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Predictive accuracy of the pneumonia severity index vs CRB-65 for time to clinical stability: Results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study

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Summary
Background: The Pneumonia Severity Index (PSI) and CRB-65 are scores used to predict mortality in patients with community-acquired pneumonia (CAP). It is unknown how well either score predicts time to clinical stability in hospitalized patients with CAP. Thus, it is also not known which score predicts time to clinical stability better.
Methods: A secondary analysis of 3087 patients from the Community-Acquired Pneumonia Organization (CAPO) database was performed. Time-dependent receiver-operator characteristic (ROC) curves for time to clinical stability were calculated for the PSI and CRB-65 scores at day seven of hospitalization. Secondary outcomes were to assess the relationship of the PSI and CRB-65 to in-hospital mortality and length of stay (LOS). ROC curves for LOS and mortality were calculated.
Results: The area under the ROC curve (AUC) for time to clinical stability by day seven was 0.638 (95% CI 0.613, 0.660) when using the PSI, and 0.647 (95% CI 0.619, 0.670) while using

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the CRB-65. The difference in AUC values was not statistically significant (95% CI for difference of −0.03 to 0.01). However, the difference in the AUC values for discharge within 14 days (0.651 for PSI vs 0.63 for CRB-65, 95% CI for difference 0.001−0.049), and 28-day in-hospital mortality (0.738 for PSI vs 0.69 for CRB-65, 95% CI for difference 0.02−0.082) were both statistically significant.

Conclusions: This study demonstrates a moderate ability of both the PSI and CRB-65 scores to predict time to clinical stability, and found that the predictive accuracy of the PSI was equivalent to that of the CRB-65 for this outcome.

Introduction

Over a million patients are hospitalized each year for community-acquired pneumonia (CAP) in the United States.[1] After decades of research and patient care, pneumonia has remained one of the top ten causes of death (currently eighth) in the United States.[2] Because of the diversity of care among physicians caring for patients with CAP, and the high rate of mortality among patients with CAP, there is a need for an accurate predictive tool to make appropriate management clear to physicians.[3,4] The widely endorsed pneumonia severity index (PSI) was originally described in 1997, followed by the British Thoracic Society score; CURB in 2001 and CRB-65 in 2004.[5,6] A significant relationship between each score and mortality has been verified.[7−10] Which score is the most useful has not been settled.

Evaluating a different outcome than mortality may be more useful to determine the better score as the US Food and Drug Administration designated time to clinical stability to be a relevant outcome to study CAP.[11] However, only two studies, to our knowledge, address how well the PSI predicts time to clinical stability,[12,13] and no study evaluates how well the CRB-65 predicts time to clinical stability. Thus no study compares the predictive ability of the two scores.[14,15]

If one score was known to have a higher predictive accuracy for time to clinical stability, then it would serve as evidence for clinicians to use that particular score to help guide decisions about switch therapy from intravenous to oral antimicrobial therapy, and decisions about hospital discharge. Researchers could compare times to clinical stability in patients receiving different antibiotic regimens to determine which one is better. On the other hand, if the two scores were known to have the same predictive accuracy for time to clinical stability, then it would provide evidence for the current Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines for CAP, which recommend using either score.

In order to allow a comparison of populations with CAP, and because the PSI and the CRB-65 scores have widespread adoption, knowing how well each score predicts short term outcomes based on patient characteristics at the time of hospitalization is needed. The present study sought to define and compare how well the PSI and the CRB-65 predicts time to clinical stability in hospitalized patients with CAP. Secondary outcomes were to assess the relationship of the PSI and CRB-65 to mortality and length of stay (LOS).

Materials and methods

Study design and population

This was an international, retrospective, observational study in which a secondary analysis was performed of the Community-Acquired Pneumonia Organization (CAPO) database including hospitalized patients ≥18 years of age. Data from June 10, 2001 until November 10, 2006 were collected from 41 hospitals in 12 countries (see appendix). The process of how the database was assembled and used was described previously.[16] Local institution review board (IRB) permission was requested, and consent was waived because this study was retrospective and observational. In each participating center primary investigators selected one or more patients from a list of hospitalized patients with a diagnosis of CAP. Severity of disease data was collected, as well as, patient demographics, culture results and appropriateness of antimicrobial therapy for patients in whom a pathogen was identified.

