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TANAFFOS

Can Procalcitonin Add to the Prognostic Power of the Severity Scoring System in Adults with Pneumonia?

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Background: The first decision confronting clinicians in the management of patients with community acquired pneumonia (CAP) is whether the patient is to be hospitalized or not. We sought to validate the pneumonia scoring system and assess the power of procalcitonin (PCT) level to predict in-hospital mortality (IHM) and intensive vasopressor and respiratory support (IVRS) requirements in patients with CAP.

Materials and Methods: A total of 120 patients with CAP were evaluated for severity of illness based on the defined scoring systems including pneumonia severity index (PSI), confusion, urea, respiratory rate, blood pressure, age>65 (CURB-65), confusion, respiratory rate, blood pressure, age>65 (CRB-65), infectious diseases society of America/American thoracic society 2007 criteria (IDSA/ATS 2007) and systolic blood pressure, multilobar infiltrate, albumin, respiratory rate, tachycardia, confusion, low oxygen, low pH (SMART-COP).Demographic, clinical, laboratory and radiographic data were collected prospectively. The accuracy of each scoring system in predicting IVRS requirement and IHM was assessed from the area under the receiver operating characteristic (ROC) curve (AUC). Level of PCT was determined by semi-quantitative PCT-Q method (BRAHMS). The accuracy of the defined scoring systems, PCT levels and each scoring system plus PCT levels in prediction of IHM and IVRS requirement was analyzed.

Results: The accuracy of PCT levels in predicting IHM and IVRS requirement based on AUC was 0.542 and 0.658, respectively and the best threshold was ≥ 2ng/mL for both of them. Adding the level of procalcitonin to different scoring systems (based on the defined scoring systems) improved the accuracy of all systems.

Conclusion: We do not suggest using the PCT level alone as a predictor for mortality and IVRS requirement. Instead, we suggest PSI plus PCT and IDSA/ATS 2007 plus PCT as accurate predictors for IHM and SMART-COP plus PCT for IVRS requirement in patients who presented with CAP.

Key words: Hospital Mortality; Pneumonia; Procalcitonin; Severity of Illness Index

INTRODUCTION

The initial management decision after diagnosis of CAP is to determine the site of care. There is significant variation in admission rates among hospitals and among individual physicians. Overestimation of the severity of CAP is common among physicians and leads to hospitalization of a significant number of patients at low risk for death. Because of this, different specialty groups have tried to develop objective site-of-care criteria or severity scoring systems (1). Several scoring systems have been proposed. These scoring systems include PSI (20

variables including age, coexisting illness and abnormal physical and laboratory findings) (2), CURB-65 (3), CRB-65 (4), American Thoracic Society 2001 Criteria (ATS) (5), IDSA/ATS (major criteria: septic shock requiring vasopressor support and mechanical ventilation; minor criteria: respiratory rate ≥30 breaths/minute, PaO_2/FiO_2 ratio ≤250, multilobar infiltrates, confusion, blood urea nitrogen ≥20 mg/dL (blood urea 7 mmol/L), leukopenia, thrombocytopenia, hypothermia or hypotension requiring fluid support) and SMART-COP (6). The predictive power of each score is calculated and validated in different studies. According to the best cut off value, severe illness is defined as PSI class ≥ 4, CURB-65 ≥3, IDSA/ATS criteria (1 or 2 major criteria or ≥ 3 minor criteria), or SMART-COP score ≥ 5.

In addition, several inflammatory markers were identified with predictive capacity of the severity of pneumonia. Among the most widely studied biomarkers are C-reactive protein (CRP) and PCT (7-11).

Herein, we conducted a study to validate each scoring system and assessed the level of serum procalcitonin for prediction of IHM and IVRS requirement alone and in combination with other severity scoring systems in adult patients with CAP.

