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Predicting mortality in patients with community-acquired pneumonia and low CURB-65 scores

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Title: Predicting mortality in patients with community-acquired pneumonia and low CURB-65 scores

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Abstract: Purpose Some patients classified as having non-severe community-acquired pneumonia (CAP) by CURB-65 subsequently die. The objective was to identify risk factors for mortality in non-severe patients and to test how risk factors might be used.

Methods Patients who had a CURB-65 score of 0-2 on admission to hospital and were alive at 30 days were compared with those who died. Identified risk factors were included in new variations of CURB-65 and new management strategies.

Results Age >65 years, blood urea >7mmol/l, bilateral/multi-lobar appearance of the chest radiograph (CXR), social situation (living alone/no fixed abode or residential/nursing care), and temperature <36°C were associated with mortality (p<0.05). A two-step approach, with initial use of CURB-65 followed by the above non-CURB-65 criteria, increased the proportion of patients correctly classified as having severe CAP who subsequently died from 54/76 (71%, 95% CI 61% to 81%) to 72/76 (95%, 95% CI 90% to 100%).

Conclusions Consideration of additional risk factors in a two-step approach can improve stratification of mortality by CURB-65. Physicians should be cautious about managing patients with CAP as outpatients if they have a CURB-65 score of 1 (or more) and have at least one of the three additional risk factors identified.

Response to Reviewers: Reviewer #1:

The here presented study examines the risk factors for mortality in patients with CAP and CURB-65 score of 0 to 2.

Patients were recruited from two Scottish hospitals and were identified by review of Acute Medical Admission Unit (AMAU) records during the winter periods, 11/2001 to 4/2002 and 11/2002 to 4/2003.

Overall, I have found the manuscript well presented and clearly written.

The study is of interest as it demonstrates that patients with CAP and a CURB-65 score of 0 to 2 may have a non-negligible mortality rate and that some additional risk factors for death could be identified at admission to the Emergency Department.

This information is not new because most experienced clinicians know, and several reports have shown, that some of the identified variables (i.e. bilateral pneumonia, low temperature) are associated with high mortality among patients with CAP. However, the present study may be of interest since it demonstrates that these variables could improve the severity index scores (CURB-65) in order to identify patients with CAP who are at risk of death. As the authors pointed out, their results must be prospectively validated in a separate cohort study.

The main weaknesses of the study are those related to the presence of possible bias and confounding. For example, selection bias could have been introduced in the present study since patients were selected only by review of AMAU records. The authors have stated some of these limitations in their Discussion.

RESPONSE: We completely agree, but did try and specifically reduce the risk of this by reviewing a wide-range of potential CAP presentations on the AMAUs (N = 1393) - This is stated in the methods section. We have added the following statement to the discussion section: "To minimise the risk of selection bias and capture a high proportion of patients presenting to the admission wards with CAP, a wide-range of potential CAP presentations were reviewed (e.g. pleuritic chest pain, shortness of breath, fever, etc.). We therefore believe our cohort to be representative of patients referred for hospital assessment of CAP in Tayside."

As the authors have demonstrated in the present study, other reports have also suggested that the current severity index scores for CAP could be improved if additional prognostic variables are included. For example, recent studies have shown that in elderly patients with pneumonia the presence of dysphagia and low functional status are associated with poor prognosis (Cabre M, Age and Ageing 2009; Medicina Clinica 2008). The authors have discussed the advantages of the two-step approach which can improve the stratification of mortality by CURB-65. However, they could also include in the Discussion a comment suggesting further investigations (i.e. new prognostic variables) or recommendations for selected group of patients (i.e. elderly) in order to improve the current severity index scores.

RESPONSE: Thank you for this helpful suggestion. We have added the following statement to the discussion: "In older patients, Cabre et al recently showed that the presence of dysphagia and low functional status are associated with a poorer prognosis and may need to be incorporated into clinical decision-making and future studies of prognostic scores in CAP [14]."

Could the authors provide any data regarding the etiology of pneumonia ?. I think it would be interesting to know the microbiological data from patients who died and survived.

RESPONSE: Thank you for this helpful suggestion. We have included the following statement in the results section: "...301 (70%) had a blood culture taken at initial assessment with 120 (28%) having atypical respiratory serology and 87 (20%) having sputum analysis performed during their admission. Seventy-one (71, 17%) patients had a positive test for at least one potential respiratory pathogen. Of these, Streptococcus pneumoniae was identified in 29 (41%), influenza A or B in 15 (21%), Gram negative enteric bacilli in 11 (15%), Haemophilus influenzae in 9 (13%), Staphylococcus aureus in 7 (10%), other streptococci in 6 (8%), and other respiratory pathogens in 3 (4.5%). The likelihood of a positive test was not significantly different in those who lived (16%) and those who died (19%)"

Results (page 7, line 22) and Table 1 "total cohort : 428", however, in Table 2 the numbers are different (patients with CURB-65 score 0-5 : 422 (61+83+121+103+48+6). Could the authors check these data?

RESPONSE: 428 patients were in the overall cohort (Table 1), but 6 patients were subsequently excluded in comparisons of the new scores (Table 2) because 1 or more of the 3 new criteria identified were missing - We could have assumed these values to be normal, which is an alternative approach. We have checked and this does not change our results or conclusions. We have added a note to Table 2 to explain this to the reader.

