Physician- and Patient-related Barriers to Diagnosis and Care of Acute Coronary Syndrome in Tanzania

by

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Thesis submitted in partial fulfillment of
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ABSTRACT

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Abstract

Background: Acute coronary syndrome (ACS) is a rare diagnosis in sub-Saharan Africa, but patient and physician-related factors that may contribute to under-diagnosis are poorly understood. Methods: A community survey was performed of adults in northern Tanzania, and respondents were asked to describe symptoms of ACS, personal healthcare-seeking preferences for chest pain, and perceptions of self-risk. A retrospective chart review was conducted at a referral hospital in northern Tanzania to determine rates of various diagnoses among admitted adults over a six-month period. A prospective observational study was conducted in the emergency department, and diagnostic workups, treatments, and diagnoses for adults with chest pain or shortness of breath were recorded. Results: Of 718 survey respondents, 277 (38.6%) stated they would present to a hospital for chest pain and 115 (16.0%) were able to identify a conventional ACS symptom. Retrospectively, ACS accounted for 9 (0.3%) adult admissions, whereas heart failure accounted for 294 (12.2%) admissions. Prospectively, among 339 adults presenting with chest pain or shortness of breath, 170 (50.1%) received an electrocardiogram, 9 (2.7%) underwent cardiac biomarker testing, and 6 (1.8%) were diagnosed with ACS. Conclusions: In northern Tanzania, community awareness of ACS symptoms is low and only a minority of adults would present to a hospital for chest pain. Full diagnostic workups are rare among patients with symptoms of possible ACS, and ACS is a rare diagnosis.

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Acknowledgements

I have been blessed with outstanding mentors and a wonderful team of collaborators and supporters. I would like to thank my entire mentorship team, including John Bartlett, Catherine Staton, Nathan Thielman, Gerald Bloomfield, Blandina Mmbaga, Matthew Rubach, Alex Limkakeng, John Crump, Sophie Galson, Charles Gerardo, Gloria Temu, and Francis Sakita. I owe them an enormous debt of gratitude for their wisdom, guidance, and patience. I would further like to thank my research team, Godfrey Kweka and Oscar Kamanga for their outstanding efforts to make this study successful. I am also deeply indebted to my collaborators and supporters at KCMC, including Frank Kimaro, Francis Karia, Gwamaka William, Vera Wright, Robert Chuwa, Cynthia Asiyo, Carolyn Simon, Sakasaka Philoteus, Eliza Kusaga, and Tumsifu Tarimo. Without their assistance managing finances, administrative tasks, data management, regulatory affairs, and procurement, this study would not have been possible. I would further like to thank the team at Duke Global Health Institute and the Hubert Yeargan Center, including Tara Pemble, Madi Smith, Cynthia Binanay, Alisa Mutter, Laura Bey, and Katherine Link for the tireless help and support over the past two years. Finally, I wish to thank the entire KCMC emergency department staff and all the individuals who participated in the study. It is my sincere hope that our work together will ultimately lead to improved ACS care at KCMC and beyond.

1. Introduction

Acute coronary syndrome (ACS) is the most common cause of death worldwide.[1] In sub-Saharan Africa (SSA), there is little data regarding the incidence or prevalence of ACS despite the recent rapid rise in risk factors like hypertension and obesity.[2, 3] A recent systematic review found only a few published reports regarding the burden prevalence of ACS in SSA, but these were performed in small non-generalizable populations and were subject to significant methodological limitations.[4] In Tanzania, for example, there are currently no rigorous ACS prevalence or incidence data available. However, the Global Burden of Disease study, using modeling based on data from other settings and local risk factor burden data, estimates that ACS is currently the fourth most common cause of morbidity in the country.[5]

In spite of such projections, ACS appears to be an uncommon diagnosis across the region.[6-8] In two recent retrospective reviews of hospital admissions at referral centers in Nigeria and Ghana, ACS accounted for less than 0.25% of all adult admissions.[6, 7] Beyond these retrospective studies suggesting ACS is rare, there have been few other published reports of ACS cases from SSA.[4, 9] Several epidemiologists have noted this paucity of data and surmised that the primary form of cardiovascular disease in SSA is stroke, rather than ACS.[10, 11] The apparent scarcity of ACS relative to stroke in SSA is curious, in light of the fact that the risk of ACS and stroke are highly correlated, at least in other world regions.[12-15] The paucity of diagnosed ACS cases

relative to risk factor burden and stroke burden in SSA has many potential explanations.

One possible contributor to under-detection of ACS in SSA may be the role of the patient.[16] If patients are not aware of the symptoms of ACS or do not seek care in the formal healthcare system for ACS symptoms, their beliefs and behavior may be driving under-recognition of ACS in SSA. Indeed, prior research regarding infectious diseases in SSA found that laypersons often ascribed fevers to non-infectious causes such as rain or dust, resulting in patients not seeking care in hospitals or clinics, potentially resulting in the underreporting of certain infections.[17] If patient beliefs about ACS are similarly affecting their healthcare-seeking behavior, then patient knowledge and practices may be buttressing the misconception that ACS in SSA is rare.[18]

Beyond understanding the role of the patient in ACS diagnosis, delineating patient knowledge, attitudes, and practices towards ACS is necessary to create educational programming to improve ACS care in SSA. If patients in SSA do not possess adequate knowledge regarding ACS and do not engage in preventative practices regarding ACS, then ACS outcomes will likely not improve without patient-centered interventions. Indeed, research regarding cardiovascular disease in high-income countries has shown that better patient knowledge and attitude results in improved uptake of preventative practices and improved clinical outcomes.[19-21] Thus, characterizing patient beliefs and behaviors is a necessary first step to develop educational and health-system interventions in SSA to curtail ACS morbidity and

mortality.

Apart from patient-related factors, physician practices may also be contributing to under-recognition of ACS in SSA. Some researchers have speculated that the ACS may be under-reported in SSA due to widespread lack of diagnostic equipment and insufficient clinician education.[8] If physicians do not regularly consider a diagnosis of ACS and do not routinely pursue the testing required for such a diagnosis, then the low numbers of reported ACS cases may be more reflective of physician practices than of low disease incidence.

However, little is known about patterns of ACS diagnosis and care in SSA. In hospitals outside SSA, patients with symptoms like chest pain or shortness of breath commonly present to the emergency department (ED) and diagnostic workups for ACS are routinely pursued for such patients.[22, 23] To our knowledge, however, there has been only one study of the management of chest pain in SSA. In a retrospective review at a single ED in South Africa, only 1.7% of patients had chest pain and 12% of these patients received a diagnosis of ACS.[24] Other than this study, there is currently no data from SSA regarding the prevalence of chest pain and shortness of breath among ED patients, the comorbidities and risk profiles of such patients, and the diagnosis and care given to such patients. Understanding such patterns of diagnosis and treatment is essential to clarifying the role of the provider in ACS under-detection in SSA.

The purpose of this study was to describe patient and physician beliefs and

behaviors surrounding ACS in northern Tanzania in order to understand barriers to ACS diagnosis and care. To do so, we conducted a cross-sectional community survey, a retrospective chart review, and a prospective hospital-based observational study in the Kilimanjaro Region of Tanzania. The contents of this thesis were taken from two published manuscripts[25, 26] and from two other manuscripts being prepared for publication.

2. Methods

This study consisted of three distinct parts: a community-based survey, a retrospective chart review, and a hospital-based prospective observational study.

2.1 Setting

This study was conducted in the Kilimanjaro Region of northern Tanzania. The community-based survey was conducted in the city of Moshi (population 184,289) and two surrounding rural districts, Moshi Rural and Hai (populations 466,740 and 210,531, respectively).[27] In 2014, the local prevalence of hypertension and glucose impairment among adults in Kilimanjaro was 28% and 22%, respectively.[28, 29] The retrospective chart review and prospective observational study were conducted in the ED at Kilimanjaro Christian Medical Centre (KCMC), a tertiary care center located in Moshi. ED physicians at KCMC have access to electrocardiography (ECG), an array of laboratory tests including troponin assays, computed tomography, and echocardiography.

2.2 Community survey methods

The methods used in the community-based survey have been previously published.[25, 26] The survey used sampling techniques recommended by the World Health Organization (WHO) for cluster-based surveys.[30] A two-stage randomized population-based cluster survey was conducted with selection of urban and rural sub-districts proportionate to population size. Within the three study districts, sixty sub-districts were selected randomly in a population-weighted manner. Quantum

Geographic Information System (QGIS, v2.18.7) was then used to generate twelve random points within each selected sub-district. The household closest to each random point was approached in person by a member of the study team for survey participation. If there were no eligible respondents at the nearest household, then the next closest household to the selected point was approached for inclusion.

The survey was performed from February 2018 to May 2018. Any household resident who self-identified as a healthcare decision maker was eligible for survey participation, but only one individual per household was enrolled. Sociodemographic information about respondents including age, sex, and level of education was collected. Participants were then asked, (1) "What are the possible causes of chest pain in an adult?" (2) "What are the symptoms of a heart attack?" (3) "Do you think you have a chance of having a heart attack?" and (4) "Where would you go if you or another adult member of your household were to have chest pain?" For questions (1) and (2), participants were asked to list as many answers as they could think of, and they were not given a picklist to choose from. For question (3), participants could choose "yes," "no," or "don't know" as responses. For question (4), participants were asked to choose from a picklist of different kinds of Tanzanian healthcare facilities, as well as self-treatment at home or traditional healer. Surveys were conducted in Swahili by trained research assistants using using Open Data Kit software (ODK v1.12.2, Seattle, Washington) on Samsung Galaxy Tab A tablets (Samsung, Seoul, Korea).

