Full Title

Non-cardiovascular death, especially infection, is a significant cause of death in elderly patients with acutely decompensated heart failure

Short title

Non-cardiovascular death in elderly ADHF

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Abstract

Background

Despite marked improvements in treatment strategies for heart failure (HF), the mortality rate of elderly patients with HF is still high. Detailed causes of death have not been fully understood.

Methods and Results

We studied 459 consecutive patients with acute decompensated HF (ADHF) emergently admitted to our hospital from 2007 to 2011. Patients were divided into 2 groups: <75 years (younger group, n=225) and ≥75 years (elderly group, n=234). All-cause death, cardiovascular death, non-cardiovascular death were assessed as adverse outcomes.

Compared with the younger group, the elderly group was characterized by a higher incidence of women and hypertensive patients and higher left ventricular ejection fraction. During a mean follow-up of 20.7 months, a total of 174 patient deaths (37.9%) occurred. All-cause death was significantly higher in the elderly group than in the younger group (46.6% vs 28.9%; P<0.0001), and this difference was caused by an increase in non-cardiovascular deaths (20.9% vs 9.3%; P<0.001), in particular, deaths due to infection (10.7% vs 4.0%; P<0.01). Cardiovascular deaths did not differ between the 2 groups.

Conclusions

Non-cardiovascular deaths, most of which were caused by infection, were frequent among elderly patients with ADHF.

Key words

ADHF

Elderly

Prognosis

Introduction

Despite significant progress in treatment strategies for heart failure (HF), mortality and morbidity remain high.[1,2] As the population ages in Japan and other industrialized countries, the prevalence of HF is increasing and its prognosis is worsening.[3,4] HF is currently one of the leading causes of death and hospitalization in especially elderly patients.[5]

During last 2 decades, many clinical trials investigating how to treat patients with HF with a reduced ejection fraction (EF) have shown that renin-angiotensin-system blockers, β-blockers, and mineralocorticoid receptor antagonists reduce the number of cardiovascular events. However, most clinical trials have enrolled patients with a mean age between 60 and 65 years whose left ventricular EF (LVEF) was less than 40% and renal function was not severely impaired. In the real world, however, the majority of patients admitted for acutely decompensated HF (ADHF) are 75 years or older. Approximately half have an EF higher than 50% and approximately two-thirds have stage 3–5 chronic kidney disease. Elderly ADHF patients have a higher prevalence of hypertension and ischemic heart disease and a lower prevalence of dilated cardiomyopathy compared with younger patients, as well as more co-morbidities.[6-9]

Thus, it is likely that treatment strategies found to effective by recent clinical trials of HF patients with reduced EF are less applicable to elderly HF patients. In order to improve prognosis and to identify optimal treatment strategies for HF in elderly patients, it is necessary to

understand the clinical characteristics and causes of death in elderly HF patients. Although earlier observational studies of elderly patients with HF have described their baseline characteristics, the causes of death in elderly patients with HF have not been fully appreciated. [3,8,10]

In this context, the aim of the present study is to determine the long-term prognosis and causes of death in patients older than 75 years of age using a medium-sized retrospective cohort, the Nara registry and analyses for heart failure (the NARA-HF study).

Methods

Patient Selection

The NARA-HF study recruited patients emergently admitted to our hospital (internal medicine/cardiology wards or CCU) with verification of ADHF (acute new-onset and acute on chronic HF) between January 2007 and March 2011. Diagnosis of HF was based on Framingham criteria for HF.[11] Patients with acute myocardial infarction, acute myocarditis, acute HF with acute pulmonary embrysm were excluded. Patients were divided into 2 groups: <75 years (younger group, n=225) and ≥75 years (elderly group, n=234). For each patient, baseline date included: age, sex, body mass index (BMI), causes of HF, medical history, vital signs, laboratory data, echocardiographic data, and medication use on admission and at discharge.

