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Severity assessment of healthcare-associated pneumonia and pneumonia in immunosuppression

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ABSTRACT

The study compares the ability of the PSI (pneumonia severity index), CURB (confusion-uraemia-respiratory rate-blood pressure) scales, and the SCAP (severe community-acquired pneumonia) score to predict 30-day mortality in health-care associated pneumonia (HCAP) patients, and analyses differences in the demographics, aetiology and outcomes of community-acquired pneumonia (CAP), HCAP and pneumonia in immunocompromised patients.

Six hundred and twenty-nine consecutive patients admitted to a tertiary care University Hospital were prospectively categorised as having CAP (n=322) or HCAP (n=307) and the HCAP patients were further sub-divided into those who were immunocompromised (n=219) or non-immunocompromised (n=88).

The 30-day mortality rate was 9.0% in the CAP group and 24.1% in the HCAP group. In the HCAP group, the PSI and SCAP scores had similar prognostic power (areas under the curve [AUC] of respectively 0.68 and 0.67 respectively), and performed better than the CURB-65 score (AUC≤0.62). Among the non-immunocompromised HCAP patients, the PSI and CURB-65 score were more sensitive than the others at every threshold, whereas SCAP was more specific than both. In the immunocompromised group, the PSI was highly sensitive but poorly specific at all thresholds.

Our results suggest that prognostic tools should be designed for the subsets of HCAP patients.

Keywords

Community acquired pneumonia, immunocompromised patients, severity scores.

INTRODUCTION

In 2005, the term "healthcare-associated pneumonia (HCAP)" was introduced by the guidelines of the American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) concerning nosocomial pneumonia [1]. This new category was based on data showing that multidrug-resistant pathogens (MDR), frequent in nosocomial infections, could be found in subjects who had on-going interactions with the healthcare system despite their status as outpatients [2,3]; the guidelines recommended intensively treating HCAP patients with a combination of broad-spectrum antimicrobial drugs active against MDR pathogens [1].

The 2005 ATS/IDSA guidelines also considered the increasing number of elderly and/or severely disabled patients resident in nursing homes, and patients who were significantly immunocompromised because of the disease and/or therapy who were more likely to experience MDR infections.

Recent observational studies have shown that between 17% and 38% of patients hospitalised for pneumonia have HCAP [4-7]. Despite the latest advances in antimicrobial therapy and improved supportive care, HCAP is a major cause of morbidity, and leads to mortality rates of about 20%, which is twice as high as those observed in patients with community-acquired pneumonia (CAP) [3-9]. HCAP patients are generally older, have more comorbidities and disabilities, and more closely resemble patients with hospital-acquired (HAP) or ventilator-associated pneumonia (VAP) than CAP patients [3,8,10]. They therefore require adequate in-patient care and the appropriate allocation of resources to intensive care unit (ICU) in order to minimise morbidity and mortality.

A number of scoring systems have been developed to improve the clinical management of CAP patients and assure better resource allocation [11-13]. The two most widely studied are the 20-variable Pneumonia Severity Index (PSI) [14] and the 5-variable Confusion, Urea, Respiratory Rate, Blood pressure, age >65 years (CURB-65) score [15]. The 8-variable severe community-

acquired pneumonia (SCAP) score has recently been developed for patients with severe CAP [16,17], and seems to be accurate for ICU admission.

There are no specific rules for HCAP patients, and the performance of the CAP prognostic tools has only been evaluated in a few mainly retrospective studies [7,18-20]. Furthermore, most of the prospective studies have investigated cohorts of HCAP patients residing in nursing homes or extended-care facilities or previously hospitalized [9,12,21]. However, HCAP is a heterogeneous disease that may be more or less severe in different patient populations and in patients with different reasons for having contacted the healthcare system [22]. In particular, it is still debated whether pneumonia in immunocompromised patients can be considered a form of HCAP or is a different entity [23], and there are no published data concerning the use of severity scores in immunocompromised outpatients non-neutropenic, or HIV-negative.

The aims of this prospective study were to compare the performance of PSI, CURB, CURB-65, CRB-65 and SCAP scores in evaluating the severity of pneumonia and predicting 30-day mortality in hospitalised HCAP patients; to discuss any differences in the demographics, aetiology and outcomes of CAP and HCAP patients, and those belonging to the different HCAP subsets; and to explore the predictive power of the scoring systems in immunocompromised (IC) and non-immunocompromised (non-IC) HCAP patients.

METHODS

Study subjects

Between 2005 and 2010, 1066 consecutive adults with pneumonia aged ≥18 years were admitted to the Internal Medicine Department of Fondazione I.R.C.C.S. Ospedale Maggiore Policlinico, an acute-care tertiary university hospital in Milan, Italy. Of these, 629 were considered eligible for this prospective observational study. CAP and immunocompromise were defined on the basis of the criteria used in the Italian study of CAP management in Internal Medicine Departments, in which the authors have been involved since 2002 [24]. The patients were classified as having HCAP if

they had been hospitalised for 2 or more days during the 90 days preceding admission; if they resided in a skilled nursing facility or other institution; if they had been undergoing chronic dialysis; if they had received home or one-day hospital infusion therapy within the preceding 30 days; if they had received home or hospital wound care; or if a member of their family was affected by MDR pathogens [1].

Immunocompromise was defined as the presence of malignancy (active solid or hematological), immunological disorders or immunosuppressive therapy (e.g. cytotoxic chemotherapy, the use of >20 mg of prednisone/day, or any other immunosuppressant in the previous four weeks), severe malnutrition or cachexia.

The exclusion criteria were VAP; HAP; suspected or known aspiration pneumonia; active tuberculosis infection, or fungal or Cytomegalovirus pneumonia; and HIV positivity. Approval from local institutional review board and the patients' informed consent was obtained. In all cases, the decision to admit and the choice of therapy was entirely at the discretion of the attending physician.

