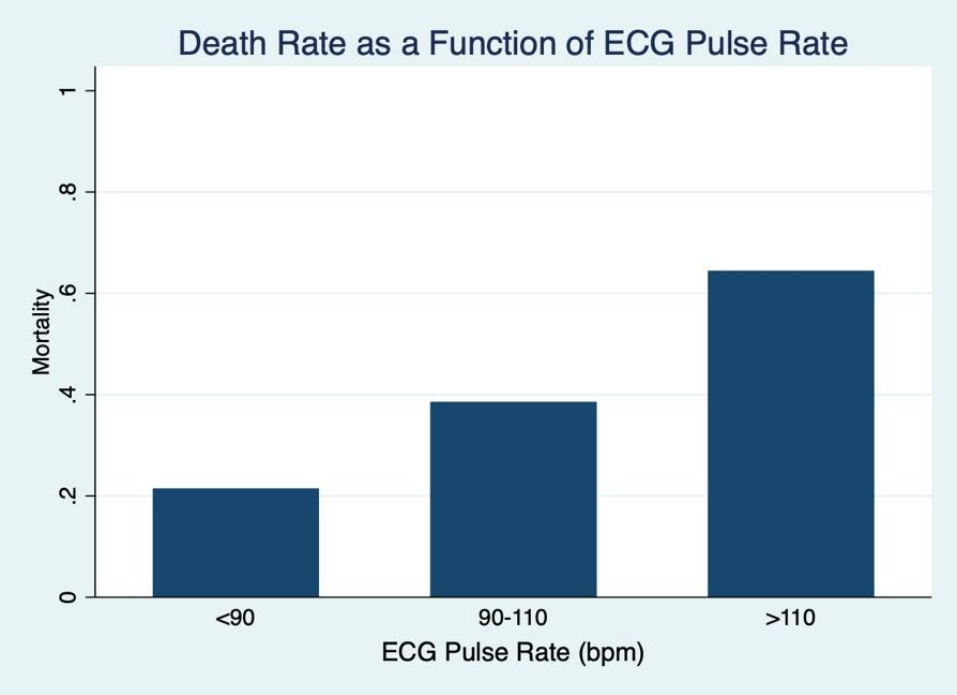

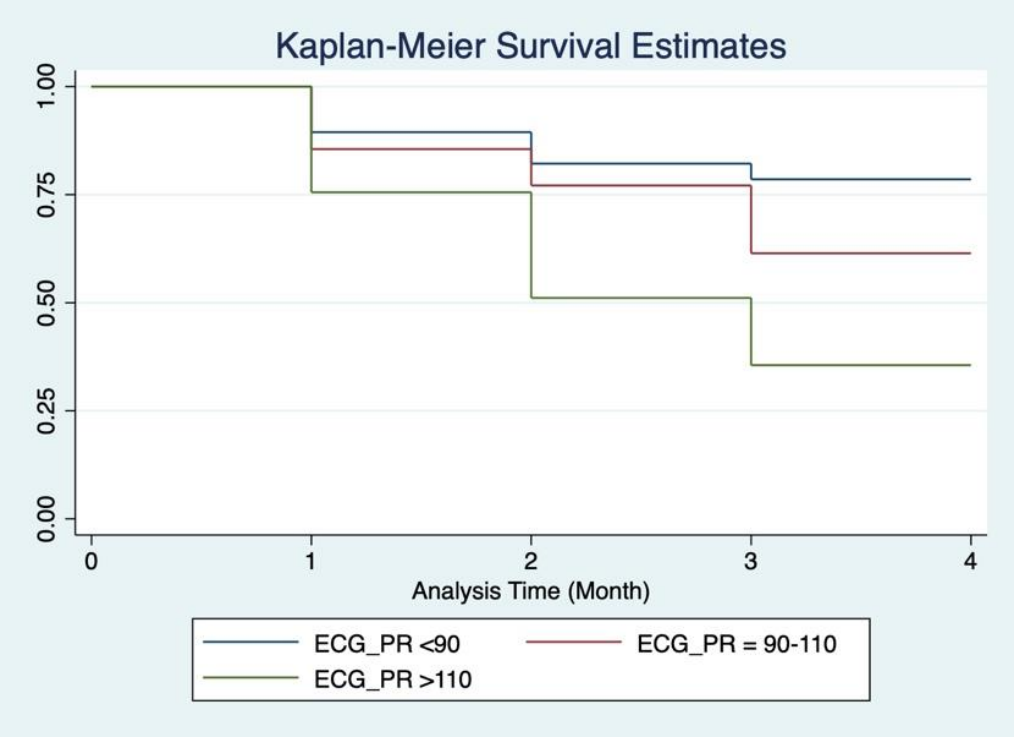

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	18
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	8-10
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-15
		(*b*) Report category boundaries when continuous variables were categorized	10-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Atrial Fibrillation and Mortality in Outpatients with Heart Failure in Tanzania: A prospective cohort study

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Atrial Fibrillation and Mortality in Outpatients with Heart Failure in Tanzania: A prospective cohort study

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Abstract

Objective: In recent years, the prevalence and mortality of heart failure (HF) and other associated cardiovascular diseases have doubled in Sub-Saharan Africa (SSA). Studies in high-income countries indicate that HF with concurrent atrial fibrillation (AF) is linked to increased mortality. Our objective was to determine the incidence and clinical outcomes of AF among heart failure patients in SSA.

