RESEARCH

Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study

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Abstract

Objectives To quantify the diagnostic accuracy of selected inflammatory markers in addition to symptoms and signs for predicting pneumonia and to derive a diagnostic tool.

Design Diagnostic study performed between 2007 and 2010. Participants had their history taken, underwent physical examination and measurement of C reactive protein (CRP) and procalcitonin in venous blood on the day they first consulted, and underwent chest radiography within seven days.

Setting Primary care centres in 12 European countries.

Participants Adults presenting with acute cough.

Main outcome measures Pneumonia as determined by radiologists, who were blind to all other information when they judged chest radiographs.

Results Of 3106 eligible patients, 286 were excluded because of missing or inadequate chest radiographs, leaving 2820 patients (mean age 50, 40% men) of whom 140 (5%) had pneumonia. Re-assessment of a subset of 1675 chest radiographs showed agreement in 94% (κ 0.45, 95% confidence interval 0.36 to 0.54). Six published "symptoms and signs models" varied in their discrimination (area under receiver operating characteristics curve (ROC) ranged from 0.55 (95% confidence interval 0.50 to 0.61) to 0.71 (0.66 to 0.76)). The optimal combination of clinical prediction items derived from our patients included absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia, and fever, with an ROC area of 0.70 (0.65 to 0.75). Addition of CRP at the optimal cut off of >30 mg/L increased the ROC area to 0.77 (0.73 to 0.81) and improved the diagnostic classification (net reclassification improvement 28%). In the 1556 patients classified according to symptoms, signs, and CRP >30 mg/L as "low risk" (<2.5%) for pneumonia, the prevalence of pneumonia was 2%. In the 132 patients classified as "high risk" (>20%), the prevalence of pneumonia was 31%. The positive likelihood ratio of low, intermediate, and high risk for pneumonia was 0.4, 1.2, and 8.6 respectively. Measurement of procalcitonin added no relevant additional diagnostic information. A simplified diagnostic score based on symptoms, signs, and CRP >30 mg/L resulted in proportions of pneumonia of 0.7%, 3.8%, and 18.2% in the low, intermediate, and high risk group respectively.

Conclusions A clinical rule based on symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough performed best in patients with mild or severe clinical presentation.

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Appendix 1: Standard operating procedure for assessment and feedback of chest radiographs
Appendix 2: Characteristics of included patients with radiography available
Appendix 3: Calibration plots of validation models, new developed "symptoms and signs" model and "symptoms and signs model + CRP"
Appendix 4: Reclassification tables comparing diagnostic risk categories of pneumonia by diagnostic models with and without CRP
Appendix 5: Nomogram relating diagnostic items of final model to probability of pneumonia

Addition of CRP concentration at the optimal cut off of >30 mg/L improved diagnostic information, but measurement of procalcitonin concentration did not add clinically relevant information in this group.

Introduction

Diagnosis of pneumonia in adults presenting with signs of lower respiratory tract infection in primary care is important because pneumonia requires specific treatment and follow-up, whereas for acute bronchitis expectant management is usually appropriate.[1]

Nonetheless, accurate diagnosis of pneumonia in primary care is difficult as it is not feasible to obtain chest radiographs in all patients with lower respiratory tract infection. Primary care physicians therefore have to rely on signs and symptoms and simple additional tests, when available. Several studies, mostly conducted in secondary care, have assessed the diagnostic value of history and findings on physical examination for pneumonia.[2-12] These diagnostic models have been validated only once in primary care.[13] The number of patients included in that validation study was small overall, but the prevalence of pneumonia was three times higher than the 6% prevalence that is usually reported in primary care.[14]

Regarding markers of inflammation, recent reviews found that C reactive protein (CRP) had limited diagnostic value for pneumonia in primary care when the probability of pneumonia is below 10%.[15 16] Studies included in this review, however, came from various settings, and the studies from primary care were small. Furthermore, the diagnostic value of another potentially important biomarker, procalcitonin,[17] has never been assessed in addition to history and clinical examination in primary care patients with lower respiratory tract infection.

We therefore studied a large group of primary care patients presenting with signs of lower respiratory tract infection, firstly, to validate published diagnostic models for pneumonia and, secondly, to quantify whether CRP and procalcitonin concentrations add information to history and physical examination, and whether these could be combined in a clinically useful diagnostic tool.

Methods

This cross sectional observational study used data from the GRACE-09 study (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org), which collected data from patients presenting with acute cough in 16 primary care networks in 12 European countries. Participating general practitioners recruited eligible patients from October 2007 to April 2010. A total of 3106 patients were included in the GRACE study.

Data analysis

Less than 0.1% of history items, 1% of physical examination items, and 5% blood test data were missing (table 1⇓). Data are rarely missing completely at random, and we therefore performed multivariate imputation by chained equations.[21-23] Missing results were imputed for all variables evaluated for the diagnostic model but not for "pneumonia," as we analysed only participants for whom this diagnostic outcome was known. To impute missing results, we used results of all variables in table 1⇓.