Data collection and evaluation

A record was made of demographic variables, clinical findings upon presentation, comorbidities, pre-admission therapy, chest radiographic findings, laboratory parameters, microbiological studies, the need for invasive mechanical ventilation, complications, the length of hospital stay (LOS), in-hospital mortality; outcome at discharge and 30 days after admission. Thirty-day all-cause mortality was assessed by reviewing the medical records and/or by telephone interview. The patients in whom 30-day mortality could not be ascertained were excluded.

Clinical prognostic models

The patients were stratified into 30-day mortality risk groups on the basis of the PSI, the CURB, CURB-65, CRB-65 scoring systems, and the SCAP score, all of which were calculated using the set of prognostic indicators collected upon admission. The parameters for each prognostic tool were converted into dichotomous variables. In the case of the PSI, the patients were divided into low-,

intermediate- and high-risk classes [14]; in the case of CURB, CURB-65 and CRB-65, they were stratified on the basis of the number of criteria met and divided into low-, intermediate- and high-risk classes [15]. The SCAP score upon admission was calculated *a posteriori* using prospectively recorded variables, and the patients were divided into low-, intermediate- and high-risk classes.[16]

Statistical analysis

Descriptive statistics were computed resorting to the Statistical Package for Social Sciences, version 17 (SPSS, Chicago, IL). Differences in the baseline characteristics between HCAP and CAP patients and, within the HCAP group between IC and non-IC patients were tested with χ^2 test or t test, as appropriate. Stepwise logistic regression was used to select the set of variables associated with 30-day mortality and to compute adjusted estimates of mortality in the CAP, HCAP IC and HCAP non-IC patients. Differences in survival between these groups were tested with log-rank test. Survival was assessed using the Kaplan-Meier product limit estimates. The performance of each prognostic rule (in terms of sensitivity, specificity, and positive and negative likelihood ratio) was assessed for different cut-off points. Exact confidence limits of sensitivity and specificity were derived from binomial distribution. The ROC curves for each prognostic score system were traced and the area under each ROC curve (AUC) were computed. The pairwise differences between the AUC of the five prognostic score systems were tested with a Wald test. SAS PROC LOGISTIC (SAS/STAT User's guide version 9, SAS Institute Inc Cary; NC) was used to fit logistic regression models, to assess the performance of the prognostic score systems, and to carry out ROC curve analysis. Two-tailed significance threshold was set at $p<0.05$ for all tests, with the exception of the pairwise comparisons between AUC. In this case the threshold was set to $p<0.005$, in accordance with Bonferroni principle.

RESULTS

Patient characteristics and outcomes

Of the 629 enrolled patients, 307 (49%) were classified as having HCAP and 322 (51%) as having CAP. Table 1 shows the characteristics of the two groups.

A percentage of 34.2% HCAP and of 48.8% CAP were older than 80 years of age ($p<0.001$), and consequently, in HCAP group the prevalence of cerebrovascular diseases (21.5% vs 32.0%; $p=0.004$) and COPD (13.7% vs 25.8%) was lower. However, HCAP had more associated comorbidities than CAP (66.1% vs 51.9%; $p<0.001$) and were more often affected by malignancy (69.4% vs 4.0%; $p<0.001$). A greater rate of HCAP (45.1%) were given antibiotics prior of hospital admission compared to CAP (27.7%; $p<0.001$). On admission X-Ray, pneumonia with multilobar involvement was found more often in HCAP (26.1%) than in CAP patients (18.9%; $p=0.035$). Malignancy of 13 CAP and 8 non-IC HCAP patients was attributable to in situ cancer (skin, prostate, uterus).

The most of dichotomous laboratory variables included in PSI, in SCAP or in CURBs scores were able to discriminate HCAP from CAP patients.

Mortality was 24.1% in the HCAP group, and 9% in the CAP group. In-hospital mortality was similar to 30-day mortality.

The univariate odds for 30-day mortality was three times higher in the HCAP group (OR 3.21; 95% CI 2.020-5.096). After adjusting for PSI, the odds in the HCAP remained higher (OR=5.56; 95% CI 2.02-15.26). At stepwise logistic regression, mortality was found to be associated with age≥80 years, multilobar involvement, blood urea nitrogen≥11mmol/L, sodium <130mEq, pulse rate≥125bpm, cerebrovascular disease, malignancy, pleural effusion and (R-squared=16.1%; residual χ^2=13.1 (18 df), p=0.78). The odds ratio adjusted for these covariates (OR=4.65; 95% CI: 1.22-17.75) was still significant. The HCAP patients had a longer LOS (p=0.004).

Table 1 – Baseline characteristics

	HCAP patients (n = 307)		CAP patients (n = 322)		
	No.	**%**	**No.**	**%**	**p value**
Demographic data					
Age (years) (mean, [range])	72.8	[26-98]	75.0	[18-102]	0.073
Age <65 years	74	24.1	67	20.8	0.340
Age ≥80 years	105	34.2	157	48.8	<0.001
Male	187	60.9	164	50.9	0.013
Antibiotics before presentation	137	45.1	88	27.7	<0.001
Active alcohol abuse	9	4.4	13	5.4	0.666
Co-morbidities					
Cerebrovascular disease	66	21.5	103	32.0	0.004
Cardiovascular disease	135	44.0	151	46.9	0.472
Chronic renal failure	89	29.0	75	23.3	0.122
COPD	42	13.7	83	25.8	<0.001
Diabetes	51	16.6	56	17.4	0.832
Chronic liver disease	44	14.3	35	10.9	0.229
Malignancy	213	69.4	13[§]	4.0	<0.001
Two or more co-morbidities	203	66.1	167	51.9	<0.001
Clinical parameters upon admission					
Altered mental status	78	25.4	92	28.6	0.419
Congestive hearth failure	41	13.4	49	15.2	0.569
Acute renal failure	24	9.0	13	4.9	0.063
Temperature <35°C or ≥40°C	6	2.0	6	1.9	1.000
°Systolic blood pressure <90 mmHg	4	1.3	3	0.9	0.719
*Systolic blood pressure <90 mmHg or diastolic ≤60 mmHg	96	31.3	61	18.9	<0.001
Pulse rate ≥ 125 bpm	20	6.5	18	5.6	0.738
Respiratory rate ≥ 30/min	61	19.9	59	18.3	0.685
Laboratory findings upon admission					
*Blood urea nitrogen ≥7 mmol/L	190	61.9	165	51.2	0.008
°Blood urea nitrogen ≥11 mmol/L	96	31.3	69	21.4	0.006
Glucose ≥250 mg/dL	13	4.2	20	6.2	0.288
Sodium <130 mEq	26	8.5	11	3.4	0.010
Hematocrit <30%	88	28.7	10	3.1	<0.001
pO2 < 60 mmHg or SaO2 <90%	71	23.1	102	31.7	0.020
pH <7.35	5	1.6	18	5.6	0.010
WBC < 4000/μL	58	18.9	4	1.2	<0.001
pO2 < 54 mmHg or PaO2/FiO2 < 250	34	11.1	44	13.7	0.336
Radiographic findings upon admission					
Pleural effusion	84	27.4	109	33.9	0.084
Multilobar involvement	80	26.1	61	18.9	0.035
Outcome measures					
LOS (d) (mean, [range])	15.1	[1-91]	13.1	[1-52]	0.004
30-day mortality	74	24.1	29	9.0	<0.001
[#]In-hospital mortality	62	20.2	26	8.1	<0.001
30-day mortality in aged ≥ 80 y	40	38.9	25	15.9	0.003
PSI score (mean, [range])	126.7	[23-226]	105.1	[8-215]	<0.001

