Predicting mortality with severity assessment tools in out-patients with community-acquired pneumonia

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Summary

Introduction: In community-acquired pneumonia, severity assessment tools, such as CRB65, CURB65 and Pneumonia Severity Index (PSI), have been promoted to increase the proportion of patients treated in the community. The prognostic accuracy of these scores is established in hospitalized patients, but less is known about their use in out-patients. We aimed to study the accuracy of these severity tools to predict mortality in patients managed as out-patients.

Methods: We performed a systematic review and meta-analysis according to MOOSE guidelines. From 1980 to 2010, we identified 13 studies reporting prognostic information for the CRB65, CURB65 and PSI severity scores in out-patients (either exclusively managed in the community or discharged from an emergency department <24 h after admission). Two reviewers independently collected data and assessed study quality. Performance characteristics across the studies were pooled using a random-effects model. Relationships between sensitivity and specificity were plotted using summary receiver operator characteristic curves (sROC).

Results: Out-patient mortality ranged from 0% to 3.5%. Four studies were identified for CRB65, 2 for CURB65 and 10 for PSI. Mortality was low for out-patients in the low-risk CRB65 classes [CRB65 0 or 1: mortality occurred in 3 of 1494 patients (0.2%)] but higher in CRB65 Groups 2–4 [mortality 13 of 154 patients (8.4%)]. Similarly, mortality was low in PSI Classes I–III [mortality 8 of 3655 patients (0.2%)] managed as out-patients but higher in Classes IV and V [mortality 32 of 317 patients (10.1%)]. CRB65 showed pooled sensitivity of 81% (54–96%), pooled specificity of 91% (90–93%) and the area under the sROC was 0.91 [standard error (SE) 0.05]. For PSI, pooled sensitivity was 92% (64–100%), pooled specificity was 90% (89–91%) and area under the sROC was 0.92 (SE 0.03). There were insufficient studies to analyse CURB65.

Conclusion: The limited data available suggest that CRB65 and PSI can identify groups of patients at low risk of mortality that can be safely managed in the community.

Introduction

The initial decision of whether a patient requires hospitalization for community-acquired pneumonia (CAP) or can be managed as an out-patient can be difficult. Evidence suggests that physicians both over and underestimate the risk of complications in patients with CAP, leading to inappropriate hospitalization for low-risk patients. In the UK, the average cost for managing pneumonia in the community was estimated at £100 per episode compared with £1700–5100 when the patient requires admission to hospital, with hospitalization accounting for...
87% of the total annual cost of managing CAP. In the USA based on figures from 1990s, the mean (±SD) treatment cost for an in-patient episode of CAP was $10,227 ± 15,342, compared with $466 ± 1038 for an out-patient episode of CAP. The authors also estimated the annual cost of treating CAP in the USA at $12.2 billion.

Aside from the financial benefits of out-patient care, many patients prefer out-patient management and data suggest that satisfaction with care is at least as good in patients managed in the community compared with hospitalized low-risk patients.

This has led to the development of severity assessment tools such as the Pneumonia severity index and CURB65/CRB65. These scores are designed to promote outpatient management by providing an objective measure of the risk of 30-day mortality based on a number of validated predictors of outcome.

Although these scores have established accuracy for prediction of mortality in hospitalized patients, most cases of lower respiratory tract infections (LRTI) or CAP internationally are managed in primary care, usually by general practitioners (GPs). Increasing the number of patients managed as outpatients using validated severity criteria has the potential to reduce hospital costs, increase patient satisfaction and reduce hospital-related complications such as MRSA and Clostridium difficile infections. Two meta-analyses have recently reviewed the use of severity criteria in hospitalized patients, finding PSI, CURB-65 and CRB-65 all predict 30-day mortality. A third study sought to study the CRB65 score alone in both hospitalized and non-hospitalized groups and found CRB-65 over-predicts the probability of 30-day mortality in community settings.

The role of severity criteria in outpatients has not been established and no meta-analysis comparing the predictive value of mortality of severity scores in outpatient populations has previously been performed. This study aimed to systematically review the published literature in relation to these pneumonia scoring systems for predicting mortality in patients managed in outpatient settings.

**Methods**

The present study was a systematic review and meta-analysis conducted according to MOOSE (meta-analysis of observational studies in epidemiology) guidelines.

