Multimorbidity in patients with acute heart failure across world regions and country income levels (REPORT-HF): a prospective, multicentre, global cohort study

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Summary

Background Multimorbidity (two or more comorbidities) is common among patients with acute heart failure, but comprehensive global information on its prevalence and clinical consequences across different world regions and income levels is scarce. This study aimed to investigate the prevalence of multimorbidity and its effect on pharmacotherapy and prognosis in participants of the REPORT-HF study.

Methods REPORT-HF was a prospective, multicentre, global cohort study that enrolled adults (aged ≥18 years) admitted to hospital with a primary diagnosis of acute heart failure from 358 hospitals in 44 countries on six continents. Patients who currently or recently participated in a clinical treatment trial were excluded. Follow-up data were collected at 1-year post-discharge. The primary outcome was 1-year post-discharge mortality. All patients in the REPORT-HF cohort with full data on comorbidities were eligible for the present study. We stratified patients according to the number of comorbidities, and countries by world region and country income level. We used one-way ANOVA, χ^2 test, or Mann-Whitney *U* test for comparisons between groups, as applicable, and Cox regression to analyse the association between multimorbidity and 1-year mortality.

Findings Between July 23, 2014, and March 24, 2017, 18 553 patients were included in the REPORT-HF study. Of these, 18 528 patients had full data on comorbidities, of whom 11 360 (61%) were men and 7168 (39%) were women. Prevalence rates of multimorbidity were lowest in southeast Asia (72%) and highest in North America (92%). Fewer patients from lower-middle-income countries had multimorbidity than patients from high-income countries (73% *vs* 85%, p<0·0001). With increasing comorbidity burden, patients received fewer guideline-directed heart failure medications, yet more drugs potentially causing or worsening heart failure. Having more comorbidities was associated with worse outcomes: 1-year mortality increased from 13% (no comorbidities) to 26% (five or more comorbidities). This finding was independent of common baseline risk factors, including age and sex. The population-attributable fraction of multimorbidity for mortality was higher in high-income countries than in upper-middle-income or lower-middle-income countries (for patients with five or more comorbidities: 61% *vs* 27% and 31%, respectively).

Interpretation Multimorbidity is highly prevalent among patients with acute heart failure across world regions, especially in high-income countries, and is associated with higher mortality, less prescription of guideline-directed heart failure pharmacotherapy, and increased use of potentially harmful medications.

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Introduction

Multimorbidity (two or more comorbidities) is common in patients with heart failure.[1–6] The reported prevalence of multimorbidity in patients with heart failure ranges between 43%[1] and 98%[6] and varies among geographical regions.[1,6,7] Multimorbidity complicates guideline-directed pharmacological treatment and worsens prognosis.[1,3,4,8,9] Additionally, comorbidities in heart failure are important drivers of poor health-related quality of life[10] and hospitalisations.[8] Previous reports on the effect of multimorbidity in heart failure included a limited number of countries, predominantly from western Europe,[2,3,6] Asia,[7] and North America[5,8] or were based on populations participating in clinical trials, in which patients with comorbidities such as (severe) renal failure or cancer are commonly excluded.[4,11] Patients with heart failure from lower-income regions report fewer comorbidities, but are at higher risk of mortality than patients from higher-income regions.[9] This finding suggests regional differences in medical surveillance or the prognostic impact of multimorbidity. Contemporaneous representative data on multimorbidity from a global heart failure population, which are needed to quantify international differences, are scarce.

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Research in context

Evidence before this study

We initially performed a systematic MEDLINE and Embase search for English, German, and Dutch language articles on the prognostic effect of multimorbidity in patients with heart failure across world regions published between Jan 1, 1990, and Dec 31, 2020. We later extended the search to articles published until Dec 31, 2022. The search terms used were ("multimorbidity" OR "comorbidity") AND "heart failure" AND ("global" OR "international" OR "worldwide" OR "multinational") AND ("outcomes" OR "mortality" OR "prognosis"). This search did not identify any global cohort study assessing prevalence and effect of multimorbidity in patients with heart failure across several world regions or different country income levels. The identified studies on multimorbidity in patients with heart failure were derived from nation-wide or region-wide registries such as The Epidemiology of Chronic Diseases and Multimorbidity, Asian Sudden Cardiac Death in Heart Failure, or the European Heart Failure Pilot Survey, which report data on the prevalence of multimorbidity in heart failure in Spain and across regions in Asia and Europe, respectively, or from international clinical trials, which only provide data limited to trial-specific inclusion criteria, often excluding important comorbidities such as (severe) renal failure. We identified no studies that reported comparable data on multimorbidity in heart failure from Latin America, the Eastern Mediterranean, and Africa.

Added value of this study

Our study adds to published registries by providing data on numerous comorbidities across 44 countries from six continents and is the first study to highlight the effect of multimorbidity on pharmacotherapy across different regions and country income levels. Our data expand on previous studies by showing a strong association between comorbidity burden and mortality risk revealing, for the first time, that (1) this association is stronger in high-income than in lower-income regions, despite a higher absolute mortality risk in lower-income regions, (2) the population attributable fraction of multimorbidity for mortality is higher in high-income than in lower-income regions, (3) the prognostic effect of multimorbidity varies between different combinations of comorbidities, and (4) multimorbidity negatively affects the quality of heart failure pharmacotherapy.

Implications of all the available evidence

The high prevalence and prognostic relevance of multimorbidity in patients with heart failure across world regions underlines the systemic nature of the heart failure syndrome and highlights that treatment of comorbidities warrants attention in the management of patients with heart failure. The observed underuse and underdosing of guideline-directed medical therapies in patients with multimorbidity with heart failure, particularly in lower-income countries, as well as higher prescription rates of medications that can cause or worsen heart failure, suggests that optimising pharmacotherapy by a multidisciplinary care team is a promising avenue to improve outcomes.

Furthermore, the effect of multimorbidity on heart failure treatment and non-heart failure related therapies for comorbidities have not been systematically evaluated.