Reviewer #2: This is a high observational study - with retrospective data analysis - in patients admitted to two Scottish hospitals for community acquired pneumonia. Low risk patients - CURB class 0 and 1 - showed a remarkable mortality and were therefore re-analysed. Bilateral infiltrates in chest x-ray (CXR), social situation and low temperature were found as additional risk factors for mortality. Re-Analysis demonstrated an increase in sensitivity using these new parameter in addition to the classical CURB score. Risk stratification of patients with CAP is an important tool to avoid hospitalisation of too healthy patients and undertreatment of more severely ill ones. An improvement of the available risk stratification scores is therefore welcome. However, the current study has a number of important limitations.

1. It is recommended to treat patients with CURB class 0 and most with CURB class I as outpatients.

RESPONSE (also see below): This is not our recommendation, it is that of the British Thoracic Society and we have therefore used this as the standard in our study; Table 5 does state this.

The here described patient group has been hospital admitted even they are low risk patients. The major reason for that may be that GP found the patient more severely ill as it seemed to be according to the CURB Score. Therefore, this is a highly selected patient population, not comparable to the majority of CURB class 0 and 1 patients.

RESPONSE: These patients were hospital assessed, but not necessarily admitted to a medical ward. We do state this in the methods section: "At both hospitals, patients were referred from primary care and the Department of Emergency Medicine to an acute medical admissions unit (AMAU) for further assessment. Patients were then discharged immediately to outpatient care or admitted to the AMAU for a short period prior to discharge or subsequently admitted to a general medical ward."

We have also added the following line to the limitations section of the discussion to provide the reader with more information about this cohort:

"Although our study was hospital based, 7% of patients were discharged within 24 hours and 16% within 48 hours."

Our cohort therefore represents patients with CAP that were hospital assessed with a small but notable proportion being discharged within 24 hours without full admission. We agree that our study is not representative of patients presenting to GPs, but that was not the purpose of this study. We believe our cohort to be representative of patients presenting with CAP to hospitals in the UK for further assessment (but not necessarily full admission). It is important to emphasise that in the UK, not all acutely ill patients referred to an AMAU by a GP (or from the emergency department) are subsequently admitted to hospital; this decision is made by the AMAU doctors not the GP or emergency department

doctors, which may be different to systems employed in other countries. Our study is therefore most relevant to doctors working in emergency departments and AMAUs in the UK, but will also be of interest and have resonance in other countries, particularly where CURB-65 is being used. The 2007 Infectious Diseases Society of America/American Thoracic Society consensus guidelines suggest CURB-65 as an appropriate score to help clinicians in making site-of-care decisions about patients with CAP.

2. The CURB Score is primarily used to assess whether a patient needs hospital care or not. It is well known that in hospital admitted patients it does not distinguish between patients who need careful observation on ICU or respiratory intermediate care unit and those who do not need this. The modified ATS Score (Ewig et al. Thorax 2004) the ISDA/ATS guidelines from 2007 and the SMART-COP Score - CID 2008 - do much better in these circumstances. Therefore I do not agree to use the CURB score alone for risk stratification in hospital admitted patients.

RESPONSE: We completely agree and do not believe we are suggesting this and, if anything, our study supports the need for additional assessments to determine the need for critical care. The objective of the original CURB-65 derivation/validation study was "...to derive and validate a practical severity assessment model for stratifying adults hospitalised with CAP into different management groups." [Thorax 2003;58:377-382]. This study was in fact hospital-based and a number of subsequent studies have shown CURB-65 to stratify mortality (but not critical care admission) reasonably well at initial hospital assessment (as in our study). The BTS base the management of CAP in the UK on this and it was therefore logical to adopt this approach in our study. To make our position clearer, however, we have added the following in the discussion: "It is important to emphasise that CURB-65 has been shown to perform poorly at predicting the need for critical care when used alone. Other scores, such as SMART-COP [13], have been shown to perform better and it may therefore be necessary to use scores that predict different outcomes sequentially at initial assessment in order to optimise patient care."

3. Some of the basic data are very hard to understand: 30 day mortality is 19%, but only 3 % of the patients has been treated on ICU? Does this mean that treatment was withheld or withdrawn? BP diast. < 60 mmHg in 24% of patients, but BP syst. < 90% only in 6 %? This is in opposite to the manuscript from Chalmers (Thorax 2008), which looked also to Scottish patients?

RESPONSE: It is well recognized that the UK has an under-provision of ICU services (we do comment on this in the discussion) and at the time of the study, the hospitals involved did not have intermediate facilities so most patients were therefore managed in respiratory, ID or general medical wards even when some critical care interventions (e.g. NIV and inotropic support) were being used. This has actually improved somewhat in recent years across the NHS, but even now a lower % of patients are managed in critical care in the UK compared with our European or North American colleagues. Also, the median age of our cohort was relatively high (74 years), which would decrease the % of patients managed in ICU.

