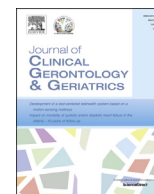


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## Original article

## Impact on mortality of systolic and/or diastolic heart failure in the elderly—10 years of follow-up

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## ABSTRACT

**Background/purpose:** There is a lack of long-term follow-up studies for elderly patients with heart failure (HF) in primary health care. There is conflicting information on prognostic differences between systolic or diastolic HF in elderly patients. Our aims were, first, to study the association between overall HF or types of HF and all-cause and cardiovascular mortality, and second, to explore the impact of N-terminal prohormone of brain natriuretic peptide (NTproBNP) and comorbidities.

**Methods:** A longitudinal, prognostic, observational primary health care study with 10 years of follow-up comparing an elderly patient population with HF (systolic and/or diastolic HF) to patients without HF was conducted. HF was diagnosed with echocardiography according to the European Society of Cardiology guidelines.

**Results:** Seventy-seven of 144 patients (102 women and 42 men; mean age, 77 years) had systolic and/or diastolic HF and were compared with 67 patients without HF (Reference group). During the 10-year follow-up, 71 (49%) patients died (women, 68%; men, 32%). In univariate Cox regression analysis, significant associations were found for overall HF [hazard ratio (HR), 1.86; 95% confidence interval (CI), 1.15–3.01], isolated systolic HF (HR, 1.95; 95% CI, 1.06–3.61), and combined (systolic and diastolic) HF (HR, 3.28; 95% CI, 1.74–6.14) with all-cause mortality, but not for isolated diastolic HF. Similar results were found for cardiovascular mortality. In multivariate analysis, age (HR, 1.11; 95% CI, 1.06–1.17), kidney dysfunction (HR, 1.91; 95% CI, 1.11–3.29), smoking (HR, 3.70; 95% CI, 2.02–6.77), and NTproBNP (HR, 1.01; 95% CI, 1.00–1.02) significantly predicted all-cause mortality, but not any type of HF.

**Conclusion:** Patients diagnosed with systolic HF had a worse prognosis for mortality compared to the reference group, but in patients with diastolic HF the prognosis for mortality was similar with that in the reference group. NTproBNP was a valuable prognostic factor in elderly patients. Emphasis should be placed on kidney dysfunction and smoking/having smoked.

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## 1. Introduction

In the elderly population (>75 years), the prevalence of heart failure (HF) is about 10%.<sup>1</sup> The prognosis for patients with HF is poor, comparable to a diagnosis of cancer.<sup>2</sup> Severe systolic HF has the most serious prognosis,<sup>3</sup> but whether diastolic HF has the same ominous prognosis as systolic HF in both younger and elderly patients is a matter of debate.<sup>3–5</sup> Elderly patients, especially females, are known to more often have diastolic HF than younger patients.<sup>6</sup>

However, most HF studies on prognosis are based on younger patients (<70 years) treated in the hospital,<sup>7</sup> but there is limited and conflicting information on prognostic differences between systolic or diastolic HF in elderly patients. Echocardiography is still the gold standard for diagnosis of HF, but there is limited use of echocardiography in primary health care (PHC) so many of these patients may be misdiagnosed and misclassified for prognostic reasons.<sup>8</sup> In PHC, elderly patients often have serious comorbidities, and the contributions of these comorbidities to the prognosis of patients with HF are often overlooked.<sup>9</sup> N-terminal prohormone of brain natriuretic peptide (NTproBNP) is a biomarker used to exclude HF,<sup>10</sup> but is also frequently used for prognostic purposes.<sup>11</sup> Its value in predicting mortality in elderly patients with systolic and/or diastolic HF requires further evaluation.

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There is a lack of long-term follow-up studies for elderly patients with HF in the PHC setting with regard to all-cause as well as cardiovascular mortality, and the prognostic impact of comorbidities.<sup>12</sup> The comorbidities may influence the prognosis beyond the type of HF in the short term; therefore, different follow-up periods need to be evaluated.

### 1.1. Aims

The primary objective of this study was to investigate the association between overall HF or specific types of HF and all-cause and cardiovascular mortality. The secondary objective was to explore the impact of NTproBNP and comorbidity on the association between overall HF or different types of HF and the risk for all-cause and cardiovascular mortality.

