Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study

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Summary

Background Most data on mortality and prognostic factors in patients with heart failure come from North America and Europe, with little information from other regions. Here, in the International Congestive Heart Failure (INTER-CHF) study, we aimed to measure mortality at 1 year in patients with heart failure in Africa, China, India, the Middle East, southeast Asia and South America; we also explored demographic, clinical, and socioeconomic variables associated with mortality.

Methods We enrolled consecutive patients with heart failure (3695 [66%] clinic outpatients, 2105 [34%] hospital in patients) from 108 centres in six geographical regions. We recorded baseline demographic and clinical characteristics and followed up patients at 6 months and 1 year from enrolment to record symptoms, medications, and outcomes. Time to death was studied with Cox proportional hazards models adjusted for demographic and clinical variables, medications, socioeconomic variables, and region. We used the explained risk statistic to calculate the relative contribution of each level of adjustment to the risk of death.

Findings We enrolled 5823 patients within 1 year (with 98% follow-up). Overall mortality was 16·5%: highest in Africa (34%) and India (23%), intermediate in southeast Asia (15%), and lowest in China (7%), South America (9%), and the Middle East (9%). Regional differences persisted after multivariable adjustment. Independent predictors of mortality included cardiac variables (New York Heart Association Functional Class III or IV, previous admission for heart failure, and valve disease) and non-cardiac variables (body-mass index, chronic kidney disease, and chronic obstructive pulmonary disease). 46% of mortality risk was explained by multivariable modelling with these variables; however, the remainder was unexplained.

Interpretation Marked regional differences in mortality in patients with heart failure persisted after multivariable adjustment for cardiac and non-cardiac factors. Therefore, variations in mortality between regions could be the result of health-care infrastructure, quality and access, or environmental and genetic factors. Further studies in large, global cohorts are needed.

Funding The study was supported by Novartis.

Lancet Glob Health 2017; 5: e665–72

Published Online
April 30, 2017
http://dx.doi.org/10.1016/S2214-109X(17)30196-1

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 9, 2017

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Introduction

Heart failure is an important global health problem, affecting about 26 million people worldwide;[1] it is associated with high mortality and is estimated to have cost about US$100 billion in 2012.[2] Most data on outcomes in patients with heart failure come from North America and Europe, with much less information from Africa, Asia, the Middle East, and South America.[3–5] The few data from low-income and middle-income countries (LMIC) suggest that mortality in patients with heart failure in these countries is greater than that in high-income countries.[6–8] However, reasons for variation in outcomes between regions remain unclear. Therefore, we designed a prospective registry of patients with heart failure in 16 countries in Africa, Asia, the Middle East, and South America to document 1-year mortality in patients from these regions, and to explore variables associated with mortality.

Methods

Study design and participants

The International Congestive Heart Failure Study (INTER-CHF) is a prospective cohort study, conducted in 108 centres in 16 countries with follow-up at 12 months. The rationale and design for this study have been published elsewhere,[9] but are briefly described here.

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See Online for appendix

Research in Context

Evidence before this study

We searched MEDLINE on Feb 10, 2017, for English-language cohort studies published since 1990 of patients with heart failure recruited from outpatient clinics or hospital settings. Studies had to include data on mortality. We used the search terms "heart failure", "global", "international", "worldwide", "outcomes", and "mortality". There were no cohort studies identified that included patients with heart failure from different world regions that compared outcomes.

Added value of this study

The current study adds to the findings of previously published local registries and randomised controlled trials by directly demonstrating that mortality in patients with heart failure was highest in Africa and India, intermediate in southeast Asia, and lowest in China, South America, and the Middle East. These differences persisted after adjustment for clinical variables, medication use, and socioeconomic variables, suggesting that a large part of the variations in mortality could be the result of unrecorded or unknown factors.

Implications of all of the available evidence

The evidence suggests that there are important differences between regions in death rates for patients with heart failure. In general, patients with heart failure from richer regions have lower mortality than do patients from poorer regions. These regional differences persist after adjustment for risk factors and treatments, which only explained about half of the risk of death. Therefore, the data suggest that regional variations in heart failure outcomes might be due to factors that are not well described or measured in the current literature. These include health-care quality, access, and infrastructure as well as environmental factors and genetics. Further research into these factors is, therefore, warranted.

We enrolled patients with a clinical diagnosis of heart failure in Africa (Mozambique, Nigeria, South Africa, Sudan, and Uganda), China, India, the Middle East (Egypt, Qatar, and Saudi Arabia), southeast Asia (Malaysia, and the Philippines), and South America (Argentina, Chile, Colombia, and Ecuador; appendix). We included consecutive heart failure patients from outpatient clinics and inpatient hospital wards at participating centres. We aimed to recruit two-thirds of the study population from out patient clinics since most previous data on heart failure have come from hospital inpatients.[4–7,10] Patients were aged 18 years or older and enrolled from academic health-care centres, community health centres, and specialist and primary care clinics. Where feasible, at least one centre in each country was in a rural area. We excluded patients with severe non-cardiac diseases that could affect survival within 1 year, and patients who were difficult to follow-up (for example, because of their migratory status).