MATERIALS AND METHODS

1. Selection and Description of Participants

Out of 166 patients with community acquired lower respiratory tract problems with chest infiltrate, 140 cases were eligible for this study. Sixteen patients with non-infectious etiologic diagnosis and four patients with extra-pulmonary infections were excluded from the study. Statistical analyses were only performed on the remaining 120 adult patients with the diagnosis of CAP admitted to Imam Reza Teaching Hospital in Mashhad, Iran. Severity of illness based on the defined scoring systems (PSI, CURB-65, CRB-65, IDSA/ATS 2007 and SMART-COP) was assessed. The diagnostic criteria for CAP included a new infiltrate on chest radiograph in a patient with either fever or clinical signs and symptoms of lower respiratory tract infection (cough, sputum production, dyspnea, pleuritic chest pain, crackles on auscultation), or both.

This study was approved by the vice chancellery, the institutional review board (IRB) and ethics committee of Mashhad University of Medical Sciences (MUMS). Written informed consents were taken from all subjects.

2. Technical Information

All patients underwent a diagnostic evaluation, including chest radiography with/without chest computed tomography (CT) scan, blood chemistry and ABG assessment, sputum/endotracheal aspirate (and possibly pleural fluid) staining and culture, blood for culture in standard aerobic/F BACTEC bottles, Binax NOW Legionella urinary antigen test (Binax, Scarborough, Maine, USA), Binax NOW Streptococcus pneumonia urinary antigen test (Binax, Maine, USA), and RT-PCR of nasopharyngeal swab specimen for influenza virus. The PCT levels were determined by a semi-quantitative solid-phase immunoassay (B.R.A.H.M.S. PCT-Q, B.R.A.H.M.S.-Diagnostica GmbH, Hennigsdorf, Germany) on 200 µl plasma. The PCT levels were categorized into four groups (< 0.5 µg/l; 0.5−< 2 µg/l; 2−< 10 µg/l; ≥ 10 µg/l) according to the provided reference scale. The test was performed within the first 12 hours of patient admission.

Demographic, clinical, laboratory and radiographic data were collected. The accuracy of defined scoring systems and PCT levels in prediction of IVRS requirement and IHM was analyzed (mechanical ventilation and/or vasopressor support during an unsuccessful CPR were not included). The PCT level factor of each scoring system as a risk factor for IHM and IVRS requirement was considered and calculated by the AUC of each new model. Patients included in our study were those who had new infiltrates on chest radiography with fever or lower respiratory signs/symptoms, (or both) and required hospital admission.

Chronic obstructive pulmonary disease (COPD) was defined clinically as the presence of a chronic productive cough for ≥ three months during two consecutive years (other causes of cough being excluded).

Bedridden status was defined as confined to bed by sickness or old age.

Opium addiction was defined as behaviors that include one or more of the following: Impaired control over drug (opioid) use, compulsive drug use or continued use.

3. Statistical Analyses

Statistical analyses were performed using SPSS software and R programming language. Discrete variables were expressed as percentage and continuous variables as mean ± standard deviation (SD) unless stated otherwise. Frequency comparison was done by the chi-square test or Fisher's exact test for categorical variables. Student's t-test or the Mann-Whitney U test was used for continuous variables. Standard definitions of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used. The accuracy of each scoring system in predicting outcome was evaluated using the ROC analysis. Discrimination was assessed by plotting ROC curve and calculating the AUC; AUC values were ranked as excellent (AUC≥0.90), good (AUC: 0.80-0.90), fair (AUC: 0.70-0.80), poor (0.60-0.70), and failed (0.50-0.60). The sensitivity and specificity of each score at the best threshold and after adding PCT levels to each score were calculated using R programming language.

RESULTS

One hundred twenty patients fulfilled the criteria for inclusion. The mean age was 50.4 ± 22.6 years (range 17-94). The male to female ratio was 1/7. The most common microbial diagnosis was S. pneumonia, followed by M. tuberculosis, S. aureus, and polymicrobial including anaerobes. The frequency of patients who presented with severe illness as judged by the PSI class ≥ 4, CURB-65 ≥3, IDSA/ATS criteria (1 or 2 major criteria or ≥ 3 minor criteria), and SMART-COP score ≥ 5 was 60.3%, 36.6%, 60.4% and 60.6%, respectively.

