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ORIGINAL ARTICLE

European Society of Cardiology guidelines and 1 year outcomes of acute heart failure treatment in Central Asia and Europe

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Abstract

Aims Outcomes reported for patients with hospitalization for acute heart failure (AHF) treatment vary worldwide. Ethnicity-associated characteristics may explain this observation. This observational study compares characteristics and 1-year outcomes of Kyrgyz and Swiss AHF patients against the background of European Society of Cardiology guidelines-based cardiovascular care established in both countries.

Methods and results The primary endpoint was 1 year all-cause mortality (ACM); the secondary endpoint was 1 year ACM or HF-related rehospitalization. A total of 538 Kyrgyz and 537 Swiss AHF patients were included. Kyrgyz patients were younger (64.0 vs. 83.0 years, $P < 0.001$); ischaemic or rheumatic heart disease and chronic obstructive pulmonary disease were more prevalent (always $P < 0.001$). In Swiss patients, smoking, dyslipidaemia, hypertension, and atrial flutter/fibrillation were more frequent (always $P \leq 0.035$); moreover, left ventricular ejection fraction (LVEF) was higher (47% vs. 36%; $P < 0.001$), and >mild aortic stenosis was more prevalent ($P < 0.001$). Other valvular pathologies were more prevalent in Kyrgyz patients ($P < 0.001$). At discharge, more Swiss patients were on vasodilatory treatment ($P < 0.006$), while mineralocorticoid receptor antagonists ($P = 0.001$), beta-blockers ($P = 0.001$), or loop diuretics ($P < 0.001$) were less often prescribed. In Kyrgyz patients, unadjusted odds for the primary and secondary endpoints were lower [odds ratio (OR) 0.68, 95% confidence interval (CI): 0.51–0.90, $P = 0.008$; OR 0.72, 95% CI: 0.56–0.91, $P = 0.006$, respectively]. After adjustment for age and LVEF, no difference remained (primary endpoint: OR 1.03, 95% CI: 0.71–1.49, $P = 0.894$; secondary endpoint: OR 0.82, 95% CI: 0.60–1.12, $P = 0.206$).

Conclusions On the background of identical guidelines, age- and LVEF-adjusted outcomes were not different between Central Asian and Western European AHF patients despite of large ethnical disparity.

Keywords ESC guidelines; Acute heart failure; Ethnicity; Outcome

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Introduction

Heart failure (HF) is a global pandemic, and while prognosis of chronic HF has continuously improved worldwide during the last decades,[1] substantial variability of short-term outcome is still reported for acute heart failure (AHF) patients living in different world regions.[2] Reason is foremost the complexity of AHF syndrome with its multiple aetiologies, diverse pheno-

types, and the variable disease severity.[3,4] Moreover, many therapeutic interventions failed to demonstrate prognostic improvement.[5] In addition, AHF management differs between regions.[6,7] And, last not least, ethnical disparity seems to play a role as suggested by the observation that well-known predictors of death in Caucasian HF patients explain only 44.2% of the variation of risk in Asian HF patients.[8]

In this complexity, identical guidelines for the care of cardiovascular disease offer to study the impact of ethnical disparity on short-term outcomes in patients with HF-related rehospitalization (HHF). The guidelines of the European Society of Cardiology (ESC) are established in most European, many Arabian, and some Central Asian countries.[9] Kyrgyzstan and Switzerland endorsed the ESC guidelines more than 10 years ago providing a common background of established cardiovascular care.[10]

On this basis, the present study compares characteristics and outcomes of Kyrgyz AHF patients with a respective Swiss cohort. As best application of the guidelines is primordial in particular for the comparison of outcomes, this study contrasts cohorts of tertiary teaching hospitals, the National Center of Cardiology and Internal Medicine (NCCIM) in Bishkek, Kyrgyzstan, and the Lausanne University Hospital [Centre Hospitalier Universitaire Vaudois (CHUV)] in Lausanne, Switzerland.

Methods

Study design, population of the catchment area, study population, and data collection

This observational two-centre-based study includes data of consecutive AHF patients with transthoracic echocardiography obtained during hospitalization for AHF treatment. The NCCIM at Bishkek, Kyrgyzstan, and the CHUV at Lausanne, Switzerland, are tertiary teaching hospitals providing ambulatory and hospital-based HF care with the option for structural intervention and device implantation. However, treatment options such as long-term continuous-flow left mechanical circulatory support or heart transplantation were available only at the CHUV. As the latter treatment is offered only to the rare patient with AHF, this difference should not impact on results of the present study. The study complies with the Declaration of Helsinki and was approved by the local ethics committees (Bishkek: local ethics committee 2019-7; Lausanne: CER-VD 2019-1158).

During the study period (2013–19), the general population of the catchment area of the CHUV was composed of Swiss (67%) and White people from other European countries (26%) while 7% were from outside of Europe; for the NCCIM, 75% of the population of the catchment area were of Central Asian origin, and 15% were of Eastern European descendance.

