Characteristics, outcomes, and predictors of 1-year mortality in patients hospitalized for acute heart failure

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Introduction

Acute heart failure (AHF) is one of the most common diseases in emergency medicine and associated with a poor prognosis. Its clinical classification has been described in the recently published guidelines of European Society of Cardiology (ESC)¹. The clinical presentation ranges from acute pulmonary congestion to pulmonary oedema and cardiogenic shock. It can also be seen as heart failure caused by hypertension, high output, or right ventricular failure.¹

Even though common and fatal at its worst, there is limited data on the epidemiology, treatment, and prognosis of AHF.²⁻⁵ The largest European survey, the Euro Heart Failure Survey (EHFS)² with 11 327 patients, includes both patients with AHF and patients with chronic heart failure (CHF) hospitalized primarily due to other reasons, as well as 17% of patients with only suspected heart failure with a follow-up of only 3 months. Only 40% of patients in EHFS had heart failure as primary cause for hospitalization, i.e. AHF.²

Aims Acute heart failure (AHF) is associated with poor prognosis and requires recurrent hospitalizations. However, studies on AHF characteristics, treatment, and prognostic factors are few. Our aim was to investigate the characteristics, treatment, and 1-year prognosis of AHF and identify prognostic factors in different clinical groups.

Methods and results We conducted a prospective multicentre study with 620 patients hospitalized due to AHF; mean age 75.1 (10.4) years, 50% male. Half of the patients had new-onset heart failure. Acute congestion (63.5%) and pulmonary oedema (26.3%) were the most common clinical presentations. Left ventricular ejection fraction (LVEF) was reported in two-thirds of patients. Half of these had preserved systolic function (LVEF ≥ 45%). At discharge, 86% of patients had beta-blockers and 76% either ACE-inhibitors or angiotensin receptor blockers in use. The 12-month all-cause mortality was 27.4%. We identified several clinical and biochemical prognostic risk factors in univariate analysis. Independent predictors of 1-year mortality were older age, male gender, lower systolic blood pressure (SBP) on admission, C-reactive protein, and serum creatinine > 120 μmol/L.

Conclusion We present the characteristics and prognosis of an unselected population of AHF patients. One-year mortality is high, and independent clinical risk factors include age, male gender, lower SBP on admission, C-reactive protein, and renal dysfunction.

Identification of prognostic risk factors in the setting of AHF is of high priority, and follow-up might be tailored in the high-risk patients. Several markers of poor prognosis have been described in CHF. Widely recognized risk factors are age, coronary artery disease (CAD), reduced left ventricular ejection fraction (LVEF), and renal dysfunction.⁶⁻⁸ Also anaemia, hyponatraemia, male gender, and diabetes have been associated with poor prognosis.⁸⁻¹⁰ The values of these prognostic factors in AHF patients are less well documented.

Finnish Acute Heart Failure Study (FINN-AKVA) is a national observational prospective multicentre study on AHF. It is the first population of all consecutive AHF patients characterized according to the ESC criteria—distinct to the EHFS survey. Our aim was to investigate the aetiology, comitant diseases, treatment modalities, morbidity, mortality, and prognostic markers of AHF.

Methods

All consecutive patients hospitalized with AHF during 3 months were enrolled at 14 university, central, and regional hospitals in Finland between 2 February 2004 and 30 May 2004. Patients with new-onset...
AHF as well as with exacerbation of CHF were included and enrolled only once during the study period. They were characterized according to the recently published ESC AHF guideline criteria to five groups on the basis of their clinical presentation on admission: cardiogenic shock, pulmonary oedema, congestive heart failure, hypertensive crisis with heart failure, and right ventricular failure. Patients with high-output heart failure were not included. Anthropometric measures, underlying diseases, precipitating factors, the most recent echocardiography findings, clinical presentation, in-hospital treatments, and medication at discharge were recorded by local research fellows. Morbidity as well as in-hospital mortality and length of stay (LOS) in the hospital were also documented. At discharge, the diagnosis of heart failure had to be confirmed. Mortality was assessed for all patients from the Finnish National Population Register. The patients gave a written consent and blood samples were drawn twice during the hospital stay and stored in –20°C. The study was approved by local ethical committees.