LOS = length of hospital stay; [&]in situ cancer; *CURB cut-off level; °PSI cut-off level; [#]also after 30 days.

Patient characteristics and outcomes in the HCAP subsets

Table 2 shows the backgrounds of HCAP patients, many of whom satisfied more than one HCAP criterion: 24.7% had been hospitalised for more than two days in the previous 90 days, 5.9% were nursing home residents, 45.8% received one-day hospital intravenous medical therapy (chemotherapy or supportive care), and 34.2% underwent home wound care or home infusion therapy. Among the 137 patients with Day Hospital access in previous 30-days, 114 were affected by hematogenous malignancies, 8 by solid malignancies and 15 by thalassemia maior or autoimmune diseases.

The majority (71.3%) were immunocompromised because of the disease and/or therapy, all of whom met at least one HCAP criterion, and none was classified as having CAP. As this was a discriminating parameter, the 219 immunocompromised patients were compared with the 88 non-immunocompromised patients. Admission from a nursing home accounted for 13.6% of the latter and 2.7% of the former (p=0.001). Malignancy of 8 non-IC HCAP patients was attributable to in situ cancer. These patients were defined as HCAP because 2 had been hospitalised for more than two days in the previous 90 days, 3 received one-day hospital intravenous medical therapy, and 2 underwent home wound care.

Table 2 – HCAP patient backgrounds

All HCAP patients	Overall[#] (n = 307)	
	No.	**(%)**
HCAP criteria		
Hospitalization for ≥2 days in previous 90 days	74	(24.7)
Day Hospital access in previous 30-days for intravenous therapy	137	(45.8)
Nursing home residents	18	(5.9)
Home wound care or home infusion therapy	105	(34.2)
Chronic dialysis	0	(0)
Immunocompromised HCAP patients°	**219**	**(71.3)**
Chemotherapy and/or immunosuppressive therapy	113	(36.8)
Long-term steroids ≥20 mg/day	40	(15.7)
Malignancy	213	(69.4)
Hematogenous malignancy	170	(55.4)
Neutropenic (*ANC <1500/μL)	16	(7.2)

[#]Including overlapping cases.
[°]All immunocompromised patients met at least one HCAP criterion
*ANC = absolute neutrophil count (ANC 501-1000: 7 patients; ANC 1001-1500: 9 patients)

Table 3 shows comorbidities, and clinical and laboratory variables in the two HCAP subsets. The non-immunocompromised patients were older (mean age 77.8 *vs* 70.8; p<0.001), and included three times more over-80 year olds than the immunocompromised patients.

The univariate odds for 30-day mortality were similar in these two groups of patients (OR=0.93; 95% CI: 0.52-1.65). Even after adjustment for the covariates selected by stepwise logistic regression, the odds ratio (OR=1.02; 95% CI: 0.35-2.96) remained close to 1.

There were no differences in PSI score or LOS between the two groups.

Table 3 – Baseline comparison of immunocompromised (IC) and non-immunocompromised (non-IC) HCAP patients

	non-IC (n = 88)		IC (n =219)		
	No.	**%**	**No.**	**%**	**p value**
Demographic data					
Age (years) (mean, [range])	77.8	[28-98]	70.8	[26-97]	<0.001
Age <65 years	15	17.0	59	26.9	0.077
Age ≥80 years	55	62.5	50	22.8	<0.001
Males	45	51.1	142	64.8	0.029
Antibiotics before presentation	32	37.2	105	48.2	0.097
Co-morbidities					
Cerebrovascular disease	46	52.3	20	9.1	<0.001
Cardiovascular disease	54	61.4	81	37.0	<0.001
Chronic renal failure	32	36.4	57	26.0	0.095
COPD	19	21.6	23	10.5	0.016
Diabetes	17	19.3	34	15.5	0.498
Chronic liver disease	13	14.8	31	14.2	0.859
Malignancy	8[&]	9.1	205	93.6	<0.001
Two or more co-morbidities	63	71.6	140	63.9	0.231
Clinical parameters upon admission					
Altered mental status	40	45.5	38	17.4	<0.001
Congestive hearth failure	15	17.0	26	11.9	0.266
Acute renal failure	9	13.4	15	7.5	0.147
Temperature <35°C or ≥40°C	2	2.3	4	1.8	1.000
°Systolic blood pressure <90 mmHg	2	2.3	2	0.9	0.324
*Systolic blood pressure <90 mmHg or diastolic ≤60 mmHg	23	26.1	73	33.3	0.276
Pulse rate ≥125bpm	10	11.4	10	4.6	0.040
Respiratory rate ≥30/min	16	18.2	45	20.5	0.752
Laboratory findings upon admission					
*Blood urea nitrogen ≥7 mmol/L	56	63.6	134	61.2	0.795
°Blood urea nitrogen ≥11 mmol/L	33	37.5	63	28.8	0.137
Glucose ≥250 mg/dL	5	5.7	8	3.7	0.531
Sodium <130 mEq	12	13.6	14	6.4	0.067
Hematocrit <30%	9	10.2	79	36.1	<0.001
pO2 <60 mmHg or SaO2 <90%	19	21.6	52	23.7	0.765
pH <7.35	4	4.5	1	0.5	0.025
WBC <4000/μL	2	2.3	56	25.6	<0.001
pO2 <54 mmHg or PaO2/FiO2 <250	9	10.2	25	11.4	0.843
Radiographic findings upon admission					
Pleural effusion	19	21.6	65	29.7	0.160
Multilobar involvement	21	23.9	59	26.9	0.667
Outcome measures					
LOS (d) (mean, [range])	13.7	[1-41]	15.7	[2-91]	0.111
30-day mortality	22	25.0	52	23.7	0.883
[#]In-hospital mortality	20	22.7	42	19.2	0.530
30-day mortality in patients aged ≥80 years	22	100	18	34.6	<0.001
PSI score (mean, [range])	122.9	[23-226]	128.2	[53-205]	0.269

