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Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study

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ABSTRACT

Background: There are few data on heart failure (HF) patients from Africa, Asia, the Middle East and South America.
Methods: INTER-CHF is a prospective study that enrolled HF patients in 108 centers in 16 countries from 2012 to 2014. Consecutive ambulatory or hospitalized adult patients with HF were enrolled. Baseline data were recorded on sociodemographics, clinical characteristics, HF etiology and treatments. Age- and sex-adjusted results are reported.
Results: We recruited 5813 HF patients: mean(SE) age = 59(0.2) years, 39% female, 65% outpatients, 31% from rural areas, 26% with HF with preserved ejection fraction, with 1294 from Africa, 2661 from Asia, 1000 from the Middle-East, and 858 from South America. Participants from Africa—closely followed by Asians—were younger, had lower literacy levels, and were less likely to have health or medication insurance or be on beta-blockers compared with participants from other regions, but were most likely to be in NYHA class IV. Participants from South America were older, had higher insurance and literacy levels, and, along with Middle Eastern participants, were more likely to be on beta-blockers, but had the lowest proportion in NYHA IV. Ischemic heart disease was the most common HF etiology in all regions except Africa where hypertensive heart disease was most common.

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Conclusions: INTER-CHF describes significant regional variability in socioeconomic and clinical factors, etiologies and treatments in HF patients from Africa, Asia, the Middle East and South America. Opportunities exist for improvement in health/medication insurance rates and proportions of patients on beta blockers, particularly in Africa and Asia.

1. Introduction

Heart failure (HF) is a major global health problem, affects approximately 26 million people worldwide, and is estimated to have cost $108 billion worldwide in 2012 [1]. While Africa, Asia, the Middle East and South America have the majority of the world's population, most HF information comes from North America and Europe [2–4]. Although systematically acquired data on HF in these developing regions are few, existing data suggest geographic variations in HF etiologies, therapies and outcomes [5–9]. Yet, despite HF being a major burden, there is very little sociodemographic information on HF patients, or etiology and management of HF, from these regions, particularly in the outpatient setting [10–13]. Therefore, we conducted the INTERnational Congestive Heart Failure (INTER-CHF) study, a prospective HF registry to document contemporary sociodemographics, clinical variables, HF etiologies and treatments—primarily targeting outpatient enrollment—in Africa, Asia, the Middle East and South America.

2. Methods

2.1. Study design

INTER-CHF is a prospective, international, multicenter, longitudinal study conducted in 108 centers in 16 countries with 12 months of follow-up (detailed design and protocol were previously published [14]). Our objectives were to assess social and clinical risk factors as well as HF etiologies and treatments in these regions.

Between September 2012 and February 2014, consecutive patients with a clinical diagnosis of HF were enrolled from outpatient clinics (2/3 of enrollment by design, as most prior HF data have come from hospital inpatient settings [6]) or inpatient hospital wards (1/3 of enrollment) of the participating centers. The participants were ≥18 years of age and provided informed consent. We excluded patients with a life expectancy less than the duration of the follow-up (12 months) due to severe non-cardiac diseases, and patients who were likely to be lost to follow-up. Ethics board approvals were obtained at all local recruiting sites and at the central coordination centre (Population Health Research Institute [PHRI], McMaster University, Hamilton, Ontario, Canada). This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutions' human research committee.

The countries participating in INTER-CHF (Fig. 1) were selected to represent the regions where existing HF data are scarce. We also built on existing collaborative networks with physicians in these regions from studies previously coordinated from PHRI, such as INTER-HEART [15]. In each country, at least one recruitment center was from a rural setting, where feasible.

2.2. Data collection

At enrollment, information on demographics, clinical risk factors, etiology and duration of HF and New York Heart Association (NYHA) functional classification were recorded. Data were additionally obtained from the participants' medical records. Information about cardiac structure and function were derived from echocardiography obtained as part of clinical care. Left ventricular ejection fraction (LVEF) was defined as preserved when ≥50% [16], and valvular heart disease was defined as at least moderate stenosis or regurgitation in ≥1 cardiac valve. Echocardiographic information on LVEF and valve disease was available in 4702 (81%) of the participants. Determination of HF etiology was based on the recruiting physician's clinical decision using all available clinical, laboratory and echocardiographic data. By design, clinical and radiographic information was prospectively collected to determine the likelihood of HF according to the Boston criteria [17], which has been shown to be more accurate than similar criteria (such as the Framingham criteria) in elderly populations [18].