Study definitions

CAP was defined as a new pulmonary infiltrate (within 24 h of admission), and associated with at least one of the following factors: a new or increased cough, an abnormal temperature (<35.8 °C or >37.8 °C), or an abnormal leukocyte count (leukocytosis, leucopenia or the absence of immature neutrophils). Pneumonia was considered as community-acquired if a patient had no history of hospitalization during the two weeks prior to admission.

The PSI and CRB-65 were calculated for each patient as described previously, except confusion was determined by noting pertinent documentation in the medical record regarding new disorientation to person, place or time rather than by knowing the Abbreviated Mental Test Score.[5,17] There are five possible rankings for each pneumonia severity score (highest is most severe). Possible PSI risk classes range from I to V, and possible CRB-65 scores range from zero to four.

Time to clinical stability was defined using the ATS criteria for switch therapy from intravenous to oral antibiotic therapy: 1) improvement in cough and shortness of breath; 2) afebrile status for ≥8 h (<37.8 °C); 3) normalizing leukocyte count by at least 10% from the previous day; and 4) adequate oral intake.[18] The first day of hospitalization was day zero. Time to clinical stability was calculated in days as the day that the above four criteria were

filled simultaneously minus the admission date. Information on criteria for clinical stability was collected for the first seven days following diagnosis or until the four criteria were met. Length of stay was calculated as the discharge date minus the admission date. Mortality was assessed as 28-day in-hospital mortality.

Statistical methods

All patients who did not meet criteria for clinical stability within seven days were considered right censored at day seven. Patients remaining in the hospital longer than 30 days were right censored at 30 days. Cumulative incidence curves[19] were estimated for time to clinical stability, LOS and mortality, and were stratified by PSI risk class and CRB-65 severity scores. Proportional hazards regression models for competing risks were fit to the three outcomes using the PSI, PSI risk class and CRB-65 as predictors.[20] To properly account for patients who died in the hospital, in-hospital mortality was treated as a competing risk in the analysis. Also, hospital discharge was treated as a competing risk when analyzing in-hospital mortality. The χ^2 test statistics[21] were used for differences in the three outcomes between the levels of both severity scores. The predictive accuracy of the fitted hazard models with the severity scores were evaluated and compared based on time-dependent measures of sensitivity, specificity, ROC curves, and areas underneath the ROC curve (AUC).[22] Predictive accuracy was calculated for clinical stability by day seven, discharge by day 14, and in-hospital mortality within 28 days. The bootstrap percentile method was used to calculate 95% confidence intervals (CI) for the time-dependent AUC measures and difference between measures.[23] All analyses were done using R version 2.8.1, with package *survivalROC* used to calculate time-dependent ROC curves and AUC values, the *cmprsk* package used for calculation of cumulative incidence curves and proportional hazards models, and the *boot* package used for all bootstrap calculations.[22,24,25] An analysis of the predictive accuracy for time to clinical stability of each score was performed using two process of care factors: appropriate antibiotics according to the IDSA/ATS 2007 guidelines for CAP (adherent, under-treated, and over-treated), and time to first antibiotic dose (whether or not received within 8 h).

Results

A total of 3085 patients were evaluated for each of the three outcomes; time to clinical stability, LOS and mortality. The PSI categorized most patients in risk class IV (37%), while the CRB-65 score categorized most patients in score 1 or 2 (59%). A total of 708 patients (23%) had pathogens identified with sensitivities. *Streptococcus pneumoniae* was identified in 310 patients, *Haemophilus influenza* in 87 patients, *Moraxella catarrhalis* in 32 patients, atypical pathogens (*Legionella, Mycoplasma* and *Chlamydia*) in 60 patients, methicillin-sensitive *Staphylococcus aureus* in 52 patients, methicillin-resistant *S. aureus* in 55 patients, and *Pseudomonas aeruginosa* in 47 patients. Fifty-nine of those patients had a combination of pathogens identified. Demographics of hospitalized patients with community-acquired pneumonia are in Table 1 along with the frequency of all of the variables for each of the scores, including nursing home status. The most common antibiotic regimens were; a β-lactam plus a macrolide (1099), a fluoroquinolone alone (651) and a β-lactam alone (598). A total of 42% of patients had monotherapy and 46% had combination therapy (Table 2). Time to first antimicrobial was somewhat shorter in high risk patients (median 4 hours) compared to low risk patients (median 5 hours; $p < 0.001$).