Design: A prospective cohort study using data collected between 10/2018-05/2020

Setting: Outpatient clinic at a tertiary hospital in Mwanza, Tanzania

Participants: 303 adult participants (aged ≥ 18 years) with HF as defined by the ESC guidelines (2016) and 100 adults with HF as defined by clinical criteria alone were enrolled into the study. Patients with comorbid medical condition that had prognosis of <3 months (i.e. advance solid tumors, advance hematological malignancies) were excluded.

Methods: Participants were screened for atrial fibrillation, and their medical history, physical exams, and sociodemographic information were obtained. Multivariable logistic regression models were used to examine factors associated with AF incidence. Cox regression models were used to analyze 3-month mortality and its associated risk factors.

Results: We enrolled 403 participants with HF (mean age 60±19 years, 234 (58%) female). The AF prevalence was 17%. In multivariable models, factors associated with AF were low income, alcohol consumption and longer duration of heart failure. At the end of the three-month follow-up, 120/403 (30%) participants died, including 44% (31/70) of those with AF. Higher heart rate on ECG, more severe New York Heart Association HF class, rural residence and anemia were significantly correlated with mortality.

Conclusion: Atrial fibrillation is common, underdiagnosed and associated with significant mortality among outpatients with HF in Tanzania (HR:1.749, 95% CI:1.162-2.633, p=0.007). Our findings additionally identify tachycardia (>110 bpm, HR:1.879, 95% CI:1.508-2.340, p<0.001) as an easily measurable, high-impact physical exam finding for adverse outcomes in HF patients.

Strengths and limitations of this study

- This study is one of the few to examine the prevalence and mortality of atrial fibrillation among outpatients with heart failure in Sub-Saharan Africa.
- This study focuses on readily accessible physical exam measures, demographics, socioeconomic and lifestyle attributes. They are inexpensive to acquire and are well adapted for risk stratification in resource limited settings.
- As a cohort study, no causal relationships can be established between the risk factors and mortality. Questionnaire data on social and personal history are contingent on patient report accuracy. Given the limitations in medical equipment, concurrent coronary artery disease, the order in which atrial fibrillation and heart failure developed, and whether heart failure was due to non-ischemic or ischemic causes were not established.
- All participants were recruited from a single healthcare facility, which may qualify the generalizability of the findings.

Introduction

As global life expectancy increases, the incidence of heart failure (HF) has risen substantially [1]. Approximately 26 million people live with heart failure worldwide [2], with low- and middle-income countries bearing the greatest burden [1,3]. From 1990 to 2013, cardiovascular disease-related deaths in Africa increased two-fold, and accounted for roughly 38% of all non-communicable disease mortalities [1,4]. Within Sub-Saharan Africa (SSA), previous studies have indicated an "epidemiological transition," whereby chronic, non-communicable diseases are gradually overtaking infectious diseases in prevalence [1,3]. In particular, heart failure constitutes roughly 9.4–42.5% of all hospital admissions and 25.6–30.0% of the cardiology clinic visits at institutions across Africa [5]. HF has a higher one-year post-hospital discharge mortality than all other diagnoses [6]. In addition to patient-level burden, HF poses significant economic strain secondary to recurrent hospitalizations, lost productivity, and pharmacologic costs [5,7].

Atrial fibrillation (AF) incidence is also escalating rapidly among new cardiovascular diagnoses [8]. Between 1990-2010, the annual deaths caused by AF grew by 2 and 1.9 fold in men and women, respectively [9]. While AF and HF are known to share common cardiometabolic risk factors, growing evidence suggests that the presence of one may precipitate the severity of the other. Compared to sinus-rhythm, comorbid AF is associated with higher all-cause mortality and hospitalization rates in patients with heart failure [10]. Furthermore, AF-related atrial remodeling, altered ventricular hemodynamics and arrhythmia-induced myopathy are linked to further heart failure progression [11].

Despite the synergistic comorbidity of AF and HF, little is known about the prevalence of atrial fibrillation among outpatients with heart failure within Sub-Saharan Africa, or its impact

on clinical outcomes. Therefore, we conducted a prospective cohort study to elucidate the prevalence, correlates and mortality associated with this patient population in Tanzania.

Methods

Overview

This clinic-based prospective cohort study involved 403 patients who were enrolled in a registry of HF. This registry was created as part of a more extensive hospital quality improvement program for heart failure patients. Data collection and follow-up spanned from October 2018 to May 2020.

Setting and Participants

The study was conducted at the outpatient clinic of Bugando Medical Center (BMC), a zonal hospital for the Lake Victoria Zone in northwest Tanzania. BMC serves a population of over 14 million with a 950-bed capacity. In each month, BMC provides care for approximately 400 patients with HF, with an average of 100 patients seen weekly. BMC is similar to other facilities that provide care for heart failure in Tanzania and Uganda [12,13].

All patients attending the outpatient clinic with a diagnosis of heart failure were screened between October and December of 2019. Patients ≥ 18 years of age and seeking heart failure care were recruited serially until the target sample size was attained (n ≥ 331). Patients with comorbid medical conditions with a prognosis of <3 months (i.e. advanced malignancy) were excluded from the study. Of the 403 enrolled patients, 303 had the diagnosis of HF objectively confirmed according to the European Society of Cardiology (ESC) 2016 guidelines [14], where 133 had heart failure with reduced ejection fraction (HFrEF) and 170 had heart failure with preserved ejection fraction (HFpEF). For the remaining 100 patients, the diagnosis of HF was

made according to the Framingham criteria, and in the absence of another primary diagnosis responsible for volume overload [15].

