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Improvement of CRB-65 as a prognostic tool in adult patients with community-acquired pneumonia

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ABSTRACT

Background: Patients with community-acquired pneumonia (CAP) often require hospitalisation. CRB-65 is a simple and useful scoring system to predict mortality. However, prognostic factors such as underlying disease and blood oxygenation are not included despite their potential to increase the performance of CRB-65.

Methods: The study included 1172 consecutive patients (830 inpatients, 342 outpatients) with CAP. Mortality, sensitivity, specificity, positive predictive value and negative predictive value, and the area under the receiver operating characteristic (ROC) curve with 95% CI were calculated. Prognostic accuracy was evaluated after adding coexisting illnesses according to the Pneumonia Severity Index (malignancy, heart failure, hepatic, renal and cerebrovascular disease) and pulse oximetry (SpO_2).

Results: Mean age was 65 years, 30-day mortality 7% (inpatients 9%, outpatients 1%). Addition of one point for the presence of ≥1 coexisting condition and one point for SpO_2 <90% increased the area under the ROC curve of CRB-65 from 0.82 (95% CI 0.77 to 0.85) to 0.87 (95% CI 0.84 to 0.90; p<0.0001).

Conclusions: Modification of CRB-65 by including hypoxaemia and presence of specified underlying diseases increased the scoring system's prognostic accuracy while retaining its independence of laboratory tests. DS CRB-65 may have the potential to further facilitate site of care decision for patients with CAP.

KEY MESSAGES

▶ Does the CRB-65 have the potential to increase its ability to predict 30-day mortality in patients with CAP, thus facilitate the site of care decision, if information regarding underlying disease and peripherally measured blood oxygenation are added?

▶ When disease and peripheral blood saturation were added to CRB-65 (DS CRB-65) the scoring systems ability to predict mortality increased.

▶ Our study indicates that the scoring system DS CRB-65 can further facilitate the site of care decision in patients with CAP, without the need for blood samples or laboratory tests, when underlying disease and peripherally measured blood oxygenation are added to the CRB-65.

High incidence and mortality and the economic impact of CAP have led to the development of predictive scoring systems to facilitate assessment of disease severity in these patients. The most thoroughly validated system is the Pneumonia Severity Index (PSI) developed by Fine et al[7] based on data from more than 50 000 patients. However, the PSI contains 20 parameters with different weights and can therefore be cumbersome to use in the emergency department (ED). The British Thoracic Society (BTS) has developed the CURB scoring system,[8 9] an acronym for each of the risk factors measured—confusion, serum urea >7 mmol/L, respiratory rate ≥ 30/min, systolic blood pressure (BP) <90 mm Hg or diastolic BP ≤60 mm Hg. Modifications of CURB include CURB-65 (CURB plus age≥65 years) and CRB-65,[10] the latter advocated for use with outpatients as no laboratory tests are required.[9 10]

These scoring systems and proposed modifications have been studied and used in patients with CAP to assess illness severity and to facilitate the decision of whether a patient should be hospitalised.[11–17] In the

INTRODUCTION

Community-acquired pneumonia (CAP) is a common cause of hospitalisation with an annual incidence of 5–12 cases/1000 persons in western countries.[1–4] In a recently published multicentre study of prospective cohorts of patients with CAP mortality at 30 days, admission to intensive care or high-dependency units was 8%.[5] The annual cost of pneumonia in Europe, as estimated by the European Respiratory Society, is €10.1 billion, with in-patient care costs of €5.7 billion.[6]

PORT study[18] underlying the PSI, accessible data on patients' previous health, partial pressure of oxygen, PaO_2 <8 kPa, measured by arterial blood gas analysis, or a peripheral blood oxygen saturation (SpO_2) <90%, measured with pulse oximetry, were of independent prognostic importance and hence were included in the PSI.[7] We recently found that the addition of these two factors significantly improved the accuracy of CRB-65 to predict 30-day mortality in patients with bacteraemic pneumococcal pneumonia.[19] The aims of the present study in unselected patients with CAP of different aetiology were to analyse whether the addition of data on underlying disease and SpO_2 <90% would improve the accuracy of CRB-65 for predicting 30-day mortality, and also to specify a scoring point level that would be useful when deciding which patients with CAP might safely be treated as outpatients.

