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## Anaemia and renal function in heart failure due to idiopathic dilated cardiomyopathy

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### Abstract

**Background:** Anaemia and renal dysfunction are common in patients with heart failure (HF). Most studies involve western cohorts with ischaemic aetiology receiving treatment likely to impair renal function.

**Aims:** To investigate the frequency of anaemia and renal dysfunction and the relationship between the two within a cohort of 163 newly diagnosed Black African idiopathic cardiomyopathy patients prior to commencing HF treatments and compare those findings to those of western HF cohorts.

**Methods:** Single-centre retrospective analysis. Anaemia defined as haemoglobin concentration <13.0 g/dL for males ( $n=85$ ) and <12 g/dL for females ( $n=78$ ). Probable renal dysfunction defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m<sup>2</sup>, using serum creatinine concentrations.

**Results:** The mean age was 48±11 years, 52% were male. Overall, 13.5% of patients were anaemic and 11.8% had evidence of renal dysfunction, while 1.2% had both. Renal dysfunction was significantly more common in older patients (mean age 58±13 vs. 47±10 years;  $p<0.001$ ).

**Conclusion:** The frequency of anaemia and renal dysfunction in this cohort was lower than that reported in western HF cohorts. These data infer a more limited relationship between HF, anaemia and renal dysfunction in patients without atherothrombotic disease; hence extrapolation of HF data from the western world to other populations should be interpreted cautiously.

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**Keywords:** Heart failure; Africa; Cardiomyopathy; Renal function; Anaemia

### 1. Introduction

Anaemia and renal dysfunction are common in patients with heart failure (HF). Neither is benign in this clinical setting. Chronic kidney disease is very common in patients with HF, and for those patients the prognosis is often quite poor [1].

Similarly, strong epidemiological associations between anaemia in HF patients and severity of HF symptoms and prognosis have been noted [2]. Given that both are common in HF and poor prognostic markers, a key clinical question in recent years has been whether these two conditions are linked? Moreover, if they are linked, do they represent a particularly poor prognostic marker or simply a reflection of progressively worsening cardiac and neurohormonal function or, indeed, reflect the common use HF treatments (e.g. ACE inhibitors, AII receptor blockers and aldosterone antagonists) that interfere with the neurohormonal activation system and therefore renal function?

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47 Determining the underlying causes (particularly independent of one another) of renal dysfunction and anaemia in  
48 patients with HF has, therefore, many clinical implications.

49 The prevalence of both anaemia [2] and renal dysfunction  
50 [1] and the relationship between these two clinical conditions  
51 within HF cohorts has been reported [3,4]. However, most  
52 studies involve western world HF cohorts with primary  
53 ischaemic aetiology, often receiving treatment likely to  
54 impair renal function and therefore confound any attempt to  
55 investigate their underlying cause(s) and relationships  
56 between the two. Alternatively, in the developing world  
57 setting, the aetiology of HF is often non-ischaemic and  
58 affected patients rarely receive standard HF treatments prior  
59 to specialist assessment and management.  
60

### 61 1.1. Study aims

62 It is within this context we had the unique opportunity to  
63 examine the frequency of anaemia and renal dysfunction and  
64 the relationship between the two within a developing world  
65 cohort of Black African patients. These patients presented  
66 with HF due to idiopathic dilated cardiomyopathy and data  
67 was recorded prior to commencing HF specific treatments.  
68 We compared our findings to those of western HF cohorts to  
69 determine if: a) the underlying prevalence and relationship  
70 between anaemia and renal dysfunction is different in devel-  
71 oping world vs. developed world cohorts and b) if so, whether  
72 this provides any insights into the relationship and prognostic  
73 importance of these conditions in patients with HF.

## 74 2. Methods

### 75 2.1. Study cohort

76 This study was a retrospective analysis of a single-centre  
77 cohort study, from which other health outcome and treatment  
78 data has been previously reported [5]. The study population  
79 consisted of newly diagnosed Black African patients with  
80 idiopathic dilated cardiomyopathy in New York Heart Asso-  
81 ciation (NYHA) functional class I to IV. Importantly, baseline  
82 data were collected prior to initiation of HF-specific  
83 treatments (ACE inhibitors, AII receptor blockers, aldoste-  
84 rone antagonists and beta-blockers ( $\beta$ -blocker)). The Com-  
85 mittee for Research in Human Subjects of the University of  
86 Witwatersrand approved the initial study protocol which  
87 conformed to the principles outlined in the Declaration of  
88 Helsinki. All subjects gave written informed consent for the  
89 collection of this data.