Study Procedures

Consented participants were interviewed using a standard questionnaire that collected clinical and demographic information such as age, sex, residence, duration of heart failure, and New York Heart Association (NYHA) functional classification. Participants were also evaluated for palpitations, shortness of breath, syncope or presyncope, exercise intolerance, chest pain and fatigue. Physical examination was performed on every participant. Blood pressure measurements were taken from the right arm using an automated blood pressure monitor after subjects had rested for at least 5 minutes. Pulse rate was determined, and noted for irregularity, regularity and amplitude, then compared to the heart rate for pulse deficit.

Height was measured using a rigid ruler attached to a wall and rounded to the nearest 0.5cm. Weight was measured without shoes, with patients wearing light clothing and recorded to the nearest 500g using the DETECTO scale. Body Mass Index (BMI) was calculated using the Quetelet equation [16] and categorized using the WHO Classification Scale, with underweight BMI classified as <18.5 kg/m^2, normal BMI as 18.5-24.9 kg/m^2, overweight BMI as 25-29.9 kg/m^2, and obese BMI as $\geq$ 30kg/m^2. Additionally, electronic medical records were reviewed to extract blood hemoglobin and serum creatinine values.

Study participants were then subjected to a resting 12-lead electrocardiography. The heart rate on ECG was recorded for all subjects. Tracings with irregular QRS Complexes and absent discrete P waves were categorized as AF, in accordance with the ESC 2016 criteria [17]. All diagnoses of atrial fibrillation were confirmed by a staff cardiologist. Patients with AF had their results communicated to the attending physician and were treated according to protocol.

Follow Up and Outcome Determination

At least three contact phone numbers were obtained at the time of enrollment, including one from the patient and two from friends and relatives. All participants were followed for a period of three months, with none lost to follow up. The research team interviewed the participants during their regularly scheduled visits on a monthly basis. Phone calls were made to those not presenting to clinic. During these interviews, information about their recent medical updates or hospitalizations were collected. If the participant could not be reached, the designated alternate contact was called to determine the patient's vital status. Mortality was ascertained via phone call to each individual family. The families confirmed the death was cardiac in origin or related to their cardiac diagnosis (HF/cardio-embolic stroke/cardio-renal syndrome). Additionally, for those who died during hospitalization, care was taken to confirm with the family member that the original admission was due to cardiac etiologies.

Statistical Analysis

By the difference in proportions calculation, a minimum sample size of 331 patients was needed to provide at least 80% power to detect the difference in mortality rates between patients with AF and those without (two-sided test with a 5% level of significance) [18]. Our pre-test estimation of AF prevalence was 16% [19,20]. For the secondary analyses, this sample size was expected to provide at least 10 observations (i.e., number of patients with AF or death events) per predictor in the final models to allow good estimates [21,22]. Stata 16.1 was the statistical analysis software used in this study. Unknowns were recorded as null prior to analysis. For tabulation purposes, we reported count for discrete variables, and mean/standard deviation or median/interquartile range for continuous variables. Logistic regression was used to determine which baseline features were most strongly correlated with atrial fibrillation, and Cox

Proportional Hazard Analysis was used to evaluate their associations with mortality. The primary outcome of interest was death within 3 months of the index visit. A p-value < 0.05 was considered statistically significant.

Patient and Public Involvement Statement

No patients involved in the design of this study.

Results

Baseline Characteristics

Baseline characteristics of the patients are described in **Table 1**. The cohort included 234 females (58.1%) and 169 males (41.9%), with a mean age of 60±19 years. Nearly one-half (186, 46.2%) were overweight or obese (≥ 25kg/m^2). Among the participants, 202 (50.1%) had health insurance. One hundred and fifty-four (154, 38.2%) self-identified as low income (less than 500,000 TZS/month). Two hundred and thirty-four participants lived in rural settings (234, 58.1%) and 169 (41.9%) lived in urban environments. One hundred and nine participants (109, 27.1%) did not receive formal education, 214 (53.1%) completed primary school, and 80 (19.9%) obtained secondary or higher degrees. The median heart failure duration in this cohort was four years (IQR 3-9), and 180 (44.7%) noted a family history of heart failure. The majority, 320 (79.4%), were diagnosed with advanced HF (III/IV NYHA class). The most predominant comorbidity was hypertension, with 323 cases (80.2%). Ninety-seven (97, 24.1%) had concurrent diabetes mellitus. Nearly half of the participants (189, 46.9%) reported a social history positive for alcohol consumption, and 77 (19.1%) had a smoking history.