The study was approved by institutional review boards or independent ethics committees at participating sites and the international coordinating centre (McMaster University, Hamilton, ON, Canada). Participants or their substitute decision maker provided written informed consent.

Procedures

At enrolment, we recorded information on demographics, clinical factors, medications, and socioeconomic factors. Echocardiograms, if done for clinical care, were used for information about left ventricular systolic function and valve disease. Left ventricular ejection fraction (LVEF) was defined as reduced when less than 40%.[11] Valvular heart disease was defined as the presence of at least moderate stenosis or regurgitation in at least one cardiac valve.

A local physician determined the cause of heart failure using all available clinical data. Although we did not specify that patients had to meet specific criteria to be included, we prospectively collected information to assess the proportion of participants who met the Boston criteria for heart failure.[12,13] Patients had follow-up visits at 6 months and 12 months, at which symptoms, medications and outcomes were recorded.

Outcomes

Primary outcome was time to all-cause mortality within 1 year. Cause of death was also recorded, and categorised by local investigators as cardiac, non-cardiac, or unknown.

Statistical analysis

We used univariable and multivariable Cox proportional hazards models for time-to-event analysis of mortality. We verified the proportionality assumptions with standard log[-log(survival)] plots. In model 1, we included 17 variables from the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) criteria,[14] plus socioeconomic variables and region, in a multivariable model. These variables (see appendix) were divided into demographic variables, clinical variables, medications, socioeconomic variables, and region to determine the effect of each level of adjustment on the conditional instantaneous risk (hazard) of death within 1 year. To calculate regional hazard of death, we used South America as the reference region because it had a low death rate.

In model 2, we performed a second analysis using the same variables as in model 1, but excluded data derived from echocardiograms (LVEF, valve disease).

We conducted a sensitivity analysis including patients who had clinical variables that fulfilled the Boston heart

failure criteria.[11] We did further analyses by admission status at enrolment (ie, hospital inpatients or clinic outpatients). In Cox proportional hazards models, we calculated the explained risk statistic to measure the

