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Predicting benign course and prolonged illness in lower respiratory tract infections: a 13 European country study

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Background. Clinicians and patients are often uncertain about the likely clinical course of community-acquired lower respiratory tract infection (LRTI) in individual patients. We therefore set out to develop a prediction rule to identify patients at risk of prolonged illness and those with a benign course.

Methods. We determined which signs and symptoms predicted prolonged illness (moderately bad symptoms lasting >3 weeks after consultation) in 2690 adults presenting in primary care with LRTI in 13 European countries by using multilevel modelling.

Results. 212 (8.1%) patients experienced prolonged illness. Illness that had lasted >5 days at the time of presentation, >1 episode of cough in the preceding year, chronic use of inhaled pulmonary medication and diarrhoea independently predicted prolonged illness. Applying a rule based on these four variables, 3% of the patients with ⩽ 1 variable present ($n = 955$, 37%) had prolonged illness. Patients with all four variables present had a 30% chance of prolonged illness ($n = 71$, 3%).

Conclusions. Most patients with acute cough (>90%) recover within 3 weeks. A prediction rule containing four clinical items had predictive value for the risk of prolonged illness, but given its imprecision, appeared to have little clinical utility. Patients should be reassured that they are most likely to recover within three weeks and advised to re-consult if their symptoms persist beyond that period.

Keywords. Acute cough, prognosis, prediction rule, primary care, prospective cohort study.

Introduction

Acute cough is one of the leading causes of consulting in primary care and one of the most frequent indications for antibiotic prescription.[1] The majority of acute cough episodes are caused by mild and self-limiting lower respiratory tract infections (LRTIs), lasting on average 2 weeks.[1–3] However, some patients have an unusually prolonged illness, lasting >3–4 weeks.[4] The wide range of symptom duration causes uncertainty and anxiety in some patients leading to repeat consultations and both under- and overprescribing of antibiotics, which is associated with unnecessary costs and risks.[5–7] On the other hand, prolonged illness is associated with more severe disease (such as pneumonia and sepsis) and with underlying lung disorders such as asthma or chronic obstructive lung disease (COPD). A large proportion of chronic lung disease remains undetected, and prolonged and recurrent signs and symptoms are often the first triggers for diagnosis.[8] Information on patient characteristics that help predict a prolonged course of LRTI would help primary care physicians reassure those with mild self-limiting illness, while providing an opportunity for those with a higher risk for an abnormal course to re-consult appropriately for further diagnostic and therapeutic interventions. Apart from improving clinical outcomes, such additional information sharing may also leave patients feeling that they have been taken seriously and more in control.[9,10]

Most existing prognostic models to guide LRTI management have been derived from hospitalized patients

and have limited applicability to primary care, where the spectrum of patients' illness is less differentiated, and includes many more with mild illness.[4,11–17] Prediction rules derived in hospitalized patients are generally complex and rely on variables that are not readily available to primary care physicians, such as urea serum levels and arterial pH.[18] Our searches identified three studies of prognostic models for use in patients with an LRTI in primary care.

The CRB-65 score (Confusion, high Respiratory rate, low Blood pressure and age ⩾65 years) was designed to predict mortality in patients with pneumonia and is therefore of limited usefulness since mortality is a rare outcome for this condition in primary care.[19] Bont *et al.* developed a tool in primary care for identifying patients with an LRTI over the age of 65 with an elevated risk for prolonged illness.[20] This rule was developed in elderly patients and it is unlikely that the same predictors (e.g. cardiac failure) apply to the younger group. Moore *et al.* studied predictors for cough duration, focussing on longer or shorter duration than the average of 12 days.[2] Patients already diagnosed with lung disease were excluded. However, a considerable proportion of patients with uncomplicated LRTI have symptoms for up to 4 weeks, including the period prior to the first consultation.[4] Thus, identifying predictors for an illness course of 3 weeks or more after the initial consultation seems most useful.