Table 1. Social, Demographic, and Past Medical History of Enrolled Patients

Patient Data (n=403)	Subclass	Number (n=403)

Sex	Female	234 (58.1%)
Age	Mean (SD)	60.2 (18.8)
Education	Informal	109 (27.1%)
	Primary	214 (53.1%)
	Secondary or Higher	80 (19.9%)
Reside	Urban	169 (41.9%)
	Rural	234 (58.1%)
Health Insurance	Yes	202 (50.1%)
Income Level	Low	154 (38.2%)
	Medium/High	249 (61.8%)
BMI Categories	Underweight	26 (6.5%)
	Normal	191 (47.4%)
	Overweight	120 (29.8%)
	Obese/Severely Obese	66 (16.4%)
History of Hypertension	Yes	323 (80.2%)
Duration of Heart Failure (Years) - Median (IQR)		4 (3-9)
Family History of Heart Failure	Yes	180 (44.7%)
NYHA Function Class	II	83 (20.6%)
	III	317 (78.7%)
	IV	3 (0.7%)
Diabetes Mellitus	Yes	97 (24.1%)
HIV	Positive	21 (5.2%)
Atrial Fibrillation	Present (ECG confirmed AF)	70 (17.4%)
Alcohol	Yes	189 (46.9%)
(Average Units of Alcohol/Day)	Median (IQR)	0 (0-10)
	Range	0-60
Cigarette Smoking	Yes	77 (19.1%)
Echo LV EF (%)	<40	133 (33.0%)
	>=40	170 (42.2%)
	Unknown	100 (24.8%)
Hemoglobin	Normal (>12g/dl)	175 (43.4%)
	Mild Anemia (10-11.9g/dl)	188 (46.7%)
	Moderate/Severe Anemia (<=9.9g/dl)	38 (9.9%)
Rheumatic Heart Disease	Positive History & AF	6 (1.5%)
	Positive History & No AF	18 (4.5%)
	Negative History & AF	64 (15.8%)
	Negative History & No AF	315 (78.2%)
Creatinine Level - Median (IQR)		94 (77-169)
Systolic Blood Pressure - Median (IQR)		122 (106-142)

Diastolic Blood Pressure - Median (IQR)		70 (66-82)
Pulse Rhythm	Regular	300 (74.4%)
	Irregular (diagnosed by clinical exam)	103 (25.6%)
Heart Rate (bpm) - Median (IQR)		79 (71-91)
Pulse Deficit (bpm) - Median (IQR)		6 (3-11)
ECG Heart Rate (bpm) - Median (IQR)		79 (67-94)
ECG Rhythm	Regular	304 (75.4%)
	Irregular	99 (24.6%)
Goal Directed Therapy	Beta-Blocker	254 (63.0%)
	ACE-inhibitor	188 (46.7%)
	Diuretic	300 (74.4%)
	Nitrates	39 (9.6%)
	Digitalis	58 (14.4%)
	ARB	156 (38.7%)
	Calcium Channel Blocker	48
	Vasodilator	35

Prevalence of Atrial Fibrillation

Of the 403 study participants with heart failure, 70 (17.4%) participants had atrial fibrillation detected on screening electrocardiogram. Of these, 29/70 (41.4%) had previously been diagnosed with atrial fibrillation and 41/70 (58.6%) were new diagnoses. Twenty-five percent (6/24) of participants with a history RHD had atrial fibrillation (**Table 1**).

Sociodemographic Correlates of Atrial Fibrillation

In a univariable logistic regression model (**Table 2**), advanced age, low income, informal education, alcohol consumption, and longer heart failure duration were significantly associated with atrial fibrillation. In the multivariable model (**Table 3**), lower income (high income aOR 0.5, 95% CI 0.3-0.9), duration of heart failure (aOR 1.05, 95% CI 1.0-1.1), and alcohol consumption (aOR 2.1, 95% CI 1.2-3.8) were associated with atrial fibrillation.

Table 2. Univariate logistic regression for sociodemographic, clinical history and anthropomorphic correlates associated with atrial fibrillation

Screening Characteristics	Subclass	AF (%)	No AF (%)	OR (95% CI)	p-value
Sex	Male	31 (18.3)	138 (81.7)	1.000	
	Female	39 (16.7)	195 (83.3)	0.890 (0.530-1.497)	0.661
Age	Mean±Std. Dev.	66.4±19.0	58.8±18.5	1.025 (1.009-1.041)	**0.002**
Education	Informal	27 (24.8)	82 (75.2)	1.000	
	Formal	43 (14.6)	251 (85.4)	0.520 (0.303-0.895)	**0.018**
Income	Low	34 (22.1)	120 (77.9)	1.000	
	Medium/High	36 (14.5)	213 (85.5)	0.597 (0.355-1.003)	**0.051**
Reside	Urban	26 (15.4)	143 (84.6)	1.000	
	Rural	44 (18.8)	190 (81.2)	1.274 (0.749-2.166)	0.372
Health Insurance	Yes	31 (15.4)	171 (84.7)	1.000	
	No	39 (19.4)	162 (80.6)	0.753 (0.448-1.264)	0.283
BMI (kg/m^2)	Underweight	4 (15.4)	22 (84.6)	1.000	
	Normal	43 (22.5)	148 (77.5)	1.598 (0.522-4.889)	0.411
	Overweight	15 (12.5)	105 (87.5)	0.786 (0.238-2.595)	0.692
	Obese	8 (12.1)	58 (87.9)	0.759 (0.207-2.774)	0.676
Duration of Heart Failure (Years) - Median (IQR)		6.5 [3-13]	4 [2-7]	1.076 (1.034-1.076)	**<0.001**
NYHA Function Class	I/II	9 (10.8)	74 (89.2)	1.000	
	III/IV	61 (19.1)	259 (80.9)	1.937 (0.918-4.083)	**0.083**
Diabetes Mellitus	No	55 (18.0)	251 (82.0)	1.000	
	Yes	15 (15.5)	82 (84.5)	0.835 (0.448-1.556)	0.57
Alcohol	No	26 (12.2)	188 (87.8)	1.000	
	Yes	44 (23.3)	145 (76.7)	2.194 (1.290-3.732)	**0.004**
Cigarette Smoking	No	53 (16.3)	273 (83.7)	1.000	
	Yes	17 (22.1)	60 (77.9)	1.459 (0.790-2.696)	0.227