We have re-read the Chalmers paper. Based on Table 3 in that paper, 18.5% of patients had a sBP <90mmHg and 28% a DBP <60mmHg. The figure for DBP is similar to our own study (24%), but we agree the % of patients in our study with a sBP <60mmHg is lower. The two studies used different inclusion/exclusion criteria and were performed in different years. In our study, a considerably higher % of patients had cardiac disease (32% versus 20%) and the median age of patients was older (74 versus 66y) so it is possible that these or other differences may explain the differential between sBP and DBP. In our overall cohort, we have also found that sBP is more predictive of mortality than DBP (data not shown), which is consistent with the findings of Chalmers et al.

4. I am not convinced that the conclusion of the low sensitivity of the CURB is to create more complex scores. In my mind, the consequence of the data is that in patients with additional risk factors a reassessment by the physician is necessary in between the first 24 to 48 hours.

RESPONSE: Thank you. We completely agree and do not think that our study is suggesting this. In fact we explicitly state that "Although the addition to CURB-65 of the risk factors identified in this study increased sensitivity and NPV, it is unlikely that a new prognostic score for CAP will usurp the CURB-65 criteria, which are now well established in the UK and elsewhere." To incorporate the reviewer's suggestion we have added the following statement to the discussion: "These patients should be carefully reassessed by the physician in the first 24 to 48 hours after admission to ensure that escalation of care is not required."

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4 **Predicting mortality in patients with community-**
5 **acquired pneumonia and low CURB-65 scores**
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4 **Abstract**

5 **Purpose** Some patients classified as having non-severe community-acquired
6 pneumonia (CAP) by CURB-65 subsequently die. The objective was to identify risk
7 factors for mortality in non-severe patients and to test how risk factors might be used.
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11 **Methods** Patients who had a CURB-65 score of 0-2 on admission to hospital and
12 were alive at 30 days were compared with those who died. Identified risk factors were
13 included in new variations of CURB-65 and new management strategies.
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17 **Results** Age >65 years, blood urea >7mmol/l, bilateral/multi-lobar appearance of the
18 chest radiograph (CXR), social situation (living alone/no fixed abode or
19 residential/nursing care), and temperature <36°C were associated with mortality
20 (p<0.05). A two-step approach, with initial use of CURB-65 followed by the above
21 non-CURB-65 criteria, increased the proportion of patients correctly classified as
22 having severe CAP who subsequently died from 54/76 (71%, 95% CI 61% to 81%) to
23 72/76 (95%, 95% CI 90% to 100%).
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31 **Conclusions** Consideration of additional risk factors in a two-step approach can
32 improve stratification of mortality by CURB-65. Physicians should be cautious about
33 managing patients with CAP as outpatients if they have a CURB-65 score of 1 (or
34 more) and have at least one of the three additional risk factors identified.
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4 **Introduction**

5 Community-acquired pneumonia (CAP) is a frequent cause of admission to hospital
6 worldwide and is the commonest infection cause of death in the United Kingdom
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10 (UK) [1]; mortality in hospitalised patients in the UK ranges from 10.5% to 25% [2-
11 54]. Certain risk factors, such as physiological status on admission to hospital and
12 age, are known to be associated with a higher risk of death. Over the past decade, a
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15 number of prognostic (severity) scores have been derived and validated, and
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17 subsequently incorporated into clinical practice. In the UK, the British Thoracic
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19 Society (BTS) recommends the use of CURB-65 for prognostic assessment in CAP
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21 and in the event of an influenza pandemic [1,65]. With CURB-65, 1 point is assigned
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23 for the presence of each of the following criteria on admission to hospital: 1) new
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25 confusion, 2) urea >7mmol/l, 3) respiratory rate ≥30/minute, 4) systolic blood
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27 pressure <90mmHg or diastolic blood pressure ≤60mmHg, and 5) age ≥65 years.
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29 CRB-65 (CURB-65 without serum urea) performs almost as well as CURB-65 and, as
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31 it does not require a blood test, is suitable for use in primary care [2].
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35 Many studies have now evaluated the use of CURB-65 in clinical practice and have
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37 shown it to have moderate performance in predicting death due to CAP [2,3,76-98]. In
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39 the original validation study by Lim et al [2], CURB-65 was shown to have a
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41 sensitivity and specificity of approximately 75%, a negative predictive value (NPV)
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43 of 97% and a positive predictive value (PPV) of 22% in predicting death within 30
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45 days at a cut-off score of 3 or more to define severe CAP. On this basis, the BTS
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47 define severe CAP by a CURB-65 score of 3 or more [1]. Patients with a CURB-65
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49 score of 0 to 2 are said to have non-severe CAP with those with a score of 0 or 1
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51 having a predicted mortality of 1.5% and those with a CURB-65 score of 2 having a
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4 predicted mortality of 9.2% (4.3% for all patients with a score of 0 to 2). The BTS
5 recommend that patients with a score of 0 or 1 are suitable for outpatient therapy, but
6 that those with a score of 2 should initially be admitted to hospital, but may be
7 suitable for oral antibiotics and an early discharge. There has been concern, however,
8 that CURB-65 sometimes initially misclassifies patients, particularly young patients,
9 who subsequently require admission to the intensive care unit (ITU) and/or die as
10 being 'low risk' (i.e. a CURB-65 score of 0 or 1) or 'moderate risk' (i.e. a CURB-65
11 score of 2) [109]. How to identify patients who by the BTS definition have non-severe
12 CAP, but who subsequently die is a pertinent question for clinical CAP research.
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23 The objective of the study we now report was to identify risk factors for mortality in
24 patients assessed in hospital with low or moderate risk CAP (i.e. a CURB-65 a score
25 of 0 to 2), and then to test how such risk factors might be used in clinical practice.
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31 **Method**

