Comorbidity Drives Mortality in Newly Diagnosed Heart Failure: A Study Among Geriatric Outpatients

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ABSTRACT

Background: Elderly heart failure (HF) patients frequently have multiple comorbidities. The prognostic impact of combined comorbidities is poorly quantified in these patients. We assessed the impact of comorbidities on 3-year mortality in geriatric outpatients with newly diagnosed HF.

Methods and Results: Of 93 geriatric outpatients with HF (mean age 82.7 years, 36.6% men), 52 patients (55.9%) died within 3 years after HF was diagnosed. Comorbidity was measured with the Charlson Comorbidity Index (CCI). Age- and gender-adjusted hazard ratio (HR) for 3-year mortality was 1.6 (95% confidence interval [CI] 0.9−3.2) for patients with 3−4 CCI points and 3.2 (95% CI 1.5−6.8) for those with >4 CCI points, compared with 1−2 CCI points. After adjustment for age, gender, left ventricular ejection fraction (LVEF), and N-terminal pro−B-type natriuretic peptide, CCI remained predictive of death (CCI 3−4: HR 1.5 (95% CI 0.7−2.9); CCI >4: HR 4.0 (95% CI 1.9−8.8)). In addition to age and gender, the c-statistics for CCI and LVEF were similar (0.63 [95% CI 0.55−0.70] and 0.64 [95% CI 0.56−0.72], respectively).

Conclusions: The majority of geriatric outpatients with new HF die within 3 years. Comorbidity, summarized in the CCI, is the strongest independent predictor of mortality. (*J Cardiac Fail 2012;18:47−52*)

Key Words: Heart failure, mortality, comorbidity.

lence of heart failure, especially in the elderly.[1,2] Survival in geriatric patients with heart failure is generally poor. Elderly heart failure patients have a wide range of both cardiovascular and noncardiovascular comorbidities, that may influence prognosis.[3,4] Although the impact of several diseases on prognosis in heart failure patients has been established,[1,5] predominantly in hospitalized patients,[6] the impact of combinations of concomitant diseases in geriatric patients is largely unknown, especially in the large group of geriatric outpatients with newly diagnosed heart failure not

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ment to assess comorbidity that has been shown to predict prognosis in a variety of patient groups (eg, patients with cancer, pneumonia, or admitted to internal wards).[7−9] In elderly heart failure patients, other than 2 studies addressing short-term (1-year) or long-term (12-year) mortality, the effect of comorbidity, as measured with the CCI, on the prognosis of heart failure has not been addressed.[10,11] We determined the impact of comorbidity, measured with the CCI, on 3-year mortality in geriatric outpatients with newly diagnosed heart failure.

Methods

Study Population

Patients referred, for a variety of reasons, to the geriatric outpatient clinic of 2 regional hospitals in The Netherlands (Elkerliek Hospital, Helmond, and Meander Medical Center, Amersfoort) who presented with symptoms of breathlessness, fatigue, ankle swelling, or any combination of these were eligible, as described in detail elsewhere.[12] Only patients with newly diagnosed heart failure in whom the symptoms had increased gradually before the diagnosis (so-called "slow-onset" heart failure) were included. Patients with acute-onset heart failure requiring emergency admission were excluded. Briefly, 206 geriatric outpatients suspected of new heart failure by a geriatrician

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underwent a comprehensive standardized diagnostic work-up. The presence or absence of heart failure was established by an outcome panel according to the diagnostic criteria for heart failure of the European Society of Cardiology, using all available diagnostic information.[13] Each of the participants, or their representatives in case of impaired cognition, gave his or her written consent. Patients were recruited between July 2003 and July 2007. The study was approved by the Medical Ethical Committees of both participating hospitals.

Comorbidity

We used the CCI, which assigns points for several medical conditions, to evaluate the severity of comorbidity with a score ranging from 1 (only heart failure present) to 30 (extensive comorbidity).[7] All diagnoses obtained from the general practitioner's referral letter, letters of other specialists retrieved from the hospital information system, and diagnoses established by the geriatricians within 2 months after the initial visit were regarded to be comorbidity. The presence or absence of heart failure according to the outcome panel was established before calculating the CCI.

Outcome

The outcome of the study was all-cause mortality within 3 years after heart failure was diagnosed. Information on vital status was obtained from the hospital information system or from the patients' general practitioners. Follow-up data were collected between July 2003 and July 2010. One patient without heart failure was lost to follow-up after the first year and was considered to have withdrawn alive as of the last date of follow-up.