2.3. Statistical methods

Baseline characteristics and other descriptive variables are reported using means and standard errors, medians and interquartile ranges, or counts and proportions as appropriate. We compared categorical data using Chi-square tests and continuous data with

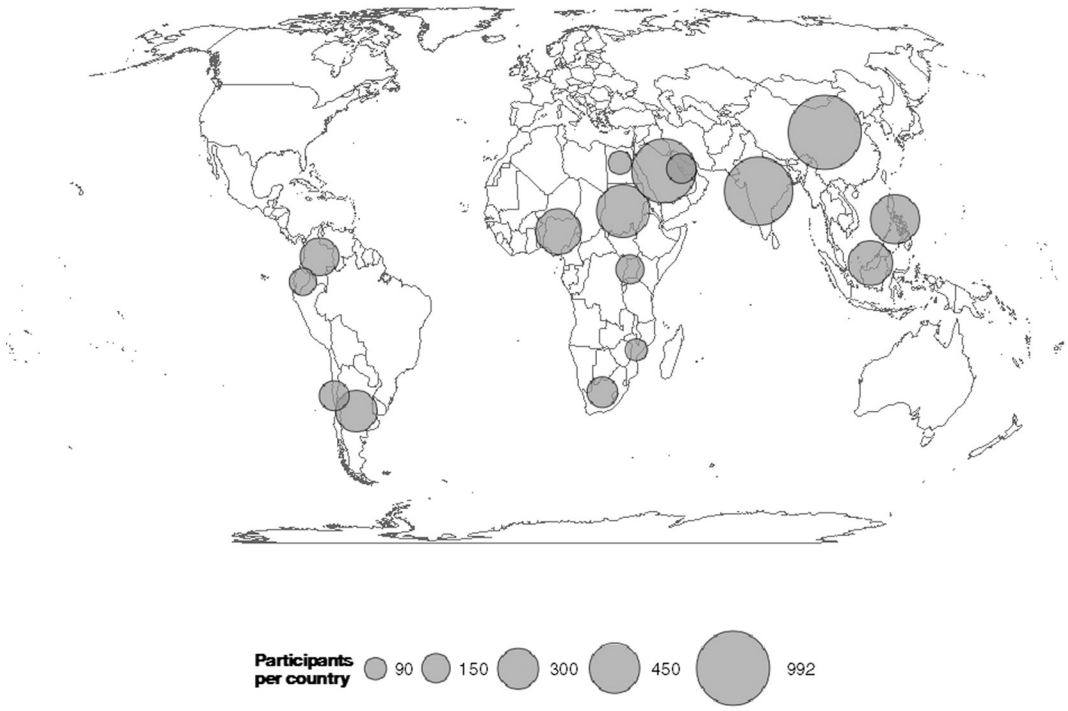

Fig. 1. INTER-CHF participant enrollment, by country. 1. Africa (1294 patients): Nigeria (383 patients), South Africa (169 patients), Sudan (501 patients), Uganda (151 patients), Mozambique (90 patients). 2. Asia (2661 patients): China (992 patients), India (858 patients), Malaysia (362 patients), Philippines (449 patients) 3. Middle East (1000 patients): Saudi Arabia (741 patients), Egypt (102 patients) Qatar (157 patients) 4. South America (858 patients): Argentina (308 patients), Chile (153 patients), Colombia (268 patients), Ecuador (129 patients). Total recruitment = 5813 patients.

ANOVA. For all reported variables (except age and sex), means or standardized proportions were adjusted for age and sex. Additional pre-specified stratified analysis was performed according to: 1) hospital inpatients and clinic outpatients; and 2) preserved and reduced LVEF, owing to differences in characteristics and management of these populations. Additionally, all enrolled participants who had clinical variables recorded that could be applied all of the three categories required for the Boston criteria for HF[17] (history; physical examination; chest radiography) were analyzed to determine whether results differed in patients with definite/possible HF according to these criteria from the overall cohort. Two-sided p-values < 0.05 were considered statistically significant. All analyses were performed using SAS version 9.1.

3. Results

Of 7176 patients screened, 5813 (81%) consecutive patients with HF were enrolled: 1294 (22%) from Africa, 2661 (46%) from Asia, 1000 (17%) from the Middle East, and 858 (15%) from South America. The numbers of participants recruited from each of the 16 countries are shown in Fig. 1. The mean(SE) age of the participants was 59(0.2) years and 2244 participants (39%) were female; 64% were outpatients, 36% were inpatients, 42% were in NYHA class III or IV, and 31% were from rural areas. Of the 81% of participants with echocardiographic data, 26% had preserved LVEF.

3.1. Regional variations in HF patient characteristics

3.1.1. Africa

Detailed baseline data according to region are shown in Table 1. African participants were the youngest (mean[SE] = 53[0.4] years), most likely to be illiterate (43%), lack health insurance (66%) and medication insurance (67%), and most likely to be in NYHA functional class IV (21%). The proportion of African participants on a beta blocker was significantly lower than in participants from other regions (48%) (Table 2). Hypertensive heart disease was the leading cause of HF (35% of cases), followed by ischemic cardiomyopathy (20%), idiopathic dilated cardiomyopathy (15%), and rheumatic valvular heart disease (7%; Fig. 2 and Appendix 2).

3.1.2. Asia

Asian participants were most likely to have been recruited from rural locations (46%), had the second highest proportions without health (47%) and medication insurance (61%) or in NYHA III/VI (13%) (Table 1), but were the second least likely (after African participants) to receive beta blockers (61%) (Table 2). Ischemic heart disease was the leading HF etiology (48%), followed by hypertensive heart disease (14%), idiopathic dilated cardiomyopathy (10%) and rheumatic valvular heart disease (9%; Fig. 2 and Appendix 2).

