

Heart failure in low- and middle-income countries: Background, rationale, and design of the INTERNATIONAL Congestive Heart Failure Study (INTER-CHF)



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Background Although heart failure (HF) has been referred to as a global epidemic, most HF information comes from high-income countries, with little information about low-income countries (LIC) and middle-income countries (MIC) in Africa, Asia, the Middle East, and South America, which make up the majority of the world's population.

Methods The INTERNATIONAL Congestive Heart Failure Study is a cohort study of 5,813 HF patients enrolled in 108 centers in 16 LIC and MIC. At baseline, data were recorded on sociodemographic and clinical risk factors, HF etiology, laboratory variables, management, and barriers to evidence-based HF care at the patient, physician, and system levels. We sought to enroll consecutive and consenting patients ≥ 18 years of age with a clinical diagnosis of HF seen in outpatient clinics (2/3 of patients) or inpatient hospital wards (1/3 of patients). Patients were followed up at 6 and 12 months post-enrollment to record clinical status, treatments, and clinical outcomes such as death and hospitalizations. In the 5,813 enrolled HF patients, the mean age was 59 ± 15 years, 40% were female, 62% had a history of hypertension, 30% had diabetes, 21% had prior myocardial infarction, 64% were recruited from outpatient clinics, 36% lived in rural areas, and 29% had HF with preserved left ventricular ejection fraction.

Conclusions This unique HF registry aims to systematically gather information on sociodemographic and clinical risk factors, etiologies, treatments, barriers to evidence-based care, and outcomes of HF in LIC and MIC. This information will help improve the management of HF globally. (*Am Heart J* 2015;170:627-634.e1.)

Heart failure (HF) is a major global health problem, affecting approximately 26 million people worldwide,¹ and is estimated to have cost \$102 billion worldwide in 2012.² Yet, the majority of information on HF comes from high-income countries, with much less from middle-income countries (MIC) and very little from low-income countries (LIC) in Africa, Asia, the Middle East, and South America, even though these regions have the majority of the world's population.³ The existing data in LIC and MIC suggest that there are substantial inter-regional and intra-regional variations in sociodemographic and clinical risk factors, etiologies, treatments, and outcomes (Table D).⁵⁻⁷ Despite

HF being a major burden in these areas of the world,⁵⁻⁸ there is a paucity of data on physician and patient knowledge, attitudes to HF, and barriers at the patient, physician, and system levels.⁹ Further studies in these underrepresented regions are needed to inform clinical practice and to build appropriate knowledge translation strategies.¹⁰ Therefore, we designed a prospective HF registry in 16 LIC and MIC to address some of these gaps in HF knowledge.

Our objectives were as follows:

1. Document sociodemographic and clinical risk factors in selected LIC and MIC with a focus inter-regional and inter-country (within region) differences.
2. Document HF etiologies in LIC and MIC.
3. Document investigations and management of HF patients in these regions.
4. Document patient and physician knowledge and perceptions about HF and potential barriers to care at the patient, physician, and system levels.
5. Document HF mortality and associated morbidity in LIC and MIC.

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Conflicts of interest: None.

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Table I. Summary of limitations of current HF data in LIC and MIC

Region	Limitations of current data
Africa	Much of the data is from Soweto, South Africa, and from patients hospitalized with HF, with a little data from as Nigeria, Mozambique, Uganda, Democratic Republic of Congo, Cameroon, and Ghana. A recent sub-Saharan African registry of acute HF patients hospitalized in urban centers has somewhat expanded knowledge, ⁴ yet information on chronic HF outpatients and data on knowledge/perceptions on HF and barriers' assessments is lacking.
Asia	Most evidence is from hospitalized HF patients in major centers in China, while HF data from other LIC and MIC Asian countries with large and growing populations, such as India, Malaysia, and the Philippines, are very limited. Therefore, there are substantial gaps in many areas of HF evidence in LIC and MIC, which are ironically the most populous regions of the world.
Middle East	The majority of data is from acute HF patients hospitalized in urban centers in Saudi Arabia, with a few studies from Qatar and the United Arab Emirates, and 1 single-center study from Egypt. Information on chronic HF outpatients, and detailed sociodemographic data with knowledge/perceptions on HF and barriers' assessments are lacking.
South America	Data are largely from single urban centers in Argentina and Brazil, with much less data from Chile and no significant published HF data from Colombia or Ecuador. There are virtually no data on knowledge and perceptions of HF among patients and physicians and also very scarce data on assessments at the patient, physician, and systems levels, on barriers to HF care.