	Overall (N=5823)	Africa (N=1294)	India (N=858)	SoutheastAsia (N=811)	Middle East (N=1000)	China (N=991)	South America (N=869)
Demographic variables							
Age (years)	59 (15)	53 (14)	56 (15)	57 (14)	56 (16)	66 (16)	67 (15)
Male sex	3495 (61%)	662 (52%)	531 (62%)	474 (59%)	721 (72%)	570 (57%)	537 (61%)
Clinical variables							
Body-mass index (kg/m^2)	26 (6·1)	26 (6·1)	23 (6·2)	26 (6)	30 (6)	24 (6.3)	29 (6.2)
Systolic blood pressure (mm Hg)	125 (23)	124 (21)	125 (21)	128 (23)	126 (22)	126 (22)	123 (24)
Diastolic blood pressure (mm Hg)	76 (13)	79 (16)	77 (12)	76 (12)	72 (13)	77 (12)	75 (13)
History of diabetes mellitus	1728 (29%)	201 (17%)	217 (26%)	328 (41%)	541 (57%)	216 (19%)	225 (21%)
History of chronic kidney disease	487 (8%)	45 (4%)	30 (3%)	107 (13%)	121 (12%)	67 (6%)	117 (11%)
Current tobacco use	554 (6%)	78 (4%)	102 (7%)	81 (6%)	132 (7%)	106 (8%)	55 (4%)
History of chronic obstructive pulmonary disease	450 (6%)	26 (2%)	139 (16%)	35 (4%)	41 (4%)	99 (8%)	110 (10%)
Reduced left ventricular ejection fraction (<40%)*	2486 (50%)	526 (54%)	392 (53%)	247 (39%)	743 (73%)	212 (27%)	366 (53%)
Valve disease*†	2286 (46%)	582 (57%)	309 (42%)	265 (40%)	479 (50%)	306 (41%)	345 (48%)
NYHA functional class III or IV	2470 (40%)	702 (56%)	415 (50%)	127 (16%)	360 (37%)	574 (56%)	292 (32%)
Admission for heart failure in previous year	1567 (27%)	420 (36%)	122 (14%)	285 (35%)	219 (22%)	308 (34%)	213 (28%)
Recruited as hospital inpatient	2105 (34%)	616 (48%)	389 (45%)	187 (23%)	310 (31%)	367 (35%)	236 (26%)
Main cause of heart failure							
Ischaemic heart disease	2433 (39%)	242 (20%)	399 (46%)	449 (56%)	521 (50%)	519 (45%)	303 (25%)
Hypertensive heart disease	1096 (17%)	392 (35%)	116 (14%)	115 (15%)	93 (10%)	165 (14%)	215 (21%)
Idiopathic dilated cardiomyopathy	838 (12%)	212 (14%)	118 (11%)	31 (3%)	220 (18%)	141 (15%)	116 (15%)
Valvular heart disease	739 (11%)	185 (11%)	135 (12%)	122 (12%)	93 (8%)	97 (11%)	107 (13%)
Endocrine or metabolic disease	224 (4%)	67 (5%)	36 (4%)	46 (6%)	14 (1%)	31 (3%)	30 (4%)
Hypertrophic cardiomyopathy	71 (1%)	3 (0·2%)	15 (1·7%)	7 (0·8%)	6 (0·6%)	14 (1·6%)	26 (3·4%)
Congenital heart disease	57 (0·5%)	4 (0·1%)	10 (0·5%)	11 (1%)	7 (0·3%)	13 (1·2%)	12 (1·5%)
Alcohol or drugs	68 (0·4%)	22 (0·7%)	6 (0·2%)	6 (0·3%)	19 (0·6%)	7 (0·4%)	8 (0·5%)
Cardiac medications							
Beta blocker	3768 (67%)	634 (48%)	495 (57%)	543 (66%)	866 (85%)	594 (60%)	636 (73%)
ACE inhibitor	2924 (49%)	774 (59%)	449 (51%)	383 (46%)	641 (62%)	336 (34%)	341 (40%)
Angiotensin receptor blocker	1443 (24%)	226 (19%)	143 (17%)	215 (27%)	191 (20%)	323 (29%)	345 (36%)
ACE inhibitor/angiotensin receptor blocker	4322 (74%)	990 (78%)	586 (68%)	593 (73%)	828 (82%)	654 (64%)	671 (76%)
Aldosterone inhibitor	2913 (48%)	787 (59%)	421 (47%)	229 (27%)	480 (46%)	533 (56%)	463 (55%)
Loop diuretic	4414 (78%)	1214 (94%)	691 (81%)	361 (45%)	878 (88%)	598 (61%)	672 (78%)
Digoxin	1550 (26%)	443 (32%)	224 (25%)	241 (29%)	186 (18%)	262 (29%)	194 (25%)
Long-acting nitrate	1075 (15%)	58 (5%)	114 (13%)	188 (23%)	256 (25%)	360 (31%)	99 (8%)
Aspirin	3293 (56%)	558 (46%)	440 (52%)	469 (58%)	753 (75%)	620 (58%)	453 (46%)
Warfarin	858 (14%)	222 (17%)	84 (10%)	81 (10%)	194 (20%)	97 (10%)	180 (22%)
Socioeconomic factors							
Illiterate	1319 (15%)	495 (43%)	229 (29%)	20 (2%)	303 (36%)	210 (15%)	62 (4%)
Education ≥ grade 5 level	2496 (42%)	714 (61%)	428 (56%)	161 (20%)	464 (54%)	423 (37%)	306 (29%)
Education grade 6 –10 level	1382 (23%)	178 (13%)	135 (15%)	312 (37%)	207 (19%)	285 (30%)	265 (32%)
Education grade 11–12 level	1047 (17%)	208 (13%)	183 (18%)	175 (19%)	161 (13%)	170 (18%)	150 (19%)
Education post secondary	896 (13%)	193 (13%)	112 (11%)	163 (18%)	168 (13%)	113 (11%)	147 (17%)
Dwelling in rural area	2080 (36%)	414 (42%)	492 (48%)	298 (37%)	261 (26%)	434 (44%)	181 (21%)
Health insurance	3345 (61%)	416 (33%)	166 (19%)	357 (44%)	743 (74%)	906 (91%)	757 (76%)

Data adjusted for age and sex. Data are mean (SD) or n (%). NYHA=New York Heart Association. ACE=angiotensin converting enzyme. *Data available for 4716 patients (81%) who had echocardiograms. †Valve disease defined as moderate or greater stenosis or regurgitation in a cardiac valve on echocardiogram; may co-exist with any of the main causes of heart failure.