Recruiting health professionals were asked to keep logs of patients who were eligible but not recruited and to record reasons for not screening patients at the end of the study. Clinical characteristics of non-recruited patients were compared with a recent observational study[24] that used the same case definition and case record form. We identified published diagnostic models for pneumonia[2-9 11 12] by selecting references from an existing validation study[13]; searching PubMed from 2003 to 2012, supplemented by checking article references; and selecting references from the recently updated guidelines from the European Respiratory Society for management of adults with lower respiratory tract infection.[25] We excluded studies that did not report a multivariable model[4 8 11] or regression coefficients of the diagnostic variables[3] or that used diagnostic tests that are not readily available in European primary care (such as leucocyte count[5] and pulse oximetry[8 11]). For the remaining models[2 6 7 9 12] we computed the probability of pneumonia for all our 2820 study patients and calculated the area under the receiver operating characteristic curve with 95% confidence intervals. Calibration of the models was graphically assessed with calibration plots[26] and tested with the Hosmer-Lemeshow statistic.

As we expected existing models to perform suboptimally in our external validation study, as previously found,[13] we determined from our data which items from history and physical examination independently contributed to the discrimination between presence and absence of pneumonia and whether the diagnostic accuracy of history taking and physical examination could be improved by blood tests. Accordingly, and given the total number of cases of pneumonia in our study (n=140), we preselected a set of 14 candidate diagnostic items that were most promising based on published literature.[2-13 27] We then calculated univariate odds ratios and 95% confidence intervals for each candidate diagnostic variable with the outcome, using logistic regression modelling. For continuous variables (age, CRP, procalcitonin), we used visual inspection to assess whether the inclusion of a non-linear component showed a clear deviation from a linear association in a graph.[26] No deviation from linearity was found.

As in most multicentre studies, individual patient data were likely to be clustered within the 12 different countries, which could affect the association of the diagnostic variables with the outcome. We accounted for such possible non-random differences within countries (clusters) using multilevel logistic regression techniques. We used a random effect for the intercept (to adjust for differences in baseline prevalence of pneumonia per cluster) as well as for each candidate variable (to adjust for differences in the associations between variable and outcome per cluster).[28-31] After we rounded the results, this multilevel analysis identified the same intercept, odds ratios (associations), and confidence intervals as the standard multivariable logistic regression analysis, and therefore we used results from the latter for all further analysis. All 14 preselected diagnostic predictors from history taking and physical examination were entered in a multivariable logistic regression model. We explicitly did not select items based on univariate results as this often leads to unstable models.[32 33] With backward selection, with P<0.10 for the likelihood ratio test, we fitted a reduced diagnostic "symptoms and signs" model and computed the ROC area and calibration plot.[26 34]

We repeated regression analyses after adding CRP and procalcitonin concentrations as continuous offset variables, while regression coefficients of symptoms and signs were unchanged ("fixed") using results from all patients. We used the areas under the curve to quantify the added value of CRP and procalcitonin beyond the "symptoms and signs" model. We also analysed results for CRP and procalcitonin at clinically relevant thresholds: >20, >30, >50, and >100 mg/L for CRP[7 8 35] and >0.25 μg/L and >0.50 μg/L for procalcitonin.[36]

As physicians usually use dichotomised test results (normal *v* abnormal) we also determined the additional benefit of CRP and procalcitonin when used in this way, if continuous results showed relevant added information. The most optimal cut-off level was assessed from the area under the curve (that is, the best trade off between sensitivity and specificity). The number of patients correctly reclassified after the addition of CRP or procalcitonin results to the diagnostic model was expressed in the net reclassification improvement,[37] with three predefined diagnostic risk groups: low (probability <2.5%), intermediate (2.5-20%), and high (>20%). This approach was chosen as this is how we anticipate CRP would be used in practice—that is, defining high, low, and intermediate risk groups based on symptoms and signs then assessing the added value of CRP based on the initial symptoms and signs model. We calculated negative and positive predictive value, sensitivity, and specificity for these three risk groups (taking one risk group compared with the other two combined), as well as and positive and negative likelihood ratios. The cut-off levels of the three risk groups were based on clinical judgment of the authors and assessment of acceptability of false negative results in other diagnostic studies in primary care.[38-41] We carried out a sensitivity analysis around these thresholds using low thresholds of 1% and 2% and high thresholds of 15% and 25%.

Because any developed model can be over-fitted, we used bootstrapping for internal validation. In 100 bootstrap samples we repeated the analyses and, by evaluating the diagnostic model performance in the bootstrap samples and in the original data, obtained a shrinkage factor to adjust regression coefficients and areas under the curve for overoptimism.[42] To make a simple tool for clinical practice, we also derived a simplified score from the regression model of symptoms signs and CRP by rounding all regression coefficients to 1 point.