We hypothesized that there would be significant variability in risk factors, investigations, and outcomes of HF as well as patient and physician perceptions and knowledge between and within the regions. We also hypothesized that the most common HF etiologies as previously described in LIC and MIC had changed compared to prior data owing to socioeconomic change, urbanization, and population migration.

Methods

Study design

INTERNATIONAL Congestive Heart Failure Study (INTER-CHF) is a prospective, international, multicenter cohort study, conducted in 108 centers in 16 countries in Africa, Asia, the Middle East, and South America with 6- and 12-month follow-ups.

Study phase

Phase I. This phase involved gathering qualitative information using consensus-building exercises with the steering committee (online [Appendix](#)), patient and physician interviews, and focus groups. We aimed to understand knowledge and attitudes toward HF and diagnostic and management practices for HF and to identify potential barriers for evidence-based HF care.

These qualitative data were then used to generate the case report forms (CRFs) for use in phase II of the study (patient recruitment) and to develop specific patient and physician questionnaires. The Patient Questionnaire included 24 questions on knowledge, attitudes, and perceptions of HF; burden and financial impact of HF; access to health care resources and therapies; quality of life; and experiences and perceived barriers to HF care. Physicians or their proxy translated this questionnaire and administered it verbally to the patients. The Physician Questionnaire included 14 written questions on knowledge, attitudes, and perceptions of HF; management approaches to HF; local infrastructure and resources for HF care; and perceived barriers to HF care. We built these questionnaires to identify strategic areas for future knowledge translation strategies.

Phase II. In phase II, we recruited 5,813 HF patients from LIC and MIC in a prospective cohort to describe social, demographic, and clinical risk factors; HF etiology; treatments; and outcomes. Participants were recruited from urban and rural areas, specialized and primary care practices, and academic and community settings in each participating country. Participants were followed up for 1 year ([Table II](#)).

Registry details

A total of 5,813 participants with HF were enrolled from 108 clinical centers in Africa, Asia, the Middle East, and South America ([Figure](#)). We aimed to recruit two-thirds of patients from outpatient clinics and one-third from hospital inpatient wards. We also purposefully involved urban and rural centers as well as primary care practitioners and specialists. Study sites were chosen based on the existence of adequate infrastructure and previous collaboration with the Population Health Research Institute (PHRI) or the regional coordinating centers.

We enrolled consecutive patients with a clinical diagnosis of HF in the participating centers who met the following criteria:

Inclusion criteria

1. Age ≥ 18 years old.
2. Informed consent.

Exclusion criteria

1. Patients considered unreliable by the investigator for follow-up visits.
2. Patients with a life expectancy less than the expected duration of the registry due to non-HF comorbidities.

Diagnosis of HF

Patients with a clinical diagnosis of HF, as determined locally by the recruiting physician, were enrolled into the study. In addition, we collected detailed

Table II. Visit/investigation schedule

Investigation/data collection	Registry period		
	Enrollment	Month 6	Month 12
Period			
Informed consent	X		
Inclusion/exclusion criteria	X		
Demographics	X		
Sex, ethnicity, occupation, marital status, living arrangements, health insurance status, literacy level			
Medical history and clinical risk factors	X		
HF symptoms, hypertension, hyperlipidemia, diabetes mellitus, tobacco use, rheumatic fever, HIV/AIDS, tuberculosis history, Chagas seropositivity, family history of HF or coronary artery disease, prior cardiac surgery, prior angioplasty, prior or current chemotherapy, alcohol or drug use			
Physical examination	X	X	X
Weight, height, jugular venous pressure, lung auscultation, third heart sound			
Vital signs	X	X	X
Pulse rate, blood pressure			
Therapy/medications	X	X	X
β-Blocker, ACE inhibitor, angiotensin receptor blocker, aldosterone inhibitors, diuretics, long-acting nitrate, digoxin, warfarin, other oral anticoagulants, acetylsalicylic acid, thienopyridine, insulin, oral hypoglycemics, reasons for medication discontinuation, alternative/traditional medical care, implantable cardiac devices			
Montreal Cognitive Assessment	X		
Echocardiography*	X		
ECG*	X		
Chest x-ray*	X		
Laboratory	X	X	X
CBC, electrolytes, creatinine, urea, BNP, or NT-proBNP			
Physician Questionnaire	X		
Field and type of practice, HF definition, diagnostic and therapeutic strategies for HF, barriers to HF care			
Patient Questionnaire	X		
Patient's understanding of HF and knowledge about HF, compliance, social support, health insurance, financial and emotional burden of HF, quality of life, income			
Outcome events		X	X
Death, hospitalization, cardiogenic shock, heart transplantation, resuscitated cardiac arrest, stroke, myocardial infarction, venous thromboembolism, hemorrhage, aortic dissection, renal failure, and sepsis			