Data Analysis

Data with a normal distribution were summarized as means with standard deviations (SD). Data with a skewed distribution were summarized as medians with interquartile ranges (25th-75th percentiles). To obtain a normal distribution, N-terminal pro−B-type natriuretic peptide (NT-proBNP) values were logarithmically transformed. Left ventricular ejection fraction (LVEF) was categorized in patients with LVEF $<35\%$, $35\%-45\%$, and $>45\%$. CCI score was categorized in subjects with a CCI score of 1−2, 3−4, and >4 points.[14] A Cox proportional hazards analysis was performed to calculate differences in survival between patients with and without heart failure and differences between patients with heart failure due to impaired (n = 49) and preserved (n = 44) LVEF after adjusting for age and gender. The ability of established determinants (ie, age, gender, LVEF, and NT-proBNP) and CCI to discriminate between patients who died and who remained alive was estimated with the use of the c-statistic, which reflects the area under the receiver operating characteristic curve.[15] The c-statistic can range from 0.5 (no discrimination, like flipping a coin) to 1.0 (perfect discrimination).[16] Multivariate proportional hazards analysis was performed to determine the independent value of comorbidity after adjusting for ''established'' determinants of mortality in heart failure. For continuous variables, the assumption of linearity was assessed with the use of restrictive cubic splines.[15]

The reproducibility (intrarater agreement) of the CCI, evaluated by retesting 21 cases (10.2% of total population), was good, with an intraclass correlation coefficient of 0.95 (95% confidence interval [CI] 0.89−0.98). None of the predictors had missing values. Data were analyzed with the use of SPSS (version 17.0 for Windows; SPSS; Chicago, IL, USA), and R (version 2.8.1; R Foundation for Statistical Computing, Vienna, Austria [http://www.R-project.org]) software.

Results

Ninety-three geriatric outpatients with newly diagnosed, ''slow-onset'' heart failure (63.4% female; mean age 82.7 ± 5.3 years) were included (Table 1). Three-year all-cause mortality was much higher (55.9%) in geriatric patients with newly diagnosed heart failure than in those without (28.3%; crude hazard ratio [HR] 2.6 [95% CI 1.7−4.1]; age and gender adjusted HR 2.2 [95% CI 1.4−3.4]; Fig. 1). Three-year mortality did not differ between patients with systolic heart failure) LVEF $<45\%$) and those with heart failure with preserved ejection fraction (HFPEF): 59.2% and 52.3%, respectively; crude HR 1.3 (95% CI 0.7−2.2); HR adjusted for age and gender 1.3 (95% CI 0.7−2.3).

Mortality increased with higher CCI score from 42.9% in the 35 patients with a CCI of 1−2 to 57.1% in those with CCI 3−4 (n = 42) and 81.3% in those with CCI >4 (n = 16). Compared with CCI 1−2, HR for death within 3 years was 1.6 (95% CI 0.8−3.0) for patients with CCI 3−4 and 3.3 (95% CI 1.5−6.9) for patients with CCI >4 (Table 2). The CCI remained predictive of mortality after adjustment for age and gender (CCI 3−4: HR 1.6 [95% CI 0.9−3.2]; CCI >4: HR 3.2 [95% CI 1.5−6.8]; Fig. 2). In addition to age and gender, the c-statistic was 0.63 for CCI (95% CI 0.55−0.70), 0.64 (95% CI 0.56−0.72) for LVEF, and 0.59 (95% CI 0.50−0.67) for NT-proBNP. Combining these determinants improved the c-statistic to 0.69 (95% CI 0.62−0.76). The CCI remained predictive of mortality after adjustment for age, gender, LVEF, and NT-proBNP (CCI 3−4: HR 1.5 [95% CI 0.7−2.9]; CCI >4: HR 4.0 [95% CI 1.9−8.8]).

Discussion

More than one-half of 93 (n = 52; 55.9%) geriatric outpatients with newly diagnosed ''slow-onset'' heart failure (ie, gradually increasing symptoms of heart failure not requiring hospital admission) died within 3 years after establishing the diagnosis. Mortality increased with more extensive comorbidity, as assessed with the CCI, 3-year mortality being 81.3% in heart failure patients with a CCI score >4. The CCI was the strongest independent predictor of mortality.