We therefore set out to determine which characteristics and clinical features of patients presenting with an LRTI in primary care, easily obtainable in primary care, predict illness duration of 3 weeks or more. In addition, we aimed to develop a prediction rule that could easily be used in primary care to predict such a prolonged illness in these patients.

Methods

Design: prospective cohort study

Setting. Data were used from the GRACE-01 (Genomic to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org) study.[3] In this observational study, data were collected in 14 primary care research networks in 13 European countries. Participating GPs were asked to recruit consecutive eligible patients from October to November 2006 and late January to March 2007; 3402 patients (1711 + 1691) were included, of which 2690 completed all measurements relevant to these analyses (see below).

Patients. Eligible patients were at least 18 years old, suffering from an acute or worsened cough (⩽28 days duration) as the main or dominant symptom, or a clinical presentation that suggested an LRTI, and who consulted their GP for the first time for this illness episode. Patients with disorders associated with immune deficiency were excluded. All subjects provided written informed consent and the study was approved by the medical ethics committees of all participating countries.

Follow-up and measurements

Clinicians recorded aspects of consenting patients' history, symptoms, co-morbidities (diabetes, respiratory and cardiovascular disease) and clinical findings (body temperature was recorded using a disposable thermometer (TempaDot®; 3M Health Care). All other items of physical examination were only performed if the physician thought it was indicated. Clinicians also recorded their management including antibiotic prescriptions, other treatment and investigations. Patients were followed up for 28 days using self-complete patient diaries. Each day until recovery, patients rated the severity of 11 symptoms and interference with normal activities/work and interference with social activities on a 7-point scale ranging from 0 ('normal/not affected') to 6 ('as bad as it can be'). In addition, patients recorded the day they felt recovered. Patients were telephoned between days 4 and 7 and after 1 month to ensure diary completion and return.

Outcome

Prolonged illness was considered present when patients reported any moderate or severe symptom (e.g. cough, shortness of breath, chest pain, muscle aching) 3 weeks or more after the consultation. Moderate and severe symptoms were defined as all symptoms with a score of 3 or higher, as was rated on the 0- to 6-point scale of the patient diaries; 3–4 weeks is regarded as the demarcation between normal and prolonged illness in LRTI.[2,4,21] Other complication-related outcomes (e.g. mortality, hospital admission) were not analysed because they were too rare in this study (0 and 1.1%, respectively).

Predictors

Potential clinically useful predictive features were investigated in the available dataset if they had been previously identified as having predictive value and were feasible to obtain in routine community-based clinical care. We collected demographic data (i.e. age, gender, educational level and household structure), as well as data on co-morbidity, present use of medication, smoking, signs and symptoms, treatment and self-stated compliance (Table 1).

Data analysis

Only cases for whom we had complete data were included in further analyses. We favoured including dichotomous variables over continuous variables, as 'the presence or absence' of a feature is generally easier to use than continuous measures in time-pressured clinical situations. All continuous predictors as well as the outcome measure were therefore dichotomized

TABLE 1 *Characteristics of patients consulting in primary care with LRTI and their association with prolonged illness (>3 weeks)*