3.1.3. Middle East

Middle Eastern participants were the second youngest (mean[SE] = 56.4[0.5] years), were most likely to be male (72%), and had the highest BMI (mean[SE] of 30[0.2] kg/m^2) of any region (Table 1). A majority of Middle Eastern participants had diabetes (56%) and hyperlipidemia (57%)—markedly higher than any other region. Participants from the Middle East also had the second lowest proportions without health (25%) and medication (27%) insurance or in NYHA IV (6.4%), and the highest proportion of patients on beta blockers (86%) (Table 2). Ischemic cardiomyopathy was the most common HF etiology (50%), followed by idiopathic dilated cardiomyopathy (19%), hypertensive heart disease (10%) and rheumatic valvular heart disease (6%; Fig. 2 and Appendix 2).

3.1.4. South America

South American participants were the oldest (mean[SE] = 67[0.5] years), were least likely to be from rural areas (21%), and had the lowest proportions of patients without health (15%) and medication insurance (16%) or who were illiterate (4%). South American participants were least likely to be in NYHA IV (4.7%) (Table 1) and had the second highest beta-blocker use (73%) (Table 2). Ischemic heart disease was the most common HF etiology (26%), followed by hypertensive heart disease (21%), idiopathic dilated cardiomyopathy (15%) and rheumatic valvular heart disease (6%; Fig. 2 and Appendix 2).

Table 1
Baseline characteristics of INTER-CHF participants, by region.

	Africa N = 1294	Asia N = 2661	Middle East N = 1000	South America N = 858	p-Value
Demographics					
Age, mean (SE)	53.4 (0.4)	60.0 (0.3)	56.4 (0.5)	67.1 (0.5)	<0.0001
Male (%)	51.8	59.1	72.3	61.2	<0.0001
Rural (%)	31.8	46.2	26.2	21.0	<0.0001
Inpatient (%)	48.6	34.9	30.6	26.1	<0.0001
Social history					
Absence of health insurance (%)	65.8	46.9	24.8	14.7	<0.0001
Absence of medication insurance (%)	67.3	61.3	27.3	15.5	<0.0001
Illiterate (%)	42.7	14.9	36.1	4.2	<0.0001
Heart failure history					
NYHA functional class I (%)	7.2	12.9	15.4	19.6	<0.0001
Functional class II (%)	36.8	44.7	46.2	49.4	<0.0001
Functional class III (%)	35.5	28.9	31	26.4	<0.0001
Functional class IV (%)	20.9	12.8	6.4	4.7	<0.0001
<1 year since of HF diagnosis (%)	53.9	44.0	26.5	32.3	<0.0001
Preserved LVEF (%)	28.8	40.7	11.1	29.0	<0.0001
HF hospitalization in past year (%)	36.4	27.7	22.1	26.9	<0.0001
Risk factors					
BMI, mean (SE)	25.5 (0.2)	24.4 (0.1)	30.0 (0.2)	28.5 (0.2)	<0.0001
Hypertension (%)	61.6	59.0	68.4	73.6	<0.0001
Diabetes mellitus (%)	17.1	27.9	56	21.9	<0.0001
Dyslipidemia (%)	21.1	26.1	57.1	48.7	<0.0001
Chronic kidney disease (%)	3.8	7.1	11.7	11.6	<0.0001
Tobacco use (ever) (%)	14.7	31.1	22.6	34.3	<0.0001
Alcohol use (any) (%)	10.8	9.1	2.5	14.9	<0.0001
Valve disease (%)	57	40.4	48	47.4	<0.0001
Prior stroke (%)	5.0	10.2	3.3	4.1	<0.0001
History of myocardial infarction (%)	8.2	22.3	19.1	18.3	<0.0001

Table 2
Heart failure medications among INTER-CHF participants, by region.

	Africa N = 1294	Asia N = 2661	Middle East N = 1000	South America N = 858	p-Value
Beta-blocker(%)	48.3	60.8	85.9	73.3	<0.0001
ACE inhibitor (%)	58.3	43.1	61.6	39.9	<0.0001
Angiotensin receptor blocker (%)	18.8	24.8	20	35.5	<0.0001
ACE Inhibitor, angiotensin receptor blocker, or both (%)	77.1	67.9	81.6	75.4	<0.0001
Aldosterone Inhibitors (%)	59.4	44.0	45.8	55.1	<0.0001
Digoxin (%)	31.9	27.6	18.0	25.0	<0.0001
Diuretic (%)	93.7	62.1	87.8	77.6	<0.001

3.2. Definition of HF

Of the 5823 participants in INTER-CHF, 3189 (55%) had variables measured in all of the 3 categories required for the Boston Criteria for HF. Of these 3189 participants, 2597 (82%) had either definite or possible HF; of these 2597 patients, very similar findings were seen, on a regional basis, compared to the entire cohort of 5823 participants (Appendix 3), with African participants being youngest (mean[SE] = 52.4[0.6] years),