2.3 Retrospective chart review methods

The ED admissions logbook was retrospectively reviewed for admissions with diagnoses of ACS, heart failure, or stroke. This logbook includes information regarding patient age and sex, vital signs, blood glucose, physician-documented diagnosis, and disposition. Admission diagnoses are copied verbatim from the patient chart and are not standardized to ICD-10 taxonomy. In cases of heart failure, the underlying etiology of heart failure is recorded in the logbook if it is known to the physician based on existing diagnostic data. All adult admission data from the logbook was retrospectively reviewed for a six-month period, from September 21st, 2017 to March 22nd, 2018. All admission data were entered into an electronic database exactly as recorded without abstraction or interpretation.

2.4 Prospective observational study methods

All KCMC ED patients aged greater than 17 years were screened by trained research assistants. Screening was conducted during one clinical shift (morning, evening, or overnight) per day, from August 20th 2018 to January 4th 2019. The number of days spent screening during morning, evening, and overnight shifts was proportional to total patient volumes during each type of shift. Inclusion criteria were (1) primary or secondary complaint of chest pain or shortness of breath and (2) age greater than 17. Patients were excluded if they reported a history of fever during the present illness, if their chest pain was secondary to trauma, or if they were unable to provide informed

consent. A standardized questionnaire regarding sociodemographic background, medical co-morbidities, and lifestyle behaviors was adapted from the WHO STEPS instrument for non-communicable disease surveillance[31] and administered to all participants. Standardized information regarding history of present illness was also collected from each enrolled patient. Participant weight and height were measured and recorded, and blood pressure was measured using the Beurer BM40 automatic blood pressure monitor (Beurer, Ulm, Germany). Enrolled patients were followed until admission or discharge from the ED; all treatments administered, prescriptions given, and diagnostic investigations ordered by the ED physician were documented by the study team. ED diagnoses were copied directly from the patient's medical record.

2.5 Language

All questionnaires used in the community survey and prospective observational study were translated into Swahili and back-translated into English to confirm content fidelity and to identify any ambiguities in language. Special attention was paid to the terms "heart attack" and "chest pain," since these terms can have different interpretations across cultures and languages. Several wording options for these terms were piloted with fifteen Tanzanians of both medical and non-medical backgrounds. They unanimously agreed that the best Swahili phrases for these concepts were "*mshituko wa moyo"* and *"maumivu ya kifua,"* respectively. They further confirmed that the Swahili phrase "*mshituko wa moyo"* does not have additional connotations such as

heartbreak or emotional fright. All study instruments were piloted with 20 Tanzanians prior to initiation of both the community survey and the prospective observational study to ensure comprehensibility.

2.6 Study definitions

2.6.1 Urban residence

Urban residence was defined as residence within Moshi Urban district.

2.6.2 Conventional myocardial symptoms

Conventional myocardial infarction symptoms were defined *a priori* as chest pain, shortness of breath, arm pain, jaw pain, diaphoresis, nausea, dizziness, or epigastric pain.

2.6.3 "Other heart problem"

In response to the community survey question regarding causes of chest pain, 'other heart problem' was defined as any response involving the heart other than a heart attack.

2.6.4 ACS

Cases of ACS in both the retrospective and prospective studies were defined as any patient with a physician-recorded diagnosis of ACS, ST elevation myocardial infarction, non-ST elevation myocardial infarction, myocardial infarction, or unstable angina.

2.6.5 Heart failure, stroke, and symptomatic hypertension

Cases of heart failure in both the retrospective and prospective study were defined by any patient with a physician-documented diagnosis of heart failure, congestive heart failure, or congestive cardiac failure. Cases of stroke were defined by a recorded diagnosis of stroke, ischemic stroke, hemorrhagic stroke, or cerebrovascular accident. Cases of symptomatic hypertension were defined by a documented diagnosis of hypertensive emergency, hypertensive urgency, or severe hypertension.

2.6.6 Hypertension

Cases of hypertension in both the retrospective or prospective study were defined as self-reported history of hypertension, physician-documented diagnosis of hypertension, or measured blood pressure ≥140/90 mmHg, as per JNC 8 guidelines.[32]

2.6.7 Diabetes

In the retrospective chart review, diabetes was defined as a documented diagnosis of diabetes mellitus or random blood glucose ≥200 mg/dL, as per American Diabetes Association guidelines.[33] In the prospective observational study, diabetes was defined by patient self-report.

2.6.8 Other cardiovascular risk factors

In the prospective observational study, hyperlipidemia, HIV infection, and current or prior tobacco use were defined by patient self-report. Personal cardiovascular disease history was defined by self-reported history of heart attack or stroke; patients

who reported a history of heart attack or stroke in a first-degree blood relative were defined as having a family history of cardiovascular disease. Patients with body mass index (BMI) ≥ 30 kg/m^2 were defined as obese, those with BMI between 25 and 30 kg/m^2 were defined as overweight, those with BMI between 17.5 and 25 kg/m^2 were defined as normal weight, and those with BMI < 17.5 kg/m^2 were defined as underweight. Sedentary lifestyle was defined as fewer than 150 minutes of moderately vigorous exercise, consistent with WHO recommendations.[34] Patients who reported not eating fruits and vegetables at least once daily were defined as having a poor diet, based on data demonstrating that daily consumption of vegetables and fruits significantly reduces risk of cardiovascular disease.[35]

2.6.9 Anginal severity

Patients who reported that their chest pain or shortness of breath were not affected by exertion were defined as having non-exertional symptoms. For all other patients, severity of angina was graded by the Canadian Cardiovascular Society (CCS) guidelines for angina pectoris.[36]

2.7 Statistical analyses

Categorical variables are presented as proportions, and continuous variables are presented as means (standard deviations) or medians (ranges). Associations between categorical variables and continuous variables were evaluated using Welch's t-test. Associations between two categorical variables were evaluated with Pearson's chi-

squared except when the expected cell count was <10, when Fisher's Exact method was used. Odds ratios and corresponding 95% confidence intervals were calculated directly from two-way contingency tables. Statistical analyses on the community survey data were performed in STATA (v15.1, StataCorp, College Station, TX, United States), all other analyses were performed using RStudio (v3.3.2, Rstudio Inc, Boston, MA, United States). Principal component analysis[37] was conducted to generate a socioeconomic score for community survey participants from nine binary variables: ownership of a vehicle, ownership of a television, ownership of a refrigerator, possession of a bank account, post-primary education, presence of electricity in the home, possession of health insurance, home floor material, and presence of a flush toilet in the home. The five-year risk of cardiovascular event for each patient in the prospective observational study was calculated via Harvard NHANES (National Health and Nutrition Examination Survey) risk score.[38] This model, which is based on age, systolic blood pressure, sex, current smoking, diabetes, and BMI, has been previously validated in SSA.[39] A statistical significance threshold of 0.05 was used in all analyses.

2.8 Ethical approval and funding

Ethical approval for this study was obtained from the Duke Health Institutional Review Board, the Kilimanjaro Christian Medical Centre Research Ethics Committee, and the Tanzania National Institutes for Medical Research Ethics Coordinating Committee. All study participants in the community survey and the prospective

observational study provided written informed consent prior to enrollment. For the retrospective chart review, the requirement for individual informed consent was waived.

The community survey was funded by Bill & Melinda Gates Foundation (grant number OPP1158210) and the remaining portions of the study were funded by the US National Institutes of Health (grant number D43TW009337).

3. Results

3.1 Community survey results

The results of the community survey have been previously published.[25, 26] A total of 718 persons participated in the survey, and their sociodemographic features are summarized in Table 1. The median (IQR) age of participants was 48 (32, 62) years, and 485 (67.5%) of respondents were female. The majority of respondents lived in rural areas (563, 78.4%) and did not have post-primary education (537, 74.8%).

Table 1. Sociodemographic features of household survey respondents, Moshi Urban, Moshi Rural, and Hai Districts, 2018 (N=718).

	n	(%)
Female	485	(67.5)
Urban residence	155	(21.6)
Education		
None	40	(5.6)
Primary	497	(69.2)
Secondary	132	(18.4)

Post-Secondary	49	(6.8)
Have health insurance	230	(32.0)
Religion		
Christian	584	(81.3)
Muslim	115	(16.0)
Other	19	(2.6)
Chagga tribe	535	(74.5)
	Median	(Range)
Age, years	48	(17, 99)
Household size, number of persons	4	(1, 13)
SES score	0.29	(0, 1.01)

SES: socioeconomic status

Table 2 presents the possible causes of chest pain in an adult identified by the participants. Weather and exercise were the most commonly mentioned causes of chest

pain, cited by 342 (47.6%) and 318 (44.3%) respondents, respectively. Ninety-four (13.1%) participants were unable to think of any causes of chest pain. Two (0.3%) respondents identified 'heart attacks' and 5 (0.7%) respondents identified 'other heart problems' as possible causes of chest pain, respectively.

Table 2. Possible causes of chest pain in an adult identified by adult residents of northern Tanzania, 2018 (N=718).

