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RESEARCH ARTICLE

# Associations of Heart Failure Onset Age with All-Cause Mortality: The Kailuan Study

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## Abstract

**Objective:** This study was aimed at investigating the correlations between heart failure onset age and all-cause mortality.
**Methods:** The study examined 186,249 patients treated at Kailuan Group hospitals who underwent medical evaluations between 2006 and 2018. Biennial health assessments were conducted, and, as of December 31, 2020, 4022 heart failure instances were identified. For each patient with new-onset heart failure, four control participants were randomly selected, matched for age (within ±1 year) and sex. Cox regression models were used to calculate the hazard ratios of all-cause mortality across age groups.
**Results:** The median follow-up duration was 5.25 (2.65, 8.63) years. All-cause mortality occurred in 1783 participants in the new-onset heart failure group and 2633 participants in in the control group. Refined multivariable Cox regression analysis revealed that patients with heart failure under 55 years of age had the highest relative mortality risk, with an HR (95% CI) 6.86 (4.42–10.64) with respect to their matched controls. Moreover, the relative mortality risk systematically decreased with increasing age of heart failure onset: HR (95% CI) 4.70 (3.73–5.92) for ages 55–64, HR (95% CI) 3.23 (3.73–3.81) for ages 65–74, and HR (95% CI) 1.69 (1.48–1.94) for 75 years or older.
**Conclusion:** Heart failure significantly elevates the risk of all-cause mortality, and the risk is more pronounced with earlier manifestation of the condition.

**Keywords:** Heart failure; Onset age; All-cause mortality; Cohort study

## Introduction

As medical advancements progress, and therapeutic treatments are refined, the acute-phase mortality rate for cardiovascular ailments has declined. This shift has led to an increase in heart failure (HF) occurrence. Between 2000 and 2015, HF prevalence in the Chinese population rose from 0.9% to 1.3% [1]. Whereas patients with HF are a predominantly older population, the number of middle-aged and younger adults receiving HF diagnoses is growing [2]. According to data from China's urban employee medical insurance in 2017, 2.5% and 3.8% of all people with HF are 35–39 and 40–44 years of age, respectively [3]. Furthermore, in contrast to their older counterparts, younger individuals

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have a higher relative risk of HF due to factors such as obesity, hypertension, diabetes, smoking habit, and prior myocardial infarction incidents [4]. This trend may potentially lead to more dire prognosis and heightened mortality risk among people diagnosed with HF at younger ages.

The China-HF study has reported an in-hospital mortality rate of 4.1% among patients with HF [5]. Despite remarkable advances in HF treatment, the mortality rate among younger patients with HF remains alarmingly high. Canadian statistics have indicated a 1-year mortality rate of 12% and a 5-year rate of 28% for this younger demographic [6]. Recent findings from Sweden's HF patient data suggest that the youngest HF cohort faces the greatest mortality risk and the shortest life expectancy, relative to those in the broader population [7]. However, this research primarily evaluated the prevalent age for HF rather than the age of HF onset. In addition, much of the current research was conducted in Western nations, thus leaving a dearth of research in China regarding the correlation between HF onset age and overall mortality risk. Thus, using the Kailuan Study data, we sought to examine the ramifications of new-onset HF for all-cause mortality in patients in multiple age groups compared with controls.

## METHODS

### Study Participants

This study monitored individuals receiving medical check-ups across 11 hospitals affiliated with the Kailuan Group, encompassing Kailuan General Hospital and its branches, spanning from 2006 to 2018. The criteria for inclusion in the new-onset HF cohort were 1) participation in Kailuan Group health examinations between 2006 and 2018; 2) initial HF diagnosis after the aforementioned health check-up; and 3) consent to participate in the study and provision of informed consent. In contrast, the exclusion criterion was a history of malignant tumor at the time of HF diagnosis. For the control cohort (those without HF), the inclusion criteria were 1) engagement in Kailuan Group health examinations between 2006 and 2018; 2) absence of any HF diagnosis after the health check-up; and 3) agreement to join the study and provision of informed consent. The exclusion criterion for this group was a history of malignant tumor during the identical matching timeframe as in the HF cohort. For every patients with newly diagnosed HF, a corresponding control was randomly chosen from the non-HF cohort that underwent medical examinations in the same timeframe, matched in a 1:4 ratio by sex and age (within ±1 year). The study's was conducted in strict accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee at Kailuan General Hospital.