LOS = length of hospital stay; *CURB cut-off level; °PSI cut-off level; [#]Also after 30 days; [&]in situ cancer.

Figure 1 shows the Kaplan-Meier plot of 30-day survival in the study cohort: the trend was similar in the immunocompromised and non-immunocompromised HCAP patients (p=0.713).

Microbiological studies

The microbiological studies were performed in 253 of 322 *CAP patients* (78.6%). and in 266 of 307 HCAP patients (86.6%). The positivity was obtained in 23.3% of CAP patients and 30.8% of HCAP. Table 4 shows the microbiological findings in the groups and subgroups. Data on *Enterococcus species* isolation have been included because *Enterococci* are considered a rare cause of lung infections, except in the setting of impaired immunity. *Enterococcus faecalis* and *Enterococcus faecium* have emerged as multi-resistant nosocomial pathogens in immunocompromised, critically ill and elderly patients with co-morbidities (stroke, hypertension, vascular disease).

Table 4 – Distribution of isolated pathogens: CAP, and immunocompromised (IC) and non-immunocompromised (non-IC) HCAP patients

Pathogens	Number (%) of patients with indicated infections							
	CAP patients		HCAP patients		HCAP non-IC		HCAP IC	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Tested	253	(78.6)	266	(86.6)	68	(77.3)	198	(90.4)
Positive	59	(23.3)	82	(30.8)	22	(32.4)	60	(30.3)
Streptococcus pneumoniae	21	(35.6)	11	(13.4)	1	(4.5)	10	(16.7)
Staphylococcus aureus	4	(6.8)	13	(15.9)	5	(22.7)	8	(13.3)
MRSA	2	(3.4)	8	(9.8)	3	(13.6)	5	(8.3)
MSSA	2	(3.4)	5	(6.1)	2	(9.1)	3	(5.0)
Pseudomonas aeruginosa	5	(8.5)	9	(11.0)	4	(18.2)	5	(8.3)
Enterococcus species	3	(5.1)	10	(12.2)	3	(13.6)	7[&]	(11.7)
Legionella species	5	(8.5)	4	(4.9)	-	-	4	(6.7)
Mycoplasma pneumoniae	2	(3.4)	4	(4.9)	2	(9.1)	2	(3.3)
Klebsiella pneumoniae	3	(5.1)	3	(3.7)	-	-	3	(5.0)
Chlamydia pneumoniae	-	-	1	(1.2)	-	-	1	(1.7)
*Other Enterobacteriaceae**	2	(3.4)	3	(3.7)	2	(9.1)	4	(6.7)
Other nonfermenting gram-negative rods°	2	(3.4)	6	(7.3)	1	(4.5)	2	(3.3)
Coagulase-negative Staphylococci[#]	4	(6.8)	7	(8.5)	1	(4.5)	6	(10.0)
E.coli	2	(3.4)	4	(4.9)	1	(4.5)	3	(5.0)
Haemophilus influenzae	1	(1.7)	3	(3.7)	-	-	3	(5.0)
Others[§]	3	(5.1)	6	(7.3)	3	(13.6)	3	(5.0)
Polymicrobial infection	6	(10.2)	9	(11.0)	3	(13.6)	6	(10.0)

**Enterobacter species. Citrobacter species. Serratia marcescens. Proteus species. Morganella species*
°*Acinetobacter species. Stenotrophomonas maltophilia. Pseudomonas fluorescens. Brevimundas*
[#]*Staphylococcus haemoliticus. hominis. epidermidis*
[§]*Brahamella. Corynebacterium. Streptococcus agalatiae. Streptococcus pyogenes. A influentia H1N1 virus*
MRSA= methicillin-resistant *Staphylococcus aureus*; MSSA= methicillin-sensitive *Staphylococcus aureus*
[&]two were *vancomycin resistant enterococci (VRE)*

Severity scores

As shown in Figure 2, all five scoring systems showed the same trend of increasing mortality with worsening risk group. In all of the risk classes of each score, mortality was higher in the HCAP group. In terms of distribution, CURB, CRB-65 and SCAP classified the largest proportion of patients as being at low risk, whereas the PSI and CURB-65 classified the lowest proportion as low risk. Among the HCAP patients, the PSI low-risk class had the lowest aggregate 30-day mortality than the low-risk classes of all of the other scores.

Comparison of severity score performance

Figure 3 shows the ROC curves, AUCs and their differences for all scores in all of the groups and subgroups. All the prognostic scores performed better in CAP patients than in HCAP patients. In the overall HCAP group, the PSI seemed to predict mortality better than the three CURB scores, though differences were not significant; also SCAP appeared to perform slightly better than CURBs curves. In the subset of non-IC HCAP patients, the performance of all prognostic scores was similar to that observed in CAP group. Among the IC HCAP patients, only the PSI and SCAP scores had prognostic value. At every threshold, reported in Table 5, the PSI was more sensitive and less specific than the CURB and SCAP scores, and also had the best negative likelihood ratio (0.19).