Cause	Number of respondents (%)
Weather	342 (47.6)
Exercise	318 (44.3)
Cigarette smoking	95 (13.2)
Dust	66 (9.2)
Tuberculosis	62 (8.6)
Food	53 (7.4)
Pneumonia	50 (7.0)

Other lung problems	42 (5.8)
Other infections	41 (5.7)
Smoke Inhalation	34 (4.7)
Alcohol	31 (4.3)
Injury	24 (3.3)
Allergy	8 (1.1)
Smells	5 (0.7)
Malaria	5 (0.7)
Other heart problems	5 (0.7)
High blood pressure	3 (0.4)
Heart attack	2 (0.3)
Others	36 (5.0)
Don't know any	94 (13.1)

The symptoms of myocardial infarctions identified by respondents are presented in Table 3. The majority of participants (403, 56.1%) were unable to name any symptom of a heart attack. The most commonly mentioned symptoms of a heart attack were feelings of worry, sadness, or anger (93, 13.0%) and headache (52, 7.1%). One hundred and fifteen (16.0%) respondents were able to identify at least one conventional symptom of a myocardial infarction. The most commonly identified conventional symptom was sweating, mentioned by 36 (5.0%) participants. Chest pain was cited as a symptom of a heart attack by 24 (3.3%) participants.

Table 3: Symptoms of a 'heart attack' cited by residents of northern Tanzania, 2018 (N=718).

Symptom	Number of respondents (%)
Don't know any	403 (56.1)
Feelings of worry, sadness, or anger	93 (13.0)
Headache	52 (7.1)
Palpitations	43 (6.0)
Sweating	36 (5.0)

Shortness of breath	35 (4.9)
Dizziness	33 (4.6)
Chest pain	24 (3.3)
Fever	20 (2.8)
High blood pressure	19 (2.6)
Unilateral paralysis	18 (2.5)
Loss of consciousness	12 (1.7)
Fatigue	10 (1.4)
Confusion	5 (0.7)
Jaw or arm pain	4 (0.6)
Nausea	3 (0.4)
Leg swelling	3 (0.4)
Epigastric pain	1 (0.1)
Others	17 (2.4)

Table 4 compares the sociodemographic features of respondents who were able to identify at least one conventional myocardial infarction symptom versus those who were not. There were no statistically significant associations between ability to identify a conventional symptom and education, urban residence, age, or socioeconomic status. There were also no significant associations between ability to identify a convention symptom and preference for a hospital for symptoms of chest pain or shortness of breath.

Table 4: Characteristics of participants who identified any conventional myocardial infarction symptom versus those who did not, northern Tanzania, 2018 (N=718).

	Able to name a conventional symptom, n (%) (N=115)	Unable to name a conventional symptom, n(%) (N = 603)	OR (95% CI)	*p*
Female	78 (67.8%)	407 (67.5%)	1.02 (0.66, 1.56)	0.945
Urban residence	25 (21.7%)	130 (21.6%)	1.01 (0.62, 1.64)	0.966

Post-primary education	23 (20.0%)	158 (26.2%)	0.70 (0.43, 1.15)	0.160
Health insurance	38 (33.0%)	192 (31.8%)	1.06 (0.69, 1.62)	0.800
Chagga tribe	85 (73.9%)	450 (74.6%)	0.96 (0.61, 1.52)	0.872
Hospital preferred facility for chest pain	47 (40.9%)	230 (38.1%)	1.12 (0.75, 1.68)	0.582
Hospital preferred facility for shortness of breath	92 (80.0%)	430 (71.3%)	1.61 (0.99, 2.63)	0.055
	Able to name a conventional symptom, mean (sd) (N=115)	Unable to name a conventional symptom, mean (sd) (N = 603)		*p*
Age, years	48.6 (18.5)	48.0 (18.0)		0.732

SES score	0.32 (0.28)	0.35 (0.30)		0.239

*p<0.05

SES: Socioeconomic status

A total of 198 (27.6%) of respondents stated they thought they had a chance of suffering a heart attack. Of the remaining respondents, 310 (43.2%) did not think they had any chance of having a heart attack and 210 (29.2%) did not know whether they were at risk. Table 5 compares the sociodemographic features of participants who perceived themselves to be at risk for a heart attack versus other respondents. Compared to others, respondents who perceived themselves to be at risk for a heart attack were more likely to be older (mean age 52.8 vs 46.3 years, p<0.001). There were no differences in gender, education, or socioeconomic status between the two groups. Self-perceived risk was not associated with increased likelihood of preferring a hospital for chest pain or shortness of breath.

Table 5: Characteristics of respondents who felt they were at risk of heart attacks versus those who did not perceive any self-risk or were unsure, northern Tanzania, 2018 (N=718).

	Perceived themselves to be at risk, n(%) (N = 198)	Did not perceive themselves to be at risk or were unsure, n(%) (N = 520)	OR (95% CI)	*p*
Female	134 (67.7%)	351 (67.5%)	1.01 (0.71, 1.43)	0.964
Urban	42 (21.2%)	113 (21.7%)	0.97 (0.65, 1.45)	0.880
Post-primary education	42 (21.2%)	139 (26.7%)	0.74 (0.50, 1.10)	0.128
Health insurance	64 (32.3%)	166 (31.9%)	1.02 (0.72, 1.45)	0.918
Identified a conventional symptom of myocardial infarction	32 (16.2%)	83 (16.0%)	1.01 (0.65, 1.58)	0.948
Chagga tribe	151 (76.3%)	384 (73.8%)	1.14 (0.78, 1.67)	0.392

Hospital preferred facility for chest pain	68 (34.3%)	209 (40.2%)	0.78 (0.55, 1.10)	0.150
Hospital preferred facility for shortness of breath	134 (67.7%)	388 (74.6%)	0.71 (0.50, 1.02)	0.062
	Perceived themselves to be at risk, mean(sd) (N = 198)	Did not perceive themselves to be at risk or were unsure, mean(sd) (N = 520)		*p*
Age, years	52.8 (17.1)	46.3 (18.2)		<0.001*
SES score	0.31 (0.27)	0.36 (0.30)		0.052

*p<0.05

SES: Socioeconomic status

Table 6 presents the responses to the question, 'Where would you seek care if you or another adult in your household had chest pain?' The most commonly selected facility was a hospital, but the majority of respondents (441, 61.4%) said they would present somewhere other than a hospital. Only 104 (14.5%) participants said they would seek care entirely outside of the formal healthcare system, either by going directly to a pharmacy for treatment, self-treating at home, or watchful waiting. No respondent said they would go to a traditional healer.

Table 6. Responses to the question 'Where would you seek care if you or another adult in your household had chest pain?' among adults in northern Tanzania, 2018 (N=718).

Facility	Number of respondents	(%)
Hospital	277	(38.6)
Dispensary	206	(28.7)
Health center	124	(17.3)
Pharmacy	60	(8.4)
Self-treatment at home	35	(4.9)

Do nothing/watchful waiting	9	(1.3)
Clinic	3	(0.4)
Traditional healer	0	(0.0)
Don't know	4	(0.6)

Table 7 compares the sociodemographic characteristics of those who stated they would seek care at a hospital for chest pain versus those who did not. Females were significantly less likely than males to prefer seeking care at a hospital (OR 0.65, p=0.008). There were otherwise no statistically significant associations observed between preference for a hospital and urban residence, education, ownership of health insurance, or age. Of the 6 respondents who identified either heart attacks or heart problems as possible causes of chest pain, one (16.7%) stated that they would present to a hospital for chest pain.

Table 7. Characteristics of respondents who would present to hospital for chest pain versus those who would not, northern Tanzania, 2018.

	Hospital first choice for chest pain, n(%) (N = 277)	Hospital not first choice for chest pain, n(%) (N= 441)	OR (95% CI)	*p*
Female	171 (61.7%)	314 (71.2%)	0.65 (0.47, 0.90)	0.008*
Urban residence	50 (18.1%)	105 (23.8%)	0.70 (0.48, 1.03)	0.068
Post-primary education	76 (27.4%)	105 (23.8%)	1.21 (0.86, 1.71)	0.276
Have health insurance	97 (35.0%)	133 (30.2%)	1.25 (0.91, 1.72)	0.174
Christian	229 (82.7%)	355 (80.5%)	1.16 (0.78, 1.71)	0.467
Chagga tribe	217 (78.3%)	318 (72.1%)	1.40 (0.98, 1.99)	0.062
Cited heart problem as possible cause of chest pain	1 (0.4%)	5 (1.1%)	0.32 (0.04, 2.72)	0.268

	Hospital first choice for chest pain mean(sd) (N = 277)	Hospital not first choice for chest pain mean(sd) (N= 441)		*p*
Age, years	49.7 (17.1)	47.0 (18.6)		0.054
SES score	0.37 (0.31)	0.34 (0.28)		0.245

SES: socioeconomic status

* $p < 0.05$

3.2 Retrospective chart review results

During the study period, 3961 adult patients presented to the KCMC ED, of whom 2418 (62.1%) were admitted. The median (range) age of admitted adult patients was 52 (18, 105) years, and 1090 (45.1%) admitted patients were male.

Of admitted patients, 204 (8.4%) had a diagnosis of stroke, 9 (0.3%) had a diagnosis of ACS, and 294 (12.2%) had a diagnosis of heart failure. Together, these diagnoses accounted for 503 (20.8%) admissions. The ratio of ACS admissions to heart failure admissions and stroke admissions was 1:32.7 and 1:22.7, respectively.

