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RESEARCH PAPER

Severity assessment for lower respiratory tract infections: potential use and validity of the CRB-65 in primary care

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Abstract

Aims: To explore the potential use of the CRB-65 rule (based on Confusion, Respiratory rate, Blood pressure and age >65 years) in adults with lower respiratory tract infection (LRTI) in primary care.

Methods: Primary care clinicians in 13 European countries recorded antibiotic treatment and clinical features for adults with LRTI. Patients recorded daily symptoms. Multilevel regression models determined the association between an elevated CRB-65 score and prolonged moderately severe symptoms, hospitalisation, and time to recovery. Sensitivity analyses used zero imputation.

Results: Respiratory rate and blood pressure were recorded in 22.7% and 31.9% of patients, respectively. A total of 2,690 patients completed symptom diaries. The CRB-65 could be calculated for 339 (12.6%). A score of ≥1 was not significantly associated with prolonged moderately severe symptoms (odds ratio (OR) 0.42, 95% CI 0.04 to 4.19) or hospitalisations (OR 3.12, 95% CI 0.16 to 60.24), but was associated with prolonged time to self-reported recovery when using zero imputation (hazard ratio (HR) 0.75, 95% CI 0.64 to 0.88).

Conclusions: Respiratory rate and blood pressure are infrequently measured in adults with LRTI. We found no evidence to support using the CRB-65 rule in the assessment of LRTI in primary care. However, it is unclear whether it is of value if used only in patients where the primary care clinician suspects pneumonia.

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See linked editorial by Marsden & Woodhead on pg 11

Introduction

Community-acquired lower respiratory tract infection (LRTI) is one of the most frequent diagnoses in medical care. Most cases are managed in primary care where an extensive diagnostic work-up for all patients is neither feasible nor cost-effective. Identifying which of the many presenting patients are likely to experience an unusual or prolonged illness course is helpful in setting realistic expectations about recovery and advising on appropriate help-seeking. Community-based clinicians rely on clinical judgement to determine which patients are likely to experience a more complicated or prolonged course. However, there is insufficient evidence on the diagnostic value of signs,

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symptoms and rapid or near patient tests to identify reliably patients likely to have a worse prognosis.[1] Clinician uncertainty and patient expectations for antibiotic treatment contribute to substantial overuse of antibiotics in most European countries. This results in substantial direct and indirect costs and serious unintended consequences including side effects from unnecessary antibiotics[2] and, most notably, a rise in bacterial resistance.[3,4]

To counteract unnecessary antibiotic use and associated pressure for selecting bacterial resistance, primary care clinicians need valid feasible tools to improve the quality of their management decisions. Prognostic models that are valid in primary care can help clinicians tailor their management strategies to the risk of complications or prolonged illness. Indeed, the development and evaluation of strategies or tools to help differentiate between serious and self-limiting LRTIs was described as a key research need by the International Primary Care Respiratory Group.[5]

The CRB-65 rule, based on Confusion, Respiratory rate, Blood pressure and age ≥65, was developed to predict the risk of admission to the intensive care unit and mortality in hospitalised patients with community-acquired pneumonia (CAP).[6,7] Although developed in the hospital setting, it has also been promoted as a tool for guiding decisions about hospital admission in patients with CAP initially managed in the community.[8-11] However, its validity in this setting has not been adequately assessed. There have been three recent systematic reviews of evidence for using severity assessment rules in the management of CAP.[10-12] Two of these excluded patients who had not had a chest x-ray.[10,11] This limited the applicability of the findings as an x-ray is not performed for most patients with LRTI managed in the community. The third review compared the use of the CRB-65 to predict 30-day mortality in hospital and community settings, and found that the rule over-predicted the probability of mortality in community settings.[12] However, while studies have evaluated the use of CRB-65 in outpatient clinics, emergency departments, and private specialist clinics,[13-16] only one study has evaluated its use in primary care, and this study was limited to older patients (aged ≥65 years) with an empirical diagnosis of pneumonia.[17] No study has yet assessed the extent to which primary care clinicians routinely assess the features that make up the CRB-65 score, the value of the CRB-65 in all adults presenting with LRTI in primary care, or whether the tool can be used to predict more severe or prolonged illness in the community.

We therefore set out to explore the extent to which components of the CRB-65 rule were routinely evaluated, and to assess its validity as a tool for predicting prognosis in adults presenting with LRTI in primary care.

Methods

Study subjects

Eligible patients were aged ≥18 years who presented with an illness where an acute or worsened cough was the main or dominant symptom or the clinical presentation suggested an LRTI, with a duration of ≤28 days.