Therefore, this analysis aimed to assess prevalence, prognostic effect, and implications for treatment of multimorbidity across world regions in the global prospective Registry to Assess Medical Practice and Longitudinal Observation for Treatment of Heart Failure (REPORT-HF) cohort study.[12]

Methods

Study design

The REPORT-HF study design and methods have been previously published.[12] Briefly, REPORT-HF was a prospective, multicentre, global cohort study that enrolled patients admitted to hospital with a primary diagnosis of acute heart failure. 18 553 patients were included between July 23, 2014, and March 24, 2017, across 358 hospitals from 44 countries on six continents using a common protocol.[12] The number of patients recruited per region or country has been published previously.[13] The study was conducted in accordance with the Declaration of Helsinki, and the protocol received institutional review board or ethics committee approval at each centre.

Participants

Our analysis included patients with full data on comorbidities available. Adult patients (aged ≥18 years) hospitalised with a primary diagnosis of decompensated chronic heart failure or new-onset acute heart failure were eligible and only excluded if they currently or recently participated in a clinical treatment trial.[12] Heart failure with reduced ejection fraction (HfrEF) was defined as a left ventricular ejection fraction of less than 40%, heart failure with mildly reduced ejection fraction (HfmrEF) was defined as a left ventricular ejection fraction of 40–49%, and heart failure with preserved ejection fraction (HfpEF) was defined as a left ventricular ejection fraction of 50% or more. Patients were only enrolled if they or their designated surrogate medical decision maker had provided written informed consent.

Procedures

Data collected during the index hospitalisation included patient demographics, clinical signs and symptoms including New York Heart Association functional class, vital signs, physical examination findings, laboratory test values, in-hospital mortality, ejection fraction assessment, medical history, and discharge medications. Using the

same case report form at all 358 sites, data were captured prospectively in a central electronic database. Sex was recorded based on clinical records or as reported by the patient. All information was reviewed by central data management, and uncertainties solved by local study monitors. Patient treatment was left to the discretion of the attending physician, but sites were encouraged to adhere to current guideline recommendations of the location.

The 44 participating countries were stratified according to a modified WHO classification into seven regions and by country income level into lower-middle-income, upper-middle-income, and high-income countries as previously reported.[13] Comorbidities were identified at enrolment by medical history, unless stated otherwise. Valvular heart disease was defined as a positive history of valve disease or valvular surgery. Patients diagnosed with coronary artery disease had a self-reported history of myocardial infarction or other chronic coronary artery disease, previous coronary artery bypass grafting or percutaneous coronary intervention, or an acute myocardial infarction as the primary precipitant of the current hospitalisation. Anaemia was defined as a history of anaemia or haemoglobin concentrations of less than 13 g/dL (men) or of less than 12 g/dL (women) during the index hospitalisation. The selection of comorbidities included in this analysis was based on data availability.

Guideline-directed medical therapy (GDMT) for heart failure was defined based on recommendations from the European Society of Cardiology (2016) and the American College of Cardiology, American Heart Association (AHA), and Heart Failure Society of America (2017).[14,15] GDMT use was only assessed in patients with HfrEF, for whom a class IA recommendation exists. Medications potentially causing or worsening heart failure were defined according to a 2016 AHA scientific statement[16] and their use was assessed in all patients in the study. These medications were stratified based on the quality of available evidence for their harmful effect: level of evidence A (multiple randomised trials or multiple populations through meta-analyses), B (non-randomised studies or only one randomised trial), and C (expert opinions, case studies, or standard of care).[16] For this analysis, only medications classified as harmful with levels of evidence A or B were considered.

Outcomes

Follow-up data were collected at 6 months and 12 months post-discharge via telephone interviews as pre-specified,[12] unless a regular follow-up visit was planned. At each data collection point, information on vital status was obtained. Vital status was assessed by telephone interviews and by national reporting databases where available.

Statistical analysis

Patients were grouped according to the number of comorbidities recorded at hospitalisation. Cardiovascular comorbidities included hypertension, coronary artery disease, atrial fibrillation or atrial flutter, and valvular heart disease. Non-cardiovascular comorbidities included anaemia, diabetes, renal failure, chronic obstructive pulmonary disease (COPD) or asthma, sleep apnoea, peripheral arterial disease, liver disease, cancer, thyroid dysfunction, stroke or transient ischaemic attack, other neurological conditions, and psychiatric conditions. Differences in demographics, medical history, and medication use were reported for subgroups by number of comorbidities. For outcome analyses, patients were grouped by the recorded number of comorbidities, considering both all comorbidities (cardiovascular and non-cardiovascular) or only non-cardiovascular comorbidities. This approach was taken because it can be difficult to distinguish if cardiovascular comorbidities are true comorbidities or the cause of heart failure. For analyses stratified by ejection fraction, patients were further grouped into a HfrEF (ejection fraction <40%) and a HfmrEF or HfpEF group (40–49% or ≥50%). For comparisons between groups, one-way ANOVA (for parametric continuous variables), χ^2 test (for categorical variables), or Mann-Whitney *U* test (for non-parametric continuous variables) was used as applicable. Specifically, the χ^2 test was used to compare absolute 1-year mortality risk in patients with different numbers of comorbidities across country income levels. We used an extension of the Wilcoxon rank-sum test for linear trend to investigate possible trends in variables across multimorbidity categories, and Cox regression analyses to investigate the association between multimorbidity and outcome. The proportionality of hazards assumption was checked using statistical tests and graphical diagnostics based on the Schoenfeld residuals. To estimate and correct for baseline risk in multivariable analyses, we corrected for variables included in the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score.[17] The variables include age, sex, left ventricular ejection fraction subgroup (HfrEF, HfmrEF, HfpEF, or unknown), systolic blood pressure, BMI, creatinine, New York Heart Association class, current smoker, diabetes, COPD, time since diagnosis of heart failure, discharge β-blocker use, and angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or angiotensin receptor-neprilysin inhibitor use upon discharge. For Cox regression analysis, we imputed the variables individually in five imputation sets. Cox regression analyses were performed on the five imputation sets separately, and estimates were pooled using Rubin's rule. We accounted for clustering effects at the site level by including cluster-robust standard errors in the Cox regression analysis. We used the punafcc package in Stata to estimate the population attributable fraction, correcting for the imputed MAGGIC risk score. Because the punafcc package does not work with the mi set command, we imputed the