Table 8 presents the etiologies of heart failure cited by clinicians for the 294 patients with admission diagnoses of heart failure. Uncontrolled hypertension was the most commonly identified cause of heart failure, cited in 124 (42.2%) cases. Only 1 (0.3%) case of heart failure was attributed to ischemic heart disease.

Table 8. Etiologies of heart failure cited by clinicians among admitted patients with heart failure, northern Tanzania, September 2017 - March 2018 (N=294).

Heart failure etiology	n	%
Uncontrolled hypertension	124	42.2%
Cardiomyopathies	29	9.9%
Dilated cardiomyopathy	25	8.5%
Post-partum cardiomyopathy	3	1.0%
HIV cardiomyopathy	1	0.3%
Valvular etiologies	10	3.4%
Rheumatic heart disease	7	2.3%

Valvular heart disease	3	1.0%
Ischemic heart disease	1	0.3%
Unknown or unspecified	128	43.5%

3.3 Prospective observational study results

During the study period, a total of 3909 patients were screened, of whom 349 (8.9%) patients were eligible for inclusion. Of eligible patients, 339 (97.1%) participants consented to enrollment in the study. Table 9 presents the characteristics and cardiovascular risk profile of enrolled patients. The median (IQR) age was 60 (46, 72) years and 144 (42.5%) patients were male. Of participants, 252 (74.3%) met the study definition for hypertension, including 203 (59.9%) who self-reported a history of hypertension and 176 (51.9%) who were noted to have an elevated blood pressure. A total of 156 (46.0%) patients were overweight or obese, and 304 (89.7%) met the study definition for poor diet. With regards to overall cardiovascular risk, 222 (65.5%) patients had greater than 10% five-year risk of cardiovascular event.

Table 9. Characteristics and cardiovascular risk factors among adults presenting to the emergency department with chest pain or shortness of breath, northern Tanzania, 2018 (N=339).

Patient Characteristics	Median	IQR
Age, years	60	(46, 72)
Systolic blood pressure, mmHg	138	(121, 155)
Diastolic blood pressure, mmHg	85	(72, 96)
	Number of patients	(%)
Male	144	(42.5)
Hypertension	252	(74.3)
Diabetes	44	(13.0)
Hyperlipidemia	39	(11.5)
History of tobacco use	109	(22.0)
Body mass index		
Underweight	28	(8.3)

Normal weight	155	(45.7)
Overweight	85	(25.1)
Obese	71	(20.9)
Self-reported history of CVD	18	(5.3)
Family history of CVD	86	(25.4)
Poor diet	304	(89.7)
Sedentary lifestyle	124	(36.6)
HIV infected	6	(1.8)
5-year risk of cardiovascular event		
<5%	74	(21.8)
5-10%	43	(12.7)
10-20%	76	(22.4)
20-30%	75	(22.1)
>30%	71	(20.9)

CVD: Cardiovascular disease

HIV: Human immunodeficiency virus

The historical features of participants' presenting illnesses are detailed in Table 10. The most common chief complaints among patients were chest pain and shortness of breath, endorsed by 122 (36.0%) and 107 (31.5%) participants, respectively. Patients reported a median duration of illness of 7 days, and 314 (92.6%) reported that their symptoms were worse with exertion.

Table 10. Historical features of present illness among adults presenting to the emergency department with chest pain and shortness of breath, northern Tanzania, 2018 (N=339)

	Number of patients	%
Chief complaint		
Chest pain	122	(36.0)
Shortness of breath	107	(31.5)
Palpitations	18	(5.3)
Leg swelling	11	(3.2)

Abdominal pain	10	(2.9)
Other	71	(20.9)
Secondary complaints		
Chest pain	139	(41.0)
Shortness of breath	137	(40.4)
Abdominal pain	66	(19.5)
Palpitations	60	(17.7)
Cough	60	(17.7)
Back pain	56	(16.5)
Leg swelling	51	(15.0)
Headache	38	(11.2)
Arm/jaw pain	35	(10.3)
Generalized weakness	28	(8.3)
Other	110	(32.4)

Duration of symptoms, median (IQR), days	7	(3, 28)
CCS grading for anginal severity		
Non-exertional symptoms	25	(7.4)
Class I	38	(11.2)
Class II	95	(28.0)
Class III	74	(21.8)
Class IV	107	(31.6)

CCS: Canadian Cardiovascular Society[36]

Table 11 summarizes the diagnostic workups, treatments, and diagnoses received by enrolled patients in the ED. Of participants, 170 (50.1%) underwent ECG testing and 9 (2.7%) underwent cardiac biomarker testing. With regard to treatment, 3 (0.9%) patients were given aspirin. The most common clinical diagnoses were symptomatic hypertension and heart failure, which were ascribed to 104 (30.7%) and 99 (29.2%) patients, respectively. Six patients (1.8%) were diagnosed with ACS. Approximately one-third of patients (116, 34.2%) were admitted to the hospital.

Table 11. Patterns of diagnosis and management of adults presenting to the emergency department with chest pain and shortness of breath, northern Tanzania, 2018 (N = 339)

	Number of patients	(%)
ECG performed	170	(50.1)
Cardiac biomarkers ordered	9	(2.7)
Other laboratory investigations ordered	246	(72.6)
Treatments administered in the ED		
Aspirin	3	(0.9)
Clopidogrel	2	(0.6)
Furosemide	33	(9.7)
Anti-hypertensive	26	(7.6)
Supplemental oxygen	24	(7.1)
Analgesic	8	(2.4)
Other	23	(6.8)

None	247	(72.9)
Diagnosis		
Symptomatic hypertension	104	(30.7)
Heart failure	99	(29.2)
PUD/gastritis	27	(8.0)
Non-specific chest pain	14	(4.1)
Pneumonia	12	(3.5)
Asthma/COPD	11	(3.2)
Malignancy	11	(3.2)
Acute coronary syndrome	6	(1.8)
Other	55	(16.2)
Admitted to hospital	116	(34.2)

PUD: peptic ulcer disease

COPD: Chronic obstructive pulmonary disease

Table 12 presents the association between various patient characteristics and the decision to obtain an ECG. Patients who received an ECG were more likely to deny a history of smoking ($p = 0.025$) and to have a chief complaint of chest pain ($p = 0.046$). There was otherwise no association between decision to obtain an ECG and overall five-year cardiovascular risk, age, hypertension, diabetes, or personal or family history of cardiovascular disease.

Table 12. Association between patient characteristics and decision to obtain an ECG for adults presenting to the emergency department with chest pain and shortness of breath, northern Tanzania, 2018 (N = 339).

	ECG obtained, n (%) (N=170)	ECG not obtained, n (%) (N=169)	OR (95% CI)	*p*
Male sex	72 (42.4)	72 (42.6)	0.99 (0.64, 1.52)	0.963
Hypertension	128 (75.3)	124 (73.4)	1.11 (0.68, 1.81)	0.686
Diabetes	18 (10.6)	26 (15.4)	0.65 (0.34, 1.24)	0.189
Hyperlipidemia	24 (14.1)	15 (8.9)	1.68 (0.85, 3.41)	0.130

History of tobacco use	45 (26.5)	64 (37.9)	0.59 (0.37, 0.94)	0.025*
Overweight or obese	84 (49.4)	72 (42.6)	1.31 (0.86, 2.02)	0.209
Personal history of CVD	9 (5.3)	9 (5.3)	0.99 (0.37, 2.64)	0.990
Family history of CVD	46 (27.1)	40 (23.7)	1.20 (0.73, 1.96)	0.473
Poor diet	156 (91.8)	148 (87.6)	1.57 (0.77, 3.29)	0.205
Sedentary lifestyle	65 (38.2)	59 (34.9)	1.15 (0.74, 1.80)	0.525
Chief complaint chest pain	70 (41.2)	52 (30.8)	1.57 (1.01, 2.47)	0.046*
Anginal symptoms	159 (93.5)	155 (91.7)	1.30 (0.57, 3.04)	0.523
>10% five-year risk of cardiovascular event	109 (64.1)	113 (66.9)	0.89 (0.56, 1.39)	0.595
	ECG obtained, mean (sd) (N =)	ECG not obtained, mean (sd) n (%) (N =)		*p*

Age, years	56.9 (18.8)	57.7 (18.7)		0.698
Systolic blood pressure, mmHg	139.2 (29.5)	140.1 (26.6)		0.762
Symptom duration, days	30.0 (73.4)	20.6 (31.7)		0.127

4. Discussion

This project consisted of three distinct studies, the results of which collectively suggest that patient and physician beliefs and behaviors may be contributing substantially to ACS under-detection in SSA.

4.1 Implications of community survey findings

To our knowledge, this paper presents the first study of community perceptions of chest pain and healthcare seeking behavior for chest pain in sub-Saharan Africa. Only a tiny fraction of participants in this survey were aware of cardiovascular causes of chest pain, and the majority of respondents said they would not present to a hospital if they or another adult in their household had chest pain. If ischemic heart disease is as common in Tanzania as is currently estimated by the Global Burden of Disease study,[5] then these findings highlight an urgent need for community education that is likely not unique to northern Tanzania.