Nearly all patients were unstable at hospital admission with 94% having a cough and/or shortness of air, 73% having a fever and 54% not tolerating oral intake. Table 3 gives the median time and inter-quartile range (IQR — 25th and 75th percentiles) until each criterion for clinical stability was met. The overall time to clinical stability was the day all four criteria were met. Table 4 depicts the median time to clinical stability, median LOS, and mortality for patients in each PSI risk class and CRB-65 score. Among the patient population, 2090 (68%) patients reached clinical stability within seven days. The relationship between the time to clinical stability and each of the severity scores (the PSI, the PSI risk class and the CRB-65) was statistically significant ($p < 0.001$).

Fig. 1 shows the cumulative incidence plots for patients reaching clinical stability stratified by both the PSI risk class and CRB-65 scores. Data over time for both scores shows that as the severity level increases, fewer patients reach clinical stability by day seven. The range of

Table 1 Demographics of hospitalized patients with community-acquired pneumonia.

	No. patients (%)
Total	$n = 3085$ (100)
Mean age (years)	65.8
PSI and CRB-65 variables	
Male	1909 (62)
Nursing home resident	178 (6)
Neoplastic disease	300 (10)
Liver disease	126 (4)
Congestive heart failure	627 (20.3)
Cerebrovascular disease	478 (16)
Renal disease	349 (11)
Altered mental status	399 (13)
Respiratory rate ≥30 breaths/min	675 (22)
Systolic blood pressure <90 mmHg	167 (5)
Temperature <35 °C or ≥40 °C	179 (6)
Heart rate ≥125 beats/min	391 (13)
pH <7.35	185 (6)
BUN >30 mg/dL	644 (21)
Sodium <130 mmol/L	195 (6)
Glucose >250 mg/dL	198 (6)
Hematocrit <30%	207 (7)
PaO_2 <60 mmHg	1161 (38)
Pleural effusion	554 (18)
Other comorbidities	
Chronic obstructive pulmonary disease	890 (29)
Diabetes mellitus	588 (19)

Table 2 Empiric antimicrobial regimens provided to patients with CAP.

Empiric treatment regimen	No. (%)
β-Lactam based regimens	1851 (60.0)
β-Lactam alone	598 (19.4)
β-Lactam + Macrolide	1099 (35.6)
β-Lactam + other[a] + Macrolide	154 (5.0)
Fluoroquinolone ± other[a]	744 (24.1)
β-Lactam + Fluoroquinolone ± other[a]	244 (7.9)
Macrolide ± other[a]	68 (2.2)
Combination regimens	
Fluoroquinolone + Macrolide ± β-Lactam ± other[a]	180 (5.8)

[a] "Other" antibiotics with the number of patients who used each: amikacin (1), aztreonam (1), chloramphenicol (2), clindamycin (62), doxycycline (3), gentamicin (13), metronidazole (28), pentamidine (2), primaquine (1), rifampin (2), trimethoprim/sulfamethoxazole (31), vancomycin (43).

Table 3 The time for each criterion to clinical stability, and the proportion of each criterion stable on the day of patient admission.

	Unstable on day 0[b]	Time to clinical stability[a]	
		Median	Inter-quartile
Criterion for Stability	No. (%)	(Days)	Range (days)
Improving symptoms[c]	2894 (94)	2	3–6
Temperature <37.8 °C	2257 (73)	1	0–3
Improving leukocytosis[d]	2459 (80)	2	1–4
Tolerating oral intake[e]	1661 (54)	1	0–3

[a] The time to clinical stability indicates the first day that all four criteria were stable.
[b] The day of admission was considered day zero.
[c] Cough and shortness of breath improving or back to baseline.
[d] Improving by at least 10% from previous day.
[e] Receiving an oral diet or oral medications.

proportions of patients who reached clinical stability by day seven was more varied with the CRB-65 (83–6% from score zero to four) than the PSI (87–46% from risk class I to V) (Table 4). The proportion of patients with CRB-65 scores of 3 or 4, however, was low (3.5%). Fig. 2 shows the ROC curves for patients reaching clinical stability within seven days. The AUC values for the PSI risk class (0.638) and CRB-65 (0.647) were nearly identical (Table 5), yielding a difference with a 95% CI that crosses zero (−0.03, 0.01). This indicates that they are equally effective at predicting which patients will reach clinical stability within seven days.