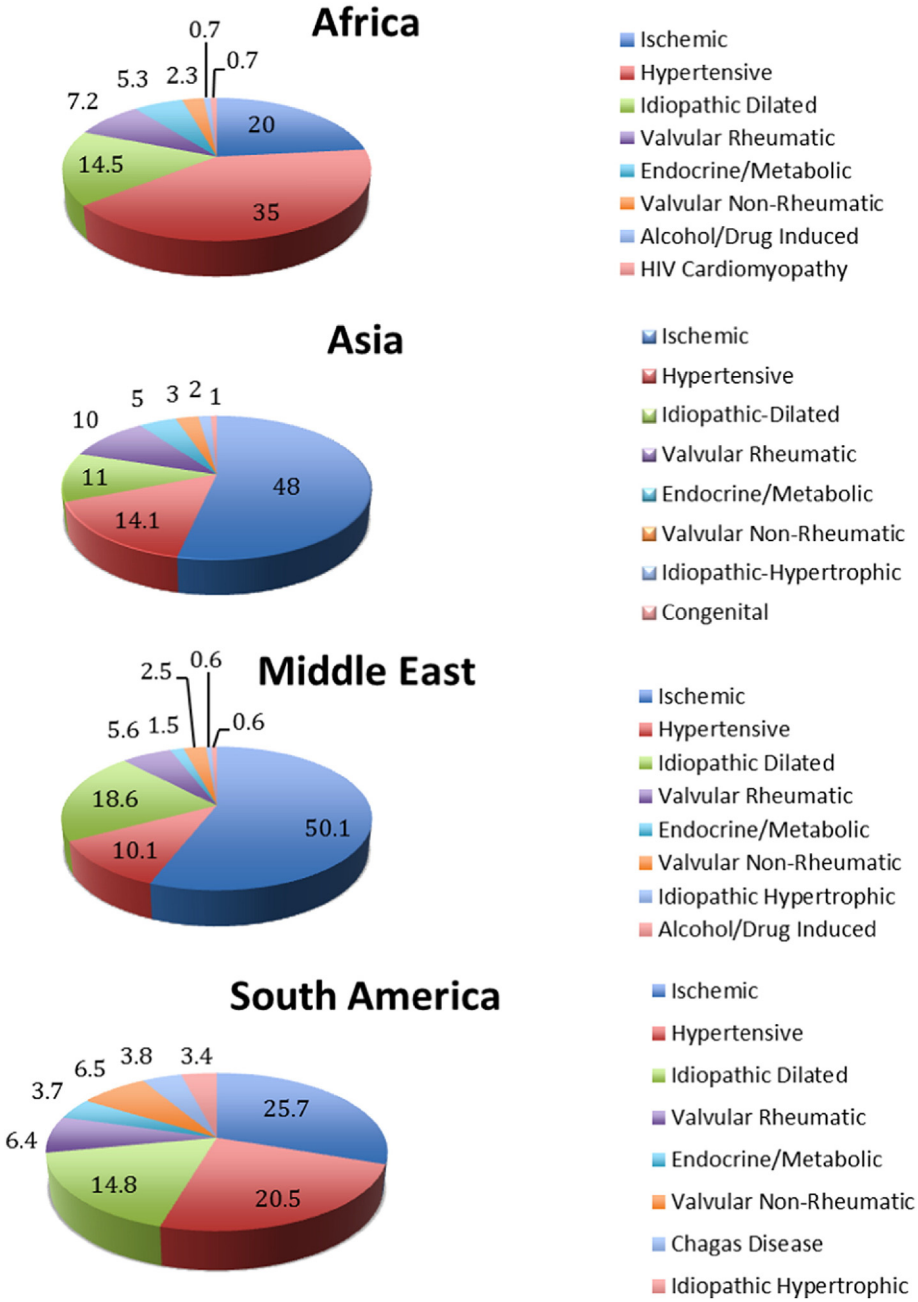

Fig. 2. Most common heart failure etiologies among INTER-CHF participants by region, adjusted for age and sex (%).

more likely to lack health insurance (72%), be illiterate (48%), be in NYHA IV (23%), and have hypertensive heart disease as the leading HF etiology.

3.3. Participants with reduced and preserved LVEF

In the 3306 INTER-CHF participants with reduced LVEF, when adjusted for age and sex, similar regional variations were seen compared to the overall cohort of 5823 participants, most notably with significantly lower proportions of African participants (52%) and Asian participants (69%) being on a beta blocker compared to Middle Eastern (88%) or South American participants (83%) (Appendix 4). Stratified analysis of the 1368 INTER-CHF participants with preserved LVEF showed similar regional trends as seen in the overall cohort.

