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A prediction rule for elder primary care patients with lower respiratory tract infections

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ABSTRACT: Prognostic scores for lower respiratory tract infections (LRTI) have been mainly derived in a hospital setting. We developed and validated a prediction rule for the prognosis of acute LRTI in elderly primary care patients.

Data, including demographics, medication use, health care use and comorbid conditions, from 3,166 episodes of patients aged ≥ 65 years visiting the general practitioner (GP) with LRTI were collected. Multiple logistic regression analysis was used to construct a predictive model. The main outcome measure was 30-day hospitalisation or death. The Second Dutch Survey of GPs was used for validation.

Increasing age, male gender, previous hospitalisation, heart failure, diabetes, use of oral glucocorticoids, previous use of antibiotics and a diagnosis of pneumonia or exacerbation of Chronic Obstructive Pulmonary Disease were independent predictors of 30-day hospitalisation or death. A prediction rule based on these variables showed that the outcome increased directly with increasing scores: 3, 10 and 31% for scores of <2 points, 3-6 and ≥7 points, respectively. Corresponding figures for the validation cohort were 3, 11, 26%, respectively.

This simple prediction rule can help the primary care physician to differentiate between high- and low-risk patients. As a possible consequence, low-risk patients may be suitable for home-treatment whereas high risk patients might be monitored more closely in a homecare or hospital setting. Further studies should assess whether information on signs and symptoms can further improve this prediction rule.

INTRODUCTION

Acute lower respiratory tract infections (LRTI) such as pneumonia and acute bronchitis are among the most common reasons to attend a general practitioner (GP), notably among elderly persons.[1] In The Netherlands, the annual incidence of pneumonia and acute bronchitis per 1,000 patients aged 65 to 74 years is 12 and 32, respectively, and this is even much higher in the very old.[2] Elderly persons are of particular concern to GPs, since they are more likely to develop complications from LRTI compared to younger patients. Correctly classifying these patients into high- or low-risk may reduce unnecessary (antibiotic) treatment in low-risk patients and improve tailoring of more intensive interventions in high-risk patients.

Severity scores are important in predicting outcome. Many guidelines use these scores to tailor management decisions.[3-6] However, the usefulness of the available studies from which scores are derived is limited for primary care physicians. First, the majority of studies included hospitalised patients[7-18] or a selected group of patients with community-acquired pneumonia (CAP) only.[7-13;15-20] While mortality is the most commonly used outcome and of importance, other more frequent complications leading to hospitalisation are relevant from a patients and physicians perspective as well. Also, most studies included only a small number of elderly. Finally, the data-analysis of some studies included the development of a prediction rule, but few validated such rule in an elderly primary care population with LRTI[7-9;12-14;16;20]. To be able to target management decisions in elderly with LRTI more efficiently, we aimed to develop a prediction rule with the use of easily obtainable data to estimate the absolute risk of elderly primary care patients with LRTI to be admitted to hospital or die within 30 days after diagnosis, and validated the rule in a large nationally representative cohort.

METHODS

Setting and study population

We retrospectively analysed medical data from two large cohorts of elderly patients with physician-attended LRTI. The first cohort was used to identify characteristics that were predictive of 30-day hospitalisation or death and to develop a prediction rule. The second cohort served to validate the predictive model.

The derivation cohort originates from patient-data stored in the database of the Utrecht GP research network (Utrecht patient cohort). In this network a structured and uniform morbidity registration system has been in use since the early nineties. Currently, thirty-five GPs of this network serve approximately 58,000 non-institutionalized persons. The patient population is representative for the Dutch population with regard to age and gender.[21] All patient data are registered in the patient record using the International Classification of Primary Care (ICPC)-codes for diagnoses. Using the computerized medical records of all elderly persons from the Utrecht patient cohort, we collected data on eligible LRTI episodes from January 1997 to February 2003 in elderly patients aged 65 years or older. During the study period, the participating physicians made their decisions concerning their treatment and possible referral of patients according to usual care.