32 *Participants*

33 The study was a retrospective analysis of data prospectively collected for the
34 evaluation of a quality improvement study [3,110]. Patients were recruited from two
35 Scottish hospitals, a 1000-bed teaching hospital and a 500-bed district general
36 hospital. At both hospitals, patients were referred from primary care and the
37 Department of Emergency Medicine to an acute medical admissions unit (AMAU) for
38 further assessment. Patients were then discharged immediately to outpatient care or
39 admitted to the AMAU for a short period prior to discharge or subsequently admitted
40 to a general medical ward.
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4 Patients were identified prospectively by review of AMAU records between the
5 periods 1st November 2001 to 31st April 2002 and 1st November 2002 to 31st April
6 2003 (i.e. the winter months of 2002 and 2003). A wide-range of potential CAP
7 presentations were reviewed (e.g. pleuritic chest pain, shortness of breath, fever, etc.).
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9 Patients were included if they were receiving an antibiotic for a lower respiratory tract
10 infection and had either a new infiltrate on the chest radiograph (CXR) or had been
11 clinically diagnosed as having CAP by a specialist registrar or consultant physician
12 and had this diagnosis recorded in the case-notes. Patients were excluded if they were
13 under 16 years old, taking immunosuppressive drugs (long term (>2 weeks)
14 prednisolone (or equivalent) of ≥ 15 mg or immunosuppressive therapy such as
15 methotrexate, azathioprine, mycophenolate, etc.), HIV positive, neutropenic
16 (neutrophil count $< 1.0 \times 10^9/l$), or had aspiration, hypostatic or hospital-acquired
17 pneumonia (as diagnosed and documented by the admitting medical team), or
18 progressive malignancy. Patients were also excluded if one or more of the CURB-65
19 criteria had not been recorded on admission to hospital, if 30-day mortality was not
20 available or if the diagnosis was changed prior to discharge from hospital or death. In
21 the UK, the BTS guidelines do not recommend treating patients with pneumonia who
22 live in a nursing home differently from those who live in their own homes, so these
23 patients were included in analyses [1]. We included patients only if they were being
24 actively managed (i.e. prescribed antibiotics with/without oxygen and/or intravenous
25 fluid therapy).

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29 For each patient, the CURB-65 and CRB-65 scores were calculated from the first
30 recorded set of observations after admission to hospital regardless of where this
31 occurred. Severe CAP was defined according to the British Thoracic Society (BTS)

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4 definition (i.e. a CURB-65 score of 3 or more). Mortality at 30-days post-admission to
5 hospital was established prospectively if the patient died in hospital and
6 retrospectively using a computer database if the patient died after discharge.
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9 Demographic, clinical and outcomes data were recorded on a piloted data collection
10 sheet and checked before being double entered into an Epi-Info database (Centers for
11 Disease Control, Atlanta and World Health Organisation, Geneva).
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16 17 *Statistical analyses*

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19 We initially identified patients with a CURB-65 score of 0 to 2. Descriptive statistics
20 for this cohort are presented as numbers and percentages. The characteristics of
21 patients with a CURB-65 score of 0 to 2 who died within 30 days of admission were
22 compared with those who lived using the χ^2 or Fisher's exact test. Characteristics
23 found to be associated with 30-day mortality by a p-value ≤ 0.05 were then used to
24 create new prognostic scores, based on CURB-65 and CRB-65, and new management
25 strategies.
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35 Mortality in the overall cohort of patients (i.e. all CURB-65 scores from 0 to 5) was
36 then stratified by CURB-65 score and the new prognostic scores and management
37 strategies. The sensitivity, specificity, PPV, NPV and area under the receiver
38 operating curve (AUROC) of the new scores were calculated. For each AUROC, 95%
39 confidence intervals (CI) are presented. For each score, the AUROC was statistically
40 compared to a null hypothesis AUROC of 0.5. All statistical analyses were performed
41 using SPSS (version 12). For all analyses a two-sided p-value of < 0.05 was
42 considered to be statistically significant.
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4 **Results**

