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Renal dysfunction in African patients with acute heart failure

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Aims In Western countries with typically elderly ischaemic acute heart failure patients, predictors and clinical outcome of renal dysfunction and worsening renal function are well described. However, the prevalence, predictors and clinical outcome of renal dysfunction in younger, mainly hypertensive acute heart failure patients from Africa, have not been described.

Methods and results From 1006 patients enrolled in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF), renal function was determined by the estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula. Worsening renal function was defined as an increase in creatinine ≥0.3 mg/dL (26.5 μmol/L) from baseline to day 7/discharge. The mean (SD) age of the patients was 52.4 (18.2) years, 481 (50.8%) were women and the predominant race was black African [932 of 946 (98.5%)]. Heart failure was most commonly a result of hypertension ($n = 363$, 39.5%) and only 7.8% had ischaemic heart failure. At hospital admission, 289 patients (30.6%) had an estimated glomerular filtration rate <60 ml/min.1.73m^2. Worsening renal function during hospitalization was detected in 53 (9.8 %) of 543 patients with a follow-up creatinine value, and was independently associated with the Western sub-Saharan region, body mass index, and the presence of rales. Worsening renal function was an independent predictor of death or readmission over 60 days [multivariable hazard ratio = 1.98 (1.07, 3.68); $P = 0.0298$] and all-cause death over 180 days [multivariable hazard ratio = 1.80 (1.02, 3.17); $P = 0.0407$].

Conclusions Renal dysfunction is also prevalent in younger non-ischaemic acute heart failure patients in Africa, but worsening renal function is less prevalent and has different predictors compared with Western cohorts. Nevertheless, worsening renal function is strongly and independently related with clinical outcome.

Keywords Africa • Outcome • Prognosis • Renal dysfunction • Worsening renal function

Introduction

Heart failure is generally considered a typical disease of Western countries. However, recent data clearly indicate that heart failure is also an important health-care problem in Africa, where it is estimated to contribute about 3–7% of all medical admissions.[1,2] The causes of heart failure in Africa are different from those outside of Africa. The recent sub-Saharan Africa Survey of Heart Failure (THESUS-HF) registry[3] showed that in sub-Saharan Africa the disease affects men and women in the most productive years of life, at an average age of 52 years and is mostly caused by hypertension and not ischaemic heart disease, as is seen in Western countries.[4] Other studies have confirmed that hypertension accounts for more than half of cases, followed by cardiomyopathies and rheumatic

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heart disease.[5] In a recent study from Abuja, Nigeria, hypertension was the cause of heart failure in 64% of patients.[6] In addition, the patients mostly present in late stages of heart failure [New York Heart Association (NYHA) class III and class IV], which may significantly worsen prognosis and increase morbidity and mortality.

Studies from Europe and North America have shown that more than half of the patients hospitalized for heart failure have some degree of impairment of renal function, and moderate to severe impairment has been reported in 30–35% of cases.[7–10] Hospitalization for acute heart failure is also associated with further worsening renal function (WRF) in 30–50% of patients, depending on the definition used.[8,9] Typical predictors of WRF in these patients are baseline chronic kidney disease, history of hypertension and diabetes, age, and use of diuretics.[11]

However, the prevalence, predictors and clinical outcome of renal dysfunction in younger, mainly hypertensive acute heart failure (AHF) patients in sub-Saharan African are not known. We therefore studied renal dysfunction at admission and WRF, the association between WRF and 180-day mortality, and 60-day death/readmission in a cohort of 1006 African patients admitted with AHF and enrolled in the THESUS-HF registry.

Methods

THESUS-HF[3] was a prospective, multicentre, international observational survey conducted in 12 hospitals from nine 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 described in detail previously.[3] 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 echocardiographic findings and was confirmed by a cardiologist. 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 on standardized case report forms at admission 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 over 6 months for the occurrence of readmissions 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.

Renal function and worsening renal function

Patients presenting with heart failure are routinely checked for renal dysfunction at presentation. More detailed investigations and follow up on previous tests are based on indications and availability of resources. The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula $(186.3 \times (\text{serum creatinine (mg/dl)})^{-1.154} \times \text{age}^{-0.203} \times (0.742$ if female$) \times (1.212$ if black African$)$ (mL/min.1.73 m^2).[12,13] Worsening renal function was defined as an absolute increase in creatinine $\geq$0.3 mg/dL (26.5 μmol/l)[14,15] from baseline to the earlier of day 7 or hospital discharge.

The relation between clinical variables, renal function and worsening renal function was evaluated. Finally, we examined clinical outcomes of patients with worsening renal function and its prognostic significance.

Statistical methods

Means ± standard deviations (SD) are presented for continuous variables, and absolute and relative frequencies for categorical variables. Differences in continuous variables between groups were compared using two-sample *t*-tests, or one-way ANOVA tests where there were more than two groups. Categorical variables were compared using chi-square tests or Fisher's exact tests where at least one group had an absolute frequency <5. To evaluate the predictors of WRF, we first examined the univariable associations between each covariate and WRF. Patients with baseline and follow-up creatinine values at day 7 (or discharge) were included in this analysis. The linearity of association between each continuously distributed predictor and WRF was assessed using restricted cubic splines (RCS) with four 'knots' with a test of the significance of the non-linear terms. Where the association was non-linear, a readily interpretable 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 (AIC). The only non-linear predictor was body mass index (BMI). A linear spline was chosen with a single knot at 18.5 kg/m^2 (the lower cut-off for a normal BMI).

Multiple imputations were used with a method that assumes multivariate normality (SAS PROC MI) 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 datasets were used. Parameter estimates were averaged across these datasets using Rubin's algorithm (SAS PROC MIANALYZE). With only 53 WRF events, the number of predictors that could be entered into a multivariable model was limited. We selected predictors that had a strong univariable association with WRF and used backwards selection in each of the seven imputation datasets, with the criterion for staying $P < 0.10$. Predictors that were significant in the majority of the imputed datasets were kept in the final model.