Data on the *validation cohort* were obtained from data of patients from the Second Dutch National Survey of General Practice (National patient cohort), conducted by the Netherlands Institute for Health Services Research (NIVEL) in 2001. The study included 359,625 patients from 163 GPs in 85 practices.[22] All GPs participated in a training programme aimed at uniform registration of diagnosis and prescriptions. Data were collected over a 12-month period in 2000/2001.

Definition of LRTI

LRTIs consisted of episodes of pneumonia, acute bronchitis and exacerbations of chronic obstructive pulmonary disease (COPD). Patients were allowed to have more than one episode of LRTI with at least three weeks and a symptom free interval in between each episode. ICPC-codes were used to select the episodes. The ICPC-criterion for pneumonia (R81) is evidence of pulmonary consolidation based on either physical examination or chest X-ray. The ICPC-criteria for acute bronchitis (R78) are coughing and fever with diffuse abnormalities on pulmonary examination like wheezing and crepitations. Since fever is often absent in elderly, we allowed for this criterion to be ignored. An exacerbation of COPD (R91, R95) was defined according to the Anthonisen criteria.[23] Criteria were met if 2 out of 3 of the following symptoms occurred: increased dyspnoea, sputum volume or sputum purulence. If 1 out of 3 symptoms was found, at least one of the following findings had to be present: upper respiratory infection (sore throat, nasal discharge) within the past 5 days, fever without other cause, increased wheezing, increased cough, or increase in respiratory rate or heart rate.[23]

Episodes from patients who were treated with antibiotics within the previous 3 weeks for another

respiratory problem were excluded. Also episodes were excluded if at the moment of presentation the patient was known to have lung cancer, a haematological malignancy or an infection with the Human Immunodeficiency virus, used immunosuppressive medication (except oral glucocorticoids), or was hospitalised during the two weeks preceding the diagnosis.
The validation cohort included patients with episodes of acute bronchitis and pneumonia only. Unfortunately the database did not allow us to use the same inclusion criteria for selecting episodes of COPD exacerbations. Therefore we choose not to use these episodes for the external validation.

Selection of potential predictor variables

The selection of potential predictive variables routinely available in the GP medical records, was based on a review based on relevant literature pertaining to the prognosis of community-acquired LRTI.[7-16;18;20;24-26] We collected demographic data including age and gender, present use of medication, pre-existing potentially risk-elevating co-morbidity and health care use in the 12 months prior to consultation including previous hospitalisation and number of GP visits. Present use of medication was described as medication used at the day of the diagnosis and at least one week prior to this day, including oral glucocorticoids and benzodiazepines or antidepressants. Prior antibiotic use was present if the last tablet of a course was taken within the month prior to diagnosis. Co-morbidity was defined as the presence of a co-morbid condition in the patient's history recorded according to the International Classification of Primary Care coding system. We recorded the presence of COPD or emphysema (R91, R95) or asthma (R96), malignancies (besides haematological malignancies and lung cancer, as they belong to the exclusion criteria), congestive heart failure (K77, K82), myocardial infarction (K75, K76), angina pectoris (K74), stroke (K90), dementia (P70), neurological diseases (N86, N87, N99), diseases of the kidney (U99) and liver (D72, D97) and diabetes (T90). The latter was indicated as present when oral diabetic medication or insulin was used.

Endpoint

The combined endpoint was defined as the occurrence of hospitalisation or death irrespective of the primary cause within 30 days after the day of diagnosis. This information was obtained from the patients' medical file. We repeated our analysis with the separate endpoint all-cause death to be able to compare our results with those of others.

Model development

Derivation of the prediction rule in the Utrecht patient cohort. All variables, except hospitalisation in the year preceding diagnosis, were classified as dichotomous variables. Hospitalisation was classified into three groups consisting of no hospitalisation, hospitalised once or more than once in the preceding year. Descriptive statistics as proportions and means (SD) using SPSS for Windows, version 12.1 (SPSS inc., Chicago, Illinois, USA) were calculated in those with or without the outcome. The absence

of a characteristic in the medical database was assumed to indicate no presence of the characteristic under study for the presence of characteristics is assumed to be accurately documented in the Utrecht GP network.[27] In case of a missing numeric variable the median value based on non-missing episodes was entered. This method was applied in cases in which the number of hospital visits (n=12), general practitioner visits (n=6) or the history of diagnoses of pneumonia (n=6) in the previous year was missing on the research registration forms.