Study design

This was a prospective observational study in 14 primary care networks in 13 European countries with clinicians recording symptoms on presentation and management. More details on this observational Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE) 01 study (www.grace-lrti.org) of acute cough have been reported elsewhere.[18-21] Ethical approval for the study was obtained in each of the 13 countries in which the study was conducted.

Data collection

Clinicians recorded aspects of patients' history, symptoms, co-morbidities (diabetes, chronic lung disease including chronic obstructive pulmonary disease (COPD) and cardiovascular disease), clinical findings, and their management including antibiotic prescription on a case report form (CRF). Clinicians indicated the presence or absence of 14 symptoms (cough, sputum production, shortness of breath, wheeze, coryza, fever during this illness, chest pain, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities, confusion/disorientation and diarrhoea) and, if present, recorded whether each symptom constituted 'no problem', a 'mild problem', a 'moderate problem', or a 'severe problem' for the patient. In addition, clinicians had the opportunity to register the age, respiratory rate and blood pressure of patients on the CRF. In order to record routine practice, we asked clinicians only to record elements of the clinical examination (other than temperature, which clinicians were asked to record for all patients) that they would routinely check in such a patient.

Patients were given a symptom diary. They were asked to rate 13 symptoms each day until recovery (or for 28 days if symptoms were ongoing) on a 7-point scale from 'normal/not affected' to 'as bad as it can be'. Patients rated the same symptoms as the clinicians except for two symptoms – namely, confusion/disorientation and diarrhoea. They were also asked to rate the impact of their illness on their social activities, an item that was not part of the clinicians' assessment. In addition, patients were asked to indicate the day on which they felt recovered from their illness and whether or not they re-consulted with healthcare services (e.g. general practitioner [GP], nurse, or out-of-hours service) or were hospitalised for the same condition.

Data analysis

We determined the proportion of patients with CRF and diary data who had confusion, respiratory rate, blood pressure, and age recorded on the CRF. CRB-65 scores were calculated by assigning one point for each of the following: presence of confusion, respiratory rate ≥30/min, systolic blood pressure <90mmHg or diastolic blood pressure ≤60mmHg, and age ≥65 years. Patients with missing data for any of these parameters were given a missing CRB-65 score. However, in order to conduct sensitivity analyses, we also calculated CRB-65 scores

imputing zero for all missing values.

Patients who had been hospitalised and patients who had re-consulted within the 4-week follow-up period were identified. Patients who reported one or more symptom as 'moderately bad' (scored as ≥3 or more on a scale of 0–6) on one or more days during the fourth week (22–28 days after the initial consultation) were identified as having a prolonged illness. We defined a CRB-65 score of ≥1 as abnormal. This was based on a literature review, an assessment of the CRB-65 score frequency distribution in our dataset, and evaluation of a Receiver Operating Characteristic (ROC) curve of CRB-65 score as a predictor of prolonged illness.

As no patients died and only a small number were hospitalised, our main analysis was the association between an elevated CRB-65 score (≥1) and prolonged illness using a two-level hierarchical logistic regression model (with patients nested within clinicians), and controlling for antibiotic prescribing. We also examined the association between an elevated CRB-65 score and hospitalisation (using the same approach) and time to recovery, using Cox proportional hazards modelling. Sensitivity analyses were conducted by fitting the same models using the zero-imputed CRB-65 scores.

Results

A total of 3,368 participants had CRF data. The number with data on confusion, respiratory rate, blood pressure, and age and the proportion that scored positively for each of these components (i.e. had confusion, increased respiratory rate, low blood pressure, or age ≥65) are shown in Table 1.

Diary data were available for 2,690 participants. Of these, 2,613 had symptom scores for the full 4-week follow-up period and 2,468 had data on the day of recovery. Of the 2,690 participants with diary data, a complete CRB-65 score could be calculated for only 339 (12.6%) (complete case dataset). Imputing zero for all missing components of the CRB-65 score gave scores for all 2,690 participants (zero-imputed dataset). The proportions of participants with each CRB-65 score and participant characteristics by CRB-65 score for the complete case and zero-imputed datasets are given in Tables 2 and 3, respectively. A total of 111 patients had a clinical diagnosis of pneumonia. Participants with a clinical diagnosis of pneumonia were slightly older than those with a diagnosis of non-pneumonic cough (mean 52.3 (range 49.0–55.7) years vs. 48.1 (range 47.5–48.7) years) and were more likely to be male (50.5% vs. 35.4%). Of those with a clinical diagnosis of pneumonia, a complete CRB-65 score could be calculated for 12.