The severity scores were also predictive of the LOS and in-hospital mortality within 28 days. A total of 260 patients died. The mortality rate ranged from 4.9% to 87.5% for each score of the CRB-65, while it ranged from 2.6% to 26.5% for each PSI risk class (Table 4). For LOS, the median value ranged from 6 to greater than 30 for each CRB-65 score, and from 5 to 14 for each PSI risk class. While the range for both outcomes was greater for the CRB-65, the patients in each PSI risk class were more evenly distributed. The PSI risk class had higher overall predictive accuracy for both LOS (AUC of 0.651 vs 0.626), and mortality (AUC of 0.738 vs 0.69), relative to the CRB-65 score (Table 5). In both cases the difference was statistically significant, as the confidence intervals for the differences both excluded zero (0.001–0.049 for LOS, 0.020–0.082 for mortality) (Figs. 3 and 4).

Low risk and high risk patients received similarly overuse and underuse of antibiotic treatment when a causative pathogen was identified (47% in risk classes I–III, 53% in risk classes IV–V, $p = 0.33$). Addition of the two process of care

Table 4 Time to clinical stability (TCS), length of stay (LOS), and mortality among hospitalized patients with community-acquired pneumonia according to two severity scores; the pneumonia severity index (PSI) and the CRB-65.

CAP Severity score	Level	No. patients	No. deaths	Median and IQR TCS[a] (days)	Proportion clinically stable by day seven (95% CI)	Median and IQR LOS (days)	Mortality (95% CI)
PSI	I	306	8	3 (2, 5)	87 (83, 91)	5 (3, 9)	2.6 (1, 4)
	II	462	8	3 (2, 6)	82 (78, 86)	5 (3, 9)	1.7 (1, 3)
	III	677	25	4 (2, 7)	75 (72, 79)	7 (4, 11)	3.7 (2, 5)
	IV	1130	84	5 (3, >7)	69 (66, 71)	8 (5, 15)	7.4 (6, 9)
	V	510	135	>7 (4, >7)	46 (42, 51)	14 (7, >30)	26.5 (23, 30)
CRB-65	0	1152	56	3 (2, 6)	83 (81, 85)	6 (3, 10)	4.9 (4, 6)
	1	1298	82	4 (3, >7)	68 (66, 71)	7 (5, 14)	6.3 (5, 8)
	2	527	67	6 (3, >7)	56 (51, 60)	10 (6, 21)	12.7 (10, 16)
	3	92	41	>7 (6, >7)	28 (19, 38)	27 (10, >30)	44.6 (34, 54)
	4	16	14	>7 (>7, >7)	6 (0, 27)	>30 (>30, >30)	87.5 (53, 97)

CAP = Community-Acquired Pneumonia, CI = confidence interval, IQR = inter-quartile range (25th percentile and 75th percentile), LOS = Length of Stay, TCS = Time to Clinical Stability.
[a] TCS was not right censored at day seven for this table.

