Bont, J., Hak, E., Hoes, A.W., Schipper, M., Schellevis, F.G., Verheij, T.J.M. A prediction rule for elderly primary-care patients with lower respiratory tract infections. European Respiratory Journal: 2007, 29(5), 269-275

A prediction rule for elderly 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. The current authors have developed and validated a prediction rule for the prognosis of acute LRTI in elderly primary-care patients.

Data including demographics, medication use, healthcare use and comorbid conditions from 3,166 episodes of patients aged 65 yrs 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.

The following were independent predictors of 30-day hospitalisation or death: increasing age; previous hospitalisation; heart failure; diabetes; use of oral glucocorticoids; previous use of antibiotics; a diagnosis of pneumonia; and exacerbation of chronic obstructive pulmonary disease. 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 and 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. Future studies should assess whether information on signs and symptoms can further improve this prediction rule.

Acute lower respiratory tract infections (LRTI) such as pneumonia and acute bronchitis are among the most common reasons to visit 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 65–74 yrs is 12 and 32, respectively, and this is even 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 with younger patients. Correctly classifying these patients as 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 only 7–13, 15–20. While mortality is the most commonly used outcome in studies of this nature, other more frequent complications leading to hospitalisation are also relevant from the patients' and physicians' perspective. Also, most previous studies have included only a small number of elderly patients. Finally, the data analysis of some studies included the development of a prediction rule, but few validated such a rule in an elderly primary-care population with LRTI 7–9, 12–14, 16, 20. To be able to target management decisions in elderly patients with LRTI more efficiently, the current authors 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 being admitted to hospital or dying within 30 days of diagnosis, and to validate the rule in a large, nationally representative cohort.

METHODS

Setting and study population

Medical data from two large cohorts of elderly patients with physician-attended LRTI was retrospectively analysed. The first cohort was used to identify characteristics that were predictive of 30-day hospitalisation or death and thence 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 (the Utrecht patient cohort). In this network, a structured and uniform morbidity registration system has been in use since the early 1990s. Currently, 35 GPs from this network serve approximately 58,000 noninstitutionalised persons. The patient population is representative of the Dutch population with regard to age and sex 21. All patient data are registered in the patient record using the International Classification of Primary Care (ICPC) codes for diagnoses. Using the computerised medical records of all elderly persons from the Utrecht patient cohort, data on eligible LRTI episodes from January 1997 to February 2003 was collected for elderly patients aged 65 yrs. During the study period, the participating physicians made their decisions concerning 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 21. 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 a 3-week symptom-free interval 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 radiograph. The ICPC criteria for acute bronchitis (R78) are coughing and fever with diffuse abnormalities on pulmonary examination, e.g. wheezing and crepitations. Since fever is often absent in the elderly, this criterion was allowed to be ignored. An exacerbation of COPD (R91, R95) was defined according to the criteria of Anthonisen et al. 22. Criteria were met if two out of three

of the following symptoms occurred: increased dyspnoea; sputum volume; or sputum purulence. If one out of three 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; increased respiratory rate; or increased heart rate 22.

Episodes from patients who were treated with antibiotics for another respiratory problem within the previous 3 weeks were excluded. Episodes were also excluded if, at the moment of presentation, the patient was known to have lung cancer, a haematological malignancy or an infection with HIV, used immunosuppressive medication (except oral glucocorticoids), or was hospitalised during the 2 weeks preceding the diagnosis.

The validation cohort included patients with episodes of acute bronchitis and pneumonia only. Unfortunately, the database did not allow the use of the same inclusion criteria for selecting episodes of COPD exacerbations. Therefore it was decided 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 of the relevant literature pertaining to the prognosis of community-acquired LRTI 7–16, 18, 20, 23–25. The following demographic data was collected: age; sex; present use of medication; pre-existing potentially risk-elevating comorbidity; and healthcare use in the 12 months prior to consultation, including previous hospitalisation and the number of GP visits. Present use of medication was described as medication used on the day of the diagnosis and 1 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 1 month prior to diagnosis. Comorbidity was defined as the presence of a comorbid condition in the patient's history recorded according to the ICPC coding system. Presence of the following was recorded: COPD or emphysema (R91, R95); 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.