TABLE 5 – Sensitivity and specificity by patient group, risk class and prognostic scores

	HCAP						CAP					
	Sensitivity		Specificity		PLR	NLR	Sensitivity		Specificity		PLR	NLR
PSI												
≥IV	**0.973**	(0.905 to 0.997)	**0.142**	(0.100 to 0.193)	**1.13**	**0.19**	**1**	(0.881 to 1.000)	**0.389**	(0.333 to 0.448)	**1.64**	**0**
≥V	**0.608**	(0.488 to 0.720)	**0.605**	(0.539 to 0.668)	**1.54**	**0.65**	**0.552**	(0.357 to 0.736)	**0.785**	(0.733 to 0.831)	**2.57**	**0.57**
CURB												
≥2	**0.541**	(0.421 to 0.657)	**0.588**	(0.522 to 0.652)	**1.31**	**0.78**	**0.759**	(0.565 to 0.897)	**0.659**	(0.601 to 0.713)	**2.2**	**0.37**
≥3	**0.216**	(0.129 to 0.327)	**0.897**	(0.851 to 0.933)	**2.1**	**0.87**	**0.207**	(0.080 to 0.397)	**0.922**	(0.885 to 0.950)	**2.64**	**0.86**
CURB-65												
≥2	**0.811**	(0.703 to 0.893)	**0.326**	(0.266 to 0.390)	**1.2**	**0.58**	**1**	(0.881 to 1.000)	**0.399**	(0.343 to 0.458)	**1.66**	**0**
≥3	**0.514**	(0.394 to 0.631)	**0.631**	(0.565 to 0.693)	**1.39**	**0.77**	**0.759**	(0.565 to 0.897)	**0.679**	(0.622 to 0.732)	**2.36**	**0.36**
CRB-65												
≥2	**0.622**	(0.501 to 0.732)	**0.536**	(0.470 to 0.602)	**1.34**	**0.71**	**0.793**	(0.603 to 0.920)	**0.556**	(0.497 to 0.614)	**1.79**	**0.37**
≥3	**0.23**	(0.140 to 0.342)	**0.893**	(0.846 to 0.929)	**2.14**	**0.86**	**0.276**	(0.127 to 0.472)	**0.891**	(0.849 to 0.924)	**2.53**	**0.81**
SCAP												
≥IV	**0.459**	(0.343 to 0.579)	**0.729**	(0.677 to 0.786)	**1.70**	**0.74**	**0.621**	(0.423 to 0.793)	**0.778**	(0.726 to 0.824)	**2.80**	**0.49**
≥V	**0.081**	(0.030 to 0.168)	**0.974**	(0.945 to 0.990)	**3.14**	**0.94**	**0.138**	(0.039 to 0.317)	**0.945**	(0.913 to 0.968)	**2.53**	**0.91**
	HCAP non-immunocompromised						HCAP immunocompromised					
	Sensitivity		Specificity		PLR	NLR	Sensitivity		Specificity		PLR	NLR
PSI												
≥IV	**1.000**	(0.846 to 1.000)	**0.242**	(0.145 to 0.364)	**1.320**	**0.000**	**0.962**	(0.868 to 0.995)	**0.102**	(0.060 to 0.158)	**1.071**	**0.378**
≥V	**0.773**	(0.546 to 0.922)	**0.652**	(0.524 to 0.765)	**2.217**	**0.349**	**0.538**	(0.395 to 0.678)	**0.587**	(0.508 to 0.662)	**1.303**	**0.786**
CURB												
≥2	**0.727**	(0.498 to 0.893)	**0.606**	(0.478 to 0.724)	**1.846**	**0.450**	**0.462**	(0.322 to 0.605)	**0.581**	(0.502 to 0.657)	**1.101**	**0.927**
≥3	**0.318**	(0.139 to 0.549)	**0.848**	(0.739 to 0.925)	**2.100**	**0.804**	**0.173**	(0.082 to 0.303)	**0.916**	(0.863 to 0.953)	**2.065**	**0.903**
CURB-65												
≥2	**1.000**	(0.846 to 1.000)	**0.288**	(0.183 to 0.413)	**1.404**	**0.000**	**0.731**	(0.590 to 0.844)	**0.341**	(0.270 to 0.419)	**1.109**	**0.789**
≥3	**0.727**	(0.498 to 0.893)	**0.606**	(0.478 to 0.724)	**1.846**	**0.450**	**0.423**	(0.287 to 0.568)	**0.641**	(0.563 to 0.713)	**1.178**	**0.900**
CRB-65												
≥2	**0.864**	(0.651 to 0.971)	**0.500**	(0.374 to 0.626)	**1.730**	**0.270**	**0.519**	(0.376 to 0.660)	**0.551**	(0.472 to 0.628)	**1.156**	**0.873**
≥3	**0.409**	(0.207 to 0.636)	**0.848**	(0.739 to 0.925)	**2.700**	**0.700**	**0.154**	(0.069 to 0.281)	**0.910**	(0.856 to 0.949)	**1.713**	**0.930**
SCAP												
≥IV	**0.909**	(0.708 to 0.989)	**0.515**	(0.389 to 0.640)	**1.875**	**0.176**	**0.519**	(0.376 to 0.660)	**0.659**	(0.581 to 0.730)	**1.521**	**0.730**
≥V	**0.318**	(0.139 to 0.549)	**0.894**	(0.794 to 0.956)	**3.000**	**0.763**	**0.115**	(0.044 to 0.234)	**0.958**	(0.916 to 0.983)	**2.753**	**0.923**

In brackets: 95% confidence intervals. PLR = positive likelihood ratio; NLR = negative likelihood ratio.