### 90 2.2. Study inclusion/exclusion criteria

91 Inclusion criteria were: 1) age  $\geq 18$  and  $< 80$  years, 2) 3)  
92 left ventricular ejection fraction  $< 45\%$  on echocardiography  
93 or radionuclide angiography, 4) sinus rhythm. Exclusion  
94 criteria were: 1) chronic obstructive pulmonary disease, 2)  
95 significant valvular heart disease, 3) history or evidence

of ischemic heart disease, 4) systolic blood pressure 96  
>180 mmHg and/or diastolic blood pressure >100 mmHg, 97  
5) pregnancy, and 6) severe liver disease, defined as enzymes 98  
>2 times the upper limit of normal. 99

### 2.3. Anaemic status 100

Consistent with other studies reporting the anaemia in HF 101  
cohorts [6–13], anaemia was defined according to World 102  
Health Organisation criteria [14], haemoglobin (Hb) con- 103  
centrations  $< 13.0$  g/dL for males and  $< 12.0$  g/dL females 104  
were classed as anaemia. 105

### 2.4. Renal function 106

Renal function was assessed via an estimated glomerular 107  
filtration rate (estimated GFR mL/min/1.73 m<sup>2</sup>) calculated 108  
using the Modification of Diet in Renal Disease (MDRD) 109  
abbreviated formula (estimated GFR mL/min/1.73m<sup>2</sup> = 110  
 $186.3 \times (\text{serum creatinine mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times (0.742$  111  
female sex)  $\times (1.212$  if African American) [15] using serum 112  
creatinine concentrations ( $\mu\text{mol/L}$ ) converted to mg/dL. An 113  
estimated GFR is preferred for the assessment of renal 114  
function over assessment of serum creatinine [16]. The 115  
MDRD formulas have been validated in several studies in 116  
different patient populations and have been used to estimate 117  
GFR in patients with HF [3,4,8,10,12,17] and include an 118  
adjustment for Black race [15], given the propensity for 119  
greater total muscle mass in this population [16]. The 120  
presence of probable renal dysfunction was identified 121  
according to a threshold of  $< 60$  mL/min/1.73 m<sup>2</sup>, a definition 122  
used in many clinical trials in HF [3,18–23] and other studies 123  
reporting renal function within HF cohorts [10,24,25] and a 124  
threshold below which complications of renal impairment 125  
appear [3]. 126

### 2.5. Cardiac function 127

An average left ventricular ejection fraction (LVEF) was 128  
calculated, using several calculations of LVEF obtained by 129  
standard clinical methods (multi-gated equilibrium cardiac 130  
blood pool scintigraphic technique and two dimensional 131  
targeted M-mode echocardiography with Doppler color flow 132  
mapping using both manual and machine calculations of 133  
LVEF) [5]. The functional capacity of each patient was 134  
determined according to NYHA classification. All patients 135  
above the age of 40 years had a coronary angiogram per- 136  
formed to rule out coronary artery disease. 137

### 2.6. Statistical analysis 138

All data analyses were performed using SPSS version 139  
12.0.1. Data are presented as percentage (%) or mean val- 140  
ues  $\pm$  standard deviation (SD). Between group differences 141  
were determined using an analysis of variance (ANOVA), or 142  
by independent samples *t*-test.  $\chi^2$  was used for analysis of 143

144 categorical variables. A Pearson correlation was used to  
 145 evaluate the relationship between continuous variables.  
 146 Testing was two-sided, and  $p$  values  $<0.05$  were considered  
 147 significant. Multiple logistic regression models were used to  
 148 determine the independent predictors of anaemia and  
 149 probable renal dysfunction: to examine potential differences  
 150 in Hb concentration or frequency of anaemia according to  
 151 age, renal function or LVEF, the cohort was grouped into  
 152 tertiles based on each of these variables.