### Data Collection

Participant demographics (e.g., birthdate, age, and sex) were recorded, along with personal lifestyle choices such as smoking habit, alcohol intake, and physical activity. Anthropometric data including height and weight; medical histories including conditions such as hypertension, diabetes, myocardial infarction, atrial fibrillation, and prior strokes; and medication regimens (e.g., antihypertensive, antidiabetic, antiplatelet, or diuretic drugs) were also documented. Blood pressure readings and blood biochemical markers were obtained. An in-depth overview has been provided in our earlier publication [8]. Biochemical evaluations were performed on venous blood samples collected after a minimum fasting period of 8 hours. A Hitachi 7600 automated biochemical analyzer was used to measure total cholesterol, triglycerides, LDL-C, fasting blood glucose, and serum creatinine concentrations. The estimated glomerular filtration rate (eGFR) was deduced with the creatinine formula endorsed by the Chronic Kidney Disease Epidemiology Collaboration [9].

### Follow-Up and Assessment of Outcomes

Follow-up for the new-onset HF cohort started at the time of HF onset, and that for the control cohort started at the time of the corresponding medical examination. In both groups, all-cause mortality was the terminal event and the conclusion of the follow-up period. For participants who did not encounter the terminal event, the follow-up concluded on December 31, 2022. Annually, skilled physicians examined hospitalization records to extract data

pertinent to HF diagnosis and intervention. Data on mortality incidents were obtained annually from the Kailuan Social Security Information System.

### Relevant Definitions

HF diagnosis was determined according to the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [10], according to examination medical records, considering HF risk factors, clinical manifestations, irregular electrocardiograms, NT-proBNP or BNP concentrations, and echocardiographic results. All-cause mortality was defined as any death occurring during the follow-up, regardless of the cause. Hypertension was characterized by (1) a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg or (2) systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg with the administration of antihypertensive drugs or a documented history of hypertension. Diabetes was defined by a fasting blood glucose (FBG) level ≥ 7.0 mmol/L or < 7.0 mmol/L with the use of antidiabetic drugs or a known history of diabetes. Body mass index (BMI) was calculated as the weight divided by the square of the height (kg/m$^2$). Smoking was characterized by consumption of a minimum of one cigarette daily, on average, during the past year, sustained for at least 1 year. Alcohol intake was defined by the consumption of ≥ 100 mL/day of white spirit (with 50% alcohol content) on average over the previous year, sustained for at least 1 year.

### Statistical Analyses

New-onset HF cohort and its corresponding control cohort were divided into four age brackets: under 55 years, 55–64 years, 65–74 years, and 75 years or older. Normally distributed metrics are presented as mean ± standard deviation, and group comparisons were made via ANOVA. Skewed distribution measurements are denoted M (P25, P75) and were assessed with the rank sum test. Categorical data are represented as cases (percentages), and rate comparisons were performed with the chi-square test. Person-year incidence rates (incidence densities) were used to assess all-cause mortality across age categories in the HF and control cohorts. Cumulative all-cause mortality rates were computed for each age bracket within the HF and control groups. The absolute mortality risk was determined for each age group in the HF and control cohorts, and is denoted as the mortality prevalence (prevalence = death count/total group count), standardized for age and sex, from which the standardized absolute risk was derived. A multivariate Cox regression model was used to assess the hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality, comparing patients with HF with their non-HF counterparts across age brackets. Model 1 accounted for age and sex. Model 2, building upon model 1, incorporated factors including smoking habit, alcohol intake, education level, physical activity, BMI, low-density lipoprotein, and hemoglobin. Model 3 further adjusted for medication regimens (e.g., antidiabetic, lipid-lowering, antiplatelet, beta-blocker, ACEI/ARB, MRA, or diuretic drugs) and was based on model 2. Sensitivity analysis excluded participants with prior histories of conditions such as myocardial infarction, atrial fibrillation, stroke, hypertension, diabetes, or renal insufficiency, and the aforementioned statistical methods were followed. All computations were performed in SAS, version 9.4 (SAS Institute, Inc, Cary, NC). A two-sided P-value less than 0.05 was considered statistically significant.