Table 1. Assessment of the components of the CRB-65 prediction rule in adults with community-acquired lower respiratory tract infections presenting in primary care

Item	Recording, N (%)	Positivity, N (%)
Confusion	3,361 (99.8)	135 (4.0)
Respiratory rate (≥30/min)	765 (22.7)	10 (1.3)
Blood pressure (systolic <90mmHg or a diastolic ≤60mmHg)	1,073 (31.9)	42 (3.9)
Age (≥65 years)	3,368 (100)	524 (15.6)

Most participants had a CRB-65 score of 0, a minority scored 1 (28.0% in the complete case dataset and 21.6% in the zero-imputed dataset), and a few scored 2 (2.7% in the complete case dataset and 0.7% in the zero-imputed dataset). No participants had scores of 3 or 4. The distribution of scores between networks varied considerably in the complete case dataset. There was less inter-network variation in the distribution of CRB-65 scores in the zero-imputed dataset, although the proportion scoring 1 or 2 varied from 10% in Helsinki to 31.8% in Utrecht. The baseline symptom severity score and the proportion receiving a prescription for antibiotics increased slightly with increasing CRB-65 score.

Data on duration of symptoms were available for 2,613 participants, 314 of whom also had complete CRB-65 scores, and data on consultations during the follow-up period were available for 2,295, 312 of whom also had complete CRB-65 scores. The median duration of moderately bad symptoms in the complete case dataset was 6 days (IQR 4, 10); 20 participants

Table 2. Characteristics of 339 adults with community-acquired lower respiratory tract infections presenting in primary care with complete data for the CRB-65 score*

	CRB-65 score			
	0	1	2	All
N (row %)	235 (69.3)	95 (28.0)	9 (2.7)	339
Age, mean (SD)	42.8 (12.4)	63.3 (15.3)	74.1 (7.5)	49.3 (16.5)
Prior duration of symptoms, median (IQR)	4 (3, 7)	5 (3, 8)	4 (3, 6)	5 (3, 7)
Baseline symptom severity score, mean (SD)	26.8 (6.0)	27.3 (6.2)	28.6 (6.9)	27.0 (6.1)
Antibiotics prescribed (column %)	165 (70.2)	70 (73.7)	7 (77.8)	242 (71.4)
Duration of moderately bad symptoms in days, median (IQR)	6 (4, 9)	7 (4, 14)	7 (5, 14)	6 (4, 10)
Prolonged illness† (N=334), N (%)	11 (4.8)	9 (9.5)	0 (0)	20 (6.0)
Hospitalisation (N=326), N (%)	5 (2.2)	5 (5.5)	0 (0)	10 (3.1)
Day recovered, median (IQR)	12 (8, 21)	15 (10, 22)	19.5 (13, 22)	13 (8, 21)

*Result of scoring presence of each of confusion, respiratory rate ≥30, systolic blood pressure <90mmHg or diastolic blood pressure ≤60mmHg, and age ≥65, with 1 point. †Moderately bad symptoms for 21–28 days.

Table 3. Characteristics of 2,690 adults with community-acquired lower respiratory tract infections presenting in primary care with complete or zero-imputed data for the CRB-65 score*

	CRB-65 score			
	0	1	2	All
N (%)	2,091 (77.7)	580 (21.6)	19 (0.7)	2,690
Network, N (row %)				
Antwerp	116 (70.7)	44 (26.8)	4 (2.4)	164
Balatonfüred	275 (85.9)	42 (13.1)	3 (0.9)	320
Barcelona	128 (75.4)	41 (24.3)	0 (0)	169
Bratislava	268 (89.6)	30 (10.0)	1 (0.3)	299
Cardiff	125 (69.1)	56 (30.9)	0 (0)	181
Helsinki	81 (90.0)	9 (10.0)	0 (0)	90
Jönköping	163 (73.4)	58 (26.1)	1 (0.5)	222
Lodz	178 (80.5)	41 (18.6)	2 (0.9)	221
Mataró	126 (70.4)	51 (28.5)	2 (1.1)	179
Milan	114 (74.5)	38 (24.8)	1 (0.6)	153
Rotenberg	144 (79.6)	39 (19.9)	1 (0.55)	181
Southampton	125 (74.4)	42 (25.0)	1 (0.6)	168
Tromsø	115 (77.7)	33 (22.3)	0 (0)	148
Utrecht	133 (68.2)	59 (30.3)	3 (1.5)	195
Age, mean (SD)	42.5 (12.7)	66.0 (14.0)	68.7 (14.1)	47.8 (16.3)
Prior duration of symptoms, median (IQR)	5 (3, 7)	6 (3, 10)	3 (2, 5)	5 (3, 8)
Baseline symptom severity score, mean (SD)	26.9 (5.9)	27.1 (6.4)	27.6 (6.3)	26.9 (6.0)
Antibiotics prescribed (column %)	1,124 (53.8)	328 (56.6)	12 (63.2)	1,464 (54.4)
Duration of moderately bad symptoms in days (N= 2,613), median (IQR)	6 (4, 11)	7 (4, 14)	7 (5, 14)	6 (4, 11)
Prolonged illness† (N=2,613), N (%)	170 (8.4)	72 (12.7)	1 (5.6)	243 (9.3)
Hospitalisation (N=2,545), N (%)	17 (0.9)	11 (2.1)	0 (0)	28 (1.1)
Day recovered, median (IQR)	13 (8, 22)	15 (10, 29)	17.5 (10.5, 22.5)	14 (9, 24)