Characteristic	Number in total population, $N = 2690$ (%)	Prolonged illness (>3 weeks), $N = 212$ (%)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Demographics				
Age >55 years	910 (33.8)	94 (44.3)	1.5 (1.1–2.0)*	NS
Male gender	973 (36.2)	78 (36.8)	1.1 (0.8–1.4)	–
Children <18 in household	980 (37.4)	78 (36.8)	0.9 (0.7–1.3)	–
Not finished high school	596 (23.1)	42 (19.8)	1.0 (0.8–1.4)	–
Smoking in the past	679 (26.0)	70 (33.0)	1.3 (1.1–1.9)*	1.6 (1.04–2.56)
Smoking now	570 (21.7)	38 (17.9)	0.8 (0.5–1.1)	–
Co-existing conditions				
>1 other cough episode lasting >1 week in the previous year	937 (37.4)	116 (54.7)	2.3 (1.7–3.2)*	1.6 (1.03–2.55)
>5 days ill before consultation	1114 (42.1)	133 (62.7)	2.5 (1.8–3.4)*	2.5 (1.56–3.95)
Respiratory co-morbidity (COPD, asthma or other lung problems)	395 (14.7)	58 (27.4)	2.5 (1.7–3.5)*	NS
Cardiac co-morbidity (Congestive heart failure, ischaemic heart disease, other)	240 (8.9)	24 (11.3)	1.4 (0.9–2.2)	–
Diabetes mellitus	126 (4.7)	7 (3.3)	0.6 (0.3–1.5)	–
Hay fever or eczema (present or past)	811 (31.3)	77 (36.3)	1.2 (0.9–1.7)	–
Current medication use				
Inhaled lung medication (e.g. bronchodilators or steroids)	282 (10.5)	55 (25.9)	3.6 (2.5–5.1)*	2.1 (1.16–3.67)
Oral steroids	16 (0.8)	4 (1.9)	3.4 (1.0–11.4)*	NS
Oral agents for diabetes	78 (2.9)	2 (0.9)	0.3 (0.06–1.2)*	NS
Insulin	25 (0.9)	1 (0.5)	0.5 (0.05–3.9)	–
Antihypertensives	546 (20.3)	54 (25.5)	1.4 (1.0–1.9)*	NS
Patient symptoms				
Cough	2682 (99.8)	212 (100)	1.8 (0–Inf)	–
Phlegm production	2071 (77.1)	175 (82.5)	1.4 (0.9–2.1)*	NS
Shortness of breath	1361 (50.7)	137 (64.6)	1.8 (1.3–2.4)*	NS
Wheeze	1004 (37.4)	105 (49.5)	1.6 (1.2–2.2)*	NS
Coryza (blocked/runny nose)	1771 (65.9)	133 (62.7)	0.8 (0.6–1.1)	–
Fever	1347 (50.2)	97 (45.8)	0.9 (0.6–1.2)	–
Chest pain	1194 (44.4)	106 (50.0)	1.3 (1.0–1.8)*	NS
Muscle aching	1336 (49.7)	112 (52.8)	1.1 (0.8–1.5)	–
Headache	1620 (60.3)	123 (58.0)	0.9 (0.7–1.3)	–
Disturbed sleep	1681 (62.6)	154 (72.6)	1.6 (1.1–2.3)*	NS
Feeling generally unwell	2167 (80.7)	184 (86.8)	1.7 (1.1–2.7)*	NS
Interference in normal activities	1862 (69.3)	167 (78.8)	1.7 (1.2–2.5)*	NS
Altered mental status	97 (3.6)	9 (4.2)	1.2 (0.6–2.6)	–
Diarrhoea	149 (5.5)	21 (9.9)	1.9 (1.2–3.2)*	2.0 (1.04–4.49)
Physical examination findings (% measured)				
Temperature >38°C (99.2%)	120 (4.5)	4 (1.9)	0.5 (0.2–1.4)	–
Auscultation abnormalities (100%)	1400 (52.0)	106 (50.0)	1.03 (0.8–1.4)	–
Wheeze (99.9%)	496 (18.5)	49 (23.1)	1.4 (1.0–1.94)*	NS
Systolic blood pressure <90 mmHg (35%)	5 (0.5)	1 (0.5)	0.7 (0.5–1.0)	–
Pulse >100/minute (44%)	21 (1.8)	0 (0.0)	0.0 (0.0–inf)	–
Respiratory rate >20/minute (23%)	82 (13.2)	4 (1.9)	0.8 (0.2–3.0)	–
Diagnosis and treatment				
Exacerbation COPD	74 (2.8)	12 (5.7)	3.3 (1.7–6.4)*	NS
Pneumonia	108 (4.0)	2 (0.9)	3.4 (1.8–6.5)*	NS
Antibiotics prescribed	1464 (54.4)	96 (45.3)	0.7 (0.5–0.9)*	NS
Use of self medication	1641 (62.8)	135 (63.7)	1.0 (0.7–1.4)	–
Extreme anxiety or depression	44 (2.2)	8 (3.8)	3.1 (1.3–7.3)*	NS