3.4. Patients recruited as hospital inpatients and clinic outpatients

Of the 5823 participants in INTER-CHF, 2105 (36%) were recruited as hospital inpatients; in this group, similar regional differences were seen compared to the overall cohort of 5823 participants. To understand whether regional variations in proportions of participants in higher NYHA functional class was related to, or independent of inpatient vs. outpatient status, we re-analyzed NYHA class in outpatient and inpatients separately. As in the overall cohort, African participants recruited as hospital inpatients were more likely to be in NYHA IV (27.4%) compared to South American (14.5%) or Middle Eastern participants (13.8%) recruited as inpatients, with Asian participants (24.5%) close behind Africans. Stratified analysis of the 3695 INTER-CHF participants recruited as clinic outpatients also showed regional variations similar to the overall cohort of 5823 INTER-CHF participants (Appendix 5); once again, African participants recruited as outpatients were most likely to be in NYHA IV (14.7%) compared to participants from other regions recruited as outpatients.

4. Discussion

The key findings of INTER-CHF are considerable variability in demographics, clinical and social factors, HF etiologies and treatments in Africa, Asia, the Middle East and South America. Most notably, African participants—followed by Asians—were least likely to have health or medication insurance or be literate, but were most likely to be in advanced NYHA functional class while least likely to be on beta-blockers. In addition, data on etiologies of HF suggest epidemiologic transition, particularly in Africa and Asia. Given the proportions of patients lacking health or medication insurance and not being on HF medications in these areas of the world—particularly in Africa and Asia—opportunities exist for interventions to ameliorate patient care and treatment.

4.1. Results in context of previous studies

INTER-CHF provides HF data on patients who have been poorly represented in prior literature: HF patients—*particularly outpatients*—from sub-Saharan Africa, South Asia, the Middle East and South America. Importantly, socio-economic information was not available from previous HF studies in Africa. In INTER-CHF, a majority of African participants did not have health or medication insurance and nearly half were illiterate. These social inequities may help explain why African INTER-CHF participants with reduced LVEF were less likely to receive beta-blockers than participants with reduced LVEF from other regions, and why African participants (both inpatients and outpatients) were more likely to be in advanced NYHA functional class; other important factors to consider are local medical culture and physician education/preference. In THESUS-HF, a prospective registry of 1006 African patients with acute HF admitted to hospital [19], participants were similar to African INTER-CHF participants in clinical characteristics, but HF was most commonly due to hypertension (45%) and rheumatic heart disease (14%), while ischemic heart disease (8%) was uncommon. Earlier data on HF in Africa [6,20,21] also suggested that rheumatic, hypertension and infectious causes were the leading HF etiologies, with <10% with ischemic heart disease. In INTER-CHF, African participants were most likely to have hypertensive or ischemic etiologies of HF, with rheumatic heart disease less common, and infectious causes very uncommon. These data may suggest transition in HF epidemiology in Africa, as previously reported in prior work [21], owing to urbanization and increase in risk factors for ischemic heart disease, although differences in sampling must be acknowledged [7].

Most HF data from Asia had previously originated from hospitalized patients in China with scant data on HF patients from India [11,13] and socio-economic features of Asian HF patients were not described. In INTER-CHF, Asian participants had significantly lower healthcare and medication insurance rates than participants in the Middle East and South America, which may contribute to the lower observed use of beta blockers in Asian INTER-CHF participants (seen in the overall cohort, but specifically when participants with reduced LVEF were analyzed separately), although physician education/preference may also play a role. As seen in African participants, the lower rate of health and medication insurance in Asian participants compared to participants in the Middle East and South America may also explain—at least in part—the higher NYHA functional class of Asians compared to these regions. In 2015, Harikrishnan et al. reported on a registry of 1205 HF hospital inpatients from a single city (Trivandrum, Kerala) [22], which indicated that the most common HF etiology was ischemic heart disease (72%). While HF data from the 1970s, 1980s and early 1990s suggested that valvular, infectious and hypertensive causes of HF were most common, more recent data suggest a major increase in ischemic heart disease in Asia [6,23]. These data, when taken together with results from INTER-CHF, suggest changes in the epidemiology of HF in Asia [11,23].

There are few HF data, particularly among outpatients, from the Middle East [24,25] with few to no socioeconomic data published on these patients. The relatively high beta-blocker and ACEi/ARB use in INTER-CHF Middle Eastern participants, compared participants from Africa and Asia, may be related to the relatively high rates of health or medication insurance relative to Africans and Asians as well as physician education/training factors. Indeed, prior data from the United States [26] and Europe [27] have suggested that physician education was a determinant of whether HF patients were taking guideline recommended therapies (particularly beta blockers and ACE inhibitors). Importantly, these regional variations in beta-blocker use did not change when INTER-CHF participants with reduced LVEF only were analyzed. Additionally, the relatively high health insurance rates may help explain the lower NYHA functional class of Middle Eastern participants compared to Africans and Asians, as they may relate to access to health care. The Gulf CARE registry of acute HF found 61% of patients were hypertensive, 50% with diabetes mellitus, and 69% with reduced LVEF and ischemic cardiomyopathy (53%) was the most common HF cause [25]. In INTER-CHF, Middle Eastern participants also had high proportions of hypertension (68%), diabetes mellitus (56%) and reduced LVEF (89%) with ischemic cardiomyopathy the main etiology. Taken together, Middle Eastern patients appear distinct from participants from other regions, being younger, yet having significantly higher prevalence of obesity and diabetes mellitus and higher rates of ischemic cardiomyopathy with depressed LVEF than HF patients from other regions. However, since the great majority of Middle Eastern participants in INTER-CHF were from Gulf countries, this observation may not be generalizable to non-Gulf state Middle Eastern HF patients.

