

# Predicting poor outcome in patients presenting to primary care with acute cough

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- 1 **Running head:** Predicting poor outcome
- 2 **Key points:** Antibiotics are prescribed to the majority of adults presenting to primary care with acute cough. We
- 3 developed a prediction rule to identify those with poor outcome, which outperforms the existing prediction rules
- 4 could help reduce antibiotic overprescribing by enabling clinicians to reassure their patients.

## 5 Abstract

6 **Background.** Accurate prediction of the course of an acute cough episode could curb antibiotic overprescribing,  
7 but is still a major challenge in primary care.

8 **Aim.** We set out to develop a new prediction rule for poor outcome (re-consultation with new or worsened  
9 symptoms or hospital admission) in adults presenting to primary care with acute cough

10 **Design and setting.** 2604 adults presenting to primary care with acute cough

11 **Method.** Important signs and symptoms for the new prediction rule were found by combining random forest and  
12 logistic regression modelling. Performance to predict poor outcome in acute cough patients was compared to that  
13 of existing prediction rules, using the models' area under the receiver operator characteristic curve (AUC), and  
14 improvement obtained by including additional test results (C-reactive protein (CRP), blood urea nitrogen (BUN),  
15 chest radiography or etiology) was evaluated using the same methodology.

16 **Results.** The new prediction rule included the baseline risk of poor outcome, interference with daily activities,  
17 number of years stopped smoking (above or below 45 years), severity of sputum, presence of crackles and  
18 diastolic blood pressure (above or below 85 mmHg), and severity of sputum. Although performance of the new  
19 prediction rule was moderate (sensitivity 62%; specificity 59%; positive predictive value 27%; negative  
20 predictive value 86%; AUC 0.62 [0.61-0.67]), it outperformed all existing prediction rules used today (highest  
21 AUC 0.53 [0.51-0.56]) and could not be improved by including additional test results (highest AUC 0.64 [0.62-  
22 0.68]).

23 **Conclusion.** The new prediction rule outperforms all existing alternatives in predicting poor outcome in adult  
24 patients presenting to primary care with acute cough and could not be improved by including additional test  
25 results.

26 **Keywords:** Acute cough, prediction rule, primary care, prognosis

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## 28 How this fits in:

29 In adults presenting to primary care with acute cough, accurate prediction of poor outcome could curb antibiotic  
30 overprescribing. The performance of existing prediction rules to predict poor outcome in these patients is very

31 poor. The new prediction rule presented in this manuscript outperforms these alternatives and could not be  
32 improved by including additional test results.

33

## Introduction

With an incidence of 30 to 50 cases per 1000 patients per year, acute cough is one of the main reasons for consulting in primary care.(1) Although antibiotic treatment for acute cough has been shown to have little or no effect, both overall and in patients with co-morbidities, and the majority of acute cough cases are caused by a self-limiting lower respiratory tract infection (LRTI), antibiotics are prescribed to over 50% of patients.(2–4) This inappropriately high level of antibiotic prescribing is explained by the difficulty to identify patients that might benefit from antibiotic treatment (e.g. suffering from a bacterial LRTI or pneumonia).(5) The best way forward is to identify early and manage differently those at high risk of an adverse outcome in which the risk for complications might outbalance the risk for unnecessary treatment, while adopting a 'wait and see approach' for the others, which are expected not to need treatment, hence adjusting treatment according to prognosis rather than diagnosis.(6,7)

Existing prognostic prediction rules include the Pneumonia Severity Index (PSI), CRB, CURB, CRB-65 and CURB-65.(8–10) These prediction rules were developed to predict mortality in patients presenting to the emergency department with community-acquired pneumonia (CAP), but CRB-65, CURB-65 and PSI could also be used to predict mortality from CAP in outpatients.(11,12) However, since death from CAP is very uncommon in outpatients, several authors suggested to consider other outcomes.(13–15) Therefore, we developed a prognostic prediction rule to predict poor outcome (re-consultation with new or worsened symptoms or hospital admission) in adults presenting to primary care with acute cough, aiming to enable general practitioners (GPs) to reassure patients at low risk and provide appropriate advice for patients at high risk. The performance to predict poor outcome in acute cough patients for the new and existing prediction rules (PSI stage I (Appendix Figure A1), CRB, CURB, CRB-65 and CURB-65) was compared and the improvement of the new prediction rule's performance by including additional test results (C-reactive protein (CRP) or blood urea nitrogen (BUN)), chest radiography and etiology was evaluated.