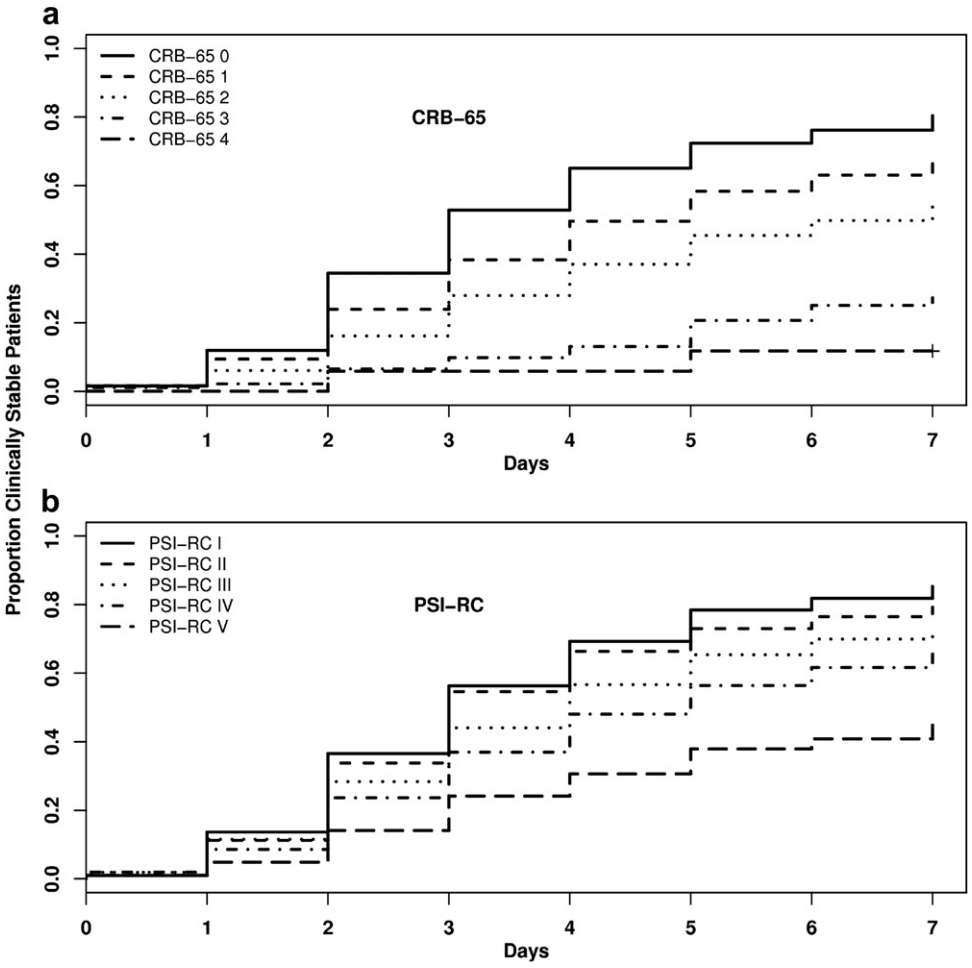

Figure 1 Cumulative incidence plots of hospitalized patients with community-acquired pneumonia reaching clinical stability for the pneumonia severity index (Fig. 1a) and CRB-65 (Fig. 1b).

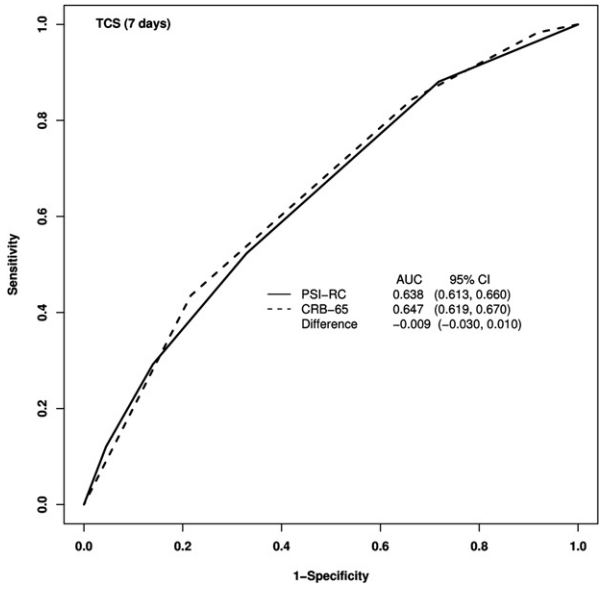

Figure 2 ROC curves for hospitalized patients with community-acquired pneumonia reaching clinical stability within 7 days for each severity score: pneumonia severity index and CRB-65.

variables increased the predictive accuracy (AUC value) of the PSI risk class for clinical stability within seven days from 0.638 to 0.658 (0.631, 0.682), and also increased the AUC value of the CRB-65 from 0.647 to 0.653 (0.630, 0.684). The additional process of care factors resulted in only marginal improvement without changing clinical significance for predicting time to clinical stability.

