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FASTTRACK CLINICAL RESEARCH

Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry

Karen Sliwa[1,2], Beth A. Davison[3]*, Bongani M. Mayosi[4], Albertino Damasceno[5], Mahmoud Sani[6], Okekuchwu S. Ogah[7], Charles Mondo[8], Dike Ojji[9], Anastase Dzudie[10], Charles Kouam Kouam[10], Ahmed Suliman[11], Neshaad Schrueder[4], Gerald Yonga[12], Sergine Abdou Ba[13], Fikru Maru[14], Bekele Alemayehu[14], Christopher Edwards[3], and Gad Cotter[3]

[1]Department of Medicine, Faculty of Health Sciences, Hatter Institute for Cardiovascular Research in Africa and the Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa; [2]Soweto Cardiovascular Research Unit, University of the Witwatersrand, Johannesburg, South Africa; [3]Momentum Research, Inc, 3100 Tower Boulevard, Suite 801, Durham, NC 27707, USA; [4]Department of Medicine, GF Jooste and Groote Schuur Hospitals, University of Cape Town, Cape Town, South Africa; [5]Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique; [6]Department of Medicine, Bayero University Kano/Aminu Kano Teaching Hospital, Kano, Nigeria; [7]Federal Medical Centre, Abeokuta, Nigeria; [8]Uganda Heart Institute, Kampala, Uganda; [9]Cardiology Unit, Department of Medicine, University of Abuja Teaching Hospital, Abuja, Nigeria; [10]Department of Internal Medicine, Douala General Hospital and Buea Faculty of Health Sciences, Douala, Cameroon; [11]Faculty of Medicine, University of Khartoum, Khartoum, Sudan; [12]Department of Medicine, Aga Khan University, Nairobi, Kenya; [13]Service de Cardiologie, Faculte de medecine de Dakar, Dakar, Senegal; and [14]Addis Cardiac Hospital, Addis Ababa, Ethiopia

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Aims Contrary to elderly patients with ischaemic-related acute heart failure (AHF) typically enrolled in North American and European registries, patients enrolled in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF) were middle-aged with AHF due primarily to non-ischaemic causes. We sought to describe factors prognostic of re-admission and death in this developing population.

Methods and results Prognostic models were developed from data collected on 1006 patients enrolled in THESUS-HF, a prospective registry of AHF patients in 12 hospitals in nine sub-Saharan African countries, mostly in Nigeria, Uganda, and South Africa. The main predictors of 60-day re-admission or death in a model excluding the geographic region were a history of malignancy and severe lung disease, admission systolic blood pressure, heart rate and signs of congestion (rales), kidney function (BUN), and echocardiographic ejection fraction. In a model including region, the Southern region had a higher risk. Age and admission sodium levels were not prognostic. Predictors of 180-day mortality included malignancy, severe lung disease, smoking history, systolic blood pressure, heart rate, and symptoms and signs of congestion (orthopnoea, peripheral oedema and rales) at admission, kidney dysfunction (BUN), anaemia, and HIV positivity. Discrimination was low for all models, similar to models for European and North American patients, suggesting that the main factors contributing to adverse outcomes are still unknown.

Conclusion Despite the differences in age and disease characteristics, the main predictors for 6 months mortality and combined 60 days re-admission and death are largely similar in sub-Saharan Africa as in the rest of the world, with some exceptions such as the association of the HIV status with mortality.

Keywords Heart failure • Prognosis • sub-Saharan Africa

* Corresponding author. Tel: +1 (919)287-1824, Fax: +1 (919)287-1825, E-mail: bethdavison@momentum-research.com

Introduction

Acute heart failure (AHF) is one of the most common reasons for admission to hospital, and a major driver for health-related cost globally. Its prevalence is shown to be high and outcomes dire in North America,[1] Europe,[2] South America,[3] Southeast Asia,[4] and recently also in sub-Saharan Africa.[5]

Despite the huge impact of this disease until recently little progress has been made in characterizing the pathophysiology of the disease. The 2012 European Society of Cardiology (ESC) guidelines on acute and chronic heart failure[6] highlight the lack of evidence-based therapy for AHF compared with the therapeutic options for chronic heart failure. Models examining predictors of outcomes such as short-term re-admission and death have very low ability to discriminate between those with and without the outcome with *c*-indexes ranging from 0.6 to 0.7,[7–9] where 0.5 represents chance and 1.0 perfect discrimination. This lack of understanding of pathophysiology and predictors of outcome in AHF is at the core of the lack of progress in its treatment with available therapies (diuretics and nitrates), such that outcomes have been largely unchanged over the last 30–40 years.[10]

Acute heart failure exacts a heavy social and economic burden on families and society in Africa. Contrary to North America and Europe where AHF affects patients with an average age of >70 years old,[1] the THESUS-HF registry[5] has shown that in sub-Saharan Africa the disease affects men and women in the most productive years of life, at an average age of 52.3 years and is mostly caused by hypertension and not ischaemic heart disease. Hence, understanding the causes for re-admission and death is especially important in this African population and may be relevant to other developing regions of the world.

In this work, we identify patient characteristics associated with 60-day re-admission or death and 180-day mortality in a cohort of 1006 African patients admitted with AHF and enrolled in the THESUS-HF registry.