Table 1: **Baseline demographic and clinical characteristics**

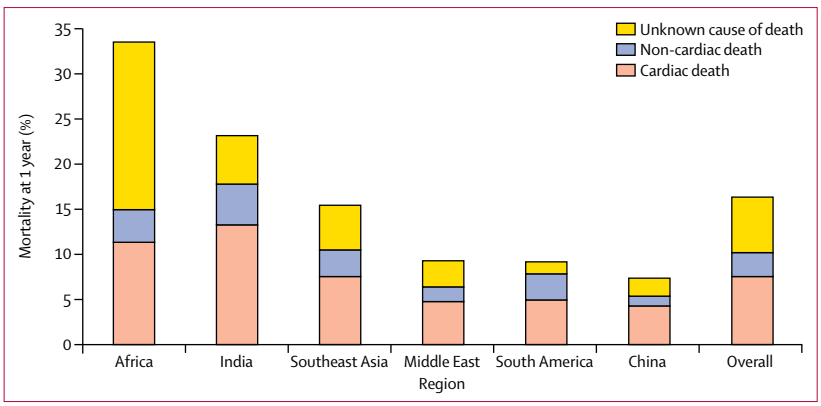

Figure 1: **Unadjusted mortality at 1 year, by region and cause**

change in randomness (entropy) due to the introduction or removal of a covariate.[15] The explained risk statistics were calculated using R software version 3.2.5, (R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc, Cary, NC, USA). Given the observational nature of this study, reported p values are considered as informative statistics. We set the threshold of p<0·001 for a finding to be considered as persuasive evidence of a meaningful finding, because of the number of research questions addressed in analysis

Results

Between September 10, 2012, and February 21, 2014, we screened 7176 consecutive patients for eligibility and

	Univariable analysis			Multivariable analysis		
	Hazard ratio (95% CI)	p	χ^{2*}	Hazard ratio (95% CI)	p	χ^{2}
Demographic variables						
Age (per 10 year increase)	1 (1·0–1·1)	0·28	1·2	1·1 (1·05–1·17)	0·005	7·7
Male sex	1 (0·9–1·2)	0·84	0	1·0 (0·9–1·3)	0·7	0·1
Clinical variables						
Enrolled as hospital inpatient	2·9 (2·5–3·6)	<0·0001	158	1·9 (1·6–2·2)	<0·0001	44
Valve disease on echocardiogram†	2·0 (1·7–2·4)	<0·0001	64	1·6 (1.3 – 1.9)	<0·0001	25
Admission for hearth failure in previous year	1·9 (1·6–2·2)	<0·0001	60	1·6 (1·3–1·9)	<0·0001	25
History of chronic kidney disease	1·7 (1·3–2·2)	<0·0001	19	1·9 (1·5–2·5)	<0·0001	24
Systolic blood pressure (per 10 mmHg increase)	0·9 (0·8–0·9)	<0·0001	30	0.92 (0.88 – 0.96)	<0·0001	17
NYHA functional class III or IV (*vs* class I and II)	2·2 (1·8–2·6)	<0·0001	83	1·4 (1·2–1·7)	0·0003	13
Body mass index (per 1 kg/m^2 increase)	0·94 (0·93–0·96)	<0·0001	52	0·97 (0·96–0·99)	0·001	11
History of chronic obstructive pulmonary disease	1·6 (1·3–2·1)	0·0002	14	1·6 (1·2–2·1)	0·001	11
History of diabetes mellitus	1·1 (0·9–1·3)	0·26	1·3	1·2 (1·0–1·5)	0·06	3·5
Reduced left ventricular function (EF <40%)	1·3 (1·1–1·5)	0·003	8·7	1·1 (0·9–1·4)	0·2	1·6
Current tobacco use	0·8 (0·6–1·1)	0·22	1·5	0·9 (0·7–1·3)	0·69	0·1
Ischaemic cause of heart failure	1·0 (0·8–1·1)	0·66	0·2	1·0 (0·8–1·3)	0·72	0·1
Medications						
ACE inhibitor or ARB use	0·7(0·6–0·8)	<0·0001	21	0·8 (0·7–0·9)	0·01	5·8
Digoxin use	1·0 (0·8–1·2)	0·83	0	0·80 (0·7–0·9)	0·03	4·7
Beta blocker use	0·6 (0·5–0·7)	<0·0001	33	0·9 (0·7–1·1)	0·17	1·9
Aldosterone inhibitor use	1·0 (0·9–1·2)	0·60	0·3	1·0 (0·8–1·2)	0·95	0
Socioeconomic factors						
Illiterate	1·8 (1·5–2·1)	<0·0001	40	1·2 (0·9–1·5)	0·13	2·2
Dwelling in rural area	1·4 (1·2–1·7)	<0·0001	17	1·2 (1·0–1·4)	0·12	2·4
No health insurance	1·6 (1·3–1·9)	<0·0001	29	0·9 (0·7–1·0)	0·12	2·4
Region (*vs* South America)						
Africa	3·7 (2·7–5·1)	<0·0001	60	3·8 (2·6–5·5)	<0·0001	48
India	2·9 (2·1–4·1)	<0·0001	37	2·9 (1·9–4·3)	<0·0001	28
Southeast Asia	1·9 (1·3–2·8)	0·0004	12	2·6 (1·7–3·9)	<0·0001	21
Middle East	1·2 (0·8–1·7)	0·43	0·6	1·3 (0·9–1·9)	0·23	1·4
China	0·8 (0·6–1·3)	0·86	0·4	0·7 (0·4–1·1)	0·14	2·1