Data were analysed with SPSS (version 17.0 for Windows) and R (version 2.11.1) including the "RMS" package by Harrell for R.[43]

Results

Patients' characteristics

During three winters (October to April) from 2007 to 2010, 294 general practitioners initially recruited 3106 adult patients. Recruitment of each participant and baseline assessments took about half an hour. Hence, in the busiest periods, time pressures resulted in only a portion of the potentially eligible patients being screened and limited completion of non-recruitment logs. The main reason reported by general practitioners for not screening was "lack of time" (rated first by 44/48, 92%), with only three (6%) reporting that individual clinical considerations limited recruitment. The population had similar clinical characteristics to the previous observational cohort recruited in these primary care networks[24] and other cohorts with lower respiratory tract infection in primary care[7 14]: the mean age of patients was 50 (SD 17) and 40% were men (table 1 ⇓). A follow-up of 28 days showed no mortality, and 11 patients (0.5%) were admitted to hospital. Patients who were excluded because radiography was not performed (n=258) or was of insufficient quality (n=28) (fig 1⇓) were no different, apart from age (see appendix 2).

Prevalence of pneumonia

Of the 2820 participants, 140 had pneumonia (5%). After reassessment, the diagnosis of presence or absence of pneumonia was concordant in 1571 of 1675 patients (94%). The positive agreement (49%) was much lower than negative agreement

(97%). Cohen's unweighted κ was 0.45 (moderate agreement) (95% confidence interval 0.36 to 0.54). Other diagnoses on chest radiography were "acute bronchitis" in 217 patients (8%) and "other diagnosis" in 462 patients (16%), of which chronic bronchitis/emphysema, cardiomegaly, atelectasis, fibrotic changes (such as old tuberculosis), and aortic changes were most commonly reported. The chest radiograph was reported as normal for 2023 (72%) patients. Most (2555, 91%)) patients underwent chest radiography within five days, and the mean duration between the first consultation for acute cough and chest radiography was 1.6 days (SD 2.6). There was no correlation between the time until radiography and presence of radiographic pneumonia (P=0.63).

Validation of existing diagnostic models

In our population the area under the curve for previously published models of signs and symptom for pneumonia varied between 0.55 and 0.68 (up to 0.71 after addition of CRP) (table 2⇓). All models showed poor calibration for pneumonia (see appendix 3), with a Hosmer-Lemeshow of P<0.001, indicating poor fit.

Diagnostic value of "symptoms and signs"

Items of history and physical examination with independent diagnostic value were absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia (>100/min), and fever (temperature ≥37.8°C) (table 1⇓). Combination of these items ("symptoms and signs" model) resulted in an area under the curve of 0.70 (95% confidence interval 0.65 to 0.75), which remained the same after internal validation. Calibration of this model was good (see appendix 3) with a Hosmer-Lemeshow test of 7.35 (df=8, P=0.50).

Added information on CRP

The mean CRP concentration was 19 mg/L (SD 35 mg/L) and 69 mg/L (SD 83 mg/L) in patients with pneumonia, with a univariate odds ratio of 1.2 (95% confidence interval 1.1 to 1.2) per 10 mg/L increase in concentration. CRP concentrations were <20, 20-30, 30-50, 50-100, and >100 mg/L in 74%, 8%, 9%, 6%, and 3% of patients, respectively. The proportion with pneumonia in these groups was 3%, 5%, 7%, 15%, and 35% respectively. Positive predictive values of CRP as a univariate (stand-alone) test were 11.8%, 14.8%, 22.5%, and 35.4% for concentrations over 20, 30, 50, and 100 mg/L, respectively. Negative predictive values were 97.4%, 97.2%, 96.8%, and 96.1%. Some 54 patients (3%) with radiographic pneumonia had a CRP concentration <20 mg/L. Compared with the total study population, these 54 patients were older (P=0.01), more often used (inhaled or oral) steroids (P=0.04), and more often had positive symptoms and signs of the clinical diagnostic model (data not shown), but the duration of illness before consultation did not differ (P=0.77).

Addition of continuous CRP concentration to the "symptoms and signs" model resulted in a multivariable odds ratio for pneumonia of 1.2 (95% confidence interval 1.1 to 1.2) per 10 mg/L rise in concentration and increased the area under the curve significantly from 0.70 (0.65 to 0.75) to 0.78 (0.74 to 0.82) (P<0.05, fig 2⇓). Calibration of the model extended with CRP was good (Hosmer-Lemeshow test 10.69, df=8, P=0.22; see appendix 4). Addition of CRP as a dichotomised variable, where 30 mg/L was the most optimal threshold, resulted in an area under the curve of 0.77 (0.73 to 0.81) with a Hosmer-Lemeshow test of 9.67 (df=8, P=0.29).