Methods

Patients and data collected

THESUS-HF[5] was a prospective, multicentre, international observational survey conducted in 12 hospitals from 9 countries in the southern, eastern, central, and western regions of sub-Saharan Africa. All patients were recruited during an admission for AHF, mostly in Nigeria, Uganda, and South Africa. Methods and results have been previously described in detail.[5] In brief, from July 2007 to June 2010 patients admitted with dyspnoea and diagnosed with AHF based on symptoms and signs (including dyspnoea, orthopnoea, dyspnoea on exercise, rales, oedema, jugular venous pulse, and oxygen saturation) and who provided written informed consent were enrolled into the study. The diagnosis was supported by echocardiographical findings and was confirmed by a cardiologist. Exclusion criteria included acute ST elevation myocardial infarction, severe renal failure (patients on dialysis or creatinine >4 mg/dL), nephrotic syndrome, or hepatic failure. Approval was obtained from the ethics committee of each participating institution and the study conformed to the principles of the Declaration of Helsinki.

Detailed data collected at admission onto standardized case report forms included medical history, medication use, laboratory values, and physical examination with symptoms and signs of heart failure. Echocardiography and electrocardiography were also performed. Human immunodeficiency virus testing was performed as clinically indicated. Patients were followed either by clinic visit or telephone contact through 6 months for the occurrence of re-admissions and death. As described in the main report, patients were classified as having either an emerging or endemic cause of heart failure. Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

Statistical methods

Cox regression models were constructed considering the time from admission to the first event; times for patients without the event of interest were censored at the earlier of the last date the patient was known to be alive or the period of interest. Prognostic models were constructed for the two outcomes of interest considering candidate predictors chosen based on data available in THESUS-HF, variables found to be predictive in other AHF studies, and clinical judgment. Participating countries were grouped into three regions: East which comprised Sudan ($n = 72$), Ethiopia ($n = 10$), Kenya ($n = 32$), and Uganda ($n = 154$); West which comprised Senegal ($n = 15$), Nigeria ($n = 425$), and Cameroon ($n = 90$); and South which comprised South Africa ($n = 132$) and Mozambique ($n = 76$). Because region was found to be significantly associated with re-admission or death, and because regional cultural and medical practice patterns might affect admission, we also constructed a model examining only patient clinical characteristics.

The linearity of association between each continuous predictor and each outcome was assessed using restricted cubic splines with four 'knots' with a test of the significance of the non-linear terms.[11] Where the association was non-linear, a readily interpreted transformation was chosen through examination of plots of the predicted log hazard ratio against the value of the predictor and changes in Akaike's information criterion. If little information was lost, the same transformation was used to model both outcomes. Multiple imputation assuming multivariate normality (SAS PROC MI) was used to handle missing values. The imputation model included all covariates under consideration for the multivariable models. The ranges of imputed values were restricted to the ranges of the observed values. Seven imputation data sets were used. Parameter estimates were averaged across these data sets using Rubin's algorithm[12] (SAS PROC MIANALYZE). SAS version 9.2 (SAS Institute, Inc, Cary, NC, USA) was used for the analyses.

We constructed a multivariable model for each of the outcomes from the candidate predictors listed in *Table 1* (except those effects that were dropped), with continuous variables included using the model forms indicated in *Tables 2–4*. For the 60-day composite endpoint, one model was assessed with the inclusion of region as a predictor and one excluding region. Backwards selection was performed in each of the imputed data sets, with the criterion for staying at $P = 0.10$. Predictors that were significant in at least four of the imputed data sets were kept in the reduced model. The discrimination of the models was evaluated using the c-index.[13] The model fit was assessed visually using calibration plots[11] which were generated from the stacked imputation data sets.[14] In these plots, patients were grouped by deciles of predicted risk, and the mean predicted risk for each group was compared with the Kaplan–Meier estimate of risk in these same groups.

Results

Of the 1006 patients included in the THESUS-HF database, one patient was excluded who had unreasonable data pertaining to both outcomes (i.e. subject had a date of death listed before admission) giving 1005 patients for this analysis. Of the 1006 patients enrolled 430 were enrolled in Nigeria, 154 in Uganda and 132 in South Africa. Patients were followed a median of 180 days.