End-point

The combined end-point 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. The analysis was repeated with the separate end-point of all-cause death to be able to compare the 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 no hospitalisation, hospitalised once or hospitalised more than once in the preceding year. Descriptive statistics such as proportions and mean±SD 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 investigation; the presence of characteristics is assumed to be accurately documented in the Utrecht GP network 26. In case of a missing numeric variable, the median value based on nonmissing episodes was entered. This method was applied in cases in which the number of hospital visits (n = 12), GP visits (n = 6) or the history of diagnoses of pneumonia (n = 6) in the previous year was missing on the research registration forms.

All episodes in the development phase of the model were used. 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 (Centre for Multilevel Modelling, Bristol, UK). The variables associated with the outcome in the multilevel univariable

analysis at a p-level 0.2 were included in a multilevel multivariable logistic regression model. Factors that were associated at a p-level <0.05 were included in the final model. Odds ratios and their corresponding 95% confidence intervals (CI) were calculated for each of the prognostic factors.

Internal validity

The model was internally cross-validated twice by a split-sampling model using two-thirds of the total derivation set. Factors were removed from the final model when the p-level was >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 = $1/(1+e^{-LP})$, where the linear predictor (LP) is computed on the basis of the coefficients of the predictors. For practical interpretation it was decided that all regression coefficients were divided by the lowest (ß[heart failure] = 0.364) and then rounded. Risk classes were defined, on the basis of the score, as 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 with the results of the derivation cohort.

RESULTS

In the derivation cohort, 3,177 episodes of LRTIs were recorded in 1,698 elderly patients. Episodes in which the diagnosis was made in hospital (n = 4) or was missing on the registration form (n = 1) were excluded, as were episodes of pleuritis (n = 6). Thus, 3,166 episodes of LRTIs were analysed in 1,693 elderly patients. 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%) episodes, of which 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, e.g. gastroenteritis, for hospitalisation or death.

The mean age of the derivation cohort was 75.5 yrs and 45% were male. One or more of the comorbid conditions was present in 85%, and COPD, diabetes, heart failure and neurological disease were present in 49, 14, 21 and 16%, respectively.

The validation cohort consisted of 2,465 episodes of LRTI, including 1,736 episodes of acute bronchitis and 729 of pneumonia. The combined end-point occurred in 178 (7.5%) episodes 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 end-point were independently associated with hospitalisation or death in the multivariate analysis: increasing age; hospitalisation in the 12 months 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]

A split-sample procedure with two-thirds of the total population showed the same results, except for the variable male sex. The male sex 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]

The calibration of the model was good ($p = 0.73$; Hosmer–Lemeshow goodness of fit test) and the AUC was 0.75 (95% CI 0.72–0.78) indicating acceptable discrimination properties. When mortality was taken as the sole end-point, the prediction rule had somewhat better discriminative power (AUC 0.76; 95% CI 0.74–0.83). 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 (table 3). Patients designated low risk (score 2) had a 97% chance of having no complications (sensitivity and specificity for a cut-off of 3 points 0.82 and 0.52, respectively). Patients with a score of 3–6 had an average risk for complications of 9.9%; patients with a score 7 had a strongly elevated risk of 31% for complications leading to hospitalisation or death (sensitivity 0.35; specificity 0.92; table 4).

[TABLE 3]

[TABLE 4]

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; 95% CI 0.71–0.78). The negative predictive value for a cut off score of 2 points was similar (97% in the national cohort and in the derivation cohort). The positive predictive value for a cut-off score of 7 points was still high, but somewhat less than observed in the derivation cohort (22% versus 31%; table 4).

DISCUSSION

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

Strength and shortcomings

The present study has several strengths. First the prediction rule was not only developed but also validated in a large representative cohort, and accuracy appeared good in both cohorts. Secondly, the prediction rule consists of only a few variables, which can be directly derived from the patients' medical file without delay or costly examinations. Also, data for the present 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 Anatomical Therapeutic Chemical coding systems. Finally, statistical power is always an issue in precisely estimating the predictive value of potential risk factors. Several thousands of episodes were included, with 274 patients experiencing an outcome; according to the rule of thumb (one predictor for 10 outcomes) the study had adequate power.

A potential limitation of the present 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, conversely, some cases of pneumonia might have been diagnosed as an acute bronchitis or an exacerbation of COPD. However, to ensure that the results would be applicable to GPs, it was 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 of COPD. Although the GPs participating in the study were trained to diagnose COPD according to guidelines in which spirometric results are necessary, the proportion of cases in which the diagnosis was made in concordance with the guidelines is unknown. Again, it was thought essential to include patients in which the COPD diagnosis was made according to daily routine, so results could be generalised to the primary-care setting.