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	0 (n=995)	1 (n=2404)	2 (n=3441)	3 (n=3923)	4 (n=3316)	≥5 (n=4449)
Age, years	54 (44–65)	60 (49–70)	64 (54–74)	67 (58–77)	70 (61–79)	73 (64–80)
Sex	..	..	..	..	..	..
Female	395 (30%)	828 (24%)	1273 (37%)	1530 (39%)	1410 (43%)	1826 (41%)
Male	694 (70%)	1576 (66%)	2168 (63%)	2393 (61%)	1906 (57%)	2623 (59%)
Predominant race	..	..	..	..	..	..
White	365 (37%)	869 (36%)	1434 (42%)	1979 (50%)	1918 (58%)	3077 (69%)
Black	18 (2%)	83 (3%)	122 (4%)	169 (4%)	167 (5%)	307 (7%)
Asian	482 (48%)	1102 (46%)	1412 (41%)	1263 (32%)	831 (25%)	642 (14%)
Native American	20 (2%)	69 (3%)	91 (3%)	94 (2%)	56 (2%)	45 (1%)
Pacific Islander	1 (<1%)	0	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Other	109 (11%)	281 (12%)	381 (11%)	417 (11%)	342 (10%)	376 (8%)
New onset heart failure	617 (62%)	1427 (59%)	1786 (52%)	1786 (46%)	1231 (37%)	1042 (23%)
NYHA class at discharge*	..	..	..	..	..	..
Class I	138/975 (14%)	390/2340 (17%)	458/3374 (14%)	488/3838 (13%)	327/3243 (10%)	221/4309 (5%)
Class II	327/975 (34%)	812/2340 (35%)	1211/3374 (36%)	1310/3838 (34%)	968/3243 (30%)	1118/4309 (26%)
Class III	119/975 (12%)	291/2340 (12%)	494/3374 (15%)	627/3838 (16%)	584/3243 (18%)	871/4309 (20%)
Class IV	34/975 (3%)	62/234 (3%)	94/3374 (3%)	127/3838 (3%)	125/3243 (4%)	182/4309 (4%)
Class missing or unknown	356/975 (37%)	785/2340 (34%)	1117/3374 (33%)	1286/3838 (34%)	1239/3243 (38%)	1917/4309 (44%)
LVEF category	..	..	..	..	..	..
<40	672 (68%)	1427 (59%)	1717 (50%)	1805 (46%)	1447 (44%)	1825 (41%)
≥40 and <50	80 (8%)	292 (12%)	518 (15%)	624 (16%)	552 (17%)	803 (18%)
≥50	133 (13%)	444 (18%)	853 (25%)	1126 (29%)	1055 (32%)	1548 (35%)
Unknown	110 (11%)	241 (10%)	353 (10%)	368 (9%)	262 (8%)	273 (6%)
Vital signs at admission						
Heart rate, bpm	93 (78–110)	90 (77–107)	90 (75–105)	86 (74–101)	85 (73–100)	81 (70–98)
Systolic blood pressure, mm Hg	120 (105–138)	126 (110–145)	130 (110–150)	130 (111–150)	132 (117–150)	132 (116–152)
Diastolic blood pressure, mm Hg	78 (68–89)	80 (70–90)	80 (70–90)	80 (70–90)	80 (70–90)	76 (65–88)
Signs and symptoms at admission†						
Dyspnoea at rest	700/874 (80%)	1762/2138 (82%)	2546/3064 (83%)	2928/3511 (83%)	2457/2933 (83%)	3202/3870 (83%)
Orthopnoea	575/797 (72%)	1412/1931 (73%)	2161/2802 (77%)	2491/3184 (78%)	2109/2670 (79%)	2868/3530 (81%)
Peripheral oedema	473/826 (57%)	1233/2054 (60%)	1915/3054 (63%)	2401/3550 (68%)	2221/2999 (74%)	3151/4068 (77%)
Pulmonary rales	445/761 (58%)	1205/1889 (64%)	1910/2842 (67%)	2314/3290 (70%)	1961/2768 (71%)	2441/3686 (66%)
Comorbidities						
Hypertension	0	640 (27%)	1781 (52%)	2755 (70%)	2698 (81%)	3931 (88%)
Valvular heart disease	0	179 (7%)	424 (12%)	676 (17%)	721 (22%)	1678 (38%)
Atrial fibrillation or atrial flutter	0	222 (9%)	651 (19%)	1102 (28%)	1262 (38%)	2528 (57%)
Coronary artery disease	0	520 (22%)	1321 (38%)	1974 (50%)	1995 (60%)	3116 (70%)
Peripheral arterial disease	0	2 (<1%)	31 (1%)	67 (2%)	146 (4%)	644 (14%)
COPD or asthma	0	90 (4%)	256 (7%)	444 (11%)	536 (16%)	1329 (30%)
Sleep apnoea	0	12 (<1%)	34 (1%)	59 (2%)	98 (3%)	441 (10%)
Anaemia	0	405 (17%)	1046 (30%)	1853 (47%)	2023 (61%)	3395 (76%)
Diabetes	0	172 (7%)	776 (23%)	1563 (40%)	1728 (52%)	2826 (64%)
Chronic kidney disease	0	26 (1%)	147 (4%)	456 (12%)	858 (26%)	2278 (51%)
Liver disease	0	17 (1%)	50 (1%)	70 (2%)	97 (3%)	333 (7%)
Cancer	0	32 (1%)	85 (2%)	132 (3%)	159 (5%)	590 (13%)
Thyroid dysfunction	0	35 (1%)	132 (4%)	225 (6%)	329 (10%)	865 (19%)
Neurological conditions	0	17 (1%)	30 (1%)	87 (2%)	118 (4%)	515 (12%)
Stroke or TIA	0	9 (<1%)	54 (2%)	147 (4%)	273 (8%)	803 (18%)
Psychiatric conditions	0	18 (1%)	34 (1%)	58 (1%)	81 (2%)	294 (7%)

Data are n (%), median IQR, or n/N (%). All variables are statistically significant (p<0·0001) apart from dyspnoea at rest (p=0·18). bpm=beats per minute. COPD=chronic obstructive pulmonary disease. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association. TIA=transient ischaemic attack. *Patients who died in hospital were not included in the denominator. †Patients without signs and symptoms reported were not included in the denominator.

