Prognostic implications of heart failure stages among Chinese community populations: insight from a nationwide population-based study

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Summary

Background In light of high burden of heart failure (HF) in China, studies of prognostic implication of HF stages are important. We aimed to evaluate the relationship between HF stages and mortality risk in Chinese community populations.

Methods Nationwide representative populations aged ≥35 years (n = 23,284, mean age 56.9 years, women 53.2%) were enrolled from 2012 to 2016. According to the international HF guidelines, participants were divided into stage A, B and C, and those who did not qualify these stages were categorized as apparently-healthy group. Association between HF stages and all-cause, cardiovascular [CV] and non-CV death was evaluated using multivariable-adjusted Cox proportional regression analysis.

Findings During a median follow-up of 4.7 years (109,902.8 person-years), 1314 deaths occurred. Age-adjusted incidence rate of all-cause death was 5.3 in apparently-healthy, 7.8 in stage A, 8.6 in stage B and 24.6 in stage C groups per 1000 person-years. In reference to apparently-healthy group, adjusted hazard ratio for all-cause death was 1.90 (95% CI: 1.47–2.45), 2.43 (95% CI: 1.89–3.13) and 6.40 (95% CI: 4.56–8.99) for stage A, B and C. Advancing HF stages were associated with increasing risks for all-cause, CV and non-CV death (P-trend <0.05). For all-cause death, population attributable fraction due to stage A, B and C were 21.2%, 33.4% and 4.9%, accounting for 1,933,385, 3,045,993 and 446,867 deaths in China in 2018.

Interpretation Advancing HF stages were associated with increasing risk mortality. Development and implementation of early screening and targeted interventions are urgently needed to reduce HF burdens in China.

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Keywords: Heart failure; Death; Preclinical stages; Population

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Research in context

Evidence before this study

The international HF guidelines define HF trajectory as stages A, B, C and D. Several studies have evaluated prognostic implications of HF stages, demonstrating that advancing HF stages were associated with increasing mortality risk. One recent study from China reported the relationship between HF stages and 1-year rate of major adverse cardiovascular events (MACE) in 1068 hospitalized patients aged ≥65 years, and the results suggested that patients with stage B and stage C/D experienced a 2–3 times higher risk of MACE. However, due to relatively small sample size, only inclusion of the elderly and hospitalized patients, and relatively short-term follow-up, implications of this study are limited.

Added value of this study

This is the first nationwide population-based representative study of prognostic implications of HF stages in Chinese community populations. There are three important findings. First, in comparison with apparently-healthy individuals, those with stage A, B and C were at a higher risk of all-cause, CV and non-CV death at 5-years' follow-up. Second, advancing HF stages were associated with increasing mortality risk in both sexes and without differences by sex. Third, prognostic implications of advancing HF stages were consistent in both young and older age groups, highlighting the importance of early screening pre-HF in younger populations.

Implications of all the available evidence

This study demonstrates prognostic implications of HF stages in Chinese community populations, and pre-HF stages (stage A and B) were associated with high mortality risk. Development and implementation of early screening and targeted interventions are urgently needed to reduce HF burdens in China.

Introduction

Approximately 8.9 million people aged ≥35 years are living with heart failure (HF) in China.[1] Due to population aging, increasing prevalence of HF risk factors, and improved management of myocardial infarction, the prevalence of HF is projected to increase further.[2] HF is associated with substantial morbidity and mortality,[3,4] high readmission rate and healthcare expenditure.[5] In light of the high prevalence and burden of HF in China, improvement in the prevention of HF development has significant implications from clinical and public health perspectives.[6]

Heart failure is a clinical syndrome characterized by continuing progression from presence of risk factors alone (at risk) to asymptomatic structural heart disease (pre-HF), symptomatic HF, and advanced HF. The international guidelines define this trajectory as stages A, B, C and D HF.[7,8] Several studies have evaluated prognostic implications of HF stages, demonstrating that advancing HF stages was associated with increasing mortality risk.[9–11] Recent study from China reported the relationship between HF stages and 1-year's rate of major adverse cardiovascular event (MACE) in 1068 hospitalized patients aged ≥65 years,[12] and the results suggested that patients with stage B and C/D experienced a 2–3 times higher risk of MACE. Due to small sample size, only inclusion of the elderly and hospitalized patients, and short-term follow-up,[12] implications of this study are limited. Data on prognostic implications of HF stages in nationwide representative populations would provide a more comprehensive view of the burden of individual HF stage in contemporary China, which could provide scientific evidence to develop targeted interventions in the future.

Accordingly, in this study using data from the echocardiography sub-cohort of the China Hypertension Survey (CHS) study, which is a nationwide population-based representative study,[13] we aimed to evaluate the mortality risk across HF stages in Chinese community populations.