MATERIALS AND METHODS
Study participants, design and underlying conditions
The study was performed at Södersjukhuset, a 600-bed inner city teaching hospital with a catchment population of approximately 500 000. By searching the hospital medical records database of the International Classification of Disease 10 (ICD-10) for patients with CAP admitted or treated as outpatients during a 16-month period from December 2008 until March 2010, a total of 1172 study patients were retrospectively included. The patients had a principal diagnosis of pneumonia (A48.1, B20.6, J09.9, J10.0, J11.0, J12.9, J13.9, J14.9-J15.2, J15.7-J15.9, J18.0, J18.1, J18.8, J18.9, J69.0, J85.1) or a principal diagnosis of bacteraemia/sepsis due to *Streptococcus pneumoniae* (A.40.3) plus a secondary diagnosis of pneumonia. For further details, see online supplementary table S1. All inpatients had new radiographic findings on chest X-ray, or chest CT, consistent with pneumonia as assessed by a radiologist. Death within 30 days of admission was set as the end point. Patients were excluded if they had been hospitalised during the preceding 2 weeks before enrolment, could not be followed for 30 days (no accessible National Population Register data) after admission or ED visit, or if radiographic findings were assessed as due primarily to congestive heart failure, pulmonary embolus, carcinoma or other abnormalities with no signs consistent with pneumonia. The principal investigator checked and extracted necessary data from the patients' medical records.

In 144 of the 342 (42%) patients sent home after visiting the ED, no chest X-ray or chest CT was performed. However, as these patients were assessed and treated after thorough clinical examination and laboratory testing as suffering from CAP, they were included in the study in order to minimise bias by falsely reducing the number of outpatients. All necessary data were available for the calculation of the two scoring systems.

As part of the triage process at the Södersjukhuset ED, vital parameters such as pulse rate, BP, temperature, SpO_2 and respiratory rate are monitored by a nurse or a healthcare assistant before patients are examined by a physician.

The underlying conditions that we used to modify CRB-65 were those identified in the PSI study as being of independent importance for the prognosis of pneumonia,[7] namely neoplastic disease defined as any cancer (except basal cell cancer or squamous cell cancer of the skin) active at the time of presentation or diagnosed within a year of presentation; liver disease defined as a clinical or histological diagnosis of cirrhosis or another form of chronic liver disease such as chronic active hepatitis; congestive heart failure defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, chest radiograph or echocardiogram; cerebrovascular disease defined as a clinical diagnosis of stroke or transient ischaemic attack or stroke documented by MRI or CT; renal disease defined as a history of chronic renal disease or abnormal serum creatinine concentration documented in the medical record.

An identical case record form was used for all patients. All clinical data of importance for the calculation of different scoring systems were collected in a similar way for all enrolled patients. The information used was given by the patient, as well as collected from patient files and laboratory databases, and was available during the day of the patient's admission or at the ED visit.

Prognostic scores
The CRB-65 score was calculated according to the original publication.[9] The lowest SpO_2 recorded, either by the ambulance crew or at the ED, was used when the DS CRB-65 score was calculated. Thus, if the patient needed supplemental oxygen when transported by ambulance before arrival at the ED, the SpO_2 measured by the crew was used if it was lower than the SpO_2 recorded on arrival at the ED.