Three-year mortality in our group of geriatric outpatients with new heart failure, being twice as high compared with those without heart failure, reflects the poor prognosis of heart failure as demonstrated earlier in the general population and in elderly hospitalized patients.[17,18] Because elderly heart failure patients are likely to have multiple cardiovascular and noncardiovascular comorbidities that influence prognosis,[4,19] we intended to determine the prognostic value of comorbidity ''as a whole'' rather than focusing on the effect of individual concomitant diseases

Table 1. Baseline Characteristics of Geriatric Outpatients with Heart Failure (n = 93)

Variable	
Age, y	82.7 ± 5.3
Male sex	34 (36.6)
Cardiovascular comorbidity and risk factors	
Ischemic heart disease, n (%)	25 (26.9)
Myocardial infarction, n (%)	17 (18.3)
Angina pectoris, n (%)	8 (8.6)
Vascular comorbidity, n (%)	55 (59.1)
Hypertension, n (%)	39 (41.9)
Diabetes mellitus, n (%)	25 (26.9)
CVA or TIA, n (%)	20 (21.5)
Atrial fibrillation, n (%)	36 (38.7)
Overweight, n (%)	31 (35.6)
Current smoker, n (%)	18 (19.4)
Noncardiovascular comorbidity	
COPD, n (%)	25 (26.9)
Cognitive impairment, n (%)	25 (26.9)
Malignancies, n (%)	15 (16.1)
Drugs	
Loop diuretic, n (%)	38 (40.9)
ACEI/ARBs, n (%)	35 (37.6)
β-Blockers, n (%)	26 (28.0)
Digitalis, n (%)	22 (23.7)
Aldosterone antagonists, n (%)	10 (10.8)
Drugs, number	6 (5–8)
NT-proBNP, pg/mL	2,295 (791–5,543)
eGFR MDRD, mL min^{-1} 1.73 m^{-2}	58 ± 20
CCI, points	3 (2–4)
LVEF, %	43 ± 14

Data are presented as number (%) of patients, mean ± SD, or median (25th–75th percentiles). Ischemic heart disease: presence of myocardial infarction, angina pectoris, coronary artery bypass grafting, or percutaneous coronary intervention; overweight: body mass index 25–30 kg/m^2; vascular comorbidity: including hypertension, diabetes mellitus, stroke, and peripheral artery disease. CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR MDRD, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease study group equation; CCI, Charlson Comorbidity Index; LVEF, left ventricular ejection fraction.

(eg, renal failure, chronic obstructive pulmonary disease, stroke, or dementia). To achieve this goal we used the CCI, a validated instrument that has been shown to predict nonsudden death in heart failure,[20] mortality, or lung transplantation within the first year after admission for right-sided heart failure in pulmonary arterial hypertension[21] and in-hospital mortality among elderly patients admitted to an internal medicine ward.[9] The strong relation between CCI and mortality testifies to the importance of various comorbidities in geriatric outpatients with heart failure. Our patient population (mean age 82.7 years; median drugs used, 6) differed from that in the study of 125 heart failure patients that failed to demonstrate an impact of CCI on 12-year mortality.[11] The mean age of those patients was 74 years, and the fact that they were using only 2 medications on average suggests limited comorbidity. Furthermore, it is possible that the CCI does not predict 12-year mortality very well, because <50% of heart failure patients tend to survive 5 years, regardless of the extent of their comorbidities.[1]

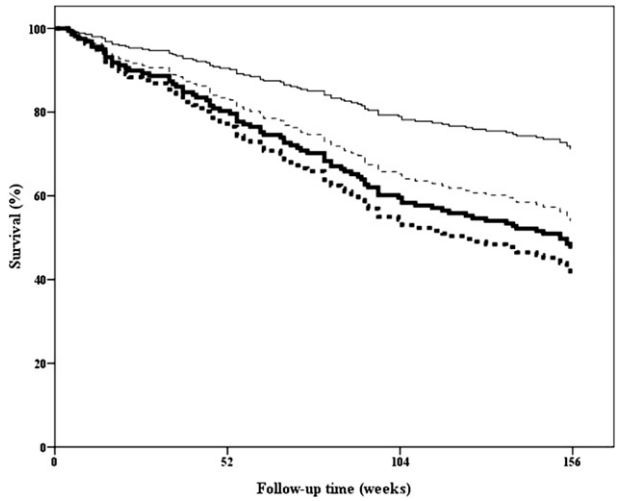

Fig. 1. Cox survival curves for geriatric patients according to the presence and type of heart failure, adjusted for age and gender. Thin solid line: heart failure absent; thick solid line: heart failure present; thin dashed line: heart failure with preserved ejection fraction; thick dashed line: systolic heart failure.