Table: **Patient characteristics according to number of comorbidities**

MAGGIC risk score per patient using the multivariate imputation by chained equations package in R.[18] The risk score was calculated for five imputation sets per patient and subsequently averaged over five imputation sets. To estimate the association between different comorbidity combinations and 1-year all cause death, we grouped patients according to commonly occurring combinations (ie, groups with at least 100 patients). We fitted a Cox regression model with the variable of the different groups and corrected for age, sex, and medication use. We tested for non-proportional hazards using the cox.zph function from the survival package in R. All analyses were performed in Stata version 16.0 or R version 3.4.2. A two-sided p<0·05 was considered statistically significant.

Role of the funding source

The funder of the study had no role in study design, conduct of the study, data collection, data management, data analysis, data interpretation or preparation, review, or approval of the manuscript.

Results

Between July 23, 2014, and March 24, 2017, 18 553 patients were included in the REPORT-HF study with acute heart failure on hospital admission at 358 sites in 44 countries; of these, 18 528 patients had full data on comorbidities (11 360 [61%] were men and 7168 [39%] were women) and were included in the analysis. Of these patients, 15 129 (82%; 9090 [60%] were men and 6039 [40%] were women) had two or more comorbidities and 4449 (24%; 2623 [59%] were men and 1826 [41%] were women) had five or more comorbidities (table). The median number of comorbidities was higher in North America, eastern Europe, and western Europe and lowest in southeast Asia and central or South America (figure 1 A–B; appendix 8 p 3–5 for baseline characteristics of participants by world region). The prevalence of multimorbidity (two or more comorbidities) was lowest in southeast Asia (72%) and highest in North America (92%; figure 1B). The proportion of patients with fewer than two comorbidities was higher in lower-middle-income and upper-middle-income countries than in high-income countries,

See Online for appendix 8

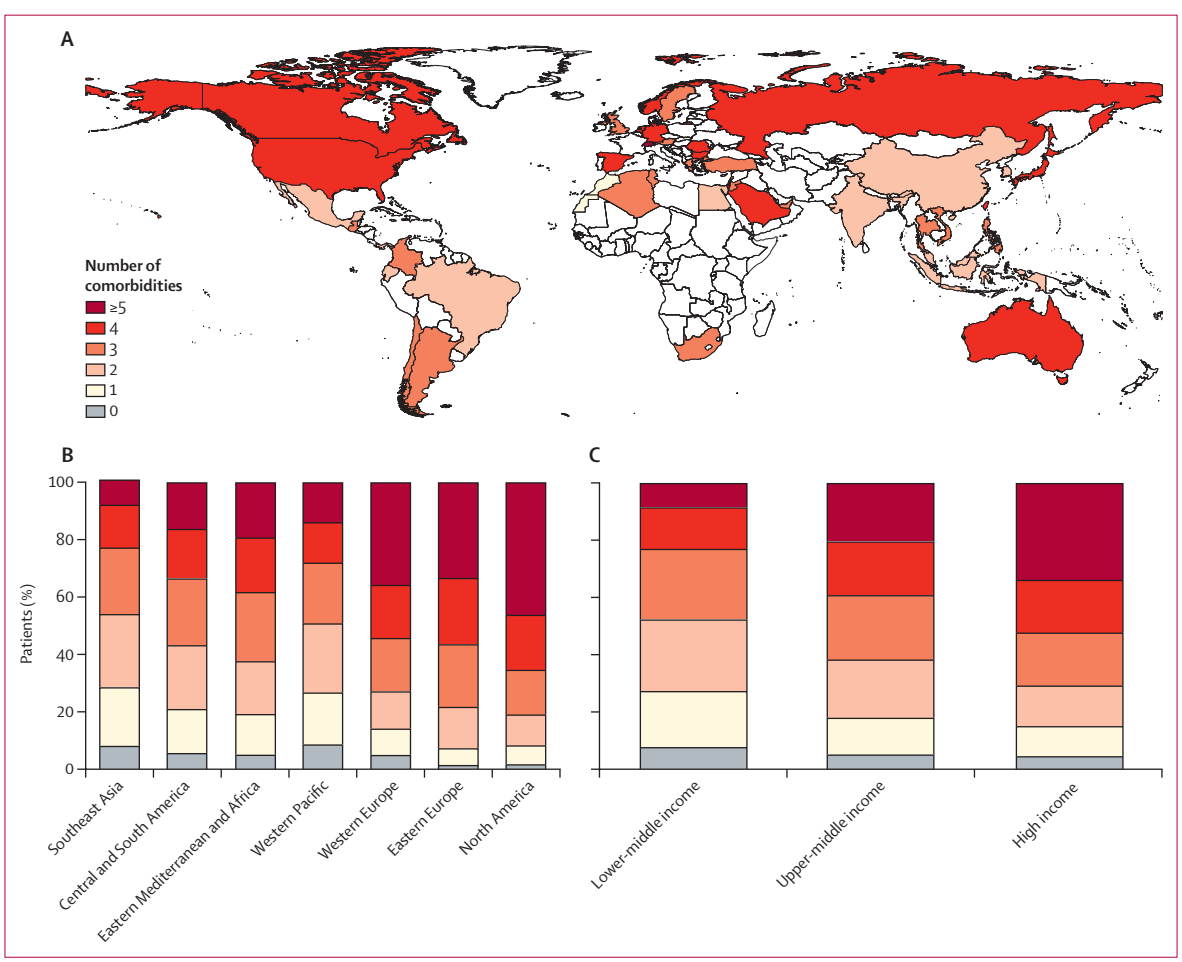

Figure 1: **Global prevalence of multimorbidity by world region and country income level**
(A) World map showing the median number of comorbidities per country. White indicates countries that were not part of the registry. (B) Comorbidity burden per world region. (C) Comorbidity burden per country income level.