We assessed the associations between WRF and clinical outcomes using a two-sided two-sample *t*-tests for length of initial hospital stay and a log-rank test for time-to-event outcomes. The associations between WRF and 60-day death or readmission and 180-day mortality were then assessed after adjusting for predictors known to be associated with each outcome in this study population (no backwards selection was done here).[16]

Results

There were a total of 1006 patients in the THESUS-HF registry. Serum creatinine on admission was available in 964 (96%) of the 1006 patients. The mean (SD) age of the patients was 52.4 (18.2) years, 481 (50.8%) were women, and the predominant race was black African (98.5%).[3]

Table 1 Patient characteristics by estimated glomerular filtration rate (eGFR)

Patient characteristics	eGFR ≤ 30, *n* = 67	eGFR 30–≤60, *n* = 222	eGFR 60–≤90, *n* = 325	eGFR >90, *n* = 332	Total, *N* = 946	*P*-value*
Age, years, mean ± SD, median (25% Q, 75% Q)	57.4 ± 16.06, 60.0 (46.0, 69.0)	58.2 ± 16.88, 60.0 (49.0, 70.0)	51.4 ± 17.10, 51.0 (39.0, 65.0)	48.5 ± 19.40, 49.0 (31.5, 65.0)	52.4 ± 18.23, 55.0 (39.0, 67.0)	<0.0001
Male sex, *n* (%)	32 (47.8%)	102 (46.0%)	160 (49.2%)	171 (51.5%)	465 (49.2%)	0.64
Black Africans, *n* (%)	65 (97.0%)	217 (97.8%)	319 (98.2%)	331 (99.7%)	932 (98.5%)	0.066
Hypertension, *n* (%)	54 (80.6%)	144 (65.2%)	171 (52.9%)	144 (43.5%)	513 (54.5%)	<0.0001
Hyperlipidaemia, *n* (%)	13 (21.0%)	17 (7.8%)	35 (10.9%)	22 (6.8%)	87 (9.2%)	0.0032
History of smoking, *n* (%)	2 (3.0%)	18 (8.1%)	32 (9.9%)	39 (11.8%)	91 (9.7%)	0.11
Malignancy, *n* (%)	0 (0.0%)	7 (3.2%)	4 (1.2%)	1 (0.3%)	12 (1.3%)	0.033
History of cor pulmonale, *n* (%)	3 (4.6%)	14 (6.4%)	25 (7.7%)	23 (7.0%)	65 (6.9%)	0.86
History of atrial fibrillation, *n* (%)	9 (13.6%)	55 (25.0%)	58 (17.9%)	56 (17.1%)	178 (18.8%)	0.059
Diabetes mellitus, *n* (%)	18 (26.9%)	33 (14.9%)	29 (9.0%)	29 (8.7%)	109 (11.5%)	<0.0001
Peripheral oedema, *n* (%)	56 (86.2%)	158 (72.2%)	202 (63.5%)	208 (63.2%)	624 (67%)	0.0006
Rales, *n* (%)	41 (75.9%)	138 (70.4%)	168 (60.0%)	174 (59.0%)	521 (63.2%)	0.0088
Body mass index, kg/m^2, mean ± SD, median (25% Q, 75% Q)	27.7 ± 7.27, 27.4 (22.51, 32.59)	25.5 ± 5.39, 25.4 (21.96, 28.76)	24.6 ± 5.76, 23.7 (20.75, 27.52)	24.3 ± 5.77, 23.4 (20.75, 27.19)	25.0 ± 5.86, 24.0 (20.91, 28.09)	<0.0001
Systolic blood pressure, mmHg, mean ± SD, median (25% Q, 75% Q)	144.4 ± 42.56, 140.0 (112.1, 170.0)	132.9 ± 35.84, 130.0 (106.0, 160.0)	128.6 ± 31.82, 122.5 (105.5, 150.0)	125.7 ± 29.33, 120.0 (103.0, 140.0)	129.7 ± 33.15, 124.0 (105.0, 150.0)	0.0001
Diastolic blood pressure, mmHg, mean ± SD median (25% Q, 75% Q)	89.5 ± 22.36, 90.0 (70.0, 104.0)	85.8 ± 21.89, 85.0 (70.0, 100.0)	84.4 ± 21.46, 80.0 (70.0, 100.0)	81.3 ± 18.92, 80.0 (70.0, 90.0)	84.0 ± 20.87, 80.0 (70.0, 100.0)	0.0076
Heart Rate, bpm, mean ± SD median (25% Q, 75% Q)	97.3 ± 17.92, 100.0 (88.0, 109.0)	106.0 ± 22.63, 105.0 (91.0, 120.0)	103.6 ± 21.83, 104.0 (90.0, 116.0)	103.3 ± 21.33, 100.0 (88.0, 116.0)	103.6 ± 21.66, 104.0 (90.0, 116.0)	0.036
LVEF %, mean ± SD median (25% Q, 75% Q)	40.7 ± 15.62, 40.0 (29.0, 52.5)	38.8 ± 15.56, 39.0 (27.0, 48.0)	37.2 ± 15.51, 35.0 (25.0, 46.0)	41.1 ± 17.41, 40.0 (28.0, 55.0)	39.2 ± 16.27, 38.0 (27.0, 50.0)	0.024
LVEF <40%, *n* (%)	29 (3.3%)	108 (12.3%)	179 (20.4%)	149 (17.0%)	465 (53.0%)	0.068
Creatinine level, µmol/L, mean ± SD, median (25% Q, 75% Q)	385.6 ± 166.40, 342.6 (267.00, 495.04)	153.4 ± 38.85, 145.9 (125.98, 174.00)	103.0 ± 16.85, 102.0 (89.30, 114.92)	69.4 ± 15.97, 70.7 (60.84, 79.56)	123.0 ± 93.43, 9.0 (78.0, 132.6)	<0.0001
BUN, µmol/L, mean ± SD, median (25% Q, 75% Q)	32.3 ± 23.89, 23.4 (18.21, 36.70)	15.1 ± 9.11, 12.6 (9.30, 18.92)	10.4 ± 8.18, 8.2 (5.60, 12.50)	8.5 ± 5.22, 7.4 (4.60, 10.71)	12.4 ± 11.36, 9.4 (6.00, 14.55)	<0.0001
Sodium level, mmol/L, mean ± SD, median (25% Q, 75% Q)	132.7 ± 7.91, 133.0 (128.0, 138.0)	135.2 ± 6.88, 135.0 (131.2, 140.0)	135.3 ± 6.42, 136.0 (132.0, 129.0)	135.2 ± 6.35, 136.0 (131.0, 140.0)	135.07 ± 6.65, 135.2 (131.0, 139.0)	0.030
eGFR, mL/min.1.73m^2, mean ± SD, median (25% Q, 75% Q)	18.6 ± 7.04, 18.4 (12.96, 24.51)	47.2 ± 8.59, 48.4 (40.48, 54.32)	75.3 ± 8.44, 75.28 (68.08, 82.63)	129.8 ± 49.36, 114.8 (101.64, 141.60)	83.8 ± 47.77, 76.9 (54.55, 103.77)	<0.0001