## 2. Methods

### 2.1. Study population

Patients were recruited from one PHC selected from northern Sweden between March 30, 2000 and March 11, 2003. The PHC has a catchment area of approximately 7800 inhabitants, of whom many are of advanced age. For many years, a computer-based registry of all patients with a diagnosis of HF had been used by the PHC. In 2001, this registry included 150 patients with a suspected diagnosis of HF on clinical grounds. The patient population comprised both registry patients and incident cases with suspected HF identified by the general practitioner (GP) at the PHC during the recruitment period. All participants had symptoms (mainly dyspnea) indicating chronic HF and were evaluated clinically by a GP prior to being referred for an echocardiography (MO) and subsequent cardiovascular consultation. The study cardiologist (KB) confirmed or refuted the diagnosis of HF based on the GP's pre-specified HF record, echocardiography results, and hospital records.

### 2.2. Diagnosis and types of HF

Global left ventricular systolic function was assessed as normal or depressed including mildly, moderately, or severely depressed. Normal systolic function corresponded to an ejection fraction (EF) of  $\geq 55\%$ , and severely depressed systolic function was considered to be an EF of  $< 30\%$ .

To evaluate the diastolic function (1) we used the mitral valve inflow pattern as the ratio of early and atrial filling velocities of the left ventricle; (2) the pulmonary vein flow was examined in the apical four-chamber view in the right upper pulmonary vein; and (3) we used the isovolumic relaxation time measured in the four-chamber view with the cursor placed between the aortic valve and the mitral valve.

In summary, if any of the above-described diastolic variables were abnormal, then diastolic dysfunction was established<sup>13–15</sup> (see Table 1).

Diagnosis of HF was established according to the European guidelines.<sup>15</sup> Patients diagnosed with left ventricular dysfunction alone had abnormal systolic and/or diastolic LV function, but had symptoms considered to be caused primarily by factors other than cardiac diseases.

We classified 170 patients (121 women and 49 men) as having HF (systolic and/or diastolic HF) or not having HF (Fig. 1). This patient population has been described in detail previously.<sup>16</sup>

In the present longitudinal, prognostic, observational study, 144 patients from the study population were included. Patients diagnosed with left ventricular dysfunction were excluded (Fig. 1). Of the 144 included patients, 77 had overall HF (systolic and/or

**Table 1**  
Distribution of echocardiographic variables for systolic and diastolic HF.<sup>a</sup>

Diagnostic variables	Systolic HF (n = 28)	Diastolic HF (n = 28)
EF $\geq 55\%$	3	28
EF 30– $< 55\%$	23	0
Abnormal E/A		15
Abnormal IVRT		13
Abnormal S/D		5
Normal E/A	13	9
Normal IVRT	8	9
Normal S/D	9	15

E/A = ratio of early (E) and atrial (A) filling; EF = ejection fraction; HF = heart failure; IVRT = isovolumic relaxation time; S/D = ratio of systolic (S) and diastolic (D) components in the pulmonary vein inflow.

<sup>a</sup> Classification for diastolic HF is as follows. The E/A ratio was classified as age-dependent and considered abnormal when E/A  $< 1$  (40–49 years), E/A  $< 0.9$  (50–59 years), E/A  $< 0.8$  (60–69 years), E/A  $< 0.7$  (70–80 years), and E/A  $< 0.7$  ( $> 80$  years).<sup>1</sup> The relation between the S and D components of the pulmonary vein inflow was assessed and S/D  $< 1$  was considered abnormal in age  $> 60$  years and S/D  $< 0.9$  was considered abnormal in age  $< 60$  years. The IVRT value was also classified by age as follows: IVRT  $> 85$  milliseconds (40–49 years), IVRT  $> 90$  milliseconds (50–59 years), IVRT  $> 95$  milliseconds (60–69 years), and IVRT  $> 100$  milliseconds ( $> 70$  years) is abnormal value and  $< 70$  ms is abnormal in all ages.<sup>13,14</sup>

diastolic HF) and were compared with 67 patients with no HF (reference group). The types of HF were defined as follows: overall HF included the three types of HF—isolated systolic HF, isolated diastolic HF, or combined systolic/diastolic HF (combined HF).

In short, details of the patients' medical history—such as hypertension, myocardial infarction (MI), atrial fibrillation (missing,  $n = 30$ ), valvular heart disease, stroke, pulmonary disease, kidney dysfunction (creatinine  $> 100$   $\mu\text{mol/L}$ ; missing,  $n = 5$ ), diabetes (both types 1 and 2), smoking habits (both smoker and ex-smoker, missing,  $n = 10$ ), use of alcohol (yes/no; missing,  $n = 16$ ), weight (missing,  $n = 8$ ), symptoms, and evidence-based medical treatment associated with prognosis—were collected from the GP's case record when the patients were examined at baseline.