Methods

Study design and participants

The is an ancillary analysis of the CHS study, which is a national representative study and has used a 4-stage stratified random sampling method to obtain a national representative subjects aged ≥15 years from 31 provinces in mainland China between 2012 and 2015. The aim of the CHS study was to estimate the prevalence of hypertension in China, and more details of the CHS study could be found in previous report.[13] In this echocardiography sub-cohort, all selected urban and rural areas were stratified into eastern, middle and western regions based on geographical locations and economic levels. Using simple random sampling method, 16 cities and 17 counties were chosen, including seven cities and seven counties from eastern regions, six cities and six counties from middle regions, and three cities and four counties from western regions. At least three communities or villages were randomly chosen from each region. Participants aged ≥35 years were randomly selected to undergo echocardiographic examination during the survey, with a response rate of 62.5% (n = 34,994).[1] After excluding those with incomplete baseline information (e.g. sex, age, and valid blood sample; n = 4958), who did not undergo echocardiographic examination (n = 1803), and who were lost to follow-up after echocardiographic examination (n = 4949), a total of 23,284 participants were included in this study (Supplemental Figure S1). All participants provided written informed consent and the

study was approved by the Ethics Committee of Fuwai Hospital (Beijing, China).

Study variables and data collection

Baseline data on sociodemographic information (age, sex, ethnicity, urbanity and education), health behaviors (smoking and drinking status), and family history of cardiovascular disease (CVD) were recorded using standardized electronic questionnaires by trained staff during the survey. Blood pressure (BP) was measured 3 times using an OMRON HBP-1300 Professional Portable Blood Pressure Monitor (OMRON, Kyoto, Japan), and average value of 3 BP readings was used. Body weight was measured using the OMRON body fat and weight measuring device (V-body HBF-371; Omron, Kyoto, Japan). Blood samples were drawn in the morning after at least 8 h overnight fasting, and laboratory analysis was performed in central core laboratory (Beijing Adicon Clinical Laboratories, INC, Beijing, China) using standardized techniques.

Echocardiographic examination

As described previously,[1,14] a commercially available Doppler ultrasonography with a 3.0 MHz transducer was used to measure echocardiographic variables by certified sonographers, who were familiar with examination protocol. Challenging cases were discussed with experts from coordination center. In this study, definitions of structural heart disease were based on the international HF guidelines,[7,8] which included concentric remodeling (CR), enlarged left atrium (LA), enlarged left ventricle (LV), left ventricular hypertrophy (LVH), left ventricular diastolic dysfunction (LVDD), left ventricular ejection fraction (LVEF) < 50%, and valvular heart disease. Specifically, CR was defined as relative wall thickness >0.42 for both sexes; enlarged LA was defined as LA anteroposterior diameter >4.0 cm for men and >3.8 cm for women, or LA diameter/height >2.61 cm/m for both sexes; enlarged LV was defined as LV end diastolic diameter/body surface area (BSA) > 30 mm/m^2 for men and >31 mm/m^2 for women; LVH was defined as left ventricular mass/BSA >115 g/m^2 for men and >95 g/m^2 for women; LVDD was defined as moderate or grade II (pseudo-normal LV filling) and severe or grade III (restrictive filling) of LVDD; valvular heart disease was defined as moderate-to-severe mitral or aortic stenosis or regurgitation.

Ascertainment of HF risk factors

Based on the international HF guidelines,[7,8] risk factors of HF included hypertension, dyslipidemia, obesity, diabetes mellitus (DM), metabolic syndrome (MS), chronic kidney disease (CKD), atherosclerotic cardiovascular disease (ASCVD, including coronary heart disease [CHD], ischemic stroke, and peripheral arterial disease [PAD]), atrial fibrillation (AF) and cardiomyopathy. Specifically, hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of antihypertensive medication in the last 2 weeks.[13] Dyslipidemia was defined as fasting plasma level of total cholesterol ≥6.2 mmol/L, triglyceride ≥2.26 mmol/L, low-density lipoprotein cholesterol ≥4.14 mmol/L, high-density lipoprotein cholesterol <1.04 mmol/L, or use of lipid-lowering medication.[15] Individuals with fasting plasma glucose (FPG) level ≥7.0 mmol/L or use of antidiabetic medication were defined as having DM.[1] Obesity was defined as body mass index (BMI) ≥ 28 kg/m^2.[16] MS was defined by presence of ≥3 of the following metabolic factors[17]: (i) BP ≥ 130/85 mm Hg or taking antihypertensive medication; (ii) abdominal obesity (waist circumference ≥90 cm for men and ≥80 cm for women); (iii) triglyceride level ≥1.69 mmol/L; (iv) high-density lipoprotein cholesterol level <1.03 mmol/L for men and <1.29 mmol/L for women; and (v) FPG level ≥5.6 mmol/L or taking antidiabetic medication. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or urinary albumin to creatinine ratio (UACR) ≥ 30 mg/g.[18] CHD was defined based on self-report of prior myocardial infarction, prior percutaneous coronary intervention or coronary artery bypass grafting. Ischemic stroke was defined based on self-report. PAD was defined as ankle-brachial index (ABI) < 0.9. AF was defined based on self-report or report on the index electrocardiogram. Cardiomyopathy was defined based on report on the index echocardiography.

