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Predictors for hospitalizations in elderly patients with clinical symptoms of heart failure: A 10-year observational primary healthcare study

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1. Introduction

Chronic heart failure (HF) occurs in 10–20% of the population aged 70–80 years. The prognosis is poor for patients with HF, and the need for hospitalization is frequent; indeed, HF is the most common cause for hospitalization at medical clinics for patients older than 65 years. In primary healthcare (PHC), elderly patients often have serious comorbidities, and the contributions of these problems to hospitalizations of patients with HF are often overlooked.

The need for markers or other instruments to identify patients at high risk for hospitalization therefore is urgent. Natriuretic peptides [N-terminal pro-hormone of brain natriuretic peptide (NTproBNP)] are relatively new markers for excluding the diagnosis of HF but also serve as prognostic tools for mortality in patients with HF. The question remains of whether these markers also can be used to predict hospitalizations. Another marker is high-sensitivity C-reactive protein (hsCRP), which indicates the grade of inflammation and also predicts cardiovascular diseases. Its value for predicting hospitalization in elderly patients with HF is unknown, however. Reduced kidney function is related to mortality in patients with heart disease, and creatinine or estimated glomerular filtration rate (eGFR) may be expected to be markers of

Methods: Between 2000 and 2003, 170 patients with HF symptoms according to their general practitioners were recruited and referred for echocardiography, biomarker measures and a final cardiology consultation. HF diagnosis was based on the general practitioner’s prespecified HF record, echocardiography, and hospital records. Records from the departments of medicine and surgery were used to identify hospitalizations. This is a 10-year longitudinal observational primary healthcare center study.

Results: During 10 years, 136 (80%) patients had 660 and 207 all-cause and cardiovascular hospitalizations, respectively. In multivariable logistic regression, age [odds ratio (OR) = 1.1, 95% confidence interval (CI) = 1.01–1.15] and underlying heart disease (OR = 3.5, 95% CI = 1.00–11.89) significantly predicted all-cause hospitalization. Age (OR = 1.1, 95% CI = 1.01–1.12), underlying heart disease (OR = 3.4, 95% CI = 1.041–1.40), and N-terminal of prohormone brain natriuretic peptide ≥ 800 ng/L (OR = 4.3, 95% CI = 1.5–12.50) significantly predicted cardiovascular hospitalizations. In Cox regression analysis, overall HF (HR = 1.8, 95% CI = 1.06–2.94) significantly predicted time to first all-cause hospitalizations while no variable independently predicted time to first cardiovascular hospitalization.

Conclusion: In patients with HF symptoms managed in primary healthcare, age, and underlying heart diseases predicted all-cause hospitalizations. N-terminal of prohormone brain natriuretic peptide added independent prognostic information for cardiovascular hospitalizations.

Keywords: biomarker comorbidity elderly heart failure hospitalization primary healthcare

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the need for hospital care. The symptoms of anemia are similar to those for HF, including breathlessness and tiredness, and anemia is rather common in patients with HF but not as well studied when it comes to predicting the need for hospitalizations in elderly patients. Cholesterol is a well-known risk factor for ischemic heart disease, especially in younger and middle-aged patients, but its role as a predictive factor for hospitalization in elderly patients with or without HF is unclear.

We hypothesized that these biomarkers and comorbidities could have the potential to independently predict all-cause or cardiovascular-related hospitalization in patients with clinical symptoms of HF. Thus, our aim with this study was to evaluate the prognostic value of biomarkers (NTproBNP, creatinine, eGFR, hemoglobin, hsCRP, and cholesterol), comorbidities and a verified diagnosis of HF for all-cause and cardiovascular hospitalizations.

2. Methods

2.1. Study population

The study population and diagnostic procedures with categorization of HF patients have been described in detail previously. In short, between the years 2000 and 2003, 170 patients with clinical symptoms of HF were recruited from one selected PHC with a catchment population of 7800 in the northern Sweden. The PHC had a computer-based registry for patients with a diagnosis of clinical symptoms of HF. This study comprises patients from the registry as well as consecutive patients who were identified by the general practitioner (GP). All patients had symptoms, essentially breathlessness, that in the GP’s clinical judgment could be caused by chronic HF.