### 2.3. NTproBNP

For analysis of NTproBNP, blood samples (plastic EDTA tubes) were taken from fasting patients who had rested for 20 minutes. After 5 minutes, the samples were centrifuged ( $1500\text{--}2000 \times g$ ) for 10 minutes at  $4^\circ\text{C}$  then stored frozen at  $-70^\circ\text{C}$ . NTproBNP was analyzed with Roche Elecsys proBNP immunoassay (Roche Diagnostic Corporations, Indianapolis, Indiana, USA; NtproBNP with missing information,  $n = 11$ ).

### 2.4. Outcome classification

Death certificates were used to identify all-cause mortality, and cardiovascular mortality was defined as International Classification of Diseases-10 codes 100–199. The same classification was used for both 3-year mortality and the 10-year follow-up (median, 4.17 years) for the 144 patients in this study.

### 2.5. Statistical analysis

Baseline characteristics were described as frequencies or means and standard deviations. Differences between groups were tested with the Student *t* test for normally distributed data, Mann–Whitney *U* test was used for nonnormally distributed continuous variables, and the Chi-square test was used for categorical variables. The association between baseline characteristics and mortality for 3-year was analyzed with logistic regression analysis and at 10 years of follow-up with Cox regression analysis. In multivariate logistic or Cox regression analyses, Model 1 included

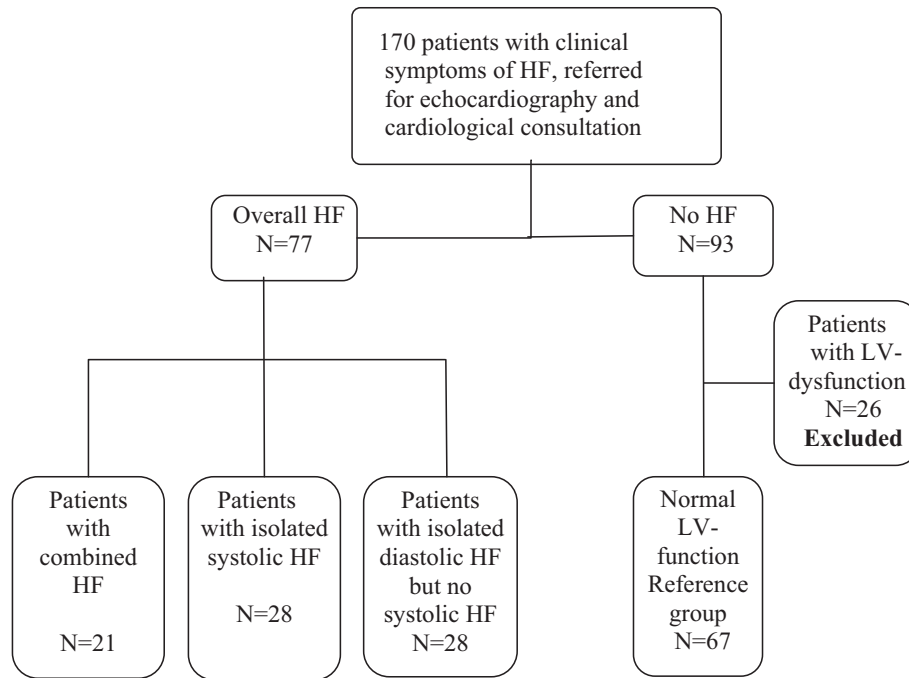


Fig. 1. Flowchart of the study population. Patients were diagnosed with heart failure (HF) or no HF, and left ventricular dysfunction.

type of HF, one at a time, and NTproBNP. Model 2 included the same variables used in Model 1 as well as other variables significantly ( $p < 0.05$ ) associated with all-cause mortality or cardiovascular mortality in the univariate analysis at 3 years or 10 years of follow-up. The results are presented as the odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (CI). In both multivariate logistic and Cox regression analyses, we primarily used overall HF (cases) together with other significant variables from the univariate analysis. For the different types of HF diagnoses, explorative analyses were done because of too few events.

The assumption of proportional hazard was graphically verified using Kaplan–Meier survival curves for 10-year mortality (figure not shown). PASW statistics (SPSS Inc., Chicago), version 18.0, was used for all statistical analyses.

Patients signed written informed consent forms for inclusion in the study, and the study was approved by the Committee of Ethics at Umeå University, Umeå, Sweden (diary number 00-276).