## Methods

### *Data*

Data on the presence of poor outcome (re-consultation with new or worsened symptoms or hospital admission) in adults presenting to primary care with acute cough were collected within the GRACE (Genomics to combat

Resistance against Antibiotics in Community-acquired LRTI in Europe; [www.grace-lrti.org](http://www.grace-lrti.org)) Network of Excellence.(5) Patients that had no outcome reported (4.4%) were excluded from analyses. To avoid computational issues, we selected countries with more than 15 poor outcome patients for further analysis (i.e. Belgium, Germany, the Netherlands, Poland, Spain and the UK; Table 1). The working data contain information on 105 variables recorded for 2604 patients. Included covariates cover information that is available to the GP on the day of consultation, concentrations of CRP and BUN, chest radiography, etiology and reported outcome (Appendix Table A1). Bacterial pathogens that were tested for include *Streptococcus pneumoniae*, *Haemophilus Influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Bordetella pertussis* and *Legionella pneumoniae*. Viral pathogens that were tested for include rhinovirus, influenza virus, coronavirus, respiratory syncytial virus, human metapneumovirus, parainfluenza virus, adenovirus, polyomavirus and bocavirus.

#### *Development of new prediction rule*

Missing covariate information was imputed, on a country-specific basis due to heterogeneity between countries, using multiple imputation by chained equations (five imputations).(16,17) To account for the difference in baseline risk of poor outcome, countries were grouped according to the observed proportion of poor outcome patients (A: < 15% (Spain), B: 15-25% (Belgium, Netherlands, Poland, UK), C: >25% (Germany)). A conditional random forest approach was then used to identify the most important variables for each imputed dataset.(18) The number of variables selected for inclusion in an imputation-specific logistic regression model was chosen based on the number of included patients (Table 1). We removed non-significant variables in a backwards fashion ( $\alpha = 0.10$ ), included interaction terms between remaining fixed effects and removed non-significant interaction terms ( $\alpha = 0.05$ ).

Variables that were significant in at least two imputation-specific models were retained in the group-specific model, which was reduced in a backwards fashion ( $\alpha = 0.05$ ). Variables that were significant in at least one group-specific model were retained in the general model, which was then reduced in a backwards fashion ( $\alpha = 0.05$ ).(19) The prediction rule was constructed using the final general model (“clinical” model) and its pooled parameter estimates, with the optimal cut-off value determined using the Youden index.(20) The procedure followed is illustrated in Figure A1 (in Appendix).

## *Validation of the new prediction rule*

The stability of the new prediction rule was evaluated using cross-validation. For this procedure, the data were split in three sets of equal size by sorting by country and assigning every first (second and third) observation to the first (second and third) dataset. Two sets were used to conduct backwards model building starting from the general model and obtain pooled parameter estimates. The third set, together with the pooled estimates, was used to determine the area under the receiver operator curve (AUC), which is the probability that for each (randomly) chosen pair (one patient with and one patient without poor outcome) the one with poor outcome is correctly identified. This AUC can range from 0.5, corresponding to no discriminative ability, to 1, corresponding to perfect discrimination.<sup>(21)</sup> This procedure was repeated three times, such that each set was used to determine the AUC once. Empirical bootstrapping was used to obtain 95% percentile confidence intervals.