Outcomes

All-cause death, cardiovascular death, and non-cardiovascular death were assessed as adverse outcomes. Cardiovascular death was defined as death due to HF, myocardial infarction, sudden death, or vascular diseases such as aortic dissection. All other causes of death were classified as non-cardiovascular death. Rehospitalization due to unexpected worsening of HF, non-fatal acute myocardial infarction, and stroke were also analyzed as cardiovascular outcomes.

Classification of Death

The cause of death was ascertained from hospital records, death certificates, by contacting the patients' physicians. When an underlying cause of death could not be identified because of insufficient information, we contacted with the patient's family on telephone if possible.

The underlying cause of death is defined as the critical condition that initiated the train of events leading directly to death. Even in the complex cases with multiple comorbidities relating to death, only one underlying cause of death assigned to each decedent. When the cause of death could not be determined in spite of an intensive investigation, the cause of death was classified as unknown.

Statistical Analysis

Continuous variables were expressed as means ± standard deviation, and comparisons between groups were performed using Student's t-test. Categorical variables were summarized as frequencies and analyzed using the chi-square test. Cumulative event-free rates during follow-up were derived using the Kaplan-Meier method. Univariate and multivariate analyses of mortality were performed using Cox proportional hazards models. Covariates considered to have potential prognostic impact (sex, BMI, hemoglobin concentration, estimated glomerular filtration rate (eGFR), brain natriuretic peptide (BNP), LVEF, and sodium level) were included in multivariable models. eGFR was calculated using the Japanese equations that take into account age, sex, and serum creatinine.[12] Results were reported as hazard ratios (HR), 95% confidence intervals (CI), and P values. The HR for outcomes in the elderly group was compared with those in the younger group. Only variables with P value <0.05 remained in the model. All statistical analysis were performed using JMP 10 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

All 459 consecutive patients were included in the analyses. The mean age was 72.4 ± 12.1 years. Forty-one percent of the patients were women. Table 1 compares the baseline clinical characteristics of the elderly patients (≥75 years old, n=234), and younger patients (<75 years old,

n=225). The elderly group had a significantly lower BMI and a higher percentage of women. Compared with the younger group, the elderly group had more HF attributable to an ischemic or valvular etiology and less to dilated cardiomyopathy. Patients in the elderly group was also more likely to have a history of hypertension and a previous myocardial infarction, whereas patients in the younger group were more likely to have diabetes mellitus. The diastolic blood pressure and heart rate on admission were significantly lower in the elderly group, but systolic blood pressure and the NYHA functional class were similar in the 2 groups. Hemoglobin, HbA1c, triglycerides, total cholesterol, and low-density lipoprotein cholesterol were significantly lower in the elderly group. In contrast, eGFR was similar between the 2 groups. There were no significant differences in the serum sodium concentration, plasma BNP level, and serum C-reactive protein level between the 2 groups. Left ventricular end-diastolic and end-systolic diameters were significantly smaller and LVEF was significantly higher in the elderly group. Moreover, the rate of LVEF $\geq$ 50% was significantly higher in the elderly group. As to medical treatment during hospital, the incidence of mechanical ventilation, including intubation and non-invasive positive pressure ventilation, percutaneous coronary intervention was similar in both groups. The patients in both groups were equally treated with catecholamine, vasodilator, carperitide, as necessary. However the incidence of dialysis and coronary artery bypass graft was higher in the younger group than in the elderly group.

Treatment on admission and at discharge

Table 2 shows the medications at discharge. The use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, and loop diuretics were similar in the 2 groups at discharge, but β-blockers were significantly less frequently used in the elderly group. The medications on admission were similar in the 2 groups.