The 2013–14 CHUV study participants were recruited from a prospective observational cohort study at the CHUV including 431 adult AHF patients[11]; 316 of the 431 patients were eligible as transthoracic echocardiography had been obtained during index hospitalization. Patients with hospitalization for AHF treatment in the years 2015–19 were derived from another prospective observational study of AHF patients (n = 221).[12] Consistent with the study inclusion criteria, consecutive Bishkek AHF patients were included only when transthoracic echocardiography was performed during index hospitalization (n = 537). Exclusion criteria were patients with AHF due to exacerbation of chronic obstructive pulmonary disease, acute pulmonary embolism, acute myocardial ischaemia, stress-related cardiomyopathy, severe valvular regurgitation or stenosis requiring immediate percutaneous or surgical intervention, and complex congenital heart disease and patients after recent cardiac surgery. Further exclusion criteria were acute metabolic, toxic, or infectious disease, pregnancy, dialysis, or when comorbidity was considered to reduce survival time to $<$1 year based on investigator's judgement (T. A. or N. S.).

Parameters of study participants were retrieved from electronic charts at both centres. Data accuracy was tested in 20% of the study population revealing 99.7% correctness (T. A. or N. S.). The primary outcome, 1 year all-cause mortality (ACM), was extracted from the national registries of Kyrgyzstan and Switzerland (accessed 12/2021). The outcome of HHF was retrieved from electronic charts of each hospital.

Variable definitions and measures

All patients entering the final analysis had a validated clinical diagnosis of AHF according to HF guidelines.[13] Rheumatic heart disease and previous myocardial infarction were documented by chart review. Tobacco abuse considered both past and current smoking. Hyperlipidaemia, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease were retrieved from each patient's chart. Atrial flutter/fibrillation was considered when paroxysmal, persistent, or permanent. Plasma natriuretic peptides measures were not available for 82.7% of study patients and not entered into the final analysis. Echocardiography was performed or proofread by board-certified cardiologists applying the respective ESC guidelines.[14] Left ventricular ejection fraction (LVEF) was assessed using biplane Simpson method. HF medication was documented pursuant to pharmacological class and captured both at admission and at discharge. Sodium-glucose cotransporter-2 inhibition was prescribed for improvement of glycaemic control in the years 2013–19; therefore, this medication was categorized as oral antidiabetic treatment.

Statistical analysis

Statistical analysis was performed with STATA 16.1 (StataCorp, College Station, TX, USA). The comparisons were made between the NCCIM and CHUV cohorts and, furthermore, between study participants with LVEF of <50% and ≥50%. This classification was chosen as the ESC guidelines recommend pharmacological HF treatment in HF patients with mid-range LVEF in analogy to evidence available for HFrEF patients.[13] Continuous variables are expressed as median ± interquartile range; categorical variables are expressed as frequencies and percentages. Comparisons of demographic, clinical, laboratory, and echocardiographic characteristics were performed using Wilcoxon's rank sum test for continuous variables and χ^2 test for categorical variables. A violin plot was used to graphically show the difference of age between the two cohorts.

To compare the study outcomes 1 year ACM (primary endpoint) and 1 year ACM or 1 year HHF (secondary endpoint), odds ratios (ORs) and predicted proportions with 95% confidence interval (95% CI) were calculated using logistic regression, both unadjusted and adjusted. Traditional cardiovascular risk factors explain only 44.2% of mortality in Asian HF patients,[8] suggesting that their impact on mortality in the two study cohorts differs. Therefore, in appreciation of the large disparity between the two study populations for the majority of parameters and in univariate analysis investigating association with 1 year ACM, we chose to adjust 1 year outcomes only for age and LVEF in analogy to the MAGGIC meta-analysis[15] to avoid maladjustment.

Furthermore, unadjusted Kaplan–Meier estimates were calculated for both cohorts in order to visualize the time to event course for 1 year ACM stratified by LVEF of <50% and ≥50%.

P-values < 0.05 were considered to represent significant difference.

Results

Demographics

Overall, 1075 patients were included into the final analysis. Asian ethnicity was present in 82% of patients of Central Asian cohort and 1.3% of the Western European cohort. Kyrgyz patients were younger (64 vs. 83 years, $P < 0.001$; Supporting Information, *Figure S1*) and less frequently female when compared with the Swiss cohort (38.8% vs. 48.6%, $P = 0.001$) (*Table 1*).