We sought to identify demographic characteristics, clinical variables, and biochemical markers with prognostic impact. \( \chi^2 \) test, independent \( t \)-test, and Cox proportional hazards regression analysis were used as appropriate. We compared 1-year mortality in relation to age, gender, body mass index (BMI), and previous medical history. The use of beta-blockers, ACE-inhibitors, and/or angiotensin receptor blockers (ARB) on admission was tested for impact on prognosis, as was the use of these medications at discharge in the population discharged alive. We further evaluated the effect of left ventricular systolic function on survival (LVEF ≤ 40%), clinical presentation, acute coronary syndrome (ACS), as well as systolic and diastolic blood pressures on admission. Biochemical variables included in the analysis were anaemia (blood haemoglobin < 120 g/L in females and < 130 g/L in males), hyponatraemia (sodium < 135 mmol/L), C-reactive protein (over median of 10 mg/L), serum creatinine > 120 µmol/L, and BNP on admission (over median of 174 pg/mL). All variables were then included in the Cox multivariable analysis to identify independent predictors of mortality. There was a large number of missing values for BMI, BNP, and LVEF. Therefore, these variables were tested both separately and all together in multivariable analyses, but since found non-significant, they were not retained in the final multivariate model. The proportional hazards assumption was confirmed using weighted residuals score test. We used SPSS 12.0.1 statistical software (SPSS Inc.). The results are given as mean (SD), median (interquartile range (IQR)), percentages [95% confidence interval (CI)], or hazard ratios (95% CI) as appropriate.

**Results**

**Patient characteristics**

Altogether 620 patients entered the study, 58% from university hospitals, 21% from central hospitals, and 21% from regional hospitals. The patient demographics are shown in Table 1 with a comparison between new-onset and acutely decompensated CHF patients. Of the latter, 40% had been hospitalized for AHF at least once during the previous 6 months.

**Clinical manifestation and hospital course**

Acute congestion (63.5%) was the most common manifestation of AHF, whereas 26.3% had pulmonary oedema. The rest had either cardiogenic shock (2.3%) or hypertensive crisis (3.1%) or right ventricular failure (4.8%). Half of the patients had a history of heart failure. Compared with patients with congestive heart failure, those with pulmonary oedema had more often a history of CAD (66 vs. 53%, \( P < 0.01 \)) as well as ACS (51 vs. 25%, \( P < 0.001 \)) and angiography (22 vs. 14%, \( P < 0.01 \)), percutaneous coronary intervention (PCI), or coronary artery bypass surgery (CABG) performed during hospital stay (15 vs. 6%, \( P < 0.001 \)), along with treatment in the cardiac care unit (CCU) and/or intensive care unit (ICU) (71 vs. 35%, \( P < 0.001 \)). Hospital stay was similar with a median of 8 (IQR 5–10) vs. 7 (IQR 6–14) days, whereas in-hospital mortality was slightly higher (10 vs. 6%, n.s.) in the pulmonary oedema group. On the contrary, compared with patients with congestive heart failure, those with pulmonary oedema had less often atrial fibrillation as a precipitating factor (20 vs. 34%, \( P < 0.01 \)).

The 14 cardiogenic shock patients were mostly men (71%), with ACS as the most common precipitating factor (64%). Eight out of nine cardiogenic shock patients with ACS underwent angiography during the hospital stay. PCI was performed in five of these patients and one patient underwent CABG during hospital stay. All shock patients needed inotropic or vasopressor support, and levosimendan was used in 71% of these patients. Invasive ventilatory support was needed in 50% of the shock patients, and 22% received intra-aortic balloon pump (IABP) support. The median in-hospital LOS was 12 days (IQR 8–25) in shock patients. All these patients were treated in the CCU and/or ICU for a total median time of 13 (IQR 5–19) days. Still, in-hospital mortality was 28.6% in the shock patients.

**Therapeutic and diagnostic management of the total study population**

Continuous positive airway pressure support was used in 26% of the patients, but invasive ventilatory support only in 4%. Intravenous furosemide infusions/bolus were given during the first 12 h to 76% of all patients, and 42% received intravenous nitrates. Inotropic treatment or vasopressors were used in 13% of the patients, and 49% of these received two or more inotropes. Levosimendan (7%), dopamine (7%), noradrenaline (5%), and dobutamine (4%) were the most commonly used. Few patients received adrenaline or milrinone.