Prognosis and Outcome

During a follow-up duration of 20.7 months, there were 109 (46.6%) deaths in the elderly group, of which 47 (20.1%) were cardiovascular deaths and 49 (20.9%) were non-cardiovascular deaths. In the younger group, 65 (28.9%) patients died: 37 (16.4%) from cardiovascular causes, and 21 (9.3%) from non-cardiovascular causes (Table 3). The mortality rate was significantly higher in the elderly group than the younger group ($P<0.0001$). Although the incidence of cardiovascular death was similar, the incidence of non-cardiovascular death in the elderly group was significantly higher ($P=0.0005$) (Table 3). Within non-cardiovascular death, the incidence and the proportion of infection-related death were significantly higher in the elderly group ($P=0.0053$) (Table 3 and Figure 1). Even after adjustment for covariates in multivariable Cox proportional hazard models, age ≥75 years was an independent predictor for non-cardiovascular death and

infection-related death, as shown in Table 4. The rehospitalization rate and the incidence of non-fatal acute myocardial infarction and stroke were similar in both groups.

As shown in the Kaplan-Meier survival curves, the elderly group had a much higher rate of all-cause death (log-rank P<0.0001) and non-cardiovascular death (log-rank P=0.0001), but there was no significant difference in the rate of cardiovascular death (log-rank P=0.0967) (Figure 2).

Discussion

The present study is a retrospective cohort study involving 459 patients with ADHF, of whom 58.6% were male. The mean age was 72.4 years. Patients in this study were slightly older than in recent large Japanese and European prospective cohort studies, namely JCARE-CRAD (mean age, 71.0 years)[3] and the Euro Heart Failure Survey II (mean age, 69.9 years)[7], respectively. Other baseline patient characteristics were similar. The mortality rate in person-years in the present study was worse than in JCARE-CRAD, but similar to the Euro Heart Failure Survey II.

To compare clinical characteristics and outcomes in elderly versus younger patients, we divided all patients into 2 groups according to age, ≥75 years and <75 years, because 75 years of age was near the median value in the present study and because individuals ≥75 years are usually called old-old people or late-stage elderly in Japan. The differences in baseline clinical characteristics between the elderly and young groups were consistent with those in previous studies.[6-8,13-15]

Elderly patients were more frequently women, and had lower BMI and higher LVEF. They were more likely to have HF of ischemic or valvular etiology. In contrast, younger patients were more likely to have dilated cardiomyopathy and diabetes mellitus as previous studies.[3,7,16]

The present study demonstrates a higher mortality rate in elderly HF patients compared to younger HF patients during a long-term follow-up period up to 20.7 months ($P<0.0001$). The incidence of non-cardiovascular death was significantly higher in the elderly group, although the incidence of cardiovascular death was similar in both groups. The proportion of non-cardiovascular and infection-related death among all deaths reached approximately 45% and 23%, respectively. Thus, a higher rate of non-cardiovascular death, especially infection-related death, probably contributed to the higher mortality rate in the elderly group. Although earlier studies reported a high incidence of non-cardiovascular death in elderly patients with HF, such studies did not focus on infection.[17,18] To our knowledge, the present study, for the first time, examined the details by telephone and careful medical record review on an individual level, which made it possible to figure out the cause of death in these ADHF patients. These findings suggest that careful care should be paid to prevent non-cardiovascular events and infection in addition to the treatment of HF itself in elderly HF patients. Recently, there is accumulating evidence that non-cardiovascular death is significant in HF patients with preserved EF. Given that elderly ADHF patients are more likely to have preserved EF than younger ones, it is likely

that elderly ADHF patients mostly die due to non-cardiovascular causes.

The rate of infection-related death increases with age even in the general population. To better understand the relationship between infection-related death and age in patients with ADHF, we compared it with that in Japanese general population, using the database from the Japanese Ministry of Health, Labour and Welfare[13]. The proportion of infection–related death is approximately 15% and 6% in the Japanese general population older than 75 years, and those aged 75 years or younger, respectively.[13] In the present study, 25 of 109 all-cause deaths (about 23%) were died from infection in the elderly group and 9 of 65 all-cause death (about 14%) were died in the younger group. Thus the infection-related death in patients with ADHF is apparently higher than in the general population in any ages. In other words, ADHF may be a risk factor for infection-related death. Therefore, physicians should pay an attention to prevent infection in ADHF patients with any ages, especially in older patients because the absolute number of infection-related death was significantly larger.