The overall IHM rate was 23.6%. The third day mortality rate was 3.3%; 19.1% of hospitalized patients admitted to the ICU; however, it was far less than actual number of patients who needed intensive care. If the actual number of patients who need ICU admission was equal to the number of patients who need IVRS, then the former would be 1.6 times more than patients admitted to the ICU (37 vs. 23). The IHM rate was higher among patients who admitted to the ICU compared to those who did not (60% vs. 14.8%; P<0.001). As expected, it was significantly higher among patients who needed IVRS compared to other patients (67.6% vs. 4.1%, P <0.001). Evaluation of different demographic, clinical, laboratory and radiographic characteristics of patients demonstrated several risk factors for IHM and IVRS requirement (Table 1). The mean length of hospital stay (LOS) was 11.43±13.2 days. Factors associated with longer LOS were: leukopenia (P=0.045), leukocytosis (P=0.021), PCT level > 0.5 ng/mL (P=0.002), presence of hypoxia on admission (P=0.001), IVRS requirement (P=0.028), ICU admission (P=0.004) and severe illness as judged by the IDSA/ATS 2007 and SMART-COP criteria (P=0.031 and P=0.009, respectively).

The associations of PCT levels with IHM and IVRS requirement were also analyzed and showed different levels of PCT; the odds ratio values for IHM were 2.95, 1.467 and 0.595 for PCT level>10ng/mL, >2ng/mL and >0.5ng/mL, respectively. The associations for IVRS requirement were: 6.846, 3.555, and 1.136 for PCT level>10ng/mL, >2ng/mL, and >0.5ng/mL, respectively (Table 2).

Comparison of PCT levels in patients with CAP of different levels of severity showed that the PCT levels increased with increasing severity of CAP according to PSI, CURB-65, SMART-COP, and IDSA/ATS scores (Table 3). It was significantly higher in patients with PSI class≥ 4 (P< 0.001), CURB-65≥ 3 (P< 0.001), SMART-COP≥ 3 (P< 0.001), and patients with severe pneumonia based on IDSA/ATS 2007 criteria (P< 0.001).

The accuracy of different scoring systems in prediction of IHM and IVRS requirement is shown in Tables 4 and 5. The accuracy of PCT levels in predicting IHM and IVRS requirement based on the AUC was 0.542 and 0.658, respectively.

Comparison between the AUC values of different scoring systems of CAP in predicting IHM and IVRS requirement showed that AUC value of each scoring system increased when we added PCT levels to them as risk factor for IHM and IVRS (Tables 4 and 5, Figure 1).

The best threshold for prediction of IVRS requirement and IHM was also re-calculated for each defined scoring system alone and after addition of PCT levels and the results are shown in Tables 4 and 5 and Figure 2.

Table 1. The relation between patient characteristics, IVRS and IHM

	IVRS		IHM	
Risk factor	**Odds Ratio**	**P value**	**Odds Ratio**	**P value**
Demographic characteristics				
Age>=65 yrs.	1.723	0.211	1.964	0.063
Female sex	1.645	0.297	1.25	0.958
Addiction	2	0.101	1.6	0.556
History of incarceration	0.968	1.000	1.75	0.387
Comorbidity	1.639		1.62	
Diabetes	0.364	0.596	2.821	0.381
IHD/CHF	0.066	0.068	1.795	0.619
COPD	1.8	0.301	2.029	0.095
Bedridden	4.31	0.054	8.1	0.02
Initial Clinical Characteristics				
Confusion	7.736	<0.001	5.416	0.001
Hypotension SBP<90	3.6	0.011	3.611	0.003
Tachycardia HR >=90	1.571	0.575	0.415	0.369
Tachypnea RR>=30	7.032	0.005	1.86	0.494
Fever T>=37.9	0.659	0.393	0.774	0.686
High grade fever T>=38.3	0.684	0.485	1.178	0.714
Initial clinical finding				
Hypoxia SaO_2=<93%	31.158	<0.001	7.723	0.001
Severe hypoxia SaO_2=<85%	11.143	<0.001	8.821	0.001
Hct<36%	1.374	0.628	1.111	0.946
Thrombocytopenia PLT:100000-150000/µl	1.453	0.464	0.542	0.251
Severe Thrombocytopenia PLT =<100000/µl	1.327	0.894	0.763	0.975
Leukopenia WBC<4000/µL	1.184	1.000	1.466	0.866
Leukocytosis WBC>12000/µL	0.875	0.8	0.403	0.142
BUN>20 mg/dl	4.16	0.012	2.204	0.138
Sodium<135 mg/dl	2.045	0.432	3.536	0.056
PCT level>0.5 ng/ml	1.091	0.843	0.644	0.331
PCT level>2 ng/ml	3.481	0.003	1.73	0.211
PCT level>10 ng/ml	6.735	0.001	3.516	0.004
Bilateral CXR involvement	4.127	0.002	1.62	0.302
Pleural effusion	1.815	0.164	1.333	0.335