Table 1 Continued

Patient characteristics	eGFR ≤ 30, *n* = 67	eGFR 30–≤60, *n* = 222	eGFR 60–≤90, *n* = 325	eGFR >90, *n* = 332	Total, *N* = 946	*P*-value*
Haemoglobin, g/L, mean ± SD	107.7 ± 26.46,	120.8 ± 24.33,	126.1 ± 22.24,	123.7 ± 21.40,	122.7 ± 23.23,	<0.0001
median (25% Q, 75% Q)	107.0 (87.0, 122.0)	120.0 (104.5, 137.0)	126.9 (113.0, 140.0)	126.0 (110.0, 137.0)	23.0 (109.0, 138.0)	
Glucose level, mmol/L,	6.1 ± 2.70,	6.3 ± 3.15,	6.2 ± 2.69,	6.0 ± 2.55,	6.11 ± 2.76,	0.61
mean ± SD, median (25% Q, 75% Q)	5.30 (4.60, 6.49)	5.18 (4.66, 6.30)	5.28 (4.80, 6.66)	5.22 (4.60, 6.49)	0.2 (4.70, 6.52)	
Previous medication use, *n* (%)						
ACE inhibitor	19 (40.4%)	34 (30.1%)	67 (37.0%)	59 (27.2%)	179 (32.1%)	0.11
Loop diuretics	25 (53.2%)	37 (33.6%)	88 (49.7%)	69 (32.2%)	219 (40%)	0.0005
β-Blockers	9 (19.1%)	24 (21.8%)	37 (21.5%)	27 (12.6%)	97 (17.8%)	0.075
Digoxin	7 (15.2%)	14 (12.5%)	42 (23.7%)	40 (18.7%)	103 (18.8%)	0.11
Hydralazine	1 (2.2%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	3 (0.5%)	0.064
Nitrates	1 (2.2%)	3 (2.7%)	5 (2.9%)	1 (0.5%)	10 (1.8%)	0.17
Aldosterone Inhibitor	7 (14.9%)	28 (25.2%)	38 (21.7%)	31 (14.6%)	104 (19%)	0.076
Statins	4 (8.9%)	8 (7.1%)	9 (5.2%)	6 (2.8%)	27 (5%)	0.13
Aspirin	14 (30.4%)	27 (23.9%)	41 (23.3%)	41 (19.1%)	123 (22.4%)	0.35
Anticoagulants	5 (11.4%)	5 (4.4%)	14 (8.0%)	11 (5.2%)	35 (6.4%)	0.28
Aetiology of heart failure						
Hypertensive CMP, *n* (%)	37 (56.9%)	96 (45.1%)	114 (36.0%)	116 (35.7%)	363 (39.5%)	
Idiopathic dilated CMP, n (%)	7 (10.8%)	30 (14.0%)	43 (13.6%)	56 (17.2%)	136 (14.8%)	
Rheumatic heart disease, *n* (%)	5 (7.7%)	27 (12.7%)	55 (17.4%)	50 (15.4%)	137 (14.9%)	
Ischaemic heart disease, *n* (%)	4 (6.2%)	24 (11.3%)	27 (8.5%)	17 (5.2%)	72 (7.8%)	
Peripartum cardiomyopathy, *n* (%)	1 (1.5%)	11 (5.2%)	31 (9.8%)	27 (8.3%)	70 (7.6%)	
Pericardial effusion tamponade, *n* (%)	5 (7.7%)	9 (4.2%)	17 (5.4%)	11 (3.4%)	42 (4.8%)	
HIV cardiomyopathy, *n* (%)	4 (6.2%)	3 (1.4%)	7 (2.2%)	9 (2.8%)	23 (2.5%)	
Endomyocardial fibrosis, *n* (%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	11 (3.4%)	13 (1.4%)	
Other, *n* (%)	2 (3.1%)	13 (6.1%)	21 (6.6%)	28 (8.6%)	64 (7.0%)	
Region						
East	14 (20.9%)	61 (27.5%)	99 (30.5%)	91 (27.4%)	265 (28.0%)	0.25
South	12 (17.9%)	47 (21.2%)	77 (23.7%)	62 (18.7%)	198 (20.9%)	
West	41 (61.2%)	114 (51.4%)	149 (45.9%)	179 (53.9%)	483 (51.1%)	

BUN, blood urea nitrogen; CMP, cardiomyopathy; HIV, human immunodeficiency virus ;LVEF, left ventricular ejection fraction.
*P-value for categorical variables from Chi-square test or Fisher's exact test if at least one cell count <5 *P*-value for continuous variables from ANOVA.

Table 2 Baseline characteristics of patients with and without a follow-up creatinine value

Baseline characteristic	Patients with FU creatinine, *N* = 543	Patients with BL creatinine, but no FU, *N* = 441	*P*-value*
Age, mean (SD) median (25%Q, 75%Q)	49.8 (17.45) 51.0 (36.0, 64.0)	55.4 (18.82) 75.0 (41.0, 70.0)	<0.0001
Male sex, *n* (%)	264 (48.6%)	218 (49.5%)	0.77
Black Africans, *n* (%)	532 (98.0%)	430 (99.1%)	0.20
Hypertension, *n* (%)	286 (52.8%)	257 (58.7%)	0.0643
Hyperlipidaemia, *n* (%)	49 (9.2%)	41 (9.7%)	0.789
History of smoking, *n* (%)	53 (9.8%)	44 (10.0%)	0.91
Malignancy, *n* (%)	3 (0.6%)	9 (2.1%)	0.034
History of cor pulmonale	38 (7.1%)	30 (6.8%)	0.88
Diabetes, *n* (%)	64 (11.8%)	50 (11.4%)	0.83
Peripheral oedema, *n* (%)	371 (69.0%)	279 (64.7%)	0.16
Rales, *n* (%)	340 (70.7%)	210 (55.3%)	<0.0001
BMI, kg/m^2 mean (SD), median (25%Q, 75%Q)	24.6 (5.93), 23.4 (20.70, 27.68)	25.2 (5.68), 24.6 (21.36, 28.65)	0.12
SBP, mmHg, mean (SD), median (25%Q, 75%Q)	127.7 (34.24), 120.0 (102.0, 150.0)	133.8 (32.80), 130.0 (110.0, 152.5)	0.0051
DBP, mmHg, mean (SD), median (25%Q, 75%Q)	83.2 (20.86), 80.0 (70.0, 100.0)	85.6 (21.15), 82.0 (70.0, 100.0)	0.075
Heart Rate, bpm mean (SD), median (25%Q, 75%Q)	106.0 (21.28), 108.0 (92.0, 120.0)	100.7 (21.79), 100.0 (88.0, 113.0)	0.0001
LVEF (%), mean (SD), median (25%Q, 75%Q)	37.7 (15.75), 36.0 (25.0, 47.0)	41.7 (16.93), 40.0 (29.0, 55.0)	0.0002
LVEF <40%, *n* (%)	289 (32.5%)	182 (20.5%)	0.006
Creatinine, µmol/L, mean (SD), median (25%Q, 75%Q)	124.0 (84.49), 103.0 (79.56, 136.18)	121.9 (101.94), 95.5 (70.72, 129.00)	0.73
BUN, mmol/L, mean (SD), median (25%Q, 75%Q)	12.6 (9.80), 10.0 (6.10, 15.35)	12.6 (13.36), 8.9 (5.72, 14.21)	0.94
Sodium, mmol/L, mean (SD), median (25%Q, 75%Q)	134.3 (6.56), 135.0 (130.0, 138.6)	136.2 (6.60), 136.2 (132.0, 140.0)	<0.0001
eGFR,ml/min.1.73m^2, mean (SD), median (25%Q, 75%Q)	79.3 (38.79), 76.2 (52.71, 98.19)	89.3 (56.38), 78.5 (57.03, 106.88)	0.0020
Haemoglobin, g/L, mean (SD), median (25%Q, 75%Q)	117.6 (23.84), 120.0 (103.0, 132.5)	127.5 (23.15), 129.0 (115.0, 143.0)	<0.0001
Glucose, mmol/L, mean (SD), median (25%Q, 75%Q)	6.3 (3.18), 5.3 (4.52, 6.79)	5.8(2.00), 5.2 (4.72, 6.19)	0.0039
Medication use (1-month before)			
ACE inhibitor, *n* (%)	89 (37.2%)	95 (28.2%)	0.022
Loop diuretics, *n* (%)	103 (43.6%)	120 (36.4%)	0.081
Beta blockers, *n* (%)	44 (18.6%)	56 (17.2%)	0.68
Digoxin, *n* (%)	48 (20.1%)	58 (17.7%)	0.47
Hydralazine, *n* (%)	3 (1.3%)	0 (0.0%)	0.074
Nitrates, *n* (%)	8 (3.4%)	2 (0.6%)	0.021
Aldosterone inhibitor, *n* (%)	57 (24.2%)	51 (15.5%)	0.0099
Statins, *n* (%)	21 (8.9%)	7 (2.2%)	0.0003
Aspirin, *n* (%)	71 (29.8%)	55 (16.7%)	0.0002
Anticoagulants, *n* (%)	24 (10.1%)	11 (3.4%)	0.0011
Aetiology of heart failure			
Endomyocardial fibroelastosis	9 (1.7%)	4 (0.9%)	
HIV CMP	10 (1.9%)	13 (3.0%)	
Hypertensive CMP	201 (37.9%)	184 (43.0%)	
Idiopathic dilated CMP	81 (15.3%)	55 (12.9%)	
Ischemic heart disease	37 (7.0%)	40 (9.4%)	
Pericardial effusion /tamponade	31 (5.9%)	14 (3.3%)	
Peripartum CMP	46 (8.7%)	26 (6.1%)	
Rheumatic heart disease	79 (14.9%)	59 (13.8%)	
Other	36 (6.8%)	33 (7.7%)	