## RESULTS

### Baseline Characteristics

Between 2006 and 2018, the Kailuan Group conducted health examinations on 186,249 individuals and identified 4328 HF cases by December 31, 2020. After exclusion of 265 participants with a history of HF at the first examination and 41 participants with a history of malignant tumors at the time of HF occurrence, 4022 new-onset HF cases remained. After 1:4 matching according to age (within ±1 year) and sex, 3998 patients with HF (average age 68.59 ± 10.93, 86.49% men) and 15,769 controls were included. Relative to controls, patients with HF had higher fasting blood glucose, BMI, heart rate, and creatinine, but lower TC, LDL-C, eGFR, and hemoglobin levels; had greater prevalence of hypertension and diabetes; and frequently used antidiabetic, lipid-lowering, antiplatelet, beta-blocker, and ACEI/ARB drugs (Table 1). Comparison of patients

**Table 1** Basic Characteristics of Participants with New-Onset Heart Failure and Controls.

| Variables | New-onset heart failure (n=3998) | Control participants (n=15,769) | P value |
|---|---|---|---|
| Age (years) | 68.59±10.93 | 68.12±10.54 | 0.0519 |
| Male, n (%) | 3458 (86.49) | 13,617 (86.35) | 0.1343 |
| Smokers, n (%) | 1209 (30.24) | 4705 (29.84) | 0.7131 |
| Drinkers, n (%) | 1072 (26.81) | 5017 (31.82) | <0.0001 |
| Physical exercise, n (%) | 1155 (28.99) | 4521 (28.67) | 0.8885 |
| Higher education or above, n (%) | 172 (4.30) | 779 (4.94) | 0.0387 |
| SBP (mmHg) | 141.20±22.66 | 141.57±21.20 | 0.2191 |
| FBG (mmol/L) | 6.73±2.89 | 5.93±1.77 | <0.0001 |
| BMI (kg/m$^2$) | 25.40±3.55 | 24.73±3.24 | <0.0001 |
| TC (mmol/L) | 4.60±1.34 | 4.97±1.27 | <0.0001 |
| LDL-C (mmol/L) | 2.45 (1.81-3.13) | 2.79 (2.27-3.34) | <0.0001 |
| Heart rate (bpm) | 82.24±32.00 | 75.10±11.80 | <0.0001 |
| Creatinine (μmol/L) | 81.00 (67.00-100.75) | 78.00 (66.00-91.90) | <0.0001 |
| eGFR (mL/min/1.73 m$^2$) | 77.38±27.58 | 83.05±16.98 | <0.0001 |
| Hb (g/L) | 137.43±22.72 | 147.37±14.81 | <0.0001 |
| Hypertension, n (%) | 2924 (73.26) | 10467 (66.38) | <0.0001 |
| Diabetes, n (%) | 1282 (32.47) | 2759 (17.50) | <0.0001 |
| Medical treatment, n (%) | | | |
| Antidiabetic agents | 773 (19.33) | 1019 (6.46) | <0.0001 |
| Lipid-lowering agents | 2474 (61.88) | 904 (5.73) | <0.0001 |
| Antiplatelet agents | 2514 (62.88) | 614 (3.89) | <0.0001 |
| Beta-blockers | 1115 (27.89) | 304 (1.93) | <0.0001 |
| ACEIs/ARBs | 1262 (31.57) | 1168 (7.41) | <0.0001 |
| MRAs | 138 (3.45) | — | <0.0001 |
| Diuretics | 512 (12.81) | — | <0.0001 |
| Cardiotonics | 264 (6.60) | — | <0.0001 |

Abbreviations: SBP, systolic blood pressure; FBG, fasting blood glucose; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; Hb, hemoglobin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

with HF with an earlier versus a later age of onset indicated that the former were more likely to smoke, drink alcohol, and lack physical exercise, as well as to have higher BMI, TC, LDL-C, eGFR, and hemoglobin levels. The likelihood of having diabetes and taking antidiabetic agents, lipid-lowering agents, antiplatelet agents, beta-blockers, and ACEIs/ARBs was also higher among patients with an earlier than a later age of onset (Table 2).