ARB=angiotensin receptor blocker; EF=ejection fraction; NYHA=New York Heart Association.*Degrees of freedom=1 for all tests. †Defined as moderate or greater stenosis or regurgitation in a cardiac valve on echocardiography. N=4347; 565 deaths; global χ^2=519; p <0·0001

Table 2: **Variables associated with all-cause mortality at 1 year**

enrolled 5823 participants (81%). Table 1 shows baseline characteristics, adjusted for age and sex, by region; further cohort data have been reported previously.[16] Mean age of the cohort was 59 years (SD 15); 2328 (39%) were female, 3549 (64%) had a history of hypertension, 1728 (29%) had a history of diabetes mellitus, 487 (8%) had a history of chronic kidney disease, and 2486 (50%) had a LVEF less than 40%. The cause of heart failure was ischaemia in 2433 (39%), hypertension in 1096 (17%), idiopathic dilated cardiomyopathy in 838 (12%), and primary valve disease in 739 (11%). 1319 (15%) of participants were illiterate and 2477 (39%) had no health insurance. As per our study design, 3695 participants (66%) were recruited from outpatient clinics and 2105 (34%) from inpatient hospital wards; 2080 (36%) were recruited in rural settings.

Follow-up data at 12 months were available in 5689/5823 (98%) of patients: 811/811 (100%) in southeast Asia, 989/991 (100%) in China, 856/858 (100%) in India, 995/1000 (99%) in the Middle East, 830/869 (95%) in South America, and 1208/1294 (93%) in Africa.

Data from echocardiograms were available for 4716 patients (81%). In model 2, with data derived from echocardiograms excluded, the number of patients for which all data were available increased from 4347 patients with 565 deaths (in model 1) to 5341 patients with 766 deaths. The events per variable (EPV) of 565 deaths/21 variables=27 (model 1), and 766 deaths/19 variables=40 (model 2), are well above the recommended threshold of 10 EPV, therefore minimising bias in parameter estimates of our Cox proportional hazards model.[17,18] Findings from model 1 are reported here, and results from model 2 are shown in the appendix.

Unadjusted all-cause mortality within 1 year was 16·5% (95% CI 15·4–17·6), and varied substantially between regions. Mean age at time of death was 56 years (SD 16) in Africa, 59 years (15) in India, 57 years (15) in southeast Asia, 60 years (14) in the Middle East, 69 years (13) in China, and 72 years (14) in South America. Despite being in the youngest cohorts at baseline, patients in Africa and India had the highest mortality (33·6% [95% CI 30·2–37·4]), 23·3% [19·9–27·0]), respectively), and participants from southeast Asian had an intermediate rate (15·0% [12·4–18·0]), compared with patients in China, South America and the Middle East patients who had the lowest rates of death (7 ·3% [5·7–9·3], 9·1% [7·1–11·4] and 9·4% [7·5–11·5], respectively).

Of the 858 deaths within 1 year, cardiac deaths were more common than non-cardiac deaths (398 [46%] and 136 [16%], respectively), and deaths from an unknown cause (324 [38%]). The proportion of deaths from an unknown cause was much higher in Africa (189 deaths, 55%) than in other regions (figure 1). When we excluded Africa from analysis, 282 (55%) deaths were from cardiac causes, 99 (19%) from non-cardiac causes, and 135 (26%) from unknown cause.

In unadjusted analyses, variables associated with death within 1 year included clinical variables, medications, socioeconomic variables and region (table 2). After multivariable adjustment, clinical and demographic variables independently associated with death within 1 year included: age (hazard ratio [HR] 1·1; 95% CI 1·05–1·17), systolic blood pressure (0·92 per 10 mm Hg increase; 0·88–0·96), body mass index (0·97 per 1 kg/m^2 increase; 0·96–0·99), history of chronic kidney disease (1·9; 1·5–2·5), New York Heart Association (NYHA) functional class III or IV heart failure (1·4; 1·2–1·7), enrolment as a hospital inpatient (1·9; 1·6–2·2), admission for heart failure in the previous year (1·6; 1·3–1·9), history of chronic obstructive pulmonary disease (1·6; 1·2–2·1), and valve disease shown on echocardiograms (1·6; 1·3–1·9). Medications associated with death rates at 1 year were ACE inhibitors or angiotensin receptor blockers (0·8; 0·7–0·9), and digoxin use at enrolment (0·8; 0·7–0·9). With South America as the reference, the variable of region was associated with 1-year mortality in Africa (3·8; 2·6–5·5), India (2·9; 1·9–4·3), and southeast Asia (2·6; 1·7–3·9). Figure 2 shows unadjusted and adjusted survival curves.