DISCUSSION

This prospective study analysed validated CAP scoring systems (PSI, CURB and its derivatives, and SCAP) as predictors of 30-day mortality in hospitalised HCAP patients including immunocompromised patients: all scores are found to be poor at predicting 30-day mortality. The analysis of the two separate groups by immunocompetence showed that in HCAP patients without immunocompromission, all scores are good at predicting 30 day mortality and PSI is the best, while in HCAP patients with immunocompromission, all scores are poor at predicting 30 day mortality.

The study also investigated the epidemiology of HCAP and the pneumonia of immunocompromised HCAP patients. Both the CAP and HCAP cohorts mainly consisted of elderly subjects with many chronic comorbidities. Cerebrovascular diseases and chronic obstructive pulmonary disease (COPD) were more prevalent in the CAP group. The most common pathogen in the CAP patients was *S. pneumoniae*, whereas the HCAP patients showed an increased incidence of pneumonia secondary to *Staphylococcus aureus* (MSSA and MRSA), Pseudomonas and other Gram-negative bacteria. The 30-day and in-hospital mortality rates in the HCAP group were respectively 24.1% and 20.2%, as previously reported [3,5,7,9]; the odds ratio for 30-day mortality with respect to CAP was 3.2.

The risk category distribution of our HCAP patients is the main difference between our study and previously published studies [3-7]. We did not enrol any patients undergoing haemodialysis or with aspiration pneumonia, and there was only a small proportion of nursing home residents, but there were many patients with cancer or who were immunocompromised as a result of therapy, thus making our HCAP cohort similar to that of Park *et al*. [25], who reported a mean PSI of 104, with 29.7% of the patients in the low-risk class, and 10.4% in the high-risk CURB-65 class. However, their study was retrospective and there may have been some missing information.

The mean PSI of the HCAP patients in our study was 126.7, and 11.4% of them were in the low-risk class. However, the PSI and SCAP scores had opposite trends in both the CAP and HCAP groups: the smallest number was in the low-risk PSI class, and the highest number in the low-risk SCAP class. In our setting, PSI could be considered more useful than CURB-65 or SCAP in ruling out serious HCAP because of its high negative and low positive predictive values for 30-day mortality at all cut-off points, whereas SCAP is probably better suited to capture abnormal vital signs in acute illness as it includes multilobar radiographic infiltrates, hypoxia, acidosis and very old age. Nevertheless, its positive predictive value in the case of HCAP was as low as that of CURB and CRB-65, which may mean that none of them is useful in guiding decision making for in-patients.

It has been argued that the HCAP population is highly heterogeneous, and that the HCAP concept may be misleading and creates confusion in the management of pneumonia [22]. However, we overcame this limitation by comparing our larger subgroup of immunocompromised HCAP patients with the subgroup of non-immunocompromised patients. Many HCAP studies [26] do not include immunocompromised patients and, although studies of immunocompromised patients have included HIV-positive subjects [5,27,28], there is a lack of data regarding the risks associated with pneumonia caused by drug-resistant pathogens in non-neutropenic cancer patients undergoing chemotherapy. Moreover, one study of neutropenic cancer patients found that no difference in risk was attributable to the type of malignancy: i.e. solid *vs* haematological malignancies [29].

The main differences between the two subgroups of immunocompromised and non-immunocompromised patients were age, cerebrovascular diseases and COPD: non-immunocompromised HCAP resembled CAP in terms of demographics and comorbidities. We did not observe any differences in admission parameters except for low haematocrit levels and leukopenia related to the underlying malignancy and/or therapy of immunocompromised. The two HCAP subgroups also had similar 30-day and in-hospital mortality rates, and it is worth noting that both showed the same trend in 30-day survival. This suggests that very elderly patients with associated comorbidities and patients with advanced malignancies have a similarly high probability of dying during pneumonia.

Some authors have attempted to find a means of predicting the mortality risk in immunocompromised pneumonia patients, mainly those with HIV-infection or neutropenia [30,31]. Sanders *et al*. [32] retrospectively investigated the performance of PSI in immunocompromised HIV-negative, and found that ranking by mortality risk reflected the groupings by different causes of immunological impairment and pointed out that the PSI was an ‘equally valid predictor of outcomes in the subset of patients not undergoing active cancer treatment’. We did not splitted our immunocompromised patients into subgroups and found that the PSI was fairly good at predicting 30-day mortality.

However, further investigations are necessary to evaluate whether any other blood biomarker or parameter could be added to the 20 variables of the PSI in order to improve its performance in immunocompromised patients. The use of CURB and its derivatives to predict 30-day mortality in (particularly immunocompromised) HCAP patients is limited by its low prognostic accuracy.

Our data show that it may be useful to use SCAP score in the clinical management of immunocompromised patients, in whom it seems to reflect acute pneumonia-related illness appropriately. SCAP was the most specific score in the highest risk class, and none of these patients survived.

Our study has a number of limitations: it involved only a single centre; younger patients with severe pneumonia admitted directly to ICUs from the Emergency Department were lost; and we were unable to determine the true impact of the patients' performance status on patient outcome. Furthermore, the large majority of the HCAP outpatients admitted because of pneumonia were affected by malignancies or were immunocompromised as a result of therapy.

The heterogeneity of the HCAP population is a major concern because it is known that the distribution and characteristics of HCAP depend on the local setting, which may affect the incidence of different causative organisms with different rates of antibiotic resistance [33]. Some authors have even claimed that immunocompromised patients should not be regarded as having HCAP, but various disease-specific characteristics should be considered when making treatment decisions [23,34].

The strong points of our study seem to be the complete prospective data collection and the homogeneity of each of the HCAP subsets, some of which may have their own distinctive epidemiology and risk factors. In conclusion, while awaiting the development of an optimal predictive instrument, it seems that combining the information offered by different and complementary prognostic systems may be useful in different groups of HCAP patients.

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Statement of Interest

None declared.