### 153 3. Results

154 The study cohort of 163 Black African patients comprised  
 155 85 males (52%) and 78 females with a mean age  $48 \pm$   
 156 11 years. The clinical characteristics of this cohort are  
 157 summarised in Table 1. All patients had left ventricular  
 158 systolic dysfunction (mean LVEF  $25 \pm 9\%$ ). Functionally, the  
 159 majority of patients were classified as NYHA Class II or III.  
 160 As newly diagnosed patients prior to substantive treatment,  
 161 no patients had been pre-treated with an ACE inhibitor or  
 162 beta-blocker at the time of assessment, although 150 patients

t1.1	Table 1	
t1.2	Clinical characteristics of the cohort	
t1.3		All patients $n=163$
	<i>Demographics</i>	
t1.5	Male/female (%)	52/48
t1.6	Age, years	$48 \pm 11$
t1.7		
	<i>Medication (mean <math>\pm</math> SD)</i>	
t1.9	Furosemide (mg/day)	$137 \pm 46$
t1.10		
	<i>Anthropometrics (mean <math>\pm</math> SD)</i>	
t1.12	Weight (kg)	$69 \pm 15$
t1.13	BMI (kg/m <sup>2</sup> )	
t1.14	Male	$24 \pm 4$
t1.15	Female	$27 \pm 6$
t1.16		
	<i>Cardiac parameters (mean <math>\pm</math> SD)</i>	
t1.18	Average LVEF (%)	$25 \pm 9$
t1.19	Systolic BP (mmHg)	$117 \pm 20$
t1.20	Diastolic BP (mmHg)	$75 \pm 18$
t1.21	NYHA Class ( $n$ )	I (11), II (69), III (54), IV (12)
t1.22		
	<i>Haematological and biochemical parameters (mean <math>\pm</math> SD)</i>	
t1.24	Haemoglobin (g/dL)	
t1.25	Male	$14.9 \pm 1.7$
t1.26	Female	$13.7 \pm 1.9$
t1.27	est GFR (mL/min/1.73m <sup>2</sup> )	$88.2 \pm 26.9$
t1.28	Se creatinine ( $\mu$ mol/L)	$97.5 \pm 31.5$
t1.29	Se sodium (mmol/L)	$139.5 \pm 4.2$
t1.30	Se uric acid ( $\mu$ mol/L)	
t1.31	Male	$492.3 \pm 124.2$
t1.32	Female	$479.5 \pm 110.0$
t1.33	Se urea (mmol/L)	$15.3 \pm 29.1$
t1.34	Se potassium (mmol/L)	$4.1 \pm 0.6$
t1.35	Se glucose (mmol/L)	$5.2 \pm 1.8$

BMI, body mass index; Average LVEF, Left Ventricular Ejection Fraction, averaged for each patient from a number of methods of calculation; NYHA Class, New York Heart Association Classification; est GFR, estimated glomerular filtration rate; Se, serum.