In South America, prior data on HF largely came from reports on hospitalized patients in single urban centers in Argentina and Brazil [28], with one multi-hospital registry of acute HF in Chile [29]; furthermore, socioeconomic data on these patients were very scarce. South American participants in INTER-CHF had among the highest literacy and health and medication insurance rates, were in the lowest NYHA class and had significantly higher rates of beta blocker usage compared to African and Asian participants (also seen in stratified analyses of

participants with reduced LVEF only). Therefore, in terms of age, and risk factor profile, South American participants were similar to reported descriptions of HF patients in North America and Europe [2–4]; however, INTER-CHF South American participants had ischemic etiology of HF in only 26% (and in 31% of patients with reduced LVEF). By contrast, in the Euro-Heart Survey, evidence of ischemic heart disease was present in 68% of participants [2] and in 65% in IMPROVE-HF [4]. However, our findings on HF etiology are similar to the pooled estimate from previous studies in South America that suggested that ischemic heart disease accounted for 33% of HF in South America [6].

4.2. Strengths and limitations

Our study of 5813 consecutive patients recruited in 108 centers in 16 countries constitutes the largest study of HF in Africa, Asia, the Middle East and South America. The standardized protocol ensured a common approach to recruitment and documentation of patient characteristics, which facilitated comparisons among regions. Yet, our sampling frame was not representative of each country, and thus future studies with random sampling of populations to identify HF in the community with long-term follow-up of participants would be needed to ensure greater representativeness. By design, higher outpatient recruitment was our focus because the majority of prior data was from hospitalized patients [6]. However, stratified analysis of inpatients and outpatients did not significantly change the overall findings. We enrolled patients with a clinical HF diagnosis because we wanted participants to represent a real-world dataset of patients who are diagnosed with, and being treated for, HF in these regions; thus, it is possible that some patients who did not in fact have HF were included in the registry. Yet, analysis of INTER-CHF participants who satisfied the Boston criteria for HF, and those with documented reduced LVEF, did not significantly change the overall findings.

5. Conclusions

INTER-CHF describes significant regional variability in sociodemographic factors, clinical characteristics, etiologies and treatments of HF patients in Africa, Asia, the Middle East and South America. Information obtained on HF etiology suggests epidemologic transition in Africa and Asia. The proportions of patients lacking health or medication insurance and not being on HF medications—particularly in Africa and Asia—point to opportunities for interventions to improve patient care and treatment for HF in these areas of the world.

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Conflict of interest

The authors have no conflict of interest to declare in respect of this manuscript.

Appendix 1. Investigators in the INTER-CHF Registry

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Appendix 2

Table 1
Heart failure etiologies among INTER-CHF participants, by region, adjusted for age and sex.

	Africa N = 1294	Asia N = 2661	Middle East N = 1000	South America N = 858	p-Value
Ischemic heart disease (%)	20.0	48.6	50.1	25.7	<0.0001
Hypertensive heart disease (%)	35.0	14.1	10.1	20.5	<0.0001
Idiopathic — dilated (%)	14.5	10.1	18.6	14.8	<0.0001
Valvular heart disease, rheumatic (%)	7.2	9.2	5.6	6.4	0.0004
Valvular heart disease, non-rheumatic (%)	2.3	2.6	2.5	6.5	<0.0001
Endocrine/metabolic (%)	5.3	4.3	1.5	3.7	<0.0001
Idiopathic — hypertrophic (%)	0.2	1.4	0.6	3.4	<0.0001
Chagas' cardiomyopathy (%)	0	0	0	3.8	<0.001
Endomyocardial fibrosis (%)	0.2	0.1	0.1	0.1	0.32
Peripartum cardiomyopathy (%)	0.15	0.03	0.13	0.04	<0.0001
Congenital (%)	0.1	0.7	0.3	1.5	<0.0001
Alcohol/drug induced (%)	0.7	0.3	0.6	0.4	0.04
Tuberculosis related heart disease (%)	0.1	0.2	0	0.3	0.07
HIV cardiomyopathy (%)	0.7	0	0	0	<0.0001
Post-chemotherapy (%)	0.1	0.1	0.4	0.5	0.01
Unknown (%)	0.6	0.9	0.3	0.4	0.12

Appendix 3. INTER-CHF participants who met the Boston HF Criteria.