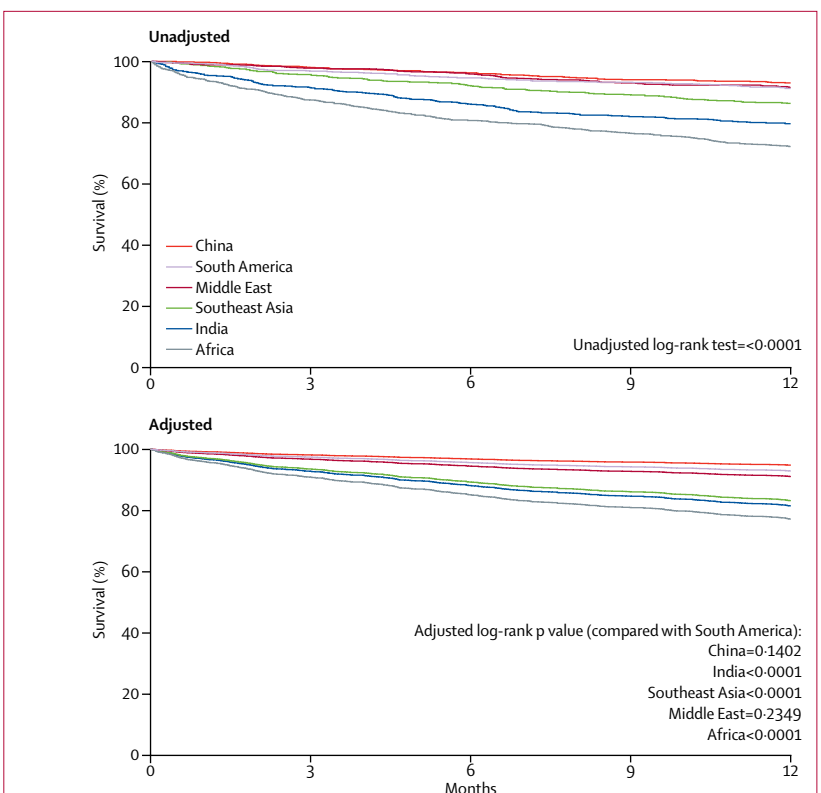

Figure 2: **Unadjusted and adjusted survival curves by region**

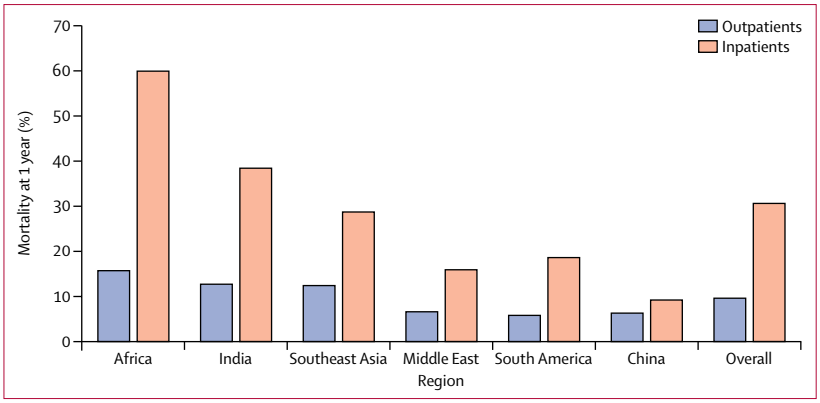

Figure 3: **Unadjusted mortality at 1 year, by admission status at recruitment and region**

In our analyses of cause-specific mortality, we noted that for cardiac death alone, results were similar to those for all-cause deaths: patients in Africa (HR 2·3; 95% CI 1·4–3·8) and India (2·5; 1·5–4·2) were at highest hazard of cardiac death, followed by those in southeast Asian (2·0; 1·2–3·4), with no increased hazard in patients in the Middle East (1·0; 0·6–7·7) or China (0·7, 0·4–1·2), compared with the South American cohort. Likewise, for non-cardiac deaths, participants in Africa (2·7; 1·2–6·2) and India (2·4; 1·0–5·9) were at highest hazard, followed by participants in southeast Asia (2·0; 0·8–4·9), the Middle East (1·4, 0·6–3.4) and China (0·5; 0·2–1·3), compared with South American patients.