NS, non-significant.
*OR (95% CI) significant at 5% level.

for further analysis. Receiver operating characteristic (ROC) curves were used to determine optimal cut-offs for dichotomization.[22] Akaike's Information Criterion (AIC) values from univariate models of dichotomous and continuous variables were compared. If the AIC difference between both was small (<2), then the minor loss of information by dichotomization was considered to be acceptable and the dichotomized outcome was used.[23]

The association between each predictor and prolonged illness was examined using univariate logistic regression analyses. Predictors associated with the

outcome in univariate analyses ($P < 0.15$) were included in a multivariable two-level model, with patients nested within clinicians. The model was reduced through exclusion of predictors with P values >0.10. By a split-sampling model using a randomly selected two-third of the total population, the model was internally cross-validated twice.[24] Factors were removed from the final model when they had a P value higher than 0.05 in the multivariable model of both split samples. The predictive accuracy of the model was estimated on the basis of the reliability (goodness of fit) using Hosmer–Lemeshow statistics.[25] The model's ability to discriminate between patients with and without prolonged illness was estimated as the area under the ROC curve of the model.[24] To facilitate interpretation of the model and its use as a prognostic rule, all coefficients from the final multivariable model were rounded to one. The ROC curve of the model with the rounded coefficients was compared to the ROC curve of the model with the parameter estimates, to see how much discriminative power a simplified model would lose. The prognostic rule was used to calculate a score for each individual patient. According to the scores, patients were divided in three groups with increasing predicted risk for prolonged illness. Also, the absolute risk of prolonged illness was calculated for the different risk groups. The same was done for the subgroups of patients over 55 years old and those prescribed an antibiotic, and their absolute risk of prolonged illness by risk group was compared to that of all patients in the analysis. In those groups, patients under and over 55 years old were compared to find possible associations between age and disease severity. The same was done for antibiotic prescription.

Results

Data from 2690 patients were analysed (Table 1). Characteristics of these 2690 patients, such as age and co-morbidity, were similar to the characteristics of the 3402 patients that were included in the GRACE 01 study.[4] The median age was 48 years (interquartile range 35–60); 36.2% were males; 23.8% had one or more co-morbid conditions. COPD, asthma, cardiac co-morbidity and diabetes were present in 5.8, 9.1, 8.9 and 4.7%, respectively. In all, 212 (8.1%) participants had an illness that lasted >3 weeks, 28 (1.1%) were hospitalized, and none died; 67% of our participants stated they felt recovered at 14 days, irrespective of antibiotic treatment. The prior duration of symptoms before consultation was 6.9 days (SD 6.7). There was a re-consultation rate of 35% [95% confidence interval (CI): 33–37%].

Of the 44 potential predictors we examined, the following were independently associated with prolonged illness (Table 2): being ill for 5 or more days at the initial consultation [odds ratio (OR): 2.5; 95% CI): 1.56–3.95], more than one episode of cough/LRTI lasting more than a week in the previous year (OR: 1.6; 95% CI: 1.03–2.55), smoking in the past (OR: 1.6; 95% CI: 1.04–2.56), use of inhaled pulmonary medication (OR: 2.1; 95% CI: 1.16–3.67), and having diarrhoea (OR: 2.0; 95% CI: 1.04–4.49).