## All-Cause Mortality by Age Group

During a median follow-up of 5.25 years, the new-onset HF group experienced 1783 all-cause mortality events, with 98, 385, 564, and 736 cases distributed across the age groups. In contrast, the control group reported 2633 events, with 55, 287, 741, and 1550 cases distributed across the age groups. The incidence of mortality in the HF group was 32.85, 55.61, 86.15, and 157.15 per 1000 person-years, whereas that in the control group was 4.70, 10.19, 26.39, and 77.51 per 1000 person-years, across the age groups. The cumulative all-cause mortality rates for the new-onset HF group were 43.48%, 53.98%, 70.87%, and 84.08%, whereas those in the control group were 8.40%, 19.42%, 41.47%, and 72.79%, across the age groups. The difference in cumulative mortality rates between the HF and control groups across age groups is illustrated in Supplementary Figure 1.

**Table 2** Basic Characteristics of Participants with New-Onset Heart Failure Across Age Groups.

| Variables | <55 (n=412) | 55-64 (n=1149) | 65-74 (n=1243) | ≥75 (n=1194) | P value |
|---|---|---|---|---|---|
| Age (years) | 49.90±5.34 | 60.51±2.68 | 69.93±2.95 | 81.41±4.96 | <0.0001 |
| Male, n (%) | 349 (84.71) | 969 (84.33) | 1073 (86.32) | 1067 (89.36) | 0.0094 |
| Smokers, n (%) | 177 (42.96) | 383 (33.34) | 342 (27.51) | 301 (25.21) | <0.0001 |
| Drinkers, n (%) | 132 (32.04) | 341 (29.68) | 309 (24.86) | 284 (23.79) | 0.0004 |
| Physical exercise, n (%) | 72 (17.48) | 294 (25.59) | 381 (30.65) | 402 (33.67) | <0.0001 |
| Higher education or above, n (%) | 25 (6.07) | 43 (3.74) | 52 (4.18) | 46 (3.85) | 0.2112 |
| SBP (mmHg) | 139.42±23.07 | 141.57±22.84 | 142.30±22.95 | 140.32±21.99 | 0.0554 |
| FBG (mmol/L) | 6.70±2.96 | 6.86±2.92 | 6.62±2.74 | 6.72±2.99 | 0.2565 |
| BMI (kg/m$^2$) | 26.04±3.87 | 25.78±3.55 | 25.25±3.49 | 24.97±3.45 | <0.0001 |
| TC (mmol/L) | 4.85±1.42 | 4.70±1.42 | 4.59±1.33 | 4.42±1.23 | <0.0001 |
| LDL-C (mmol/L) | 2.55 (1.87-3.19) | 2.50 (1.87-3.23) | 2.51 (1.82-3.15) | 2.34 (1.70-3.00) | <0.0001 |
| Heart rate (bpm) | 78.00 (70.00-90.00) | 78.00 (70.00-91.00) | 78.00 (68.00-90.00) | 80.00 (70.00-93.00) | 0.0937 |
| Creatinine (μmol/L) | 79.60 (66.90-100.00) | 78.00 (65.00-97.0) | 81.00 (68.00-100.00) | 83.00 (70.00-104.74) | 0.0003 |
| eGFR (ml/min/1.73 m$^2$) | 96.27 (74.44-105.89) | 91.75 (71.33-98.98) | 82.52 (64.44-91.30) | 73.56 (56.14-84.04) | <0.0001 |
| Hb (g/L) | 145.65±21.75 | 141.65±22.60 | 137.96±20.93 | 129.31±22.69 | <0.0001 |
| EF (n=2816) | | | | | 0.2935 |
| ≥50% | 240 (76.19) | 687 (80.44) | 695 (79.79) | 643 (82.86) | |
| 40-49% | 47 (14.92) | 101 (11.83) | 108 (12.40) | 77 (9.92) | |
| <40% | 28 (8.89) | 66 (7.73) | 68 (7.81) | 56 (7.22) | |
| NYHA class (n=3221) | | | | | <0.0001 |
| I | 12 (3.29) | 18 (1.84) | 19 (1.95) | 9 (1.00) | |
| II | 194 (53.15) | 566 (57.81) | 523 (53.64) | 419 (46.45) | |
| III | 108 (29.59) | 267 (27.27) | 293 (30.05) | 325 (36.03) | |
| IV | 51 (13.97) | 128 (13.07) | 137 (14.05) | 148 (16.41) | |
| Hypertension, n (%) | 299 (72.57) | 849 (73.89) | 952 (76.59) | 823 (68.93) | 0.0006 |
| Diabetes, n (%) | 135 (32.77) | 426 (37.08) | 426 (34.27) | 305 (25.54) | <0.0001 |
| Medical treatment, n (%) | | | | | |
| Antidiabetic agents | 83 (20.15) | 274 (23.85) | 268 (21.56) | 142 (11.90) | <0.0001 |
| Lipid-lowering agents | 258 (62.62) | 767 (66.75) | 792 (63.72) | 651 (54.52) | <0.0001 |
| Antiplatelet agents | 262 (63.59) | 773 (67.28) | 836 (67.26) | 637 (53.35) | <0.0001 |
| Beta-blockers | 121 (29.37) | 370 (32.20) | 389 (31.30) | 229 (19.18) | <0.0001 |
| ACEI/ARB | 129 (31.31) | 420 (36.55) | 434 (34.92) | 273 (22.86) | <0.0001 |
| MRA | 6 (1.46) | 36 (3.13) | 47 (3.78) | 43 (3.60) | 0.1245 |
| Diuretics | 34 (8.25) | 110 (9.57) | 173 (13.92) | 189 (15.83) | <0.0001 |
| Cardiotonics | 24 (5.83) | 76 (6.61) | 80 (6.44) | 78 (6.53) | 0.8449 |