Added information on procalcitonin

The mean procalcitonin concentration was 0.09 µg/L (SD 0.6 µg/L) overall and 0.38 µg/L (SD 2.6 µg/L) in patients with pneumonia, with a univariate odds ratio of 1.3 (95% confidence interval 1.2 to 1.4) per 0.1 µg/L increase in concentration. Procalcitonin concentrations were ≤0.25, 0.25-0.50, and >0.50 µg/L in 94%, 3%, and 3% of patients, respectively. The proportion of pneumonia in these groups was 5%, 7%, and 18%, respectively. Addition of continuous procalcitonin to the "symptoms and signs" model resulted in a multivariable odds ratio for pneumonia of 1.1 (95% confidence interval 1.1 to 1.2) per 0.1 µg/L rise in concentration and increased the area under the curve to 0.72 (0.68 to 0.77; P>0.05) and 0.71 (0.67 to 0.76) after internal validation (fig 2⇓). Calibration of the model extended with procalcitonin was good (Hosmer-Lemeshow test 7.56, df=8, P=0.48).

Because of the limited added value of continuous procalcitonin results, it was not further analysed.

Diagnostic risk classification

Table 3⇓ shows the diagnostic risk classification by the model with and without CRP. Based on symptoms and signs only, in the 665 patients with a low (<2.5%) estimated probability of pneumonia, 11 (2%) actually had pneumonia (positive likelihood ratio 0.3, negative likelihood ratio 1.2, negative predictive value 98%, sensitivity 8%, specificity 76%). In the 63 patients with a high (>20%) estimated probability, 24 actually had pneumonia (positive likelihood ratio 11.8, negative likelihood ratio 0.8, positive predictive value 38%, sensitivity 17%, specificity 99%). The positive likelihood ratio of an intermediate diagnostic risk, which included most patients, was 1.01 and the negative likelihood ratio was 0.97. Addition of CRP increased the number of patients with estimated low risk to 1556 (31, 2%) had pneumonia, positive likelihood ratio 0.4, negative likelihood ratio 1.8, negative predictive value 98%, sensitivity 22%, specificity 43%) and the number of patients with estimated high risk to 132 (41, 31%) had pneumonia, positive likelihood ratio 8.6, negative likelihood ratio 0.7, positive predictive value 31%, sensitivity 29%, specificity 97%). In the intermediate risk class the positive and negative likelihood ratios were 1.2 and 0.9, respectively. In 1640 patients (58%), addition of CRP did not change the estimated risk class. The net reclassification improvement was 28% (95% confidence interval 17% to 30%). A threshold of 2% and 1% for low probability resulted in a net reclassification improvement of 26% (16% to 36%) and 10% (4% to 27%), respectively. With 15% and 25% as a threshold for high probability, the net reclassification improvement was 24% (14% to 34%) and 26% (16% to 3%5), respectively (see appendix 4). Re-analysis with presence of pneumonia according to the (secondly) centrally read radiographs as the reference test showed a net reclassification improvement of 28% (19% to 37%).

CRP in intermediate risk group

Most reclassifications of diagnostic risk considered patients with intermediate risk based on symptoms and signs. Of the 1987 patients without pneumonia who were classified as intermediate risk based on symptoms and signs, after addition of CRP >30 mg/L 957 were reclassified (correctly) to low risk and 64 were reclassified (incorrectly) to high risk. Of the 105 patients with pneumonia classified as intermediate risk, addition of CRP reclassified 27 to low risk and 22 to high risk (table 3⇓).

Diagnostic classification by a simplified diagnostic score

Rounding of all regression coefficients in the model including symptoms signs and CRP >30 mg/L to 1 point resulted in the simplified diagnostic score presented in table 4⇓. The proportions of pneumonia were 0.7%, 4%, and 18%, respectively, in the estimated low, intermediate, and high risk class.

Because the simplified score in table 4 had a considerably lower diagnostic accuracy than the model that used the results of the original β coefficients, we developed a nomogram to enable physicians to use the original β coefficients (see appendix 5). The nomogram allows for calculation of the added value of CRP in all patients but is mainly meant to enable targeted use of a CRP test in patients at intermediate risk based on symptoms and signs alone.

Discussion

Main findings

Pneumonia was diagnosed by chest x radiography in 140 (5%) of the 2820 patients presenting to primary care with acute cough. The optimal combination of symptoms and signs for predicting pneumonia was absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia, and fever. Signs and symptoms were useful in correctly identifying patients with a "low" (<2.5%) or "high" (>20%) diagnostic risk in 26% of patients. In the 74% of patients in whom diagnostic doubt remained (estimated risk 2.5%-20%), measurement of C reactive protein (CRP) concentration helped to correctly exclude pneumonia. A simplified diagnostic score based on symptoms, signs, and CRP concentration resulted in proportions of pneumonia of 0.7%, 4%, and 18% in the low, intermediate, and high risk group, respectively. Measurement of procalcitonin concentration had no clinically relevant added value in this setting.