Abbreviations: ACE, Angiotensin-converting enzyme; BNP, brain natriuretic peptide; CBC, complete blood count.
*Results/findings if available.

information to compare the clinical diagnosis of HF with the Boston criteria for HF,¹¹ which has been suggested to be more accurate for the diagnosis of HF than other criteria.¹²

Follow-up visits

The main objectives at the 6- and 12-month in-person visits were to determine if the patients experienced outcome events and/or changes in medications and other therapies. These visits could be performed by telephone for participants who would otherwise be lost to follow-up. Data were collected on symptom status,

medications (with dose), and clinical events. Deaths were recorded, and their causes ascertained locally by review of relevant clinical documents and information from patient relatives or close friends. Details on morbidity were ascertained locally by review of hospitalizations, new diagnoses and treatments, investigations, and surgical procedures, supplemented as needed by interviews with patient relatives or close friends. Morbidity outcomes included cardiac death, cardiogenic shock, resuscitated cardiac arrest, cardiac transplantation, HF requiring hospitalization, myocardial infarction, stroke, venous thromboembolism, hemorrhage, sepsis,

Figure



Countries involved in INTER-CHF with recruitment numbers. 1. Asia (2,661 patients): China (992 patients), India (858 patients), Malaysia (362 patients), and the Philippines (449 patients). 2. Africa (1,294 patients): Nigeria (383 patients), South Africa (169 patients), Sudan (501 patients), Uganda (151 patients), and Mozambique (90 patients). 3. Middle East (1,000 patients): Saudi Arabia (741 patients), Egypt (102 patients), and Qatar (157 patients). 4. South America (858 patients): Argentina (308 patients), Chile (153 patients), Colombia (268 patients), and Ecuador (129 patients). Total recruitment is 5,813 patients.

and renal failure. The primary outcome of the study was all-cause mortality.

Data collection

At the time of enrollment, a baseline CRF was completed by the physician or their proxy and contained social, demographic, and clinical risk factors; treatment, etiology, laboratory data; and both patient and physician questionnaires (Table II). The completed CRF was transmitted via iDataFax to the central coordinating center, PHRI, in Canada for review, validation, and analysis.

Countries and regions for patient enrollment

The countries in INTER-CHF were selected to represent a significant proportion of the population in the regions poorly represented in the current literature. We built on existing collaborative networks with physicians in these regions from previous studies coordinated (INTERHEART¹³ and PURE¹⁴ studies).

Central coordinating center

The PHRI at Hamilton Health Sciences/McMaster University in Hamilton, Ontario, Canada, was the coordinating center for this study. The PHRI team created

the CRFs and study protocol, provided sites with the manual of operations, developed and maintained the study database, received data from sites, ensured high data quality, and performed the statistical analyses.

National and international coordination

National leaders were chosen based on local leadership, expertise, and prior international research collaboration with PHRI. They established a National Coordination Office (NCO) in each of the participating countries. The NCO in each country identified the local sites to recruit HF patients, with at least 1 site being in a rural setting whenever feasible. The NCO kept a record of all patients recruited in the given country. Any questions regarding submitted CRFs were communicated to the recruiting center through the NCO.

Funding source. INTER-CHF was funded by an unrestricted educational grant from Novartis, with additional internal funding from PHRI.