Table 2 Continued

Baseline characteristic	Patients with FU creatinine, $N = 543$	Patients with BL creatinine, but no FU, $N = 441$	*P*-value*
Region			
East	99 (70.7%)	168 (38.1%)	<0.0001
South	143 (26.3%)	64 (14.5%)	
West	301 (55.4%)	209 (47.4%)	
Country			
Cameroon	10 (1.8%)	77 (17.5%)	
Ethiopia	9 (1.7%)	1 (0.2%)	
Kenya	17 (3.1%)	15 (3.4%)	
Mozambique	72 (13.3%)	4 (0.9%)	
Nigeria	285 (52.5%)	125 (28.3%)	
Senegal	6 (1.1%)	7 (1.6%)	
South Africa	71 (13.1%)	60 (13.6%)	
Sudan	68 (12.5%)	4 (0.9%)	
Uganda	5 (0.9%)	148 (33.6%)	

BL, baseline; FU, follow up; BMI, body mass index; SBP, systolic blood pressure, DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CMP, cardiomyopathy; HIV, human immunodeficiency virus.
*P-value is from two-sided *t*-tests for continuous variables, or chi-square tests for categorical variables (Fisher's exact if at least one cell count is <5).

Table 3 Clinical outcomes in patients with and without a follow-up creatinine value

	Patients with BL and FU creatinine, $N = 523$	Patients with BL creatinine, but no FU. $N = 441$	*P*-value*
Length of initial hospital stay (days), mean(SD), median (25% Q, 75% Q)	10.2 (10.83), 8.0 (6.0, 11.0)	8.1 (7.34), 7.0 (4.0, 9.0)	0.0009
Initial hospitalization mortality, *n* (%)	22 (15.1%)	15 (5.8%)	0.91
Rehospitalization to day 60, *n* (%)	45 (10.4%)	23 (6.6%)	0.070
Death to day 60, *n* (%)	50 (10.6%)	36 (9.3%)	0.66
Death of readmission to day 60, *n* (%)	77 (16.5%)	47 (12.3%)	0.13
Death to day 180, *n* (%)	90 (20.4%)	50 (13.5%)	0.029

BL, baseline; FU, follow up.
*P-value is from two-sided t-test for length of stay (LOS), log-rank test for time to event outcomes %'s represent K-M event rates for time to event outcomes.

The comorbid conditions present were 11.5% of patients with diabetes, 18.8% with atrial fibrillation, 9.2% with hyperlipidaemia and 15.2% with anaemia. Left ventricular ejection fraction (LVEF) was 39.2 ± 16.3%, with 465 (53.0%) of patients with an LVEF of less than 40%. The initial systolic blood pressure was 129.7 ± 33.2 mmHg and heart rate was 103.6 ± 21.7 bpm.

Heart failure was most commonly caused by hypertension ($n = 363$, 39.5%) followed by idiopathic dilated cardiomyopathy ($n = 136$, 14.8%) and rheumatic valvular heart disease ($n = 137$, 14.9%). Ischaemic heart failure was present in only 72 (7.8%) of the patients.

Mean creatinine at admission was 123.0 ± 93.43 μmol/L [median 99.0 ~~mg/dL~~, interquartile range (IQR) 78.0–132.6 ~~mg/dL~~] and eGFR was 83.8 ± 47.8 mL/min (median 76.7 mL/min, IQR 54.6–103.8 mL/min).

Table 1 shows the patients characteristic according to the eGFR. They were categorized as follows: eGFR < 30 mL/min, 30–≤60 mL/min, 60–≤90 mL/min and >90 mL/min. Patients with a lower eGFR (≤60 ml/min; $n = 289$, 30.6%) were significantly older and had more hypertension, diabetes, and hyperlipidaemia. They also showed more evidence of congestion (rales and peripheral oedema), and had higher body mass indices. Laboratory results showed that they had higher creatinine and blood urea nitrogen and lower haemoglobin levels.

Five hundred and forty-three (53%) patients had baseline and follow-up creatinine. This group was significantly younger, had more evidence of congestion (rales), a higher heart rate, and lower eGFR, LVEF, and haemoglobin levels compared with those with only a baseline value. They were also more likely to receive renin–angiotensin aldosterone system inhibition ($n = 453$; *Table 2*).