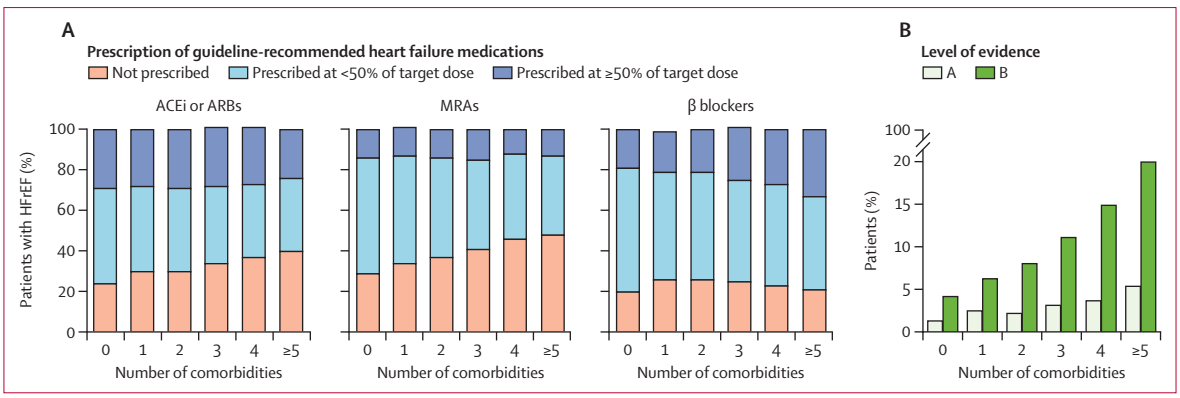

Figure 2: **Prescription rates of heart failure medications and potentially harmful drugs by comorbidity burden at hospital discharge**
(A) Differences in the prescription of guideline-recommended heart failure medications at hospital discharge in patients with HFrEF according to the number of comorbidities. (B) Prescription of medications that can cause or worsen heart failure according to number of comorbidities in all patients in the registry. ACEi=angiotensin-converting enzyme inhibitor. ARBs=angiotensin receptor blockers. HFrEF=heart failure with reduced ejection fraction. MRAs=mineralocorticoid receptor antagonists.

meaning that fewer patients from lower-middle-income countries had multimorbidity than patients from high-income countries (73% *vs* 85%, p<0·0001; figure 1C). Differences between regions remained significant when correcting for age and sex (appendix 8 p 6).

With an increasing number of comorbidities, patients were older, more likely to have presented with decompensated chronic heart failure than with new-onset heart failure, had a higher New York Heart Association class (ie, worse symptoms) at discharge, and had HfpEF more often (table).

Patients with HfrEF with a higher number of comorbidities were less likely to receive GDMT for heart failure at discharge, including ACEi, ARBs, and mineralocorticoid receptor antagonists (MRAs; p_{trend}<0·0001 for all; figure 2A). The fraction of patients receiving β blockers at hospital discharge was similar across patients with different numbers of comorbidities (figure 2A). The association between number of comorbidities and use of GDMT was consistent, when considering only non-cardiovascular comorbidities (appendix 8 p 12), and was observed across different country income levels (appendix 8 p 11). However, overall, a higher fraction of patients was on GDMT in higher-income than in lower-income countries (appendix 8 p 11). With an increasing number of comorbidities, the use of potentially heart failure-worsening medication was more common (p_{trend}<0·0001; figure 2B) at all income levels (appendix 8 p 13). The most commonly used potentially harmful drugs were antidiabetic, antihypertensive, and pulmonary medications (appendix 8 pp 7–8).

At 1-year follow-up, 3457 (19·6%) of 17 608 patients had died and 470 (2·5%) patients were lost to follow-up. The regional percentages for loss to follow-up are in appendix 8 (p 9).

Patients with more comorbidities were at a higher mortality risk with 1-year mortality increasing from 13% in patients without comorbidities to 26% in patients with five or more comorbidities (figure 3 A–B). This finding was consistent after correction for all baseline risk factors captured by the MAGGIC risk score, including age and sex. Having three or more comorbidities significantly increased all-cause mortality in a multivariable model adjusting for variables included in the MAGGIC risk score (figure 3B). Obesity as a comorbidity was captured in only 19 146 (49·4%) patients. Sensitivity analyses including obesity in the model did not change the observed association between comorbidity burden and mortality risk (appendix 8 p 10). The association between the number of comorbidities and mortality was independent of left ventricular ejection fraction ($p_{interaction}$=0·32). The absolute 1-year mortality risk by number of comorbidities and country income level in patients with HfpEF or HfmrEF and patients with HfrEF is in appendix 8 (p 14). Comparing the absolute 1-year mortality risk in patients with different numbers of comorbidities across country income levels indicated a stronger association between multimorbidity and mortality in high-income than in lower-income regions (p<0·0001), but patients from lower-middle-income countries had a higher absolute mortality risk (figure 3C). The estimated population attributable fraction for 1-year all-cause mortality related to number of comorbidities increased as the number of comorbidities increased, particularly in high-income countries, and was greater in high-income than in lower-income countries: the fraction of 1-year all-cause mortality risk in patients with acute heart failure explained by the presence of five or more comorbidities was 61% in high-income countries, but only 27% in upper-middle-income countries, and 31% in lower-middle-income countries (figure 3D).