Figure 1

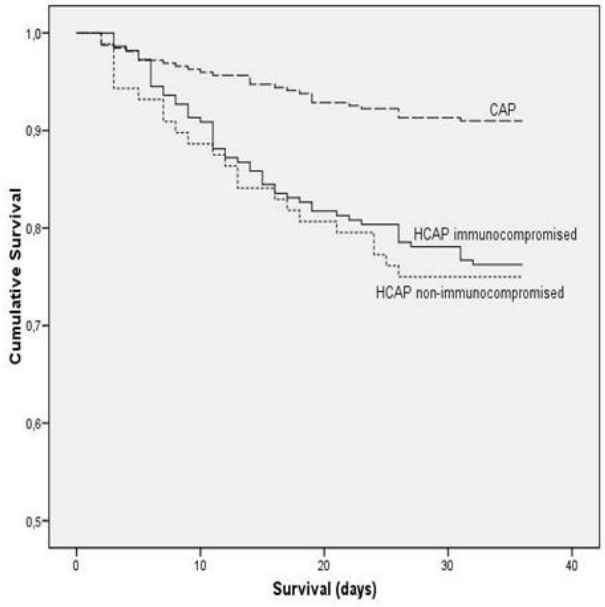


Figure 2

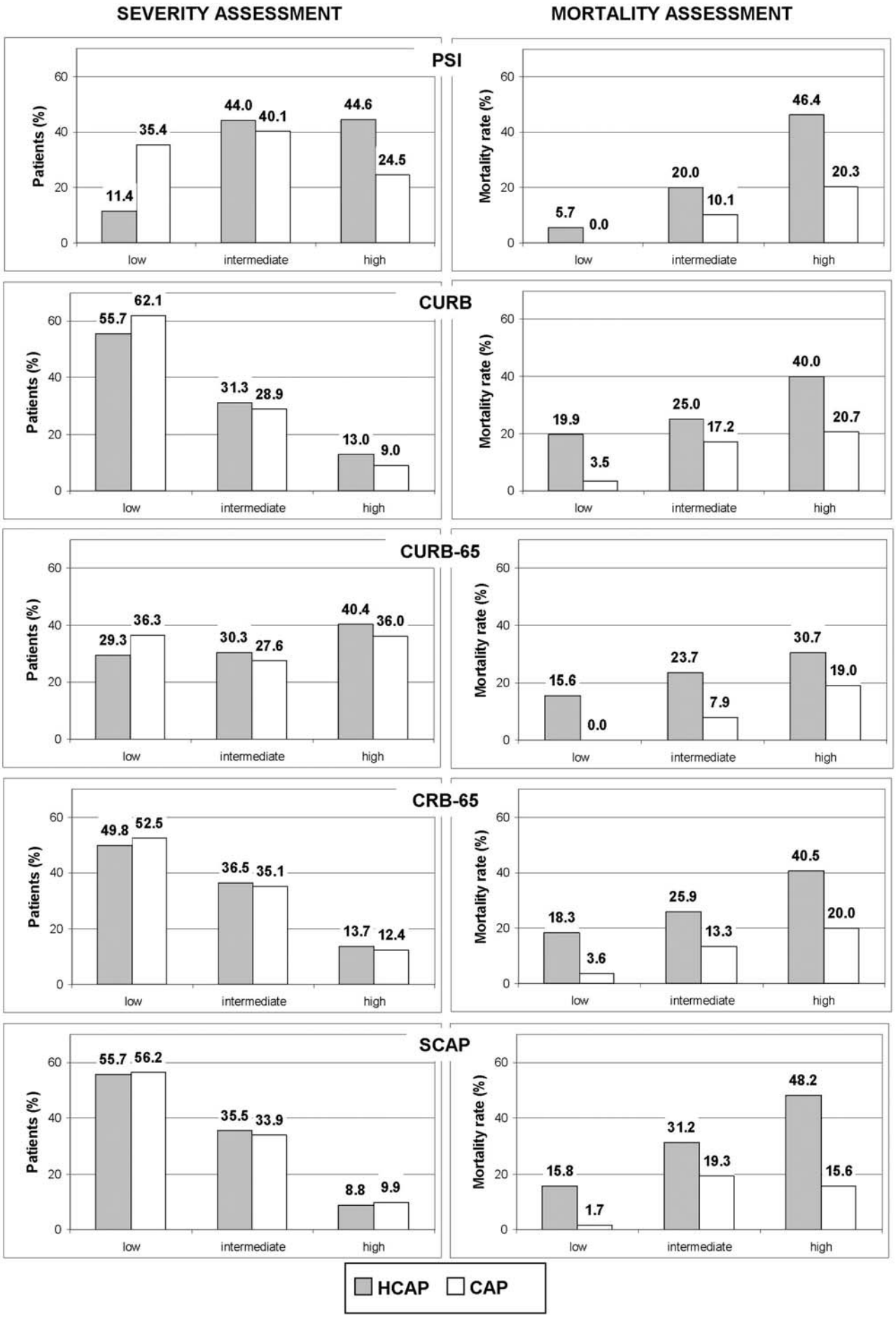
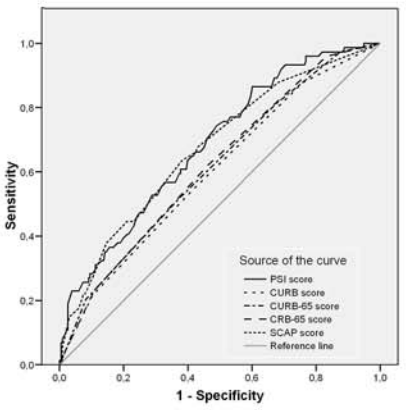

SEVERITY ASSESSMENT
MORTALITY ASSESSMENT
PSI
Patients (%)
11.4
35.4
44.0
40.1
44.6
24.5
Mortality rate (%)
5.7
0.0
20.0
10.1
46.4
20.3
CURB
Patients (%)
55.7
62.1
31.3
28.9
13.0
9.0
Mortality rate (%)
19.9
3.5
25.0
17.2
40.0
20.7
CURB-65
Patients (%)
29.3
36.3
30.3
27.6
40.4
36.0
Mortality rate (%)
15.6
0.0
23.7
7.9
30.7
19.0
CRB-65
Patients (%)
49.8
52.5
36.5
35.1
13.7
12.4
Mortality rate (%)
18.3
3.6
25.9
13.3
40.5
20.0
SCAP
Patients (%)
55.7
56.2
35.5
33.9
8.8
9.9
Mortality rate (%)
15.8
1.7
31.2
19.3
48.2
15.6
0
20
40
60
low
intermediate
high
HCAP
CAP