IVRS: Intensive Vasopressor and Respiratory Support; IHM: In-Hospital Mortality; Yrs.: Years Old; IHD: Ischemic Heart Disease; CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; SBP: Systolic Blood Pressure; HR: Heart Rate; RR: Respiratory Rate; T: Temperature; SaO_2: Arterial oxygen saturation; Hct: Hematocrit; PLT: Platelets; WBC: White Blood Cells; BUN: Blood Urea Nitrogen; PCT: Procalcitonin; CXR: Chest X-ray.

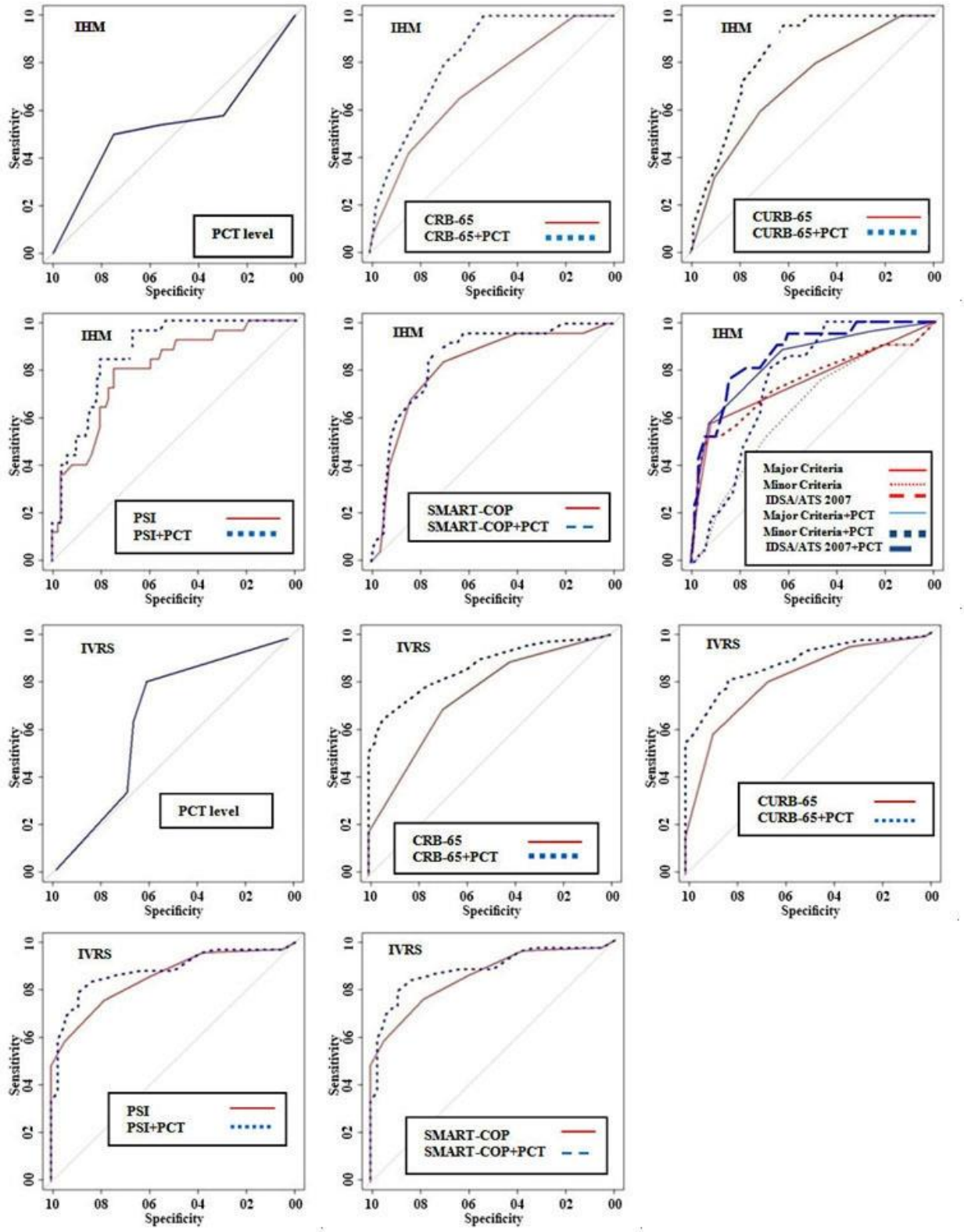

Figure 1. ROC curve of PCT level, scoring systems, and scoring systems plus PCT level in prediction of hospital mortality and IVRS requirement

Table 2. Frequency of IHM and IVRS and LOS in patients with CAP

PSI Class	IHM	P value	IVRS	P value	LOS (days)	P value	ICU	P value
I	0	<0.001	0	<0.001	7	0.98	0	<0.001
II	4.3%		2 (8.7%)		6.9±5.5		0	
III	4.5%		3 (14.3%)		10.6±12.1		2(9.1%)	
IV	20%		7 (23.3%)		10.6±8		4(13.3%)	
V	48.7%		25 (65.8%)		15.7±18.8		17(45.9%)	
CURB-65								
0	0	<0.001	0	<0.001	7.5±8.3	0.096	0	<0.001
1	5 (14.7%)		4 (12.1%)		8.3±6		2 (5.9%)	
2	5 (21.7%)		8 (34.8%)		13.3±12.8		6 (26.1%)	
3	7 (31.8%)		12 (54.5%)		14.1±15.8		7 (31.8%)	
4	7 (50%).		11 (78.6%)		18.7±24.6		6 (42.9%)	
5	2 (66.7%)		1 (50%)		5±1.4		0	
SMART-COP								
I	1 (5.3%)	<0.001	0	<0.001	5.4±2.5	0.003	0	<0.001
II	1 (4%)		2 (8%)		9.7±1.9		2 (8.7%)	
III	6 (18.2%)		13 (40.6%)		14.5±11.9		7 (30.4%)	
IV	19 (59.4%)		22 (68.8%)		14.5±19.7		14 (60.9%)	
IDSA/ATS 2007								