When considering non-cardiovascular comorbidities only, the association between comorbidity burden and mortality was similar: having one or more non-cardiovascular comorbidities was associated with a significantly higher 1-year mortality risk and there was a stronger association between the number of non-cardiovascular comorbidities and mortality risk in

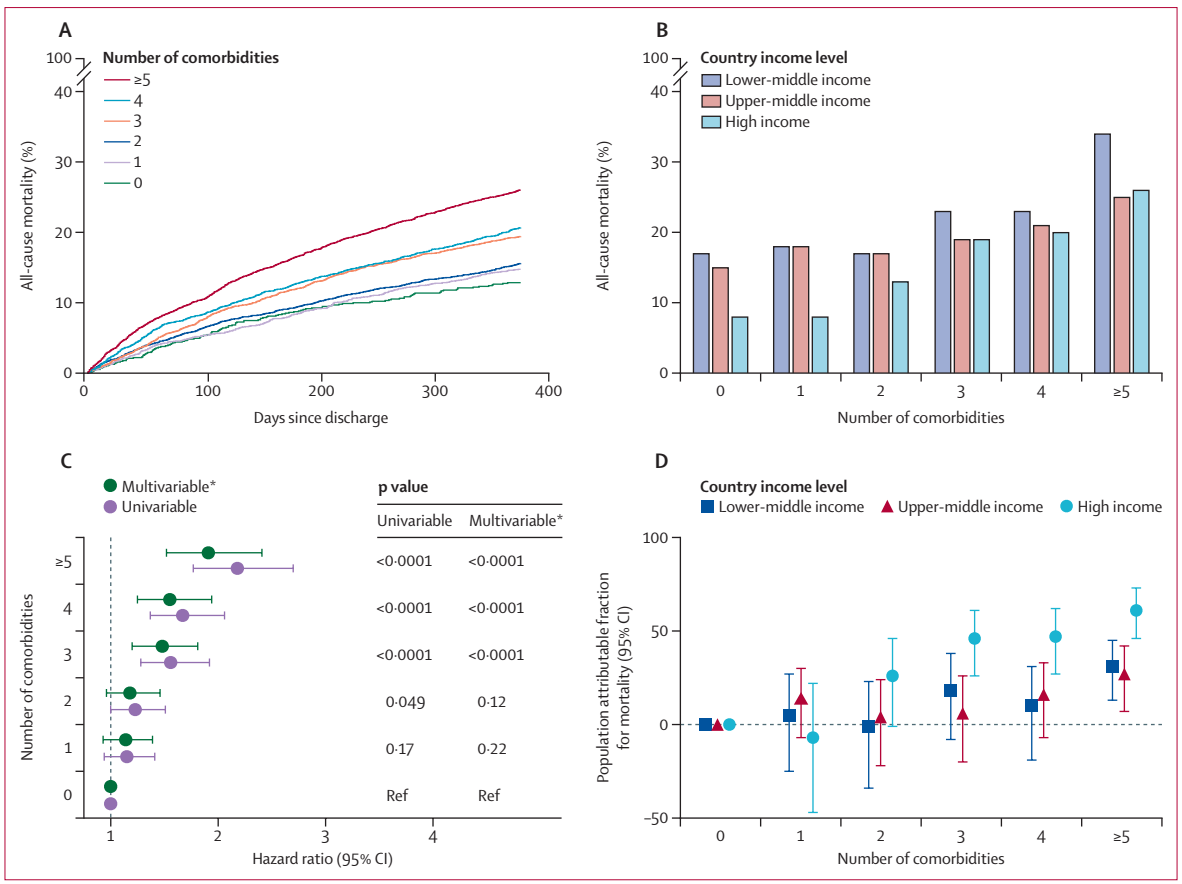

Figure 3: **All-cause 1-year mortality risk according to comorbidity burden and country income levels and population attributable fraction for mortality by number of comorbidities and country income levels**

(A) Kaplan-Meier curves showing global 1-year all-cause mortality stratified by number of comorbidities. (B) Univariable and multivariable analysis of all-cause mortality risk according to number of comorbidities. The reference (Ref) is no comorbidity. (C) Absolute 1-year all-cause mortality risk by number of comorbidities and country income levels (unadjusted analysis). (D) Population attributable fractions for 1-year all-cause mortality by number of comorbidities and country income levels in percent. *Adjusted for the variables included in the MAGGIC risk model.[17]

high-income than in lower-income countries (appendix 8 p 15). Strikingly, in patients with three or more non-cardiovascular comorbidities, the comorbidity-population attributable fraction was more than two-fold higher in high-income than in lower-income countries (in patients with three non-cardiovascular comorbidities: 20% [95% CI 13–26] in lower-middle-income, 17% [11–22] in upper-middle-income, and 42% [34–48] in higher-income countries), driven by the higher fraction of patients with three or more non-cardiovascular comorbidities in high-income countries (appendix 8 p 15).

Hazard ratios for 1-year mortality for specific combinations of comorbidities that were present in more than 100 patients are shown in figure 4. If two comorbidities were present, the combination of anaemia with either coronary artery disease or valvular heart disease was associated with increased risk, compared with having no comorbidities. The most adverse combinations of three comorbidities were anaemia and coronary artery disease with either hypertension or diabetes. Conversely, 1-year mortality tended to be lower in patients with hypertension and either coronary artery disease, atrial fibrillation, or diabetes, although this association did not reach significance.

Discussion

We report four main findings. First, multimorbidity was highly prevalent in this global population hospitalised for acute heart failure, and there were important regional differences. North America, western Europe, and eastern Europe had the highest prevalence of multimorbidity, and southeast Asia and the western Pacific had the lowest prevalence of multimorbidity. Second, patients with multimorbidity received less GDMT and were prescribed more medications potentially causing or worsening heart failure at hospital discharge. Third, multimorbidity was strongly associated with increased 1-year all-cause mortality risk with different combinations of comorbidities conferring differential mortality risks. Fourth, the multimorbidity-associated population attributable risk for mortality was greater in high-income than in lower-income countries.