As shown in the Kaplan-Meier curve of infection-related death in elderly ADHF patients, difference in survival rate is becoming obvious after about 800 days later. However, the Kaplan-Meier curve of non-cardiovascular death is spreading gradually from the beginning. We cannot explain clearly for the difference. One possible explanation is higher incidence of cancer related death in the elderly group than the younger group within 800 days after the recruitment.

Besides, given that older patients would be more likely rehospitalized by non-HF causes, such as cancers or infection after discharge, they would more easily die of infection. Therefore we also examined the Kaplan-Meier survival curves of patients except subsequent hospitalization for all diseases other than HF. The rate of infection-related death remained higher in the elderly group than in younger group (log-rank P=0.0332, data not shown).

At discharge, prescription rates for ACE inhibitors, ARBs, mineralocorticoid receptor blockers, and diuretics in both groups of patients were similar; β-blockers were less used in the elderly group. One possible examination is higher prevalence of HF with preserved EF in the elderly patients. Medications had a similar effect on the prevention of cardiovascular death and HF-related rehospitalization in elderly patients, suggesting that these regimens could work effectively in both young and elderly patients with ADHF. Previous studies reported that cardiovascular events were more common in the elderly group than in the younger group.[3,8] The reason for the discrepancy is not clear at present, but the relatively high usage of ACE inhibitors, ARBs, or both, in the elderly group in this study might be related to the better cardiovascular outcomes observed. Another possible explanation is that in these studies, they compared clinical outcomes in octogenarians with those in younger patients.

Study Limitations

There are several limitations to this study. The major limitation is that it was middle-sized, retrospective in design, and based at a single center. Thus, the evidence level is not high, but details on the cause of death could be obtained from more than 95% of patients. Although we compared outcomes between elderly and younger patients, we did not collect data on variables that probably influence prognosis in the elderly, such as exercise tolerance and activities of daily living. Respiratory function and the incidence of chronic obstructive lung disease were not examined. As far as we know, a wide QRS wave influences adverse outcomes in ADHF, but we did not measure QRS wave width on admission. We used only the Framingham Criteria for the diagnosis of ADHF in order to include 'real world' HF patients. Many patients had both cardiac and renal failure. There were some patients in whom it was difficult to determine whether pulmonary edema was cardiac or renal in nature.

Conclusion

The present study demonstrates that adverse outcomes including all-cause death and non-cardiovascular death in elderly patients were significantly poorer than in younger patients. Although there was no difference in the incidence of cardiovascular death between the 2 groups, non-cardiovascular death, mostly caused by infection, was more frequent among elderly patients with ADHF. These findings indicate the need to prevent infections for better prognosis. Moreover,

we need more information on elderly patients with HF in order to design preventive and therapeutic strategies specifically directed towards them.

Disclosure

None

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Table 1. Baseline Characteristics of HF Patients According to Age