Clinical characteristics and comorbidities

Table 1 shows that body mass index was higher in Kyrgyz patients. Kyrgyz AHF patients had a lower average systolic blood pressure but higher diastolic blood pressure at ad-

Table 1 Demographic and clinical characteristics of patients hospitalized for acute heart failure in Central Asia and Western Europe

	Number of observations	All (*n* = 1075)	Central Asian cohort (*n* = 538)	Western European cohort (*n* = 537)	*P*-value
Demographic characteristics					
Asian ethnicity (%)	1075	448 (41.7)	441 (82.0)	7 (1.3)	<0.001
Age (years)	1075	74 (62–84)	64 (56–72)	83 (75–88)	<0.001
Female sex (%)	1075	470 (43.7)	209 (38.8)	261 (48.6)	0.001
Clinical characteristics					
SBP at admission (mmHg)	1070	130 (111–150)	130 (110–150)	134 (118–153)	<0.001
DBP at admission (mmHg)	1069	80 (68.0–90.0)	80 (70.0–90.0)	76 (63.0–89.0)	<0.001
HR at admission (b.p.m.)	1073	88 (73–106.0)	89 (74.0–108.0)	85 (72.0–105.0)	0.210
BMI (kg/m^2)	1050	27.3 (23.6–31.6)	28.4 (24.4–32.3)	26.3 (22.9–30.7)	<0.001
BSA (m^2)	1050	1.9 (1.7–2.0)	1.9 (1.7–2.0)	1.8 (1.7–2.0)	<0.001
Rheumatic heart disease (%)	1075	47 (4.4)	47 (8.7)	0 (0.0)	<0.001
Ischaemic heart disease (%)	1075	671 (62.4)	418 (77.7)	253 (47.1)	<0.001
Comorbidities					
COPD (%)	1075	298 (27.7)	173 (32.2)	125 (23.3)	0.001
Smoking (%)	1075	366 (34.0)	120 (22.3)	246 (45.8)	<0.001
Atrial fibrillation/flutter (%)	1075	589 (54.8)	255 (47.4)	334 (62.2)	<0.001
History of myocardial infarction (%)	1075	467 (43.4)	243 (45.2)	224 (41.7)	0.253
History of heart failure (%)	1075	891 (82.9)	518 (96.3)	373 (69.5)	<0.001
Hyperlipidaemia (%)	1075	526 (48.9)	246 (45.7)	280 (52.1)	0.035
Hypertension (%)	1075	833 (77.5)	388 (72.1)	445 (82.9)	<0.001
Diabetes mellitus (%)	1075	350 (32.6)	170 (31.6)	180 (33.5)	0.502

BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
P-value compares parameters between Central Asian and Western European acute heart failure patients.

mission (always $P < 0.001$). Heart rate was not different between the two cohorts. The prevalence of ischaemic heart disease was higher in Kyrgyz patients (77.7% vs. 47.1%; $P < 0.001$), while the prevalence of previous myocardial infarction was not different between groups. A total of 32.6% study participants was suffering from type 2 diabetes without significantly different prevalence between Central Asians and Western Europeans. Chronic obstructive pulmonary disease was more frequent in Kyrgyz patients (32.2% vs. 23.3%; $P = 0.001$) despite of an overall lower prevalence of tobacco consumption (22.3% vs. 45.8%; $P < 0.001$). In contrast, Swiss AHF patients had a higher prevalence of hypertension (82.9% vs. 72.1%; $P < 0.001$) and atrial fibrillation/flutter (62.2% vs. 47.4%; $P < 0.001$) (*Table 1*).

Laboratory characteristics

Laboratory measures were obtained at admission and, except for creatinine levels, always significantly different. Haemoglobin and haematocrit levels were higher in Central Asians while white blood cell count and glucose levels were lower in Kyrgyz patients. Regarding serum electrolytes, median levels for sodium and potassium were within the normal range but always higher in Western Europeans (*Table 2*).

Echocardiographic parameters

Central Asian patients had significantly lower LVEF and higher left ventricular end-diastolic diameters or indexed left ventricular mass (always $P < 0.001$). Furthermore, the prevalence of >mild regurgitation of the aortic, mitral, or tricuspid valves was higher in Central Asians while >mild aortic stenosis was more frequent in Western Europeans (always $P < 0.001$); mitral stenosis was more prevalent in Central Asians, in particular, in participants with LVEF $\geq$ 50% (always $P \leq 0.009$) (*Table 3* and Supporting Information, *Tables S3* and *S6*).

Drug and device treatment

HF medication use is shown separately for each cohort at admission and discharge; prescription is shown as a function of the pharmacological class (*Figure 1*). During hospitalization, HF drug prescription increased in both cohorts and for all pharmacological classes except for angiotensin receptor blockers (ARBs) that decreased by 5.2% at discharge in Swiss AHF patients (*Figure 1*). At admission, the percentage of Kyrgyz AHF patients with prescription of beta-blockers, angiotensin-converting enzyme inhibitors (ACE-Is), ARBs, and loop diuretics was overall lower when compared with Swiss patients (*Figure 1*); moreover, the percentage was not different between LVEF subgroups (Supporting Information, *Table S4*) while being different between LVEF subgroups in Swiss AHF