The GP registered data from the examination of the patient into a prespecified HF record. Patients then were referred for an echocardiography (performed by M.O.) and subsequent cardiovascular consultation. The study cardiologist (K.B.) confirmed or refuted the diagnosis of HF according to European Society of Cardiology guidelines based on the GP’s prespecified HF record, echocardiography results and hospital records. Underlying heart disease included patients with myocardial infarction, hypertension, atrial fibrillation (AF), ischemic heart disease, angina pectoris, and those with a cardiac murmur as a proxy for valvular disease (8 patients with mitral insufficiency, 4 with aortic stenosis, and 3 with aortic insufficiency; 11 patients had unspecified cardiac murmurs).

AF was verified by an electrocardiogram analysis. The diagnosis of HF was validated with echocardiography. No other clinical variables were validated. There were missing values for smoker, or ex-smoker (n = 12), and alcohol (n = 17). All other categorical variables were classified as yes or no.

2.2. Biomarkers

For administrative reasons, blood samples for NTproBNP and hsCRP were taken in 159 patients. Blood sampling took place before the echocardiographic examination from fasting patients who had rested for 20 minutes. After 5 minutes, the samples were centrifuged (1500–2000 × g) for 10 minutes at 4 °C then stored frozen at −70 °C.

For analysis of hsCRP, a solid-phase, chemiluminescent immunometric assay (Immulite Analyzer; Diagnostic Products Corporation, Los Angeles, CA, USA) was used. NTproBNP was analyzed using the Roche Elecsys proBNP immunoassay. There is no general consensus on the best cut-off value for NTproBNP to predict hospitalizations, and different values have been suggested depending on the clinical setting (e.g., emergency departments or PHC centres). Our cutoff level for NTproBNP of ≥ 800 ng/L was an estimated mean value for clinical purposes based on findings from three studies.

The results for creatinine, hemoglobin, and cholesterol analyses were collected from the GP’s pre-specified HF record. The eGFR was calculated with the equation from the Modification of Diet in Renal Disease study.

2.3. Outcome classification

To register hospitalizations for 10 years of follow-up, medical records at the Medical and Surgical Departments in Skellefteå County Hospital, Skellefteå, Sweden were used. Classification was defined according to ICD-10 for all-cause and cardiovascular hospitalization diagnoses (100–199 and transitory ischemic attack, G45.9).

2.4. Statistical analysis

Baseline characteristics are presented as frequencies or means and standard deviations. Chi-square and Fisher’s exact tests were used for categorical variables. The association between baseline characteristics and hospitalizations for 10 years of follow-up was analyzed with logistic regression analysis and time to first hospitalization with Cox regression analysis. In multivariable logistic and Cox regression analyses, the categorical variable NTproBNP ≥ 800 ng/L was used instead of the continuous variable.

We used two different models for multivariable logistic or Cox regression analyses. Model 1 included age and sex as fixed covariates and those variables that significantly (p < 0.05) predicted hospitalizations in univariable analysis. Model 2 tested all variables from model 1 and with the addition of overall HF compared to those with no HF. The results are presented as an odds ratio (OR) and hazard ratio (HR) with the 95% confidence interval (CI). The assumption of proportional hazard was checked graphically using Kaplan–Meier survival curves for time to first hospitalization. PASW statistics (SPSS Inc., Chicago, USA) version 18.0, was used for all statistical analyses.

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

3. Results

3.1. At 10 years of follow-up

A total of 136 of 170 (80%) patients were hospitalized for any reason, 90 (53%) for cardiovascular causes; see baseline characteristics in Table 1. In total, there were 660 all-cause hospitalizations and 207 hospitalizations for cardiovascular reasons. A total of 25 patients (18%) had only one hospitalization, and all others had two or more. Of special note, all patients with AF had at least one all-cause hospitalization. The most common cause of hospitalization was cardiovascular disease (Figure 1). Of 77 patients (84%) with overall HF, 65 contributed to 351 all-cause hospitalizations, and 46 patients out of 77 (60%) with overall HF accounted for 127 hospitalizations due to cardiovascular diseases. The mean number of hospitalizations/patient did not differ significantly between patients with overall HF and no HF (4.56 ± 4.53 vs. 3.15 ± 3.53, p = 0.064) for all-cause hospitalization or between overall HF and no HF (1.65 ± 2.51 vs. 0.88 ± 1.31, p = 0.052) for cardiovascular hospitalization.