Discussion

The CRB-65 has been shown to have an association with mortality and, to a lesser degree, with LOS, but never with time to clinical stability until now. With that relationship established, the score's ability to predict time to clinical stability was compared to the PSI, and found to be equivalent. Neither score performed outstandingly well with AUC values of approximately 0.6 for predicting which patients would reach clinical stability within seven days. The present study more broadly validates the PSI and CRB-65 scores. It showed that two pneumonia specific mortality models used to quantify severity at the time of patient presentation are also both associated to an equivalent degree with a non-mortal downstream patient outcome; time to clinical stability.

Table 5 Area under the ROC curve (AUC) for outcomes among hospitalized patients with community-acquired pneumonia for the pneumonia severity index (PSI), PSI risk class and the CRB-65 score.

Outcome	PSI	PSI-RC	CRB-65	PSI-RC − CRB-65
	AUC 95% CI	AUC 95% CI	AUC 95% CI	Difference 95% CI
TCS within 7 days	0.652 (0.627, 0.674)	0.638 (0.613, 0.660)	0.647 (0.619, 0.670)	−0.009 (−0.030, 0.010)
Discharge within 14 days	0.659 (0.633, 0.685)	0.651 (0.625, 0.674)	0.626 (0.600, 0.655)	0.025 (0.001, 0.049)
In-hospital 28-day Mortality	0.756 (0.722, 0.784)	0.738 (0.712, 0.765)	0.69 (0.651, 0.720)	0.049 (0.020, 0.082)

CI, Confidence Interval; ROC, Receiver-Operating Characteristic curve; TCS, Time to Clinical Stability.

A longer LOS and higher mortality were associated with incrementally higher PSI and CRB-65 scores as they were in previous studies.[7–10,14,26,27] In the present study, as elsewhere,[26,28] the PSI was statistically better at predicting both LOS and mortality when compared to the CRB-65.

The present study revealed that the PSI and CRB-65, although adequate and generally comparable, are not ideal severity scores. Analyzing the two scores with additional information regarding processes of care improved their predictive accuracy by only a slight margin. The tools lack perfect sensitivity and specificity as summarized in their ROC curves. When plotting the ROC curves for LOS and mortality, an ideal score would rise vertically and then turn 90° to finish as a horizontal line. As seen in both Figs. 3 and 4, neither score approached the model curve form. The fair predictive accuracy of the scores for time to clinical stability was not unexpected because they were originally designed to predict mortality.

There are two implications of finding that the PSI and CRB-65 scores predict time to clinical stability equivalently: clinical practice and research. Physicians in the hospital emergency department may use either score to assist with a disposition decision. The place of patient care (*e.g.*, ICU, ward, home) is an important implication of correctly predicting risk at admission. In the clinical setting, ease of use may be emphasized as a quality so that such a tool (*i.e.*, CRB-65) may be readily adopted.[28] For this reason, it has been recommended that validation studies for severity scores be limited to data that is only available in real time.[27] The strength of a severity score, however, is clinical research, not clinical practice, so a tool may be practical without being necessarily easy to use. A tool that can stratify populations and normalize variables, such as antimicrobial regimens and co-morbid illnesses, most accurately is preferred. At present, the PSI and CRB-65 perform equivalently for this research purpose, which provides the basis for evidence-based clinical practice.

Regarding the context of other studies, certain longitudinal, observational studies of hospitalized patients with CAP comparatively had approximately 36% of patients with combination therapy (β-lactam plus either a macrolide or a fluoroquinolone) and 50% with monotherapy (β-lactam alone, or fluoroquinolone alone).[12,29] Using these definitions of mono and combination therapy, the present study had 21% patients with monotherapy and 36% with