Table 3. Multivariate logistic regression of demographic factors associated with atrial fibrillation

Variable	aOR (95% CI)	p-value
Age	1.006 (0.987-1.025)	0.564
Education (Formal)	0.659 (0.354-1.223)	0.186
Income (Med/High)	0.531 (0.306-0.920)	**0.024**
Duration of Heart Failure (Years)	1.049 (1.000-1.100)	**0.050**
NYHA (III/IV)	1.347 (0.612-2.962)	0.459

Alcohol Consumption	2.083 (1.150-3.771)	**0.015**

Clinical and Physical Exam Correlates of Atrial Fibrillation

By univariate logistic regression (**Table 4**), irregular pulse rhythm, higher baseline heart rate, and greater pulse deficit were linked to AF prevalence. Conversely, higher systolic blood pressure at baseline was associated with a decreased risk of having atrial fibrillation. With respect to physical exam findings, in the multivariate analysis (**Table 5**), irregular pulse rhythm (OR 38.0, 95% CI 15.3-94.4) and pulse deficit (OR 1.1, 95% CI 1.0-1.2) are strongly suggestive of AF presence.

Table 4: Univariate logistic regression for physical exam correlates of atrial fibrillation

Screening Characteristics	Subclass	AF (%)	No AF (%)	OR (95% CI)	p-value
Systolic Blood Pressure - Median (IQR)		117 [97-134]	124 [107-145]	0.985 (0.974-0.996)	**0.009**
Diastolic Blood Pressure - Median (IQR)		69 [64-82]	70 [67-82]	0.996 (0.977-1.016)	0.699
Pulse Rhythm	Regular	7 (2.3)	293 (97.7)	1.000	
	Irregular	63 (61.2)	40 (38.8)	**65.925 (**28.237-153.915**)**	**<0.001**
Heart Rate (bpm) - Median (IQR)		85 [74-102]	78 [70-89]	1.026 (1.013-1.040)	**<0.001**
Pulse Deficit (bpm) - Median (IQR)		11 [10-13]	5 [3-8]	1.328 (1.233-1.431)	**<0.001**

Table 5. Multivariate logistic regression for screening factors associated with atrial fibrillation

Variable	OR (95% CI)	p-value
SBP	0.987 (0.967-1.007)	0.186
DBP	1.019 (0.988-1.051)	0.240
Pulse Rhythm (Irregular)	38.001 (15.292-94.436)	**<0.001**

Heart Rate	1.003 (0.984-1.022)	0.778
Pulse Deficit	1.110 (1.018-1.211)	**0.018**

Three Month Mortality

At the end of the three-month follow-up, 120 (29.8%) participants died, including 44.3% and 26.7% of those with and without AF, respectively. Among the clinical variables (**Table 6**), the factor most significantly associated with three-month mortality was higher heart rate on ECG (Hazard Ratio (HR) 1.88, 95% CI 1.508-2.340). Other noteworthy risk factors for death include atrial fibrillation (HR 1.75, 95% CI 1.162-2.633), worse heart function (III/IV) on the NYHA scale (HR 1.64, 95% CI 0.981-2.738), rural residence (HR 1.47, 95% CI 1.006-2.150), and anemia (HR 1.33, 95% CI 1.012-1.738). Conversely, higher education, higher ejection fraction (≥40%) and baseline systolic blood pressure within the normal range were associated with decreased hazard ratio. By multivariate analysis (**Table 7**), increased ECG heart rate remained significantly associated with mortality. Collinearity was noted between AF and other measures of heart failure, and the singular inclusion of AF displayed statistically significant mortality hazards when other diluting factors were omitted (**Table 8**). On stratified analysis, death rate increased significantly with each increment in ECG heart rate, with a three-month mortality of 21.5% for those with HR below 90 bpm, 38.6% for those between 90-110 bpm and 64.4% for patients with >110 bpm at baseline (**Figure 1&2**). Additional analyses comparing the AF prevalence and three-month mortality data for participants with echocardiograph confirmed heart failure (according to the ESC criteria) against those participants diagnosed based on clinical criteria alone was conducted. In the HFrEF cohort, death rate at 3-months was similar for those with AF and those without. For both HFpEF and clinical criteria diagnosis, there was a marked increase in the 3-month mortality in those with AF (**Table 9**).