We used all episodes in the development phase of the model. Since most patients had more than one episode and within-person dependency could be present, data were analysed by means of multilevel logistic regression in MlwiN (Center for Multilevel Modelling, Bristol). The variables associated with the outcome in the multilevel univariable analysis at a p-level of 0.2 or lower were included in a multilevel multivariable logistic regression model. Factors that were associated at a p-level lower than 0.05 were included in the final model. Odds ratios [OR] and their corresponding 95% confidence intervals [95% CI] were calculated for each of the prognostic factors.
Internal validity. We internally cross-validated our model twice by a split-sampling model using 2/3 of the total derivation set. Factors were removed from the final model when the p-level was higher than 0.05 in the multivariable model of both split samples. The calibration of the final multivariable logistic regression model was determined by the Hosmer-Lemeshow goodness-of-fit statistic. The area under the receiver-operating curve (ROC) was used to assess the model's discriminative ability. The ROC gives the probability that high-risk patients can be distinguished from low-risk patients when the prediction rule is applied. An area under the curve (AUC) estimate of 0.5 indicates no discrimination whereas an estimate of 1.0 indicates perfect discrimination.

In the final stage the regression coefficients of the derived multivariable model were used to construct the prediction rule. The predicted probability of outcome equals $1/1+e^{-LP}$ where the linear predictor is computed on the basis of the coefficients of the predictors. For practical interpretation we choose to divide all regression coefficients by the lowest (beta [heart failure]=0.364) and rounded them. We defined risk classes on the basis of the score into low-, medium- and high-risk groups.

External validation of the prediction rule in the National patient cohort. The National patient cohort was used to validate the prediction rule. The AUC of the model in this cohort was compared with the ROC of the model in the derivation cohort. Next, the National cohort was also divided into low-, medium- and high risk groups on the basis of the score and the incidence of outcomes and compared to the results of the derivation cohort.

RESULTS

In the derivation cohort we recorded 3,177 episodes of LRTIs in 1,698 elderly patients. We excluded episodes in which the diagnosis was set in hospital (n=4) or was missing on the registration form (n=1). We also excluded episodes of pleuritis (n=6). Thus we analysed 3,166 episodes of LRTIs in 1,693 elderly. Acute bronchitis was diagnosed in 1,120 episodes, 1,523 episodes were diagnosed as an exacerbation of COPD and pneumonia was diagnosed in 523 episodes. 30-day hospitalisation or death occurred in 274 (8.7%) of all episodes and 76 (2.4%) were fatal. In 72% of episodes the reason for hospitalisation or death was primarily LRTI-related and in 20% the cause was cardiovascular. In the remaining 8% there were other reasons, like gastroenteritis, for hospitalisation or death.
The mean age of the derivation cohort was 75.5 years and 45% had the male gender. One or more of the comorbid conditions were present in 85% and COPD, diabetes, heart failure and neurological disease were present in respectively 49%, 14%, 21% and 16%.

The validation cohort consisted of 2,465 episodes of LRTI, including 1,736 episodes of acute bronchitis and 729 of pneumonia. The combined endpoint occurred in 178 episodes (7.5%) and 59 (2.4%) patients died within 30 days.

Derivation of the prediction rule.

The following of the 20 potential predictors examined for an association with the endpoint were independently associated with hospitalisation or death in the multivariate analysis: increasing age, hospitalisation in 12 month prior to diagnosis, heart failure, use of insulin, use of oral glucocorticoids, use of antibiotics in the month prior to diagnosis, and type of diagnosis (table 1).

Table 1. Univariable and/or multivariable multilevel associations between characteristics and the endpoint 'hospitalisation or death within 30 days' in the total derivation set (n=3,166).