Variable (N = 2597)	Africa N = 624	Asia N = 1034	Middle East N = 584	South America N = 355	p-Value
Age, years [mean(SEM)]	52.4(0.60)	60.5(0.47)	57.7(0.63)	68.3(0.79)	<.0001
Male (%)	53.8	58.1	72.5	50.1	<.0001
Body mass index, kg/m^2 [mean (SEM)]	24.9(0.27)	24.1(0.20)	30.3(0.27)	29.2(0.36)	<.0001
No health insurance (%)	71.6	49.9	23.3	22.1	<.0001
No medication insurance (%)	71.9	60.1	26.8	22.2	<.0001
Illiterate (%)	47.6	18.2	37.6	5.03	<.0001
Rural (%)	35.3	53.2	25.6	24.2	<.0001
Inpatient (%)	59.2	49.2	45.4	51.5	<.0001
NYHA class I (%)	5.18	6.07	6.59	10.1	0.0543
NYHA class II (%)	35.4	35.3	42.1	39.4	0.0293
NYHA class III (%)	36.9	36.7	41.3	41.1	0.1796
NYHA class IV (%)	22.5	21.8	9.98	9.65	<.0001
<1 year since of HF diagnosis (%)	59.3	45.2	28.9	42.2	<.0001
Hypertension (%)	56.7	53.5	70.6	76.7	<.0001
Diabetes mellitus (%)	17	26.1	60.5	23.4	<.0001
Dyslipidemia (%)	19	26.5	59.9	45.4	<.0001
Chronic kidney disease (%)	4.7	6.42	12.6	13.8	<.0001
Tobacco use (ever) (%)	11.6	32.5	21.5	40.1	<.0001
Alcohol use (any) (%)	8.07	10.5	2.17	18.4	<.0001
Preserved LVEF (%)	26.9	39.2	9.91	31.2	<.0001
Valve disease (%)	57	48.3	53.7	56	0.0066
Prior stroke (%)	3.77	10	3.89	4.44	<.0001
History of myocardial infarction (%)	6.54	17.1	19.9	13.5	<.0001
CHF hospitalization in prior year (%)	38.6	29.9	27.3	35.2	0.0002
Beta blocker (%)	43	53.1	84.4	64.1	<.0001
ACE inhibitor, ACEi (%)	57.6	42.9	61.8	41.8	<.0001
Angiotensin receptor blocker, ARB (%)	19.9	22.1	18.5	28.7	0.0032
ACEi/ARB (%)	77.5	65	80.3	70.5	<.0001
Aldosterone inhibitors (%)	65.1	48.5	47.3	51.5	<.0001
Diuretic (%)	96.2	72.3	91.2	88.8	<.0001
Digoxin (%)	34.6	32.8	20	24.5	<.0001
Etiology: ischemic (%)	21.2	45.6	52.9	24.1	<.0001
Etiology: hypertensive (%)	32	13.2	9.53	22.6	<.0001
Etiology: idiopathic — dilated (%)	15.2	10.9	16.2	12.8	0.0075
Etiology: valvular rheumatic (%)	7.66	10.1	6.16	7.64	0.032
Etiology: valvular, non-rheumatic (%)	2.07	2.66	3.22	8.27	<.0001

Appendix 4. INTER-CHF participants with reduced left ventricular ejection fraction (<50%).

Variable (N = 3306)	Africa N = 681	Asia N = 1253	Middle East N = 886	South America N = 486	p-Value
Age, years [mean (SEM)]	52.2(0.54)	58.5(0.41)	56.1(0.49)	66.1(0.65)	<.0001
Male (%)	57.7	69	75.3	68.4	<.0001
Body mass index, kg/m^2 [mean (SEM)]	25.0(0.24)	24.6(0.18)	29.9(0.21)	28.1(0.29)	<.0001
No health insurance (%)	71.8	51.7	25.8	11.2	<.0001
No medication insurance (%)	73.5	60.8	28.2	12.9	<.0001
Illiterate (%)	40.7	15.8	36.1	3.24	<.0001
Rural (%)	30.4	47.8	25.2	20.7	<.0001
Inpatient (%)	43.9	36.4	31.1	23.3	<.0001
NYHA class I (%)	6	10.9	15.4	19.2	<.0001
NYHA class II (%)	37.8	43.2	46.4	47.7	0.0021
NYHA class II (%)	35.7	28.2	29.7	28.5	0.0081
NYHA class IV (%)	21.1	17.1	6.93	4.15	<.0001
<1 year since of HF diagnosis (%)	53.1	44.9	26.7	30.5	<.0001
Hypertension (%)	62.1	55.3	67.4	67.5	<.0001
Diabetes mellitus (%)	15.4	32.7	57.2	20.1	<.0001
Dyslipidemia (%)	23.3	25.1	56.8	50.5	<.0001
Chronic kidney disease (%)	4.31	8.23	11.5	12.2	<.0001
Tobacco use (ever) (%)	15.1	35.9	24	37.8	<.0001
Alcohol use (any) (%)	10	9.79	2.41	11.9	<.0001
Valve disease (%)	59.8	41.7	50.3	50.3	<.0001
Prior stroke (%)	4.37	7.71	3.3	4.46	<.0001
History of myocardial infarction (%)	8.43	26.3	19.2	23.8	<.0001
CHF hospitalization in prior year	39.4	33.7	23.3	31.7	<.0001
Beta blocker (%)	51.7	69.5	88.4	82.8	<.0001
ACE inhibitor, ACEi (%)	60.6	56.2	65.6	43	<.0001
Angiotensin receptor blocker, ARB (%)	20.5	21.6	19.1	37.3	<.0001
ACEi/ARB (%)	80.8	77.7	84.7	79.8	0.0011
Aldosterone inhibitors (%)	64.6	56.9	50	67.7	<.0001