274 **Table 6. Univariate Cox Hazard Model with death as outcome**

Patient Data (n=403)	Subclass	No Death (%)	Death (%)	HR (95% CI)	P>|z|
Sex	Female	157 (67.1)	77 (32.9)	1.304 (0.898-1.894)	0.163
	Male	126 (74.6)	43 (25.4)		
Age				1.000	0.998
Reside	Urban	129 (76.3)	40 (23.7)	1.471 (1.006-2.150)	**0.046**
	Rural	154 (65.8)	80 (34.2)		
Education	Informal	68 (62.4)	41 (37.6)	0.689 (0.472-1.004)	**0.053**
	Formal	215 (73.1)	79 (26.9)		
Income Level	Low	103 (66.9)	51 (33.1)	0.827 (0.576-1.188)	0.303
	Medium/High	180 (72.3)	69 (27.7)		
Health Insurance	Yes	147 (72.8)	55 (27.2)	1.183 (0.826-1.694)	0.359
	No	136 (67.7)	65 (32.3)		
BMI Categories	Underweight/Normal	148 (68.2)	69 (31.8)	0.876 (0.610-1.258)	0.474
	Overweight/Obese	135 (72.6)	51 (27.4)		
Hypertension	Yes	227 (70.3)	96 (29.7)	0.982 (0.628-1.536)	0.936
	No	56 (70.0)	24 (30.0)		
HF Duration (Years)				1.282 (0.767-2.141)	0.343
NYHA	I/II	66 (79.5)	17 (20.5)	1.639 (0.981-2.738)	**0.059**
	III/IV	217 (67.8)	103 (32.2)		
Diabetes	Yes	70 (72.2)	27 (27.8)	0.903 (0.588-1.386)	0.641
	No	213 (69.6)	93 (30.4)		
AF	Absent	244 (73.3)	89 (26.7)	1.749 (1.162-2.633)	**0.007**
	Present	39 (55.7)	31 (44.3)		
Alcohol	Yes	132 (69.8)	57 (30.2)	1.051 (0.735-1.504)	0.785
	No	151 (70.6)	63 (29.4)		
Smoking	Yes	53 (71.6)	21 (28.4)	0.964 (0.602-1.544)	0.879
	No	230 (69.9)	99 (30.1)		
Echo LV EF (%)	<40	86 (64.7)	47 (35.3)	0.736 (0.488-1.111)	0.144
	>=40	126 (74.1)	44 (25.9)		
	Unknown	71 (71)	29 (29)		
Hb	Normal (>12g/dl)	131 (74.9)	44 (25.1)	1.326 (1.012-1.738)	**0.041**
	Mild (10-11.9g/dl)	129 (68.6)	59 (31.4)		
	Moderate/Severe Anemia (<=9.9g/dl)	23 (57.5)	17 (42.5)		
Creatinine Level				0.996 (0.990-1.002)	0.200
SBP				0.992 (0.985-1.000)	**0.051**

DBP				0.991 (0.977-1.005)	0.195
ECG Heart Rate				1.017 (1.012-1.023)	**<0.001**
ECG HR Category (bpm)	<90	216 (78.6)	59 (21.5)	1.879 (1.508-2.340)	**<0.001**
	90-110	51 (61.5)	32 (38.6)		
	>110	16 (35.6)	29 (64.4)		

Table 7. Multivariate Cox Hazard Ratio

Patient Data	HR (95% CI)	p-value
Reside	1.288 (0.821-2.021)	0.271
Education	0.841 (0.535-1.322)	0.453
Income Level	0.964 (0.631-1.471)	0.863
NYHA Function Class	1.275 (0.701-2.318)	0.426
AF	1.030 (0.629-1.687)	0.907
Echo LV EF (%)	0.910 (0.578-1.431)	0.682
ECG Heart Rate	1.015 (1.009-1.021)	**<0.001**
Hemoglobin	1.062 (0.760-1.485)	0.723
SBP	0.996 (0.987-1.005)	0.377

Table 8. Multivariate Cox Hazard Ratio (without collinear measures of heart failure)

Patient Data	HR (95% CI)	p-value
Reside	1.343 (0.912-1.979)	0.136
Education	0.813 (0.551-1.200)	0.297
Income Level	0.931 (0.645-1.345)	0.704
AF	1.541 (1.012-2.345)	**0.044**
Hemoglobin	1.217 (0.925-1.602)	0.161
SBP	0.995 (0.987-1.003)	0.23

Table 9. Stratified Analysis of HFpEF, HFrEF, Clinical Criteria Diagnosis and AF

Heart Failure Condition	**AF/History of AF**	**N**	**3-Month Mortality (% of Subgroup N)**
HFrEF – Echo Diagnosis	Yes	35	12 (34.3%)
	No	98	35 (35.7%)
HFpEF – Echo Diagnosis	Yes	27	13 (48.1%)
	No	143	29 (20.3%)
Clinical Criteria Alone	Yes	8	7 (87.5%)
	No	92	18 (19.6%)

Discussion

In this study, we sought to elucidate the prevalence and correlations of atrial fibrillation, as well as the significant 3-month mortality risk factors for heart failure patients in Tanzania. Atrial fibrillation was common among our cohort: nearly one out of six (17.4%) ambulatory adults had AF that was evident on a screening electrocardiogram. This high prevalence is similar to other reports from East Africa [19], and is likely a result of poor post-diagnosis linkage to care [23]. Of note, patients were more likely to be symptomatic if they were alcohol consumers, more elderly, or had longer heart failure duration. These are common risk factors for disruptions in cardiac electrophysiology, and in particular, heavy drinking is linked to sudden-onset supraventricular arrhythmias [24]. Unlike age and HF duration, decreasing alcohol consumption is a lifestyle adjustment that patients can readily make to reduce their risk of developing AF. In addition, we found that socioeconomic factors associated with poverty, such as less education and lower monthly income, were correlated with atrial fibrillation. Previous studies [19,25] cited these attributes as major barriers to outpatient care access, and potential contributors to poorer outcomes.