Community awareness that life-threatening cardiovascular conditions like ACS could cause chest pain was extremely low in this study population. This finding stands in contrast to the results of multiple studies from a wide range of settings outside of Africa which found that large majorities of respondents recognized chest pain as potentially having a cardiac origin without being prompted by a picklist.[40-42] Thus, the findings of this study suggest that knowledge of ACS symptoms is much lower in northern Tanzania than in other settings across the globe. There has been no study of

perceptions of chest pain elsewhere in sub-Saharan Africa, and additional research is needed to establish whether knowledge of ACS is similarly poor in other African communities. Increasing knowledge of ACS symptoms is an important public health goal because prior research has shown that such knowledge is associated with faster presentation to an appropriate healthcare facility.[43]

A large number of participants in this study ascribed chest pain to environmental causes like weather, dust, and smoke inhalation. This finding is consistent with the results of other studies in sub-Saharan Africa that have described widespread community beliefs in weather conditions as a cause of other physical symptoms like fever.[17, 44] Infectious causes of chest pain, such as pneumonia, tuberculosis, and malaria, were also cited much more frequently by participants than cardiac causes. This difference may be reflective of the long-standing emphasis on infectious disease in this community, in terms of research, resources, and education. There are, however, no existing data about common causes of chest pain in Tanzania and data regarding the prevalence of ischemic heart disease in the country is sorely lacking. Thus, further research is needed to describe the actual causes of chest pain in Tanzania and local burden of ACS in order to determine the magnitude of the discrepancies between actual and perceived causes of chest pain.

In order to fully understand community knowledge of ACS, participants were also asked to list all the symptoms of ACS, rather than list causes of chest pain generally.

This study is among the first to examine community knowledge of ACS symptoms in SSA. In a community with high prevalence of risk factors,[28, 29] knowledge of ACS symptoms was limited. These findings again underscore a grave need for educational programming to improve community awareness of ischemic heart disease.

The vast majority of respondents were unable to name any conventional symptom of ACS, consistent with the results of the few other studies regarding knowledge of myocardial infarction symptoms in SSA.[45, 46] Knowledge of symptoms was especially poor in our study setting, with only 16% of participants able to name a single symptom, the lowest proportion reported in SSA to date.[45, 47] Lack of knowledge of the symptoms of this life-threatening condition was not confined to a single segment of the population; low levels of knowledge were observed across all ages, genders, tribes, education levels, and socioeconomic strata. Thus, the need for community educational programming in northern Tanzania is particularly acute, especially given the high local prevalence of risk factors.[28, 29] In recent years, the Tanzanian Ministry of Health, the Tanzanian Cardiac Society, and others have increased efforts to educate the community about symptoms of heart disease via media programming, which have emphasized chest pain, shortness of breath, and dizziness as potential warning signs.[48-50] The results presented here suggest that such efforts have not yet resulted widespread community recognition of the symptoms of ACS in northern Tanzania.

Less than a third of participants in this study felt that they were at any risk of having a myocardial infarction despite the high local prevalence of cardiovascular risk factors.[28, 29] Older respondents were more likely to consider themselves to be at risk, but otherwise lack of self-perception of risk was not limited to any specific gender, education level, socioeconomic stratum, urban or rural setting, or tribe. Thus, efforts by clinicians, public health officials, and community leaders are needed to emphasize personal risk of cardiovascular disease in educational programming. These efforts would again be more effective if informed by data regarding local burden of disease, but such data are presently lacking in Tanzania. Therefore, establishing the local prevalence of ischemic heart disease is essential to formulating a public health response to the observed low levels of knowledge of myocardial infarction symptoms and perception of self-risk.

Less than half of respondents reported that they would present to the hospital for chest pain, a preference that was prevalent across socioeconomic strata, tribal and religious affiliations, education levels, and urban and rural settings. This again stands in contrast to studies from outside Africa, which have found that the majority of respondents would call an ambulance or present directly to the emergency department for chest pain.[51] Many participants in this study said they would seek care in other healthcare facilities such as dispensaries or health centers, but in the northern Tanzanian context such facilities would not be appropriate for ACS symptoms because they lack

capacity for basic diagnostic testing such as electrocardiogram or cardiac biomarker testing. Women were less likely than men to state that they would present to a hospital. Such gender differences have been observed in some settings like Peru,[40] but not in other settings like the United Kingdom.[42] Age was not a significant predictor of healthcare seeking behavior for chest pain in this study population, perhaps because many of the commonly cited explanations for chest pain such as weather and dust are not associated with age. Thus, there is a tremendous need for community educational interventions regarding appropriate care-seeking for chest pain in northern Tanzania, with particular attention to females, older residents, and other high-risk sub-populations. There have been no other studies of healthcare seeking behavior for chest pain in sub-Saharan Africa, and additional research is needed to establish whether similar patterns of care-seeking exist in other African settings.

In this population, knowledge of myocardial infarction symptoms and perception of self-risk were not associated with preference for hospital care for common symptoms of cardiovascular disease such as chest pain and shortness of breath. Therefore, educational interventions regarding ACS ought to include information about appropriate care seeking for ACS symptoms rather than just recognition of such symptoms or emphasizing personal cardiovascular risk. Previous research in Tanzania found that among patients admitted to referral hospitals with severe febrile illness, seeking care at multiple lower level health facilities and experiencing delays in accessing

referral hospitals was associated with increased mortality.[52] It is unknown whether such patterns of delays within the healthcare system are also associated with increased mortality for cardiovascular diseases in Tanzania.

The community survey study had several limitations. First, participants were asked to report their care seeking behavior for a hypothetical case of chest pain rather than to report actual healthcare utilization during any prior episodes of chest pain. If respondents selected a hospital because they perceived it to be the most socially acceptable answer, this may have resulted in an overestimation in the true proportion of patients who would present to a hospital. Furthermore, patients were only asked to identify causes of chest pain generally, without specifying acuity or associated symptoms. Adding such details may have resulted in a larger proportion of respondents identifying cardiovascular causes of chest pain and selecting a hospital as their preferred facility for chest pain. Finally, this survey was only given to self-identified healthcare decision makers. This was done in an attempt to survey only those whose opinions might guide actual healthcare seeking behavior, but exclusion of other adults may have resulted in a sample that was not truly representative of the local community. Furthermore, the survey was conducted in homes during daytime hours, which may have resulted in under-representation of males and individuals with certain occupations. Finally, information about individual respondents' cardiovascular risk profiles was not collected which would have allowed for a more nuanced analysis of

perceptions of self-risk. Nonetheless, given the known high local burden of risk factors like hypertension, the low proportion of adult respondents in this study who felt they were at risk of a heart attack, and the lack of association between age and perception of self-risk observed in our study, there is clearly a need for increased awareness of cardiovascular risk in northern Tanzania.

In conclusion, the results of the community survey suggest that, in northern Tanzania, community knowledge of ACS symptoms is low, recognition of personal risk of ACS is uncommon, and only a minority of residents would present to a hospital for possible symptoms of ACS like chest pain. These findings, taken together, suggest that patient knowledge and healthcare seeking behavior may be contributing to under-detection of ACS in SSA. These findings also highlight an urgent need for community education regarding ACS in northern Tanzania.

4.2 Implications of retrospective chart review findings

Heart failure and stroke were the most common admission diagnoses at a tertiary care center in northern Tanzania, accounting for more than one-fifth of all hospital admissions. ACS was an exceedingly rare admission diagnosis, and ischemic heart disease was rarely cited as a cause of heart failure. The large discrepancy between admissions for ACS versus other forms of cardiovascular disease raises important epidemiologic questions. These findings underscore the urgent need for public health interventions to combat cardiovascular disease in Tanzania.

Stroke accounted for nearly one in ten adult admissions in this study, similar to the proportion reported in Cameroon and Ghana.[53, 54] The burden of stroke observed in our study was substantially more than what has been reported outside SSA: in the United States (US), for example, all acute cerebrovascular disease accounted for only 2.0% of adult hospitalizations in 2014.[55]

Heart failure was the leading cause of hospitalization in northern Tanzania, accounting for more than one in ten adult admissions. This is also markedly higher than what has been observed outside SSA: heart failure accounted for 3.0% of adult admissions in the US in 2014.[55] Even compared to other settings in SSA, the 12.2% of hospital admissions due to heart failure observed in our study is high: recent studies in Zimbabwe,[56] Ghana,[6] and Nigeria[57, 58] reported that heart failure accounted for 4.7-9.6% of adult admissions. In northern Tanzania, this single diagnosis consumes substantial inpatient hospital resources, and public health interventions are needed to prevent costly hospitalizations. Although cost data was not collected in this study, previous studies in SSA have demonstrated that heart failure hospitalizations are catastrophically expensive for patients.[59] Uncontrolled hypertension was the most commonly identified etiology of heart failure while ischemic heart disease was rarely cited as a cause of heart failure in our study, consistent with the results of other studies across SSA.[60, 61] This stands in stark contrast to Europe and North America, where the majority of heart failure is due to ischemic heart disease.[62]