(continued on next page)

Appendix 4 (*continued*)

Variable (N = 3306)	Africa N = 681	Asia N = 1253	Middle East N = 886	South America N = 486	p-Value
Diuretic (%)	95.9	74.8	89.8	78.7	<.0001
Digoxin (%)	39.7	33.9	19	28.1	<.0001
Etiology: ischemic (%)	20.1	53.8	52.2	31	<.0001
Etiology: hypertensive (%)	35.5	8.56	7.46	14	<.0001
Etiology: idiopathic — dilated (%)	19.8	18	22.1	21	0.1236
Etiology: valvular rheumatic (%)	5.56	4.58	5.49	3.31	0.3151
Etiology: valvular non-rheumatic (%)	2.51	1.79	1.6	5.39	0.0002
Etiology: endocrine/metabolic (%)	0.67	4.07	1.04	4.54	<.0001

Appendix 5. INTER-CHF participants recruited as outpatients.

Variable (N = 3695)	Africa N = 678	Asia N = 1717	Middle East N = 690	South America N = 610	p-Value
Age, years [mean(SEM)]	52.1(0.56)	59.6(0.36)	55.6(0.57)	66.9(0.60)	<.0001
Male (%)	47.1	58.2	69.7	64.6	<.0001
Body mass index, kg/m^2 [mean (SEM)]	26.3(0.24)	24.7(0.15)	30.1(0.24)	28.4(0.26)	<.0001
No health insurance (%)	71.2	46	27	11.9	<.0001
No medication insurance (%)	73.7	63.6	28.6	12.8	<.0001
Illiterate (%)	33.3	11.8	35.6	4.79	<.0001
Rural (%)	24.9	43.7	25.4	22.4	<.0001
NYHA class I (%)	9.69	15.9	20.4	23.8	<.0001
NYHA class II (%)	43.3	52.5	52.2	53.9	0.0003
NYHA class II (%)	32.7	24.5	23	21.1	<.0001
NYHA class IV (%)	14.7	6.41	3.11	1.45	<.0001
<1 year since of HF diagnosis (%)	52.3	37.1	20.9	29.1	<.0001
Hypertension (%)	70.8	60.2	67.7	71.8	<.0001
Diabetes mellitus (%)	12.6	26.8	53.6	20.4	<.0001
Dyslipidemia (%)	22.1	28.7	59.6	49.8	<.0001
Chronic kidney disease (%)	3.88	6.46	9.78	10.5	<.0001
Tobacco use (ever) (%)	14.2	30.1	23.4	30.7	<.0001
Alcohol use (any) (%)	14.8	7.72	2.64	12.6	<.0001
Preserved vs depressed	27.1	42	11.1	28.3	<.0001
Valve disease	47.1	40.3	46.1	47	0.0047
Prior stroke	3.84	10.9	3.06	3.29	<.0001
History of MI	9.5	22	18.9	18.8	<.0001
CHF hospitalization in prior year	28.1	24.6	19.6	25.1	0.0036
Beta blocker (%)	46.4	64.7	87.8	77.7	<.0001
ACE inhibitor (%)	63	41.8	61.2	42.4	<.0001
Angiotensin receptor blocker, ARB (%)	17.9	27.8	21.8	36.5	<.0001
ACEi/ARB (%)	82	70.1	84	79.2	<.0001
Aldosterone inhibitors (%)	51.8	43.5	47.3	57.5	<.0001
Diuretic (%)	90.8	55.6	85.4	75.6	<.0001
Digoxin (%)	38.4	29.3	19.4	26.7	<.0001
Etiology: ischemic (%)	14.7	46.7	46.7	24.4	<.0001
Etiology: hypertensive (%)	46.7	14.9	10.2	18.4	<.0001
Etiology: idiopathic — dilated (%)	10.5	10.7	22.1	15.6	<.0001
Etiology: valvular rheumatic (%)	5.36	8.94	4.44	6.74	<.0001
Etiology: valvular non-rheumatic (%)	2.64	2.94	1.6	5.9	0.0002
Etiology: hypertrophic (%)	0.29	1.52	0.71	4.09	<.0001
Etiology: Chagas' (%)	0	0	0	4.3	<0.001
Etiology: endocrine/metabolic (%)	2.53	3.53	1.58	4.39	0.0163

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