Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care

E Hak, J Bont, AW Hoes and TJM Verheij


**Background.** Uncertainty about the prognosis of lower respiratory tract infections (LRTI) hinders optimal management in primary care.

**Objective.** We determined prognostic factors for a severe complicated course of LRTI among elderly patients in primary care.

**Methods.** In a retrospective clinical database study we examined 455 patients with a first LRTI episode; 226 with physician-diagnosed acute bronchitis or lung exacerbations and 229 with pneumonia. Multivariate logistic regression analysis was used to assess independent associations of the potential predictors with the endpoint.

**Results.** Occurrence of the combined endpoint 30-day home-treated complications from LRTI (4.4%) or hospitalisation (4.6%), or all-cause mortality (5.3%) was 14.3%. In a logistic regression model, increasing age [odds ratio (OR) 1.04; 95% confidence interval (95% CI) 1.00–1.08], male sex (OR 3.12; 95% CI 1.66–5.87), heart failure (OR 5.14; 95% CI 2.33–11.34), stroke or dementia (OR 3.36; 95% CI 1.18–9.58), use of antidepressants or benzodiazepines (OR 1.89; 95% CI 1.02–3.52) and a diagnosis of pneumonia (OR 4.24; 95% CI 2.17–8.28) were independent predictors.

**Conclusion.** GPs need to be aware of readily available prognostic factors that can be used in primary care to complement physical examination and laboratory data in LRTI to guide preventive and therapeutic management decisions.

**Keywords.** Elderly, epidemiology, general practice, prognosis, respiratory tract infection.

Introduction

Community-acquired lower respiratory tract infections (LRTI) like acute bronchitis, pneumonia and exacerbations of chronic lung disease rank among the most common reasons why people visit their GP. Annual incidence of LRTI is 50 per 1000 patients and the occurrence is considerably higher among seniors. The nation-wide costs associated with LRTI for the US were estimated to be $4.4 billion. In The Netherlands, case fatality from pneumonia was estimated at 2.2% in 1990 and recent figures suggest that pneumonia annually leads to more than 50 000 years of life lost.

Immediate treatment of LRTI in primary care is usually empirical and based on medical history, clinical signs and symptoms without evidence-based weighing of prognostic factors. Accurate and systematic assessment of the patients’ risk of developing complications from LRTI as an indication for immediate treatment—as has for example been advocated for patients at high risk for development of cardiovascular disease—is not included in primary care guidelines due to a lack of accurate predictive models. Verheij *et al.* did not find prognostic patient characteristics for a prolonged course of LRTI among adults. However, Houston, amongst others, reported that apart from an atypical clinical picture, neurologic disease, cancer, and recent use of antibiotics in the medical history were independent risk factors for 30-day mortality among elderly with LRTI.

As in secondary care, prognostic factors from medical
history that are readily available to the primary care physician could complement clinical diagnostic data to further rationalise management of elderly with LRTI, for example by aggressive treatment of high-risk co-morbid conditions or withholding prescription of antibiotics in low-risk patients. We determined prognostic factors for the risk of serious morbidity and mortality from LRTI among non-institutionalised patients aged ≥60 years in primary care using easily obtainable routine information from computerised medical records.

Methods

Patients and setting

We studied patients aged 60 years or over who visited a general practice of the Utrecht GP research network in the period March 1998 to February 2000. Twenty-three GPs of this network serve approximately 50 000 persons. The patient population with regard to age and gender distribution is representative for the Dutch population as a whole. Twenty-percent live in urban areas, 24% in middle-sized towns and 56% in rural areas. A protocol-led morbidity registration system has been in use since the early nineties. All patient contact data are registered in routine medical care using computerised medical records. For diagnoses the International Classification of Primary Care (ICPC)-codes have been in use and the Anatomical Therapeutically Classification (ATC)-codes is applied to classify medical drug prescriptions. All diagnostic coding is performed by the GP. In addition, uniform diagnosis, registration and management of respiratory disease has been the primary object of continuing medical education. During the study period, the participating physicians made their decisions concerning their treatment and possible referral of patients independently.