Abbreviations: SBP, systolic blood pressure; FBG, fasting blood glucose; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; Hb, hemoglobin; EF, ejection fraction; NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

## Multifactorial Cox Regression Analysis of Age at Onset of Heart Failure on All-Cause Mortality

In a multivariable Cox regression analysis adjusting for variables including age, sex, smoking habit, alcohol consumption, education level, physical exercise, body mass index, low-density lipoprotein, hemoglobin, and medication use (including antidiabetic agents, lipid-lowering agents, antiplatelet agents, beta-blockers, ACEIs/ARBs, MRAs, and diuretics), the influence of HF onset age on all-cause mortality was evaluated. Relative to participants in the control group, patients with new-onset HF consistently exhibited greater risk of all-cause mortality across all age brackets. Notably, the most pronounced risk was identified in patients below 55 years of age, with an HR 6.86 (95% CI: 4.42–10.64). As the age of HF onset increased, the relative mortality risk progressively decreased: HR 4.70 (95% CI: 3.73–5.92) for 55–64 years, HR 3.23 (95% CI: 3.73–3.81) for 65–74 years, and HR 1.69 (95% CI: 1.48–1.94) for 75 years or older (Table 3).

## Absolute Risk of All-Cause Mortality by Age Group

We assessed the absolute risk of all-cause mortality across various age groups of HF onset, standardizing the results according to age and sex. Across the age groups, the standardized prevalence (95% CI) was 23.79 (19.08–28.50), 33.50 (30.16–36.85), and 45.38 (41.63–49.13), 61.58 (57.14–66.03) in the new-onset HF group, and 3.34 (2.46–4.22), 6.23 (5.51–6.95), 14.85 (13.78–15.92), and 34.27 (32.56–35.97) in the control group. These findings underscored that patients with new-onset HF consistently exhibited greater absolute mortality risk than controls across all age brackets, and this risk was amplified with increasing age of onset (Table 4).

## Sensitivity Analysis

We performed sensitivity analyses (Supplementary Tables 1–5), omitting participants with prior histories of conditions such as myocardial infarction, atrial fibrillation, stroke, hypertension, and renal

**Table 3** HR (95% CI) For All-Cause Mortality Among Patients with New-Onset Heart Failure Versus Controls, Across Age Groups.

| Onset age | New-onset heart failure | | Control participants | | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|---|---|
| | Case/total | Rate | Case/total | Rate | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| <55 | 98/412 | 32.85 | 55/1648 | 4.70 | 6.73 (4.82-9.38) | 5.44 (3.83-7.73) | 6.86 (4.42-10.64) |
| 55-64 | 385/1149 | 55.61 | 287/4607 | 10.19 | 5.37 (4.60-6.26) | 4.22 (3.57-4.99) | 4.70 (3.73-5.92) |
| 65-74 | 564/1243 | 86.15 | 741/4989 | 26.39 | 3.25 (2.91-3.63) | 2.88 (2.55-3.24) | 3.23 (3.73-3.81) |
| ≥75 | 736/1194 | 157.15 | 1550/4525 | 77.51 | 1.94 (1.78-2.12) | 1.62 (1.47-1.80) | 1.69 (1.48-1.94) |

The rate is per 1,000 person-years. Model 1: adjusted for age, sex; model 2: adjusted for smoking habit, alcohol consumption, educational level, physical exercise, body mass index, low-density lipoprotein, and hemoglobin, based on model 1; model 3: further adjusted for medication use (including antidiabetic drugs, lipid-lowering drugs, antiplatelet drugs, beta-blockers, ACEIs/ARBs, MRAs, and diuretics), based on model 2.