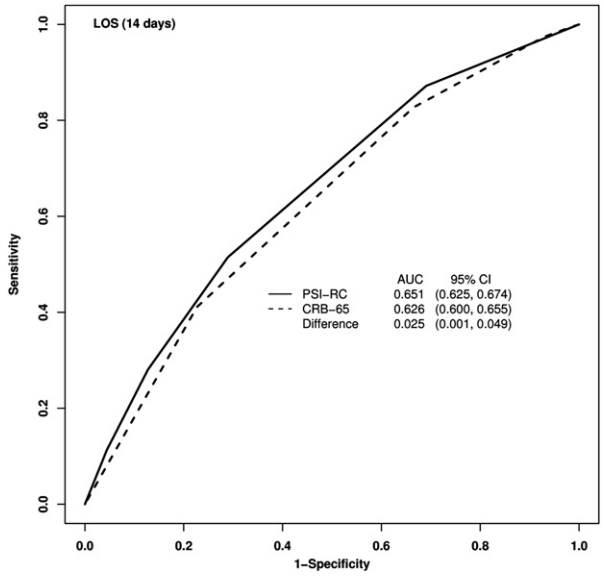

Figure 3 ROC curves for hospitalized patients with community-acquired pneumonia being discharged within 14 days for each severity score: pneumonia severity index and CRB-65.

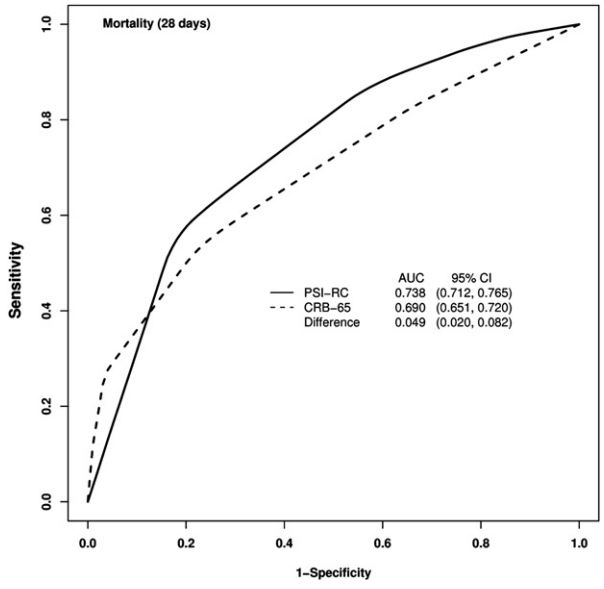

Figure 4 ROC curves for hospitalized patients with community-acquired pneumonia dying within 28 days for each severity score: pneumonia severity index and CRB-65.

combination therapy. Mortality rates in other patients with risk classes I, II and III were 0.4%, 0.7% and 2.8%, respectively.[5] Mortality rates in other patients with CRB-65 scores 0, 1 and 2 were 1.2%, 5.3% and 12.2%, respectively.[10]

The present study also had several limitations. Although the overall mortality (~10%) was similar to related studies, the mortality for patients with lower risk classes and CRB-65 scores was higher. One explanation is that the mortality of non-US patients with a low risk class was elevated (risk class I 4.6% vs 0.7%). There is also the possibility that low risk class patients had factors not captured by either score, such as hypoxia or sepsis.[30] When evaluating CRB-65, we did not use an objective mechanism to evaluate "confusion", such as the Abbreviated Mental Test Score, but rather subjective information documented in the medical record.[6] Another limitation was the sample selection. All of the patients were admitted through the Emergency Department, and thus more likely to be severely ill and aged. In contrast, the PSI and CRB-65 were created for a more ambulatory population to determine hospital admission status. So, the overall predictive accuracy of our study population, with a mean PSI risk class of 3.3, matched the lower predictive accuracy for mortality of the population found by Man et al.[27] with a mean PSI risk class of 3.5, and was in contrast to the higher accuracy of two other study populations with mean PSI risk classes of 2.7 each.[14,26] Although, a large number of patients were included, only 16 patients had a CRB-65 score of 4.

The present study was strengthened by several factors. The results reproduced the well-known relationships between the PSI and CRB-65 severity scores with LOS,[14,15,27] and with mortality.[7–10,26] Robust statistics developed for time-to-event data, not used in previous studies comparing pneumonia severity scores, were used in the present study.[22] The findings are more generalizable because the present study was international, large, and used lenient inclusion criteria which facilitated including patients with multiple medical comorbidities in the observational review.

Overall, the PSI and CRB-65 were each significantly associated with time to clinical stability. However, the predictive accuracy of each score for time to clinical stability leaves room for improvement, and research to create a new score or to modify existing scores is encouraged. This work augments what is already known about severity adjustment from the perspective of CAP research by providing evidence to use either the PSI or CRB-65 when analyzing time to clinical stability.

Conflict of interest statement

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Appendix

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