Table 2 Admission laboratory characteristics of patients hospitalized for acute heart failure treatment in Central Asia and Western Europe

	Number of observations	All (n = 1075)	Central Asian cohort (n = 538)	Western European cohort (n = 537)	P-value
Haemoglobin (g/L)	1075	130 (112–146)	140 (125–154)	120 (106–135)	<0.001
Haematocrit (%)	892	39 (34–43)	42 (37–46)	37 (33.0–41.0)	<0.001
Leucocytes (10^9/L)	1074	7.6 (6.2–9.6)	7 (5.8–8.5)	8.3 (6.8–10.7)	<0.001
Glucose (mmol/L)	1036	6.2 (5.1–7.6)	5.3 (4.6–6.7)	6.9 (5.8–8.4)	<0.001
Creatinine (mmol/L)	1072	107.7 (89–136)	105.2 (91–127)	111 (86–149)	0.151
Sodium (mmol/L)	934	138 (135–141)	136 (133–139)	139 (136–142)	<0.001
Potassium (mmol/L)	1054	4.2 (3.9–4.7)	4.1 (3.8–4.5)	4.3 (4.0–4.7)	<0.001

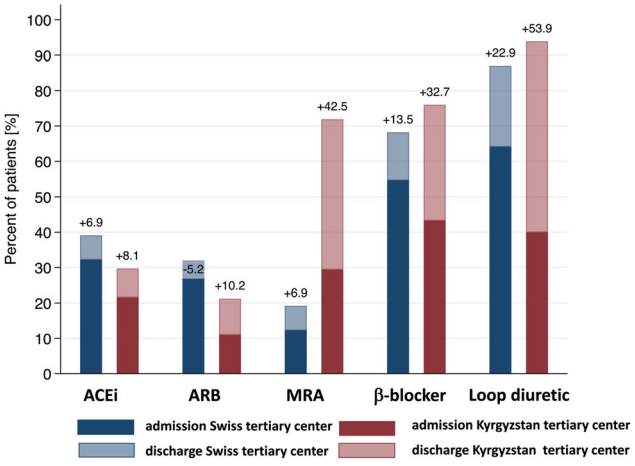
Measures were performed in laboratories working in accordance with ISO 15189 or 17025.

Table 3 Echocardiographic characteristics of patients hospitalized for acute heart failure treatment in Central Asia and Western Europe

	Number of observations	All (n = 1075)	Central Asian cohort (n = 538)	Western European cohort (n = 537)	P-value
LVEF (%)	1075	42 (29–55)	36 (26–47)	47 (35–60)	<0.001
LVEDD indexed (mm/m^2)	941	30 (26–35)	31 (27–35)	29 (25–34)	<0.001
LVM indexed (g/m^2)	922	117 (93–147)	132 (103–162)	105 (85–129)	<0.001
>Mild mitral regurgitation (%)	1075	882 (82.0)	489 (90.9)	393 (73.2)	<0.001
>Mild mitral stenosis (%)	1075	50 (4.7)	37 (6.9)	13 (2.4)	0.001
>Mild aortic regurgitation (%)	1075	457 (42.5)	272 (50.6)	185 (34.5)	<0.001
>Mild aortic stenosis (%)	1075	109 (10.1)	20 (3.7)	89 (16.6)	<0.001
>Mild tricuspid regurgitation (%)	1075	676 (62.9)	394 (73.2)	282 (52.5)	<0.001

LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVM, left ventricular mass.

Figure 1 Change of heart failure drug treatment between admission and discharge in Kyrgyz and Swiss patients hospitalized for acute heart failure treatment. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.



patients (Supporting Information, *Table S7*). At discharge, the percentage of Central Asian AHF patients on beta-blockers, ACE-Is, ARBs, and loop diuretics was largely increased (*Figure 1*), again without significant difference between LVEF subgroups (Supporting Information, *Table S4*). In the Western European cohort, at admission, the portion of AHF patients on beta-blockers, ACE-Is, ARBs, and loop diuretics was overall higher (*Figure 1*), in particular, in AHF patients with LVEF $<$ 50% (Supporting Information, *Table S7*). Different to the Kyrgyz patients, the increase of the portion of Swiss AHF patients on beta-blockers, ACE-Is, ARBs, and loop diuretics at discharge was more important in the $<$50% LVEF group when compared with those with LVEF $\geq$ 50% (Supporting Information, *Table S7*). For antagonists of the mineralocorticoid receptor antagonist (MRA), baseline prescription was higher in Central Asians (*Figure 1*) and the increase of MRA administration was more important across both LVEF groups during hospitalization when compared with Western Europeans. In contrast, in Western Europeans, the increase of MRA treatment at discharge was mostly limited to the $<$50% subgroup (Supporting Information, *Table S7*).