### 3. Results

#### 3.1. All-cause mortality during 10 years of follow-up

Seventy-one (49%) of 144 patients died during the 10-year follow-up period. Of those who died, 48 (68%) were women and 23 (32%) were men. The mean age was 81 years at baseline. Of those who died, 25 patients (35%) died of HF, eight patients (11%) died of cancer, eight patients (11%) died of stroke, five patients (7%) died of lung disease, four patients (6%) died of sudden cardiac death, four patients (6%) died of MI, and three patients (4%) died of dementia. Overall, HF was present in 45 (63%) patients distributed into 16 (22%) patients with combined HF, 17 (24%) patients with isolated systolic HF, and 12 (17%) patients with isolated diastolic HF (Table 2).

Among the patients with systolic HF, 76% died from cardiovascular diseases, five patients (29%) died of HF, four patients (24%) died of stroke, one patient (6%) died of sudden cardiac death, and one patient (6%) died of MI; of the 24% from

noncardiovascular causes, two patients (12%) died of cancer and one patient (6%) died of lung disease. In patients with diastolic HF, the causes of death were equally distributed (50% each) between cardiovascular [4 patients (33%) died of HF and 2 patients (17%) died of stroke], and noncardiovascular causes [2 patients (17%) died of lung disease, 1 patient (8%) died of cancer, and 1 patient (8%) died of dementia].

Table 2

Characteristics at baseline, for patients dead ( $n = 71$ ) or alive ( $n = 73$ ) after 10 years of follow-up.

Characteristic	Dead		Alive	
	<i>n</i>	Mean (SD) or <i>n</i> (%)	Mean (SD) or <i>n</i> (%)	<i>p</i>
Age, y	144	81 ± 6.1	73 ± 8.5	<0.001
Female	102	48 (47)	54 (53)	0.401
Weight, kg	136	73 ± 14.5	76 ± 16.1	0.173
Smoker or ex-smoker	34	21 (62)	13 (38)	0.073
Hx of alcohol	27	13 (48)	14 (52)	0.973
Hx diabetes	19	12 (63)	7 (37)	0.195
Hx hypertension	64	30 (47)	34 (53)	0.602
Hx myocardial infarction (MI)	32	19 (59)	13 (41)	0.196
Hx atrial fibrillation	22	15 (68)	7 (32)	0.086
Hx valvular disease	22	13 (59)	9 (41)	0.319
Hx underlying heart disease	122	63 (52)	59 (48)	0.187
Hx stroke	18	11 (61)	7 (39)	0.284
Hx pulmonary disease	16	9 (56)	7 (44)	0.556
Kidney dysfunction (creatinine > 100 μmol/L)	38	28 (74)	10 (26)	<0.001
Systolic HF	28	17 (61)	11 (39)	0.050
Diastolic HF	28	12 (43)	16 (57)	0.713
Combined systolic and diastolic HF	21	16 (76)	5 (24)	0.003
Overall HF	77	45 (58)	32 (42)	0.019
Reference group	67	26 (39)	41 (62)	0.019
NTproBNP (ng/L)	13,321	1942 ± 3739	530 ± 1471	<0.005
ACE or ARB and BB	21	12 (57)	9 (43)	0.437

ACE = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blocker; BB = beta blocker; Hx = history; HF = heart failure; NTproBNP = natriuretic peptide; SD = standard deviation.

**Table 3**

Univariate and multivariate Cox regression analyses concerning the influence of HF on all-cause mortality during 10 years of follow-up.

	n cases/n reference group	Univariate analysis			Model 1		Model 2	
		HR	95% CI	p	HR	95% CI	HR	95% CI
Systolic HF	28/67	1.95	1.06–3.61	0.033	1.83	0.96–2.80	1.78	0.83–3.82
Diastolic HF	28/67	1.14	0.57–2.25	0.716				
Combined HF	21/67	3.28	1.74–6.14	<0.001	2.25	1.08–4.67	1.97	0.88–4.44
Overall HF	77/67	1.86	1.15–3.01	0.012	1.64	0.96–2.80	1.39	0.78–2.47

CI = confidence interval; HF = heart failure; HR = hazard ratio; Model 1 = adjustment for natriuretic peptide; Model 2 = adjustment for natriuretic peptide, age, kidney dysfunction, and smoking habits.

**Table 4**

Univariate Cox regression analysis for comorbidities for all-cause and cardiovascular mortality at 10 years of follow-up.