Diagnosis of pneumonia and non-pneumonia LRTI

Patients were eligible for inclusion in the retrospective cohort study if they had a record of a physician-diagnosed first LRTI episode including a diagnosis of “non-pneumonia” LRTI (i.e. acute bronchitis; ICPC code R78 or exacerbation of chronic obstructive pulmonary disease [COPD]; codes R91 and R95 with added qualification “exacerbation”) or pneumonia (code R81). The criteria for the diagnosis of acute bronchitis (R78) according to the ICPHHC-2 were presence of cough and scattered or generalised abnormal chest signs. Patients with cough only were excluded from the analysis. No specific criteria according to the ICPHHC-2 are available for the diagnosis exacerbations of COPD and we relied on the diagnosis of the GP. Since only few patients had COPD exacerbations and risks of these patients appeared similar to those with acute bronchitis, we choose to combine them to gain power in the analysis. Diagnostic criteria of pneumonia (R81) were either a confirmation by X-ray or the presence of 3 or more of the following signs/symptoms: (a) decreased intensity for breath sounds; (b) dullness on chest percussion; (c) inspiratory crackles; (d) bronchophony; (e) fever (≥38°C); and (f) local chest pain on deep inhalation. All records were scrutinised by two trained medical students to verify the final diagnosis given by the GP after all diagnostic information including X-ray results was obtained.

We further excluded few patients from the study if they had a record of: prior infection with HIV or immune deficiency (B90); prior immunosuppressive medication use; or hospitalisation in 2 weeks prior to the visit to their GPs.

Definition of potential predictors

After extensive literature search, we identified several potential predictors from medical history that are routinely available for patients with LRTI in Dutch general practice: demographic data (age, sex and private health insurance cover or Sick Fund), health care use in the 12 months prior to consultation as well as common co-morbidity including the presence of COPD (R91/R95), lung cancer (R84), other malignancies (Y77, X76, L71, D75, X75), heart failure (K77), coronary artery disease (K76), myocardial infarction, neurological diseases including stroke (K90), multiple sclerosis (N86), Parkinson’s disease (N87), dementia (P70), diabetes (T89, T90), and alcohol abuse (P15). In addition, information was available on prior use of antidepressants and tranquilisers, respiratory and cardiac medication, diabetic medication and antibiotics taken more or less than one month before diagnosis. Since in diagnostic data are not routinely encoded in the medical records, information on clinical signs and symptoms as well as laboratory findings could not validly be retrieved. All patient data were collected by review of the medical records by two trained physicians and stored anonymously in a database.

Primary endpoint

The combined endpoint was defined as the occurrence of physician-diagnosed and recorded (1) dysregulation of metabolic control of diabetes, stroke, acute heart failure and myocardial infarction or hospitalisation for respiratory disease and these complications or (2) death from all causes within 30 days after a first LRTI diagnosis. Since there is no ICPC code available for dysregulation of diabetes, we relied on the text given by the GP.

Model development

We used the complete data of 229 study patients with a diagnosis of pneumonia and of a similarly sized random sample of 226 of 688 non-pneumonia LRTI cases that occurred during the research period to develop the model. In line with other primary care based studies, absence of a characteristic in the
medical database was assumed to indicate no presence of the characteristic under study. Age was a continuous variable, all other variables were classified as dichotomous variables with presence as indicator and absence as reference. Descriptive statistics as proportions and means (SD) were calculated to describe baseline characteristics in the two outcome groups (with or without endpoint) using SPSS for Windows, version 9.0 (SPSS Inc., Chicago, Illinois, USA). The construction of the prognostic model started with a univariate assessment of the associations of each characteristic and the endpoint by estimation of odds ratio’s (OR) and their corresponding 95% confidence interval (95% CI) for the total study population. In the next stage we applied multivariate logistic regression modelling to select those variables that were associated with the endpoint with a \( P \)-value < 0.05 as criterion for entry.\(^{16,17}\) Forward selection was additionally performed to verify whether any previously deleted potentially relevant characteristic was incorrectly eliminated from the model. Before estimating the performance of the rule in the two separate diagnostic groups, we also tested for statistical interaction between the variable diagnosis (pneumonia versus non-pneumonia LRTI) and the other main predictors of the final model. No statistically significant interactions were observed in our dataset which indicates that associations in the pneumonia group between the predictors and endpoint are not statistically significant different from those associations among patients with non-pneumonia LRTI. For each patient we calculated the individual probability of the outcome from the final model (predicted probability).\(^{18}\)