Characteristic	No hospitalisation or death (N=2,892)	Hospitalisation or death (N=274)	Univariable OR (95%CI)	Multivariable OR (95%CI)
Demographics				
Age ≥ 80 years	751 (26%)	109 (40%)	2.0 (1.5-2.8)	1.8 (1.3-2.4)
Male gender	1,287(45%)	147 (54%)	1.4 (1.0-1.9)	NS
Health care use[#]				
GP visit for pneumonia ≥1	114 (3.9)	26 (9.5)	1.7 (0.9-2.9)	NS
Hospitalisation ≥1	422 (15)	106 (39)	2.3 (1.6-3.2)	2.0 (1.4-2.8)
Hospitalisation ≥2	97 (3.4)	48 (18)	4.4 (2.7-7.0)	3.5 (2.1-5.7)
Co-morbidity				
COPD/emphysema/ asthma	1379 (48)	157 (57)	1.3 (1.0-1.8)	NS
Malignancies	399 (14)	43 (16)	1.2 (0.8-1.8)	NS
Diabetes[¶]	263 (9.1)	56 (20)	2.3 (1.5-3.4)	1.9 (1.3-2.8)
Congestive heart failure	572 (20)	102 (37)	2.3 (1.6-3.1)	1.4 (1.0-2.0)
Myocardial infarction	319 (11)	30 (11)	1.0 (0.6-1.6)	NS
Angina Pectoris	481 (17)	62 (23)	1.3 (0.9-1.9)	NS
Stroke	185 (6.4)	22 (8.0)	1.2 (0.7-2.1)	NS
Dementia	55 (1.9)	9 (3.3)	2.1 (0.9-4.7)	NS
Neurological disease	166 (5.7)	19 (6.9)	1.5 (0.9-4.7)	NS
Renal disease	74 (2.6)	12 (4.4)	1.7 (0.7-3.8)	NS
Liver disease	29 (1.0)	4 (1.5)	1.5 (0.4-5.2)	NS
Medication use[+]				
Oral glucocorticoids	109 (3.8)	46 (17)	3.7 (2.2-6.1)	2.6 (1.6-4.3)
Benzodiazepines or antidepressants	717 (25)	85 (31)	1.3 (0.9-1.7)	NS
Antibiotics < 1 month[§]	161 (5.6)	36 (13)	2.3 (1.4-3.5)	1.8 (1.2-2.9)
Diagnosis				
Acute bronchitis	1,079 (37)	41 (15)	reference	
Exacerbation COPD	1,389 (48)	134 (49)	2.4 (1.6-3.5)	1.9 (1.3-2.8)
Pneumonia	424 (15)	99 (36)	5.6 (3.7-8.4)	5.0 (3.3-7.5)

OR= odds ratio. CI= confidence interval. GP= general practitioner. COPD= chronic obstructive pulmonary disease. NS= NS not statistically significant (P>0.05). # Health care use was measured over the year preceding the diagnosis. ¶ Diabetes was registered as present if the patient used diabetic medication. + Maintenance medication had to be used for at least a week at the start of the episode. § In case of antibiotics, the last tablet had to be taken within the previous month.

A split-sample procedure with 2/3 of the total population showed the same results, except for the variable male gender. Male gender was not a significant predictor ($p>0.05$) in both split samples and was therefore removed from the final model. All other variables showed similar results.
A score was assigned to each predictor variable resulting in the final prediction model (table 2).

Table 2. Prediction rule for estimating the probability of 30-day hospitalisation or death from LRTI in elderly.

Characteristic	Regression coefficient (B)	Score
Diagnosis		
Acute bronchitis	0	
Exacerbation of COPD	0.643	2
Pneumonia	1.608	4
Age category		
65-79	0	
≥80	0.575	2
Congestive heart failure	0.364	1
Diabetes	0.629	2
Using oral glucocorticoids	0.966	3
Hospitalisation in prior year		
0	0	
1	0.676	2
≥2	1.239	3
Using antibiotics in previous month	0.615	2