5 Of 1393 patients with presentations that might have represented CAP, 503 patients
6 were included in our original study. The main reasons for exclusion were: diagnosis
7 was unclear (276, 31%); chronic obstructive pulmonary disease without pneumonia
8 (98, 11%); non-pneumonia respiratory tract infection (79, 9%); other respiratory
9 conditions (72, 8%); pulmonary embolus (55, 6%); and heart failure (52, 6%). Of the
10 included patients, 75 (15%) were excluded from this study because one or more of the
11 CURB-65 criteria had not been recorded on admission to hospital or 30-day mortality
12 could not be ascertained or the diagnosis had been changed prior to discharge from
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21 hospital or death; see Table 1. Of the remaining 428 patients (Table 1), 301 (70%) had
22 a blood culture taken at initial assessment with 120 (28%) having atypical respiratory
23 serology and 87 (20%) having sputum analysis performed during their admission.
24 Seventy-one (71, 17%) patients had a positive test for at least one potential respiratory
25 pathogen. Of these, *Streptococcus pneumoniae* was identified in 29 (41%), influenza
26 A or B in 15 (21%), Gram negative enteric bacilli in 11 (15%), *Haemophilus*
27 *influenzae* in 9 (13%), *Staphylococcus aureus* in 7 (10%), other streptococci in 6
28 (8%), and other respiratory pathogens in 3 (4.5%). The likelihood of a positive test
29 was not significantly different in those who lived (16%) and those who died (19%).
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41 Two hundred and sixty-six (266, 62%) patients had a CURB-65 score of 0 to 2 at
42 initial assessment. Table 1 shows the demographic and clinical characteristics of this
43 cohort and the differences between those who lived and those who died. A social
44 score was determined by considering whether a patient lived alone (in their own home
45 or not) or was of no fixed abode or required residential or nursing care. Social score,
46 bilateral or multi-lobar changes on the CXR, and a temperature <36°C were found to
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4 be significantly associated with 30-day mortality. These were used to create new
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6 prognostic scores by adding 1 point for the presence of each of these criteria to the
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8 CURB-65 and CRB-65 scores. Bilateral or multi-lobar changes on the chest
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10 radiograph was not added to new variations of CRB-65 as CXRs are not rapidly
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12 available to the majority of general practitioners in the UK. Of the existing CURB-65
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14 criteria, age over 65 years and a serum urea >7mmol/L were also significantly
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16 associated with 30-day mortality. These were used to create a new variation of
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18 CURB-65 in which 2 points (instead of 1) was scored for the presence of each of
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20 these criteria. The performance of these scores is shown in Table 2. Although the new
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22 scores improved stratification of mortality and sensitivity (at the expense of
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24 specificity) and NPV at a cut-off score of 3 or more to define severe CAP (2 or more
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26 for CRB-65), performance as measured by AUROC did not significantly improve
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28 (Table 3).
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31 We then used the three identified non-CURB-65 criteria in a two step approach,
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33 initially applying the CURB-65 criteria followed by the three new criteria. Table 4
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35 shows CURB-65 score stratified by the number of new risk factors and 30-day
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37 mortality. For patients with a CURB-65 score of 1 or 2, there was a significant
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39 association between the number of new criteria present at admission to hospital and
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41 subsequent mortality. Table 5 shows the stratification of mortality and ITU admission
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43 by the two-step approach compared to CURB-65 used alone. The two-step approach
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45 resulted in an increase in the proportion of patients who died who were initially
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47 classified as having severe CAP from 54/76 (71%, 95% CI 61% to 81%) to 72/76
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49 (95%, 95% CI 90% to 100%). Stratification of the need for ITU admission did not
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4 change. A higher proportion of patients were classified as having severe CAP by the
5 two-step approach (37% versus 56%).
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9 Further analyses showed that in the CURB-65 = 0 to 2 cohort, only pulse oximetry
10 <92% was significantly associated with ITU admission (P = 0.02), although there was
11 a trend towards significance for male sex (P = 0.07) and lack of availability of the oral
12 route (P = 0.1).
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21 Discussion