Table 1 Candidate predictors for re-admission and death

Variable	*N*	*n*	Distribution (%) for dichotomous; 25th %ile, median, 75th %ile for continuous	% missing	Comments
Hx of DM	1004	114	(11.4)	0.2	
Hx of IHD	1004	82	(8.2)	0.2	
Valvular disease	1000	272	(27.2)	0.6	
HIV positive	992	65	(6.6)	1.4	
Hypertension	1002	556	(55.5)	0.4	
Hyperlipidaemia	981	90	(9.2)	2.5	
HX of stroke	1005	25	(2.5)	0.1	
HX of PVD	1003	12	(1.2)	0.3	
Current or former smoker	1002	98	(9.8)	0.4	
Malignancy	1003	13	(1.3)	0.3	
Hx of depression	1004	33	(3.3)	0.2	
Hx of dementia	1004	22	(2.2)	0.2	
Hx of atrial fibrillation	998	184	(18.4)	0.8	
Hx of pericardial Disease	1000	53	(5.3)	0.6	
Hx of Cardiomyopathy	994	416	(41.8)	1.2	
Hx of cor pulmonale	995	72	(7.2)	1.1	
Age, years	996		39, 55, 67	1.0	
Male sex	1005	494	(49.2)	0.1	
White race	999	15	(1.5)	0.7	Dropped from consideration as there were no events for either outcome in 15 white subjects
Ejection fraction, %	930		27, 38, 50	7.6	
BMI, kg/m^2	968		20.9, 24.0, 28.0	3.8	Extreme values of 214.5 and 121.4 set to missing for analysis
BUN, mg/dL	971		16.5, 26.6, 42.0	3.5	Values <6 set to missing
Creatinine, mg/dL	970		0.89, 1.12, 1.5	3.6	Values <0.4 set to missing
Glucose, mg/dL	878		84.0, 93.7, 117.0	12.7	
Haemoglobin, g/dL	967		10.7, 12.3, 13.7	3.9	
Lymphocytes, %	839		20.0, 30.0, 39.6	16.6	
Sodium, mmol/L	946		131.0, 135.8, 139.1	6.0	
Cholesterol, mg/dL	649		124.0, 152.1, 187.0	35.5	Not measured in large proportion of study population
Total WBC, $/mm^3$ or /cumm or/μL or /mcL	963		5200, 6800, 8980	4.3	
Systolic BP, mmHg	994		106, 126.5, 150	1.2	
Diastolic BP, mmHg	992		70, 80, 100	1.4	Collinear with systolic BP. Dropped from consideration
Heart rate, b.p.m.	997		90, 104, 116	0.9	
Respiration, breaths/min	989		26, 29, 34	1.7	
Orthopnoea, (0/1 vs. 2/3)	838	741	(88.4)	16.7	
Peripheral oedema, (0/1 vs. 2/3)	990	665	(67.2)	1.6	
Rales, (0/1 vs. 2/3)	880	565	(64.2)	12.5	
lifestyle (emerging = 1, endemic = 0)	980	507	(51.7)	2.6	
Region	1006		East: 268, South: 208, West: 530	0	

Ninety-five patients died and 74 were readmitted through 60 days; 138 patients experienced a death or re-admission through 60 days, where the first event was re-admission for 74 patients and death for 64 patients. A total of 151 patients died through 180 days after admission. A total of 38 candidate predictors were considered. The distribution and proportion of unavailable values for each predictor are given in *Table 1*. A total of 522 (51.9%) patients were missing at least one candidate variable when cholesterol was not included as a predictor; one variable was missing for 284 patients, two for 162 patients, three for 72 patients, and four or more for 140 patients. We also considered cholesterol as a predictor, although it is measured only when clinically indicated in African patients with AHF. With the inclusion of

Table 2 Models for all-cause death or re-admission through 60 days

Predictor	HR for a change of	Univariable models		Multivariable model	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Hx of DM	Yes/no	1.29 (0.81, 2.08)	0.2862		
Hx of IHD	Yes/no	1.00 (0.55, 1.81)	0.9948		
Valvular disease	Yes/no	1.04 (0.72, 1.52)	0.8275		
HIV positive	Yes/no	1.57 (0.88, 2.80)	0.1241		
Hypertension	Yes/no	0.86 (0.62, 1.20)	0.3756		
Hyperlipidaemia	Yes/no	0.40 (0.17, 0.95)	0.0373	0.47 (0.20, 1.12)	0.0891
HX of stroke	Yes/no	0.27 (0.04, 1.98)	0.1984		
HX of PVD	Yes/no	1.13 (0.27, 4.66)	0.8644		
Current or former smoker	Yes/no	0.76 (0.41, 1.43)	0.3995		
Malignancy	Yes/no	5.07 (2.25, 11.45	<0.0001	5.04 (2.19, 11.56)	0.0001
Hx of depression	Yes/no	1.21 (0.49, 2.97)	0.6831		
Hx of dementia	Yes/no	0.92 (0.29, 2.92)	0.8933		
Hx of atrial Fibrillation	Yes/no	1.34 (0.90, 1.99)	0.1509		
Hx of pericardial disease	Yes/no	1.29 (0.67, 2.47)	0.4423		
Hx of cardiomyopathy	Yes/no	0.96 (0.68, 1.35)	0.8133		
Hx of cor plmonale	Yes/no	2.50 (1.57, 4.00)	0.0001	1.75 (1.07, 2.87)	0.0268
Age, years	10	0.95 (0.87, 1.04)	0.2443		
Male Sex	Yes/no	1.16 (0.83, 1.63)	0.3756		
Ejection fraction, %[a]	50 vs. 27	0.94 (0.73, 1.21)	0.0523	0.89 (0.79, 1.14)	0.1355
BMI, kg/m^2	5	1.04 (0.90, 1.20)	0.6127		
BUN, mg/dL[a]	Doubling	1.39 (1.18, 1.63)	<0.0001	1.46 (1.23, 1.73)	<0.0001
Creatinine, mg/dL[a]	1.55 vs. 0.90	1.40 (1.07, 1.83)	0.0095		
Glucose, mg/dL	10	0.99 (0.95, 1.03)	0.5489		
Haemoglobin, g/dL	1	0.92 (0.86, 0.99)	0.0238		
Lymphocytes, %	5	0.96 (0.90, 1.03)	0.2275		
Sodium, mmol/L	5	0.87 (0.77, 0.98)	0.0263		
Total WBC, /mm^3 or /cumm or /μL or /mcL[a]	Doubling	1.10 (0.84, 1.43)	0.4833		
Cholesterol, mg/dL	10	0.98 (0.94, 1.02)	0.2423		
Systolic BP, mmHg	10	0.91 (0.86, 0.96)	0.0009	0.91 (0.86, 0.97)	0.0017
Heart rate, b.p.m.	5	1.04 (1.00, 1.08)	0.0300		
Respiration, breaths/min	5	1.07 (0.97, 1.18)	0.1836		
Orthopnoea[b]	(2/3 vs. 0/1)	1.78 (0.89, 3.56)	0.1033		
Peripheral oedema[c]	(2/3 vs. 0/1)	1.60 (1.08, 2.37)	0.0194		
Rales[d]	(2/3 vs. 0/1)	2.16 (1.38, 3.38)	0.0008	2.18 (1.36, 3.50)	0.0012
Heart failure cause[e]	(emerging = 1, endemic = 0)	0.78 (0.56, 1.09)	0.1497		
Region	(South vs. West)	1.32 (0.89, 1.94)	0.0141	1.83 (1.21, 2.78)	0.0025
Region	(East vs. West)	0.62 (0.39, 0.97)		0.78 (0.48, 1.27)	
C-statistic (95% confidence interval)				0.6986 (0.6521–0.7451)	