When data were stratified by patients' admission status, we noted that of the 2105 patients recruited as hospital inpatients, unadjusted mortality within 1 year was markedly higher (30·6%, 95% CI 28·0–33·3), than in the 3695 patients recruited from outpatient clinics (9·6%, 8·6–10·6) (figure 3). As in the overall cohort, patients recruited as hospital inpatients in Africa had the highest adjusted hazard of death within 1 year (HR 3·7; 95% CI 2·2–6·2), followed by inpatients in India (2·4; 1·4–4·0) and southeast Asia (2·4; 1·3–4·4), with no increased hazard of death in the Middle East (1·1; 0·6–1·9), or China (0·4; 0·2–0·8), compared with the South American cohort. For patients recruited as outpatients, findings were similar, with highest hazard of death in Africa (4·2; 2·3–7·5) and India (4·1; 2·2–7·6), followed by southeast Asia (3·3; 1·9–5·9), the Middle East (1·7; 1·0–3·0), and China (1·2; 0·8–2·2).

Of the 5823 participants in INTER-CHF, 3189 (55%) had all required variables measured for the Boston Criteria for heart failure. Of these 3189 participants, 2597 (81%) had either definite or probable heart failure. In this stratum patients with either definite of probable heart failure, regional patterns in hazard ratios noted for the overall cohort remained: participants in Africa (HR 2·8; 95% CI 1·7–4·3) and India (2·7; 1·6–4·3) had the highest hazard of death, followed by those in southeast Asia (2·2; 1·3–3·9), the Middle East (0·9; 0·6–1·5), and China (0·6; 0·3–1·1), compared with South American patients.

	Value (%)	Standard error (%)
Demographic variables	0·2	0·4
Demographic + clinical variables	35	2·7
Only demographic variables	0·1	0·1
Only clinical variables	35	2·7
Demographic + clinical variables + medications	36	2·7
Only demographic variables	0	0·1
Only clinical variables	33	2·8
Only medications	2·1	1
Demographic + clinical + medications + socioeconomic variables	39	2·6
Only demographic variables	0·2	0·3
Only clinical variables	29	2·8
Only medications	1·7	0·9
Only socioeconomic variables	3·4	1·2
Demographic + clinical + medications + socioeconomic variables + region	46	2·4
Only demographic variables	0·7	0·6
Only clinical variables	25	2·6
Only medications	1·1	0·6
Only socioeconomic variables	0·7	0·5
Only region	12	3·0

Demographic, clinical, medication, socioeconomic variables and region account for 46% of explained relative risk of death in the overall cohort. The remainder of risk is unexplained. N=4347; 565 events.

Table 3: **Explained risk analysis for independent variables included in Cox proportional hazards (model 1) of all-cause mortality in the overall cohort at 1 year**

We used the explained-risk statistic[15] to determine the relative contributions of each of demographic and clinical variable, medications, socioeconomic variable and region to the risk of death within 1 year in the overall cohort. These variables, together, explained 46% of the risk of death. Of the explained risk, clinical variables alone accounted for 53%, and region for 35%, with lesser contributions from demographic variables, medications ,and socioeconomic variables (2% for each; table 3).

Discussion

We have observed substantial variations in mortality between regions in patients with heart failure—rates were higher in poorer regions and lower in richer regions, and differences persisted after multivariable modelling. Although data from international studies in clinic outpatients (that is, patients with chronic heart failure) are few, they do also suggest regional differences in heart failure outcomes. In an analysis of regional differences observed in the PARADIGM-HF study[19] (a randomised trial of sacubitril/valsartan versus enalapril, in which 10 521 patients from 1043 centres in 47 countries entered the run-in period), Kristensen and colleagues analysed data from 8399 patients with chronic heart failure with reduced LVEF in six geographical regions. They showed

that the adjusted risk of cardiovascular death was greater in Latin America and Asia-Pacific than in North America and Europe; patients from the Asia-Pacific region were also significantly younger than patients from western countries. A pooled analysis of 53 local and regional studies also reported that the mean age of patients with heart failure in LMIC was a decade younger than in high-income countries.[8] In INTER-CHF, patients in Africa, India, and southeast Asia were approximately 10 years younger than patients in South America and China, but had much higher mortality. This finding may be related to patients with heart failure presenting later for medical care (that is, when they are sicker) in low-income compared with high-income regions, and late presentation being associated with a worse prognosis.[20] This finding may also be related to the overall lower life expectancies in LMIC compared with high-income countries.[21]