Statistical analysis
For statistical analysis, the computer software used were SAS V.9.0, SAS V.JMP 5.0 (SAS Institute, Cary, North Carolina USA) and NCSS 07.1.1. Fisher's exact test was used to test differences in proportions between groups and the t test to analyse differences between groups' means (except for age and the difference between median values where the Wilcoxon/Kruskal-Wallis rank sum test was used). For each scoring system, an empirical receiver operating characteristic (ROC) curve was constructed and the area under the curve (AUC) was measured to compare the accuracy of the scoring systems for the prediction of death within 30 days of admission. To test the statistical difference between AUCs of the empirical ROC curves, the results of DeLong *et al* were applied.[20] The Youden Index was used in order to find accurate cut-off points for DS

CRB-65 (sensitivity+specificity−1). For all analyses, p<0.05 was considered to indicate a statistical significance. All p values were two sided.

RESULTS

A total of 1172 patients (591 female, 581 male) with CAP were included in the study. Of these, 342 were treated as outpatients. Overall mortality within 30 days of ED assessment was 7% (80/1172). Mortality among admitted patients was 9% (75/830) and among outpatients 1% (5/342). The mortality was higher in men, 8% (49/581), than in women, 5% (31/591) (p=0.04). Age differed significantly between survivors and non-survivors (table 1).

However, no gender difference in age was noted (females, mean age 64 years, median age 66 years, males, mean age 65 years, median age 68 years). Male gender, any cardiac disease (except hypertension) and cerebrovascular, renal and malignant diseases were all significantly associated with mortality (table 1). Moreover, altered mental status, respiratory rate≥30/min, systolic BP <90 mm Hg or diastolic BP≤60 mm Hg, ICU-treatment, invasive mechanical ventilation and use of non-invasive ventilation (NIV) were all factors significantly associated with a fatal course (table 2).

Assessment of severity criteria for 30-day mortality

Table 3 shows the sensitivity, specificity and negative and positive predictive values of the two scoring systems, CRB-65 and DS CRB-65, for assessment of mortality.

Table 1 Clinical and demographic data for patients who survived and for those patients who died

Characteristics	Survived (n=1092)	Died (n=80)	p Value*
Age, years			
Median	66.0	82.5	<0.0001
Mean	63.7	80.3	
Range	18–100	45–99	
Male, N (%)	532 (49)	49 (61)	0.04
Chronic cardiac disease, N (%)			
Hypertensive	287 (26)	25 (31)	0.4
Coronary artery	165 (15)	20 (20)	0.02
Heart failure	112 (10)	31 (39)	<0.0001
Cardiac all†	481 (44)	53 (66)	0.0002
Other chronic disease, N (%)			
Cerebrovascular	119 (11)	25 (31)	<0.0001
Pulmonary	296 (27)	23 (29)	0.8
Liver	35 (3)	1 (1)	0.5
Renal	76 (7)	17 (21)	<0.0001
Diabetes mellitus	136 (12)	15 (19)	0.1
Malignancy	66 (6)	10 (12)	0.03
HIV	8 (1)	0	1

*Fisher's exact test was used, except for age where the Wilcoxon/Kruskal-Wallis rank sum test was used.
†Cardiac all, total number of patients with a medical history of any heart disease.

Table 2 Physical examination, laboratory findings and ICU treatment in patients who survived and in those who died

Findings	Survived (n=1092) N (%)	Died (n=80) N (%)	p Value*
Altered mental status	53 (5)	14 (18)	0.0001
Respiratory rate ≥30/min	229 (21)	45 (56)	0.0001
Systolic BP <90 mm Hg			
±Diastolic BP ≤60 mm Hg	149 (4)	31 (39)	0.0001
Body temperature <35°C or ≥40°C	26 (2)	3 (4)	0.4
SpO_2 <90%	323 (30)	62 (78)	0.0001
ICU treatment†	67 (9)	14 (19)	0.01
Invasive mechanical ventilation†‡	12 (2)	5 (7)	0.01
Non-invasive ventilation†	23 (3)	9 (12)	0.001

*Fisher's exact test.
†Only 830 of the patients admitted were analysed.
‡Invasive mechanical ventilation, ventilatory support with patient intubated or tracheostomised.
BP, blood pressure; ICU, intensive care unit; NIV, non-invasive ventilator support with patient not intubated or tracheostomised; SpO_2, saturation of peripheral oxygen measured by pulse oximetry.