Before hospitalization, 23% of the study patients had undergone either coronary angiography or PCI or CABG, and during hospitalization, these were performed to 17% of the patients. Of the ACS patients, 37% underwent angiography, PCI, or CABG during hospitalization (PCI 5%), whereas 11% had undergone angiography, PCI, or CABG only before hospitalization. Pacemakers were present in 9% of all patients on admission, 12% in the CHF patients, and 6% in de novo patients. Of all patients, 6% had paced rhythm on admission, and of these, 49% had right ventricular pacing and the rest had physiological pacing.

Data from echocardiography were available in 71% of the patients, of which 72% had been performed during hospital stay. Two-thirds of all patients had LVEF reported and half of these had preserved systolic function (LVEF ≥ 45%) (Table 1). Regarding distinct types of hospitals, echocardiography was available in only 32% of patients in regional hospitals, in contrast to 68% in central hospitals and 78% in university hospitals. The echocardiograms were least often performed to the oldest patients (data not shown).

Overall, the median LOS was 7 days (IQR 5–11). CCU care was needed in 39.5% of the patients for a median of 2 (IQR 2–4) days. ICU care was given to 11.9% of the patients for a median of 3 (IQR 2–5) days. In-hospital mortality was
7.1%. Although 78% of the patients were hospitalized from home, only 58% were discharged directly to home and the others either to regional hospitals or nursing homes for further rehabilitation.

The medication on admission and at discharge is shown in Table 2. Before hospitalization, nine out of 10 patients received cardiovascular medication. ARBs were mostly used as an alternative to ACE-inhibitors because only eight patients received both. ACE-inhibitors/ARBs were prescribed more often to patients with systolic dysfunction than with preserved systolic function [85% if LVEF < 45% and 73% if LVEF ≥ 45% (P = 0.004), 70% if LVEF missing]. The patients without prescribed ACE-inhibitors/ARBs at discharge had higher creatinine levels (111 vs. 95 μmol/L, P = 0.001) compared with those discharged with these medications. Of the patients with systolic dysfunction, 92% received beta-blockers at discharge, whereas in patients with preserved systolic function and with unknown systolic function, the use was 86 and 78%, respectively (P = 0.001). Use of beta-blockers and/or ACE-inhibitors/ARBs at discharge and differences in age and echocardiographic data are shown in Table 3. At discharge, ~90% of all patients had either aspirin or oral anticoagulant in use. Two-thirds of our patients with a known history of hypercholesterolaemia had lipid-lowering agents in use.

**Follow-up**

The cumulative 3-month and 6-month mortality rates were 15.0 and 20.0%. At 1 year, 171 patients (27.4%) had died. One-year mortality was higher in the decompensated CHF (33.5%) than in the de novo group (21.1%, P < 0.001). Demographic and biochemical variables associated with all-cause mortality at 12 months are shown in Table 4. In patients with C-reactive protein above or below median, the proportion with diagnosed infection was similar. Using Cox multivariable analysis, we identified older age, male gender, lower systolic blood pressure (SBP) on admission, C-reactive protein > 10 mg/L, and creatinine > 120 μmol/L as independent prognostic factors (Table 5). The 12-month mortality in the congestive group was 25.1%, and in the pulmonary oedema group, it was 31.9%. Mortality in the cardiogenic shock group was high, reaching 35.7% at 12 months. In the right ventricular heart failure group, all patients were
discharged alive, but 12 month mortality was as high as 43.3%. Best prognosis was seen in the hypertensive heart failure group, with no in-hospital mortality and 84.2% survival at 1 year.

Discussion

FINN-AKVA, a national observational prospective multicentre study yields new important information on real-life AHF patients. It is the first population of all consecutive AHF patients characterized according to the ESC criteria—distinct to the EHFS survey.

Decompensated CHF and new-onset heart failure

For the first time, we describe significant differences between patients with new-onset heart failure and acutely decompensated CHF. In this study, half of the patients had new-onset (de novo) heart failure, a greater number than in the previous literature. This may have been due to meticulous screening of the patients to the present study. The majority of de novo patients were men, and they were younger than patients with CHF. Importantly, de novo patients had more often ACS as the precipitating factor. Moreover, there was a significant difference in the distribution of underlying diseases in these two groups: e.g. diabetes, valvular diseases, and chronic kidney disease were more common in patients with CHF. Only history of hypertension was equally common in both groups. The finding that de novo patients more often had ACS and atrial fibrillation as precipitating factor could imply that cardiac dysfunction in some forms of de novo heart failure is transient in nature and might thus be curable along with the precipitating factor. This might explain, at least partly, the better survival of de novo patients at 1 year, which is a novel finding.