[a]Appropriate transformation used due to the non-linear relationship between predictor and outcome.
[b]Orthopnoea defined as: 0 = none, +1 = 1 pillow (10 cm), +2 = 2 pillow (20 cm), +3 = 3 pillow (>30 cm).
[c]Peripheral oedema defined as: 0, complete absence of skin indentation with mild digital pressure in all dependent areas; 1+, indentation of skin that resolves over 10–15 s; 2+, identation of skin is easily created with limited pressure and disappears slowly (15–30 s or more); 3+, large areas of indentation easily produced and slow to resolve (.30 s).
[d]Rales defined as: 0, no rales after clearing with cough; 1, moist or dry rales heard in lowerone-third of 1 or both lung fields that persist after cough; 2, moist or dry rales heard throughout the lower half to two-thirds of 1 or both lung fields; 3, moist or dry rales heard throughout both lung fields.
[e]Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

cholesterol 646 (64.3%) of the patients were missing a value for at least one predictor. Models were run for each outcome including and excluding cholesterol as a predictor. Despite the high number of patients with unavailable baseline cholesterol, the variables that stayed in the model for the outcomes were the same whether or not cholesterol was included.

Univariable associations with the composite outcome, and the final multivariable models with and without consideration of the

Table 3 Models for all-cause death or re-admission through 60 days, excluding region

Predictor	HR for a change of	Univariable models		Multivariable model	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Hx of DM	Yes/no	1.29 (0.81, 2.08)	0.2862		
Hx of IHD	Yes/no	1.00 (0.55, 1.81)	0.9948		
Valvular disease	Yes/no	1.04 (0.72, 1.52)	0.8275		
HIV positive	Yes/no	1.57 (0.88, 2.80)	0.1241		
Hypertension	Yes/no	0.86 (0.62, 1.20)	0.3756		
Hyperlipidaemia	Yes/no	0.40 (0.17, 0.95)	0.0373	0.49 (0.21, 1.19)	0.1156
HX of stroke	Yes/no	0.27 (0.04, 1.98)	0.1984		
HX of PVD	Yes/no	1.13 (0.27, 4.66)	0.8644		
Current or former smoker	Yes/no	0.76 (0.41, 1.43)	0.3995		
Malignancy	Yes/no	5.07 (2.25, 11.45)	<0.0001	4.31 (1.89, 9.82)	0.0005
Hx of depression	Yes/no	1.21 (0.49, 2.97)	0.6831		
Hx of dementia	Yes/no	0.92 (0.29, 2.92)	0.8933		
Hx of atrial Fibrillation	Yes/no	1.34 (0.90, 1.99)	0.1509		
Hx of pericardial disease	Yes/no	1.29 (0.67, 2.47)	0.4423		
Hx of cardiomyopathy	Yes/no	0.96 (0.68, 1.35)	0.8133		
Hx of cor pulmonale	Yes/no	2.50 (1.57, 4.00)	0.0001	2.03 (1.24, 3.32)	0.0048
Age, years	10	0.95 (0.87, 1.04)	0.2443		
Male sex	Yes/no	1.16 (0.83, 1.63)	0.3756		
Ejection fraction, %[a]	50 vs. 27	0.94 (0.73, 1.21)	0.0523	0.97 (0.75, 1.26)	0.0981
BMI, kg/m^2	5	1.04 (0.90, 1.20)	0.6127		
BUN, mg/dL[a]	Doubling	1.39 (1.18, 1.63)	<0.0001	1.42 (1.19, 1.68)	<0.0001
Creatinine, mg/dL[a]	1.55 vs. 0.90	1.40 (1.07, 1.83)	0.0095		
Glucose, mg/dL	10	0.99 (0.95, 1.03)	0.5489		
Haemoglobin, g/dL	1	0.92 (0.86, 0.99)	0.0238		
Lymphocytes, %	5	0.96 (0.90, 1.03)	0.2275		
Sodium, mmol/L	5	0.87 (0.77, 0.98)	0.0263		
Total WBC, /mm^3 or /cumm or /μL or /mcL[a]	Doubling	1.10 (0.84, 1.43)	0.4833		
Cholesterol, mg/dL	10	0.98 (0.94, 1.02)	0.2423		
Systolic BP, mmHg	10	0.91 (0.86, 0.96)	0.0009	0.92 (0.87, 0.98)	0.0048
Heart rate, b.p.m.	5	1.04 (1.00, 1.08)	0.0300	1.04 (1.00, 1.08)	0.0723
Respiration, breaths/min	5	1.07 (0.97, 1.18)	0.1836		
Orthopnoea[b]	(2/3 vs. 0/1)	1.78 (0.89, 3.56)	0.1033		
Peripheral oedema[c]	(2/3 vs. 0/1)	1.60 (1.08, 2.37)	0.0194		
Rales[d]	(2/3 vs. 0/1)	2.16 (1.38, 3.38)	0.0008	2.04 (1.31, 3.16)	0.0016
Heart failure cause[e]	(emerging = 1, endemic = 0)	0.78 (0.56, 1.09)	0.1497		
C-statistic (95% confidence interval)				0. 6826 (0.6375–0.7294)	