At the end of the three-month follow-up, almost half of the patients with atrial fibrillation died (44.3%). Participants with heart failure and concurrent AF experienced a 75% higher risk of dying in the first three months after enrollment compared to those with heart failure alone. This finding aligns with data from the Framingham Heart Study, which indicated a 1.5–1.9-fold increased mortality risk for patients with atrial fibrillation, further highlighting the need for early detection and treatment [26]. Anemia, a common condition in lower-income countries, was significantly linked to mortality in our study participants, a finding corroborated by other reports from Tanzania [19]. Lower systolic blood pressure was also associated with reduced survival,

which was possibly a consequence of severely diminished left ventricular function [27]. Finally, rural residence emerged as one of the significant predictors of mortality for HF outpatients. In developing regions, wealthier populations often congregate in urban areas, leading to significant disparities in healthcare access and physician-shortages in rural communities [28]. These barriers contribute to delayed diagnosis of existing conditions as well as severely limited treatment options, thus further exacerbating the disease burden.

In both univariate and multivariate models of mortality, elevated heart rate on ECG was the strongest independent predictor of death within three months [29–31]. Above the bounds of normal resting heart rate (>110 bpm), an increase of 20 beats per minute was associated with >65% increased risk of death; a finding which remained significant even after adjusting for the presence of atrial fibrillation and other possible confounders. Furthermore, nearly 40% of people with ECG heart rates between 90-110 (i.e. controlled by current guidelines) are dead at the end of the three-month study period. It is likely that higher heart rate signals heart failure exacerbation. Our data identify a heart rate of >125 beats per minute as extraordinarily high risk; therefore, this cutoff could help risk-stratify patients to appropriate care (i.e., admission vs. outpatient).

Atrial fibrillation is specifically associated with higher mortality in the participants with confirmed heart failure with preserved ejection fraction as well as those with heart failure diagnosed based on clinical criteria alone. In fact, participants with atrial fibrillation in these two groups had higher mortality than those participants with confirmed heart failure with reduced ejection fraction. One possible explanation may be that those with worsened heart function necessitate more physician visits. The greater contact with the healthcare system allows for more regular screenings, and any incidental findings to be noted and addressed in a timelier manner.

Despite the growing global burden of AF, electrocardiograms are not routinely conducted in many HF clinics in low-income communities (9). Barriers to AF screening include the relative paucity of medical devices such as electrocardiograms, supplies such as electrocardiogram paper, and available specialty physicians per capita (12,13,21). Encouragingly, our data imply that physical examination findings such as irregularly irregular pulse rate and pulse deficit are highly sensitive to detect patients with atrial fibrillation. Both measures can be ascertained with only palpation and a stethoscope and remain useful in clinical environments where electrocardiogram machines are not available.

There are limitations to this study. All participants were recruited from a single healthcare facility. Therefore, the heart failure patients included in this study may have different risk profiles than patients in other geographic locations and clinics. However, our study facility follows identical standards of care and the same protocols as other East African heart failure clinics, which promotes the generalizability of the results. Some aspects of the questionnaire, such as social history, rely on patient self-report, which may suffer from recall bias. Another study limitation is that we did not assess for rate-control medication adherence. This information could have helped differentiate deaths due to AF alone from those caused by poor drug adherence. While none of the subjects had a history of coronary artery disease, the diagnosis cannot be objectively ruled out from the existing clinical data. Additionally, because the focus of this study is the presence of atrial fibrillation and heart failure, the order in which the two conditions developed, and whether heart failure was due to non-ischemic or ischemic causes were not recorded.

Conclusions

Our data highlights the compounding morbidity and mortality of AF and HF in low- and middle-income countries. Atrial fibrillation is common, underdiagnosed and is associated with high mortality. In resource-limited settings, the presence of irregular heart rate and pulse deficit, along with affirmative responses to alcohol consumption and chronic heart failure should push atrial fibrillation forward on the differential. Heightened resting heart rate should alert physicians to possible HF-related mortality. Common predictors that emerged for both AF and death are associated with systemic impediments to healthcare access and disparities in fiscal and human resource distribution. Thus, in order to effectively alleviate cardiovascular disease burden in Tanzania and other medically underserved regions, in general, there needs to be wider availability of preventative care and targeted screening of atrial fibrillation, particularly among vulnerable populations in rural communities. Our findings also provide a reminder to clinicians in low-income countries that physical examination still matters, and that HF patients with high heart rate deserve more careful clinical scrutiny.

Figure Legends

Figure 1. Three-month mortality per categorical heart rate.