Severe	24 (36.9%)	<0.001	35 (54.7%)	<0.001	13.8±16.2	0.013	21 (32.8%)	<0.001
Non-severe	3 (6.8%)		2 (4.7%)		7.9±6.6		1 (2.3%)	

IVRS: Intensive Vasopressor and Respiratory Support; IHM: In-Hospital Mortality; LOS: Length of Hospital Stay; CAP: Community Acquired Pneumonia; PSI: Pneumonia Severity Index; ICU: Intensive Care Unit; IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society.

Table 3. The PCT levels in patients with CAP of different levels of severity

PCT level	>10 ng/mL	2-10 ng/mL	0.5-2 ng/mL	<0.5 ng/mL
PSI Classes				
I	0	0	0	1 (2.9%)
II	0	1 (5.9%)	8 (34.8%)	13 (38.2%)
III	4 (10.8%)	6 (35.3%)	4 (17.45)	7 (20.6%)
IV	11 (29.7%)	6 (35.3%)	6 (26.1%)	5 (14.7%)
V	22 (59.5%)	4 (23.5%)	5 (21.7%)	8 (23.5%)
Total	37 (100%)	17 (100%)	23 (100%)	34 (100%)
SMART-COP				
I	1 (2.8%)	1 (6.7%)	5 (22.7%)	11 (33.3%)
II	3 (8.3%)	4 (26.7%)	9 (40.9%)	7 (21.2%)
III	9 (25%)	7 (46.7%)	7 (31.8%))	9 (27.3%)
IV	23 (63.9%)	3 (20%)	1 (4.5%)	6 (18.2%)
Total	36 (100%)	15 (100%)	22 (100%)	33 (100%)
CURB-65				
0	1 (2.9%)	0	1 (4.5%)	1 (2.9%)
1	4 (11.8%)	8 (53.3%)	10 (45.5%)	
2	7 (20.6%)	3 (20%)	6 (27.3%)	13 (38.2%)
3	11 (32.4%)	3 (20%)	3 (13.6%)	7 (20.6%)
4	8 (23.5%)	1 (6.7%)	2 (9.1%)	5 (14.7%)
5	3 (8.8%)	0	0	8 (23.5%)
Total	34 (100%)	15 (100%)	22 (100%)	34 (100%)
IDSA/ATS 2007				
Severe	31 (88.6%)	9 (56.3%)	10 (43.4%)	15 (45.5%)
Non-severe	4 (11.4%)	7 (43.8%)	13 (56.5%)	18 (54.5%)
Total	34 (100%)	16 (100%)	23 (100%)	33 (100%)