The calibration of the model was good (Hosmer-Lemeshow goodness-of-fit test $p=0.73$) and the area under the receiver-operating curve (AUC) was 0.75 (95% confidence interval 0.72 to 0.78) indicating acceptable discriminating properties. When mortality was taken as the sole endpoint, the prediction rule had somewhat better discriminative power (AUC 0.76 with a 95% confidence interval of 0.74 to 0.83). Finally, patients were divided into risk classes according to their score. In the total group of patients with LRTI the risk of complications markedly increased with a higher score. Importantly, similar increases in risks with increasing scores were observed for the separate diagnostic categories of acute bronchitis, exacerbations of COPD and pneumonia. Patients designated to the low-risk class (score of 2 or lower) had a 97% chance of an uncomplicated course (sensitivity and specificity for a cut-off ≥3 points respectively 0.82 and 0.52). Patients with a score 3-6 had an average risk for complications of 9.2%; patients with a score of ≥7 had a strongly elevated risk of 31% for complications leading to hospitalisation or death (sensitivity 0.35, specificity 0.92). (table 3)

Table 3. 30-day hospitalisation or death for different risk classes in the derivation cohort for the total population and for the different diagnoses.

	Total derivation cohort N=3,166		**Acute bronchitis N=1120**		**Exacerbation of COPD N=1,523**		**Pneumonia N=523**	
RISK CLASS	N	Hospitalisation or death %	N	Hospitalisation or death %	N	Hospitalisation or death %	N	Hospitalisation or death %
In all	**3,166**	**8.7**	**1,120**	**3.7**	**1,523**	**8.8**	**523**	**18.9**
Group 1 (score ≤2)	1,564	3.2	925	2.6	639	4.1	#	
Group 2 (score 3-6)	1,288	9.9	187	7.5	722	9.6	379	11.6
Group 3 (score ≥7)	314	30.9	8	37.5	162	24.1	144	38.2

A diagnosis of pneumonia gives 4 points, therefore there is no low risk-class.

External validation of the prediction rule

The National patient cohort in which the prediction rule was validated consisted of episodes of acute bronchitis and pneumonia only. The prediction rule showed acceptable discriminative performance in this cohort (AUC 0.74 with a 95% confidence interval (CI) of 0.71 to 0.78). The negative predictive value for a cut off score of 2 points or less was similar (97% in the National cohort and in the derivation cohort). The positive predictive value for a cut off score of 7 points or higher was still high, but somewhat less than observed in the derivation cohort (26% versus 31%). (table 4.)

Table 4. 30-day hospitalisation or death in different risk classes in the derivation- and validation-cohort.

	Derivation cohort N=3,166					**Validation cohort N=2,465**				
RISK CLASS*	N	Hospitalisation or death %	Mortality %	Sensi-tivity	Speci-ficity	N	Hospitalisation or death %	Mortality %	Sensi-tivity	Speci-ficity
In all	**3,166**	**8.7**	**2.4**			**2,465**	**7.3**	**2.4**		
Low risk	1,564	3.2	0.5	0.82#	0.52#	1,953	5.3	1.6	0.42#	0.81#
Medium risk	1,288	9.9	2.8			462	14.5	5.4		
High risk	314	30.9	10.5	0.35¶	0.92¶	50	22.0	6.0	0.06¶	0.98¶

Low risk = score ≤2; medium risk = score 3-6; high risk = score≥7. # Sensitivity and specificity were calculated for a cut-off of ≥3; ¶ Sensitivity and specificity were calculated for a cut-off of ≥7

DISCUSSION

We derived a prediction rule incorporating eight easily applicable items to estimate the probability of 30-day hospitalisation or death in elderly primary care patients with LRTI.

Strength and shortcomings

This study has several strengths. The prediction rule was not only developed but also validated in a large representative cohort and accuracy appeared good in both cohorts. Second, the prediction rule consists of only few variables that can be directly derived from the medical patient file without delay or costly examinations. Also, data for this study were derived from databases of high quality. The GPs participating in the networks have been using the *ICPC*-coding system for diagnoses for several years and received continuing medical education in applying the ICPC- and ATC-coding systems. Finally, statistical power is always an issue to precisely estimate the predictive value of potential risk factors. We included several thousands of episodes with 274 patients experiencing an outcome and according to the rule of thumb (1 predictor for 10 outcomes) we had adequate power.