*Result of scoring presence of each of confusion, respiratory rate ≥30, systolic blood pressure <90mmHg or diastolic blood pressure ≤60mmHg, and age ≥65 with 1 point; missing values were imputed by a score of 0. †Moderately bad symptoms for 21–28 days.

(6.0%) had a prolonged illness (duration of moderately bad symptoms ≥21 days), 173 (55.5%) re-consulted, and 10 (3.1%) were hospitalised. In the zero-imputed dataset the median duration of moderately bad symptoms was 6 days (IQR 4, 11); 243 (9.3%) had a prolonged illness, 1,167 (50.9%) re-consulted, and 28 (1.1%) were hospitalised. The area under the curve of the ROC curve for the CRB-65 score predicting a prolonged illness was 0.57 (95% CI 0.46 to 0.68) using the complete case dataset and 0.54 (95% CI 0.51 to 0.57) using the zero-imputed dataset. A cut-off point of ≥1 had 45.0% sensitivity, 69.8% specificity, and positive and negative predictive values of 8.6% and 95.2%, respectively, for detecting those who had a prolonged moderately severe illness in the complete case dataset and sensitivity, specificity and positive and negative predictive values of 30.0%, 78.5%, 12.5% and 91.6%, respectively, in the zero-imputed dataset.

The results of regression analyses assessing the relationship between a CRB-65 score of ≥1 and prolonged moderately severe illness, hospitalisation, and time to recovery, controlling for antibiotic prescribing, are given in Table 4.

An elevated CRB-65 score was not significantly associated with a prolonged moderately severe illness, controlling for antibiotic prescribing, using either a complete case analysis (OR 0.42, 95% CI 0.04 to 4.19) or zero-imputed scores (OR 1.17, 95% CI 0.76 to 1.81) (Table 4). However, an elevated CRB-65 score was significantly associated with a reduction in the rate of recovery (hazard ratio (HR) 0.75, 95% CI 0.64 to 0.88) in the zero-imputed dataset. An elevated CRB-65 score was not significantly associated with hospitalisation (OR 2.93, 95% CI 0.77 to 11.17).

Discussion

Summary of main findings

Primary care clinicians recorded the components required to calculate a CRB-65 prediction score in only a minority of patients in this observational study of acute cough/LRTI in adults. Respiratory rate was recorded in less than a quarter of participants and blood pressure in less than a third. The recording of CRB-65 items varied between networks. However, the distribution of CRB-65 scores (within the zero-imputed dataset) was fairly consistent.

A CRB-65 score of ≥1 was associated with a prolonged time to self-reported recovery but did not predict prolonged moderately bad symptoms (≥3 weeks following the consultation) or hospitalisation.

Strengths and limitations of the study

The study benefited from being a purely observational study –

Table 4. Associations between CRB-65 score and antibiotic prescribing, and prolonged illness, hospitalisations, and rate of recovery

	Term		
	CRB-65 ≥1	Antibiotic prescription	Interaction
Logistic regression models	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Model 1: Prolonged moderately severe illness, complete case (N=334, GPs=36)	0.42 (0.04 to 4.19)	0.49 (0.13 to 1.77)	6.55 (0.50 to 85.42)
Model 2: Prolonged moderately severe illness, zero-imputed (N=2,613, GPs=80)	1.17 (0.76 to 1.81)	0.64 (0.47 to 0.88)†	1.72 (0.95 to 3.09)
Model 3: Hospitalisations, complete case (N=326, GPs=35)	3.12 (0.16 to 60.24)	2.26 (0.21 to 24.54)	0.64 (0.02 to 18.41)
Model 4: Hospitalisations, zero-imputed (N=2,545, GPs=80)	2.93 (0.77 to 11.17)	2.12 (0.74 to 6.10)	0.64 (0.12 to 3.30)
Survival analysis models	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Model 5: Time to recovery, complete case (N=322, GPs=35)	0.67 (0.41 to 1.11)	0.95 (0.69 to 1.29)	1.07 (0.60 to 1.91)
Model 6: Time to recovery, zero imputed (N=2,468, GPs=78)	0.75 (0.64 to 0.88)†	1.08 (0.98 to 1.18)	1.08 (0.88 to 1.33)