Study participants with acute heart failure enrolled as inpatients in clinical trials have shown that patients from North America and Europe had lower mortality rates than did patients from South America and Asia, with few data from the Middle East, Africa, South Asia or China.[10,22,23] In a retrospective analysis of the ASCEND-HF trial[24] (a randomised trial of nesiritide versus placebo in 7141 hospitalised patients with acute heart failure from 398 sites in 30 countries), patients from Latin America had the highest adjusted 180-day mortality (17·3%), followed by western Europe, North America, Asia-Pacific, with Central Europe (9·3%) having the lowest mortality. Local registries have also reported data on mortality in inpatients with heart failure. A study of 1009 patients with heart failure admitted to hospitals in sub-Saharan Africa reported an unadjusted 6-month mortality of 17·8%, which is probably an underestimate because of the substantial losses to follow-up.[25] In a registry of 1205 patients hospitalised with heart failure in India, the 90-day mortality rate was 24·3%.[26] In a hospital registry of 5005 patients with heart failure from Gulf states, mortality at 1 year was 20%.[27] Therefore, data from other studies accord with our findings of variations in outcomes between regions and also high mortality by region. Our study also provides new data on outcomes in outpatients with chronic heart failure, and in several countries and regions not previously studied.

In INTER-CHF, both cardiac and non-cardiac factors were associated with all-cause mortality, consistent with data from western populations.[28] However, in our study, multivariable adjustment including these factors only explained about half the mortality risk, the remainder being unexplained. Importantly, when compared with other regions in this study, patients in Africa were much younger, more symptomatic, more often treated with digoxin, had little education, low rates of health-insurance, and were more often from a rural area. Similar patterns were observed in India. These were the countries with highest mortality. Therefore, country-level, environmental, wealth, and healthcare infrastructure, quality and access factors would need to be addressed if these differences in outcomes were to be further explained. Indeed, in a systematic review by Callender and colleagues[8] of earlier regional heart failure studies, higher mortality in lower-income regions was thought to be partly the result of differing health systems, quality of care, and variations in health-care access. In addition, genetic and genomic factors may also influence regional variations in heart failure outcomes, but were not recorded in INTER-CHF. Therefore, measuring and understanding health systems, environmental and societal issues, and genetic and genomic markers in future international heart failure studies could help in understanding the causes of the regional variations in outcomes. Information on health systems could assist in developing strategies to further reduce mortality in patients with heart failure.

The 5823 patients with heart failure enrolled in this study from 108 centres in 16 countries constitute a large study of heart failure in Africa, Asia, the Middle East and South America. However, some randomised trials in patients with heart failure that included different regions were larger.[19,24] By using a standardised protocol and approach, comparisons of patient characteristics and outcomes between regions are possible. Furthermore, the high follow-up rate of 98% gives confidence in our findings. As with most registries, we were unable to randomly sample clinical sites or populations, for practical reasons. However, data from INTER-CHF are similar to data collected elsewhere in other studies.[8,19] Although representativeness and potential ascertainment bias are inherent challenges in data collection for registries, the consistent data from other studies from specific regions validate our findings. Furthermore, variability in decisions about the causes of heart failure and death are possible, but are a reality of clinical practice, not only in LMIC but also in western countries. Unpublished data from the PURE study, which is community based, also show that mortality after a diagnosis of heart failure was lowest in high-income countries, intermediate in middle-income countries and highest in low-income countries.

In this heart failure cohort study in 16 countries, mortality was highest in Africa and India, intermediate in southeast Asia, and lowest in China, South America, and the Middle East. These regional differences persisted after multivariable adjustment including both cardiac and non-cardiac factors. Therefore, the large regional differences in death in patients with heart failure could be influenced by unmeasured variables, requiring further study in large, global cohorts of patients with heart failure.

Contributors

HD contributed to study design, literature search, data analysis, data interpretation, figures, and writing. KT contributed to study design, data interpretation, and writing. JZ, AR, KFA, AE, LP-V, PL-J, KK, KY, AO, KS, CM, FL, DP, AB, ME, AD, and KT contributed to study design, data collection, and data interpretation. EB-C contributed to data

interpretation and writing. KB and SI contributed to data analysis, data interpretation, and figures. MHY, MDH, and KH contributed to study design and data interpretation. AG contributed to study design, and data collection. RM contributed to study design, and data interpretation. SIB contributed to data analysis, data interpretation, and writing.
SY contributed to study design, data analysis, data interpretation, and writing.

Declaration of interests

JZ has received grants from Bayer. DP has received grants from Novartis. MH has received grants from the World Heart Federation. All other authors declare no competing interests.

Acknowledgments

Novartis staff provided assistance and support for the study. We thank the Saudi Heart Association, and the Deanship of Scientific Research at King Saud University, Riyadh, Saudi Arabia (Research group number: RG -1436-013) for research coordination and assistance.

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