PCT: Procalcitonin; CAP: Community Acquired Pneumonia; PSI: Pneumonia Severity Index; ICU: Intensive Care Unit; IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society.

Table 4. The AUC*, best threshold, sensitivity, specificity, PPV, and NPV of different scoring systems of CAP in prediction of IVRS requirement

Predicting the need for IVRS	AUC	Best Threshold	Sensitivity	95% Confidence Interval		Specificity	95% Confidence Interval		PPV	NPV
				Lower Limit	Upper Limit		Lower Limit	Upper Limit		
PSI	0.805	122	80.2%	71%	88.1%	75.6%	62%	89.1%	87.1%	65.1%
CURB-65	0.806	2	57.9%	46.3%	69.5%	88.8%	77.7%	97.2%	90.9%	52.4%
CRB-65	0.745	2	69%	57.7%	78.8%	69.4%	55.5%	83.3%	81.6%	53.1%
IDSA/ATS Minor										
SMART-COP	0.853	6	75.7%	65.7%	85.7%	64.8%	78.3%	91.8%	86.8%	63%
PCT level	0.658	>2ng/ml	81.3%	72%	90.6%	61.1%	44.4%	77.7%	81.3%	61.1%
PSI+PCT	0.858	>2ng/ml	86%	77.7%	93%	75%	58.3%	88.8%	87.3%	72.9%
			83%	75%	91.6%	77%	61.1%	91.6%	88.2%	70%
CURB-65+PCT	0.835	>2ng/ml	96%	88%	100%	61.8%	51.3%	72.3%	45.2%	97.9%
CRB-65+PCT	0.865	>2ng/ml	64.7%	52.9%	76.4%	94.2%	85.7%	100%	95.6%	57.8%
IDSA/ATS Minor.PCT	0.828	>2 ng/ml	67.1%	54.6%	78.1%	96.6%	90%	100%	97.7%	58%
SMART-COP+PCT	0.881	>2ng/ml	79.1%	68.6%	88%	88.8%	77.7%	97.2%	92.9%	69.5%

*AUC: 0.90-1 = Excellent; 0.80-0.90 = Good; 0.70-0.80 = Fair; 0.60-0.70 = Poor; 0.50-0.60 = Failed

AUC: Area Under the Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value; IVRS: Intensive Vasopressor and Respiratory Support;

LOS: Length of Hospital Stay; CAP: Community Acquired Pneumonia; PSI: Pneumonia Severity Index; ICU: Intensive Care Unit; IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society.

Table 5. The AUC*, best threshold, sensitivity, specificity, PPV, and NPV of different scoring systems of CAP in prediction of IHM