Strengths and limitations

This is the first study to quantify the independent diagnostic value of symptoms, signs, and additional diagnostic value of inflammatory markers for pneumonia in patients presenting with acute cough in primary care that included an adequate number of cases of pneumonia. All blood samples were analysed in the same laboratory with standardised procedures. Serum CRP and procalcitonin concentrations were measured by conventional venous blood tests in a diagnostic laboratory and not with a point of care test. The added value of CRP might be different and could be lower when measured with a point of care test in general practice. Nonetheless, agreement between point of care test results and a conventional reference test has been shown to be good.[44]

Given how common lower respiratory tract infections are, many more eligible patients presented during the recruitment period than were approached about participation in this study, and therefore we probably did not achieve the goals of recruiting all consecutive, eligible patients. Nevertheless, we do not believe that there was important clinical selection bias because feedback from recruiting clinicians during and after the study was that the time required to recruit and assess each patient made sequential recruitment of every eligible patient impossible.

Chest radiographs were examined by local radiologists. We attempted to increase uniformity in assessment by implementing a protocol for reporting. While there was some variability

between observers, the moderate unweighted κ of 0.45 was similar to that reported in other studies.[18] [20]

We did not attempt to distinguish between bacterial and viral pneumonia as this is not feasible in routine primary care.[14] [45] All available relevant guidelines advocate identification of patients with pneumonia and treatment with antibiotics without further aetiological testing.[14]

Comparison with other studies

Absence of a runny nose and presence of dry cough, breathlessness, chest pain, diarrhoea, fever, and crackles have previously been found to have diagnostic value for pneumonia in primary care populations.[7] [9] "Tachycardia" and "diminished vesicular breathing" have diagnostic value in secondary care populations.[3] [6] [8] [11] We were able to confirm the predictive value of most of these items, apart from chest pain and diarrhoea. Differences between our findings and those from previous studies could relate to the difference in prevalence of pneumonia, inclusion criteria, and outcome definition.

Our finding that CRP concentration can be low in people with pneumonia is not new. Flanders and colleagues reported on a small subgroup of patients with pneumonia who had a CRP of less than 11 mg/L.[3] In the 54 patients with pneumonia with low CRP in our study, the estimated diagnostic risk of pneumonia was high (n=3) or intermediate (n=51) based on history and physical examination results as defined in our model. These findings emphasise that CRP test results should be interpreted together with clinical findings.

Of the factors known to lower CRP—such as steroid use[46] and duration of disease[47]—only steroid use (including both oral and inhaled steroids) was significantly more prevalent in the group of patients with pneumonia with low CRP concentration. Exclusion of all steroid users from our analyses resulted in a similar association between CRP concentration and pneumonia.

Procalcitonin concentrations in our study were higher in patients with pneumonia and comparable with previous findings in patients with lower respiratory tract infection in primary care.[17] [48] They did not, however, add meaningful diagnostic information. Holm and colleagues showed a clear association between procalcitonin concentration and radiographic pneumonia as well as bacterial infection,[17] but the positive predictive value was too low to be useful in clinical practice. Our findings support this conclusion. Moreover, Holm and colleagues studied a population with a higher prevalence of pneumonia (13%) and did not combine history and physical examination with procalcitonin test results.[17]

Implications for practice and conclusions

Although the diagnostic "symptoms and signs" model presented in this study assigned an intermediate diagnostic risk of pneumonia to most patients, history taking and physical examination alone enabled general practitioners to correctly identify a small group of patients at high risk. Chest radiography and/or (empirical) antibiotic treatment should therefore be considered in these patients. In these more severely ill patients, point of care tests, including CRP, do not seem to be useful. In patients with a low risk of pneumonia based on symptoms and signs, it seems justified to withhold further diagnostic investigation and not to treat with antibiotics.

CRP has additional diagnostic value in patients with an intermediate diagnostic risk of pneumonia as determined by symptoms and signs alone, especially in appropriately excluding pneumonia. Procalcitonin has no additional diagnostic value in primary care.

The simplified score derived from the regression models is more suitable for uptake in daily care than the regression models. The downside of the simplified score is that it is less precise and contains less diagnostic information. To determine whether our diagnostic model improves clinical outcomes in everyday practice would require an implementation study in which general practitioners use point of care CRP testing with outcomes such as patient recovery and the unnecessary prescription of antibiotics. Further research should also determine the performance of CRP in other settings where pneumonia is more prevalent or where patients are more severely ill.