To date, little research has been done regarding the burden of ACS among hospital admissions in SSA. ACS was a very uncommon diagnosis in northern Tanzania, accounting for 0.3% of adult admissions. The paucity of ACS admissions in our study again stands in contrast to data from outside SSA: in the US, myocardial infarction accounted for 2.0% of adult hospitalizations in 2014.[55] Moreover, the scarcity of ACS admissions relative to other cardiovascular admissions in northern Tanzania is particularly notable. The ratio of ACS admissions to heart failure admissions was approximately 1:33 in our study, however in the US, this ratio was 1:1.5 in 2014.[55] Similarly, the ratio of ACS admissions to stroke admissions in our study was 1:23, whereas in the US in 2014 this ratio was 1:1.0.[55] This disparity in ACS diagnoses versus other cardiovascular diagnoses does not appear to be unique to East Africa: a recent study in Ghana reported that the ratio of ischemic heart disease admissions to heart failure admissions was 1:12.[6]

The apparent difference in the distribution of cardiovascular disease phenotypes in SSA versus other world regions raises many pressing epidemiologic questions. Possible explanations for the disparity include widespread under-detection of ACS in SSA or a combination of unique environmental or genetic risk factors leading to a predilection for certain forms of cardiovascular disease. Some have postulated that ACS may be under-diagnosed in SSA due to poor community awareness and delayed healthcare seeking, inadequate physician training, and lack of diagnostic and treatment

capacity.[8] Alternatively, some have argued that hypertension is the dominant cardiovascular risk factor in SSA whereas atherosclerosis, hyperlipidemia, and smoking are relatively more common in the rest of the world, which may explain the different phenotypes of cardiovascular disease in SSA.[63] Others have raised the possibility of unique genetic or environmental factors that may predispose Africans to stroke and heart failure versus ACS.[64, 65] Ultimately, a combination of these factors may explain the low burden of ACS relative to other forms of cardiovascular disease in Tanzania and SSA at large. However, the findings presented here emphasize the need for multiple avenues of research to understand patient care-seeking behavior, physician diagnostic practices, and the true burden of disease of ACS in SSA.

This study had several limitations. This study reported the clinical diagnoses according to the admitting physician, but the clinical and diagnostic data supporting these diagnoses were not reviewed and therefore no evaluation of the accuracy of these clinical diagnoses is possible. However, evidence from SSA suggests that clinical diagnoses of stroke have >80% positive predictive value for stroke.[66, 67] Similarly, studies outside SSA have shown that clinical diagnoses of heart failure are generally accurate.[68, 69]

In conclusion, heart failure and stroke are the two most common admission diagnoses among adults in northern Tanzania and consume a large proportion of inpatient resources. ACS is an extremely rare diagnosis in northern Tanzania relative to

other forms of cardiovascular disease, and further research is needed to ascertain the reasons for this discrepancy.

4.3 Implications of prospective observational study findings

To our knowledge, this is the first prospective study from SSA of patterns of diagnosis and treatment of patients with possible ACS. We found large numbers of patients presenting to the ED with chest pain and shortness of breath, many of whom were high-risk. However, few of these patients underwent full evaluation for ACS, and ACS testing was not targeted to higher risk patients. Ultimately, very few patients received a diagnosis of ACS, and even fewer were treated with medications known to reduce mortality in ACS such as aspirin. Taken together, these findings demonstrate that in northern Tanzania, diagnostic workups for ACS are not routine even among high-risk patients presenting to the ED. These observations support speculation that physician practices may be contributing to ACS under-detection in SSA.

We observed large numbers of patients presenting to the ED with chest pain and shortness of breath. This is notable, given that a recent study found that the majority of adults in northern Tanzania would not present to a hospital for chest pain.[25] This suggests that the number of patients observed in this study likely represent only a fraction of those with potential ACS symptoms in the wider community. The median duration of illness at time of hospital presentation among patients in this study was seven days, indicating that even those who do seek hospital care for such symptoms do

not do so promptly. Such delayed presentation stands in stark contrast to care-seeking behavior in high income countries, where median presentation times for patients with chest pain or other potential ACS symptoms are typically less than four hours.[70-73] Even in other low- and middle-income countries (LMICs) such as Pakistan and India, the majority of patients with possible ACS symptoms presented to hospital within twelve hours.[74-76] To our knowledge, this is the first report of pre-hospital delays among patients with chest pain and shortness of breath in SSA, and the results are discouraging. The reasons for the pronounced delay in care-seeking observed in our study are likely myriad, but lack of patient education may be contributing to the problem. A recent community survey found that the vast majority of Tanzanians did not associate chest pain or shortness of breath with potentially fatal cardiovascular diseases like ACS,[25, 26] suggesting that lack of patient appreciation for the potential seriousness of these symptoms may explain such delayed care-seeking. Further research is needed to understand other barriers to prompt hospital presentation.

By conventional standards, the patients presenting in this study were at high risk for ACS. They all had chest pain or shortness of breath, and nearly all of them had anginal symptoms. Moreover, a large majority of them had risk factors like hypertension and approximately two-thirds had an overall five-year risk of cardiovascular event greater than 10%. Despite this, diagnostic workups for ACS were not routine. Only half of enrolled patients underwent ECG testing, and this testing was

not targeted to the most high-risk patients. High-risk patients were in fact slightly less likely to receive an ECG than other patients, although this difference was not statistically significant. Fewer than 3% of enrolled patients underwent cardiac biomarker testing, an essential part of the diagnostic workup for ACS.[22] Although there have been no other studies of diagnostic workups for chest pain and shortness of breath in SSA, our results are similar to what has been observed in other LMICs. In an ED-based study in Pakistan, for example, 55% of adults presenting with chest pain received an ECG and 5% had cardiac biomarker testing performed.[77] Additional study is needed to determine if the patterns of diagnostic workups observed in our study are representative of physician practices across SSA. In Tanzania, many healthcare facilities do not have access to electrocardiogram and cardiac biomarker testing,[78] and so complete diagnostic workups for ACS may be even rarer in other hospitals.

Consistent with other studies from SSA,[6, 7, 24] ACS was a rare diagnosis in our study, attributed to only 1.8% of patients with chest pain or shortness of breath. However, given the proportion of patients who did not undergo ECG or cardiac biomarker testing, it remains unclear whether the low number of ACS cases is reflective of low disease burden, frequent misdiagnosis, or both. The majority of patients received a diagnosis of symptomatic hypertension or heart failure, two diagnoses that arguably require exclusion of ACS. Less than 1% of enrolled patients received empiric treatment

with aspirin, an inexpensive and widely available treatment known to reduce mortality in ACS.[79]

When compared to standards of care in high income settings where ACS is a leading cause of mortality,[22, 80] the patterns of diagnosis and treatment for ED patients with chest pain and shortness of breath observed in this study would be considered inadequate. However, assessing the appropriateness of these patterns of care is difficult without knowledge of the local burden of disease. Like most countries in SSA, there are currently no data regarding the burden of ischemic heart disease in Tanzania.[4, 8] Thus, establishing the prevalence of ACS in this patient population is necessary to determine what interventions are required to improve care. Regardless, the results presented here suggest that physician diagnostic practices may be contributing to the perception of ACS is rare in Tanzania, which may in turn reinforce patterns of incomplete diagnostic workups. Additional research is needed to understand physician-perceived barriers to care which contribute to incomplete workups and low rates of ACS diagnosis and treatment.

This study had several limitations. First, this study relied on patient self-report to identify some cardiovascular risk factors, such as diabetes and hyperlipidemia. Given the large proportion of adults in SSA with undiagnosed diabetes and other risk factors,[81-83] this likely resulted in an underestimation of the risk profile of this patient population. Similarly, social desirability bias may have affected participants' responses

to questions regarding cigarette smoking, exercise, and HIV infection, again leading to an underestimation of cardiovascular risk. Additionally, although the kinds of diagnostic investigations ordered by physicians were recorded by the study team, the results of such testing were not collected. This data would have led to a better assessment of the appropriateness of the clinical diagnoses given to enrolled patients.

In conclusion, large numbers of adults present to the ED in northern Tanzania with chest pain and shortness of breath, but marked delays in care-seeking are common. The majority of these patients are at high risk for ACS, but full diagnostic workups for ACS are infrequent and ACS is rarely diagnosed. Further study is needed to understand physician- and patient-related barriers to care and to quantify the true local burden of disease.

5. Conclusion

In conclusion, this study identified multiple patient and physician-related barriers to ACS diagnosis and care in northern Tanzania. We found that there is little community knowledge of ACS and its symptoms, that the majority of adults do not perceive themselves to be at risk of ACS, and that patients who do seek care for potential ACS symptoms do so after prolonged delays. We further found that ED physicians rarely initiate complete diagnostic workups for ACS even for patients who are high-risk, and that ACS is an extremely uncommon diagnosis. These findings highlight an urgent need for patient and physician educational interventions to improve quality of care and to fully understand the burden of ACS in Tanzania.

References

1. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;**388**(10053):1459-1544. doi: 10.1016/s0140-6736(16)31012-1.

2. Campbell NR, Lemogoum D; Hypertension in sub-Saharan Africa: a massive and increasing health disaster awaiting solution. *Cardiovasc J Afr* 2015;**26**(4):152-4.

3. Tibazarwa K, Ntyintyane L, Sliwa K, et al.; A time bomb of cardiovascular risk factors in South Africa: results from the Heart of Soweto Study "Heart Awareness Days". *Int J Cardiol* 2009;**132**(2):233-9. doi: 10.1016/j.ijcard.2007.11.067.