[a]Appropriate transformation used due to the non-linear relationship between predictor and outcome.
[b]Orthopnoea defined as: 0 = none, +1 = 1 pillow (10 cm), +2 = 2 pillow (20 cm), +3 = 3 pillow (>30 cm).
[c]Peripheral oedema defined as: 0, complete absence of skin indentation with mild digital pressure in all dependent areas; 1+, indentation of skin that resolves over 10–15 s; 2+, indentation of skin is easily created with limited pressure and disappears slowly (15–30 s or more); 3+, large areas of indentation easily produced and slow to resolve (.30 s).
[d]Rales defined as: 0, no rales after clearing with cough; 1, moist or dry rales heard in lowerone-third of 1 or both lung fields that persist after cough; 2, moist or dry rales heard throughout the lower half to two-thirds of 1 or both lung fields; 3, moist or dry rales heard throughout both lung fields.
[e]Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

geographic region are given in *Tables 2* and *3*, respectively. Adjusted for geographic region malignancy, cor pulmonale, higher admission BUN level, and presence of rales were found to significantly increase the risk of death or re-admission within 60 days, while hyperlipidaemia, and higher systolic blood pressure reduced the risk (*Table 2*). Unlike for other continuous predictors, the association of ejection fraction with the log hazard ratio was non-linear, with risk increasing for patients with ejection fraction both less than and greater than ~40%. Patients enrolled in Southern centres were at higher risk of the composite outcome, while those enrolled in Eastern centres were at lower risk, compared with those enrolled in Western centres. Considering region, the c-index for the

Table 4 Models for all-cause death through 180 days

Predictor	HR for a change of	Univariable models		Multivariable model	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Hx of DM	Yes/no	1.25 (0.80, 1.97)	0.3260		
Hx of IHD	Yes/no	0.56 (0.27, 1.15)	0.1121		
Valvular disease	Yes/no	1.05 (0.73, 1.51)	0.7882		
HIV positive	Yes/no	1.98 (1.20, 3.29)	0.0081	1.62 (0.94, 2.78)	0.0805
Hypertension	Yes/no	0.76 (0.55, 1.04)	0.0859		
Hyperlipidaemia	Yes/no	0.43 (0.20, 0.96)	0.0382		
HX of stroke	Yes/no	0.77 (0.24, 2.43)	0.6544		
HX of PVD	Yes/no	0.92 (0.22, 3.79)	0.9074		
Current or former smoker	Yes/no	0.57 (0.29, 1.12)	0.1050	0.51 (0.25, 1.03)	0.0592
Malignancy	Yes/no	4.26 (1.76, 10.33)	0.0014	3.00 (1.22, 7.35)	0.0166
Hx of depression	Yes/no	1.16 (0.47, 2.85)	0.7474		
Hx of dementia	Yes/no	1.48 (0.61, 3.63)	0.3883		
Hx of atrial fibrillation	Yes/no	1.17 (0.79, 1.74)	0.4371		
Hx of pericardial disease	Yes/no	0.89 (0.43, 1.81)	0.7384		
Hx of cardiomyopathy	Yes/no	1.18 (0.86, 1.63)	0.3060		
Hx of Cor pulmonale	Yes/no	2.14 (1.33, 3.44)	0.0017	1.99 (1.22, 3.24)	0.0057
Age, years	10	0.93 (0.85, 1.01)	0.0845		
Male sex	Yes/no	1.08 (0.78, 1.49)	0.6409	1.38 (0.97, 1.96)	0.0699
Ejection fraction, %	5	0.96 (0.92, 1.02)	0.1657		
BMI, kg/m^2	5	1.01 (0.88, 1.16)	0.9101		
BUN, mg/dL[a]	Doubling	1.27 (1.08, 1.50)	0.0033		
Creatinine, mg/dL[a]	1.55 vs. 0.90	1.37 (1.14, 1.65)	0.0020	1.36 (1.12, 1.64)	0.0051
Glucose, mg/dL	10	0.98 (0.95, 1.02)	0.3820		
Haemoglobin, g/dL	1	0.91 (0.85, 0.97)	0.0050	0.93 (0.87, 1.00)	0.0488
Lymphocytes, %	5	1.00 (0.93, 1.07)	0.9657		
Sodium, mmol/L	5	0.87 (0.78, 0.99)	0.0294		
Cholesterol, mg/dL	10	0.95 (0.91, 0.99)	0.0282		
Total WBC, /mm^3 or /cumm or /μL or /mcL[a]	Doubling	1.14 (0.89, 1.46)	0.3060		
Systolic BP, mmHg	10	0.86 (0.81, 0.91)	<0.0001	0.86 (0.81, 0.91)	<0.0001
Heart rate, b.p.m.[a]	116 vs. 90	1.29 (0.99, 1.67)	0.0165	1.34 (1.01, 1.81)	0.0845
Respiration, breaths/min	5	1.02 (0.93, 1.13)	0.6641		
Orthopnoea[b]	(2/3 vs. 0/1)	2.69 (1.30, 5.56)	0.0079	1.86 (0.85, 4.08)	0.1194
Peripheral oedema[c]	(2/3 vs. 0/1)	2.26 (1.50, 3.40)	<0.0001	1.91 (1.23, 2.97)	0.0043
Rales[d]	(2/3 vs. 0/1)	2.11 (1.41, 3.18)	0.0003	1.60 (1.03, 2.50)	0.0380
Heart failure cause[e]	(emerging = 1, endemic = 0)	0.72 (0.52, 0.99)	0.0431		
Region	(South vs. West)	1.21 (0.84, 1.76)	0.0042		
Region	(East vs. West)	0.53 (0.34, 0.83)			
C-statistic (95% confidence interval)				0.7231 (0.6849–0.7451)	