Steering committee

The steering committee (online Appendix) was responsible for the design, execution, analysis, and reporting of the study. Its members hold primary responsibility for publication of the study results. The committee convened

Table III. Baseline characteristics of patients in INTER-CHF

Characteristic	Mean (SD) or (%) (%, N = 5813)
Age (y)	59 (15)
Male (%)	60
Body mass index (kg/m ²)	26 (6)
Systolic blood pressure (mm Hg)	125 (22)
Diastolic blood pressure (mm Hg)	76 (13)
Heart rate (beats/min)	81 (17)
Rural (%)	36
Distance from home to nearest health care facility ≤ 25 km (%)	86
Clinic outpatients (%)	74
Time of HF diagnosis < 1 y (%)	42
Hypertension (%)	62
Diabetes mellitus (%)	30
Hyperlipidemia (%)	35
Chronic kidney disease (%)	9
Tobacco use (ever, %)	37
Alcohol use (any, %)	14
Rheumatic fever history (%)	4
History of myocardial infarction (%)	21
HF hospitalization in past year (%)	30
Prior stroke (%)	7
Prior coronary angioplasty/stent (%)	15
Left ventricular ejection fraction $< 50\%$ (%)	71
Valve disease (\geq moderate in ≥ 1 valve on echocardiogram, %)	46

regularly by teleconference or in-person meetings to monitor study progress, execution, and management.

Statistical considerations

Baseline characteristics, risk factors, and etiologies will be described using summary statistics (means and SDs, medians and interquartile ranges, and counts and proportions). We expect that approximately 20% of participants would develop the primary outcome of mortality at 1-year follow-up.¹⁵⁻¹⁷ With a sample size of 5,000 participants, we would be able to determine the mortality rate at 1 year with 95% confidence, with a precision of $\pm 1\%$. Subsequent additional funding allowed for the recruitment of 813 additional patients. The morbidity outcomes will be summarized individually, with stratification for hospital inpatients versus clinical outpatients.

Ethical considerations

Before study initiation, the investigators obtained approval from the local institutional review boards or independent ethics committees for the protocol, consent form, and subject recruitment materials/process. Informed consent was obtained from each patient or their legally accepted representative.

Minimizing risk of bias

To minimize the risk of bias of our results, we enrolled consecutive patients. We also maximized external

validity and encouraged participant diversity by recruiting ambulatory and hospitalized participants, urban and rural areas, as well as general and specialized practices. Moreover, in each region, we recruited HF patients from between 3 and 5 countries.

Enrollment results

Between September 2012 and February 2014, 5,813 patients (age 59 ± 15 years, 40% female, 62% with a history of hypertension, 30% diabetes, 21% prior myocardial infarction, 29% with HF preserved ejection fraction) were enrolled, with 2,661 patients from Asia, 1,294 from Africa, 1,000 from the Middle East, and 858 from South America. Table III lists HF patient baseline characteristics. Our sampling strategies were successful with 64% participants recruited from outpatient clinics and 36% from rural areas. Sites were polled to determine the number of HF patients screened versus enrolled in the study; the results indicate that 7,176 patients were screened for the 5,813 patients enrolled (81%).

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Discussion

Heart failure is an important cause of morbidity and mortality and has been referred to as a global epidemic,¹⁸⁻²³ yet existing data on LIC and MIC are likely not representative of these entire regions. Detailed, systematically acquired data on HF patients are very limited in LIC and MIC across Africa, Asia, the Middle East, and South America. Without knowing the specific causes of HF, its treatment, and outcomes in these regions, appropriate therapy cannot be explored, much less applied.

Studies from China,²⁴⁻²⁹ mostly investigating hospital inpatients, have suggested that coronary heart disease (CHD), hypertensive, and rheumatic causes of HF are most common. However, substantial changes have occurred over the last 2 decades with a major decrease in rheumatic and a major increase in ischemic causes of HF.^{24,30} Importantly, HF data from other LIC and MIC Asian countries with large and growing populations, such as India,³¹⁻³³ Malaysia,^{34,35} and the Philippines (no published data), are very scarce. INTER-CHF recruited 2,661 patients in Asia, of whom 992 were from China; this will allow detailed comparisons with published data from China, allowing INTER-CHF to help fill current gaps in outpatient HF patient data from China. Importantly, 858 INTER-CHF patients were from India, and 449 patients from the Philippines, providing the first systematically acquired HF data from these countries.