Outcomes

The association of variables with 1 year ACM is shown in Supporting Information, *Table S1* for the whole study collective and separately for the Kyrgyz and Swiss study cohorts. Altogether, the Kyrgyz and Swiss study cohorts differ largely with respect to associations between single parameters and 1 year ACM, highlighting the disparity between the two study groups.

The primary and secondary outcomes differed between the cohorts with lower unadjusted odds for Kyrgyz patients (1 year ACM: OR 0.68, 95% CI: 0.51–0.90, P = 0.008; 1 year ACM or HHF: OR 0.72, 95% CI: 0.56–0.91, P = 0.006) (*Figure 2*), and the unadjusted Kaplan–Meier estimates suggest that this difference is related to a less important early event rate in Kyrgyz patients (Supporting Information, *Figure S2*).

However, no significant difference remained between the two study cohorts when adjusting for age and LVEF neither for the primary endpoint (OR 1.03, 95% CI: 0.71–1.49, P = 0.894) nor for the secondary endpoint (OR 0.82, 95% CI: 0.60–1.12, P = 0.206) (*Figure 2*).

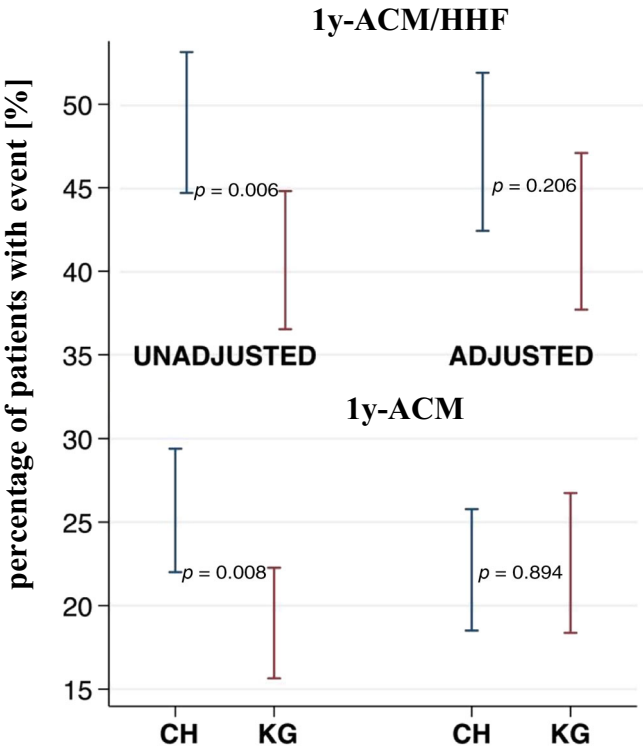
Discussion

This study compares demographic, biological, and clinical characteristics, HF drug change during HHF, and 1 year outcomes between Kyrgyz and Swiss AHF patients. The particularity of this study is that characteristics and outcomes of HF care in Kyrgyzstan and Switzerland are contrasted on the background of ESC guidelines that are established in both countries. Characteristics of the Kyrgyz and Swiss study participants differed largely; nonetheless, 1 year ACM and the combined endpoint of 1 year ACM or HHF were not different between Kyrgyz and Swiss HF patients when adjusted for age and LVEF.

HF represents a significant burden to Asian and European societies with prevalences varying from 1.3% to 6.7% among Asian regions while ranging from 1.0% to 4.4% across European countries.[16–19] Asian and European HF populations also differ with respect to 1 year outcomes, with 1 year ACM ranging from 7.4% in Northeast Asian patients to 13% in Southeast Asian patients[8] while varying from 6.9% to 11.3% among European regions.[20] Reason for this heterogeneity of HF-related outcome is multifold and has been linked with unequal access to medical care,[2] regional diversity of AHF and chronic HF management,[7,21] and variable genetic background due to ethnical disparity.[22]

This complexity motivated the present comparison of characteristics and 1 year outcomes between patients hospitalized for AHF treatment in Kyrgyzstan or Switzerland since both National Societies of Cardiology endorsed the ESC guidelines more than 10 years ago.[10,23] This provides the unique opportunity to investigate the impact of ethnical disparity on outcomes against the background of common guidelines for cardiovascular care. In order to reassure best application of the guideline-directed medical therapy, we compared patients hospitalized for treatment of AHF at two tertiary centres: the National Center of Cardiovascular Care and Internal Medicine, Bishkek, Kyrgyzstan, and the Lausanne University Hospital in Switzerland. Implementation of guidelines, as well as recruitment of study participants in tertiary

Figure 2 Adjusted and unadjusted predicted proportions for the outcome 1 year all-cause mortality (ACM) and composite outcomes 1 year ACM or heart failure-related rehospitalization (HHF) in Kyrgyzstan (KG) and Switzerland (CH) patients. Adjusted for age and left ventricular ejection fraction.