Patients and clinical groups

As previously reported, the average age of the patients in our study was high and women were older than men. CAD and hypertension were the most common cardiovascular underlying factors of heart failure in our study. Patients in our study were classified for the first time with similar criteria as those in the ESC guidelines on AHF, except that no high-output heart failure patients were included. Those patients, actually, are difficult to recognize, and their treatment is principally aimed at the factors causing high-output circulation. Indeed, the identification of curable, causative, and predisposing factors is essential in the management of all patients with AHF. Acute congestion, the most common form of AHF, was most often precipitated by atrial fibrillation, whereas pulmonary oedema and cardiogenic shock were more often caused by ACS. In fact, half of the
pulmonary oedema patients and most of those with cardiogenic shock had no history of CAD or CHF. Interestingly, the majority of AHF patients with a history of CAD did not have ACS on admission.

Echocardiography
Preserved LVEF is a common finding in patients with AHF and in elderly CHF patients. Half of our patients with information on LVEF had preserved systolic function (LVEF ≥ 45%) and one-third had LVEF over 50%. However, transient systolic heart failure cannot be excluded. LVEF was more frequently reported in university and central hospitals than in regional hospitals, to a same degree as in a previous study from two European academic hospitals. In regional hospitals, echocardiography is mostly performed by internists in contrast to university hospitals with more cardiologists. Anyhow, like in EHFS, echocardiography was not performed to a third of all patients. The probability of not having echocardiogram increased with age and was higher in women than men. The patients lacking an estimate of the LVEF also carried the worst prognosis. However, we did not record reasons for not performing an echocardiogram.

Table 4
Patient characteristics by vital status at 12 months and results of univariate Cox regression analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Deceased (95% CI) n = 171</th>
<th>Alive (95% CI) n = 449</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>78.0 (9.4)</td>
<td>74.0 (10.6)</td>
<td>0.0001</td>
<td>1.04*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.02–1.05</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>57.0 (49.2–64.5)</td>
<td>48.0 (43.3–52.7)</td>
<td>0.05</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.98–1.79</td>
</tr>
<tr>
<td>Male gender (HR adjusted for age)</td>
<td>1.8**</td>
<td>1.31–2.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) mean (SD)</td>
<td>25.9 (5.3)</td>
<td>28.2 (6.3)</td>
<td>0.004</td>
<td>0.5**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.31–0.83</td>
</tr>
</tbody>
</table>

Table 5
Adjusted hazard ratios for predictors of mortality at 12 months from multivariable Cox regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 year increase)</td>
<td>1.6</td>
<td>1.30–1.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.5</td>
<td>1.02–2.17</td>
<td>0.04</td>
</tr>
<tr>
<td>SBP (per 10 mmHg increase)</td>
<td>0.9</td>
<td>0.80–0.94</td>
<td>0.0003</td>
</tr>
<tr>
<td>C-reactive protein &gt;10 mg/L</td>
<td>1.9</td>
<td>1.32–2.65</td>
<td>0.0005</td>
</tr>
<tr>
<td>Creatinine &gt;120 µmol/L</td>
<td>1.9</td>
<td>1.29–2.69</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Adjusted for variables in Table 4. Non-significant adjusted HR not shown.

Medication
Owing to other cardiovascular diseases, a large proportion of even the new-onset heart failure patients had beta-blocker and ACE-inhibitor/ARB in use on admission. During hospital stay, especially these medications, as well as furosemide, digoxin, spironolactone, aspirin, and oral anticoagulants
were frequently initiated to the de novo patients and also to a number of decompensated CHF patients. Surprisingly, the use of beta-blockers, ACE-inhibitors/ARBs, or both on admission did not affect long-term prognosis. In fact, the decompensation and need for hospitalization in patients with CHF could partly be regarded as a treatment failure. This seems to emphasize that AHF and CHF are in themselves two different conditions.

Beta-blocker and ACE-inhibitor/ARB therapy were better implemented in our patients than before, and lipid-lowering agents and especially beta-blockers were more often used than in a recent Italian survey. The use of ARBs in heart failure has increased noticeably. Patients without prescribed beta-blockers or ACE-inhibitors/ARBs at discharge were older and had higher LVEF, a possible explanation for not prescribing these medications. Also, patients without ACE-inhibitors/ARBs at discharge had higher average creatinine levels than those with medication prescribed, although these features cannot be considered as contraindications.