TABLE 2 *Prediction rule for estimating the probability of prolonged illness (>3 weeks) in patients consulting in primary care with LRTI*

Characteristic	Regression coefficient (B)	Score[a]
Existing disease >5 days at first consultation	0.7427	1
>1 other episode of cough lasting >1 week in the previous year	0.7618	1
Use of inhaled pulmonary medication	0.7243	1
Having diarrhoea	0.6233	1

[a]To facilitate interpretation of the model and its use as a prognostic rule, all coefficients from the final multivariable model were rounded to one, without affecting the calibration of the model significantly.

A split-sample procedure with 2/3 of the total population showed the same results, except for the past smoking variable, that showed no significance in the split sample procedure (OR: 1.33; 95% CI: 0.61–2.90). In a second split-sample model, past smoking again showed no significant differences, and so this variable was removed from the prediction rule.

A score was assigned to each predictor variable resulting in the final prediction model (Table 2).

The model was well calibrated (Hosmer–Lemeshow goodness-of-fit test $P = 0.48$) and the area under the receiver-operating curve (AUC) was 0.704 (95% CI 0.67–0.74) indicating acceptable discriminating properties (Fig. 1). Simplification of the model, with the same weight for all the 4 predictors, resulted in an AUC of 0.694 (95% CI 0.66–0.73). There was no significant correlation between the independent predictors (all $P > 0.80$).

Finally, the prediction rule was used to divide the patients into risk classes according to their calculated score. Patients were designated to the low-risk class with a score of 1 or lower, the intermediate risk class with score 2–3 and high risk class with a score of 4 (all four predictors present). For each risk class, the probability of a complicated outcome (prolonged illness) was computed by counting the actual patients with prolonged illness in that risk group. The risk of prolonged illness markedly increased with a higher score (Fig. 2). Similar increases in risk with increasing scores were observed in the elderly ($n = 891$, Table 3) and patients in whom antibiotics was prescribed ($n = 1427$, data not shown). In the patients designated to the low-risk class (score 0 or 1, $n = 955$, 37%) 97% had an uncomplicated course. Their risk of prolonged illness was one-third compared to the patients in the intermediate group (score 2 or 3, $n = 1458$, 56%) where

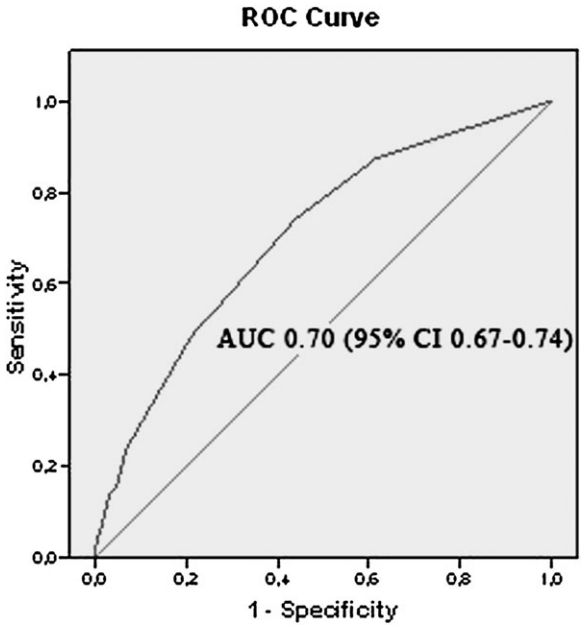

FIGURE 1 *Receiver operating characteristic curve of prediction rule for prolonged illness (>3 weeks) in adult patients consulting in primary care with LRTI. ROC curve showing a discrimination of 0.70 (95%CI 0.67–0.74) for the new prediction rule, which consist offour items which can be taken from the medical history: illness that had lasted >5 days prior to the first consultation, more than one episode of cough in the preceding year, chronic use of inhaled pulmonary medication and diarrhoea*