Definition of HF stages

Based on the international HF guidelines,[7,8] individuals with HF risk factors alone were grouped as stage A (at-risk for HF; n = 8234); with asymptomatic structural heart disease were grouped as stage B (pre-HF; n = 10,099); and with structural heart disease plus self-report of prior HF diagnosis, or prior or current HF symptoms/signs were grouped as stage C (symptomatic HF; n = 312). As reported in our prior study,[1] typical HF symptoms included exercise intolerance, shortness of breath at exertion, lower extremities swelling, and orthopnea; and less typical symptoms included worsening cough when lying flat, increased urination frequency at night, rapid or irregular heartbeat, feel depressed, feel severe thirst and abdominal swelling. No patient with stage D was included in the CHS study. Participants who were not qualified for stage A, B, or C were categorized as apparently-healthy group (n = 4639). Criteria and classifications of HF stages are presented in Supplemental Table S1.

Study outcomes

Outcomes of this study included all-cause, cardiovascular (CV) and non-CV death. Specifically, CV death was defined as the death primarily due to underlying CVD such as CHD and stroke; and death due to non-CVD such as cancer or respiratory disease were defined as

non-CV death. Outcomes were retrospectively collected by study staff in the 14 provinces through directly contacting the participants' immediate relatives and healthcare providers. These events were further confirmed using the national mortality surveillance system for death registration and mortality surveillance of China, and accuracy of these data has been demonstrated.[19]

Statistical analysis

Baseline characteristics were described according to HF stages, and continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequency (proportion). Between-group differences were assessed using one-way ANOVA or χ^2 test as appropriate. Cumulative rate of outcomes according to HF stages was displayed using Kaplan–Meier method, with comparisons using log-rank test. Age-adjusted incidence rate of mortality was calculated. Intra-class correlation coefficient (ICC) was calculated before application of two-level Cox regression model. ICCs were 0.046, 0.078 and 0.040 in all-cause, CV and non-CV death models; and a two-level regression model was applied when ICC is greater than 0.04.[20] We therefore applied a two-level Cox proportional regression model to evaluate the association between HF stages and outcomes in order to reduce regional effect. Fix of two-level Cox proportional regression model and ICC calculation were performed using the R package 'lme4'. Age, sex, urbanity, ethnicity, education, smoking and drinking status were included in the model based on prior reports.[21,22] Hypertension, diabetes and other comorbidities were used to define stage A, which were not included in the model. We additionally evaluated the association between HF stages and outcomes by sex and age (<65 and ≥ 65 years) using Cox proportional regression model. A test for linear trend was conducted and a *P*-trend value across HF stages was reported. Population attributable fraction (PAF) is used to measure disease burden attributable to a given risk factor.[23] To estimate mortality burden related to individual HF stage, we calculated PAF using following formula: PAF = P*(HR −1)/(P*[HR − 1] + 1), wherein *P* was referred to population prevalence of individual HF stage and HR was referred to adjusted HR of death related to individual HF stage. We derived 95% confidence interval (CI) of PAF by bootstrap. Attributable death related to individual HF stage was computed by multiplying PAF and estimated number of all-cause (n = 9,119,739), CV (n = 4,105,957) and non-CV (n = 5,013,782) death in China in 2018 according to the report of the China Health Statistical Report of 2018 (https://navi.cnki.net/knavi/yearbooks/YSIFE/detail?uniplatform=NZKPT). All statistical analyses were conducted using survey modules of SAS software version 9.4 (SAS Institute, Inc). Two-sided *P*-values <0.05 were considered as statistically significant.

Ethics approval and consent to participate

All participants provided written informed consent and the study was approved by the Ethics Committee of Fuwai Hospital (Beijing, China).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among the cohort, proportion of participants in apparently-healthy, stage A, B and C groups were 17.9%, 36.2%, 44.5% and 1.3%, respectively. From apparently-healthy to stage C groups, mean age was 49.6, 56.5, 60.0 and 63.5 years, and proportion of women was 54.3%, 48.0%, 57.2% and 45.8%. Baseline characteristics across HF stages are summarized in Table 1.

Mortality risk across HF stages

After a median follow-up of 4.7 years (109,902.8 person-years), 1314 deaths (584 CV deaths and 730 non-CV deaths) occurred. Cumulative mortality rate increased with advancing HF stages (Fig. 1A–C; all Log-rank $P < 0.0001$). Age-adjusted incidence rate of all-cause death increased with advancing HF stages, from 5.3 in apparently-healthy group, to 7.8 in stage A, 8.6 in stage B, and 24.6 in stage C per 1000 person-years (Table 2). After adjusting for covariates, in reference to apparently-healthy group, hazard ratio (95% CI) for all-cause death in stage A was 1.90 (95% CI: 1.47–2.45), stage B 2.43 (95% CI: 1.89–3.13), and stage C 6.40 (95% CI: 4.56–8.99; *P*-trend <0.0001). Advancing HF stages were associated with increasing CV and non-CV death risks.