Characteristic	Total (n=459)	Age <75years (n=225)	Age ≥75years (n=234)	P value
Demographic				
Age, years	72.4±12.1	62.8±9.92	81.6±4.68	<0.0001
Male, %	58.6	64.9	52.6	0.0074
BMI, kg/m^2	23.1±4.11	24.21±4.47	22.09±3.41	<0.0001
Causes of HF, %				
Ischemic	40.3	33.3	47.0	0.0028
Valvular	18.3	14.2	22.2	0.0267
Dilated cardiomyopathy	12.6	20.0	5.6	<0.0001
Hypertensive	6.1	6.7	5.6	0.6190
Medical history, %				
Hypertension	80.6	76.9	84.2	0.0375
Diabetes mellitus	47.1	52.9	41.5	0.0141
Dyslipidemia	36.6	39.6	33.8	0.2087
CKD stage 4 or 5	38.6	40.4	36.8	0.4165
Smoking	18.3	24.9	12.0	0.0004
Old myocardial infarction	26.1	17.8	34.2	<0.0001
Dialysis	7.8	11.1	4.7	0.0107
Procedures, %				
PCI	22.0	17.3	26.5	0.0167
CABG	6.5	6.7	6.4	0.9115
CRT or ICD	2.2	2.2	2.1	0.9500
NYHA class on admission, %				0.7444
II	10.2	10.7	9.8	
III	39.2	40.4	38.0	
IV	50.5	48.9	52.1	
Vital signs on admission				
Heart rate, beats/min	92.9±25.6	95.5±26.4	90.4±24.6	0.0316
SBP, mmHg	142.8±35.7	144.7±37.5	140.9±33.8	0.2538
DBP, mmHg	80.1±22.9	82.6±25.1	77.7±20.3	0.0218
MBP, mmHg	100.6±25.8	103.1±27.5	98.34±23.9	0.0503
Echocardiographic parameters				
LVEF, %	48.16±15.95	46.32±16.52	50.01±15.17	0.0187

LVEF ≥ 50%, %	47.6	42.0	53.2%	0.0234
LV EDD, mm	53.95±9.97	55.57±10.49	52.32±9.16	0.0012
LV ESD, mm	40.42±11.6	42.28±12.29	38.53±10.59	0.0015
LAD, mm	44.45±8.38	44.26±8.50	44.64±8.28	0.6845
Laboratory data on admission				
BUN, mg/dl*	27.0 (19.0-60.7)	28.0 (18.5-46.0)	26.0 (19.0-44.5)	0.5319
eGFR, ml/min/1.73m^2*	39.5 (16.3-60.7)	38.9 (12.9-63.6)	39.6 (19.4-59.0)	0.6284
CRP, mg/dl*	0.70 (0.20-2.50)	0.60 (0.20-2.25)	0.85 (0.20-2.93)	0.1446
Hemoglobin, g/dl	11.2±2.5	11.68±2.71	10.7±2.10	<0.0001
HbA1c, %	5.85±1.00	5.99±1.12	5.71±0.85	0.0058
Triglyceride, mg/dl	88.5±39.3	96.6±42.8	80.7±33.8	<0.0001
Total cholesterol, mg/dl	168.3±42.8	172.7±46.8	164.0±38.2	0.0328
HDL cholesterol, mg/dl	49.8±20.4	49.9±22.5	49.7±18.1	0.9216
LDL cholesterol, mg/dl	100.9±38.1	104.5±41.6	97.2±33.8	0.0454
Na, mEq/l	138.9±4.68	138.8±4.23	139.1±5.08	0.2108
K, mEq/l	4.26±0.85	4.29±0.79	4.25±0.91	0.4513
Plasma BNP, pg/ml*	798 (398–1540)	800 (367–1418)	781 (401–1692)	0.5353

Data are shown as percentages, means ± standard deviation or medians (25th and 75th percentile)*

HF, heart failure; BMI, body mass index; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, Mean blood pressure; LV, left ventricular; EF ejection fraction; EDD, end-diastolic diameter; ESD, end-systolic diameter; LAD, left atrial diameter; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BNP, B-type natriuretic peptide.