**Search criteria**

A search was conducted of Medline and EMBASE databases for articles on major MeSH terms ‘Severity of Illness Index’ and ‘Pneumonia’ between 1981 and 2010. We also performed separate Pubmed searches for text terms ‘CURB65’, ‘CRB65’, ‘CURB-65’, ‘CRB-65’, ‘Pneumonia Severity Index’, ‘severity scores’, ‘prognosis’, ‘mortality’, ‘predict’ and text terms ‘pneumonia’, ‘community-acquired pneumonia’ and ‘CAP’. We limited articles to those published in the English language. Full articles of all potentially appropriate peer-reviewed abstracts were reviewed. The search strategy omitted ‘outpatient’ as a text term as studies containing out-patient data are often combined with in-patient data. The search strategy was supplemented by reviewing of reference lists, bibliographies and the investigator files.

**Data extraction**

Two investigators independently assessed articles to determine study eligibility. Non-relevant studies were excluded based on title and abstract review only. Potentially relevant studies were reviewed by at least two researchers who carried out data extraction and quality assessment in a blinded fashion. Any disagreement between abstractors was resolved independently by a third abstractor.

**Study inclusion and study quality assessment**

All studies were considered eligible if they fulfilled the following criteria: original publications; data on at least 20 out-patients contained in manuscript; inclusion of unselected patients with community acquired pneumonia; exclusion of non-CAP diagnoses, e.g. non-pneumonic exacerbation of COPD; calculation of severity score based on admission data.

There are no widely accepted quality criteria for observational studies. In order to assess quality, each study was assessed by the following criteria that represent important sources of bias: (i) inclusion: patients recruited consecutively and in an unbiased fashion according to a standard definition of CAP; (ii) follow-up: were the patients appropriately followed up to determine survival; (iii) severity score measurement: severity score calculated according to standard definition and calculated at presentation; and (iv) potential confounding: potential confounders considered and accounted for. Each paper was also given an overall assessment taking into account each category. Two reviewers independently assessed quality and the agreement between the two reviewers was measured using the κ-statistic.
Definition of out-patient care

For the purposes of this analysis, out-patient care was defined as patients exclusively managed in primary care or patients discharged from the emergency department (within 24 h). All other patients not meeting this definition were regarded as hospitalized patients and were excluded from the analysis. Where definitions in included papers were unclear, authors were contacted to clarify this.

Primary outcome

The primary outcome for this study was 30-day mortality.

Statistical analysis

We compared outcomes between high- and low-risk out-patients, the incidence of each outcome in the mild to intermediate CAP and severe CAP groups were calculated and these odds ratios were weighted by the inverse of their variance and pooled across all studies using a Dersimonian/Laird random-effects model. For each severity score, pooled sensitivity and specificity are reported. A priori we specified that out-patient management should be considered safe if it was associated with a <1% mortality rate at 30 days. This is a recognized cut-off in the literature based on the findings of the original PORT study that defined the cut-offs points for the pneumonia severity index. PSI groups I–III are considered suitable for out-patient treatment, where mortality rates were 0, 0.6 and 0.9%, respectively.6 Similarly, for CRB65, group 0 are considered suitable for out-patient treatment and had a 0.9% mortality rate in the original derivation study.7 We therefore present the observed: predicted risk ratios for each study and the pooled risk ratio assuming a predicted risk of mortality of 1%. A risk ratio <1 indicates a <1% mortality for low-risk patients. Statistical heterogeneity was assessed using Cochrans Q-(chi-square) test and Higgins I^2 tests. For the Cochrans Q-test, P<0.1 was considered to represent significant heterogeneity. For the Higgins test, I^2 <25% indicates low heterogeneity, 25–50% moderate and >50% severe heterogeneity.

A summary receiver operator characteristic curve (sROC) was constructed describing the relationship between sensitivity and specificity across the included studies. For each score, the area under the sROC curve (AUC) is reported.

Results

Studies included

A total of 858 abstracts were reviewed and 60 papers were potentially eligible and were reviewed in detail (Figure 1). The majority of studies reviewed were not included as they only contained data on in-patients, did not report data for any of the severity scores under investigation or did not report mortality.

Fifteen studies6,8,14–25 were identified meeting the criteria to be assessed with data from 13 studies as a further 2 were excluded as they had insufficient numbers of out-patients or data not displayed.24,25 Thirteen studies were included in the final meta-analysis (details in Table 1). Nine were prospective cohort studies,6,8,14,15,17,19–22 one was retrospective case review16 and three were data from randomized controlled trials.18,22,23 Only one paper included data exclusively collected in out-patients,8 the other studies reported data on patients initially assessed in hospital and subsequently managed in the community.