With a CRB-65 score 0, 32% (376/1172) of all patients were classified as at low risk. Among these patients, only one patient died. Using the DS CRB-65 score 0–1 as a definition of low risk, 51% (596/1172) of all patients would be included, of whom two patients died. If DS CRB-65 score 0–2 was defined as low risk, 71% (835/1172) of all patients would be included, of whom 2% (14/835) died, representing 18% of all deaths.

DS CRB-65 score≥2 predicted 98% and score≥3 82% of all deaths. CRB-65 scores 1–4 predicted 99% of the deaths.

A statistically significant (p<0.0001) difference between the AUCs of the CRB-65 and DS CRB-65 ROC curves was observed (figure 1). The AUC, Z-value and 95% CI of the ROC curves of each of the tested severity scoring systems are demonstrated in table 4.

When the Youden Index was calculated to find an accurate cut-off score for DS CRB-65 regarding 30-day mortality, the highest value (0.58) was found for score ≥3 (sensitivity 82%, specificity 75%), and the second highest value (0.52) for score ≥2 (sensitivity 98%, specificity 54%).

Analysis of DS CRB-65 without the SpO_2 factor but including the underlying disease ('D CRB-65') regarding the prediction of 30-day mortality revealed the ROC curve AUCs (95% CI) for CRB-65 and D CRB-65 as 0.82 (0.77 to 0.85) and 0.85 (0.82 to 0.88), respectively (p=0.002 for the difference). The DS CRB-65 ROC curve AUC was 0.87 (0.84 to 0.90), compared to an ROC curve AUC of D CRB-65 of 0.82 (0.77 to 0.85) (p=0.03 for the difference). The same kind of analysis

Table 3 Sensitivity, specificity, positive and negative predictive values of 30-day mortality of the two different prediction rules CRB-65 and DS CRB-65*

	30-day mortality	Cut-off	Sensitivity	Specificity	PPV	NPV
CRB-65						
0	1/376 (0)	≥0	100	0	7	NA
1	18/471 (4)	≥1†	99	34	10	100
2	35/247 (14)	≥2	76	76	19	98
3	24/74 (32)	≥3	32	95	33	95
4	2/4 (50)	4	2	100	50	93
DS CRB-65						
0	0/295 (0)	≥0	100	0	7	NA
1	2/301 (1)	≥1	100	27	9	100
2	12/239 (5)	≥2	98	54	14	100
3	19/195 (10)	≥3	82	75	20	98
4	30/106 (28)	≥4	59	91	33	97
5	16/34 (47)	≥5	21	98	47	94
6	1/2 (50)	6	1	100	50	93

*Data presented as number total (%).
†Cut-off point accepted as threshold to define high-risk groups according to original study design.[9]
CRB-65, PPV, positive predictive value; NPV, negative predictive value.

for the prognostic performance of CRB-65 and DS CRB-65 regarding the need for ICU treatment in the 830 patients who were hospitalised revealed the ROC curve AUCs of 0.67 (0.60 to 0.77) and 0.70 (0.65 to 0.75), respectively (p=0.02 for the difference), and finally also the need for ICU treatment and/or death within 30 days was 0.73 (0.68 to 0.77) versus 0.78 (0.74 to 0.82), p<0.0001 for the difference.

DISCUSSION

In the management of patients with CAP at the ED, it is often difficult for the physician to determine which patients may safely be selected for outpatient treatment

and which patients would benefit from hospital admission. If the patient can be safely treated as an outpatient, costs are reduced and the risk of nosocomial infections eliminated. Most patients also prefer outpatient treatment and are able to resume normal activity sooner than those hospitalised.[21] A well-functioning severity scoring system can facilitate the site of care decision about this.