Patients with a follow-up creatinine value also had a longer length of stay, and had a higher rate of readmission and death (*Table 3*). In particular, a higher proportion of patients with follow-up creatinine

Table 4 Characteristics of patients with and without worsening renal function (WRF)

Patient characteristics	WRF, *N* = 53	no WRF, *N* = 470	Total, *N* = 523	*P*-value*
Age, years, mean ± SD median (25% Q, 75% Q)	50.6 ± 15.71 55.0 (40.0, 63.0)	50.0 ± 17.64 51.0 (36.0, 65.0)	50.1 ± 17.44 51.0 (36.0, 64.0)	0.82
Male sex, *n* (%)	30 (56.6%)	223 (47.5%)	253 (48.4%)	0.21
Black Africans, *n* (%)	52 (98.1%)	461 (98.1%)	513 (98.1%)	1.00
Hypertension, *n* (%)	30 (56.6%)	239 (51.0%)	269 (51.5%)	0.44
Hyperlipidaemia, *n* (%)	4 (7.8%)	44 (9.5%)	48 (9.3%)	1.0
History of smoking, *n* (%)	4 (7.5%)	46 (9.8%)	50 (9.6%)	0.81
Malignancy, *n* (%)	0 (0.0%)	3 (0.6%)	3 (0.6%)	1.0
History of cor pulmonale, *n* (%)	6 (11.3%)	31 (6.7%)	37 (7.2%)	0.22
History of atrial fibrillation, *n* (%)	6 (11.3%)	86 (18.4%)	92 (17.7%)	0.20
Diabetes mellitus, *n* (%)	6 (11.3%)	56 (11.9%)	62 (11.9%)	0.90
Peripheral oedema, *n* (%)	43 (81.1%)	312 (67.1%)	355 (68.5%)	0.037
Rales, *n* (%)	43 (91.5%)	281 (67.7%)	324 (70.1%)	<.0001
Body mass index, kg/m^2, mean ± SD, median (25% Q, 75% Q)	27.0 ± 7.85 25.5 (21.37, 32.72)	24.5 ± 5.69 23.4 (20.70, 27.52)	24.7 ± 5.99 23.5 (20.72, 27.77)	0.024
Systolic blood pressure, mmHg, mean ± SD, median (25% Q, 75% Q)	133.9 ± 39.15, 130.0 (105.0, 150.0)	125.8 ± 32.14, 120.0 (100.0, 145.0)	126.7 ± 32.97, 120.0 (101.0, 146.5)	0.15
Diastolic blood pressure, mmHg, mean ± SD, median (25% Q, 75% Q)	86.1 ± 25.27, 84.0 (70.0, 100.0)	82.3 ± 19.86, 80.0 (70.0, 96.0)	82.7 ± 20.49, 80.0 (70.0, 97.0)	0.29
Heart rate, Bpm, mean ± SD, median (25% Q, 75% Q)	105.26 ± 17.22, 107.0 (92.0, 114.0)	105.77 ± 21.75, 108.0 (90.0, 120.0)	105.7 ± 21.32, 108.0 (92.0, 120.0)	0.84
LVEF %, mean ± SD, median (25% Q, 75% Q)	39.1 ± 14.98, 39.0 (26.70, 50.30)	37.2 ± 15.79, 35.0 (25.0, 45.0)	37.4 ± 15.71, 35.0 (25.0, 47.0)	0.43
LVEF % <40, *n* (%)	27 (5.3%)	262 (51.6%)	289 (56.9%)	0.45
Creatinine level, μmol/L, mean ± SD, median (25% Q, 75% Q)	120.8 ± 82.49, 101 (79.56, 129.97)	124.4 ± 84.79, 103.8 (79.56, 136.97)	124.0 ± 84.49, 103.0 (79.56, 136.18)	0.77
BUN, mmol/L, mean ± SD, median (25% Q, 75% Q)	12.2 ± 6.77, 11.06 (6.80, 15.89)	12.3 ± 9.59, 9.9 (6.00, 14.98)	12.29 ± 9.34, 10.0 (6.1, 15.0)	0.95
Sodium level, mmol/L, mean ± SD, median (25% Q, 75% Q)	134.0 ± 6.39, 134.0 (129.5, 138.0)	134.4 ± 6.61, 135.0 (130.0, 139.0)	134.4 ± 6.58, 135.0 (130.0, 139.0)	0.71
eGFR, ml/min.1.73m^2, mean ± SD, median (25% Q, 75% Q)	86.2 ± 44.30, 77.2 (60.57, 106.17)	78.5 ± 38.09 75.9 (52.71, 96.66)	79.3 ± 38.79 76.2 (52.71 98.19)	0.17
Haemoglobin, g/L, mean ± SD, median (25% Q, 75% Q)	117.9 ± 24.31, 120.0 (105.0, 132.0)	118.7 ± 22.66, 120.0 (105.0, 133.0)	118.7 ± 22.81, 120.0 (105.0, 133.0)	0.80
Glucose level, mg/dL, mean ± SD, median (25% Q, 75% Q)	5.9 ± 2.59, 5.20 (4.70, 6.19)	6.4 ± 3.28, 5.38 (4.60, 6.92)	6.4 ± 3.22, 5.3 (4.60, 6.83)	0.25
Previous medication use, *n* (%)				
ACE inhibitor	9 (37.5%)	77 (36.7%)	86 (36.8%)	0.94
Loop diuretics	13 (54.2%)	87 (42.0%)	100 (43.3%)	0.26
β-Blockers	4 (16.7%)	37 (17.8%)	41 (17.7%)	1.0
Digoxin	6 (25.0%)	40 (19.0%)	46 (19.7%)	0.49
Hydralazine	0 (0.0%)	3 (1.4%)	3 (1.3%)	1.0
Nitrates	0 (0.0%)	8 (3.8%)	8 (3.5%)	1.0
Aldosterone Inhibitor	6 (25.0%)	49 (23.8%)	55 (23.9%)	0.90
Statins	2 (8.7%)	18 (8.6%)	20 (8.6%)	1.0
Aspirin	7 (29.2%)	62 (29.7%)	69 (29.6%)	0.96
Anticoagulants	2 (8.3%)	22 (10.6%)	24 (10.4%)	1.0
Aetiology heart failure				
Hypertensive CMP, *n* (%)	21 (41.2%)	167 (36.4%)	188 (36.0%)	
Idiopathic dilated CMP, *n* (%)	9 (17.7%)	72 (15.7%)	81 (15.5%)	
Rheumatic heart disease, *n* (%)	8 (15.7%)	71 (15.5%)	79 (15.1%)	
Ischaemic heart disease, *n* (%)	3 (5.9%)	32 (7.0%)	35 (6.7%)	
Peripartum cardiomyopathy, *n* (%)	3 (5.9%)	43 (9.4%)	46 (8.8%)	
Pericardial effusion tamponade, *n* (%)	3 (5.9%)	25 (5.5%)	28 (5.4%)	
HIV cardiomyopathy, *n* (%)	2 (3.9%)	8 (1.7%)	10 (1.9%)	
Endomyocardial fibrosis, *n* (%)	0 (0.0%)	9 (2.0%)	9 (1.7%)	
Other, *n* (%)	2 (3.9%)	32 (7.0%)	34 (6.1%)	
Region				
East	5 (9.4%)	93 (19.8%)	98 (18.7%)	0.048
South	11 (20.8%)	129 (27.5%)	140 (26.8%)	
West	37 (69.8%)	248 (52.8%)	285 (54.5%)	

ACE, angiotensin converting enzyme; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction.
*P-value for categorical variables from chi-square test or Fisher's exact test if at least one cell count <5 *P*-value for continuous variables from ANOVA.