Morality disk associated with HF stages by sex and age

There were no significant interactions of HF stages and sex for outcomes. Specifically, in women, age-adjusted incidence rate of all-cause, CV and non-CV death increased with advancing HF stages. In reference to apparently-healthy group, there was a trend toward increasing risk of all-cause, CV and non-CV death with advancing HF stages (*P*-trend <0.05). Similar findings were noted for men (Supplemental Table S2). In both age groups, adjusted risk for all-cause, CV and non-CV death increased with advancing HF stages (Supplemental Table S3); and there was no significant interactions of HF stages and age for outcomes.

Estimated mortality cases attributable to individual HF stage

For all-cause death, PAFs due to stage A, B and C were 21.2%, 33.4% and 4.9%, respectively (Table 3). It was estimated that 1,933,385 (95% CI: 1,896,906–1,960,744) deaths could be attributable to stage A, 3,045,993 (95%

Characteristics	Apparently healthy (n = 4167)	Stage A (n = 8438)	Stage B (n = 10,367)	Stage C (n = 312)	*P*-value	*P-trend*
Age (years)	49.6 ± 10.9	56.5 ± 12.7	60.0 ± 13.1	63.5 ± 13.1	<0.001	<0.001
Age group, n (%)					<0.001	<0.001
<65 years	3662 (87.9)	5929 (70.3)	6276 (60.5)	157 (50.3)		
≥65 years	505 (12.1)	2509 (29.7)	4091 (39.5)	155 (49.7)		
Sex, n (%)					<0.001	<0.001
Men	1903 (45.7)	4392 (52.1)	4434 (42.8)	169 (54.2)		
Women	2264 (54.3)	4046 (48.0)	5933 (57.2)	143 (45.8)		
Han ethnicity, n (%)	3561 (85.5)	7507 (89.0)	9345 (90.1)	276 (88.5)	<0.001	<0.001
Rural area, n (%)	2384 (57.2)	4134 (49.0)	6271 (60.5)	182 (58.3)	<0.001	<0.001
Education ≥ High school, n (%)	960 (23.1)	1839 (21.8)	1600 (15.5)	47 (15.1)	<0.001	<0.001
Current smoker, n (%)	1130 (27.1)	2267 (26.9)	2358 (22.8)	79 (25.3)	<0.001	<0.001
Current drinker, n (%)	1200 (28.8)	2622 (31.1)	2510 (24.2)	76 (24.4)	<0.001	<0.001
Family history of CVD, n (%)	377 (9.1)	1531 (18.1)	1689 (16.3)	65 (20.8)	<0.001	<0.001
Systolic BP (mmHg)	117.5 ± 10.6	135.1 ± 19.1	136.4 ± 21.4	137.6 ± 22.5	<0.001	<0.001
Diastolic BP (mmHg)	71.9 ± 7.9	79.2 ± 11.0	77.7 ± 11.6	78 ± 12.9	<0.001	<0.001
Heart rate (bpm)	74.8 ± 10.2	76.3 ± 11.0	76.2 ± 11.4	77.6 ± 11.8	<0.001	<0.001
Waist circumference in men (cm)	81.3 ± 7.9	88.3 ± 9.6	84.7 ± 10.5	86.0 ± 10.7	<0.001	<0.001
Waist circumference in women (cm)	77.5 ± 7.6	85.3 ± 9.7	83.0 ± 10.7	81.1 ± 11.2	<0.001	<0.001
Body mass index (kg/m^2)	23.0 ± 2.4	25.5 ± 3.4	24.4 ± 3.7	24.3 ± 3.7	<0.001	<0.001
Total cholesterol (mmol/L)	4.5 ± 0.7	4.8 ± 1.0	4.9 ± 1.0	4.7 ± 1.0	<0.001	<0.001
LDL-cholesterol (mmol/L)	2.6 ± 0.6	2.8 ± 0.9	2.9 ± 0.8	2.7 ± 0.8	<0.001	<0.001
HDL-cholesterol (mmol/L)	1.5 ± 0.3	1.3 ± 0.3	1.4 ± 0.4	1.4 ± 0.4	<0.001	0.0002
Triglyceride (mmol/L)	1.0 ± 0.4	1.7 ± 1.2	1.5 ± 1.0	1.4 ± 0.9	<0.001	<0.001
Fasting plasma glucose (mmol/L)	5.1 ± 0.6	5.8 ± 1.7	5.7 ± 1.6	5.9 ± 1.8	<0.001	<0.001
HF risk factor, n (%)						
Hypertension	0	4469 (53.2)	5098 (49.4)	176 (56.6)	<0.001	<0.001
Dyslipidemia	0	4023 (47.7)	3475 (33.5)	97 (31.1)	<0.001	<0.001
Obesity	0	1954 (23.4)	1660 (16.2)	39 (12.8)	<0.001	<0.001
Diabetes mellitus	0	1188 (14.2)	1152 (11.3)	51 (16.5)	<0.001	<0.001
Metabolic syndrome	0	3354 (39.8)	3173 (30.6)	97 (31.1)	<0.001	<0.001
Chronic kidney disease	0	2164 (29.0)	2337 (26.2)	116 (43.5)	<0.001	<0.001
ASCVD	0	963 (11.6)	1069 (10.4)	37 (12.0)	<0.001	<0.001
Atrial fibrillation	0	87 (1.0)	132 (1.3)	37 (11.9)	<0.001	<0.001
Cardiomyopathy	0	10 (0.1)	45 (0.4)	22 (7.5)	<0.001	<0.001
Structural heart disease, n (%)						
Concentric remodeling	0	0	6921 (69.3)	88 (29.4)	<0.001	<0.001
Enlarged LV	0	0	1800 (18.0)	110 (36.4)	<0.001	<0.001
Enlarged LA	0	0	1103 (11.1)	62 (20.2)	<0.001	<0.001
LVH	0	0	2976 (30.3)	105 (37.1)	<0.001	<0.001
LVDD	0	0	557 (5.8)	60 (21.0)	<0.001	<0.001
LVEF <50%	0	0	99 (1.0)	220 (70.7)	<0.001	<0.001
Valvular heart disease	0	0	947 (9.1)	62 (19.9)	<0.001	<0.001
Antihypertensive therapy, n (%)	0	2197 (26.0)	2520 (24.3)	112 (35.9)	<0.001	<0.001
Antidiabetic therapy, n (%)	0	585 (6.9)	601 (5.8)	27 (8.7)	<0.001	<0.001
Lipid-lowering therapy, n (%)	0	515 (6.1)	437 (4.2)	19 (6.1)	<0.001	<0.001