Table 2	Clinical characteristics of the cohort according to estimated glomerular filtration rate			t2.1
	est GFR $<60$ mL/ min/1.73 m <sup>2</sup>	est GFR $\geq 60$ mL/ min/1.73 m <sup>2</sup>	$p$	t2.2
				t2.3
	<i>Demographics</i>			
	Number of patients (% of cohort)	19 (12)	142 (88)	t2.5
	Male/female (%)	42/58	54/46	ns t2.6
	Age (years)	$58 \pm 13$	$47 \pm 10$	$<0.001$ t2.7 t2.8
	<i>Medication (mean <math>\pm</math> SD)</i>			
	Furosemide (mg/day)	$146 \pm 63$	$137 \pm 44$	ns t2.10 t2.11
	<i>Cardiac measures (mean <math>\pm</math> SD)</i>			
	LVEF averaged (%)	$26.2 \pm 11.2$	$25.3 \pm 8.8$	ns t2.13
	NYHA class ( $n$ )	I (3), II (6), III (6), IV (3)	I (7), II (63), III (48), IV (9)	t2.14
	<i>Systolic blood pressure (mmHg)</i>			
		$123 \pm 18$	$117 \pm 20$	ns
	<i>Diastolic blood pressure (mmHg)</i>			
		$80 \pm 12$	$74 \pm 13$	$<0.05$ t2.16 t2.17
	<i>Haematological and biochemical parameters (mean <math>\pm</math> SD)</i>			
	est GFR (mL/min/1.73m <sup>2</sup> )	$46.7 \pm 10.8$	$93.7 \pm 23.3$	$<0.001$ t2.19
	Se creatinine ( $\mu$ mol/L)	$154.6 \pm 42.1$	$89.9 \pm 20.0$	$<0.001$ t2.20
	Se sodium (mmol/L)	$138.4 \pm 5.7$	$139.6 \pm 3.9$	ns t2.21
	<i>Se uric acid (<math>\mu</math>mol/L)</i>			
	Male	$602.0 \pm 130.3$	$476.2 \pm 116.7$	$<0.05$ t2.23
	Female	$586.7 \pm 187.2$	$457.1 \pm 78.7$	ns t2.24
	Se urea (mmol/L)	$11.0 \pm 7.9$	$15.8 \pm 30.9$	ns t2.25
	Se potassium (mmol/L)	$4.5 \pm 0.9$	$4.1 \pm 0.5$	$<0.05$ t2.26
	<i>Haemoglobin (g/dL)</i>			
	Male	$14.2 \pm 1.8$	$14.3 \pm 1.9$	ns t2.27
	Female	$14.6 \pm 1.9$	$14.9 \pm 1.7$	ns t2.28
	Female	$13.9 \pm 1.8$	$13.6 \pm 1.9$	ns t2.29
	Anaemia (%)	10.5	14.1	t2.30
	Male $<13$ g/dL ( $n$ )	1	10	ns t2.31
	Female $<12$ g/dL ( $n$ )	1	10	ns t2.32

BMI, body mass index; Average LVEF, Left Ventricular Ejection Fraction, averaged for each patient from a number of methods of calculation; NYHA Class, New York Heart Association Classification; est GFR, estimated glomerular filtration rate; Se, serum.

(92%) were being treated with furosemide (mean dose of  $137 \pm 46$  mg/day). t2.33

#### 3.1. Anaemia 165

Overall, 13.5% of patients were anaemic at the time of 166  
 assessment, with greater frequency in females (14.1%, mean 167  
 Hb  $13.7 \pm 1.9$  g/dL) compared to males (12.9%, mean Hb 168  
 $14.9 \pm 1.7$  g/dL) although the proportion of anaemic patients 169  
 was not significantly different between the sexes ( $p=1.0$ ). 170  
 Anaemic females ( $n=11$ ) were significantly younger than non- 171  
 anaemic females ( $42 \pm 13$  years vs.  $50 \pm 12$  years:  $p=0.04$ ), 172  
 although no significant difference in age was detected between 173  
 anaemic males ( $n=11$ ) and non-anaemic males ( $52 \pm 11$  years 174  
 vs.  $48 \pm 11$  years:  $p>0.05$ ). Mean averaged LVEF was 175  
 significantly lower in anaemic females than non-anaemic 176  
 females ( $23.5 \pm 4.2\%$  vs.  $27.6 \pm 8.9\%$ :  $p=0.025$ ). Mean serum 177

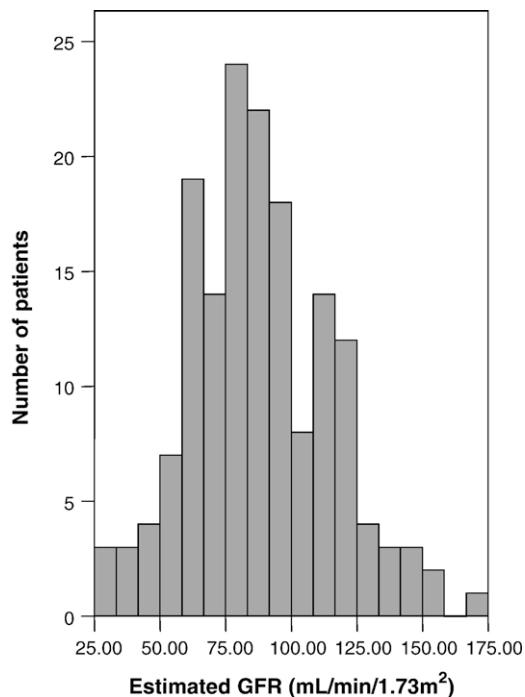


Fig. 1. Distribution of estimated glomerular filtration rate.