What is already known on this topic

Studies have evaluated the diagnostic accuracy of signs and symptoms for pneumonia, but there is limited evidence applicable to primary care

The added diagnostic value of C reactive protein (CRP) and procalcitonin concentrations to clinical signs and symptoms is unknown

What this study adds

Symptoms and signs (absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia, and fever) have moderate diagnostic accuracy for pneumonia in patients who present in primary care with acute cough

CRP concentration at the optimal threshold of >30 mg/L adds some diagnostic information by increasing diagnostic certainty in the patients when doubt remains after history and physical examination

Procalcitonin concentration adds no clinically relevant information in primary care

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Tables

Table 1| **Association between diagnostic variables and pneumonia in 2820 patients presenting with acute cough in primary care. Figures are numbers (percentages) unless mentioned otherwise**

Diagnostic variable	Missing	Total (n=2820)	Pneumonia present (n=140, 5%)	OR (95% CI)		P value
				Univariable	Multivariable*	
History (day 1)						
Mean (SD) age (years)	0 (0.0)	50 (17)	54 (15)	1.1 (1.0 to 1.2)†	1.1 (0.9 to 1.2)†	0.118
Men	0 (0.0)	1128 (40)	62 (44)	1.2 (0.9 to 1.7)	NA	—
Current smoker	2 (0.1)	779 (28)	64 (30)	1.1 (0.8 to 1.5)	NA	—
Mean (SD) No of days' illness before consultation	30 (1.1)	10 (10)	9 (6)	1.0 (0.9 to 1.0)	NA	—
Cough	2 (0.1)	2818 (100)	140 (100)	0.1 (0.0 to 0.8)	NA	—
Severe cough	0	931 (33)	56 (40)	1.4 (1.0 to 2.0)	1.1 (0.7 to 1.6)	0.724
Phlegm	2 (0.1)	2239 (79)	120 (86)	1.6 (1.0 to 2.6)	NA	—
Breathlessness	1 (0.0)	1594 (57)	96 (69)	1.7 (1.2 to 2.5)	1.4 (1.0 to 2.1)	0.025
Severe breathlessness	0	197 (7)	17 (12)	1.9 (1.1 to 3.4)	1.3 (0.7 to 2.4)	0.419
Runny nose absent	1 (0.0)	808 (29)	61 (44)	2.0 (1.4 to 2.8)	1.9 (1.3 to 2.7)	<0.001
Fever	3 (0.1)	989 (35)	82 (59)	2.8 (2.0 to 3.9)	NA	—
Chest pain	3 (0.1)	1304 (46)	80 (57)	1.6 (1.1 to 2.2)	1.2 (0.8 to 1.7)	0.402
Severe chest pain	0	141 (5)	13 (9)	2.1 (1.2 to 4.0)	1.5 (0.8 to 3.1)	0.224
Diarrhoea	2 (0.1)	199 (7)	15 (11)	1.6 (0.9 to 1.8)	1.5 (0.8 to 1.8)	0.165
Interference with daily activities	1 (0.0)	1759 (62)	96 (69)	1.3 (0.9 to 1.9)	NA	—
Any comorbidity (pulmonary, cardiac, diabetes mellitus)‡	4 (0.1)	768 (27)	50 (36)	1.5 (1.1 to 2.2)	1.0 (0.7 to 1.5)	0.960
Physical examination (day 1)						
General toxicity	5 (0.2)	739 (26)	43 (31)	1.3 (0.9 to 1.8)	1.1 (0.7 to 1.6)	0.728
Diminished vesicular breathing	15 (0.5)	362 (13)	31 (22)	2.0 (1.3 to 3.1)	1.7 (1.1 to 2.6)	0.013
Crackles	13 (0.5)	265 (9)	45 (32)	5.3 (3.6 to 7.7)	3.5 (2.3 to 5.2)	<0.001
Tachycardia (pulse >100 beats/min)	36 (1.3)	111 (4)	17 (12)	3.8 (2.2 to 6.6)	2.3 (1.3 to 4.3)	0.003
Tachypnoea (>24 breaths/min)	67 (2.4)	55 (2)	6 (4)	2.4 (1.0 to 5.7)	1.4 (0.9 to 2.0)	0.421
Blood pressure <90/60 mm Hg	58 (2.1)	71 (3)	9 (6)	2.9 (1.4 to 5.9)	NA	—
Temperature >37.8°C	27 (1.0)	158 (6)	22 (16)	3.5 (2.1 to 5.7)	2.5 (1.4 to 4.4)	<0.001
Blood test results (day 1)						
CRP (mg/L):						
Mean (SD)	142 (5.0)	19 (35)	69 (83)	1.2 (1.1 to 1.2)§	1.1 (1.1 to 1.2)§	<0.001
>20	142 (5.0)	726 (26)	85 (61)	4.9 (3.5 to 7.0)	3.5 (2.4 to 5.0)	<0.001
>30	142 (5.0)	501 (18)	74 (53)	5.9 (4.2 to 8.4)	3.8 (2.7 to 5.5)	<0.001
>50	142 (5.0)	255 (9)	58 (41)	8.9 (6.2 to 12.9)	4.8 (3.2 to 7.1)	<0.001
>100	142 (5.0)	96 (3)	34 (24)	13.5 (8.5 to 21.5)	6.0 (3.6 to 10.0)	<0.001
Procalcitonin (µg/L):						
Mean (SD)	156 (5.5)	0.09 (0.6)	0.37 (2.6)	1.2 (1.1 to 1.3)¶	1.2 (1.1 to 1.3)¶	<0.001
>0.25	156 (5.5)	107 (6)	20 (14)	2.8 (1.7 to 4.6)	2.2 (1.3 to 3.8)	<0.001
>0.50	156 (5.5)	78 (3)	14 (10)	4.5 (2.5 to 8.3)	3.2 (1.7 to 6.3)	<0.001