Predicting IHM	AUC	Best Threshold	Sensitivity	95% Confidence Interval		Specificity	95% Confidence Interval		PPV	NPV
				Lower Limit	Upper Limit		Lower Limit	Upper Limit		
PSI	0.796	122	80%	64%	96%	74.7%	64.3%	83.9%	47.6%	92.8%
CURB-65	0.712	3	60%	40%	80%	71.2%	61.2%	81.3%	39.4%	85%
CRB-65	0.699	2	65.3%	46.1%	84.6%	62.9%	53%	72.9%	36.1%	85%
IDSA/ATS 2007	0.747	---	52.3%	33.3%	76.1%	93.3%	86.6%	98.6%	68.7%	87.5%
IDSA/ATS 2007 Major	0.751	2	57.6%	38.4%	76.9%	92%	86.3%	96.5%	68.1%	88%
IDSA/ATS 2007 Minor	0.635	2	76.2%	57.1%	90.4%	46.6%	36%	58.6%	28.5%	87.5%
SMART-COP	0.817	6	84%	68%	96%	70%	60%	80%	46.6%	93.3%
PCT level	0.542	>2ng/ml	50%	30.7%	69.2%	75%	65.4%	84.5%	38.2%	82.9%
PSI+PCT	0.869	>2ng/ml	84%	68%	96%	80.4%	71.9%	89%	56.7%	94.2%
CURB-65+PCT	0.835	>2ng/ml	96%	88%	100%	61.8%	51.3%	72.3%	45.2%	97.9%
CRB-65+PCT	0.822	>2ng/ml	100%	100%	100%	53.2%	41.5%	64.9%	41.9%	100%
SMART-COP+PCT	0.852	>2ng/ml	88%	72%	100%	73.6%	63.1%	82.9%	52.3%	94.9%
IDSA/ATS 2007+PCT	0.868	>2ng/ml	76.1%	57.1%	95.2%	84.5%	76%	92.9%	59.2%	92.3%
IDSA/ATS Major.PCT	0.838	>2 ng/ml	88.4%	76.9%	100%	62.6%	51.8%	72.3%	42.5%	94.5%
IDSA/ATS Minor.PCT	0.756	>2ng/ml	80.9%	61.9%	95.2%	67.6%	56.3%	77.4%	42.5%	92.3%

*AUC: 0.90-1 = Excellent; 0.80-0.90 = Good; 0.70-0.80 = Fair; 0.60-0.70 = Poor; 0.50-0.60 = Failed

AUC: Area Under the Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value; IHM: In-hospital Mortality; LOS: Length of Hospital Stay; CAP: Community Acquired Pneumonia; PSI: Pneumonia Severity Index; ICU: Intensive Care Unit; IDSA: Infectious Diseases Society of America; ATS: American Thoracic Society.

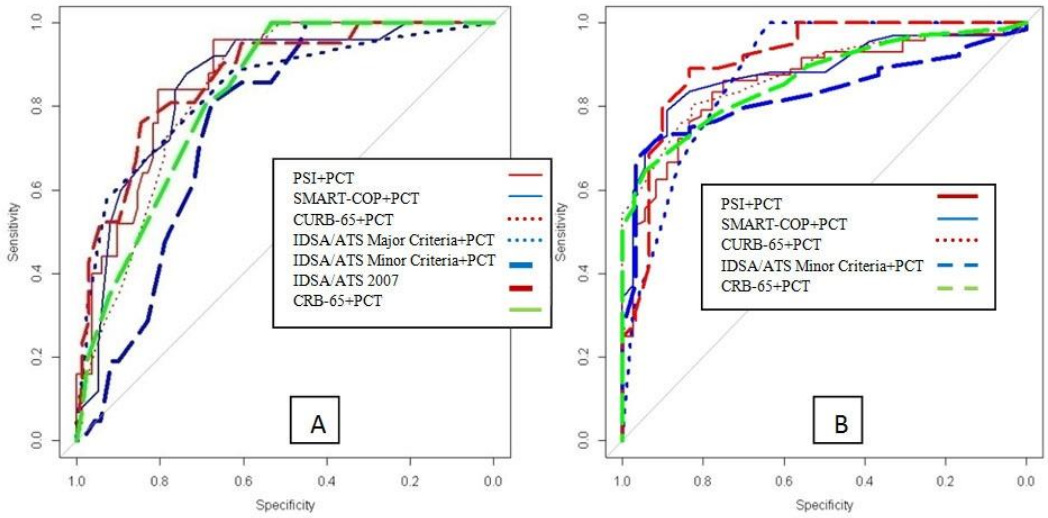

Figure 2. Comparative ROC curve of suggested models in prediction of IHM (A) and IVRS requirement (B)