**Model evaluation**

The reliability of the multivariate logistic regression model was determined by the Hosmer-Lemeshow goodness-of-fit statistic.\(^{17}\) The area under the receiver-operating-curve (ROC) was used to assess the model’s discriminative ability.\(^{18,19}\) The area under the ROC can be explained as the probability that the logistic regression model will assign a higher probability of the outcome to a randomly chosen patient with an outcome than to a randomly chosen patient without outcome. An area under the curve (AUC) estimate of 0.5 indicates no discrimination (like flipping of the coin) whereas an estimate of 1.0 indicates perfect discrimination. Models with AUC values between 0.70 and 0.79 are generally considered as having moderate and \( \geq 0.80 \) as good discriminative properties.

**Results**

Mean age of the study population was 75 years (SD 8.6 years, range 60 years to 99 years), 45% of the patients were male and 66% insured through the Sick Fund. Of the 226 patients with non-pneumonia LRTI, 195 had acute bronchitis and 31 had a diagnosis of an acute exacerbation of their COPD. Mean age, gender and insurance cover did not differ substantially between patients with non-pneumonia LRTI or pneumonia.

In all, 65 (14.2%) endpoints were recorded; 24 (5.3%) were fatal, and non-fatal events occurred in the remaining 41 cases: 21 (4.6%) hospitalisations, 15 (3.3%) heart failure, two (0.4%) stroke, two (0.4%) metabolic dysregulation of diabetes, and one (0.2%) myocardial infarction. Most endpoints were recorded among pneumonia cases (\( n = 51 \) versus 14 among non-pneumonia LRTI). Of the seventeen potential predictors examined for an association with the endpoint (Table 1), six were found to be significantly associated with the endpoint in multivariate analysis (Table 2). The reliability of the final model was good (goodness-of-fit test \( P = 0.59 \)) and the model discriminated satisfactorily between those with and without an endpoint (AUC-value 0.82; 95% CI 0.76–0.87). Though the discriminative capacity of the model for patients with pneumonia appeared lower than for patients with non-pneumonia LRTI, the differences in AUC values were neither substantial nor statistically significant and acceptably good (AUC-value 0.74; 95% CI 0.67–0.82 for pneumonia versus an AUC-value 0.82; 95% CI 0.70–0.94 for non-pneumonia).

In the elderly with an endpoint, a markedly higher mean age (78 versus 74 years) and higher prevalence of males

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without endpoint (( n = 390 ))</th>
<th>With endpoint (( n = 65 ))</th>
<th>Univariate ( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>74.1 (8.5)</td>
<td>78.0 (8.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>162 (41.5)</td>
<td>41 (63.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sick Fund</td>
<td>263 (67.4)</td>
<td>37 (56.9)</td>
<td>0.098</td>
</tr>
<tr>
<td><strong>Co-morbidity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>24 (6.2)</td>
<td>21 (32.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia/stroke</td>
<td>11 (2.8)</td>
<td>9 (13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 (2.8)</td>
<td>4 (6.2)</td>
<td>0.163</td>
</tr>
<tr>
<td>Peripheral Arterial disease</td>
<td>12 (3.1)</td>
<td>2 (3.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Lung disease</td>
<td>57 (14.6)</td>
<td>14 (23.1)</td>
<td>0.084</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31 (7.9)</td>
<td>11 (16.9)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Prior health care use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior hospitalisation</td>
<td>8 (2.1)</td>
<td>5 (7.7)</td>
<td>0.011</td>
</tr>
<tr>
<td>Antidepressants/</td>
<td>131 (33.6)</td>
<td>29 (44.6)</td>
<td>0.085</td>
</tr>
<tr>
<td>benzodiazepines use</td>
<td>81 (20.8)</td>
<td>13 (20.0)</td>
<td>0.887</td>
</tr>
<tr>
<td>Corticosteroids use</td>
<td>42 (10.8)</td>
<td>10 (15.4)</td>
<td>0.279</td>
</tr>
<tr>
<td>Oral prednisone use</td>
<td>47 (12.1)</td>
<td>11 (16.9)</td>
<td>0.276</td>
</tr>
<tr>
<td>Bronchodilator use</td>
<td>21 (5.4)</td>
<td>1 (1.5)</td>
<td>0.181</td>
</tr>
<tr>
<td>Antibiotics &lt;1 months</td>
<td>128 (33.8)</td>
<td>20 (30.8)</td>
<td>0.744</td>
</tr>
<tr>
<td>Antibiotics &gt;1 months</td>
<td>175 (44.9)</td>
<td>51 (78.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosis pneumonia</td>
<td>261 (66.9)</td>
<td>38 (58.5)</td>
<td>0.183</td>
</tr>
</tbody>
</table>