**Table 4** Absolute Risk of All-Cause Mortality in Different Age Groups in the New-Onset Heart Failure Group and Control Group.

| Onset age | New-onset heart failure | Crude ratio | Standardized ratio | Control participants | Crude ratio | Standardized ratio |
|---|---|---|---|---|---|---|
| | Case/total | | (95% CI) | Case/total | | (95% CI) |
| <55 | 98/412 | 23.79 | 23.79 (19.08-28.50) | 55/1648 | 3.34 | 3.34 (2.46-4.22) |
| 55-64 | 385/1149 | 33.51 | 33.50 (30.16-36.85) | 287/4607 | 6.23 | 6.23 (5.51-6.95) |
| 65-74 | 564/1243 | 45.37 | 45.38 (41.63-49.13) | 741/4989 | 14.85 | 14.85 (13.78-15.92) |
| ≥75 | 736/1194 | 61.64 | 61.58 (57.14-66.03) | 1550/4525 | 34.25 | 34.27 (32.56-35.97) |

insufficiency. Re-evaluation with the Cox proportional hazards regression model across all age groups indicated that the relative mortality risk of patients with new-onset HF compared with the control group remained consistent with the primary findings. When participants with a diabetes history were excluded, the 55–64 age bracket of patients with HF exhibited the most pronounced relative mortality risk, with an HR (95% CI) 5.29 (4.00–7.00). This risk declined with increasing age of onset.

## Discussion

Our findings based on Kailuan Study data indicated that patients with HF with an onset age younger than 55 years, as compared with age- and sex-matched controls without HF, exhibited the greatest relative risk of all-cause mortality. Intriguingly, as the onset age of HF increased, the relative mortality risk decreased. Nonetheless, the absolute mortality risk of patients with HF rose consistently with advancing age.

Data from the CHARM-preserved, I-PRESERVE, and TOPCAT studies have indicated that younger patients with HFpEF have more severe symptoms, poorer quality of life, and a higher frequency of cardiovascular fatalities than their older counterparts [11]. The SwedeHF study has further indicated that patients with HF 18–34 years of age have the greatest mortality risk, with an HR 38.3 (95% CI 8.70–169), and this risk decreases with age. Specifically, patients 45–54 years of age with HF exhibited a 4.61-fold elevated mortality risk [7]. Our analysis mirrored these findings, revealing that participants with new-onset HF showed a progressively decreasing risk of all-cause mortality with increasing age; the risks in the age brackets of <55 years, 55–64 years, 65–74 years, and ≥75 years were 6.86-fold, 4.70-fold, 3.23-fold, and 1.69-fold, respectively, in patients with HF compared with matched controls. This trend persisted even after exclusion of individuals with prior medical conditions such as myocardial infarction, atrial fibrillation, stroke, hypertension, or renal insufficiency. Notably, our study spanned an extensive age spectrum and started follow-up from the point of definitive HF diagnosis, thereby mitigating the influence of HF progression on outcomes, and bolstering the reliability of our conclusions.

In our research, after adjustment for the use of specific medications (including hypoglycemic agents, lipid-lowering agents, antiplatelet agents, beta-blockers, ACEIs/ARBs, MRAs, and diuretics), we observed an augmented relative risk of all-cause mortality across all age groups for patients with new-onset HF. A reasonable interpretation for this finding may be that the types of medications reflect not only the coexisting conditions of HF but also the underlying causes associated with HF. For example, hypoglycemic agents and antiplatelet agents might suggest a concurrent presence of HF such as diabetes or coronary artery disease. They could also point towards arising from diabetes-related complications that impact both large and small blood vessels. Therefore, the mortality risk in HF is elevated not by the medication itself but by the underlying condition for which the drug is prescribed.