## *Evaluation of the new prediction rule*

The new prediction rule's performance to predict poor outcome was compared to that of five existing prediction rules (PSI stage I, CRB, CURB, CRB-65 and CURB-65) using their AUCs.<sup>(8–10)</sup> The improvement in discriminative ability obtained by including information on biomarkers (CRP or BUN), chest radiography and etiology was evaluated using the AUCs after inclusion of these components (separately). Empirical bootstrapping was used to obtain 95% percentile confidence intervals.

Sensitivity, specificity positive and negative predictive values (PPV and NPV, respectively) with and without inclusion of CRP, BUN, chest radiography and etiology were compared. A cut off for poor outcome of 20% was selected, and a sensitivity analyses around this threshold was conducted, using thresholds of 15% and 25%.

To provide a tool for clinical practice, we derived a simplified prediction rule by dichotomizing continuous covariates (diastolic blood pressure and number of years stopped smoking) and retaining only the covariate level with the highest impact on the predicted odds of poor outcome for multi-level covariates.

## **Results**

Countries with < 15 poor prognosis patients were excluded from the analyses (France (7 out of 30 patients), Italy (0 out of 18 patients), Slovakia (5 out of 139 patients), Slovenia (6 out of 73 patients) and Sweden (8 out of 103

patients)). The analyses did include 2604 patients, of which 521 experienced poor outcome, divided over six countries (Table 1). Baseline characteristics for these patients are given in Table A2.

Variable importance plots for all imputed datasets can be consulted in the Appendix (Figures A2-A4). The final model for group A shows that the odds of poor outcome is affected by the presence of lung diseases other than asthma or chronic obstructive pulmonary disorder ( $p = 0.0031$ ), the presence of coughing attacks ( $p = 0.0308$ ) and the presence of crackles upon physical examination by the GP ( $p = 0.0022$ ). The final model for group B shows that the odds of poor outcome is affected by the use of antidepressants ( $p = 0.0204$ ), the severity of interference with daily activities ( $p = 0.0016$ ), the number of years since the patient stopped smoking ( $p = 0.0069$ ) and the severity of sputum as assessed by the patient ( $p = 0.0005$ ). The final model for group C shows that the odds of poor outcome is affected by the patient's smoking status (stopped smoking less or more than 45 years ago;  $p = 0.0090$ ) and diastolic blood pressure (above or below 85mmHg;  $p = 0.0038$ ). Pooled odds ratios for group-specific models are reported in the Appendix (Tables A3-A5).

The "clinical" model contains variables related to the patient's context (baseline risk of poor outcome ( $p < 0.0001$ )), the patient's symptoms obtained during an interview by the GP (severity of interference with daily activities ( $p < 0.0001$ )), the patient's general information obtained through the patient diary (the number of years since the patient stopped smoking (less or more than 45 years ago;  $p = 0.0045$ )) and self-assessment of symptoms obtained through the patient diary (severity of sputum as assessed by the patient ( $p = 0.0047$ )), the patient's signs upon clinical examination by the GP (presence of crackles ( $p = 0.0117$ ) and diastolic blood pressure (above or below 85mmHg;  $p = 0.0020$ )). Pooled odds ratios are reported in Table 2. The final prediction rule (RISSC85) was obtained using pooled parameter estimates. The optimal Youden cut-off was 0.18, which implies that a patient is classified to be at low risk for poor outcome when the predicted probability is below this threshold, and at high risk when it is above this threshold.

#### *Validation of the new prediction rule*

The three-fold cross-validation approach reveals that out of the nine predictors present in the full general model, similar variables were kept in the "clinical" model and the three reduced general models, with the three most significant variables present in all models. AUCs for all reduced general models were comparable (Table A6), indicating that the stability of the "clinical" model is acceptable. *Evaluation of the new prediction rule*

Comparing the AUCs of five existing prediction rules (PSI stage I, CRB, CURB, CRB-65 and CURB-65) and RISSC85 demonstrates that RISSC85 outperforms all existing prediction rules (Table 3).