Developed and advocated in North America, the PSI[7] is still the most thoroughly evaluated index for identifying patients with low-risk CAP suitable for outpatient management.[7 22-24] As the PSI is cumbersome to use with 20 parameters with different weights, the less complicated CURB-65 is recommended in the latest guidelines from the Infectious Diseases Society of America and the American Thoracic Society.[24] However, CURB-65 cannot be used without laboratory resources—a blood sample has to be taken and the result of serum urea analysis awaited before a definitive assessment can be made and a decision taken. The further simplified CRB-65 can be used without laboratory resources and was originally advocated for use in the outpatient setting. There is a lack of randomised studies where CRB-65 has been tested regarding its possibility to avoid unnecessary hospital admission. Moreover, it is unknown how far CRB-65 is actually implemented and used in the outpatient setting. However, it has been shown that
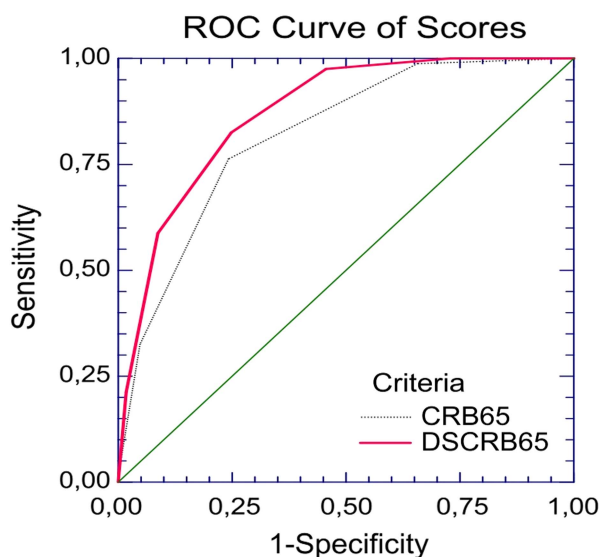

Figure 1 Comparative receiver operating characteristic (ROC) curves and the area under the curve (AUC) in association with 30-day mortality for severity scores CRB-65 (AUC 0.82) and DS CRB-65 (AUC 0.87), (p<0.0001 for the difference); for further details, see table 4.

Table 4 ROC curves of severity scores in association with 30-day mortality

	AUC	SE	Z-value*	95% CI
CRB-65	0.82	0.02	15.4	0.77 to 0.85
DS CRB-65	0.87	0.02	22.6	0.84 to 0.90

*To test AUC >0.5.
AUC, area under the curve; ROC, receiver operating characteristic.

CRB-65 can be used in outpatients to assess CAP severity and risk of death.[25] CRB-65 has been studied in more than 6000 patients, representing a mix of patients seen in the community and in hospitals and, based on these studies, is widely recommended for use in EDs.[10] In two meta-analyses of the ability of different severity indices to predict death from pneumonia, CRB-65 proved to be equivalent to the more complex PSI and CURB-65.[26 27]

When deciding the appropriate site of care in patients with suspected CAP, the Swedish Society of Infectious Diseases recommends the use of CRB-65 for patients with CAP seen in hospital EDs, since it has the advantage of not requiring venous blood samples.[28] The British Thoracic Society recommends that general practitioners use the CRB-65 score in primary care when deciding whether hospitalisation of a patient with CAP is warranted.[29]

In the developing process of the PSI, underlying diseases and poor oxygenation—information easily obtained in the ED—were independently associated with mortality.[30] The importance of underlying diseases for prognosis is supported by several recent studies[12 19 31–33] and may partly be reflected in the independent prognostic importance of high serum urea and low serum albumin.[9 33–35]