For assessment of the Pneumonia Severity Index (PSI), 10 studies were identified6,14,16,18–23 for CBR65 criteria was assessed in 48,15,17,19 and CURB65 data was only present in 2 papers17,19 so there was insufficient data to perform an meta-analysis for CURB65. All studies for CBR65 and PSI used 30 (or 28 days) mortality as outcome measures and reported mortality rates ranged from 0 to 3.5%.

Quality assessment

Two reviewers independently assessed quality, for: (i) inclusion, six studies were rated as good, five as moderate and two as suboptimal; (ii) follow-up, four studies rated as good, one as moderate, three as suboptimal and five studies were unclear;
Table 1  Details of 13 studies meeting the inclusion criteria

<table>
<thead>
<tr>
<th>References</th>
<th>Study population</th>
<th>Score(s) assessed</th>
<th>Setting</th>
<th>N</th>
<th>Age (mean)</th>
<th>Out-patient mortality rate (%)</th>
<th>Study objective/conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlas et al.</td>
<td>Prospective enrolment with retrospective case control</td>
<td>PSI (only Classes I–III)</td>
<td>Boston, USA, 1996–97</td>
<td>94</td>
<td>NR</td>
<td>0</td>
<td>Assessment of risk-based algorithm to manage low-risk patients as out-patients</td>
</tr>
<tr>
<td>Bont et al.</td>
<td>Prospective elderly (&gt;65 years) patients with CAP in the community</td>
<td>CRB65</td>
<td>Primary care, The Netherlands, 2005–06</td>
<td>314</td>
<td>77.3</td>
<td>3.5</td>
<td>CRB65 identifies low-risk patients, out-patient outcomes should focus on less severe criteria</td>
</tr>
<tr>
<td>Bauer et al.</td>
<td>Prospective cohort study in both out-patients and in-patients</td>
<td>CRB65</td>
<td>10 centres Germany, 2003–04</td>
<td>482</td>
<td>53 ± 17</td>
<td>0.6</td>
<td>Recommend use of CBR65 in out-patients</td>
</tr>
<tr>
<td>Campbell et al.</td>
<td>Retrospective case based review</td>
<td>PSI (Classes I and II combined)</td>
<td>Nova Scotia, Canada, 1999–2001</td>
<td>867</td>
<td>NR</td>
<td>2.5</td>
<td>Assessing adherence to clinical practice guideline</td>
</tr>
<tr>
<td>Capelastegui et al.</td>
<td>Prospective cohort study both in-patients and out-patients</td>
<td>CURB65, CRB65</td>
<td>Galdakao Hospital, Basque region, Spain, 2000–04</td>
<td>676</td>
<td>46.8 ± 17.9</td>
<td>0.1</td>
<td>Validation of severity scores recommending CBR65 in out-patients</td>
</tr>
<tr>
<td>Carratala et al.</td>
<td>Randomized trial to compare treatment settings</td>
<td>PSI (only risk Classes II and III)</td>
<td>two centres, Barcelona, Spain, 2000–01</td>
<td>110</td>
<td>65.5 ± 11.8</td>
<td>0.9</td>
<td>Identification of cohort that can safely be managed as out-patients</td>
</tr>
<tr>
<td>Chalmers et al.</td>
<td>Prospective cohort study</td>
<td>PSI, CURB 65, CRB65</td>
<td>two hospitals, Edinburgh, UK 2005–08</td>
<td>176</td>
<td>NR</td>
<td>2.3</td>
<td>Modification of the CURB65 score</td>
</tr>
<tr>
<td>Espana et al.</td>
<td>Prospective study</td>
<td>PSI</td>
<td>Single centre, Bizkaia, Spain, 2000–2001</td>
<td>221</td>
<td>NR</td>
<td>0.1</td>
<td>Causes of admission in low-risk PSI classes</td>
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</tbody>
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(continued)
<table>
<thead>
<tr>
<th>References</th>
<th>Study population</th>
<th>Score(s) assessed</th>
<th>Setting</th>
<th>N</th>
<th>Age (mean)</th>
<th>Out-patient mortality rate (%)</th>
<th>Study objective/conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine et al.</td>
<td>Prospective cohort study, validation arm includes in-patients and out-patients</td>
<td>PSI</td>
<td>five Hospitals, USA and Canada, 1991–94</td>
<td>944</td>
<td>NR</td>
<td>0.6</td>
<td>Validation of PSI</td>
</tr>
<tr>
<td>Ortega et al.</td>
<td>Prospective cohort study</td>
<td>PSI (Classes I and II)</td>
<td>Single centre, Barcelona, Spain, date not specified</td>
<td>48</td>
<td>NR</td>
<td>0</td>
<td>PSI to be used alongside clinical criteria in decision for treatment setting</td>
</tr>
<tr>
<td>Renaud et al.</td>
<td>Randomized controlled trial, including in-patients and out-patients</td>
<td>PSI</td>
<td>16 Hospitals, France, 2002–03</td>
<td>164</td>
<td>NR</td>
<td>2.8 (28 day)</td>
<td>Randomized controlled trial using PSI to determine site of care</td>
</tr>
<tr>
<td>Renaud et al.</td>
<td>Prospective cohort study, including in-patients and out-patients</td>
<td>PSI</td>
<td>14 hospitals, Catalonia, Spain, 2003</td>
<td>287</td>
<td>NR</td>
<td>0.3 (28 day)</td>
<td>Validation of PSI in European population</td>
</tr>
<tr>
<td>Yealy et al.</td>
<td>Cluster randomized controlled trial, both in-patients and out patients</td>
<td>PSI (only Classes I–III)</td>
<td>Connecticut and Pennsylvania, USA, 2001</td>
<td>1061</td>
<td>NR</td>
<td>0.01</td>
<td>Implementation of treatment guidelines in CAP</td>
</tr>
</tbody>
</table>