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; HDL, high density lipoprotein; LA, left atrium; LDL, low density lipoprotein; LV, left ventricle; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

Table 1: **Baseline characteristics of participants according to heart failure stages.**

CI: 3,009,514–3,091,592) deaths attributable to stage B, and 446,867 (95% CI: 383,029–519,825) deaths attributable to stage C in China in 2018. Estimated CV and non-CV deaths attributable to individual HF stage are presented in Table 3.

Discussion

To our knowledge, this is the first nationwide population-based study of prognostic implications of HF stages in Chinese community populations. There are three main findings. First, in comparison with

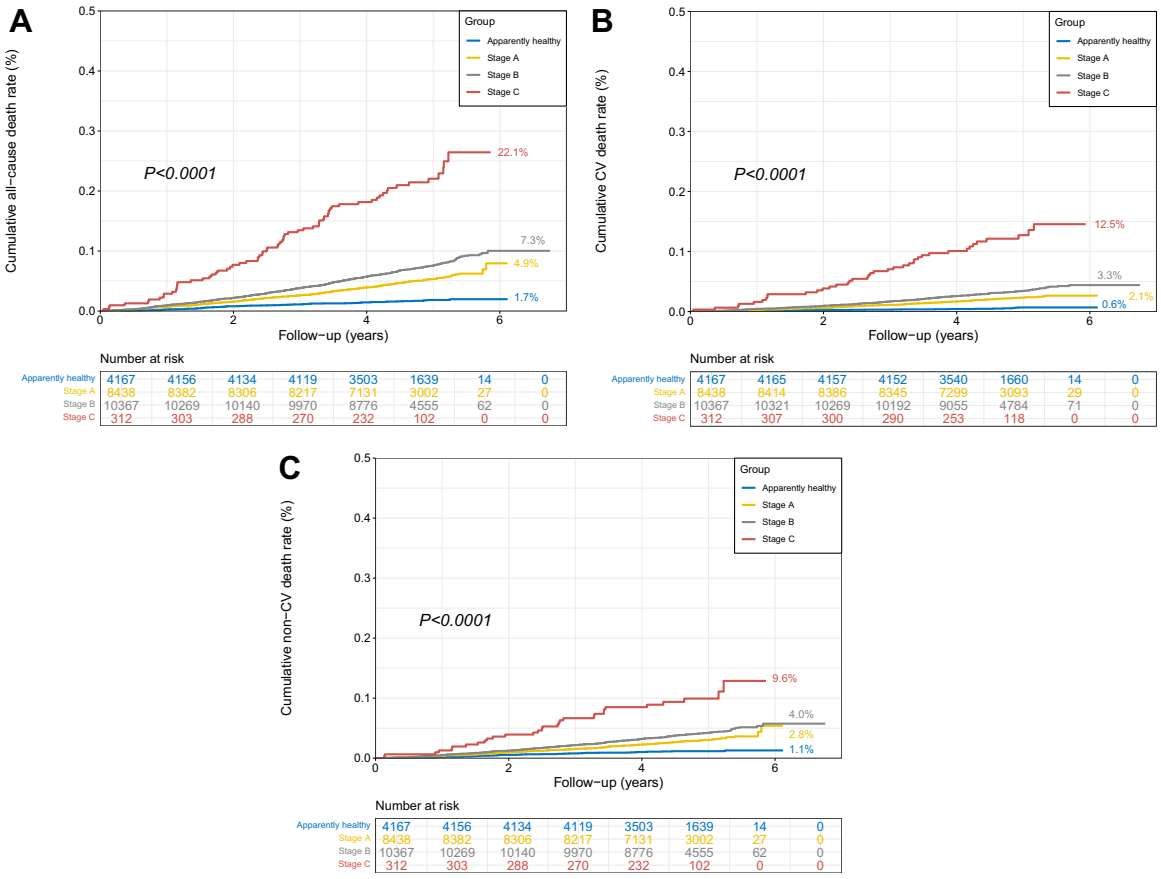

Fig. 1: **Cumulative rate of outcomes at 5-years' follow-up**. **A** showed cumulative rate of all-cause death according to the HF stages, with a log-rank $P < 0.0001$. **B** showed the cumulative rate of CV death according to the HF stages, with a log-rank $P < 0.0001$. **C** showed the cumulative rate of non-CV death according to the HF stages, with a log-rank $P < 0.0001$. CV, Cardiovascular; HF, Heart failure.

apparently-healthy individuals, those with stage A, B or C were at a higher risk of all-cause, CV and non-CV death at 5-years' follow-up. Second, advancing HF stages were associated with increasing mortality risk for both sexes and without differences by sex. Third, prognostic implications of advancing HF stages were consistent in both young and older age groups, highlighting the importance of early screening HF in younger populations.

Prognostic implications of HF stages have been well studied. In the Olmsted County Study, Ammar et al. reported that 5-years' survival rate was 97%, 96%, 75% and 20% in stage A, B, C and D.[9] In the Framingham Study, Xanthakis et al. found that over a mean follow-up of 7 years, mortality risk increased by 2-fold in stage B and 8-fold in stage C/D in comparison with apparently-healthy individuals.[10] In the Atherosclerosis Risk in Communities study, Shah et al. reported a trend toward increasing death rate with advancing HF stages.[11] However, due to differences in healthcare systems and sociodemographic, these observations are unlikely to be extrapolated to other population groups. We found that 5-years' survival rates across HF stages in Chinese community populations are similar to the Olmsted County study.