Predictor variables	n cases/n reference group	Missing n cases/n reference group	All-cause mortality			Cardiovascular mortality		
			HR	95% CI	p	HR	95% CI	p
Age (per year)	77/67	0/0	1.11	1.07–1.15	<0.001	1.19	1.12–1.26	<0.001
Female	48/54	0/0	0.77	0.47–1.27	0.310	0.70	0.38–1.27	0.239
Weight (per kg)	74/62	3/5	0.99	0.97–1.00	0.128	0.98	0.96–1.00	0.070
Smoker or ex-smoker	23/11	2/8	1.88	1.12–3.17	0.017	1.82	0.94–3.51	0.073
Hx alcohol	15/12	7/9	1.04	0.56–1.92	0.902	0.71	0.30–1.69	0.435
Hx diabetes	11/8	0/0	1.62	0.87–3.01	0.131	1.40	0.60–3.31	0.439
Hx underlying heart disease	71/51	0/0	1.63	0.78–3.41	0.192	1.72	0.68–4.35	0.250
Hx hypertension	40/24	0/0	0.89	0.55–1.42	0.622	0.71	0.39–1.28	0.256
Hx myocardial infarction	23/9	0/0	1.39	0.82–2.36	0.216	1.59	0.85–2.98	0.145
Hx atrial fibrillation	15/7	16/14	1.74	0.97–3.15	0.064	2.35	1.20–4.58	0.012
Hx valvular disease	13/9	0/0	1.43	0.78–2.61	0.248	1.46	0.68–3.12	0.333
Hx stroke	11/7	0/0	1.28	0.67–2.43	0.458	1.74	0.87–3.51	0.120
Hx pulmonary disease	8/8	0/0	1.34	0.66–2.70	0.413	1.18	0.47–2.99	0.724
Kidney dysfunction (Creatinine > 100 µmol/L)	25/13	3/2	2.81	1.72–4.60	<0.001	3.88	2.15–7.00	<0.001
BB and ACE or ARB	15/6	0/0	1.28	0.69–2.37	0.435	1.03	0.44–2.42	0.950
NTproBNP (per ng/L)	72/61	5/6	1.01	1.01–1.02	<0.001	1.02	1.01–1.02	<0.001

ACE = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blocker; BB = beta blocker; Cases = overall HF; Hx = history; CI = confidence interval; HR = hazard ratio; NtproBNP = natriuretic peptide; reference group = no heart failure.

The survival rate of the elderly patients in the present study with combined HF was 24% after 10 years. The corresponding figure for overall HF was 42%, and was 39% for isolated systolic HF. The 10-year survival rate for those with isolated diastolic HF was 57%.

In univariate Cox regression analysis, significant associations were found for overall HF, isolated systolic HF, combined HF, and all-cause mortality, but not for isolated diastolic HF (Table 3). Age, smoking habits, kidney dysfunction, and NTproBNP were significantly associated with all-cause mortality (Table 4).

In multivariate Cox regression, overall HF was not associated with mortality in Model 1 or 2 (Table 3). The impact of comorbidities on mortality is shown in Table 5.

Combined HF remained significant in Model 1 (HR, 2.3; 95% CI, 1.1–4.7), but was not significantly associated with all-cause mortality in Model 2 (HR, 2.0; 95% CI, 0.9–4.4). Systolic HF was not significantly associated with all-cause mortality in either Model 1 or 2 (Table 3).

If overall HF was replaced with combined HF in Model 2, age (HR, 1.1; 95% CI, 1.03–1.17), smoking habits (HR, 4.1; 95% CI,

1.7–9.7), and NTproBNP (HR, 1.02; 95% CI, 1.00–1.03) remained significantly associated with all-cause mortality.

When isolated systolic HF replaced overall HF in Model 2, age (HR, 1.11; 95% CI, 1.04–1.18) and smoking habits (HR, 3.8; 95% CI, 1.7–8.3) remained significantly associated with all-cause mortality.

### 3.2. Cardiovascular mortality during 10 years of follow-up

Of the 71 patients who died, 47 (66%) patients (mean age, 83 years) died from cardiovascular disease. Of these patients, 31 (66%) were women and 16 (34%) were men. Overall HF was present in 31 (66%) patients, comprising 12 (25%) with combined systolic and diastolic HF, 13 (28%) with isolated systolic HF, and six (13%) with isolated diastolic HF.

In univariate Cox regression analysis, there was an association between overall HF, isolated systolic HF, combined HF, and the risk for cardiovascular mortality, but not between isolated diastolic HF (data not shown) and cardiovascular mortality. Age, kidney

**Table 5**

Results from Cox regression model for overall HF adjusted for NTproBNP, age, kidney dysfunction on all-cause mortality but also atrial fibrillation on cardiovascular mortality, 10 years of follow-up.