*N refers to the number of patients in the out-patient categories in each study. Mortality reported at 30 days unless otherwise stated.  
aData from prospective enrolment cohort.
(iii) severity score, 11 studies rated as good and two as moderate; and (iv) potential confounding, five studies were rated as good, six as moderate and two as suboptimal. Overall six studies were rated as good, five as moderate and two as suboptimal. There was good agreement between the two reviewers (κ-statistic 0.75).

**Meta-analysis**

**CURB65**

Two studies were available with CURB65 criteria and consequently a meta-analysis was not feasible. Capelastegui et al. reported data in 676 out-patients and Chalmers et al. report data in 176. Each study had one death in the out-patient group and both with CURB65 ≥ 2.

**CRB65 as a predictor of 28–30 day mortality**

Four papers8,15,17,19 were identified with 1648 patients. Pooled data shows CRB65 = 0, 0% mortality (879 patients), CRB65 = 1, 0.5% mortality (615 patients), CRB65 = 2, 6.3% mortality (126 patients), CRB65 = 3, 13.2% mortality (28 patients) and no patient was CRB65 ≥ 4.

Using the recommended cut-off for hospital admission (CRB65 > 0) to define requirement for hospitalization, only three studies could be included, as the Bont et al. study only included patients aged >65 years. In this analysis, pooled sensitivity was 100% (48–100%), pooled specificity 65% (62–68%) with no significant heterogeneity. Further analysis was limited due to the low number of events.

Using CRB65 > 1 to define hospital admission, pooled sensitivity was 81% (54–96%) and pooled specificity was 91% (90–93%). Area under the sROC was 0.91 (SE 0.05). The pooled diagnostic odds ratio for a CRB65 score ≥ 2 was 16.47 (4.9–55.4) with no significant heterogeneity (Cochran Q 0.33, P = 0.8). These estimates were significantly limited by the low event rate. The sROC curve for 30-day mortality using CRB65 is shown (Figure 2).

Comparing the performance of CRB65 in patients with CRB65 0 to 1 (low-risk patients) to the preset 1% level of mortality, CRB65 was associated with a relative risk of 0.35 (0.10–1.16), P = 0.09 with no significant heterogeneity (χ² = 2.70, df = 3, P = 0.44, I² = 0%) (Figure 3).

**PSI**

Ten studies were identified for PSI6,14,16,18–23 with 3972 patients. Combining PSI I–III, mortality was 8 of 3655 patients (0.2%), whereas with PSI

Classes IV and V mortality was 32 in 317 patients (10.1%).

Comparing low-risk (PSI I–III patients) against high-risk (PSI IV/V) classifications, only six studies could be pooled (two studies14,21 reported no mortality and two18,23 only contained data for PSI low-risk groups). Pooled sensitivity was 92% (64–100%) and pooled specificity was 90% (89–91%). Negative likelihood ratio (NLR) was 0.21 (0.08–0.59) and area under the sROC was 0.92 (SE 0.03). The sROC curve for mortality for PSI is shown (Figure 2).

The risk of death in low-risk patients as classified by the PSI (PSI I–III) was compared to the preset 1% predicted level of mortality. PSI had a relative risk of 0.35 [0.17–0.72], P = 0.004 with no significant heterogeneity (χ² = 5.18, df = 8, P = 0.74, I² = 0%) (Figure 4).