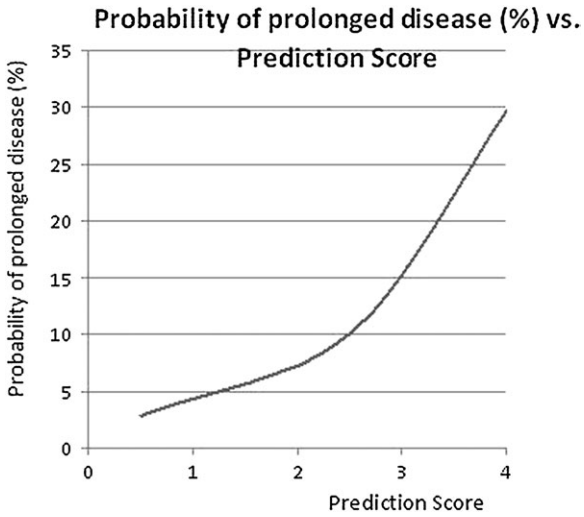

FIGURE 2 *Plot showing relation between the probability of prolonged illness as a function of the score based on the new prediction rule. The new prediction rule consists of four items from medical history: illness that had lasted >5 days prior to the first consultation, more than one episode of cough lasting more than 1 week in the preceding year, chronic use of inhaled pulmonary medication and diarrhoea. For each score, the probability of prolonged illness was computed by counting the actual patients with prolonged illness in the total population. The risk of prolonged illness markedly increased with a higher score*

10% had a prolonged course. This is in accordance to the baseline rate of prolonged illness that is 8.1%. In patients with an high risk (score 4, $n = 71$, 3%) almost 30% had a prolonged illness (Table 3, sensitivity 0.76, specificity 0.74).

Discussion

Main findings

This 13 country, prospective study of LRTI in primary care found that 8% of all the patients presenting to primary care with LRTI experienced an illness course lasting 3 weeks or more. Independent predictors of such a prolonged illness were: duration of illness for longer than 5 days at the time of the first consultation, more than one previous episode of cough in the preceding year, use of inhaled pulmonary medication and having diarrhoea.

Strengths and limitations

A major strength of our study is that we had broad inclusion criteria and we did not simply recruit patients who underwent additional diagnostic tests, which would have increased the risk of selection bias and limited applicability. In addition, this was an observational rather than randomized study. Therefore, there was probably less selection bias compared to many randomized trials as treatment was always according to usual care in our population. Fewer patients might agree to participate in placebo-controlled trials than in an observational study as they may not want to run the risk of being randomized to a particular treatment, or placebo, when feeling unwell. This was the first study of LRTI to prospectively record symptom presentation, examination findings, management and patient self-reported symptom severity using standardized tools in a large number of countries recruited during the same time periods. Recruitment was for two periods over a single winter, and findings by recruitment period were similar.[3]

The clinicians who participated were all affiliated to a research network and so may not have been representative of all GPs in their country. However, management by more research-minded clinicians is unlikely to have influenced disease severity or the relationship between patient characteristics and a prolonged course because patient self-reported symptom severity was used to assess the outcome variable. Although a subjective measure, reported outcome by patients themselves is clinically relevant since the patient's own sense of well-being determines their help seeking behaviour and thus re-consultation. However, the disadvantage of using patient self-reported diary data to determine symptom severity is diversity

TABLE 3 *Frequency of prolonged illness in adults and elderly presenting in primary care with LRTI, by three risk groups based on the new prediction rule*

Risk class	Total study population			Age over 55 years		
	$N = 2612$[a]			$N = 891$		
	N	Mean disease duration (days)	Prolonged illness (%)	*N*	Mean disease duration (days)	Prolonged illness (%)
All	2612	12	212 (8.1%)	891	13	94 (10.6%)
Low risk (score 0–1)	955	12	28 (2.9%)	253	12	5 (2.0%)
Intermediate (score 2–3)	1458	14	149 (10.2%)	527	14	64 (12.1%)
High risk (score 4)	71	21	21 (29.6%)	43	22	15 (34.9%)

[a]Information on outcome is missing for 78 out of 2690 patients.

of symptom registration. Since the study involved 13 European countries, there is no guarantee that perceptions of health and symptom reporting were consistent. We do not know how cultural differences influenced the results. Response bias was not relevant to clinician-recorded data as there was a 99% completion rate. Patient diary completion rates ranged from 60% to almost 100% between networks, with a high overall response rate of 80%. It is possible that non-responders deteriorated more than responders, but given the generally benign natural clinical course of this condition, this is unlikely. Ascertainment bias was minimized by a standardized data collection protocol used by all networks.