[a]Appropriate transformation used due to the non-linear relationship between predictor and outcome.
[b]Orthopnoea defined as: 0 = none, +1 = 1 pillow (10 cm), +2 = 2 pillow (20 cm), +3 = 3 pillow (>30 cm).
[c]Peripheral oedema defined as: 0, complete absence of skin indentation with mild digital pressure in all dependent areas; 1+, indentation of skin that resolves over 10–15 s; 2+, indentation of skin is easily created with limited pressure and disappears slowly (15–30 s or more); 3+, large areas of indentation easily produced and slow to resolve (.30 s).
[d]Rales defined as: 0, no rales after clearing with cough; 1, moist or dry rales heard in lowerone-third of 1 or both lung fields that persist after cough; 2, moist or dry rales heard throughout the lower half to two-thirds of 1 or both lung fields; 3, moist or dry rales heard throughout both lung fields.
[e]Endemic causes included rheumatic heart disease, cardiomyopathies, and infective causes, while emerging causes included hypertension and ischaemic heart disease.

multivariable model was 0.70, indicating a moderate degree of discrimination (*Table 2*). The same multivariable predictors were obtained when region was not considered, except that heart rate also entered the model (*Table 3*). The *C*-index for this multivariable model (0.68) was slightly less than for that including region.

Univariable associations and the multivariable model of death through 180 days are given in *Table 4*. Known HIV positivity, malignancy, cor pulmonale, male sex, lower haemoglobin, lower systolic blood pressure, and presence of orthopnoea, peripheral oedema, and rales were found to increase risk, while current or former

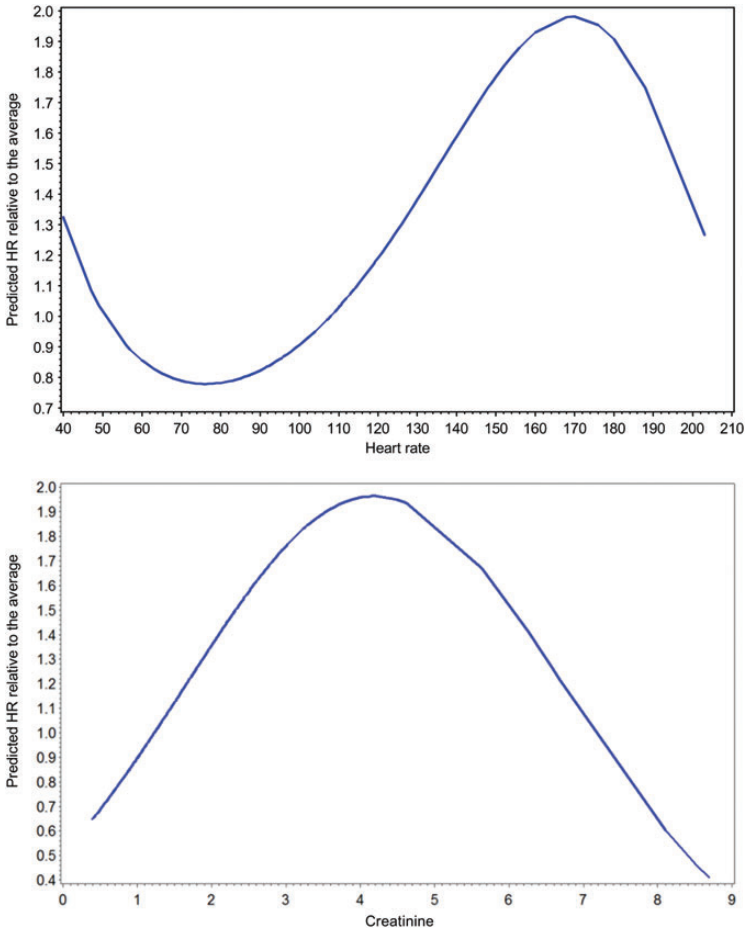

Figure 1 Non-linear associations of continuous predictors with all-cause death through 180 days.