Adding continuous CRP concentration to the “clinical” model resulted in an odds ratio for poor outcome of 1.010 [0.990-1.031] per 10 mg/L rise in concentration. Adding continuous BUN concentration to the model resulted in an odds ratio for poor outcome of 0.970 [0.803-1.185] per 10 mg/dL rise in concentration. The AUC of the “clinical” model did not improve significantly after addition of CRP or BUN (Table 4). Because of the limited added value of continuous CRP and BUN, they were not analyzed further as dichotomized covariates.

Including chest radiography resulted in an odds ratio for poor outcome of 0.927 [0.623-1.380] if pneumonia is detected on the radiograph. Adding bacterial etiology resulted in an odds ratio for poor outcome of 1.324 [1.047-1.677] if a bacterial agent was detected. Addition of viral etiology resulted in an odds ratio for poor outcome of 0.821 [0.672-1.004] if a viral agent was detected. Addition of other information on etiology resulted in an odds ratio for poor outcome of 1.247 [0.882-1.765] if only a single bacterial agent was detected, 0.745 [0.583-0.952] if only a single viral agent was detected, 1.162 [0.511-2.646] if multiple bacterial agents (but no viral agent) were detected, 1.281 [0.780-2.109] if multiple viral agents (but no bacterial agent) were detected and 1.161 [0.824-1.634] if both viral and bacterial agents were detected. The AUC of the “clinical” model did not improve significantly after adding chest radiography or etiology (Table 4).

Performance of the prediction rule with and without additional covariates (CRP, BUN, chest radiography, bacterial, viral and general etiology) was comparable, with sensitivities between 62% and 63%, specificities between 57% and 59%, PPVs between 27% and 28%, and an NPV of 86% (Tables A7-A12). Using a 15% threshold resulted in sensitivities between 85% and 87%, specificities between 27% and 32%, PPVs between 23% and 24%, and NPVs between 89% and 90%. Using a 25% threshold resulted in sensitivities between 32% and 36%, specificities between 80% and 82%, PPVs between 30% and 32%, and an NPV of 83%.

Selection of the covariate level with the highest impact resulted in an AUC of 0.59 [0.57-0.62] (Table 4). With a score of 3 or above indicating poor outcome, the simplified RISSC85 has 43% sensitivity, 73% specificity, 28% PPV and 84% NPV. Using 2 or 4 as threshold for poor outcome resulted in 89% and 9% sensitivity, 24% and 96% specificity, 22% and 32% PPV, and 90% and 81% NPV, respectively (Table 5).

## Discussion



## Summary

Poor outcome occurred in 521 (20%) of the 2604 adult patients presenting to primary care with acute cough. All important predictors for poor outcome in these patients are readily available to primary care clinicians as RISSC85 is based on information related to the patient's baseline risk of poor outcome, severity of interference with daily activities, number of years stopped smoking above or below 45 years, severity of sputum at the day of consultation, presence of crackles and diastolic blood pressure above or below 85mmHg).() (). It is a bit peculiar that, while a person indicating sputum to be a severe problem has in increased odds of poor prognosis, a person rating sputum as a very severe problem does not have an increased odds of poor prognosis. The only somewhat plausible explanation we came up with was that patients ranging their symptoms as extreme were exaggerating, while patients rating their symptoms as severe were modest but actually really ill. The performance of RISSC85 was moderate (sensitivity 62%; specificity 59%; PPV 27%; NPV 86%; AUC 0.62 [0.61-0.67]), but it outperformed all existing prediction rules used today and including information on BUN, CRP, chest radiography and etiology did not improve its performance. This indicates that, currently, RISSC85 is the best available option to predict poor outcome in adult patients presenting to primary care with acute cough.

## Strengths and limitations

This study is the first in which a prognostic prediction rule for adult acute cough patients in primary care was developed, and uses one of the largest datasets to date. Up to now, prediction rules that were developed to predict mortality in patients presenting to the emergency department with CAP were used instead, corroborating the need to develop a new prediction rule. There were very few hospital admissions so the outcome does not reflect major complications, but mostly individuals returning with bothersome, new or worsening symptoms.