Adjusted: for age and LVEF.
ACM = all-cause mortality, CH = Switzerland, HFrR = heart failure related rehospitalisation, KG = Kyrgyzstan

centres, does not guarantee best application of best guideline-directed medical therapy. But, in both cohorts, prescription of most HF drugs increased from admission to discharge and this increase was even more important in Kyrgyz AHF patients, substantially narrowing the considerable gap of prognostic HF drugs prescription between both cohorts present at admission.

As expected, the Kyrgyz and Swiss study populations differed with respect to their profiles with a higher portion of female sex (48.6%) in the latter while only 38.8% were women in the former. Moreover, Kyrgyz patients had a higher prevalence of chronic obstructive bronchopneumopathy, while smoking, diabetes, dyslipidaemia, hypertension, and atrial fibrillation were more frequent in Western Europeans. Similar differences have been demonstrated in previous reports,[2,6,17,20] and this overall distinct risk profile may, at least in part, explain the finding that traditional cardiovascular risk factors explain only 44.2% of mortality in Asian HF patients.[8]

Kyrgyz and Swiss AHF patients also differed largely with respect to age as median age was 83 years in Western Europeans while Kyrgyz patients were much younger (64 years). The relatively young age of the Kyrgyz AHF patients contrasts to reports from the Japanese Kyoto-HF registry (80 years) or Japanese study participants in the EVOLUTION-HF study.[24,25] However, national registries of other Asian countries report younger age for their HF patients (China: 65 years; Korea: 68.5 years; Thailand: 67 years; India: 61.2 years; Gulf countries: 59 years; and South Asia: 61 years). In contrast, the higher age of the Swiss study population corresponds to records from large contemporary registries, which had included predominantly White patients.[26]

Kyrgyz and Swiss study patients were furthermore largely different with regard to the portion of AHF patients with preserved LVEF, which accounted for 49.9% of all Swiss AHF patients but was only 18.8% of the Kyrgyz AHF patients. The 49.9% of AHF patients with preserved LVEF in the Swiss population correspond to the 46% of respective AHF patients reported from the Get With The Guidelines registry, which had included mostly White patients with HHF hospitalization in the United States.[26] In Asian patients, however, the REPORT-HF registry indicates a 28% proportion of AHF patients with preserved LVEF for Southeast Asia,[2] while the ASIAN-HF registry reports a variable portion of HF with preserved ejection fraction patients varying from 14.9% to

24.6% for South and Northeast Asia.[8] Altogether, this suggests that the prevalence of HF subtypes in the present study corresponds to reports published for Western and South and Northeast Asian regions.

Unadjusted logistic regression analysis of primary and secondary outcomes showed, in the present study, a significantly lower incidence in Kyrgyz AHF patients. However, this difference was no longer present after adjustment for age and LVEF. We chose to adjust only for these two parameters in acknowledgement that these two real-world study populations present large difference across most anthropometric, clinical, and biological parameters. Therefore, we were concerned whether multi-adjusting on the basis of univariable analysis disrespects the heterogeneous risk related to the distinct environmental, clinical, and genetic factors in both countries. We adjusted nonetheless for the parameters age and LVEF, in appreciation of the different age and LVEF distributions of the two study populations as visualized in the violine plot. Both parameters are central determinants of ACM in chronic HF as demonstrated by the MAGGIC meta-analysis.[15] In the present cohort, age was related with the primary endpoint in univariable analysis while LVEF was related with the primary outcome only in Central Asian patients. However, the not significant association of LVEF with 1 year ACM in Western Europeans is in accordance with the observation in the MAGGIC meta-analysis showing that the risk for mortality is similar across HF subtypes.[15]

The achievement of not different outcomes in a statistical analysis staying close to the real-world situation went along with a significant increase of the portion of AHF patients on prognostic HF drug treatment at discharge in either study population. In Kyrgyz patients, this increase was observed across the LVEF subgroups while noticeable increase of the number of Swiss HF patients on prognostic HF drug treatment was limited to patients with LVEF $< 50\%$. This explains why at discharge, more Kyrgyz AHF patients were on beta-blocker when compared with Swiss patients (76% vs. 68%). Moreover, a large difference with respect to MRA treatment was noticeable, which was at discharge more often prescribed in Kyrgyz patients (71.9% vs. 19.2%). This large difference of the latter is intriguing; however, MRA treatment is known to vary largely across all world regions: For example, the REPORT-HF registry demonstrates MRA application in 38% of Southeast Asian patients, 45% in the Japanese patients, and 63% in Western European HF patients, while MRA treatment was applied in only 14% of AHF patients documented by the Get With The Guidelines registry in the United States.[26] Application of MRA was not associated with survival benefit in the GREAT and the Kyoto-HF registry[27,28] but related with a significant reduction of incident rehospitalization in the Kyoto-HF registry,[28] which may explain, at least in part, the lower incidence of the secondary endpoint in Kyrgyz patients.