Several risk models to help physicians in estimating prognosis in heart failure patients exist, eg, the Seattle Heart Failure Model (SHFM)[22] and the scoring systems of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study[6] and the Acute Decompensated Heart Failure Registry (ADHERE).[23] The SHFM predicts 5-year mortality based on information obtained from participants with severe systolic heart failure (median age 65 years, 24% women) of the Prospective Randomized Amlodipine Survival Evaluation (PRAISE1) study.[24] The EFFECT study included patients (mean age 76.3 years, 50.5% women) admitted with acute heart failure to determine 30-day and 3-year mortality, and the ADHERE registry determined in-hospital mortality in patients (mean age 72.4 years, 52% women) admitted with acute heart failure.[25] Ours is the first study to determine the prognostic impact of comorbidity in elderly heart failure outpatients (mean age 82.7 years, 63.4% women) not requiring hospitalization, including both systolic heart failure and HFPEF. In contrast to the 3 established risk models, we included measurements of natriuretic peptides, that are known to be important predictors in heart failure. Renal function is important in determining the prognosis of heart failure.[1,5] In our patient group, all 7 patients with an estimated glomerular filtration rate <30 mL min^{-1} 1.73 m^{-2} died within 86 weeks after heart failure was diagnosed (data not shown). Unfortunately, the CCI uses serum creatinine to estimate renal function, rather than the glomerular filtration rate according to the Modification of Diet in Renal Disease study group equation, which is more accurate in elderly patients.[26] The CCI defines moderate or severe renal disease as serum creatinine of ≥3 mg/dL (265 μmol/L) which was present in only 1 patient, who died within 12 weeks. It is imaginable that the CCI underestimates the severity of renal dysfunction in elderly patients.

Table 2. Three-year mortality in 93 geriatric outpatients with heart failure in relation to established determinants and Charlson Comorbidity Index (CCI)

Variable	Alive (n = 41)	Deceased (n = 52)	HR (95% CI)		
			Crude	Adjusted for Age and Gender	Adjusted for Age, Gender, LVEF, NT-proBNP, and CCI
Age, y	82.4 ± 5.7	82.9 ± 5.1	1.1 (0.7−1.9)	1.2 (0.7−2.1)	1.3 (0.7−2.4)
Male sex	13 (31.7)	21 (40.4)	1.3 (0.8−2.3)	1.4 (0.8−2.4)	1.3 (0.7−2.4)
LVEF					
>45%	21 (51.2)	23 (44.2)	–	–	–
35%−45%	14 (34.1)	9 (17.3)	0.7 (0.3−1.5)	0.7 (0.3−1.5)	0.6 (0.2−1.3)
<35%	6 (14.6)	20 (38.5)	2.0 (1.1−3.7)	2.2 (1.1−4.1)	2.1 (1.0−4.7)
NT-proBNP, pg/mL	1,883 (760−3,507)	2,925 (851−7,500)	1.2 (0.9−1.5)	1.2 (1.0−1.6)	1.1 (0.8−1.4)
CCI					
1−2 points	20 (48.8)	15 (28.8)	–	–	–
3−4 points	18 (43.9)	24 (46.2)	1.6 (0.8−3.0)	1.6 (0.9−3.2)	1.5 (0.7−2.9)
>4 points	3 (7.3)	13 (25.0)	3.3 (1.5−6.9)	3.2 (1.5−6.8)	4.0 (1.9−8.8)

Hazard ratio (HR) of CCI 3−4 and >4 points compared with CCI 1−2 points; HR of LVEF 35%−45% and <35% compared with LVEF >45%. HR increases per 10 years of age and per ln NT-proBNP. CI, confidence interval; other abbreviations as in Table 1.