4. Hertz JT, Reardon JM, Rodrigues CG, et al.; Acute myocardial infarction in sub-Saharan Africa: the need for data. *PLoS One* 2014;**9**(5):e96688. doi: 10.1371/journal.pone.0096688.

5. IHME. *Tanzania*. http://www.healthdata.org/tanzania (Date Accessed 2016 Accessed, date last accessed)

6. Appiah LT, Sarfo FS, Agyemang C, et al.; Current trends in admissions and outcomes of cardiac diseases in Ghana. *Clin Cardiol* 2017;**40**(10):783-788. doi: 10.1002/clc.22753.

7. Kolo PM, Fasae AJ, Aigbe IF, et al.; Changing trend in the incidence of myocardial infarction among medical admissions in Ilorin, north-central Nigeria. *Niger Postgrad Med J* 2013;**20**(1):5-8.

8. Nkoke C, Luchuo EB; Coronary heart disease in sub-Saharan Africa: still rare, misdiagnosed or underdiagnosed? *Cardiovasc Diagn Ther* 2016;**6**(1):64-6. doi: 10.3978/j.issn.2223-3652.2015.08.01.

9. Shavadia J, Yonga G, Otieno H; A prospective review of acute coronary syndromes in an urban hospital in sub-Saharan Africa. *Cardiovasc J Afr* 2012;**23**(6):318-21. doi: 10.5830/cvja-2012-002.

10. Moran A, Forouzanfar M, Sampson U, et al.; The epidemiology of cardiovascular diseases in sub-Saharan Africa: the Global Burden of Diseases, Injuries and Risk Factors 2010 Study. *Prog Cardiovasc Dis* 2013;**56**(3):234-9. doi: 10.1016/j.pcad.2013.09.019.

11. Ntsekhe M, Damasceno A; Recent advances in the epidemiology, outcome, and prevention of myocardial infarction and stroke in sub-Saharan Africa. *Heart* 2013;**99**(17):1230-5. doi: 10.1136/heartjnl-2012-303585.

12. Hurst RT, Ng DW, Kendall C, et al.; Clinical use of carotid intima-media thickness: review of the literature. *J Am Soc Echocardiogr* 2007;**20**(7):907-14. doi: 10.1016/j.echo.2007.02.028.

13. Stein JH, Korcarz CE, Hurst RT, et al.; Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;**21**(2):93-111; quiz 189-90. doi: 10.1016/j.echo.2007.11.011.

14. Jeevarethinam A, Venuraju S, Weymouth M, et al.; Carotid intimal thickness and plaque predict prevalence and severity of coronary atherosclerosis: a pilot study. *Angiology* 2015;**66**(1):65-9. doi: 10.1177/0003319714522849.

15. Kablak-Ziembicka A, Tracz W, Przewlocki T, et al.; Association of increased carotid intima-media thickness with the extent of coronary artery disease. *Heart* 2004;**90**(11):1286-90. doi: 10.1136/hrt.2003.025080.

16. Temu TM, Bahiru E, Bukachi F, et al.; Lay beliefs about hypertension among HIV-infected adults in Kenya. *Open Heart* 2017;**4**(1):e000570. doi: 10.1136/openhrt-2016-000570.

17. Hertz JT, Munishi OM, Sharp JP, et al.; Comparing actual and perceived causes of fever among community members in a low malaria transmission setting in northern Tanzania. *Trop Med Int Health* 2013;**18**(11):1406-15. doi: 10.1111/tmi.12191.

18. Walker AR, Walker BF, Segal I; Some puzzling situations in the onset, occurrence and future of coronary heart disease in developed and developing populations, particularly such in sub-Saharan Africa. *J R Soc Promot Health* 2004;**124**(1):40-6.

19. Abbott LS, Slate EH; Improving Cardiovascular Disease Knowledge among Rural Participants: The Results of a Cluster Randomized Trial. *Healthcare (Basel)* 2018;**6**(3). doi: 10.3390/healthcare6030071.

20. Lee TW, Lee SH, Kim HH, et al.; Effective intervention strategies to improve health outcomes for cardiovascular disease patients with low health literacy skills: a systematic review. *Asian Nurs Res (Korean Soc Nurs Sci)* 2012;**6**(4):128-36. doi: 10.1016/j.anr.2012.09.001.

21. Magnani JW, Mujahid MS, Aronow HD, et al.; Health Literacy and Cardiovascular Disease: Fundamental Relevance to Primary and Secondary Prevention: A Scientific Statement From the American Heart Association. *Circulation* 2018;**138**(2):e48-e74. doi: 10.1161/cir.0000000000000579.

22. Amsterdam EA, Kirk JD, Bluemke DA, et al.; Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. *Circulation* 2010;**122**(17):1756-76. doi: 10.1161/CIR.0b013e3181ec61df.

23. Pitts SR, Niska RW, Xu J, et al.; National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *Natl Health Stat Report* 2008(7):1-38.

24. Geyser M, Smith S; Chest pain prevalence, causes, and disposition in the emergency department of a regional hospital in Pretoria. *Afr J Prim Health Care Fam Med* 2016;**8**(1):e1-5. doi: 10.4102/phcfm.v8i1.1048.

25. Hertz JT, Madut DB, Tesha RA, et al.; Perceptions of chest pain and healthcare seeking behavior for chest pain in northern Tanzania: A community-based survey. *PLoS One* 2019;**14**(2):e0212139. doi: 10.1371/journal.pone.0212139.

26. Hertz JT, Madut DB, Tesha RA, et al.; Knowledge of myocardial infarction symptoms and perceptions of self-risk in Tanzania. *Am Heart J* 2019;**210**:69-74. doi: 10.1016/j.ahj.2019.01.003.

27. *United Republic of Tanzania 2012 Population and Housing Census.* Dar es Salaam, Tanzania: Ministry of Finance, 2013.

28. Galson SW, Staton CA, Karia F, et al.; Epidemiology of hypertension in Northern Tanzania: a community-based mixed-methods study. *BMJ Open* 2017;**7**(11):e018829. doi: 10.1136/bmjopen-2017-018829.

29. Stanifer JW, Cleland CR, Makuka GJ, et al.; Prevalence, Risk Factors, and Complications of Diabetes in the Kilimanjaro Region: A Population-Based Study from Tanzania. *PLoS One* 2016;**11**(10):e0164428. doi: 10.1371/journal.pone.0164428.

30. WHO. *World Health Organization Vaccination Coverage Cluster Surveys: Reference Manual.* Geneva: World Health Organization, 2018.

31. WHO. *WHO STEPS Instrument: The WHO STEPwise approach to noncommunicable disease risk factor suveillance*.

https://www.who.int/ncds/surveillance/steps/instrument/STEPS_Instrument_V3.2.pdf (Date Accessed, date last accessed)

32. James PA, Oparil S, Carter BL, et al.; 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama* 2014;**311**(5):507-20. doi: 10.1001/jama.2013.284427.

33. ADA; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;**41**(Suppl 1):S13-s27. doi: 10.2337/dc18-S002.

34. WHO. *Global Recommendations on Physical Activity for Health.* Geneva: World Health Organization, 2010.

35. Aune D, Giovannucci E, Boffetta P, et al.; Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol* 2017;**46**(3):1029-1056. doi: 10.1093/ije/dyw319.

36. Campeau L; Letter: Grading of angina pectoris. *Circulation* 1976;**54**(3):522-3.

37. Vyas S, Kumaranayake L; Constructing socio-economic status indices: how to use principal components analysis. *Health Policy Plan* 2006;**21**(6):459-68. doi: 10.1093/heapol/czl029.

38. Gaziano TA, Young CR, Fitzmaurice G, et al.; Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008;**371**(9616):923-31. doi: 10.1016/s0140-6736(08)60418-3.

39. Gaziano TA, Abrahams-Gessel S, Alam S, et al.; Comparison of Nonblood-Based and Blood-Based Total CV Risk Scores in Global Populations. *Glob Heart* 2016;**11**(1):37-46.e2. doi: 10.1016/j.gheart.2015.12.003.

40. Pastorius Benziger C, Bernabe-Ortiz A, Miranda JJ, et al.; Sex differences in health care-seeking behavior for acute coronary syndrome in a low income country, Peru. *Crit Pathw Cardiol* 2011;**10**(2):99-103. doi: 10.1097/HPC.0b013e318223e375.

41. Adamson J, Donovan J, Ben-Shlomo Y, et al.; Age and sex interaction in reported help seeking in response to chest pain. *Br J Gen Pract* 2008;**58**(550):318-23. doi: 10.3399/bjgp08X279670.

42. Chaturvedi N, Rai H, Ben-Shlomo Y; Lay diagnosis and health-care-seeking behaviour for chest pain in south Asians and Europeans. *Lancet* 1997;**350**(9091):1578-83. doi: 10.1016/s0140-6736(97)06243-0.

43. Song L, Yan HB, Yang JG, et al.; Impact of patients' symptom interpretation on care-seeking behaviors of patients with acute myocardial infarction. *Chin Med J (Engl)* 2010;**123**(14):1840-5.

44. Chibwana AI, Mathanga DP, Chinkhumba J, et al.; Socio-cultural predictors of health-seeking behaviour for febrile under-five children in Mwanza-Neno district, Malawi. *Malar J* 2009;**8**:219. doi: 10.1186/1475-2875-8-219.