Study limitations

Interpretation of the study results has to consider that this observational study enrolled the study participants in teaching hospitals with tertiary centres for HF care. Therefore, the study might not represent patients with limited access to the healthcare services especially in Kyrgyzstan, where NCCIM serves as unique referral centre. Furthermore, patients were included only when echocardiography had been performed at index hospitalization, which might have excluded AHF patients presenting with another profile. In addition, we have to acknowledge that the retrospective observational study suffers from the large absence of natriuretic peptide measures both at the NCCIM and at the University Hospital of Lausanne. Last not least, interpretation of the study results has to consider that prescription of discharge HF drugs at 1 year time interval after HHF was not assessed, a bias this study shares with many other studies.[29] In fact, results from the EVOLUTION-HF suggest that drug discontinuation occurs for all HF drugs across Western Europeans, Americans, and North East HHF patients and most often during the first 3 months.[25] This may explain the high early mortality in the present study and many other studies investigating AHF populations.[29] The EVOLUTION-HF furthermore suggests that many Western European, American, and Asian patients remain on the HF drug dose prescribed at discharge from HHF[25]; however, even a low drug dose level has been shown to improve survival.[30] Altogether, as similar change of HF drug medication occurs across different world regions after discharge from HHF, and, moreover, the two cohorts were treated in tertiary hospitals and followed in urban catchment areas, there is good reason to assume that application of the guidelines-directed medical therapy was respected in the follow-up of the study participants.

Conclusions

This observational study including consecutive Kyrgyz and Swiss patients with hospitalization for AHF treatment shows that 1 year ACM or the combined endpoint of 1 year ACM or HHF were not different when adjusted for age and LVEF. This suggests that application of ESC guidelines has the potential to outperform ethnic disparity.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariable analysis showing associations of parameters with 1-year all-cause mortality for all study participants.
Table S2. Baseline characteristics and outcomes of Central Asian AHF patients with hospitalisation separated by LVEF <50% and LVEF ≥50%.
Table S3. Echocardiographic parameters of Central Asian AHF patients with hospitalisation separated by LVEF <50% and LVEF ≥50%.
Table S4. Prescription of medical treatment of Central Asian AHF patients during hospitalisation separated by LVEF <50% and LVEF ≥50%.
Table S5. Baseline characteristics and outcomes of Western European AHF patients with hospitalisation separated by LVEF <50% and LVEF ≥50%.
Table S6. Echocardiographic parameters of Western European AHF patients with hospitalization separated by LVEF <50% and LVEF ≥50%.
Table S7. Prescription of medical treatment of Western European patients during hospitalisation separated by LVEF <50% and LVEF ≥50%.
Figure S1. Distribution of age and sex in the Kyrgyz and Swiss study population.
Figure S2. Unadjusted Kaplan–Meier survival estimates of 1-year all-cause mortality as a function of LVEF for Kyrgyzstan and Switzerland patients hospitalised for treatment of AHF.

References

1. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: A systematic review and meta-analysis. *Eur J Heart Fail* 2019;**21**:1306-1325. doi:10.1002/ejhf.1594
2. Tromp J, Bamadhaj S, Cleland JGF, Angermann CE, Dahlstrom U, Ouwerkerk W, *et al*. Post-discharge prognosis of patients admitted to hospital for heart failure by world region, and a national level of income disparity (REPORT-HF): A cohort study. *Lancet Glob Health* 2020;**8**:e411-e422. doi:10.1016/S2214-109X(20)30004-8
3. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, *et al*. EuroHeart Failure Survey II (EHFS II): A survey on hospitalized acute heart failure patients: Description of population. *Eur Heart J* 2006;**27**:2725-2736. doi:10.1093/eurheartj/ehl193
4. Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, *et al*. Congestion in heart failure: A contemporary look at physiology, diagnosis and treatment. *Nat Rev Cardiol* 2020;**17**:641-655. doi:10.1038/s41569-020-0379-7
5. Njoroge JN, Teerlink JR. Pathophysiology and therapeutic approaches to acute decompensated heart failure. *Circ Res* 2021;**128**:1468-1486. doi:10.1161/CIRCRESAHA.121.318186
6. Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC Jr, *et al*. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol* 2008;**52**:1640-1648. doi:10.1016/j.jacc.2008.07.056
7. Follath F, Yilmaz MB, Delgado JF, Parissis JT, Porcher R, Gayat E, *et al*. Clinical presentation, management, and outcomes in the acute heart failure global survey of standard treatment (ALARM-HF). *Intensive Care Med* 2008;**52**:1640-1648. doi:10.1007/s00134-010-2113-0
8. MacDonald MR, Tay WT, Teng TK, Anand I, Ling LH, Yap J, *et al*. Regional variation of mortality in heart failure with reduced and preserved ejection fraction across Asia: Outcomes in the ASIAN-HF registry. *J Am Heart Assoc* 2020;**9**:e012199. doi:10.1161/JAHA.119.012199
9. www.escardio.org. Guidelines and National Cardiac Societies. Accessed 2.02.2023.
10. www.swisscardio.ch. Accessed 2.02.2023
11. Garnier A, Rouiller N, Gachoud D, Nachar C, Voirol P, Griesser AC, *et al*. Effectiveness of a transition plan at discharge of patients hospitalized with heart failure: A before-and-after study. *ESC Heart Fail*. 2018;**5**:657-667. doi:10.1002/ehf2.12295
12. Hullin R, Tzimas G, Barras N, Abdurashidova T, Soborun N, Aur S, *et al*. Decongestion improving right heart function ameliorates prognosis after an acute heart failure episode. *ESC Heart Fail* 2020;**7**:3901-3909. doi:10.1002/ehf2.12983
13. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2022;**24**:4-131. doi:10.1002/ejhf.2333
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233-270. doi:10.1093/ehjci/jev014
15. Pocock SJ, Ariti CA, McMurray JJV, Maggioni A, Kober L, Sqire IB, *et al*. Predicting survival in heart failure: A risk score based on 39372 patients from 30 studies. *Eur Heart J* 2013;**34**:1404-1413. doi:10.1093/eurheartj/ehs337