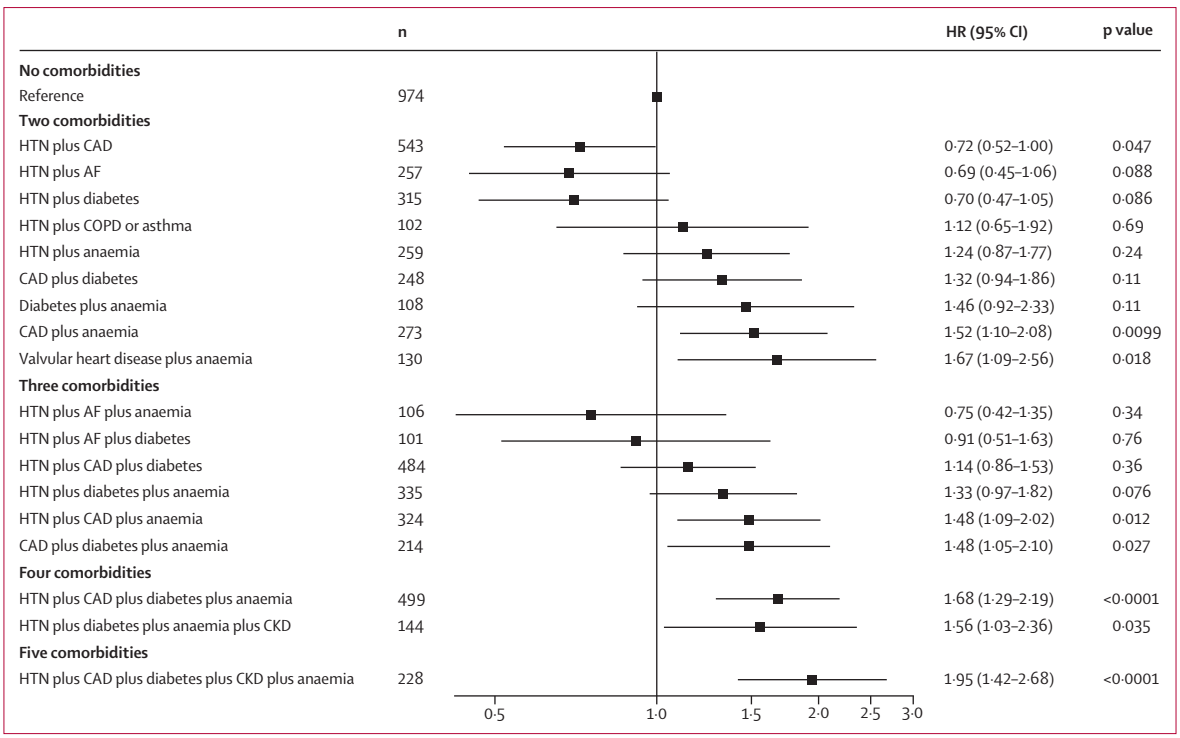

Figure 4: **12-month mortality risk for specific combinations of comorbidities present in more than 100 study participants**
HRs are adjusted for age, sex, and discharge medication. AF=atrial fibrillation. CAD=coronary artery disease. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. HR=hazard ratio. HTN=hypertension.

The high prevalence of multimorbidity in REPORT-HF participants is consistent with that in other published heart failure registries, although reported multimorbidity prevalence rates differ widely between studies. The European Heart Failure Pilot Survey showed that 74% of patients with chronic heart failure had at least one comorbidity, and 43% of patients had more than two, and that the prevalence of comorbidities differed per geographical region in Europe.[1] The Epidemiology of Chronic Diseases and Multimorbidity (EpiChron) Cohort,[6] a national heart failure registry in Spain, reported a much higher prevalence of multimorbidity (98%). However, in EpiChron, heart failure was counted as one of at least two chronic diagnoses defining multimorbidity,[6] and thus a wider range of patients were classified as multimorbid, in contrast to our definition of multimorbidity (heart failure plus at least two comorbidities). In REPORT-HF, over 80% of western European patients had multimorbidity, similar to previous studies.[1,11] The Cardiovascular Research Network PRESERVE study, a cross-sectional cohort study in North America, observed that more than 80% of heart failure patients had three or more comorbidities.[19] Similarly, in REPORT-HF 92% of patients in North America had multimorbidity and 81% of patients had three or more comorbidities. The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry reported that 81% of patients with chronic heart failure had two or more comorbidities; the most common groups of co-occurring comorbidities varied between different countries in Asia;[7] and the prevalence of multimorbidity in southeast (eg, Thailand, Indonesia, and the Philippines) and south Asia (India) in ASIAN-HF was significantly lower than in northeast Asia (eg, China, South Korea, and Japan).[20,21] Our analysis is in line with these previous results—southeast Asia having the lowest prevalence of multimorbidity—and extends them by including more countries and world regions. Our study is the first analysis of multimorbidity in a global prospective heart failure population that includes, for example, Latin America, the Eastern Mediterranean region, and African region, which were excluded from earlier publications. Overall, the high prevalence of multimorbidity in patients with heart failure in this and previous studies underlines heart failure as a systemic disease affecting multiple organ systems.

Notably, our study does not reflect changes in multimorbidity patterns that might have occurred due to COVID-19, because follow-up was completed before the pandemic. COVID-19-related hospitalisations are usually not due to acute heart failure and COVID-19 is not regarded as a comorbidity in heart failure. However, several reports showed that COVID-19 is associated with higher mortality in people with more comorbidities.[22] Furthermore, post-COVID-19 condition (also known as long COVID) probably increases the risk of other diseases, such as diabetes and cardiovascular disease.[23]

Therefore, the multimorbidity prevalence might have increased in heart failure populations due to COVID-19. The true population impact of COVID-19 on the prevalence of multimorbidity among patients with heart failure remains unknown and deserves further study.

Prescription of ACEis, ARBs, and MRAs was less frequent in patients with multimorbid HfrEF. Our data corroborate that multimorbidity might complicate treatment with GDMT for heart failure.[1,24] We observed similar prescribing patterns of GDMT in high-income and in lower-income countries, although the total percentage of patients on GDMT was lower in lower-income than in high-income countries, as reported previously.[25,26] This observation was independent of disease severity and more common in patients without health insurance,[26] suggesting less access to or awareness of GDMT for heart failure in lower-income than in higher-income countries. Previous studies showed that medication side-effects and contraindications are more frequent in patients who are sicker and frailer,[1,24] which could help explain why patients with multimorbidity received less GDMT than those without multimorbidity. Additionally, a higher prevalence of polypharmacy and fear of potential drug–drug interactions in patients with multimorbidity might have increased reluctance by treating physicians to prescribe more drugs, even if indicated by guidelines. Our findings corroborate that following hospitalisation for acute heart failure, a multidisciplinary team approach would be desirable to achieve optimal medical therapy for patients with multimorbidity.[27,28]

Our data demonstrate that the chance of receiving potentially harmful medications increases with comorbidity burden in heart failure, rising to approximately 20% in patients with five or more comorbidities. For example, similar to a prospective cohort study in Medicare beneficiaries with heart failure in North America,[29] in REPORT-HF, dipeptidyl peptidase-4 inhibitors, which potentially worsen heart failure,[16] were frequently prescribed to individuals with diabetes. The selective serotonin reuptake inhibitor (SSRI) citalopram was also commonly prescribed in REPORT-HF. According to the 2016 AHA Scientific Statement,[16] citalopram is the only SSRI with a level of evidence A for precipitation or induction of heart failure, suggesting that the use of alternative antidepressants might be preferable in heart failure. The use of potentially heart failure-worsening medication represents an avoidable cause for increased morbidity and more frequent exacerbation in heart failure, if safe and effective alternatives exist.