In 1988, Neff called pulse oximetry 'the fifth vital sign'.[36] Bewick *et al* revealed in their study that $SpO_2 \leq 90\%$, as a single parameter, was found in a significant proportion (28%) of patients admitted with CAP, while retaining a specificity of 76% for 30-day mortality or critical care admission,[37] and Buising *et al* observed in univariate as well as in multivariate statistical analyses that SpO_2 could successfully replace the 'U' (urea) in the CURB scoring system when assessing patients with CAP in the ED.[38] Poor oxygenation has also in other reports, including the recently proposed scoring systems A-DROP,[11] SMART-COP[12] and SCAP,[13] been identified as an independent prognostic factor.[11 39]

In the present study, we aimed to investigate the accuracy in predicting 30-day mortality of our proposed modified CRB-65 scoring system, DS CRB-65,[19] in consecutive patients with CAP of different aetiology assessed in a Swedish teaching hospital ED. In our previous study[19] DS CRB-65 performed significantly better than CRB-65 in an international cohort of patients with bacteraemic pneumococcal CAP. Among these patients, the presence of underlying disease in accordance with the PSI[7] (malignancy, heart failure, cerebrovascular, renal and liver disease) as well as $SpO_2 < 90\%$ or $PaO_2 < 8$ kPa was independently associated with 30-day mortality. We simplified the calculation of DS CRB-65 by letting the existence of one or more of the five diseases (D) increase the score sum by one point and the presence of a low SpO_2 or a low PaO_2 (S) also by one point. For the present calculation of 'S' in DS CRB-65, no blood tests or arterial blood gases were taken, and hence only SpO_2 was measured.

In the group of patients studied, the accuracy was satisfactory with both CRB-65 (score 0) and DS CRB-65

(score 0–1), since only one and two deaths, respectively (of a total of 80 deaths), were recorded among patients classified as at low risk. However, the comparison of ROC curve AUCs for the end point 30-day mortality revealed a significant difference between CRB-65 and DS CRB-65. Moreover, with CRB-65, only 32% were classified as at low risk, while with DS CRB-65, 51% were identified as at low risk, still with low mortality among patients so classified (0.3%). Thus, when compared to CRB-65, DS CRB-65 may represent an improved tool in the initial assessment of patients with CAP, while keeping its independence of laboratory tests. Based on our findings, we concluded that patients with score 0–1 are probably suitable for home treatment in most cases. In patients with a score of 2, a short stay in hospital or other supervised treatment as outpatients may be considered. A score≥3 represents cases of severe pneumonia and inpatient treatment should be the rule.

Some limitations to our study should be acknowledged. The study was retrospective and all patients were recruited from one hospital. In 144 patients (42% of all patients who visited the ED without being admitted), chest radiography or chest CT was not performed, and two of these patients died. Yet this had no statistically significant impact on the study results when the 1028 patients, all radiologically examined, were analysed separately (ROC curves AUCs and 95% CIs for CRB-65 and DS CRB-65 were 0.81, 0.76 to 0.84 and 0.86, 0.82 to 0.89, respectively, p<0.0001 for the difference). Seven patients with HIV and CAP were included, as well as one with unknown HIV status who turned out to be HIV positive and infected with *Pneumocystis jirovecii*. This eighth patient with HIV was initially assessed as suffering from CAP. All patients with HIV survived 30 days. Excluding these eight HIV patients from the ROC curve analysis revealed no statistically significant impact on the study results (ROC curves AUCs and 95% CIs for CRB-65 and DS CRB-65 were 0.82, 0.77 to 0.85 and 0.87, 0.83 to 0.90, respectively, p<0.0001 for the difference).

In conclusion, this study indicates that in patients with CAP, adding data on the existence of some specified underlying disease and the presence of hypoxaemia to the simple CRB-65 prognostic score will improve its accuracy in predicting 30-day mortality, while retaining independence of laboratory tests. The improved score can easily be used in the ED, as well as outside hospitals in order to facilitate the decision whether a patient with suspected CAP should be admitted to hospital or not. New studies or reanalysis of data from previous studies from different settings and geographical areas may be needed to further evaluate and determine the role of DS CRB-65 as a scoring system for early risk assessment of patients with CAP.

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