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23 Our results suggest that patients with non-severe CAP (as defined by a CURB-65
24 score of 0 to 2) who subsequently die have risk factors for death that could be
25 recognised by physicians at initial hospital assessment (i.e. social situation and
26 temperature <36°C) or shortly after admission to hospital (i.e. bilateral or multi-lobar
27 CXR appearance). Physicians should be cautious therefore about managing patients
28 with CAP as outpatients if they have a CURB-65 score of one (or more) and have at
29 least one of the additional risk factors identified in this study (mortality was at least
30 9% in this cohort). These patients should be carefully reassessed by the physician in
31 the first 24 to 48 hours after admission to ensure that escalation of care is not
32 required. Mortality was significantly higher in non-severe patients who were older
33 than 65 years or who had a urea >7mmol/l; these should therefore be considered as
34 cardinal risk factors for mortality regardless of overall CURB-65 score or the
35 presence or absence of additional risk factors. Similar to our study, Challen et al
36 previously showed that the inclusion of a social situation score (lives alone or no fixed
37 abode), to an early warning score in their study, can improve the performance of
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4 prognostic scores in lower respiratory tract infection [12]. A number of recent
5 studies confirm our finding that bilateral or multi-lobar chest radiograph findings is an
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7 important risk factor for physicians to consider in CAP [13,14].
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11 Although the addition to CURB-65 of the risk factors identified in this study
12 increased sensitivity and NPV, it is unlikely that a new prognostic score for CAP will
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14 usurp ~~the CURB-65 criteria~~, which ~~is~~ are now well established in the UK and
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16 elsewhere. Physicians are likely to implicitly or explicitly use criteria other than those
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18 in CURB-65 during clinical decision making, however, and our two-step approach
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20 provides objective evidence for which risk factors might be used and how they might
21
22 be incorporated into clinical practice. In contrast to CURB-65 used alone, the two-
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24 step approach identified a cohort of patients with zero mortality (and 2% probability
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26 of admission to ICU) and significantly increased the correct classification of severe
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28 CAP (according to the BTS definition). Physicians can be reassured therefore that
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30 patients with a CURB-65 score of 0 or 1, but with no additional risk factors are very
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32 unlikely to die or require escalation of care. Adding oxygenation status (the only risk
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34 factor for ICU admission in this study) to these criteria may further reduce the
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36 probability of managing a patient as an outpatient who subsequently requires
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38 admission to critical care. CURB-65 has been shown to perform poorly at predicting
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40 the need for critical care when used alone. Other scores, such as SMART-COP [14],
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42 have been shown to perform better and it may therefore be necessary to use scores
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44 that predict different outcomes sequentially at initial assessment in order to optimise
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46 patient care.
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4 Although the criteria used were different, our two-step approach is similar to that
5 suggested in the 2001 BTS guidelines, which suggested the initial use of the CURB
6 criteria followed by application of two pre-existing risk factors (age >50 years and
7 chronic illness) and two additional risk factors (chest radiograph appearance and pulse
8 oximetry). The CURB-65 criteria alone were subsequently felt to be less complex
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13 than the two-step approach and were therefore included in the 2004 update, although
14 the performance of CURB and CURB-65 was similar. In older patients, Cabre et al
15 recently showed that the presence of dysphagia and low functional status are
16 associated with a poorer prognosis and may need to be incorporated into clinical
17 decision-making and future studies of prognostic scores in CAP [15].
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27 Based on our results, a two-step approach may have the advantage of identifying a
28 cohort of patients with lower mortality than CURB-65 can identify when used alone.
29 Additionally, the two-step approach reduces misclassification of those who die in the
30 middle cohort of patients (i.e. those who require initial admission, but who may be
31 suitable for an early discharge). Disadvantages are the increase in patients classified
32 as having severe CAP, the slightly reduced number of patients who would initially be
33 treated as outpatients (assuming the criteria are strictly followed in clinical practice),
34 and the increased complexity, which could reduce use. However, data from the
35 Scottish National Audit Project for Community-Acquired Pneumonia (SNAP-CAP)
36 shows that less than one-third of low risk patients (according to the CURB-65 criteria)
37 are currently managed as outpatients in Scotland [personal communication, Peter
38 Davey], which suggests that physicians may not feel completely comfortable with the
39 CURB-65 criteria for the identification of low risk patients or other factors may exist.
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51 It is therefore possible that in clinical practice, the two-step approach may actually
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4 result in more low risk patients being managed as outpatients by increasing physician
5 reassurance. The greater number of patients classified as having severe CAP could
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7 have implications for antibiotic stewardship, but would ensure that intravenous
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9 therapy is targeted at almost all of those who die.
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11 12 13 **Limitations**

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15 As with all observational studies, our results could have been affected by bias or
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17 confounding. To minimise the risk of selection bias and capture a high proportion of
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19 patients presenting to the admission wards with CAP, a wide-range of potential CAP
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21 presentations were reviewed (e.g. pleuritic chest pain, shortness of breath, fever, etc.).
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23 We therefore believe our cohort to be representative of patients referred to hospital for
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25 assessment of CAP in Tayside. Although our study was hospital based, 7% of patients
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27 were discharged within 24 hours and 16% within 48 hours.
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32 As the data were collected for quality improvement research, we used a pragmatic
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34 definition of CAP. One advantage of this is that patients in our cohort are more likely
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36 to represent the patients that clinicians treat as CAP in the real world. It is important
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38 that severity scores are tested in real world cohorts as well as in gold-standard
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40 research cohorts, which tend to exclude more patients. Mortality (19%) in our cohort
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42 was higher than reported in some studies (e.g. Lim et al [2]). This is likely to be due
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44 to the higher proportion of patients who were over 65 years old (69% versus 58%),
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46 had a CURB-65 score of 3 or more (38% versus 29%), and had cardiovascular disease
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48 (32% versus 18%). The latter is consistent with the epidemiology of cardiovascular
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50 disease in Scotland [164]. The age specific and overall mortality reported in this study
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52 is similar to that reported by Trotter et al in a recent large UK epidemiological study
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[4]. In contrast, the proportion of patients admitted to ITU was relatively low, which is likely to reflect clinical practice in the UK and the older age of this cohort. Our results, and the approach adopted in this study, therefore require prospective validation in a separate cohort of patients

In summary, the application of additional risk factors in a two-step approach can improve the stratification of mortality by CURB-65. Physicians should be cautious about managing patients with CAP as outpatients if they have a CURB-65 score of 1 (or more) and have at least one of three additional risk factors identified in this study.

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9 **Transparency declarations**