178 urea concentrations were significantly lower in anaemic males  
179 than non-anaemic males ( $6.9 \pm 1.6$  mmol/L vs.  $16.7 \pm$   
180  $30.8$  mmol/L:  $p=0.009$ ). Anaemic males and females had  
181 significantly lower mean Hb, as was to be expected, than their  
182 non-anaemic counterparts ( $p<0.001$ ). No significant differ-  
183 ence in the mean Hb or frequency of anaemia was detected  
184 according to averaged LVEF tertiles or NYHA Class.

185 A weak positive correlation was detected between Hb and  
186 LVEF with borderline significance in females ( $r=0.224$ :  
187  $p=0.057$ ), but not in males ( $r=0.118$ :  $p=0.290$ ).

188 There was no difference in the mean Hb or frequency of  
189 anaemia according to age tertiles for the cohort as a whole,  
190 however when considered according to sex, the mean Hb  
191 decreased significantly between the youngest and the oldest  
192 tertiles ( $<42$  vs.  $\geq 53$  years;  $15.5 \pm 1.6$  g/dL vs.  $14.2 \pm 1.7$  g/dL:

$p=0.008$ ) and the middle and the oldest tertiles ( $42-52$  years  
vs.  $\geq 53$  years;  $15.2 \pm 1.5$  g/dL vs.  $14.2 \pm 1.7$  g/dL:  $p=0.033$ )  
for males only. A small positive correlation was detected  
between Hb and age in females ( $r=0.223$ :  $p=0.05$ ), and a  
weak negative correlation between Hb and age in males ( $r=-$   
 $0.322$ :  $p=0.003$ ) was identified.

On multiple logistic regression analysis (males and  
females combined) none of the following variables were  
significant predictors of anaemia (age, sex, serum creatinine,  
estimated GFR, NYHA Class or LVEF).

Overall, the frequency of anaemia found in this cohort  
(13.5%) was lower than that reported in western HF cohorts  
which have employed the same definition of anaemia [6–  
8,10–13,26].

### 3.2. Renal function

Approximately 11.8% of the cohort (8 males and 11  
females) demonstrated signs of probable renal dysfunction as  
evidenced by estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup> (see  
Table 2). The mean serum creatinine concentration for the  
whole cohort was  $97.5 \pm 31.5$   $\mu$ mol/L, the value varied  
significantly ( $p<0.001$ ) according to sex, ( $106.5 \pm 33.2$  for  
males vs.  $87.7 \pm 26.4$   $\mu$ mol/L for females). The mean  
estimated GFR was  $88.1 \pm 26.9$  mL/min/1.73 m<sup>2</sup> and was  
slightly higher in males ( $90.9 \pm 26.4$  mL/min/1.73 m<sup>2</sup>)  
compared to females ( $85.2 \pm 27.2$  mL/min/1.73 m<sup>2</sup>) though  
not significantly so ( $p=0.180$ ). Fig. 1 and Table 2 summarise  
this data, of note, patients with an estimated GFR  $<60$  mL/  
min/1.73 m<sup>2</sup> were significantly older, had significantly  
greater mean serum creatinine, potassium and uric acid  
concentrations relative to those with a higher estimated GFR  
( $\geq 60$  mL/min/1.73 m<sup>2</sup>).