NA=not analysed.

Table 1 (continued)

Diagnostic variable	Missing	Total (n=2820)	Pneumonia present (n=140, 5%)	OR (95% CI)		P value
				Univariable	Multivariable*	

*Variables entered in model, based on literature: age, breathlessness, runny nose, chest pain, diarrhoea, comorbidity (pulmonary, cardiac, or diabetes), general toxicity, diminished vesicular breathing, crackles, tachycardia, tachypnoea, temperature >37.8°C. Both backward and forward selection showed same results. ORs after internal validation are shown.

†Per 10 years.

‡Pulmonary comorbidity=history of asthma or COPD (chronic obstructive pulmonary disease). Cardiac comorbidity=history of heart failure or ischaemic heart disease.

§Per 10 mg/L increase.

¶Per 0.10 µg/L increase.

Table 2| Diagnostic value of published models to identify radiographic pneumonia in derivation (original) studies and in GRACE participants

Study population (setting*)	Pneumonia prevalence (derivation study)	Linear predictor	Discrimination ROC area (95% CI)			Calibration‡ (P value)
			Derivation study	Validation†	Validation in GRACE participants	
Diehr, 1984[2]	1819 (ED)	3%	−2 for rhinorrhoea, −1 for sore throat, +1 for night sweats, +1 for myalgia, +1 for sputum, +2 for respiratory rate >25, +2 for temperature >37.7°C	—	—	0.67 (0.62 to 0.72)	7816 (<0.001)
Singal, 1989[12]	225 (ED)	16%	−3.539, +0.884 for cough, +0.681 for fever, +0.464 for crackles, +0.030 for 5.0 (pretest probability of pneumonia§)	0.75 (0.71 to 0.79)	0.58 (0.45 to 0.70)	0.68 (0.62 to 0.73)	250 (<0.001)
Heckerling, 1990[6]	1134 (ED)	5%	−1.705, +0.494 for temperature >37.7°C, +0.428 for pulse >100 beats/min, +0.658 for rales, +0.638 for decreased breath sounds, +0.691 for absence of asthma	0.82 (0.78 to 0.86)	0.63 (0.50 to 0.75)	0.65 (0.59 to 0.70)	832 (<0.001)
Melbye, 1992[9]	402 (OHD)	5%	+ 4.7 for fever (reported by patient) with duration of illness of >1 week, −4.5 for coryza, −2.1 for sore throat, +5.0 for dyspnoea, +8.2 for chest pain, lateral +0.9 for crackles	—	0.49 (0.37 to 0.62)	0.65 (0.60 to 0.70)	1890 (<0.001)
Hopstaken, 2003[7] (signs and symptoms)	246 (GP)	13%	−2.74, +1.02 for dry cough, +1.78 for diarrhoea, +1.13 for temperature ≥38°C	0.76 (NA)	0.62 (0.50 to 0.75)	0.55 (0.50 to 0.61)	394 (<0.001)
Hopstaken, 2003[7] (signs, symptoms, CRP)	246 (GP)	13%	−4.15, +0.91 for dry cough, +1.01 for diarrhoea, +0.64 for temperature ≥38°C, +2.78 for C reactive protein ≥20 mg/L	0.80 (NA)	0.69 (0.58 to 0.80)	0.71 (0.66 to 0.76)	334 (<0.001)

NA=not available.

*Setting: ED=emergency department, OHD=out of hours department, GP=general practice.

†In Graffelman.[13]

‡ Hosmer and Lemeshow test. After adjustment of intercept (to correct for difference in prevalence between derivation and validation cohorts), calibration remained poor (P<0.01).

§Pre-test probability of pneumonia was proportion of patients with pneumonia (5%) in our dataset.