In sub-Saharan Africa, most information comes from Soweto and Cape Town, South Africa, and suggests that hypertensive, infectious, and rheumatic causes are the leading HF etiologies.³⁶⁻³⁸ Heart failure data from other sub-Saharan

African countries such as Nigeria,³⁹ Mozambique,⁴⁰ Uganda,⁴¹ Democratic Republic of Congo,⁴² Cameroon,⁴³ and Ghana⁴⁴ are sparse, and nearly all come from hospitalized patients with acute HF.^{45,46} In INTER-CHF, 1,294 participants in sub-Saharan Africa were recruited, of whom 169 were from South Africa, allowing direct comparisons with the data published from this region. Of note, the 703 HF patients recruited from Nigeria, Uganda, and Mozambique in INTER-CHF will provide much needed outpatient HF data and will be more detailed than that previously published. Importantly, the 501 INTER-CHF participants from Sudan will provide the first systematically acquired data on HF patients from this country.

In the Middle East, although Saudi Arabia and Qatar have some representation in the HF literature, HF patients in outpatient settings are not well represented.^{4,47} Even though Gulf states are considered high-income countries, they have a large migratory worker population from South Asia (in some cases, outnumbering the native population) coming from lower socioeconomic classes and seeking medical care in these countries.^{48,49} Only 1 single-center retrospective study of 155 patients reports on HF in Egypt.⁵⁰ The 1,000 INTER-CHF participants from these 3 Middle Eastern countries will help fill important gaps in understanding HF patients from these regions: particularly in outpatient HF populations (which is lacking), in migratory (non-national) patients, and will provide important outcome data, which is currently not well represented.

In South America, the current data are largely from single urban centers, suggesting that CHD and hypertension are the leading causes of HF, with rheumatic and Chagas disease playing smaller but important roles.⁵¹ Although most existing South American HF data come from hospitalized patients in Argentina^{52,53} and Brazil,^{54,55} there are very few data from Chile⁵⁶ and virtually none from Colombia or Ecuador. Of the 858 South American participants in INTER-CHF, detailed data from the 159 HF patients from Chile will provide novel data, and of particular note, the 395 participants from Colombia and Ecuador will provide the first detailed data in HF patients from these countries.

In 2014, Callender et al⁸ conducted a systematic review and meta-analysis of HF studies in LIC and MIC, identifying 42 studies reporting on acute hospital HF care (232,550 patients) and 11 studies on chronic HF in 5,358 ambulatory patients. When all of the previously available data were pooled in this study, the mean age in LIC and MIC was 50 and 60 years, respectively, and 58% of patients were male,⁸ compared to a mean age of 59 years with 60% male and 64% clinic outpatients in INTER-CHF; the latter represents a major difference with the study of Callender et al, where only 2.2% of the HF population described were clinic outpatients. In addition, although they describe significant inter-regional and

intra-regional variability, the heterogeneity in the included studies that had different primary objectives and that report on patients from 1980 to 2012 may limit the internal validity of their results.⁸ Before INTER-CHF, no systematic HF study in LIC and MIC used standardized enrollment criteria with uniform CRFs and longitudinal patient follow-up, compared urban versus rural settings in countries, and focused on chronic HF outpatients.¹

Currently, in LIC and MIC, scant information is available on knowledge and perceptions of HF among patients and physicians or assessments of barriers to HF care at the patient, physician, and system levels. Given the detailed data on knowledge, perceptions, attitudes, quality of life, and data on barriers to care that the patient and physician questionnaires in INTER-CHF have systematically collected, these important gaps will begin to be filled.

Registry impact

INTER-CHF is the largest systematic evaluation of HF in LIC and MIC. Preliminary participant characteristics suggest achievement of goals sampling rural and urban populations as well as ambulatory and hospitalized patients. Acquiring high-quality information on the demographics, social and clinical risk factors, etiologies, and treatments of HF patients in these countries is a key step before treatments can be further improved. Systematically collected data on patients' and physicians' perceptions of HF and appreciation of barriers to optimal HF care will be critical for the development of knowledge translation strategies, locally sensitive HF guidelines, and research programs.

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Appendix. INTER-CHF Steering Committee

Argentina: Andres Orlandini, MD; **Chile:** Fernando Lanas, MD; **China:** Zhu Jun, MD; **Colombia/Ecuador:** Patricio Lopez Jaramillo, MD; **Egypt:** Mohamed Elmaghawry, MD; **India:** Ambuj Roy, MD; Prabhakar Dorairaj, MD; **Malaysia:** Khalid Yusoff, MD; **Mozambique:** Albertino Damasceno, MD; **Nigeria:** Kamilu Karaye, MD; **Philippines:** Lia Palileo, MD;

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