[9] While prior major meta-analysis of 60 studies showed that in community patients with chronic or stable HF, 5-years' survival rate was 57%,[3] which was lower than ours and the Olmsted County Study.[9] The relatively higher survival rate of our study could be due to the following reasons. First, stage C was partly defined based on self-report of prior HF diagnosis, which might result in misclassification of symptomatic HF. Second, due to the nature of population-based survey study, participants with stage C could be relatively stable, which might also explain a relatively higher survival rate at 5-years' follow-up.

In patients with HF, LA enlargement is commonly noted on echocardiogram. While in this study, participants who were classified as Stage C (symptomatic HF) were based on presence of structural heart disease plus

HF stages	All-cause death					
	Person-years	Number of events	Crude incidence rate[a]	Age-adjusted incidence rate[a]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Apparently healthy	19217.6	70	3.6	5.3	1.00 (ref)	1.00 (ref)
A	38456.9	414	10.8	7.8	2.97 (2.31–3.83)	1.73 (1.34–2.24)
B	48094.8	761	15.8	8.6	4.31 (3.38–5.51)	2.17 (1.69–2.79)
C	1337.9	69	51.6	24.6	14.31 (10.27–19.96)	5.72 (4.08–8.02)
HR P_{trend}	–	–	–	–	<0.001	<0.001
HF stages	**Cardiovascular death**					
	Person-years	Number of events	Crude incidence rate[a]	Age-adjusted incidence rate[a]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Apparently healthy	19334.2	23	1.2	1.9	1.00 (ref)	1.00 (ref)
A	38931.9	177	4.6	3.1	3.83 (2.48–5.92)	2.02 (1.30–3.14)
B	48973.0	345	7.0	3.6	5.87 (3.85–8.95)	2.78 (1.81–4.27)
C	1409.9	39	27.7	11.0	23.26 (13.89–38.93)	7.93 (4.70–13.37)
HR P_{trend}	–	–	–	–	<0.001	<0.001
HF stages	**Non-cardiovascular death**					
	Person-years	Number of events	Crude incidence rate[a]	Age-adjusted incidence rate[a]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Apparently healthy	19217.6	47	2.4	3.4	1.00 (ref)	1.00 (ref)
A	38456.9	237	6.2	4.6	2.53 (1.85–3.46)	1.59 (1.15–2.18)
B	48094.9	416	8.6	4.9	3.51 (2.60–4.75)	1.81 (1.33–2.48)
C	1337.9	30	22.4	12.7	9.28 (5.87–14.67)	4.08 (2.56–6.51)
HR P_{trend}	–	–	–	–	<0.001	<0.001

CI, confidence interval; HF, heart failure; HR, hazard ratio. Age-adjusted incidence rate used the 2010 Chinese standard population (≥35 years old) and was presented per 1000 person-years. Adjusted for age, sex, ethnicity, urbanity, education, smoking and drinking status, and district. [a]Incidence rate was presented as per 1000 person-years.