In our study, although a pronounced relative risk of all-cause mortality was evident in younger patients with HF compared with their older counterparts, the substantial mortality effects of HF in the older demographic must be noted. Our findings indicated that the absolute mortality risks for patients with HF across the age brackets of <55 years, 55–64 years, 65–74 years, and ≥75 years were 23.79%, 33.51%, 45.37%, and 61.64%, respectively. When standardized, these risks were 23.79 (19.08–28.50), 33.50 (30.16–36.85), 45.38 (41.63–49.13), and 61.58 (57.14–66.03), respectively, translating to a 37.28% greater in absolute mortality risk in older (≥75 years) than younger (<55 years) people. Notably, prior research on HF mortality has emphasized relative risk, which can lead to an overestimation of the effect, thereby overshadowing the actual absolute risk [12]. Our study underscores that the real-world absolute mortality risk in older patients with HF is indeed higher than that in younger patients.

The heightened relative risk of all-cause mortality in younger patients with HF may be attributable to several mechanisms. First, HF is frequently associated with various cardiac structural anomalies, such as augmented left ventricular mass, increased pulmonary artery systolic pressure, and diminished left ventricular ejection fraction. These parameters indicate the likelihood of HF onset and subsequent mortality [13–19]. Younger patients with HFpEF

have been shown to have a more pronounced left ventricular mass index and higher incidence of left ventricular hypertrophy than their older counterparts [11]. In addition, a left ventricular ejection fraction below 50% is a standalone predictor of both short-term and long-term mortality in the younger demographic [20], thus implying poorer prognosis among younger patients with HF. Second, younger individuals, in contrast to older individuals, show a rapid escalation in HF risk factors including obesity, hypertension, diabetes, and smoking habit. These elements amplify the mortality rate in HF. Moreover, the activation of the renin-angiotensin-aldosterone system in HF induces sodium and water retention, thus culminating in dilutional hyponatremia. Notably, hyponatremia has been recognized as an independent determinant of 1-year and 4-year mortality rates in young patients with HF [20, 21]. Consequently, more aggressive and rigorous treatment strategies are imperative to mitigate mortality in patients with early-onset HF.

This study has multiple merits. Notably, this extensive prospective cohort initiated follow-up from the time of disease diagnosis. The entire study cohort was covered by the Municipal Social Insurance Institution, included in the hospitals' discharge register, and received biennial medical evaluations, thus ensuring comprehensive tracking of participants' outcome events. Moreover, the inclusion of age-and sex-matched control groups without HF substantially mitigated the influence of potential confounders. Notably, prior investigations of the age-associated implications of HF have been conducted predominantly in Western nations, and differences may exist in disease prevalence and age-specific incidence rates across diverse populations. This study decreases this knowledge gap by presenting findings from an Asian demographic.

However, the current study has several limitations. First, the participants consisted primarily of active and retired personnel from the Kailuan Group and were predominantly men, thus potentially introducing selection bias. However, we sought to mitigate the influence of sex on the results by incorporating it as a factor in the multifactorial Cox regression analysis. Another constraint was the lack of detailed information on death classification and all-cause mortality, thus hindering identification of specific death causes. In addition, because the study's median follow-up period was relatively brief, by the end of the follow-up, not all outcome events for participants might have been fully captured.

## Conclusion

Our study indicates a pronounced link between HF and elevated risk of all-cause mortality. Notably, the relative risk of all-cause mortality was greater with younger ages of HF onset.

## Data Availability Statement

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

## Ethics Statement

The project protocol was approved by the ethics committee of Ethics Committee of the Kailuan Medical Group and was by the guidelines of the Helsinki Declaration, and all study individuals in this project signed an informed consent form at enrollment.

## Author Contributions

Wei Li conceived and designed the study, analyzed the data, and drafted and revised the manuscript. Haibo Gao conceived and designed the study and revised the manuscript. Xuemei Zhao and Yifei Wang analyzed the data and revised the manuscript. Shouling Wu and Jing Yang collected clinical data, followed patients, and revised the manuscript. Qi Zhang conceived and designed the study, and drafted and revised the manuscript. All authors read and approved the final manuscript.

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## Conflict of Interest

The authors declare no conflicts of interest.

## Supplementary Material

Supplementary material for this paper is obtainable at the following link https://cvia-journal.org/wp-content/uploads/2023/12/supplementary_file.pdf.

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