Table 5 Predictors of worsening renal function

Predictor	Unit increase	Univariable models		Multivariable model	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Baseline Creatinine, µmol/L	88.4	0.95 (0.69, 1.31)	0.7720	0.77 (0.53, 1.11)	0.16
History of cor pulmonale	Yes vs. No	1.73 (0.68, 4.41)	0.2497		
Male sex	Male vs. Female	1.45 (0.82, 2.56)	0.2079	1.81 (0.97, 3.39)	0.062
BMI, ≤18.5 kg/m^2	5	0.10 (0.02, 0.42)	0.0018	0.06 (0.01, 0.29)	0.0005
BMI, >18.5 kg/m^2	5	1.58 (1.27, 1.98)	<0.0001	1.78 (1.39, 2.28)	< 0.0001
History of atrial fibrillation	Yes vs. No	0.57 (0.23, 1.36)	0.2050		
Systolic blood pressure,, mmHg	10	1.07 (0.99, 1.16)	0.0908		
Peripheral oedema	2/3 vs. 0/1	2.13 (1.04, 4.38)	0.0395		
Rales	2/3 vs. 0/1	3.50 (1.48, 8.28)	0.0043	3.56 (1.38, 9.17)	0.0088
Region	South vs. West	0.57 (0.28, 1.16)	0.0559	0.60 (0.27, 1.35)	0.060
	East vs. West	0.36 (0.14, 0.94)		0.31 (0.11, 0.87)	

BMI, body mass index; CI, confidence interval; OR, odds ratio.

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alues than without follow-up creatinine values died in-hospital (22 or 15.8% versus 15 or 5.8%).

Worsening renal function was evident in 53 (9.8%) patients with follow-up creatinine values available. The characteristics of patients with and without WRF are shown in *Table 4*. Patients with WRF were essentially similar to those without WRF in their characteristics, except that they had more evidence of congestion (peripheral oedema and rales).

Univariable and multivariable predictors of worsening renal function are presented in *Table 5*. Upon multivariable adjustment, significant predictors of WRF were BMI, the presence of rales, and geographic region. The risk of WRF decreased with increasing BMI until approximately 18.5 kg/m^2, above which the risk increased with increasing BMI.

Clinical outcomes by the occurrence of WRF are shown in *Table 6*. Those with WRF had a similar length of hospital stay as those without WRF, but a higher rate of 60-day mortality or readmission and a higher 180-day mortality rate. *Figure 1* is a Kaplan–Meier plot of cumulative incidence of death by worsening renal function to day 180.

Univariable and multivariable models predicting clinical outcome are presented in the Supporting Information *Tables S1* and *S2*. After multivariable adjustment for other prognostic factors, worsening renal function was an independent predictor of death or readmission over 60 days [adjusted hazard ratio (HR) = ~~1.98 (1.07, 3.68); *P* = 0.0298~~] and all-cause death over 180 days [adjusted HR = ~~1.80 (1.02, 3.17); *P* = 0.0407~~].

Table 6 Patient outcome by worsening renal function (WRF)

	WRF, *N* = 53	No WRF, *N* = 470	*P*-value*
Length of initial hospital stay (days), mean(SD), median (25% Q, 75% Q)	10.3 (7.08), 8.0 (6.5, 12.0)	10.2 (11.16), 8.0 (6.0, 11.0)	0.93
Initial hospitalization mortality, *n* (%)	5 (18.8%)	17 (14.6%)	0.10
Rehospitalization to day 60, *n* (%)	6 (14.5%)	39 (10.0%)	0.39
Death to day 60, *n* (%)	11 (22.8%)	39 (9.2%)	0.0034
Death or readmission to day 60, *n* (%)	13 (26.9%)	64 (15.3%)	0.032
Death to day 180, n (%)	15 (32.0%)	75 (19.1%)	0.020

WRF: ≥0.3 mg/dL (26.5 µmol/l) increase in creatinine compared with baseline.
*p-value is from two-sided t-test for LOS, log-rank test for time to event outcomes.

Discussion

Our study is the first multicentre registry from sub-Saharan Africa that provides insight into the prevalence, predictors, and clinical outcome of the renal dysfunction in AHF patients on this continent. The major findings of this study were that renal dysfunction was also frequently found at hospital admission for heart failure in this younger, mostly non-ischaemic patients. Although data for WRF was available in half of the patients studied, it was less prevalent and has different predictors compared with Western cohorts. Nevertheless, WRF was strongly and independently related to clinical outcome.

The prevalence of renal dysfunction (31% of patients with a eGFR <60 mL/min) in our cohort was similar to Western countries,[7–10,17] despite younger age. This relatively high prevalence might be related to the large number of patients with hypertensive heart failure, as the deleterious effects of hypertension on the kidneys are well known. In addition, AHF affects the haemodynamic and neurohormonal milieu, which leads to functional impairment or permanent kidney damage, regardless of the comorbidities.[18] The presence of comorbidities such as diabetes, atrial fibrillation, and anaemia as well as the serum creatinine values on admission of our patients were similar to those documented

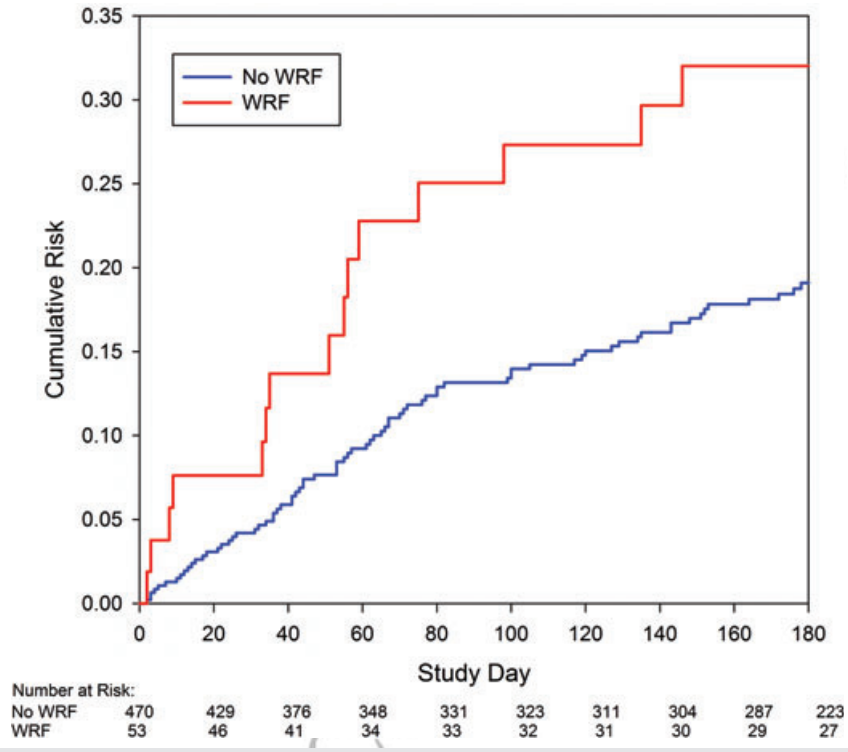

Figure 1 Kaplan–Meier plot of cumulative incidence of death by worsening renal function (WRF) to day 180.

in previous studies.[8,15,19] Inglis and co- workers[20] found renal dysfunction in only 12% of African heart failure patients with idiopathic dilated cardiomyopathy, which might be explained by the less deleterious effect of non-hypertension-related heart failure on the kidneys.