\(^a\) See Methods section for corresponding ICPC codes.
(63% versus 42%), heart failure (32% versus 6%), stroke or dementia (14% versus 3%), prescribed antidepressants or benzodiazepines (45% versus 34%) and a diagnosis of pneumonia (79% versus 45%) as compared to patients without an endpoint were observed. All other potential predictors appeared neither in the overall study population nor in the subgroups statistically significant predictors (P > 0.10). Except for heart failure, all other predictors had similar point estimates of association with the separate outcome death and the discriminative AUC-value even increased from 0.82 to 0.86.

Discussion

Our study identified easily obtainable prognostic factors from medical history to enable practising physicians to determine risks of a complicated course among elderly with pneumonia and non-pneumonia LRTI. The strengths of the study include the large number of GPs who participated in the study and the representative patient population for the Netherlands as a whole. Also, the GPs underwent regular training in diagnosis, registration and management.

Safe strategies to target antibiotic use and medical treatment of high-risk co-morbid conditions, and to monitor patients more closely would lead to cost-savings. Apart from the clinical picture which is not always clear in elderly persons, clinical management might be more rationalised using risk stratification based on medical history as a complementary set to the diagnosis itself. Most available models have been developed to assess the severity of community acquired pneumonia (CAP). However, application of these models to primary care is hindered by the selection of hospitalised patients and scoring systems requiring chest radiography, invasive tests and laboratory analyses. Seppä and colleagues studied elderly primary care patients with lower respiratory tract infections, but they focused on LRTI severe enough to indicate pneumonia. They found that aggravation of concurrent illness, a respiratory rate of ≥25/min and CRP levels above 100 mg/L were independently associated with 30-day mortality. In fact, a large proportion of patients actually had pneumonia (82%) with higher risks for a severe outcome than the large group of patients with non-pneumonia LRTI.

The prognostic factors determined in the logistic regression model discriminated well between those with and without the occurrence of the combined severe outcome (AUC-value of 0.82) and even more for the separate outcome death (AUC-value of 0.86). This means that other important information such as clinical signs and symptoms and results of physical examinations may further increase the discriminative value, but are not essential to differentiate these patients according to their risk. In this study, age (OR 1.04 per year increase) and male gender (OR 3.12) were independently associated with the combined endpoint. In earlier studies among patients with CAP, controversial observations on the prognostic value of age have been reported.Our results are supported by some and in contrast with others. Most of these latter studies included only a low percentage of elderly or differentiated between the very old and younger. Surprisingly most studies did not observe an increased risk according to gender. We found that males were clearly at higher risk for a severe outcome than females independently of other characteristics. We did not have valid information on smoking behaviour and it is well known that males smoke more often than females which can explain the observed difference. In addition, our findings may be