Table 2. Medications at Discharge of HF Patients According to Age

	Total (n=459)	**Age<75years (n=225)**	**Age≥75years (n=234)**	**P value**
β-blockers, %	42.8	48.4	37.3	0.0163
ACE inhibitors, %	55.9	53.8	57.9	0.3698
ARBs, %	38.7	41.3	36.1	0.2458
ACE inhibitors or ARBs, %	82.3	83.6	81.1	0.4939
Diuretics, %	75.8	73.8	77.7	0.3296
Loop diuretics, %	73.4	72.0	74.7	0.5169
MR blockers, %	26.4	24.4	28.3	0.3462
Ca channel blockers, %	31.7	32.4	30.9	0.7226
Statin, %	24.9	30.2	19.7	0.0095
Aspirin, %	43.7	39.1	48.0	0.0533
Digitalis, %	12.5	14.7	10.3	0.1570
Warfarin, %	27.5	29.8	25.3	0.2857

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MR, mineralocorticoid receptor.

Table 3. Causes of Death According to Age

	Total (n=459)	Age <75years (n=225)	Age ≥75years (n=234)	P value
All-cause death, n (%)	174(37.9)	65(28.9)	109(46.6)	<0.0001
Cardiovascular death, n (%)	84(18.3)	37(16.4)	47(20.1)	0.3126
Acute myocardial infarction, n (%)	8(1.7)	4(1.8)	4(1.7)	0.9554
Congestive heart failure, n (%)	48(10.5)	19(8.4)	29(12.4)	0.1653
Sudden death, n (%)	21(4.6)	11(4.9)	10(4.3)	0.7524
Stroke, n (%)	6(1.3)	3(1.3)	3(1.3)	0.9614
Vascular death, n (%)	1(0.2)	0(0)	1(0.4)	0.2454
Non-cardiovascular death, n (%)	70(15.3)	21(9.3)	49(20.9)	0.0005
Infection, n (%)	34(7.4)	9(4.0)	25(10.7)	0.0053
Cancer, n (%)	14(3.1)	4(1.8)	10(4.3)	0.1138
Gastrointestinal bleeding, n (%)	7(1.5)	3(1.3)	4(1.7)	0.7419
Kidney dysfunction, n (%)	6(1.3)	2(0.9)	4(1.7)	0.6850
Trauma, n (%)	3(0.7)	2(0.9)	1(0.4)	0.5362
Multiple organ failure, n (%)	4(0.9)	1(0.4)	3(1.3)	0.3228
Respiratory dysfunction, n (%)	1(0.2)	0(0)	1(0.4)	0.2454
Lung bleeding, n (%)	1(0.2)	0(0)	1(0.4)	0.2454
Unknown, n (%)	20(4.4)	7(3.1)	13(5.6)	0.1960
Rehospitalization with HF, n (%)	123(26.8)	63(28.0)	60(25.6)	0.6663
Acute myocardial infarction, n (%)	8(1.7)	4(1.8)	4(1.7)	0.9554
Cerebral infarction, n (%)	25(5.4)	15(6.7)	10(4.3)	0.2727

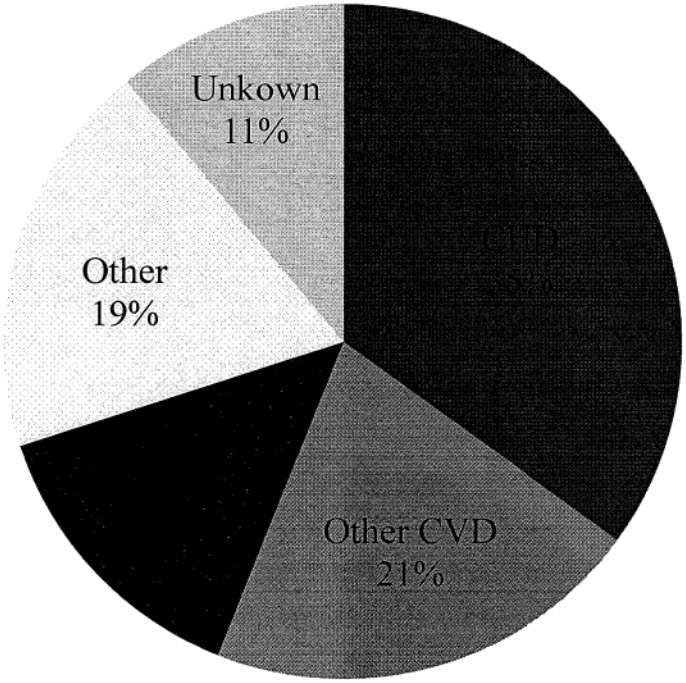
Table 4. Unadjusted and Adjusted HRs for Adverse Outcomes