Figure 3

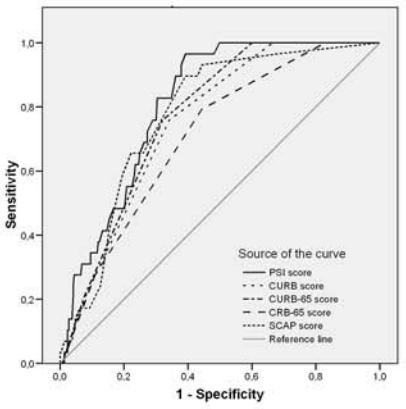


HCAP patients

	Area	95% CI	p
PSI score	0.68	0.62 to 0.75	<0.0001
CURB score	0.6	0.53 to 0.67	0.0027
CURB-65 score	0.62	0.55 to 0.69	0.0006
CRB-65 score	0.62	0.55 to 0.69	0.0003
SCAP score	0.67	0.6 to 0.74	<0.0001

Contrast	Difference	p
PSI v CURB	0.08	0.0116
PSI v CURB-65	0.07	0.0244
PSI v CRB-65	0.06	0.0499
PSI v SCAP	0.01	0.6972
CURB v CURB-65	-0.01	0.1938
CURB v CRB-65	-0.02	0.3466
CURB v SCAP	-0.07	0.0084
CURB-65 v CRB-65	0	0.7809
CURB-65 v SCAP	-0.06	0.0389
CRB-65 v SCAP	-0.05	0.063

H_0: Difference between areas = 0. H_1: Difference between areas ≠ 0.

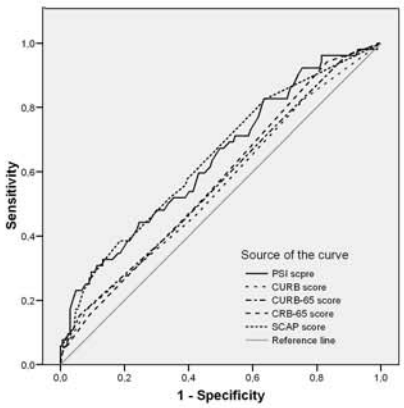


CAP patients

	Area	95% CI	p
PSI score	0.81	0.75 to 0.87	<0.0001
CURB score	0.75	0.69 to 0.82	<0.0001
CURB-65 score	0.77	0.71 to 0.83	<0.0001
CRB-65 score	0.71	0.63 to 0.79	<0.0001
SCAP score	0.78	0.7 to 0.85	<0.0001

Contrast	Difference	p
PSI v CURB	0.06	0.0682
PSI v CURB-65	0.04	0.1785
PSI v CRB-65	0.1	0.0036
PSI v SCAP	0.03	0.2738
CURB v CURB-65	-0.02	0.0003
CURB v CRB-65	0.04	0.0158
CURB v SCAP	-0.02	0.5582
CURB-65 v CRB-65	0.06	0.001
CURB-65 v SCAP	-0.01	0.8797
CRB-65 v SCAP	-0.07	0.0952

H_0: Difference between areas = 0. H_1: Difference between areas ≠ 0.

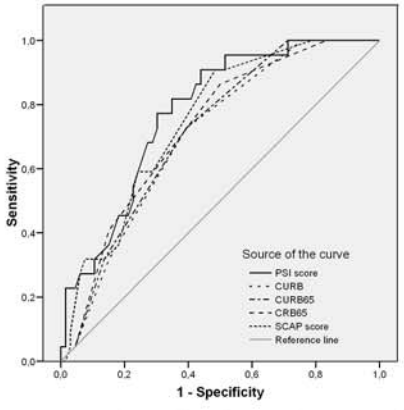


HCAP immunocompromised patients

	Area	95% CI	p
PSI score	0.64	0.55 to 0.73	0.0009
CURB score	0.55	0.47 to 0.64	0.1158
CURB-65 score	0.57	0.48 to 0.65	0.0637
CRB-65 score	0.57	0.49 to 0.65	0.0428
SCAP score	0.64	0.56 to 0.73	0.0005

Contrast	Difference	p
PSI v CURB	0.09	0.0354
PSI v CURB-65	0.07	0.0485
PSI v CRB-65	0.07	0.089
PSI v SCAP	0	0.9113
CURB v CURB-65	-0.01	0.3797
CURB v CRB-65	-0.02	0.49
CURB v SCAP	-0.09	0.0087
CURB-65 v CRB-65	0	0.8256
CURB-65 v SCAP	-0.08	0.0354
CRB-65 v SCAP	-0.07	0.056

H_0: Difference between areas = 0. H_1: Difference between areas ≠ 0.



HCAP non-immunocompromised patients

	Area	95% CI	p
PSI score	0.78	0.68 to 0.88	<0.0001
CURB score	0.7	0.6 to 0.81	0.0001
CURB-65 score	0.71	0.61 to 0.82	<0.0001
CRB-65 score	0.72	0.62 to 0.83	<0.0001
SCAP score	0.75	0.64 to 0.85	<0.0001

Contrast	Difference	p
PSI v CURB	0.07	0.1786
PSI v CURB-65	0.06	0.2419
PSI v CRB-65	0.05	0.3412
PSI v SCAP	0.03	0.4789
CURB v CURB-65	-0.01	0.0743
CURB v CRB-65	-0.02	0.4736
CURB v SCAP	-0.05	0.349
CURB-65 v CRB-65	-0.01	0.7376
CURB-65 v SCAP	-0.03	0.4723
CRB-65 v SCAP	-0.02	0.6001

H_0: Difference between areas = 0. H_1: Difference between areas ≠ 0.

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