On multiple logistic regression analysis (males and fe-  
males combined) an estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup>  
was more common in older patients (odds ratio [OR]  
1.140 per year, 95% CI 1.052 to 1.234:  $p=0.001$ ); patients  
with higher serum potassium concentrations (OR 4.363 per  
mmol/L, 95% CI 1.407 to 13.528:  $p=0.011$ ) and higher  
serum urea concentrations (OR 1.069 per mmol/L, 95% CI

t3.1 Table 3

t3.2 International comparisons of estimated prevalence of renal dysfunction (adapted from Ref. [1])

t3.3	Trial (test treatment)	Number of patients	Creatinine exclusion ( $\mu$ mol/L)	Mean age (y)	Mean creatinine ( $\mu$ mol/L)	Mean est GFR (mL/min/1.73m <sup>2</sup> )	% est GFR $<60$ mL/min/1.73 m <sup>2</sup>
t3.4	Current cohort	161 <sup>a</sup>	NA	48	97.5	88.2	11.8
t3.5	CONSENSUS [20] (Enalapril)	243	$>330$	71	133	45 <sup>b</sup>	–
t3.6	SOLVD (Enalapril) [3]	6630	$>177$	60	106	70.4	32
t3.7	DIG (Digoxin) [19]	6800	$>265$	63	112	61.6 (median)	46
t3.8	CIBIS-2 (Bisoprolol) [22]	2647	$\geq 300$	61	103	77.5 <sup>b</sup>	33
t3.9	COMET (carvedilol vs. metoprolol) [21]	3029	Not reported	62	99 (median)	67.2	–
t3.10	CHARM (candesartan) [18]	2680	265	66	97 (median)	69 (median)	35
t3.11	CARE-HF (Cardiac resynchronisation therapy) [23]	813	Not reported	66 (median)	106 (median)	60 (median)	~50

t3.12 <sup>a</sup> 161 patients with serum creatinine concentration data.

t3.13 <sup>b</sup> Calculated using Cockcroft–Gault formula.

231 1.020 to 1.121:  $p=0.005$ ), but not serum Hb concentration  
232 nor the presence of anaemia.

233 The frequency of patients with probable renal dysfunction  
234 (estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup>) is not consistent  
235 across all reported HF cohorts in the literature (see Table 3).  
236 Overall 11.8% of the cohort had an estimated GFR of  
237  $<60$  mL/min/1.73 m<sup>2</sup>.

### 238 3.3. Anaemia and renal function

239 Although no statistically significant differences in the  
240 frequency of anaemia according to renal function were  
241 detected, (see Table 2), the frequency of anaemia in those  
242 patients with an estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup>, was  
243 10.5%, compared to 14.1% of those with an estimated GFR  
244  $\geq 60$  mL/min/1.73 m<sup>2</sup> only 2 patients (1.2%) of the cohort  
245 ( $n=161$  with a calculated estimated GFR) had both anaemia  
246 and probable renal dysfunction.

247 When the cohort was divided into tertiles based on  
248 estimated GFR, no significance in the mean Hb or the fre-  
249 quency of anaemia was detected, between the groups when  
250 the cohort was considered as a whole or by sex.

251 A small negative correlation was evident ( $r=-0.221$ ,  
252  $p=0.513$ ), between estimated GFR and Hb concentration in  
253 anaemic females. Conversely, a modest positive correlation  
254 was detected in anaemic males between estimated GFR and  
255 Hb concentration ( $r=0.601$ ,  $p=0.051$ ). There was no cor-  
256 relation between estimated GFR and Hb when the cohort  
257 was considered as a whole irrespective of anaemia status  
258 ( $r=0.046$ ,  $p=0.562$ ).

## 259 4. Discussion

260 This is the first study of anaemia and renal dysfunction in  
261 a cohort of patients with HF from a developing world setting.  
262 Based on potentially important differences in the age and  
263 gender balance, race, underlying aetiology of HF and  
264 treatment history, these data provide potentially important  
265 insights into similar reports from the western world. As such,  
266 we found a lower frequency of underlying anaemia and renal  
267 dysfunction in this cohort of HF patients (13.5% and 11.8%  
268 respectively) when compared to typical reports from western  
269 HF cohorts.