	Age <75years (n=225)	Age ≥75years (n=234)	P value
All-cause death			
Unadjusted HR (95%CI)	1	1.903 (1.403-2.601)	<0.0001
Adjusted HR (95%CI)	1	2.026 (1.383-3.006)	0.0003
Cardiovascular death			
Unadjusted HR (95%CI)	1	1.439 (0.936-2.227)	0.0971
Adjusted HR (95%CI)	1	1.340 (0.794-2.284)	0.2733
Non-cardiovascular death			
Unadjusted HR (95%CI)	1	2.652 (1.612-4.519)	<0.0001
Adjusted HR (95%CI)	1	3.253 (1.726-6.461)	0.0002
Infection-related death			
Unadjusted HR (95%CI)	1	3.224 (1.557-7.317)	0.0013
Adjusted HR (95%CI)	1	7.093 (2.533-24.072)	<0.0001

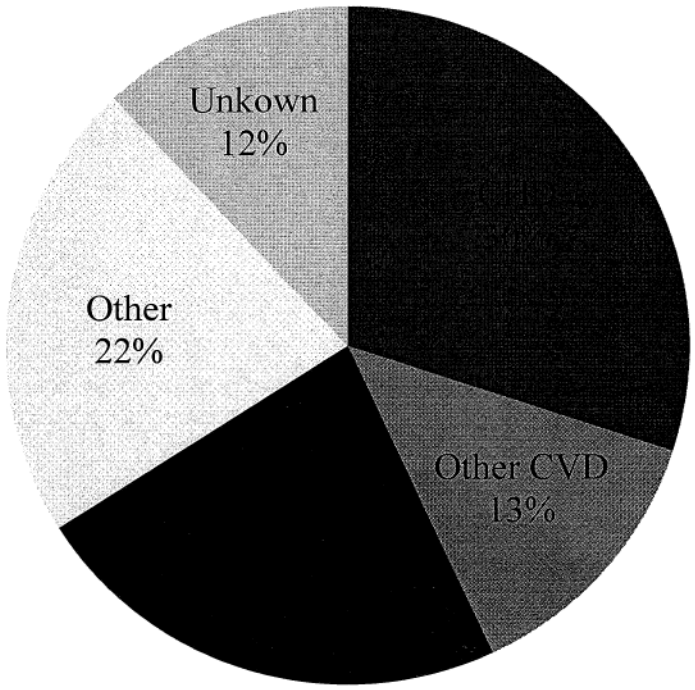
A Cox regression model was used, and was adjusted for the following covariates: sex, BMI, Hb, eGFR, BNP, Na, and LVEF. Patients < 75 years old were the reference group.