A potential limitation of our study is the lack of radiographic evidence for pneumonia. Thus differentiation between pneumonia and acute bronchitis or an exacerbation of COPD is difficult. Therefore, it is possible that pneumonia is overestimated and, on the other hand, some cases of pneumonia might have been diagnosed as an acute bronchitis or an exacerbation of COPD. However, to ensure that our results would be applicable to GPs we decided to follow the same procedure as in routine primary care in which diagnostic tests are much less often applied and diagnosis is made in the majority of cases on the basis of medical history and physical examination only. The same diagnostic uncertainty is present regarding the diagnosis COPD. Although the general practitioners participating in this study were trained to diagnose COPD according to our guidelines in which spirometric results are necessary, it is unknown in what percentage of cases the diagnosis was made in concordance with the guidelines. Again we thought that it was essential to include patients in which the diagnosis COPD was made according to daily routine so results could be generalised to the primary care setting. Further, the retrospective design did not allow for the inclusion of data based on clinical examination and symptoms stated by patients. For instance guidelines for the management of pneumonia in the community of The British Thoracic Society are based on confusion, high respiratory rate, low blood pressure and high age (CRB-65 score).[3;28] These predictive variables are derived from a study where patients were included in a hospitalised setting.[16] In a primary care setting future prospective studies should look at possible improvement of our predictive model with such clinical data. Until then, we think that the results of our study can support the primary care physician in assessing severity of LRTI in elderly.

Some issues should be mentioned about the validation process. Data of the validation cohort were also retrospectively collected. Although a prospective cohort might have been better, this cohort was

comparable in the methods of registration of diagnoses, treatment and outcome. Also, the derivation and validation cohort differed in some respects. The latter did not include COPD exacerbations for we were unable to apply the same criteria in selecting these episodes as in the derivation cohort. This resulted in fewer patients using oral glucocorticoids and fewer patients with heart failure in the validation cohort. Nevertheless the sample size was adequate to show an almost similar discriminative ability of the prediction rule.

Comparison with other studies

Some of the predictor variables were confirmed by other studies. Age is a well-known risk factor,[7;12;14;16;25;29;30] although there are several studies claiming differently.[9;13;15;18;20;24;26] The age-related waning of immunological functions and the presence of co-morbidities due to age-associated diseases largely explain complications in the very old.[31] Therefore, if all co-morbid conditions were taken into account, age would most probable show a less strong association with a poor outcome. Another reason for not finding age as a predictor in other studies is the low number of elderly included in most other studies.

In accordance with Fine et al.[12] and comparable to our previous study,[25] we found an association between a complicated course and heart failure. Although it is sometimes difficult to differentiate between heart failure and LRTI, it is likely that both illnesses can influence each other. For example, it is known that respiratory tract infections can cause aggravation of heart failure leading to hospitalisation or death.[32] Also studies have shown a preventive effect of influenza vaccination for heart failure indicating the interaction between LRTI and heart failure.[33;34]

It was already shown that diabetes is related to an increased risk for getting infections.[35] We have shown, similar to other studies,[36;37] that having diabetes also worsens the prognosis of a LRTI.

The use of oral glucocorticoids was indicative for the outcome as well. Oral glucocorticoids can mask symptoms of infection and can cause deterioration of an infection and therefore increase the risk on a complicated course. On the other hand patients with severe COPD most likely will already use oral glucocorticoids in advance. Consequently, use of oral glucocorticoids most likely acts as a marker for severe COPD and naturally patients with severe COPD have a worse prognosis.
Antibiotics used in the previous month also appeared predictive for poor outcome. This predictor has been found before by Houston et al[26] and is probably indicative for a pre-existent poor health status, like previous hospitalisation

In conclusion, this prediction rule can help GPs to distinguish elderly patients with LRTI with high and low risk of severe complications leading to hospitalisation or death. A more accurate prediction of

the expected course of infection can help the general practitioner to better target preventive and therapeutic management.

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