Furthermore, the retrospective design did not allow for the inclusion of data based on clinical examination and symptoms stated by patients. For instance, guidelines of the British Thoracic Society for the management of pneumonia in the community are based on confusion, high respiratory rate, low blood pressure and increasing age (CRB-65 score) 3, 27. These predictive variables are derived from a study in which patients were included in a hospitalised setting 16. Future prospective studies in a primary-care setting should look at possible improvement of the present predictive model with such clinical data. Until then, the current authors think that the results of the present study can support the primary-care physician in assessing the severity of LRTI in elderly patients.

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 because the same criteria could not be applied 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 have been confirmed by other studies. Age is a well-known risk factor 7, 12, 14, 16, 25, 28, 29, although several studies claim differently 9, 13, 15, 18, 20, 23, 25. The age-related waning of immunological functions and the presence of comorbidities due to age-associated diseases largely explain complications in the very old 30. Therefore, if all comorbid conditions were taken into account, age would most probably 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 subjects included in most other studies.

In accordance with Fine et al. 12 and comparable to a previous study by the current authors 24, an association was found between heart failure and the occurrence of complications resulting in 30-day hospitalisation or death. 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 31. In addition, other studies have shown a preventive effect of influenza vaccination for heart failure, indicating the interaction between LRTI and heart failure 32, 33.

It has already been shown that diabetes is related to an increased risk of getting infection 34. It is also presently shown, in a similar manner to previous studies 35, 36, that having diabetes also worsens the prognosis of a LRTI.

The use of oral glucocorticoids was also indicative of outcome. Oral glucocorticoids can mask symptoms of infection and cause deterioration of an infection; therefore increasing the risk of complications resulting in 30-day hospitalisation or death. Conversely, patients with severe COPD will most likely already use oral glucocorticoids. 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. 25, and is probably indicative of a pre-existent poor health status, such as previous hospitalisation.

CONCLUSION

This prediction rule can help general practitioners to distinguish elderly patients with lower respiratory tract infections 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.

ACKNOWLEDGEMENTS

The authors would like to thank N. Boekema (Utrecht, the Netherlands) for her contribution to the data management. The authors also thank the general practitioners of the Utrecht GP network and the Dutch morbidity study for supplying data.

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TABLES

TABLE 1 Univariable and/or multivariable multilevel associations between characteristics and the end-point "hospitalisation or death within 30 days" in the total derivation set#

Characteristic	No hospitalisation or death	Hospitalisation or death	Univariable OR (95%CI)	Multivariable OR (95%CI)
Subjects n	2892	274		
Demographics				
Age ≥80 yrs	751 (26)	109 (40)	2.0 (1.5–2.8)	1.8 (1.3–2.4)
Males	1287 (45)	147 (54)	1.4 (1.0–1.9)	NS
Healthcare 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)
Comorbidity				
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	1079 (37)	41 (15)	reference	
COPD exacerbation	1389 (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)

Data are presented as n or n (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; GP: general practitioner; COPD: chronic obstructive pulmonary disease; NS: nonsignificant (p>0.05). #: n=3,166; ¶: healthcare 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 ≥1 week at the start of the episode; /: in the case of antibiotics, the last tablet had to be taken within the previous month.

TABLE 2 Prediction rule for estimating the probability of 30-day hospitalisation or death from lower respiratory tract infection in elderly patients

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

COPD: chronic obstructive pulmonary disease.

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

Risk class	Total derivation cohort		Acute bronchitis		Exacerbation of COPD		Pneumonia	
	Subjects n	Hospitalisation or death %	Subjects n	Hospitalisation or death %	Subjects n	Hospitalisation or death %	Subjects n#	Hospitalisation or death %
All	3166	8.7	1120	3.7	1523	8.8	523	18.9
Group 1 (score ≤2)	1564	3.2	925	2.6	639	4.1		
Group 2 (score 3-6)	1288	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

COPD: chronic obstructive pulmonary disease. #: A diagnosis of pneumonia gives 4 points, therefore there is no low-risk class.

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

Risk class	Derivation cohort					Validation cohort				
	Subjects n	Hospitalisation or death %	Mortality %	Sensitivity	Specificity	Subjects n	Hospitalisation or death %	Mortality %	Sensitivity	Specificity
All	3166	8.7	2.4			2465	7.3	2.4		
Low	1564	3.2	0.5	0.82#	0.52#	1953	5.3	1.6	0.42#	0.81#
Medium	1288	9.9	2.8			462	14.5	5.4		
High	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.