smoking reduced risk (*Table 4*). The associations of creatinine and heart rate with the log hazard ratio for mortality were non-linear (*Figure 1*). Patients with a higher heart rate were generally at increased risk; while the model-predicted risk appears to fall again, this is likely because of undue influence of a few patients with extreme heart rates (six patients with HR >170 b.p.m.). The model-predicted association with creatinine was an apparent inverted U shape with patients with creatinine levels of ~1.9 mg/dL at highest risk; risks appear to decrease with values >4 mg/dL; however, very few (32) patients had these extreme values. The *C*-index for the multivariable model was 0.72.

Calibration plots, comparing observed event rates with those predicted by the models, are given in *Figure 2* for death or re-admission through Day 60 (with, *Figure 2A*, and without, *Figure 2B* consideration of region) and in *Figure 3* for mortality through Day 180. Risks predicted by the models were generally close to those observed among patients grouped by deciles of predicted risk.

Discussion

The current manuscript is an analysis of the THESUS registry.[5] As previously noted the main finding of the THESUS registry points to the fact that patients who present with AHF in sub-Saharan Africa are younger, less have ischaemic heart disease or risk factors for ischaemic heart disease (such as smoking) and many more have valvular (mostly rheumatic) heart disease and are hypertensive. As has been found in other studies,[7–9] the main predictors of either re-admission or death in the model that excludes region (*Table 3*) are a history of malignancy and severe lung disease, admission systolic blood pressure, heart rate and signs of congestion (rales), kidney function (BUN), and echocardiographic ejection fraction. In the model in which region has been included (*Table 2*), the Southern African region seems to confer a higher risk of re-admission suggesting that cultural and health economics-related factors may contribute to the decision to re-admit a patient after an AHF event, as opposed to outpatient clinic treatment. Interestingly, some factors that routinely contribute to similar models in North America and Europe have a lesser role in sub-Saharan Africa. These should be confirmed in further studies in potentially larger number of patients and more hospitals. Most notably age and sodium levels at admission may have potentially less of a predictive effect in sub-Saharan Africa. Age may have a lesser role in this population because these patients are almost 20 years younger on average than AHF patients in North American and European registries. Sodium may play a lesser role

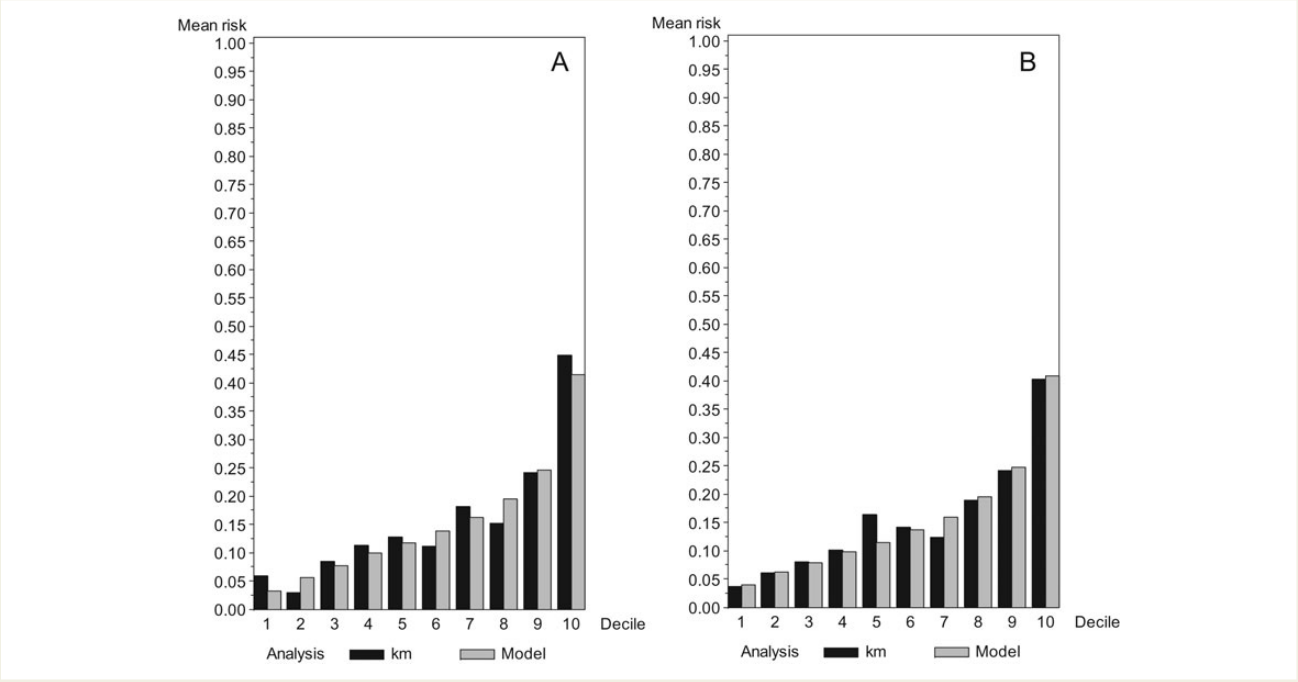

Figure 2 (*A*) Calibration plot for multivariable model for all-cause death or re-admission through 60 days. Model including region. (*B*) Calibration plot for multivariable model for all-cause death or re-admission through 60 days. Model excluding region.