Table 2: **Cox proportional regression analyses for 5-years' mortality risk according to heart failure stages.**

HF Stages	All-cause death		
	PAF (95% CI), %	Cases attributable to HF in the present cohort (95% CI)	Cases attributable to HF in China (95% CI)
A	21.2 (20.8–21.5)	279 (273–283)	1,933,385 (1,896,906–1,960,744)
B	33.4 (33.0–33.9)	439 (434–445)	3,045,993 (3,009,514–3,091,592)
C	4.9 (4.2–5.7)	64 (55–75)	446,867 (383,029–519,825)
HF Stages	**Cardiovascular death**		
	PAF (95% CI), %	Cases attributable to HF in the present cohort (95% CI)	Cases attributable to HF in China (95% CI)
A	27.3 (26.8–27.7)	159 (157–162)	1,120,926 (1,100,396–1,137,350)
B	43.3 (42.8–43.8)	253 (250–256)	1,777,879 (1,757,350–1,798,409)
C	7.1 (6.0–8.2)	41 (35–48)	291,523 (246,357–336,688)
HF Stages	**Non-cardiovascular death**		
	PAF (95% CI), %	Cases attributable to HF in the present cohort (95% CI)	Cases attributable to HF in China (95% CI)
A	17.8 (17.5–18.2)	130 (128–133)	892,453 (877,412–912,508)
B	25.8 (25.4–26.2)	188 (185–191)	1,293,556 (1,273,501–1,313,611)
C	3.3 (2.8–3.8)	24 (20–28)	165,455 (140,386–190,524)

CI, confidence interval; HF, heart failure; PAF, population attributable fraction.

Table 3: **Estimated attributable risk and number of mortality events attributable to heart failure stages.**

self-report of prior HF diagnosis, or prior or current HF symptoms/signs. The relatively low percentage of HF patients with enlarged LA could be partly due to self-report of HF diagnosis. In addition, it also could be due to the fact that the participants in the survey were in a stable condition, and LA enlargement due to volume expansion might be improved with decongestion or improvement in LV function.

Importantly, both ours and prior studies demonstrate that survival rate decreased markedly at the transition from stage B to stage C,[9–11] highlighting the importance of early screening those with at risk of developing symptomatic HF and timely implementing targeted interventions to prevent HF progression.

Identification and management of individuals at risk for symptomatic HF

Although early screening individuals with stage B has been recommend by the international HF guidelines,[7,8] efficient and cost-effective strategies haven't yet been developed. Electrocardiogram is cheap and universally available but with low sensitivity; echocardiogram has a relatively high sensitivity and specificity while limited by a relatively high cost, less accessibility, and operator-dependent; cardiac magnetic resonance is a gold standard for cardiac structure and function assessment but is limited by an extremely high cost, low accessibility and time-consuming.[24] In the last decade, machine-learning based models using easily obtained clinical and electrocardiographic variables have been developed to identify individuals with existing or at risk of developing structural heart disease.[25–27] This strategy may be cost-effective,[25–27] while more studies are needed to evaluate the performance of these models in diverse population groups and clinical settings.

Importantly, two clinical trials have demonstrated that natriuretic peptide is useful to identify asymptomatic individuals who are at risk of developing symptomatic HF.[28,29] Pandey et al. reported that a biomarker score which comprises cardiac troponin, natriuretic peptide, C-reactive protein and LVH on echocardiogram is helpful to determine HF risk in individuals with diabetes and pre-diabetes.[30] Potter et al. found that clinical risk assessment is adequate to classify low and high HF risk; while incorporating echocardiographic data is helpful to reclassify 61% of intermediate-risk patients.[31] Indeed, combinations of clinical factors, serum markers and imaging data can facilitate us to identify high-risk populations, while more efforts are needed to evaluate how to implement these strategies in daily clinical practice and at the population level in both cost-effective and convenient ways, given that a large proportion of high-risk people are living in the community.[32] Furthermore, it will be clinically important if these strategies can be used to facilitate the development of targeted interventions for high-risk populations.