Numerous determinants of the prognosis of heart failure have been identified,[1,27] of which age, gender, and severity of heart failure (reflected in LVEF and NT-proBNP) are generally considered to be the ''established'' determinants. Of these four established determinants, only LVEF <35% influenced prognosis. The observation that male gender does not predict mortality in geriatric patients with heart failure is consistent with earlier studies in the elderly.[28] In contrast with earlier studies, neither age nor NT-proBNP predicted 3-year mortality in the present group of elderly heart failure patients (mean age 82.7 years) with high NT-proBNP levels (median 2,295 pg/mL). The impact of ejection fraction was modest; mortality rates did not differ between patients with systolic heart failure (LVEF <45%) and those with HFPEF. The observation that mortality was higher in patients with LVEF <35% is in line with the results of the recently published report of the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC).[29]

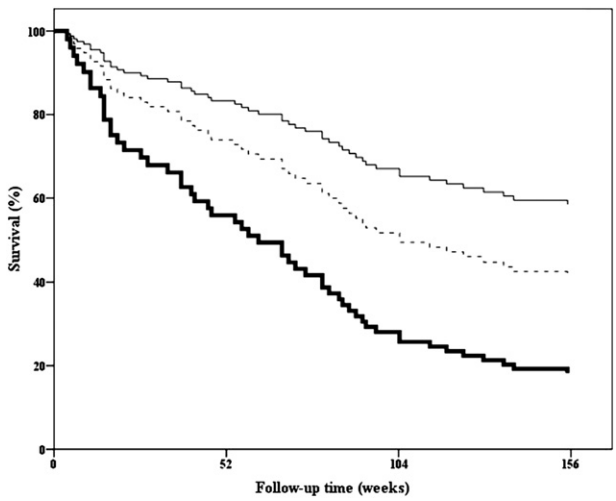

Fig. 2. Cox survival curves for geriatric patients with heart failure according to Charlson Comorbidity Index (CCI), adjusted for age and gender. Thin solid line: CCI 1−2 points; thin dashed line: CCI 3−4 points; thick solid line: CCI >4 points.

Most prognostic studies in heart failure to date were performed in patients with known heart failure,[11] eg, when admitted for decompensated heart failure,[10,18,19] and in general population samples screened for the prevalence of heart failure.[17] In these studies the actual duration of heart failure can vary appreciably. In daily practice, however, physicians establish a diagnosis, directly followed by an assessment (implicitly or explicitly) of the prognosis of the individual patient, to determine the optimal treatment strategy taking into account both life expectancy and quality of life. The major strength of our study is that we determined prognosis in patients with newly diagnosed heart failure reflecting everyday practice, which only few studies have done before.[30,31] Another strength is that we studied elderly outpatients with a wide range of comorbidity, who are generally excluded from clinical trials[32] but who are frequently treated by general practitioners, geriatricians, internists, and cardiologists.[33] As such this is the first prognostic study of geriatric outpatients with newly diagnosed heart failure (mean age 82.7 years, 63.4% female) with a wide range of both cardiovascular and noncardiovascular comorbidity. Although the results in our study may not come as a surprise, they have not been established before in this population.

The main limitation of our study relates to the small number of patients (n = 93) with heart failure, resulting in a lack of power to analyze multiple determinants of prognosis. Elderly patients with multiple comorbidities and with newly detected heart failure had a poor prognosis. This raises the question of whether this is attributable to an inherent poor prognosis in these patients or, at least in part, to poor adherence to evidence-based heart failure medication following the diagnosis, albeit that evidence from randomized trials on the efficacy of heart failure therapy in these patients is very limited. However, no detailed information on the use of heart failure medication following the diagnosis was available in this study.

Thist study shows that the prognosis of geriatric outpatients with newly diagnosed heart failure is determined to

a large extent by the severity of concomitant diseases. Explicitly taking comorbidity into consideration (eg, by means of the CCI) will facilitate treatment decisions and discussing of the various options with elderly heart failure patients and their caregivers. In those with a high CCI (and thus with a limited life expectancy), the focus is likely to be on symptom relief per se (eg, by diuretics), whereas in those with a low CCI, in addition to relief of symptoms, aiming to improve prognosis, eg, by initiating and uptitrating beta-blockers and angiotensin-converting enzyme inhibitors, could be a treatment goal.

In conclusion, the majority of geriatric outpatients with newly diagnosed heart failure not requiring hospital admission die within 3 years after establishing the diagnosis. Comorbidity, as summarized in the CCI, is the strongest independent predictor of 3-year mortality. It follows that routine application of the CCI may be of help in adequately managing this group of patients.

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Disclosures

None.

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