The proportion of patients with HF compared to patients without HF did not differ significantly for being hospitalized for all-cause (84% vs. 79%, p > 0.05) or for cardiovascular reasons (60% vs. 46%, p > 0.05).
3.2. All-cause hospitalization at 10 years of follow-up

In logistic regression univariable analysis, age, male sex, AF, underlying heart disease, NTproBNP > 800 ng/L and eGFR < 60 mL/min/1.73 m² were significantly associated with all-cause hospitalization during 10 years of follow-up (Table 2).

In multivariable model 1, after the addition of age and sex, age and male sex remained significantly associated with risk for all-cause hospitalization. In multivariable model 2, after adjustment also for overall HF, age and underlying heart disease remained significantly associated with all-cause hospitalization (Table 3). In univariable Cox regression analysis for time to first all-cause hospitalization, NTproBNP as the continuous variable (HR = 1.02, 95% CI = 1.01–1.02) and dichotomized variable (≥ 800 ng/L; HR = 2.1, 95% CI = 1.43–3.13), hemoglobin (HR = 0.98, 95% CI = 0.96–0.99), continuous hsCRP (HR = 1.03, 95% CI = 1.01–1.05), cardiac murmur (HR = 1.7, 95% CI = 1.03–2.65), and overall HF (HR = 2.4, 95% CI = 1.60–3.53) were significantly associated with time to first all-cause hospitalization.

In multivariable Cox regression analysis model 1, NTproBNP > 800 ng/L (HR = 1.7, 95% CI = 1.08–2.60) and hemoglobin (HR = 0.98, 95% CI = 0.97–0.998) remained significantly associated with all-cause hospitalization. In multivariable model 2, after the addition of overall HF, only overall HF remained significant (HR = 1.8, 95% CI = 1.06–2.93) (Figure 2).

3.3. Cardiovascular hospitalization at 10 years of follow-up

In univariable logistic regression analysis, age, diabetes, AF, underlying heart disease, and NTproBNP > 800 ng/L were significantly associated with cardiovascular hospitalization (Table 2).

In multivariable model 1, age and NTproBNP ≥ 800 ng/L remained significantly associated with cardiovascular hospitalization. In multivariable model 2, age, underlying heart disease and NTproBNP ≥800 ng/L remained significant (Table 4). In univariable Cox regression analysis, NTproBNP as a continuous (HR = 1.02, 95% CI = 1.01–1.02) and dichotomized variable (≥ 800 ng/L; HR = 2.3, 95% CI = 1.23–4.17) along with creatinine (HR = 1.01, 95% CI = 1.00–1.03), hsCRP (HR = 1.04, 95% CI = 1.00–1.08), and overall HF (HR = 2.4, 95% CI = 1.26–4.50) were significantly associated with time to first cardiovascular hospitalization. In multivariable models 1 and 2, when age, sex, and overall
HF were added, none of the variables in the multivariable analysis remained significant.

4. Discussion

Our main findings were that age and underlying heart disease significantly predicted all-cause hospitalization in multivariable analysis. In addition, overall HF independently predicted time to first all-cause hospitalization. By contrast, NTproBNP > 800 ng/L, elevated creatinine, elevated hsCRP, and overall HF were significantly associated with time to first cardiovascular hospitalization, but only in the univariable analysis.