10 DR has no conflict of interests. DN has served on Advisory Boards for Janssen Cilag
11 (UK Anti-Infectives), Wyeth (UK tigecycline), Novartis (UK daptomycin), Optimer
12 (Global, Optima-80) and received honoraria for speaking from Novartis, Johnson &
13 Johnson, Pfizer and Wyeth. PD has served on Advisory Boards for Johnson and
14 Johnson (Global Anti-infectives) and Wyeth (UK tigecycline), received honoraria for
15 speaking from Johnson & Johnson, Optimer, Pfizer, Wyeth and received research
16 funding from Boehringer Ingelheim, Glaxo Smith Kline and Pfizer. GB has received
17 support to attend conferences/meetings from Sanofi-Aventis, Gilead, Pfizer, Chiron
18 and Janssen Cilag, received honoraria for speaking/DVD development from Sanofi-
19 Aventis, and served on an advisory board for Wyeth (UK tigecycline).
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31 **Contributors:** DR analysed and interpreted the data, and wrote the 1st draft of the
32 manuscript. PD and DN were involved in developing the initial idea, interpreting the
33 data, and edited the 2nd draft of the manuscript. GB had the initial study idea,
34 collected and analysed the data, and edited the 1st draft of the manuscript. GB is the
35 guarantor and had full access to all of the data in the study and takes responsibility for
36 the integrity of the data and the accuracy of the data analysis.
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43 **Funding:** The original quality improvement project was funded by NHS Education
44 Scotland and The Chief Scientist Office, Scotland.
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47 **Ethical approval:** Collection of data was approved by both Tayside University
48 Hospitals NHS Trust's medical ethics committee and Caldicot guardian
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Table 1 Demographic and clinical characteristics of non-severe (CURB-65 = 0 to 2) CAP patients

Demographic and clinical variables	Total cohort	Excluded patients	CURB-65 = 0 to 2 patients			χ^2 or Fisher's exact test P value
			Total	Mortality in those with the variables (%)	Mortality in those without the variable (%)	
Number	428	75	266	-	-	-
Male sex	201 (47%)	34 (45%)	138 (52%)	14 (10%)	9 (7%)	NS
Age >65 years	296 (69%)	61 (81%)	140	19/140 (14%)	4/126 (3%)	0.003
Living alone	154/426 (36%)	30 (40%)	81 (30%)	11/81 (14%)	12/185 (6.5%)	0.05
Living in own home	358 (84%)	52 (69%)	240 (90%)	17/240 (7%)	6/26 (23%)	0.015 ^F
Antibiotics given before admission	150/364 (41%)	25/65 (38%)	95/244 (39%)	9/95 (9.5%)	11/149 (7%)	0.6
Oral route not available	92/420 (22%)	15/74 (20%)	38/262 (14.5%)	6/38 (16%)	17/224 (8%)	0.1 ^F
CRP >50	293 (69%)	48/69 (70%)	168/232 (72%)	12/168 (7%)	8/64 (12.5%)	NS
SaO ₂ <92%	141 (33%)	19/74 (26%)	64/262 (24%)	5/64 (8%)	18/198 (9%)	NS
Chronic disease						
Chronic disease	277 (65%)	56 (75%)	162 (61%)	15/162 (9%)	8/104 (8%)	NS
Heart disease	134/426 (31%)	27/74 (36%)	69/264 (26%)	8/69 (12%)	15/195 (8%)	NS
Lung disease	147/427 (34%)	26 (35%)	97/265 (37%)	6/97 (6%)	17/168 (10%)	NS
Diabetes	51 (12%)	12 (16%)	23/266 (9%)	1/23 (4%)	22/243 (9%)	NS

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Bilateral/multi-lobar CXR	69/423 (16%)	7 (9%)	38/265 (14%)	8/38 (21%)	14/227 (6%)	0.006 ^F
CURB-65 score						
0	61(14%)	-	61 (23%)	0 (0%)	-	-
1	83 (19%)	-	83 (31%)	3 (13%)	-	-
2	122 (29%)	-	121 (46%)	20 (87%)	-	-
New confusion	131 (31%)	29/68 (43%)	21 (8%)	2/21 (9.5%)	21/245 (8.5%)	NS
Blood urea >7 mmol/L	246 (58%)	48 (64%)	96 (36%)	18/96 (19%)	5/170 (3%)	<0.001
White cell count <4 >12 x 10 ⁹ /L	233 (54%)	39 (52%)	143 (54%)	12/143 (8%)	11/123 (9%)	NS
Temp. < 36 ⁰ C	40 (9%)	13/75 (17%)	20 (7.5%)	5/20 (25%)	18/246 (7%)	0.02 ^F
Respiratory rate >30/min.	92 (22%)	5/26 (19%)	23/266 (12%)	1/33 (3%)	22/233 (9%)	NS
Pulse >125/min.	43 (10%)	5 (7%)		1/26 (4%)	22/240 (9%)	NS
sBP <90mmHg	25 (6%)	6 (8%)	8 (3.01%)	1/8 (12.5%)	22/258 (8.5%)	NS
dBP ≤60mmHg	104 (24%)	22 (29%)	37 (13.91%)	3/37 (8%)	20/229 (9%)	NS
ITU admission	14 (3%)	0 (0%)	8/264 (3%)	2/8 (25%)	21/256 (8%)	NS
30-day mortality	79 (19%)	11 (15%)	23 (9%)	-	-	-

Key: NS = not significant; F = Fisher's exact test; CRP = C-reactive protein; Temp. = temperature; BP = blood pressure; ITU = intensive therapy unit

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Table 2 Stratification of mortality by variations of CURB-65/CRB-65 and associated performance characteristics