Figure 2. Kaplan-Meier Curve for three-month survival of adults with heart failure

List of Abbreviations

AF	Atrial Fibrillation
BP	Blood Pressure
DBP	Diastolic Blood Pressure

EF	Ejection Fraction
HF	Heart Failure
HIV	Human Immunodeficiency Virus
LV	Left Ventricle
SBP	Systolic Blood Pressure
SSA	Sub-Saharan Africa
TZS	Tanzanian Shilling

Declarations

Ethics approval and consent to participate

This study was approved by the CUHAS-BMC joint Ethics and Review Committee (CREC408/2019). All participants provided written informed consent before enrollment. Research was performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

The datasets and statistical code are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

EA & YC: study design, investigation, formal analysis, and original draft preparation, EM: investigation and review & editing, AM: study design and review & editing, GAK & JRK: review & editing, FK & RNP: study design, supervision, and review & editing. All authors read and approved the final manuscript.

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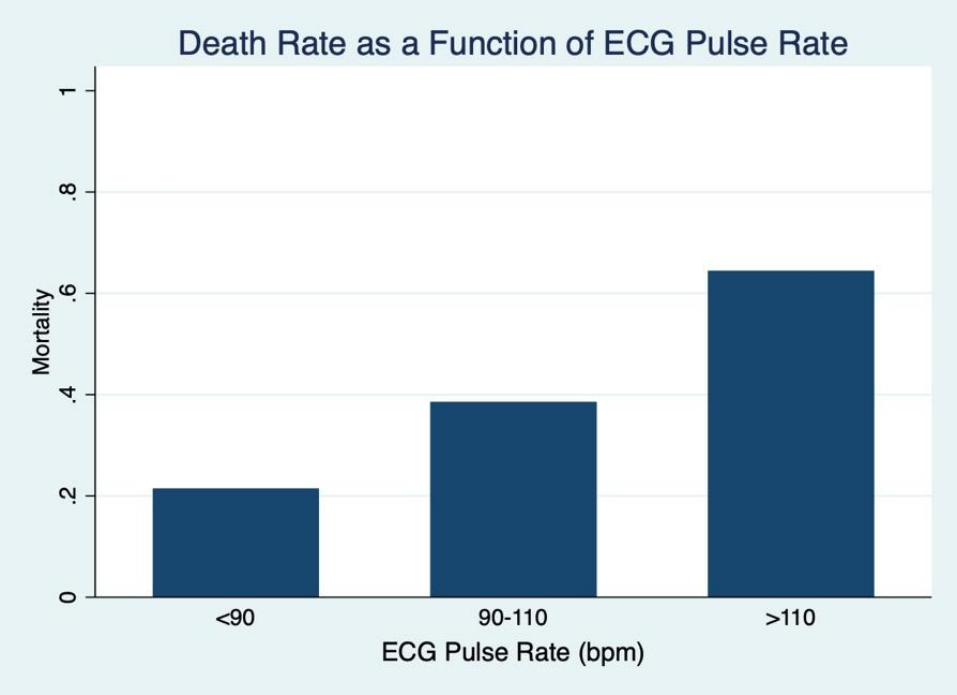

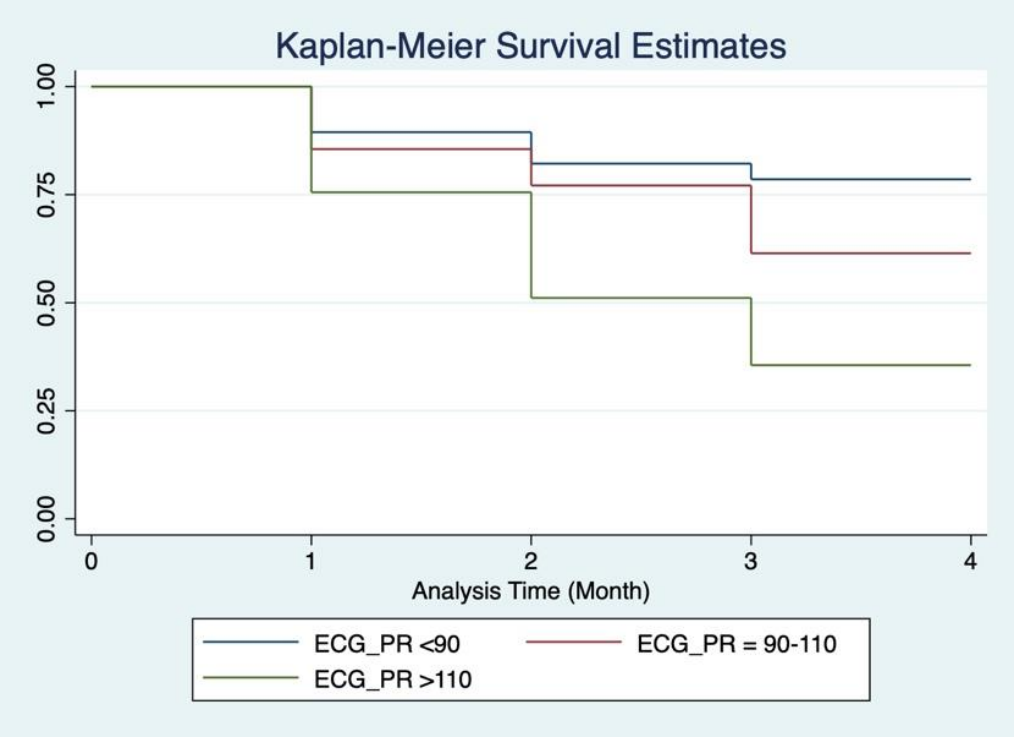

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	18
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	8-10
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-15
		(*b*) Report category boundaries when continuous variables were categorized	10-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.