An epidemiologic study from Olmsted County comprising 1077 patients with HF and with a mean follow-up of 4.7 years (our study: 6.4 years of mean follow-up) demonstrated that 83% of their patients had at least one hospitalization. Their patients were in the same age range as ours, but they all had HF. Our patients had suspected HF, and 80% were still hospitalized. As in our study, those authors found that the majority of hospitalizations were due to noncardiovascular causes. Their univariable risk factors for all-cause hospitalizations were age, male sex, hypertension, diabetes, chronic obstructive pulmonary disease, anemia, and creatinine clearance < 30 ml/min, which was somewhat similar to our findings except for diabetes and chronic obstructive pulmonary disease.
A diagnosis of HF in these older patients seems to matter when it comes to risk for time to first hospitalization. In a survey on HF-related hospitalizations in the USA between 1979 and 2004, Fang et al. reported increasing admissions to the hospital with increasing age. They emphasized the importance of treating noncardiac conditions in patients with HF to decrease hospitalizations. By contrast, a registry study from Sweden between the years 1987 and 2006 on patients with a diagnosis of HF revealed another pattern of increasing admission to the hospital for younger (<45 years) patients with HF while in patients aged 54–84 years, hospitalizations peaked in the 1990s but then decreased.

Our findings highlight the importance of identifying underlying heart disease because these patients were included due to a suspicion of HF. In these older patients, there was an association not only with cardiovascular hospitalization but more importantly also with all-cause hospitalization, suggesting a fragility of these patients to which comorbidities beyond heart diseases may have contributed. Of special note, all patients with AF had at least one all-cause hospitalization, which calls attention to this disorder with regard to both rate and rhythm control as well as anticoagulation considerations.

Studies are lacking on the prognostic importance of cardiac murmurs in PHC. A study from Copenhagen showed that in hospitalized unselected patients, a murmur was present in 22% and increased the risk of 1-year mortality after adjustment for age and sex, but there was no information about whether a murmur was associated with a risk for re-hospitalization. Our study extends the present knowledge, with 15% of hospitalized patients having a cardiac murmur and 80% of these patients hospitalized at 10 years of follow-up. The authors of the Copenhagen study also pointed out the importance of heart auscultation for noncardiologists and concluded that detection of a murmur in an elderly person admitted to the hospital is strongly prognostic. In our study, cardiac murmur at the PHC also seemed to be of value to predict time to re-hospitalization.

Figure 2. Cox regression analysis with hazard ratio (HR) and confidence interval (CI) for time to first all-cause hospitalization in patients with overall heart failure (HF) compared to patients without HF after adjustment for age, sex, NTproBNP >800 ng/L, hemoglobin, and CRP (model 2). CRP = C-reactive protein; NTproBNP = N-terminal pro-hormone of brain natriuretic peptide.

Table 4
Multivariate logistic regression analysis for cardiovascular hospitalization at 10 years of follow-up in patients with clinical symptoms of heart failure.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;, n = 159</th>
<th>OR 95% CI</th>
<th>p</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;, n = 133</th>
<th>OR 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.01–1.11</td>
<td>0.014</td>
<td>1.1</td>
<td>1.01–1.12</td>
<td>0.030</td>
</tr>
<tr>
<td>Male</td>
<td>1.7</td>
<td>0.74–3.73</td>
<td>0.220</td>
<td>1.2</td>
<td>0.49–2.95</td>
<td>0.696</td>
</tr>
<tr>
<td>History diabetes</td>
<td>2.3</td>
<td>0.74–7.15</td>
<td>0.151</td>
<td>2.4</td>
<td>0.73–7.91</td>
<td>0.148</td>
</tr>
<tr>
<td>History underlying heart disease</td>
<td>2.5</td>
<td>0.99–6.18</td>
<td>0.050</td>
<td>3.4</td>
<td>1.04–11.40</td>
<td>0.044</td>
</tr>
<tr>
<td>NTproBNP &gt; 800 ng/L</td>
<td>3.6</td>
<td>1.47–8.87</td>
<td>0.005</td>
<td>4.3</td>
<td>1.50–12.50</td>
<td>0.007</td>
</tr>
<tr>
<td>Overall HF (systolic &amp;/or diastolic HF)</td>
<td>0.9</td>
<td>0.36–2.03</td>
<td>0.716</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HF = heart failure; NTproBNP = N-terminal prohormone of brain natriuretic peptide; OR = odds ratio.
<sup>a</sup> age and sex and significant variables from the univariate analysis; <sup>b</sup> all variables from Model 1 and addition of overall HF.
first cardiovascular hospitalization. This outcome calls attention to the clinical value of cardiac auscultation even in the present era of new modern technologies of biomarkers and echocardiography. In a study by Adlbrecht et al.,13 1203 primary care patients were screened to evaluate the predictive value of NTproBNP for time to first all-cause hospitalization with 12 months of follow-up. That study included patients with hypertension, diabetes mellitus, coronary artery disease or suspected HF and showed that NTproBNP was an independent predictor for time to all-cause hospitalization. In our study, both NTproBNP and underlying heart disease were independent predictors for cardiovascular hospitalization; however, our patients were comparatively older, and the follow-up time was much longer.