Besides identifying high-risk individuals, effective interventions that can prevent or slow HF progression are crucial. Undoubtedly, risk factors control is essential across HF stages. Ameliorating abnormal cardiac structure and function is important to reduce incident HF. Recent studies showed that sodium glucose co-transporter 2 (SGLT2) inhibitor improved LVH in individuals with diabetes[33,34]; and angiotensin receptor neprilysin inhibitor (ARNI) was associated with a greater improvement in cardiac remodeling than classic antihypertensive drugs in patients with hypertension[35] and pre-HF.[36] In patients with diabetes and CKD, in comparison with placebo, SGLT2 inhibitor reduced incident HF.[37–40] However, these benefits of SGLT2 inhibitor in a broader population group is undetermined. In addition, the PARADISE-MI trial showed that in patients with acute myocardial infarction, ARNI was not superior to ramipril in reducing incident HF.[41] Taken together, more studies are needed to investigate whether use of these novel medications can prevent HF development in those with pre-HF.

Mortality risk across HF stages in China

Among individuals with stage A and B, proportion of those who died of non-CVD was slightly higher than that of CVD, which were likely due to existing comorbidities leaded to death before progressing to symptomatic HF.[10] Indeed, in those with obesity, increase in body weight not only leads to HF progression and HF-related death, but also causes other health problems such as metabolic dysfunction-associated steatotic liver disease and malignant diseases. Long-standing uncontrolled diabetes could lead to diabetic nephropathy and end stage renal disease, resulting in renal-related death. These observations underscore the importance of management of both CV and non-CV comorbidities. Furthermore, in light of evidence from HF clinical trials,[42–44] increasing uptake of SGLT2 inhibitor and ARNI and adhering to guideline-directed medication therapy could have the potential to reduce mortality risk in patients with stage C.

Ammar et al. reported that there might be a sex-specific mortality risk across HF stages.[9] Owing to small number of deaths, the conclusion was undetermined. Xanthakis et al. found that there was no significant interaction between sex and HF stages for death.[10] In this study, advantaged by large sample size and event rates, we found that there was no significant interaction of HF stages and sex for mortality. We also did not find significant interactions of HF stages and age for mortality, highlighting the importance of early screening pre-HF in younger populations due to the potential of greater life gain. The estimated number of all-cause death attributable to stage A, B and C together was around 5 million, and it is urgently needed to develop and implement early screening and targeted

interventions for pre-HF and HF at the population level in China.

Clinical implications

Findings of this study have several clinical implications. First, these results confirm that HF staging is helpful to classify mortality risk in Chinese community populations. Second, risk factors control and use of medications that can ameliorate abnormal cardiac structure and function should be broadly adopted to prevent HF progression. Third, more efforts should be allocated to younger individuals who are at pre-HF and high risk of developing symptomatic HF.

Strengths and limitations

The study is strengthened by rigorous sampling method, enabling us to obtain nationally representative populations and thus assuring the representativeness of these findings. Second, leveraging large sample size and event rates, we were able to evaluate prognostic value of HF stages in subpopulation groups. Third, we specifically evaluated CV and non-CV death rate across HF stages, which has revealed differences in the mode of death across HF stages. There are also several limitations of this study. First, some parameters used to define stage A (e.g. cardiotoxic agents) and stage B (e.g. natriuretic peptide) have not been captured, which might lead to underestimate of prognostic impacts of HF stages. Second, due to small numbers of incident HF (n = 55) at follow-up, we did not have statistical power to evaluate the relationship between HF stages and incident HF; furthermore, the incidence of HF-related death was also not evaluated. Third, data on managements (e.g. SGLT2 inhibitor or ARNI) at follow-up, which could influence the morality, were unavailable. These data could help us better understand the effective and practical strategies for HF prevention and intervention in real-world situation. Fourth, global longitudinal strain is better than LVEF in identifying individuals with subclinical LV systolic dysfunction, and lack of these data might lead to inaccurate estimation of the burden of stage B. Last but not least, due to unknown or unmeasured confounding and biases, it is uncertain as to the potential benefits of interventions that are implemented to target the specific HF stages in Chinese community populations.

Conclusions

Our study demonstrates the prognostic implications of HF stages in Chinese community populations, and even stage A and B were associated with a high mortality risk. Development and implementation of early screening and targeted interventions at the population level are urgently needed to reduce HF burdens in China.

Contributors

ZW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. ZW: conceptualization, data curation, methodology, writing—review & editing, supervision, funding acquisition; YF: conceptualization, writing-review & editing; CZ: conceptualization, methodology, formal analysis, writing-original draft preparation; AC: conceptualization, methodology, formal analysis, writing-original draft preparation; XW: investigation; JQ: formal analysis, investigation; QS: investigation; RG: investigation; XC: investigation; YT: investigation; ZH: investigation; GF: writing—review & editing; GL: writing—review & editing. Acquisition, analysis, or interpretation of data: All authors.

Data sharing statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of interests

Dr Fonarow has consulted for Abbott, Amgen, AstraZeneca, Bayer, Boehinger Ingelheim, Cytokinetics, Eli Lilly, Johnson & Johnson, Medtronic, Merck, Novartis, and Pfizer. The other authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101072.

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