Predictor variables	Multivariate analysis All-cause mortality			Multivariate analysis Cardiovascular mortality		
	HR	95% CI	p	HR	95% CI	p
Overall HF	1.32	0.74–2.36	0.347	1.06	0.50–2.23	0.881
NTproBNP (per ng/L)	1.01	1.00–1.02	0.012	1.01	1.00–1.02	0.036
Age (per year)	1.11	1.05–1.16	<0.001	1.14	1.07–1.21	<0.001
Kidney dysfunction (creatinine > 100 µmol/L)	1.91	1.11–3.29	0.020	2.15	1.05–4.38	0.036
Smoker or ex-smoker	3.70	2.02–6.77	<0.001			
History of atrial fibrillation				1.58	0.71–3.51	0.264

CI = confidence interval; HF = heart failure; HR = hazard ratio; NTproBNP = natriuretic peptide.



dysfunction, atrial fibrillation, and NTproBNP were significantly associated with cardiovascular mortality (Table 4).

In multivariate Cox regression, overall HF was not associated with mortality in Model 1 or 2. The impact of comorbidities on mortality is shown in Table 5.

Combined HF remained significant in Model 1 (HR, 2.8; 95% CI, 1.1–7, 0), but was not significantly associated with cardiovascular mortality after further adjustment in Model 2 (HR, 1.0; 95% CI, 0.3–3.3). Systolic HF was not significantly associated with cardiovascular mortality in Model 1 or 2 (data not shown).

If overall HF was replaced with combined HF in Model 2, age (HR, 1.13; 95% CI, 1.04–1.22) and NTproBNP (HR, 1.02; 95% CI, 1.00–1.03) remained significantly associated with cardiovascular mortality. When isolated systolic HF replaced overall HF in Model 2, age (HR, 1.15; 95% CI, 1.07–1.24) and kidney dysfunction (HR, 2.5; 95% CI, 1.1–5.7) remained significantly associated with cardiovascular mortality.

### 3.3. All-cause mortality at 3 years

Twenty-five (15%) patients out of 144 had died after 3 years. Of those who died, 16 (64%) were women and nine (36%) were men, and their mean age was 80 years at baseline. Overall HF was found in 19 (76%) patients, of whom eight (32%) had combined HF, five (20%) had isolated systolic HF, and six (24%) had isolated diastolic HF.

The 3-year mortality data demonstrated that patients with systolic HF mainly died from cardiovascular causes compared with noncardiovascular causes (80% vs. 20%). For patients with diastolic HF, the proportions for cardiovascular versus noncardiovascular mortality were 33% versus 67%.

In univariate logistic regression analysis, overall HF (OR, 3.3; 95% CI, 1.2–8.9) and combined HF (OR, 6.3; 95% CI, 1.9–21.1) were significantly associated with all-cause mortality, but did not remain significant after adjustment for NTproBNP.

Age, smoking habits, NTproBNP, and kidney dysfunction were significantly associated with all-cause mortality in univariate analysis. The only variable that remained significant after adjustment in Model 2 was smoking habits, with an OR of 8.1 (95% CI, 2.4–26.7) when overall HF was included in the model. When overall HF was replaced with combined HF, smoking habits had an OR of 7.1 (95% CI, 1.3–40.5).

### 3.4. Cardiovascular mortality at 3 years

Sixteen (57%) of 25 patients (mean age, 83 years at baseline) died from cardiovascular disease. Of those who died, nine (56%) were women and seven (44%) were men. Overall HF was found in 13 (81%) patients, of whom seven (43%) had combined HF, four (25%) had isolated systolic HF, and two (13%) had isolated diastolic HF.

In univariate logistic regression analysis, overall HF (OR, 4.3; 95% CI, 1.2–15.9) and combined HF (OR: 10.7; 95%CI: 2.7–46.4) were significantly associated with cardiovascular mortality, but did not remain significant after adjustment for NTproBNP.

Age and smoking habits were significantly associated with cardiovascular mortality in univariate analysis and remained significant in Model 2 when overall HF was included in the model (age: OR 1.19, 95% CI 1.01–1.39; smoking habits: OR 28.0, 95% CI 4.3–183.2). When combined HF replaced overall HF in Model 2, only smoking habits (OR, 47.7; 95% CI, 2.8–825.3) remained significant.