The number of included poor outcome cases as well as the total number of included patients was rather low in some countries (< 15 and < 150, respectively in Slovakia, Sweden, Slovenia, France and Italy). Therefore, these countries were excluded from the analysis and this study focused on a limited number of countries (6). The prediction rule can however still be used in other countries, by estimating their baseline risk for poor outcome using literature or personal experience, after which the country can be classified into group A, B or C. If computing this risk is not possible, the country could be assumed to have an average baseline risk for poor outcome (15-25%).

Even though we included a lot of variables in building this prediction model, note that we were not able to include some covariates that have previously been shown to increase the risk of hospitalization or death from pneumonia, e.g. high blood glucose levels and the use of proton pump inhibitors (22,23).

In this study, we performed an internal validation of the prediction rule, showing its stability. However, before this prediction rule can be fully trusted for use in practice, an external validation in the form of an implementation study would be needed to determine whether it can be used to improve patient management, e.g. avoiding adverse events.

#### *Comparison with existing literature*

Currently, there are no prediction rules for poor outcome in adults presenting to primary care with acute cough. The only alternative available is the use of prognostic prediction rules that were developed to predict mortality in patients presenting to the emergency department with CAP (e.g. PSI and CRB).(9,10) Although the use of these prediction rules has been demonstrated to predict mortality in outpatients,(11,12) we showed that they perform poorly in predicting poor outcome as defined here for adult patients presenting to primary care with acute cough (Table 3).

The new prediction rule could potentially be improved further and while other authors suggest the use of e.g. CRP (5) to improve the predictive ability for pneumonia, we found that the inclusion of diagnostic markers (CRP, BUN), chest radiography and etiology did not improve the model's predictive ability.

Van Vugt *et al.* showed that the GP's ability to diagnose pneumonia, based on their clinical judgement, is better than the prediction model based on signs and symptoms (24). The covariate indicating whether the history taking was suggestive of pneumonia or not was however not retained as an important predictor in any of the (group-specific) models, indicating that the clinical judgement on the presence of pneumonia does not contribute to the prognostic assessment of an adult acute cough patient. And while Teepe *et al.* showed that patients with mild unsuspected pneumonia benefitted from amoxicillin treatment,(25) also the covariate *Intervention* (indicating whether the patient received amoxicillin or placebo) was not retained in any of the (group-specific) models, indicating that amoxicillin does not provide protection against poor outcome in adult acute cough patients.

228 *Implications for practice*

229 Although the predictive ability of RISSC85 is suboptimal, it is the best currently available option to predict poor  
230 outcome in adult patients presenting to primary care with acute cough. Given that PPV is only 27% while NPV  
231 is 86%, this tool will be more suitable for reassuring patients with acute cough that, given their symptoms, the  
232 risk of poor outcome is low. GPs could hence use the (simplified) RISSC85 to differentiate between patients  
233 where a 'wait and see approach' is appropriate and careful reassurance is the preferred treatment strategy, and  
234 those more at risk for poor outcome, who could then be more explicitly advised about key symptoms and signs  
235 that require re-consultation, and possibly offered a delayed prescription. (26)  
236 Obtaining CRP, BUN, etiology and chest radiography have no added prognostic value, and hence can be avoided  
237 when the motive is purely predicting poor outcome.

238 *Conclusion*

239 The new prediction rule (RISSC85) outperforms all existing alternatives in predicting poor outcome in adult  
240 patients presenting to primary care with acute cough and its performance could not be improved by including  
241 additional test results (CRP, BUN, chest radiography, etiology).

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361 **Tables**

362 **Table 1.** Number of total patients and patients with poor outcome for countries included in the working data.