†p<0.05.

clinicians were not asked to alter their usual practice in any way and only to record items (other than age) if they would normally check them – and is therefore likely to be representative of everyday practice. It is the largest prospective observational study of LRTI to date with data from 13 European countries, and therefore should provide results that are highly generalisable. Data were collected on mortality, hospitalisations, daily symptom scores, and day of recovery, and this allowed for analyses using a number of outcomes.

Calculable CRB-65 scores were available for 12.6% of participants with follow-up data and, as such, our estimates of the distribution of CRB-65 scores – especially at the level of country-specific GP research network – do not have a high degree of precision. Furthermore, we did not have power to detect small associations between an elevated CRB-65 and poor outcomes in this dataset. For these reasons, we used zero imputation for sensitivity analyses. Given the high recording rate for confusion (99.8%) and the universal recording of age, only respiratory rate and blood pressure scores were imputed with any frequency. The rate of positivity for these items was low (1.3% for respiratory rate and 3.9% for blood pressure), and likely to be even lower when universally recorded (we believe clinicians are more likely to measure these parameters if the patient looks unwell, and they are more likely to be abnormal in such patients), and therefore the error rate from this approach is likely to be low. The finding that the coefficients in the analyses using the complete case and zero-imputed datasets were broadly similar supports this. Less than 5% of participants had a clinical diagnosis of pneumonia, and non-pneumonic LRTI is much less likely to be associated with systemic signs and symptoms than pneumonia. We conducted sensitivity analyses in the group with pneumonia and found no significant association. However, we did not have sufficient power to detect meaningful associations in this group. We also conducted a sensitivity analysis using re-consultation within 4 weeks as an outcome and again found no significant association between elevated CRB-65 scores and outcome.

Comparison with existing literature

No other study has examined the value of CRB-65 in predicting prolonged illness in primary care. One primary care-based study assessing the discriminatory value of CRB-65 for predicting mortality in older patients (≥65 years) with CAP found a 30-day mortality rate of 3.5% and good evidence for the discriminatory value of CRB-65.[17]

Elevated CRB-65 scores (≥1) resulted primarily from age ≥65 years (positivity for confusion, elevated respiratory rate and low blood pressure were low in this study). Age has been found to be a predictor of death and hospitalisation in other studies.[22-24] However, it is still not clear whether age can be used as an independent predictor of prolonged time to recovery or whether the association between CRB-65 (driven largely by age) and prolonged time to recovery observed in this study (using zero imputation) is confounded by other risk factors such as co-morbid conditions.

An alternative prognostic rule for older patients (aged ≥65 years) with LRTI in the community based on an assessment of seven easy-to-measure characteristics (diagnosis, age, congestive heart failure, diabetes, using oral glucocorticoids, hospitalisations in previous year, and use of antibiotics in previous month) has been found to have reasonable performance (area under the ROC curve=0.75) in predicting death or hospitalisation within 30 days of diagnosis.[25] The same rule has been shown to have similar properties in older diabetic patients[26] but has not yet been evaluated in younger patients.

Implications for future research and clinical practice

We found that respiratory rate and blood pressure are measured infrequently in patients presenting in primary care with LRTI.

Routine CRB-65 assessment would therefore require a change in the routine clinical assessment of most patients with acute LRTI. However, it is not yet clear whether GPs are good at identifying patients in whom these parameters should be measured or, if they were measured universally, whether they would be more predictive. We found no good evidence that the CRB-65 score is valuable in the assessment of patients with LRTI in the community. However, an elevated CRB-65 score – mediated largely through scoring a point for age ≥65 years – was associated with a prolonged time to recovery when using zero imputation. Further prognostic studies are needed to assess the value of age in multivariable analyses that include a wider range of potential explanatory variables and that aim to produce a new rule for predicting prolonged illness for LRTI in primary care. Larger studies will be needed to assess the value of CRB-65 in predicting mortality and hospitalisations, especially in patients where a GP suspects pneumonia.

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