High levels of hsCRP have been shown to predict time to first hospitalization for patients with HF.14 Compared to our patients, the patients in the previous report were much younger, having a mean age of 63 years. Low cholesterol is a known predictor for mortality but also for re-hospitalization15 in elderly patients hospitalized with HF, but we found no association for hospitalization in our study. A systematic review by Damman et al.16 on patients with HF demonstrated that worsening renal function (defined as an increase in serum creatinine of > 0.5mg/dl) was associated with a modest increase overall for all-cause hospitalization. In our study, impaired renal function defined as eGFR ≤ 60 ml/min/1.73 m² was associated with all-cause hospitalization and elevated serum creatinine levels with time to first cardiovascular hospitalization, but only in univariable analysis.

4.1. Clinical implications

Our study adds the following clinical information to be considered in the management of elderly patients in PHC with clinical symptoms of HF and a risk for future hospitalization: First is the importance of registering the underlying heart disease(s) with special attention to AF; second is the importance of diagnosing the presence of HF and taking elevated NTproBNP into account; and third is examining and validating cardiac murmurs in the patients. The above suggestions need to be tested in future prospective studies with clearly validated heart diseases. Moreover, our cutoff value for NTproBNP should be regarded as exploratory, and further prospective studies are needed to identify the most accurate cutoff value to predict hospitalizations in elderly patients in primary healthcare. Larger studies are also needed to identify other biomarkers as additional prognostic tools.

4.2. Strengths and limitations

The strength of the present study is the long-term follow-up in a rather unselected group of patients with clinical symptoms of HF. The diagnosis of HF was validated with echocardiography. Our study has a number of limitations, however. First, it is a single-center study, and the study population is limited. Second, data for clinical variables except for HF and AF were not validated. The levels of creatinine, hemoglobin, and cholesterol were registered from the GP’s prespecified HF record. Some data for clinical variables were missing for unknown reasons. For underlying heart diseases, missing data were regarded as absence of disease.

Another limitation is that the number of patients in Tables 3 and 4 differ compared to the number in Table 1. Compared with baseline characteristics for all 170 patients, age, sex, underlying heart disease, diabetes, overall heart failure, NTproBNP, and eGFR did not differ significantly in mean values or proportions among the patients presented in Tables 3 and 4. This suggests that patients in Tables 3 and 4 share almost the same characteristics as all 170 patients.

We realize that the limited number of patients and hospitalizations may have introduced a type 2 error that could limit the full understanding of the real value of our studied biomarkers for hospitalizations in elderly patients. Elevated hsCRP, a high level of creatinine and low hemoglobin were all significant in univariable analysis for time to first hospitalization, suggesting that they may have a predictive value, but this possibility needs to be confirmed in larger studies.

5. Conclusion

In this long-term follow-up study in patients with clinical symptoms of HF managed in PHC, age, and underlying heart diseases were predictors for hospitalization. Special attention should be paid to AF because all patients with this condition were hospitalized. Cox regression demonstrated that patients with HF were at greater risk for all-cause hospitalization compared to those without HF. High NTproBNP added further independent prognostic information about risk for cardiovascular hospitalizations. No other studied biomarker contributed to prediction of all-cause or cardiovascular hospitalizations.

Conflicts of interests

The authors have no conflicts of interest to report.

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