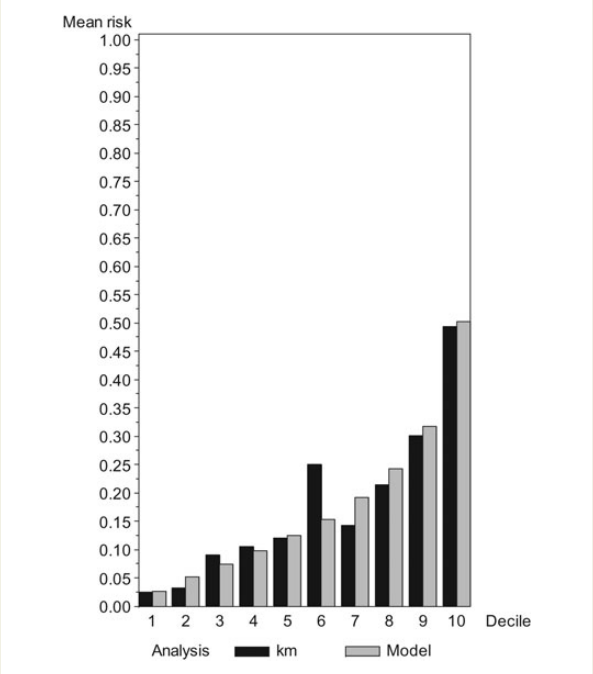

Figure 3 Calibration plot for multivariable model for all-cause death through Day 180.

since most patients are young and the most common cause of heart failure is hypertension which may be associated with less neurohormonal activation than end-stage ischaemic cardiomyopathies which are more prevalent in North America and Europe, especially among the sickest AHF patients who are more commonly re-admitted after discharge.

The main predictors of 180-day mortality include malignancy, severe lung disease, smoking history, systolic blood pressure, heart rate, and symptoms and signs of congestion (orthopnoea, peripheral oedema, and rales) at admission, kidney dysfunction (BUN), anaemia, and being HIV positive. Again, many of these predictors are the same as those reported in similar studies in North America and Europe, although some notable differences are apparent. Again, the interpretation of these differences should be tempered by the fact that the study is relatively small and was recruited in a selected group of hospitals, mostly advance medical centres in each country. The role of HIV positivity as a predictor of adverse outcome is important. Sodium was not found to be a predictor of mortality in the current study (as is the case of re-admission and death), suggesting again that neurohormonal activation involving the renin–angiotensin system may have a lesser role in the HF process in sub-Saharan Africa, a finding in line with the reduced efficacy of ACEi in African Americans,[15] suggesting that other therapies such as combination of hydralazine and nitrates should be further explored in this population. Finally, the association of smoking with less adverse outcome may relate to the diagnosis of AHF being wrong and the breathlessness was due to lung disease, and this misdiagnosis led to the associated cigarette smoking being seen as conferring survival advantage.

Similar to other studies in which short-term re-admission and death and intermediate-term mortality were modelled in AHF the strength of the predictive models are modest with *C*-indexes in the range of 0.68–0.72. These *C*-indexes suggest that although some of the variability in outcomes can be explained by the factors examined,

other causes for re-admission and death after an AHF are still unknown in sub-Saharan Africa as in the rest of the world.

Limitations

The present study is an analysis of the patients enrolled in the THESUS-HF study and as such shares certain limitations with the original cohort. The majority of the patients were recruited in a limited number of hospitals mainly in Nigeria, Uganda, and South Africa. Most importantly loss to follow-up and missing laboratory data and clinical signs assessments were higher than in studies conducted in other regions. Loss to follow-up is common in the population studied due to a number of factors such as working opportunities if still well (migrant workers), or need to be taken care of if not well. Some tests are not performed as routinely in these institutions as in institutions participating in other studies. Secondly, this registry has been performed in selected centres and may represent only AHF patients seen in specialized centres. Thirdly, HIV infection has emerged as an important factor that predicts outcome in patients with AHF in sub-Saharan Africa. Future studies should aim not only to ensure testing of cases for heart failure, but also explore the contribution of degree of immunosuppression (by CD4+ T cell count testing), and the impact of anti-retroviral therapy. Finally, a larger sample size with significant numbers of participants at each site will be needed to provide valid comparisons between patients from various countries in Africa. The small size of the database obviated a split-sample approach to model validation; validation in another sub-Saharan African cohort would provide greater confidence in the findings.

Conclusions

Despite being one of the most common causes for hospital admissions both globally and in sub-Saharan Africa, our knowledge of the pathophysiology of AHF is limited. In the present study, the predictive models for 60-day re-admission or death and 180-day mortality are of the modest predictive value suggesting that some of the factors contributing to the morbidity and mortality in AHF are unknown. For the most part, the main predictors for these adverse outcomes are similar in sub-Saharan Africa as in the rest of the world although with some notable exceptions such as the association of the HIV status with mortality and lack of prediction by sodium on both re-admission and deaths.

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