### 270 4.1. Anaemia

271 The frequency of anaemia in this current cohort was  
272 13.5% overall, a figure notably different to that reported by  
273 studies examining anaemia in western HF cohorts. For  
274 example, the prevalence of anaemia reported in western  
275 world HF cohorts applying the WHO definition of anaemia  
276 [14] ranges from 15.9–57% [6–8,10–13,26]. O'Meara and  
277 colleagues [12,17] have recently reported in a cohort of HF  
278 patients from the three CHARM trials that 26% of the cohort  
279 ( $n=2653$ , 33–35% female, 10–16% black) was identified  
280 with anaemia. Interestingly, a greater percent of anaemic

281 patients ( $n=677$ ) were black (16%) than non-anaemic 281  
282 patients ( $n=1976$ ) (10% black) in this cohort [12]. Of note 282  
283 also, in a cohort of 148 patients with HF (mean age 283  
284 64.5 years, 26% female, 48% ischaemic aetiology and 30% 284  
285 dilated cardiomyopathy), 57% were anaemic [11]. Similarly, 285  
286 Go et al. [8] have also recently reported in a large cohort of 286  
287 older HF patients (mean age 71.8 years, 46% female, 10% 287  
288 black) that 43% of patients were identified as anaemic 288  
289 according to WHO standards [8]. 289

290 In the western world overall, anaemia is often reported to 290  
291 be associated with older age, greater HF severity and renal 291  
292 dysfunction with reported rates as high as 70% [2]. 292

293 Notwithstanding the difficulty in making firm compar- 293  
294 isons due to the plethora of definitions used to identify 294  
295 underlying anaemia in this context [2] there do appear to be 295  
296 some important differences in the frequency and character- 296  
297 istics of anaemia in this Black African cohort. Clearly, the 297  
298 reasons are likely to be multifaceted. The most obvious 298  
299 difference between the cohort in the analysis and western HF 299  
300 cohorts considered here [6–8,10–13,26] is their age and the 300  
301 sex distribution; with a mean age 48 years and 48% of the 301  
302 population being female, this must account for a consider- 302  
303 able part of this difference. 303

304 The underlying cause of anaemia in this Black African 304  
305 cohort is largely unknown. We were not able to identify 305  
306 whether the low Hb observed in some patients is indicative 306  
307 of haemodilution. However, with 150 patients prescribed a 307  
308 mean furosemide dose of 137 mg/day, severe fluid overload 308  
309 in these patients would most probably have been limited. 309  
310 Significantly, these patients were all new presentations of 310  
311 idiopathic dilated cardiomyopathy, and data were collected 311  
312 prior to commencement of specific HF treatments. It is 312  
313 reasonable to suggest that confounding factors notwithstand- 313  
314 ing (e.g. a higher proportion of menstruating females), the 314  
315 anaemia found in this cohort is different to that reported in 315  
316 greater concentrations in western chronic HF cohorts, where 316  
317 low haemoglobin may be influenced by underlying vascular 317  
318 (atherothrombotic), in particular renovascular disease and 318  
319 chronic disease status; reflective of systemic organ dysfunc- 319  
320 tion due to deterioration of the HF syndrome [27]. 320

### 321 4.2. Renal function

322 We also found potentially important differences in renal 322  
323 function in this Black African cohort compared to typical 323  
324 western HF cohorts. Whilst the mean serum creatinine and 324  
325 mean serum sodium concentrations of the whole cohort were 325  
326 within the accepted normal range, the mean serum urea 326  
327 concentration was notably elevated above the accepted 327  
328 normal range, a finding which may possibly be evidence of 328  
329 some degree of pre-renal dysfunction in this cohort. On 329  
330 examination of the patients identified with probable renal 330  
331 dysfunction (estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup>), mean 331  
332 serum potassium concentrations were significantly higher; 332  
333 however, this value was within the accepted normal range. 333  
334 Diastolic blood pressure was also found to be significantly 334

335 higher in this group, perhaps reflective of neurohormonal  
336 activity. For males, the mean serum uric acid concentration  
337 was significantly higher than that of male patients with  
338 normal renal function. Conversely, serum uric acid concen-  
339 trations were elevated above the accepted normal range  
340 irrespective of estimated GFR, a finding which may be  
341 reflective of the use of furosemide in this cohort.

342 Twelve percent of patients in this current cohort had an  
343 estimated GFR  $<60$  mL/min/1.73 m<sup>2</sup>, indicative of probable  
344 renal dysfunction, a rate considerably lower than that  
345 reported by large HF clinical trials [3,18–23]. The mean  
346 estimated GFR in this current study was also higher,  
347 suggestive that this current cohort of HF patients has better  
348 renal function than patients enrolled in some of the large HF  
349 clinical trials [3,18–23]; this is to be expected, given the  
350 young age of this population and the absence of a chronic HF  
351 profile.