Intravenous diuretics were used in three-fourths of the patients in our study. Many patients had the precipitating factor treated and obviously did not have significant fluid overload. Spironolactone was rather infrequently used, since only one-third of the patients with a history of systolic heart failure were discharged with this medication. However, the use was similar to EHFS. Inotropes are needed in AHF to support and to stabilize haemodynamics if basic treatment modalities are not sufficient. The more common use of inotropes in our study than in EHFS is most likely explained by a minority of patients in EHFS having AHF; however, in a recent Italian study with more severe AHF patients, inotropes were required more often. We show for the first time prevalence of the use of levosimendan, a calcium sensitizer, in an ordinary AHF population. This seems to emphasize that AHF and CHF are in themselves two different conditions.

In multivariable analysis, we found older age, male gender, lower SBP on admission, admission C-reactive protein level, and renal dysfunction to be independently associated with prognosis in AHF patients. Although mortality increases progressively with declining LVEF in CHF, in our study, LVEF ≤ 40% was not independently associated with outcome. Among biochemical variables, a strong relationship between renal dysfunction and mortality has been reported both in CHF and in AHF. Our results confirm these findings and the importance of the cardiorenal syndrome. C-reactive protein is a novel prognostic risk marker in heart failure, and in our analysis, elevated C-reactive protein levels were indeed associated with worse prognosis. Certainly, in acute cardiac decompensation, elevated C-reactive protein levels may reflect concomitant infection, with impact on survival. However, in our study, C-reactive protein above median was an independent predictor of mortality irrespective of whether infection was diagnosed or not.

We also found a relationship between higher SBP on admission and better 1-year survival. The association between blood pressure and in-hospital outcome was recently reported. In contrast to previous reports in CHF, anaemia, hyponatraemia, and diabetes did not emerge as predictors of mortality in our population. BNP values obtained on admission were not predictive of long-term outcome on multivariable analysis. Indeed, in a previous study evaluating serial BNP measurements in AHF, predischarge BNP values had better prognostic significance compared with admission values. Our findings are representative of an unselected population hospitalized for AHF. In contrast, patients in randomized clinical trials are younger, the proportion of women is smaller than in real-life, and moderate-to-severe renal dysfunction and significant anaemia are common exclusion criteria.

This paper describes the first population of all consecutive AHF patients characterized according to the ESC criteria from a wide range of hospitals. The all-cause mortality at 12 months in our study is similar to a recently published data. Owing to the short 3 month follow-up in EHFS I, no comparison can be done on long-term prognosis; however, the 3 month mortality data are rather similar. Survival was expectedly better in patients with less severe presentation of heart failure. A third of the pulmonary oedema patients died during the 1 year follow-up, although a 40% 1-year mortality has been reported. The mortality in patients with cardiogenic shock was high, although less than previously reported. Interestingly, all deaths in cardiogenic shock patients occurred in the first 3 months. Surprisingly, mortality in right ventricular heart failure increased steadily after discharge. The outcome was in fact worst among clinical classes. Almost half of these patients had either dilated cardiomyopathy or end-stage heart failure, which most probably accounts for the negative prognosis. Hypertensive crisis on the other hand was interestingly associated with a fairly good survival. Owing to the limited number of patients in these latter three groups, the results should, however, be interpreted with caution.

Conclusion

FINN-AKVA is a large multicentre study comprising a broad spectrum of patients with AHF. AHF patients are on average old and the amount is still to increase due to growing old age groups. New-onset AHF patients are as
common as those with exacerbation of CHF. These two groups differ in regard to co-morbidities, precipitating factors, and mortality. As a whole, 1-year mortality is high and independent clinical risk factors include age, male gender, lower SBP on admission, C-reactive protein, and renal dysfunction. LOS in hospital is fairly long. Better understanding of AHF may help develop protocols for trials to improve prognosis of patients with AHF. Indeed, in contrast to studying AHF as a single entity, more refined trials, which take into account diverse aetiologies and manifestations of AHF, are needed. To this point, there is still room for improvement in adherence to diagnostic and therapeutic strategies as described in the recently published guidelines.1,8

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Conflict of interest: none declared.

Appendix
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References