CURB-65 score	Mortality Number (%) <i>(N = 422*)</i>	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
CURB-65					
0	0/61 (0%)	100	0	18	NC
1	3/83 (4%)	100	17	21.5	100
2	19/121 (16%)	96	41	26	98
3	26/103 (25%)	71 (59.5 to 81)	70 (65 to 75)	34 (27 to 43)	92 (88 to 95)
4	26/48 (54%)	37	92	52	87
5	2/6 (33%)	3	99	33	82
CRB-65					
0	0/74 (0%)	100	0	18	NC
1	20/152 (13%)	100	21	22	100
2	27/131 (21%)	74 (62 to 83)	59.5 (54 to 65)	28.5 (22 to 35)	91 (87 to 94.5)
3	27/59 (46%)	38	89.5	45	87
4	2/6 (33%)	3	99	33	82
CURB-65 + CXR + Social status + Temperature					
0	0/45 (0%)	100	0	18	NC
1	0/65 (0%)	100	13	20	100
2	2/72 (3%)	100	32	24	100
3	22/92 (24%)	97 (91 to 100)	52 (47 to 57)	31 (25 to 37)	99 (96 to 100)
4	23/83 (28%)	68	72	35	91
5	20/50 (40%)	38	90	45	87
6	8/14 (57%)	12	98	60	83
7	1/1 (100%)	1	100	100	82
CU²RB-65²					
0	0/61 (0%)	100	0	18	NC
1	0/31 (0%)	100	18	21	100
2	3/60 (5%)	100	27	23	100
3	6/44 (14%)	96 (89 to 99)	43 (38 to 48.5)	27 (22 to 33)	98 (94 to 100)
4	16/84 (19%)	88	54	30	95
5	23/89 (26%)	67	74	40	94

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6	26/47 (55%)	37	93	53	87
7	2/6 (33%)	3	99	33	82
CRB-65 + Social status + Temperature					
0	0/59 (0%)	100	0	18	NC
1	6/96 (6%)	100	17	21	100
2	22/116 (19%)	92 (84 to 97)	43 (38 to 48.5)	26 (21 to 32)	96 (92 to 98.5)
3	25/94 (27%)	63	70	32	90
4	18/47 (38%)	30	90	40	85
5	5/10 (50%)	7	99	50	83
6	0/0 (0%)	-	-	-	-

Key: CI = confidence interval

* 6 patients were excluded from the overall cohort of 428 because one of the additional (new) criteria were missing

Table 3 Area under the receiver operating curves for variations of CURB-65/CRB-65

Score	AUROC	95% CI	P-value
CURB-65	0.78	0.73 to 0.83	<0.001
CRB-65	0.73	0.67 to 0.79	<0.001
CURB-65 + CXR + Social status + Temp.	0.80	0.75 to 0.85	<0.001
CU²RB-65²	0.79	0.74 to 0.84	<0.001
CRB-65 + Social status + Temp.	0.74	0.68 to 0.79	<0.001

Key: AUROC = area under the receiver operating curve; CI = confidence interval; Temp. = temperature

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Table 4 Mortality stratified by CURB-65 score and additional risk factors

Additional risk factors	0	1	2	3	χ^2 for trend (P value)	≥ 1	Total
CURB65 score							
0	0/45 (0%)	0/14 (0%)	0/2 (0%)	-	NS	0/16 (0%)	0/61 (0%)
1	0/51 (0%)	1/27 (4%)	2/5 (40%)	-	12.62 P<0.001	3/32 (9%)	3/83 (4%)
2	1/43 (2%)	14/60 (23%)	4/18 (22%)	-	6.49 P=0.01	18/78 (23%)	19/121 (16%)
≥ 3	13/42 (31%)	26/81 (32%)	14/32 (44%)	1/2 (50%)	NS	41/115 (36%)	54/157 (34%)

Key: NS = not significant

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Table 5 Two-step mortality stratification using additional risk factors versus CURB-65 used alone

CURB-65 score followed by additional risk factors								
CURB65 score	0		1		2		≥3	
Additional factors score	None	≥1	None	≥1	None	≥1	None	≥1
Mortality by CURB-65 and additional factors	0/45 (0%)	0/16 (0%)	0/51 (0%)	3/32 (9%)	1/43 (2%)	18/78 (23%)	13/42 (31%)	41/115 (36%)
ITU by CURB-65 and additional factors	1/61 (1.6%)		1/51 (2%)	1/32 (3%)	2/43 (5%)	3/78 (4%)	6/157 (4%)	
Proposed new management strategy	Home/outpatient			Admit (non-severe)		Admit (severe)		
Number	112 (26.5%)			75 (18%)		235 (56%)		
30-day mortality	0/112 (0%)			4/75 (5%)		72/235 (31%)		
ITU admission	2/112 (2%)			3/75 (4%)		9/235 (4%)		
CURB-65 used alone								
CURB-65 score	0		1		2		≥3	
Mortality by CURB-65 only	0/61 (0%)		3/83 (4%)		19/121 (16%)		54/157 (34%)	
ITU by CURB-65 only	1/61 (1.6%)		2/83 (2.4%)		5/121 (4%)		6/157 (4%)	
Management strategy by BTS guidelines	Home/outpatient				Admit (non-severe)		Admit (severe)	
Number	144 (42%)				121 (29%)		157 (37%)	
30-day mortality	3/144 (2%)				19/121 (16%)		54/157 (34%)	
ITU admission	3/144 (2%)				5/121 (4%)		6/157 (4%)	

Key: ITU = intensive therapy unit