Country	Included patients	Poor outcome patients (%)	Group	Number of covariates
Spain	594	86 (14.5)	A	7
Belgium	388	76 (19.6)	B	10
Poland	590	120 (20.3)	B	
UK	518	113 (21.8)	B	
Netherlands	325	75 (23.1)	B	
Germany	189	52 (27.5)	C	5

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**Table 2.** Pooled odds ratios [95% confidence intervals (CI)] for parameters in the “clinical” model.

Parameter	Odds ratio [95% CI]	Parameter	Odds ratio [95% CI]
<u>Patient's context</u>		<u>General patient information (patient diary)</u>	
Group B	1.672 [1.282-2.180]	Years stopped smoking high (> 45 years ago)	1.006 [1.002-1.010]
Group C	2.271 [1.515-3.406]	<u>Patient's symptoms (patient diary)</u>	
<u>Patient's symptoms (interview)</u>		Sputum very small problem	0.547 [0.332-0.902]
Some interference daily activities	1.369 [1.093-1.714]	Sputum small problem	0.962 [0.658-1.406]
Severe interference d. activities	2.413 [1.667-3.491]	Sputum moderate problem	1.038 [0.748-1.439]
<u>Patient's signs (clinical examination)</u>		Sputum severe problem	1.303 [0.926-1.837]
Crackles not present	0.662 [0.488-0.899]	Sputum very severe problem	1.270 [0.842-1.915]
Diastolic blood pressure high (> 85 mmHg)	0.986 [0.977-0.995]	Sputum could not be worse	0.767 [0.455-1.295]

**Table 3.** Area under the receiver operator curve (AUC) and 95% bootstrap confidence intervals (CI) for the new and five existing prediction rules.

	AUC [95% CI]
<b>Pneumonia Severity Index</b>	0.51 [0.50-0.54]
<b>CRB rule</b>	0.53 [0.51-0.55]
<b>CURB rule</b>	0.53 [0.51-0.55]
<b>CRB-65 rule</b>	0.53 [0.51-0.56]
<b>CURB-65 rule</b>	0.53 [0.50-0.56]
<b>RISSC85</b>	0.62 [0.61-0.67]

**Table 4.** Area under the receiver operator curve (AUC) and 95% bootstrap confidence intervals (CI) for the new prediction rule (RISSC85), RISSC85with inclusion of C-reactive protein (CRP), blood urea nitrogen (BUN), chest radiography (X-ray) and information on presence of bacterial (BAC) and viral (VIR) agents (ETIO) and the simplified RISSC85.

	AUC [95% CI]
<b>RISSC85</b>	0.63 [0.61-0.67]
<b>RISSC85+ CRP</b>	0.63 [0.61-0.67]
<b>RISSC85+ BUN</b>	0.63 [0.61-0.67]
<b>RISSC85+ X-ray</b>	0.63 [0.61-0.67]
<b>RISSC85+ BAC</b>	0.64 [0.62-0.67]
<b>RISSC85+ VIR</b>	0.64 [0.62-0.67]
<b>RISSC85+ ETIO</b>	0.64 [0.62-0.68]
<b>Simplified RISSC85</b>	0.59 [0.57-0.62]

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**Table 5.** Diagnostic risk classification of poor outcome according to the simplified RISSC85 in 2001 patients with acute cough, and sensitivity, specificity, positive and negative predictive values for different threshold.

Score (risk category)	No of patients with poor outcome (n=398)	No of patients without poor outcome (n=1603)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
5	7	5	2	100	58	80
4	27	66	9	96	32	81
3	139	367	43	73	28	84
2	181	783	89	24	22	90
1	40	330	99	3	20	93
0	4	52				

Score calculated as +1\*Group (B or C) +1\*interference with daily activities + 1\*crackles + 1\*diastolic blood pressure low (below 85mmHg) + 1\*years stopped smoking high (more than 45 years ago) + 1\* sputum (severe).

Using 3 (full line), 2 (dashed line) or 4 (dotted line) as a threshold, the number of patients above the respective line get a positive test result while numbers below the line get a negative test result.

PPV: positive predictive value; NPV: negative predictive value