45. Boateng D, Wekesah F, Browne JL, et al.; Knowledge and awareness of and perception towards cardiovascular disease risk in sub-Saharan Africa: A systematic review. *PLoS One* 2017;**12**(12):e0189264. doi: 10.1371/journal.pone.0189264.

46. Temu TM, Kirui N, Wanjalla C, et al.; Cardiovascular health knowledge and preventive practices in people living with HIV in Kenya. *BMC Infect Dis* 2015;**15**:421. doi: 10.1186/s12879-015-1157-8.

47. Aminde LN, Takah N, Ngwasiri C, et al.; Population awareness of cardiovascular disease and its risk factors in Buea, Cameroon. *BMC Public Health* 2017;**17**(1):545. doi: 10.1186/s12889-017-4477-3.

48. *National Noncommunicable Disease Strategy.* Dar es Salaam: Tanzania Ministry of Health and Social Welfare, 2008.

49. Michuzi O; Siku ya moyo duniani kuadhimishwa Septemba 29 kwa kupima magonjwa wa moyo. *Mtaa Kwa Mtaa*. Dar es Salaam, 2018.

50. *Standard treatment guidelines & national essential medicines list Tanzania mainland.* Dar es Salaam: Ministry of Health, Community Development, Gender, Elderly, and Children, 2017.

51. Liao L, Whellan DJ, Tabuchi K, et al.; Differences in care-seeking behavior for acute chest pain in the United States and Japan. *Am Heart J* 2004;**147**(4):630-5. doi: 10.1016/j.ahj.2003.10.006.

52. Snavely ME, Maze MJ, Muiruri C, et al.; Sociocultural and health system factors associated with mortality among febrile inpatients in Tanzania: a prospective social biopsy cohort study. *BMJ Glob Health* 2018;**3**(1):e000507. doi: 10.1136/bmjgh-2017-000507.

53. Sarfo FS, Akassi J, Awuah D, et al.; Trends in stroke admission and mortality rates from 1983 to 2013 in central Ghana. *J Neurol Sci* 2015;**357**(1-2):240-5. doi: 10.1016/j.jns.2015.07.043.

54. Lekoubou A, Nkoke C, Dzudie A, et al.; Stroke admission and case-fatality in an urban medical unit in sub-Saharan Africa: a fourteen year trend study from 1999 to 2012. *J Neurol Sci* 2015;**350**(1-2):24-32. doi: 10.1016/j.jns.2015.02.002.

55. *Healthcare Cost and Utilization Project (HCUP) Fast Stats*. https://www.hcup-us.ahrq.gov/faststats/NationalDiagnosesServlet (Date Accessed 2017 Accessed, date last accessed)

56. Bardgett HP, Dixon M, Beeching NJ; Increase in hospital mortality from non-communicable disease and HIV-related conditions in Bulawayo, Zimbabwe, between 1992 and 2000. *Trop Doct* 2006;**36**(3):129-31. doi: 10.1258/004947506777978217.

57. Onwuchekwa AC, Asekomeh GE; Pattern of heart failure in a Nigerian teaching hospital. *Vasc Health Risk Manag* 2009;**5**:745-50.

58. Osuji CU, Onwubuya EI, Ahaneku GI, et al.; Pattern of cardiovascular admissions at Nnamdi Azikiwe University Teaching Hospital Nnewi, South East Nigeria. *Pan Afr Med J* 2014;**17**:116. doi: 10.11604/pamj.2014.17.116.1837.

59. Ogah OS, Stewart S, Onwujekwe OE, et al.; Economic burden of heart failure: investigating outpatient and inpatient costs in Abeokuta, Southwest Nigeria. *PLoS One* 2014;**9**(11):e113032. doi: 10.1371/journal.pone.0113032.

60. Bloomfield GS, Barasa FA, Doll JA, et al.; Heart failure in sub-Saharan Africa. *Curr Cardiol Rev* 2013;**9**(2):157-73.

61. Damasceno A, Mayosi BM, Sani M, et al.; The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med* 2012;**172**(18):1386-94. doi: 10.1001/archinternmed.2012.3310.

62. Khatibzadeh S, Farzadfar F, Oliver J, et al.; Worldwide risk factors for heart failure: a systematic review and pooled analysis. *Int J Cardiol* 2013;**168**(2):1186-94. doi: 10.1016/j.ijcard.2012.11.065.

63. Owolabi MO, Ugoya S, Platz T; Racial disparity in stroke risk factors: the Berlin-Ibadan experience; a retrospective study. *Acta Neurol Scand* 2009;**119**(2):81-7. doi: 10.1111/j.1600-0404.2008.01077.x.

64. Owolabi M, Sarfo F, Howard VJ, et al.; Stroke in Indigenous Africans, African Americans, and European Americans: Interplay of Racial and Geographic Factors. *Stroke* 2017;**48**(5):1169-1175. doi: 10.1161/strokeaha.116.015937.

65. Stewart S, Carrington MJ, Pretorius S, et al.; Elevated risk factors but low burden of heart disease in urban African primary care patients: a fundamental role for primary prevention. *Int J Cardiol* 2012;**158**(2):205-10. doi: 10.1016/j.ijcard.2011.01.022.

66. Aiwansoba IF, Ibiene OE, Ashinedu UR, et al.; Benin stroke score in the diagnosis of acute brain infarct: a pilot study in Senegalese Africans. *Ann Afr Med* 2014;**13**(4):157-60. doi: 10.4103/1596-3519.142278.

67. Nyandaiti YW, Bwala SA; Validation study of the Siriraj stroke score in North-east Nigeria. *Niger J Clin Pract* 2008;**11**(3):176-80.

68. Kelder JC, Cramer MJ, van Wijngaarden J, et al.; The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation* 2011;**124**(25):2865-73. doi: 10.1161/circulationaha.111.019216.

69. Lokuge A, Lam L, Cameron P, et al.; B-type natriuretic peptide testing and the accuracy of heart failure diagnosis in the emergency department. *Circ Heart Fail* 2010;**3**(1):104-10. doi: 10.1161/circheartfailure.109.869438.

70. Ruane L, J HG, Parsonage W, et al.; Differences in Presentation, Management and Outcomes in Women and Men Presenting to an Emergency Department With Possible Cardiac Chest Pain. *Heart Lung Circ* 2017;**26**(12):1282-1290. doi: 10.1016/j.hlc.2017.01.003.

71. Bruins Slot MH, Rutten FH, van der Heijden GJ, et al.; Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care. *Fam Pract* 2012;**29**(3):332-7. doi: 10.1093/fampra/cmr089.

72. Angerud KH, Thylen I, Sederholm Lawesson S, et al.; Symptoms and delay times during myocardial infarction in 694 patients with and without diabetes; an explorative cross-sectional study. *BMC Cardiovasc Disord* 2016;**16**(1):108. doi: 10.1186/s12872-016-0282-7.

73. Bugiardini R, Ricci B, Cenko E, et al.; Delayed Care and Mortality Among Women and Men With Myocardial Infarction. *J Am Heart Assoc* 2017;**6**(8). doi: 10.1161/jaha.117.005968.

74. Ahmed S, Khan A, Ali SI, et al.; Differences in symptoms and presentation delay times in myocardial infarction patients with and without diabetes: A cross-sectional study in Pakistan. *Indian Heart J* 2018;**70**(2):241-245. doi: 10.1016/j.ihj.2017.07.013.

75. Alexander T, Mullasari AS, Kaifoszova Z, et al.; Framework for a National STEMI Program: consensus document developed by STEMI INDIA, Cardiological Society of India and Association Physicians of India. *Indian Heart J* 2015;**67**(5):497-502. doi: 10.1016/j.ihj.2015.05.017.

76. Khan MS, Jafary FH, Faruqui AM, et al.; High prevalence of lack of knowledge of symptoms of acute myocardial infarction in Pakistan and its contribution to delayed presentation to the hospital. *BMC Public Health* 2007;**7**:284. doi: 10.1186/1471-2458-7-284.

77. Paichadze N, Afzal B, Zia N, et al.; Characteristics of chest pain and its acute management in a low-middle income country: analysis of emergency department surveillance data from Pakistan. *BMC Emerg Med* 2015;**15 Suppl 2**:S13. doi: 10.1186/1471-227x-15-s2-s13.

78. Masanja H, Smithson P, Ipuge Y. *Tanzania Service Availability and Readiness Assessment (SARA) 2012.* Dar es Salaam: Ifakara Health Institute, Tanzania Ministry of Health and Social Welfare, 2013.

79. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;**2**(8607):349-60.

80. Naghavi M; Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;**390**(10100):1151-1210. doi: 10.1016/s0140-6736(17)32152-9.

81. Ataklte F, Erqou S, Kaptoge S, et al.; Burden of undiagnosed hypertension in sub-saharan Africa: a systematic review and meta-analysis. *Hypertension* 2015;**65**(2):291-8. doi: 10.1161/hypertensionaha.114.04394.

82. Manne-Goehler J, Atun R, Stokes A, et al.; Diabetes diagnosis and care in sub-Saharan Africa: pooled analysis of individual data from 12 countries. *Lancet Diabetes Endocrinol* 2016;**4**(11):903-912. doi: 10.1016/s2213-8587(16)30181-4.

83. Hall V, Thomsen RW, Henriksen O, et al.; Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review. *BMC Public Health* 2011;**11**:564. doi: 10.1186/1471-2458-11-564.