**Discussion**

Out-patient management of community acquired pneumonia has the potential to reduce costs related to hospitalization, improve patient satisfaction and reduce complications related to hospitalization such as MRSA and *C. difficile* infections. The use of validated severity criteria has been proposed as a mechanism to increase the number of patients managed in the community. The results of this meta-analysis suggest that out-patient management of selected low-risk patients is safe, with a very low mortality rate observed for patients in low-risk CRB65 (0 or 1) and PSI groups (I–III) managed in
Currently guidelines suggest that patients with a CRB65 score of 1 should be managed with short hospitalization. Our results suggest that in selected patients, out-patient management of this group is associated with a low mortality rate. In contrast to the data in low-risk patients, patients with PSI score >3 and CRB65 score >1 had a relatively high mortality (10.1 and 8.4%, respectively) when managed in the community. It is possible that some of the mortality in this group represented patients in whom hospital admission was inappropriate. Marrie and Huang26 demonstrated that for selected patients in PSI Classes IV and V, out-patient management was safe and associated with low mortality. The available data, however, does not support out-patient management in these patient groups.

The CURB65 and PSI were originally derived and validated in hospitalized patients and GPs may not have access to areas such as pulmonary radiography or laboratory investigations in order to complete the scoring systems. To overcome this factor the CRB65 system has been advocated27 as these variables should be immediately available to the GP. Direct application of these scores from secondary to primary care at first seems reasonable. However, using a score with the main aim of predicting mortality may not be appropriate in primary care given low rates of death in this population. Another difficulty faced would be the ‘cut-off’ required to classify patients—a mild CAP in a 66-year-old patient will trigger a severity point but this may not be, on its own, sufficient for requiring hospital assessment. Conversely, patients with co-morbidities may indeed require hospital assessment with a CRB65 score of 0. Therefore these scores, as with all severity scoring systems, must be assessed in conjunction with physician judgement.

This meta-analysis demonstrates that there is a relatively little data in the literature on the use of scoring systems in out-patient managed community acquired pneumonia. The majority of the data presented here were derived from patients initially assessed in hospital and discharged within 24 h. This is a significant limitation of the analysis and further studies in exclusively out-patient populations are required.
From the data, we present we have shown both CRB65 and PSI are good at identifying low-risk patients, who are at a low risk of death, and therefore are confidently managed as out-patients. From the available data neither PSI nor CRB65 scores show superiority in this regard. As CRB65 is easier to calculate and does not rely on laboratory parameters, CRB65 may be more useful for primary care physicians. Only one study has been performed, using our inclusion criteria, exclusively in out-patients. Bont et al. also chose to study a population over the age of 65 years and found that age alone was not a requirement of hospital admission. They suggest patients in CRB65 2 could also be managed in the community (when age >65 years), but this would depend on local resources and ability to closely monitor patients at home. They also acknowledge that future studies assessing out-patients with respiratory infections should look at parameters other than mortality as outcome measures. Although more complex, a major advantage of the pneumonia severity index is that implementation of this score has been shown to safely increase the proportion of patients treated in the community. In a recent meta-analysis, we demonstrated that this was associated with no increase in readmissions, mortality or any adverse effect on patient satisfaction with care.

Limitations of this meta-analysis must be acknowledged. This study was limited by the relatively small number of studies especially for CRB65 and CURB65. In addition, as mentioned above, only one study exclusively including out-patients was identified. More studies in primary care are therefore needed. Although we identified high-mortality rates in moderate to high-risk patients managed in the community, a number of potential confounders must be considered; first, patient factors such as patient preference for out-patient care, despite medical advice may lead to more high-risk patients being managed as out-patients. Furthermore, on occasion, there may be a number of patients where CAP may be seen as a terminal event and therefore a decision is made against hospitalization given prognostic considerations. Therefore, some of the mortality observed in out-patients is likely to represent patients in whom hospitalization was deemed inappropriate. As well as patient considerations, the attending physician may not estimate the severity correctly leading to a higher proportion managed in the community or conversely the physician may deem it safe to manage a patient in the community despite the severity score. Future studies should also assess the importance of each of these factors in management of patients with CAP in the community and should also include markers of failed out-patient management, such as subsequent hospitalization.

In conclusion, patients in the low-risk CRB65 and PSI classes are at low risk of death when managed as out-patients but further studies are needed in out-patient cohorts.

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A.R.A. and J.D.C. conceived the study design. A.R.A., J.D.C. and A.H. reviewed the literature, extracted the data, analysed the data and drafted the manuscript. All authors approved the submitted manuscript. A.R.A. acts as the guarantor of the paper.

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References