### Table 2

Multivariate associations of clinical characteristics with endpoints in total patient population (n = 455), patients with pneumonia (n = 226) and acute bronchitis (n = 229). Percentages are given, unless stated otherwise.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 455)</th>
<th>Pneumonia (n = 226)</th>
<th>Non-pneumonia (n = 229)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)*</td>
<td>P-value</td>
<td>Odds Ratio (95% CI)**</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.04 (1.00–1.08)</td>
<td>0.050</td>
<td>1.05 (1.00–1.09)</td>
</tr>
<tr>
<td>Male</td>
<td>3.12 (1.66–5.87)</td>
<td>&lt;0.001</td>
<td>2.52 (1.23–5.15)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5.14 (2.33–11.34)</td>
<td>&lt;0.001</td>
<td>3.13 (1.25–7.86)</td>
</tr>
<tr>
<td>Dementia/ stroke</td>
<td>3.36 (1.18–9.58)</td>
<td>0.023</td>
<td>3.35 (1.03–10.9)</td>
</tr>
<tr>
<td>Antidepressants/ benzodiazepines</td>
<td>1.89 (1.02–3.52)</td>
<td>0.044</td>
<td>1.58 (0.78–3.22)</td>
</tr>
<tr>
<td>Diagnosis pneumonia</td>
<td>4.24 (2.17–8.28)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Likelihood ratio test (LR): P < 0.001; Hosmer-Lemeshow goodness-of-fit test: P = 0.59.
** Likelihood ratio test (LR): P < 0.001; Hosmer-Lemeshow goodness-of-fit test: P = 0.89.
*** Likelihood ratio test (LR): P < 0.001; Hosmer-Lemeshow goodness-of-fit test: P = 0.75.
NA: not applicable.
explained by the larger range of outcomes under study including both home-treated and hospitalised or even fatal severe complications and the rather unselected group of primary care patients with large range of risks.

In many prediction studies, co-morbidity has been shown to be independently associated with higher risks of mortality. In another study such an association was not reported, but often the presence of certain high-risk co-morbidity was used as an exclusion criterion.

In the present study, we observed higher risks for those with coexisting stroke or dementia and especially those with congestive heart failure which have previously been reported as high-risk diseases for example for development of complications from influenza. We probably did not have enough statistical power to show a statistically significant association between lung disease and the combined outcome. The point estimate of the odds ratio was much higher than 1 (1.9), however, not statistically significant \((P = 0.19)\). Most probably, more important predictive information was present in the other significant factors.

Surprisingly, the use of antidepressants or benzodiazepines was independently associated with a severe prognosis. This finding could not be supported by other studies. However, it has been described that frailty, depression and use of benzodiazepines are highly intercorrelated, hence the use of these medications might be an indicator of frailty.

Finally, our data confirm a higher risk among patients with a diagnosis of pneumonia as compared to those without such a diagnosis. In all, 14/226 (6%) of the non-pneumonia group and 51/229 (22%) of the pneumonia group developed a complication. Since this was a retrospective cohort study, we were not able to verify the diagnoses made by the participating physicians. However, to be applicable to GPs who do not have immediate access to radiography or spirometric measurements to confirm their symptom-based diagnosis this type of study is suitable to meet our primary objective.

Our study had some potential limitations that need to be discussed. The assessment of predictors and endpoints was retrospective and could not be blinded. However, we trained the physicians to register the information as it was available in the patient records. From a previous large database study, we know that information collected by review of medical records is largely in accordance with information given by patients themselves. Since most predictors were confirmed by previous findings, we therefore do not expect serious bias by this design. Another limitation of our study is that we did not have data on whether the patient was immediately referred to the hospital. Therefore, it is possible that some of the worst cases were recorded as not having received antibiotics whereas in fact they received the antibiotics in the hospital. Furthermore, more diagnostic data from physical examination or laboratory tests were not available in the database since these are not routinely collected by the GPs. Despite a high discriminative capacity of the history model, it might be that additional tests from physical examination or laboratory such as respiratory rate and CRP levels can further improve the discriminative capacity.

In conclusion, complications in lower respiratory tract illness are frequent, notably when a diagnosis of pneumonia is made. We have demonstrated that primary care physicians may use the model to more rationally classify patients at high or low risk for severe outcomes, hence allowing them to more rationally select them for appropriate preventive and therapeutic care. Future studies should be conducted to validate its findings and applicability in primary care and to determine the additional value of tests from physical examination and laboratory.

**Declaration**

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Ethical approval: not applicable.

Conflicts of interest: none.

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