16. Martinez-Amezcua P, Haque W, Khera R, Kanaya AM, Sattar N, Lam CSP, *et al*. The upcoming epidemic of heart failure in South Asia. *Circ Heart Fail Circ Heart Fail* 2020;**13**:e007218. doi:10.1161/CIRCHEARTFAILURE.120.007218
17. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015;**17**:884-892. doi:10.1002/ejhf.319
18. Seferovic PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, *et al*. The Heart Failure Association Atlas: Heart failure epidemiology and management statistics 2019. *Eur J Heart Fail* 2021;**23**:906-914. doi:10.1002/ejhf.2143
19. Guo Y, Lip GY, Banerjee A. Heart failure in East Asia. *Curr Cardiol Rev* 2013;**9**:112-122. doi:10.2174/1573403x11309020004
20. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, *et al*. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2018;**20**:1505-1535. doi:10.1002/ejhf.1236
21. Ouwerkerk W, Tromp J, Cleland JGF, Angermann CE, Dahlström U, Ertl G, *et al*. Association of time-to-intravenous furosemide with mortality in acute heart failure: Data from REPORT-HF. *Eur J Heart Fail* 2023;**25**:43-51. doi:10.1002/ejhf.2708
22. Ntsui NAB, Sliva K. Impact of racial and ethnic disparities on patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2021;**78**:2580-2588. doi:10.1016/j.jacc.2021.10.021
23. Nicholls M. The 2014 ESC Guidelines on the diagnosis and management of hypertrophic cardiomyopathy have been published. *Eur Heart J* 2014;**35**:2849-2850. doi:10.1093/eurheartj/ehu375
24. Yaku H, Ozasa N, Morimoto T, Inuzuka Y, Tamaki Y, Yamamoto E, *et al*. Demographics, management, and in-hospital outcome of hospitalized acute heart failure syndrome patients in contemporary real clinical practice in Japan—Observations from the prospective, multicenter Kyoto Congestive Heart Failure (KCHF) registry. *Circ J* 2018;**82**:2811-2819. doi:10.1253/circj.CJ-17-1386
25. Savarese G, Kishi T, Vardeny O, Adamsson Eryd S, Bodegård J, Lund LH, *et al*. Heart failure drug treatment—Inertia, titration, and discontinuation: A multinational observational study (EVOLUTION HF). *JACC Heart Fail* 2023;**11**:1-14. doi:10.1016/j.jchf.2022.08.009
26. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, *et al*. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol* 2017;**70**:2476-2486. doi:10.1016/j.jacc.2017.08.074
27. Gayat E, Arrigo M, Littnerova S, Sato N, Parenica J, Ishihara S, *et al*. Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: A propensity-score matched study. *Eur J Heart Fail* 2018;**20**:345-354. doi:10.1002/ejhf.932
28. Yaku H, Kato T, Morimoto T, Inuzuka Y, Tamaki Y, Ozasa N, *et al*. Association of mineralocorticoid receptor antagonist use with all-cause mortality and hospital readmission in older heart failure adults with acute decompensated heart failure. *JAMA Netw Open* 2019;**2**:e195892. doi:10.1001/jamanetworkopen
29. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, *et al*. The global health and economic burden of hospitalisations for heart failure: Lessons learned from hospitalised heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123-1133. doi:10.1016/j.jacc.2013.11.053
30. Soborun N, Müller M, Abdurashidova T, Tzimas G, Schukraft S, Lu H, *et al*. Already low drug dose antagonism of the renin-angiotensin aldosterone system decreases 1-year mortality and rehospitalization in old heart failure patients. *Biomed Pharmacother* 2022;**154**:113615. doi:10.1016/j.biopha.2022.113615