Overall, the cumulative comorbidity burden was strongly associated with mortality risk, in accordance with several previous reports.[1,3,4,8] Expanding on evidence from previous studies, the design of the REPORT-HF registry enabled assessment of the association between multimorbidity and mortality risk on both the individual and the population level at a global scale. Although the individual mortality risk associated with multimorbidity was higher in lower-middle-income countries than in high-income countries, the fraction of deaths attributable to multimorbidity on the population level was greater in high-income than in lower-income countries, reflecting the higher prevalence of multimorbidity in high-income regions. The association between comorbidity burden and mortality was weaker in lower-income countries than in high-income countries, and the differences in mortality risk between lower-income and high-income countries were greatest in patients with no or one comorbidity. These findings suggest that a larger residual risk remains in lower-income countries, which is likely multifactorial. Issues such as undiagnosed comorbidities, limited access to health care, fewer physician contacts, low-resource living situations, and inadequate nutrition, and possibly the interaction among them, might play a role. Cardiovascular comorbidities are common in patients with heart failure, and it is often difficult to distinguish if they are true comorbidities, or the cause of heart failure. Importantly, the observed associations between comorbidity burden and mortality risk remained valid when considering only non-cardiovascular comorbidities.

Finally, our analyses revealed substantial differences in the magnitude of risk for different comorbidity combinations after acute heart failure. For example, a combination of coronary artery disease and anaemia with either diabetes or hypertension was associated with a higher relative mortality risk in patients with three comorbidities compared with other combinations of three comorbidities, such as hypertension, anaemia, and atrial fibrillation. These data suggest that beyond the number of comorbidities (quantity), the combination (quality) of comorbidities is an important determinant of clinical outcomes.

Strengths of this study include the large patient number and the prospective, global design. REPORT-HF enrolled patients in 44 countries from six continents, providing an unprecedented scale of regional granularity. Notably, however, for logistical and policy reasons no low-income country and a comparably low number of Black people were included in the study. Although patients were identified on hospitalisation for a primary diagnosis of acute heart failure, the findings are consistent with other reports and should be applicable to a more general population with heart failure. Nevertheless, despite use of a common case report form across all sites, variations in availability of diagnostic tools and regional standards caused regional differences in data quality and collection. Local practice and sociocultural differences might also have influenced reporting of information related to comorbidities and prescribing patterns of medications. REPORT-HF required written informed consent from every participant, which might have introduced a selection bias towards younger, healthier patients, with fewer

comorbidities. Data collection to assess medications and comorbidities was performed during the index hospitalisation only. Differences in medication adherence and new diagnoses following admission therefore might not be considered in the analysis. It was not possible to consider, for example, new diagnoses made after hospital discharge, because they were not recorded. Most comorbidities were only identified via medical history. This approach might have resulted in an underestimation of the actual prevalence of some comorbidities, such as valvular diseases, where diagnosis by echocardiography would have been more reliable. Similarly, the included comorbidities were selected according to data availability and not all comorbidities relevant to heart failure patients could be included. Importantly, the enrolment period of REPORT-HF ended in March, 2017, before the COVID-19 pandemic. The pandemic might have changed disease patterns and local practices, which this report would not reflect. Lastly, due to concerns with the quality of the available data, mortality analyses were not stratified by cause of death and therefore did not differentiate between cardiovascular and non-cardiovascular deaths.

This first assessment of multimorbidity from a global, prospective, cohort study demonstrates high prevalence of multimorbidity in populations with heart failure across world regions, but also significant differences related to regional and country income level. More comorbidities were associated with higher mortality risk, less prescription of GDMT, yet more use of potentially heart failure-worsening medication, especially in high-income countries. Our results highlight the systemic nature of heart failure and call for a multidisciplinary diagnostic and therapeutic approach to optimise heart failure management and improve outcomes.

Contributors

JT and WO had full access to and verified the data in the study. TG, LMSG, and WO prepared the figures and tables. TG and LMSG wrote the first draft of the Article with input from CEA, JT, WO, KD, and GAR. The study was designed by CEA, JT, JGFC, UD, KD, GE, MH, SVP, MG, AS, AO, CSPL, GF, GAR, and SPC. Critical revisions of the Article were provided by GAR, WTT, JGFC, CEA, UD, KD, GE, MH, SVP, MG, AS, AO, CSPL, GF, and SPC. All authors had full access to the data. All authors shared the final responsibility for the decision to submit the manuscript for publication.

Equitable partnership declaration

See Online for appendix 9

The authors of this paper have submitted an equitable partnership declaration (appendix 9). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health's* broader goal to decolonise global health

Declaration of interests

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Data sharing

Novartis provided copies of the REPORT-HF database to two independent academic groups in Singapore and Glasgow, led by REPORT-HF Steering Committee members. Data can only be shared further with the agreement of Novartis. The publications group of the REPORT-HF study meets regularly to discuss manuscript development. Proposals for further analyses may be submitted to the group and will be judged based on their feasibility, originality, and scientific merit. Applicants might be asked to meet the costs of data preparation and statistical analysis and are expected to involve REPORT-HF investigators in manuscript development. Applications should be made to Gerasimos Filippatos (geros@otenet.gr), Sean Collins (sean.collins@vumc.org), Carolyn Lam (carolyn.lam@duke-nus.edu.sg), or John Cleland (john.cleland@glasgow.ac.uk).

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