Furthermore, certain aspects of physical examination were performed only when the physician considered this necessary. Since there were few severely unwell patients in this cohort, predictors of severe disease, such as elevated pulse or respiratory rate, were infrequently measured. Their predictive value should therefore be interpreted with caution. However, when performing a zero-imputation analysis, in which a zero was imputed for all missing values for the clinical signs (pulse, respiratory rate and blood pressure), the same results were found. During data collection, GPs were asked to record clinical signs only when they thought it was indicated. We believe clinicians are more likely to measure a parameter if they are concerned that it may be abnormal, and therefore, the error rate from this zero-imputation approach is likely to be low.

As expected in this primary care cohort, the low rate of hospitalization and infrequently measured heart and respiratory rate suggest that pneumonia was not a frequent diagnosis. Slowly resolving respiratory tract infection or underlying (undiagnosed) chronic pulmonary disease is the most likely explanations for prolonged illness in this cohort. Persistent cough is related to undetected chronic lung disease: Van Schayck *et al.*[26] found in 27% of all people with chronic cough a forced expiratory volume < 80%. Broekhuizen *et al.*[27] detected COPD in 29% of elderly patients with chronic cough. The items that significantly predicted prolonged illness (e.g. inhaled pulmonary medication use, previous cough episodes) support this hypothesis. However, prolonged duration of symptoms before the first consultation might also be associated with other phenomena, like consultation behaviour. Further etiologic research is necessary to clarify these relations.

Comparison with other studies

Increasing age, hospitalization during the 12 months prior to diagnosis, heart failure, treatment with insulin or oral glucocorticoids, use of antibiotics in the month prior to diagnosis and type of diagnosis (i.e. acute bronchitis, COPD or pneumonia) have been independently associated with a complicated outcome, defined as hospitalization or death in elderly primary care patients with LRTI.[20] The current study used different end points and patients had other co-morbidity and were less frail, making comparisons difficult between the two study populations.

Our results are congruent with Moore's finding of a longer illness course in those with a longer duration of symptoms prior to consultation and restricted activities on the day of first consulting.[2] We also found that variables from clinical examination did not predict prolonged illness duration. Only a history of diarrhoea, which is likely to indicate severe disease, had some predictive value. Inhaled pulmonary medication use and previous cough episodes probably identify people with underlying chronic lung problems.[8] Moore's study excluded such patients.

The association between diarrhoea and prolonged illness could perhaps be explained by the release of cytokines and other inflammation mediators, leading to malabsorption in the intestines, combined with an adrenergic stress reaction.[28] Possibly some patients had a mild undetected pneumonia with prolonged course since Hopstaken *et al.*[29] found that diarrhoea was related to the presence of pneumonia in patients with acute cough.

Implications for practice and research

Although four readily available symptoms were found to be clearly related to the risk of prolonged illness, these predictors do not seem to be useful for daily practice. When all four predictors were present, still 70% of those patients did not have a prolonged course. In addition, the vast majority of patients with prolonged disease (83%) had not all four predictors present. Given the imprecision of existing approaches, predicting a prolonged course does not seem feasible.

Instead, patients should be re-assured that their illness most likely will subside within 3 weeks and be advised to re-consult if their symptoms persist beyond 3–4 weeks since previous studies have shown that the small group of patients with protracted symptoms has increased risk for underlying chronic lung disease.

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Conflict of interest: All authors declare that there are no potential conflicts of interest.

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