## 4. Discussion

Our main finding was that overall HF, isolated systolic HF, and combined HF, but not diastolic HF, were significantly associated

with all-cause and cardiovascular mortality after 10 years of follow-up. Only combined HF remained significant after adjusting for NTproBNP, but not after further adjusting for age, smoking habits, and kidney dysfunction. Another important finding was that smoking habits was the only studied variable that predicted all-cause mortality after both 3 years and 10 years of follow-up.

The results after 3 years and 10 years of follow-up revealed that the presence of systolic HF—in contrast with diastolic HF—was a determinant of prognosis, although not significant after adjustments. Our reference group comprised patients with symptoms such as dyspnea and fatigue, but these were not classified as HF symptoms because they were considered more likely to be caused by other diseases. For women in the reference group, the survival rate was 57% after 10 years of follow-up, which was the same as that found for women of the same age in the Swedish population. For males, the survival rate was 78% compared with 51% for Swedish males.<sup>17</sup> Thus, the men in our reference group may have been healthier than those in the general Swedish population, but were also younger (73 years vs. 75 years). The difference in survival rate for males should be interpreted with caution because of the limited number of males ( $n = 13$ ) in our reference group.

In contrast to our findings, a registry study in hospitalized patients with preserved systolic function, defined as  $EF \geq 40\%$ , and those with left ventricular systolic dysfunction ( $EF < 40\%$ ) showed no significant difference in unadjusted all-cause mortality after 60–90 days of follow-up after hospital discharge.<sup>18</sup> The patients with preserved systolic function were in parity in terms of age, and included more females and patients with a history of hypertension than our patients with isolated diastolic HF. By contrast, the previous study consisted of a hospitalized, prespecified subset of patients with HF, and the follow-up time was short compared with that used in our study.

Results from a meta-analysis also pointed in the same direction as our study—that patients with HF and preserved left ventricular ejection fraction (HF-PEF) had a 32% lower risk of death than patients with HF and systolic dysfunction.<sup>19</sup> Their patients with HF-PEF were at significantly lower risk of death than those with HF-REF also after adjustment for age, sex, hypertension, diabetes, atrial fibrillation, and etiology of HF. In our study, we found in the univariate logistic regression analysis at 3 years, an HR of 0.80 for patients with isolated diastolic HF when compared to patients with isolated systolic HF, although it is not significant, probably because of the limited number of patients. The above meta-analysis ( $n = 50,991$  patients) included both observational studies and randomized trials with 3 years of follow-up but their patients were younger and with fewer women than in our study.

The Olmsted community study of patients with preserved EF ( $\geq 50\%$ ) and reduced EF ( $\leq 50\%$ ) from a random sample of all potential HF cases, including both hospitalized individuals and outpatients, showed different results compared with ours.<sup>20</sup> There were more males and fewer patients with a history of hypertension, and the mortality rate was 86% compared with 49% in our study with the same follow-up time. Noncardiovascular causes accounted for 49% of deaths in their patients with preserved EF, which was similar to our results (50%). By contrast, noncardiovascular causes accounted for 36% of deaths in their patients with reduced EF compared with 24% in our patients with systolic HF. This may suggest that patients in the Olmsted community study<sup>20</sup> with reduced EF had more severe illness than our patients.

Obviously, our patients with systolic HF died more often from cardiovascular than noncardiovascular causes than did patients with diastolic HF. This may be because cardiovascular comorbidities increase with time, and/or an increasing death rate among patients with systolic HF.

NTproBNP is a well-known prognostic factor, but has mostly been studied in younger patients. Only combined HF together with NTproBNP remained significantly associated with a risk of mortality after 10 years of follow-up. This strengthens the notion that NTproBNP is a strong prognostic factor even in elderly patients with HF.

After 3 years and 10 years of follow-up, smoking habits had a greater impact on all-cause mortality than a diagnosis of HF. After 10 years of follow-up, kidney dysfunction, NTproBNP, and age were also significantly associated with all-cause mortality.

The Olmsted study<sup>20</sup> found that advanced age, male sex, diabetes, smoking, and kidney disease were associated with an increased risk of mortality. Our results are in line with the results of that study except for the sex differences. Diabetes seemed to be an important comorbidity factor in our study at 3 years in univariate analysis of all-cause mortality with borderline significance ( $p = 0.090$ ). The findings for diabetes mellitus (DM) merit further investigations in these elderly patients. There are a number of potential prognostic factors that may affect prognosis in patients with DM. These include associated atherosclerotic complications, hypoglycemia episodes, and drug interaction.<sup>21,22</sup>