Concomitant renal dysfunction is one of the main independent risk factors for prolonged hospitalization, rehospitalization, and short- and long-term mortality in AHF.[21–23] In patients with chronic heart failure, baseline eGFR has been demonstrated to be a stronger predictor for all-cause mortality than LVEF and NYHA functional class.[24] Similarly, a decrease in GFR is directly associated with the rate of in-hospital mortality. In a meta-analysis, Smith *et al.*[7] reported that annual mortality rates were 26% in patients without renal dysfunction, 41% in the patients with any impairment of renal function. and 51% in patients with moderate to severe impairment. Overall, they found that any degree of renal impairment was associated with a 56% increase in relative mortality risk. Renal dysfunction was found to be a predictor of outcome both in heart failure patients with reduced ejection fraction (HFrEF) and heart failure patients with preserved ejection fraction (HFpEF) and was suggested to be a more powerful predictor of outcome in patients with HFpEF.[11]

Although the prevalence of renal dysfunction at baseline was relatively high, worsening renal function was found to be less prevalent than that reported in many previous studies.[8,9,25,26] This is likely to be because our patients were younger, had less previous myocardial infarctions, and probably less atherosclerotic kidneys. Although they had a high prevalence of chronic kidney disease, the kidneys could probably handle acute hypoperfusion better than atherosclerotic kidneys. However, this prevalence may still be an overestimation as there might have been selection in favour of more severe heart failure patients with poorer renal function, in whom renal function was more frequently measured.

The predictors of WRF in this study were BMI, signs of congestion (peripheral oedema and rales) and being in the Western African region. These are different from the factors found by other workers, which include diabetes[15,27,28] elevated systolic blood pressure,[7,27,28] NYHA class,[7,19] tachycardia, and female sex.[25] In a recent updated meta-analysis of WRF and outcomes in heart failure by Damman and colleagues,[11] other predictors found were age, diuretic use, baseline GFR, anaemia, vascular disease/ischaemic heart disease, and LVEF. Only one previous study showed a higher BMI to be a predictor of WRF.[11] We found both lower BMI and higher BMI to be predictors of WRF. Patients with a very low BMI might be cachectic, which carries a poor prognosis by itself, and WRF may be a marker of a poor functional and clinical status of cachectic heart failure patients. We cannot explain why a higher BMI was related to a higher risk of WRF, although it is well known that obese patients tend to hyperfiltrate, which might result in a limited 'spare capacity' when kidneys are challenged with hypoperfusion during an episode of AHF.

Similar to the findings of other studies conducted mostly in Europe and North America,[15,25,29,30] we found that patients who presented with signs of congestion were more likely to develop

WRF than those who had a less severe congestion The systemic/pulmonary congestion increases central venous pressure, which is directly transmitted to the renal vein affecting renal perfusion pressure. Different reports have highlighted that higher CVP is associated with decreasing GFR.[17,31,32] In addition, a direct effect on renal perfusion pressure—high renal venous pressure—results in increased interstitial intrarenal pressure because the kidney has a tight capsule. This increased pressure causes collapsing of tubules and directly opposes filtration, resulting in decreased GFR.[33] How autoregulation responds to increased renal venous pressure is unknown, although higher levels of intrarenal angiotensin II and activation of the sympathetic nervous system have been proposed, which could indirectly influence arteriolar tone.[34] However, the association between WRF and venous congestion remains complex, as was recently described by Testani and Damman.[35]

In a recent meta-analysis of WRF during RAAS inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction by Clark and colleagues,[36] WRF was associated with poorer outcome in both RAAS inhibitor and placebo groups, compared with patients who did not develop WRF. In addition the RAAS inhibitor group, despite having more frequent WRF, was associated with lower overall mortality than the placebo group and that benefit was attained in patients both with and without WRF. This may indicate that WRF by itself is a biased prognosticator.[37] In our study, even though the frequency of WRF is low, there was no difference in RAAS inhibition between those with WRF and those without (angiotensin-converting enzyme inhibition was 36.7% vs. 37.5% , $P = 0.94$; aldosterone inhibition 23.8% vs. 25.0%, $P = 0.9$).

Although the length of hospital stay of our patients was comparable to that found in other European registries,[38–41] there was no difference between those who developed WRF and those who did not. Other studies have shown that the development of WRF is associated with prolonged hospital stay.[15,21] The reason for this difference is not apparent but result from different management strategies in diverse medical centres as well as economic reasons, as in many hospitals in sub-Saharan Africa how long a patient remains on admission is determined by the affordability of the services.

Worsening renal function was an independent predictor of death or readmission over 60 days and all-cause death over 180 days. It has been shown that WRF is associated with a poor prognosis in most previous studies.[8–10,25,42] The cause of WRF in AHF has not been completely elucidated but is thought to result from decreased renal perfusion and venous congestion, while endothelial dysfunction, neurohormonal activation, and inflammation play a mediating role.[31,43] These patients also generally have more severe disease, developing a vicious cycle with more congestion leading to poor renal perfusion and further accelerating the heart failure.

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.[3] 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, missing laboratory data, and clinical signs assessments were higher than in studies conducted in other regions.

This registry was performed in selected centres and may represent only AHF patients seen in specialized centres. In addition, we did not measure renal haemodynamics or GFR by clearance methods, the eGFR formula used is only a surrogate marker of real GFR, but has been shown to be the most accurate in heart failure.[12] Finally, the fact that almost half of the patients do not have follow-up creatinine values for calculation of WRF calls for caution in the interpretation of the WRF data.

Conclusion

The present study shows that renal dysfunction is frequently present in younger non-ischaemic AHF patients in Africa. Worsening renal function, although calculated in half of the patients with available follow-up creatinine values, is less prevalent and has different predictors compared with Western cohorts. Nevertheless, in these patients, WRF was associated with the severity of congestion and appeared to be a strong and independent predictor of adverse clinical outcomes.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Predictors of death or readmission through 60 days

Table S2. Predictors of all-cause death through 180 days

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References

1. Antony KK. Pattern of cardiac failure in northern savanna Nigeria. *Trop Geogr Med* 1980;**32**:118–125.
2. Oyoo GO, Ogola EN. Clinical and socio demographic aspects of congestive heart failure patients at Kenyatta National Hospital, Nairobi. *East Afr Med J* 1999;**76**:23–27.
3. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schreuder N, Yonga G, Ba SA, Maru F, Alemayu B, Edwards C, Davison BA, Cotter G, Sliwa K. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries: results of the sub-Saharan Africa Survey of Heart Failure. *Arch Internal Med* 2012;**172**:1386–1394.
4. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;**149**:209–216.
5. Cotter G, Cotter-Davison B, Ogah OS. The burden of heart failure in Africa. *Eur J Heart Fail* 2013;**8**:829–831.
6. Ojji DB, Stewart S, Ajayi S, Manmak M, Sliwa K. A predominance of hypertensive heart failure in the Abuja Heart Study cohort of urban Nigerians: a prospective clinical registry of 1515 *de novo* cases. *Eur J Heart Fail* 2013;**15**:835–842.
7. Smith GL, Lichtman JH, Bracken MB, Shilpak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006;**47**:1987–1996.
8. Akhter MW, Aronson D, Bitar F, Khan S, Singh S, Singh RP, Burger AJ, Elkayam U. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. *Am J Cardiol* 2004;**94**:957–960.