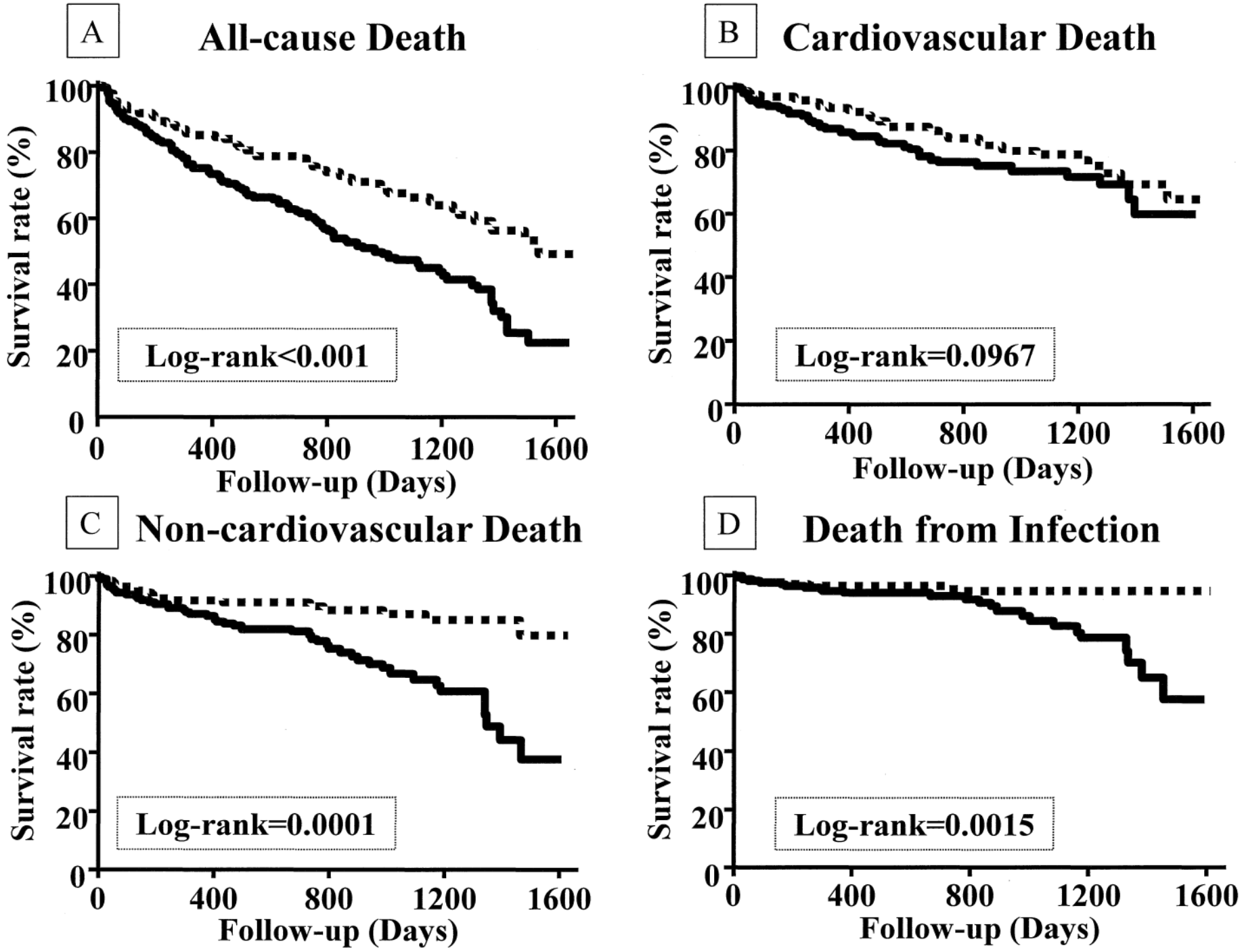
HR, hazard ratio; CI, confidence interval. All other abbreviations are as per Table 1.

Age < 75 years



Age ≥ 75 years




A
All-cause Death
Survival rate (%)
100
80
60
40
20
0
Log-rank<0.001
0
400
800
1200
1600
Follow-up (Days)
B
Cardiovascular Death
Survival rate (%)
100
80
60
40
20
0
Log-rank=0.0967
0
400
800
1200
1600
Follow-up (Days)
C
Non-cardiovascular Death
Survival rate (%)
100
80
60
40
20
0
Log-rank=0.0001
0
400
800
1200
1600
Follow-up (Days)
D
Death from Infection
Survival rate (%)
100
80
60
40
20
0
Log-rank=0.0015
0
400
800
1200
1600
Follow-up (Days)