#### 352 4.3. Anaemia and renal function

353 Only 2 patients (1.2%) were identified with probable  
354 renal dysfunction as well as being anaemic. Although no  
355 differences were detected in the frequency of anaemia  
356 according to declining renal function, a modest positive  
357 relationship was detected between renal function and Hb in  
358 the presence of anaemia, for males. However this relation-  
359 ship was weaker and negative in nature between estimated  
360 GFR and Hb concentration in anaemic females. The negative  
361 nature of this relationship for anaemic females in conjunction  
362 with the significant difference in the mean ages of anaemic  
363 and non-anaemic women may reflect the influence of men-  
364 strual status on Hb concentration and the influence of age on  
365 estimated GFR. Hence, older women in this cohort may have  
366 a lower estimated GFR due to the influence of age on renal  
367 function, yet they are more than likely postmenopausal and  
368 have slightly greater serum Hb concentrations than their  
369 menstruating peers, who are younger and have better renal  
370 function. Considering that prevalence of anaemia in non-  
371 pregnant women of the developing world is estimated to be  
372 as high as 40–50% [14] and the prevalence of iron deficiency  
373 anaemia in European menstruating women is estimated at 1–  
374 14% [28], the anaemia seen in female patients in this cohort  
375 may not be associated with HF but rather a commonly  
376 occurring outcome associated with menstruation.

377 The absence of a notable positive relationship between  
378 renal function and the presence of anaemia in this HF cohort  
379 as a whole differs considerably from the typical sequelae of  
380 HF often observed in western HF cohorts, that anaemia is  
381 common, its prevalence increases with the severity of HF,  
382 declining renal function and increasing age [2].

#### 383 4.4. Comparisons with other heart failure cohorts

384 These data reported suggest that we may not be able to  
385 rely on the data reported from western HF cohorts and  
386 extrapolate those findings to developing world HF cohorts.

These data from a cohort of HF patients not yet exposed to  
ACE inhibitors and beta-blockers do, however, stimulate  
consideration that the anaemia and renal dysfunction  
observed commonly in western HF patients may not be the  
result of underlying pathological processes but perhaps  
merely a side effect from otherwise beneficial pharmaco-  
logical treatments of HF.

#### 4.5. Limitations

394 There are several limitations to this current analysis. The  
395 data is a retrospective analysis of secondary data and as such  
396 not all variables were available for the 163 patients, and no  
397 substantial conclusions may be made from these data alone.  
398 The sample size of the study is relatively small and the  
399 potential problem of Type II error in being under-powered to  
400 detect clinically significant differences based on age, sex,  
401 renal dysfunction and anaemic status was highly likely.  
402 There was also considerable difference in the number of  
403 patients in this current study compared to that of the studies  
404 for which comparisons are made. At the stage of data col-  
405 lection no further investigations into the cause of anaemia  
406 had been performed. Future prospective studies involving  
407 detailed follow-up soon to be undertaken in this population  
408 [29] will allow greater study of these differences between HF  
409 cohort of the western and developing worlds.  
410

#### 4.6. Summary

411 Despite these limitations, these unique data provide an  
412 important counter-point to data derived from predominantly  
413 western cohorts with HF where high rates of underlying  
414 anaemia and renal dysfunction are reported. Whilst the  
415 definition of anaemia differs significantly amongst research-  
416 ers [2], it is known that within most western cohorts of HF  
417 for which the prevalence of anaemia is reported, anaemia is  
418 common, its prevalence increases with the severity of HF,  
419 declining renal function and increasing age [2]. In this cohort  
420 we have found that although anaemia was present in some  
421 patients it was not particularly common. Moreover, the  
422 frequency of anaemia did not increase with the severity of  
423 HF, or with increasing age or with decreasing renal function.  
424 Overall, these data suggest a more limited relationship  
425 between HF, anaemia and renal dysfunction in Black African  
426 patients without atherothrombotic disease. As previous data  
427 were predominantly derived from western cohorts, this study  
428 suggests that any extrapolation of current HF data to non-  
429 western populations should be interpreted with caution.  
430

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436

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