9. Smith GL, Vaccarino V, Kosiborod M, Litchman JH, Cheng S, Watnick SG, Krumhols HM. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail* 2003;**9**:13–25.
10. Van Kimmenade RRJ, Januzzi JL Jr, Baggish AL, Lainchbury JG, Bayes-Genis A, Richards AM, Pinto YM. Amino terminal pro-brain natriuretic peptide, renal function, and outcomes in acute heart failure: redefining the cardiorenal interaction. *J Am Coll Cardiol* 2006;**48**:1621–1627.
11. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2013; Oct 27; [Epub ahead of print]
12. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation* 2006;**114**:1572–1580.
13. O'Meara E, Chong KS, Gardner RS, Jardine AG, Neilly JB, McDonagh TA. The Modification of Diet in Renal Disease (MDRD) equations provide valid estimation of glomerular filtration rates in patients with advanced heart failure. *Eur J Heart Fail* 2006;**8**:63–67.
14. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004;**147**:331–338.
15. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). *Eur Heart J* 2006;**27**:1216–1222.
16. Sliwa K, Davison BA, Mayosi BM, Damasceno A, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam Kouam C, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Cotter G. Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry. *Eur Heart J* 2013;**40**:3151–3159.
17. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol* 2008;**51**:1268–1274.
18. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. *Eur Heart J* 2012;**33**:2135–2143.
19. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei Cas L. Worsening renal function in patients hospitalized for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail* 2008;**10**:188–195.
20. Inglis SC, Stewart S, Papachan A, Vaghela V, Libhaber C, Veriava Y, Sliwa K. Anaemia and renal function in heart failure due to idiopathic dilated cardiomyopathy. *Eur J Heart Fail* 2007;**4**:384–390.
21. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail* 2002;**8**:136–141.
22. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol* 2006;**47**:1–8.
23. Klein L, Massie BM, Leimberger JD, O'Connor CM, Pina IL, Adams KF Jr, Califf RM, Gheorghiade M. OPTIME – CHF Investigators. Admission or changes in renal function during hospitalization for worsening heart failure predict post discharge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail* 2008;**1**:25–33.
24. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000;**102**:203–210.
25. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients > or = 65 years of age with heart failure. *Am J Cardiol* 2000;**85**:1110–1113.
26. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999;**138**:285–290.
27. Damman K, Jaarsma T, Voors AA, Navis G, Hillege HL, van Veldhuisen DJ, on behalf of the COACH investigators. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). *Eur J Heart Fail* 2009;**11**:847–854.
28. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004;**43**:61–67.
29. Kociol RD, Greiner MA, Hammill BG, Phatak H, Fonarow GC, Curtis LH, Hernandez AF. Long-term outcomes of Medicare beneficiaries with worsening renal function during hospitalization for heart failure. *Am J Cardiol* 2010;**105**:1786–1793.
30. Testani JM, McCauley BD, Kimmel SE, Shannon RP. Characteristics of patients with improvement or worsening in renal function during treatment of acute decompensated heart failure. *Am J Cardiol* 2010;**106**:1763–1769.
31. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009;**53**:582–588.
32. Uthoff H, Breidthardt T, Klima T, Aschwanden M, Arenia N, Socrates T, Heinisch C, Noveanu M, Frischknecht B, Baumann U, Jaeger KA, Mueller C. Central venous pressure and impaired renal function in patients with acute heart failure. *Eur J Heart Fail* 2011;**13**:432–439.
33. Braam B, Cupples WA, Joles JA, Gaillard C. Systemic arterial and venous determinants of renal haemodynamics in congestive heart failure. *Heart Fail Rev* 2012;**17**:161–175.
34. Fiksen-Olsen MJ, Strick DM, Hawley H, Romero JC. Renal effects of Angiotensin II inhibition during increases in renal venous pressure. *Hypertension* 1992;**19**(2 Suppl):137–141.
35. Testani JM, Damman K. Venous congestion and renal function in heart failure … it's complicated. *Eur J Heart Fail* 2013;**15**:599–601.
36. Clark H, Krum H, Hopper I. Worsening renal function during renin–angiotensin–aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. *Eur J Heart Fail* 2014;**16**:41–48.
37. Damman K, McMurray JJ. Why and when should we worry about worsening renal function? *Eur J Heart Fail* 2014;**16**:4–5.
38. Rudiger A, Harjola VP, Muller A, Mattila E, Saila P, Nieminen M, Follath F. Acute heart failure: clinical presentation, one-year mortality and prognostic factors. *Eur J Heart Fail* 2005;**7**:662–670.
39. Zannad F, Mebazaa A, Juilliére Y, Cohen-Solal A, Guize L, Alla F, Rougé P, Blin P, Barlet MH, Paolozzi L, Vincent C, Desnos M, Samii K, EFICA Investigators. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: the EFICA study. *Eur J Heart Fail* 2006;**8**:697–705.
40. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L, EuroHeart Survey Investigators. Euro Heart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
41. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M, Italian survey on Acute Heart Failure Investigators. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J* 2006;**27**:1207–1215.
42. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999;**138**:285–290.
43. Smilde TD, Damman K, van der Harst P, Navis G, Daan Westenbrink B, Voors AA, Boomsma F, van Veldhuisen DJ, Hillege HL. Differential associations between renal function and 'modifiable' risk factors in patients with chronic heart failure. *Clin Res Cardiol* 2009;**98**:121–129.

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AQ5. Is the text OK now: **length of stay (LOS)**

AQ6. Please define: **K-M**

AQ7. Does the following text make sense (something missing?): **Patients with a follow-up creatinine value also had a longer length of stay?**

AQ8. Does the following text make sense (e.g. type of creatinine values): **higher proportion of patients with follow-up creatinine values than without follow-up creatinine values?**

AQ9. **Author: GFR or eGFR?**

AQ10. Please define: **CVP**

AQ11. Is the text OK now: **In addition, a direct effect on renal perfusion pressure—high renal venous pressure—results in increased interstitial intrarenal pressure**

AQ12. Please define: **RAAS**

AQ13. Is the text OK now: **Finally, the fact that almost half of the patients do not have follow-up creatinine values for calculation of WRF calls for caution in the interpretation of the WRF data**

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