#### 4.1. Methodological considerations

Our study was planned and performed in the late 1990s and performed during the first years of 2000. During that time, HF with preserved ejection (HF-PEF) was not used as a diagnostic criterion but diastolic HF was the main definition although not uniformly agreed upon. We have used the proposal made by the European Society of Cardiology guidelines 2001. For the diagnosis of CHF, the response to treatment was also included. HF-PEF is still difficult to define, and there is no consensus on the optimal cutoff value for EF. It is also important to emphasize that a normal EF is not equivalent to a normal systolic function. In our study, we had three cases with  $EF \geq 55\%$  although they were categorized as having systolic HF. One case had aortic stenosis with left ventricular hypertrophy. The two others had severe mitral incompetence with large afterload reductions. These three cases responded very well to drug and surgical treatment, which explains why they were classified as systolic HF according to earlier guidelines.

#### 4.2. Clinical implications

Our study provides further knowledge on elderly patients with HF who are managed mainly in the PHC setting, with follow-up for 10 years: first, the prognostic importance of systolic HF rather than diastolic HF in these patients should be considered; second, the importance and often overlooked impact of comorbidities, especially renal dysfunction but also diabetes, should be considered. Third, the impact of smoking/having smoked should not be forgotten, even in elderly patients. Taken together for the GP in clinical practice who wants to predict 10-year outcome, systolic HF, NTproBNP, renal dysfunction, and smoking habits are the main predictors of mortality. If the GP has a patient with isolated systolic HF or kidney dysfunction, the prognosis is poor in 10 years for both all-cause and cardiovascular mortality, and the need for NTproBNP is not obviously necessary unless there is a requirement for more precise prognostic information. By contrast, according to this study, if an elderly patient has a high NTproBNP value, the 10-year prognosis is poor for both all-cause and cardiovascular mortality.

#### 4.3. Limitations

The study population is limited. Data for clinical variables were collected from the GP's prespecified HF record, but were not

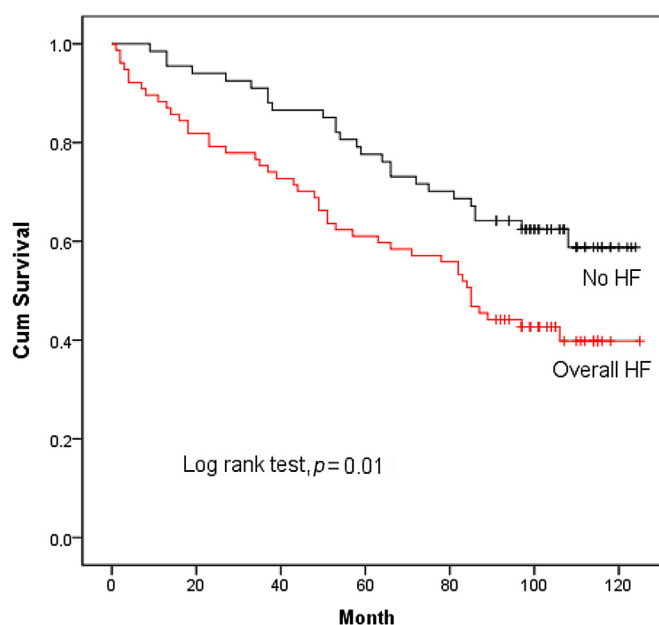


Fig. 2. Kaplan–Meier plots showing proportions of patients who were alive during 10 years of follow-up for 77 patients with overall heart failure (HF) and 67 patients with no HF at baseline.

validated. Some data for clinical variables were missing for unknown reasons. For clinical diseases, missing data were regarded as absence of disease. Validation was done for HF, but not for any other clinical diseases. The Cox analyses for diastolic HF should be interpreted with caution because of some violations of the curves in the Kaplan–Meier plot (Fig. 2).

#### 4.4. Strengths

The major strengths of this study are the long-term, 10-year follow-up, and inclusion of protocol-based patients from one PHC, and that HF was verified by echocardiography in all patients. The reference group consisted of patients with symptoms suggestive of HF, but who were not considered to have HF. This resembles daily clinical practice when the GP encounters a patient with breathlessness and fatigue.

### 5. Conclusion

In this long-term follow-up study, a patient with a diagnosis of systolic HF had a worse prognosis for mortality than a patient with diastolic HF when compared with the reference group. Age is not modifiable, but recognizing and counseling patients on smoking habits remains of great importance in elderly patients seen in the PHC setting. Attention to comorbidities such as kidney dysfunction and DM should also be emphasized.

#### Conflicts of interest

The authors have no conflicts of interest to report.

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