Table 3| Reclassification: comparison of diagnostic risk for presence of pneumonia by diagnostic model with and without addition of measurement of C reactive protein (CRP). Figures are numbers of patients (%)

Risk according to "symptoms and signs" model (without CRP)	Risk according to "symptoms and signs" model plus CRP >30 mg/L							
	Patients with pneumonia				Patients without pneumonia			
	<2.5%	2.5-20%	>20%	Total	<2.5%	2.5-20%	>20%	Total
<2.5%	4 (36)*	7 (64)	0 (0)	11	568 (87)	86 (13)	0 (0)	654
2.5-20%	27 (26)	56 (53)*	22 (21)	105	957 (48)	966 (49)	64 (3)	1987
>20%	0 (0)	5 (21)	19 (79)*	24	0 (0)	12 (31)	27 (69)	39
Total	31	68	41	140	1525	1064	91	2680

*Patients classified in agreement according to model with and without CRP >30 mg/L. Of all patients with pneumonia 29 (22+7+0) are reclassified to higher risk groups, and 32 (27+5) to lower risk groups. For patients without pneumonia this is 150 (86+64) and 969 (957+12), respectively. Reclassification improvement is −2% among patients with pneumonia (29-32 of 140) and 30% among patients without pneumonia (957-150 of 2680), resulting in net reclassification improvement of −2+30=28% (95% CI 0.17 to 0.40).

Table 4| Diagnostic risk classification of pneumonia by simplified diagnostic score in 2820 patients with acute cough

Score (risk category)	Symptoms and signs + CRP >30 mg/L*	
	No of patients (% of 2820)	No with pneumonia (observed prevalence)
0 (low)	572 (20.3)	4 (0.7)
1-2 (intermediate)	1902 (67.4)	73 (3.8)
≥3 (high)	346 (12.3)	63 (18.2)
All	2820 (100)	140 (0.05)

*Score: 1×absence of runny nose+1×breathlessness+1×crackles+1×diminished vesicular breathing+1×raised pulse (>100/min)+1×fever (temperature >37.8°C) 1×raised CRP (>30 mg/L).
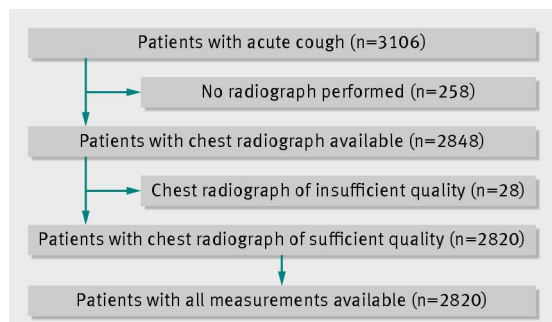
Figures

Fig 1 Recruitment and flow of participants with acute cough to determine diagnosis of pneumonia
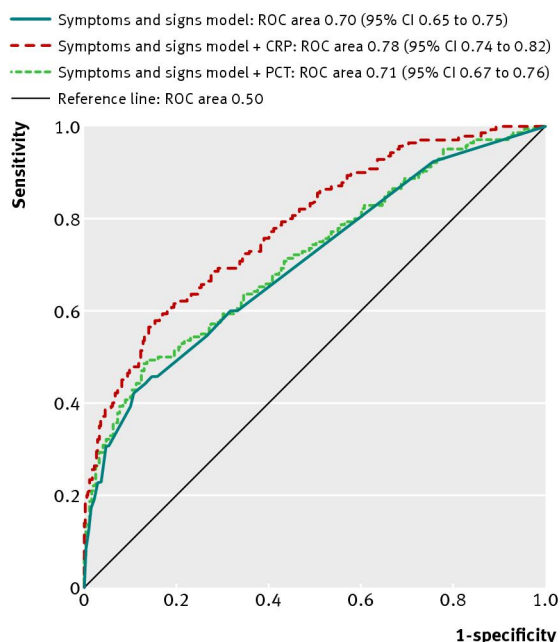

Fig 2 ROC curves of symptoms and signs and added value CRP and procalcitonin (continuous results). Linear predictors for estimated risk of pneumonia: symptoms and signs=1/(1+exp−(−3.984+0.446×breathlessness+0.698×absence of runny nose+0.596×diminished vesicular breathing+1.404×crackles+0.961×tachycardia+0.980×temperature >37.8°C)); symptoms signs and CRP=1/(1+exp−(−4.270+0.446×breathlessness+0.698×absence of runny nose+0.596×diminished vesicular breathing+1.404×crackles+0.961×tachycardia+0.980×temperature >37.8°C+0.130×(CRP/10))); symptoms signs and PCT=1/(1+exp−(−4.023+0.446×breathlessness+0.698×absence of runny nose+0.596×diminished vesicular breathing+1.404×crackles+0.961×tachycardia+0.980×temperature >37.8+0.160×(PCT×10)))