DISCUSSION

Almost all of the major decisions regarding management of CAP, including diagnostic and treatment issues revolve around the initial assessment of severity (1). Several studies assessed and compared different scoring predictors of pneumonia severity. Some authors concluded that there is no significant difference in the capability of each scoring system to effectively predict CAP mortality (12), whereas others noted that different severity scores have different strengths and weaknesses as prediction tools (13). In our study, patients with CAP were evaluated for severity of illness according to different scoring systems and the association between several demographic, clinical, laboratory and radiographic characteristics and prognosis was analyzed. We found several risk factors that significantly increased patient's need for IVRS and/or IHM. Risk factors for IVRS requirement (in decreasing order of significance) included hypoxia, altered mental status, tachypnea, bedridden status, blood urea nitrogen (BUN)>20 mg/dL, bilateral involvement, hypotension, PCT level>2ng/mL, hyponatremia and opium addiction. Factors related to increased IHM were bedridden status, hypoxia, confusion, hypotension, hyponatremia, diabetes mellitus, BUN>20 mg/dL and COPD.

Several biomarkers and cytokines have been proposed as potential predictors of pneumonia. Among them the predictive capability of CRP and PCT has been most widely studied and validated. The PCT has been widely studied for its usefulness in decision-making of whether to use antibacterial agents in patients with pneumonia or not (14). According to a meta-analysis conducted by Li et al, PCT-guided antibiotic therapy in patients with respiratory tract infections reduces antibiotic use without affecting overall mortality or LOS in the hospital (15). More recently, analysis of eight trials (n=3,492) addressed initiation and/or discontinuation of antibiotics in patients with acute upper and lower respiratory tract infections, which provided evidence that PCT guidance reduces antibiotic duration and prescription rates. There is also evidence that PCT guidance did not increase mortality, hospital LOS or ICU admission rates (14).

The most recent international consensus guidelines defined elevated serum PCT level as a warning sign of incipient severe sepsis and septic shock (16). It has also been shown that PCT levels predict bacteremia (17, 18). Johansson et al. found that median PCT levels were higher in bacteremic patients (than in those without bacteremia), in patients with non-bacteremic pneumococcal etiology

(than in those infected with other bacteria) and in patients with pneumococcal etiology (as compared with viral etiology). They suggested high level of PCT to be a good marker for invasive disease and pneumococcal etiology (19).

Numerous studies have been conducted on the potential role of PCT as a prognostic biomarker (20-24). They found that PCT levels increase with increasing severity of sepsis and organ dysfunction. Several other studies have shown that PCT levels help predict the severity of pneumonia and may predict survival based on the magnitude of the result (9-11). It has been suggested that PCT should be regarded as a prognostic rather than a diagnostic factor in patients with CAP (25). Christ-Crain et al. found gradual increase of PCT levels with increasing severity of CAP, classified according to PSI score ($P< 0.001$) (26). Similarly, another study conducted by Albrich et al. showed its usefulness as a severity marker for pneumococcal pneumonia in HIV-infected adults (27). The prognostic value of PCT has also been demonstrated in patients with VAP. Abula et al. found that the increased PCT levels in VAP patients were associated with poor control of infection and subsequent deterioration (28). Also, PCT levels were associated with severity of pneumonia in our patients. We found that the PCT levels were significantly higher in patients with PSI class≥ 4, CURB-65≥ 3, SMART-COP≥ 3 and patients with severe pneumonia based on IDSA/ATS 2007 criteria. Menéndez et al. found that serum levels of CRP, IL6 and PCT were good predictors of early treatment failure, and that adding the PSI risk classes did not improve the sensitivity or negative predictive values (29). In another study conducted by Menéndez et al, among other biomarkers and cytokines including PCT, CRP, IL6, IL8, IL10 and TNFα, PCT had the highest positive correlation with PSI, CURB65 and CRB65 scales (30). However, while we calculated the power of PCT levels in predicting the outcome of pneumonia, the accuracy of PCT levels in predicting IHM and IVRS requirement based on the area under the ROC curve (AUC) was only 0.542 and 0.658, respectively; the best threshold was ≥ 2ng/mL for both of them. In a similar study, Menéndez et al. found AUC of only 0.66 (0.56-0.76) for PCT levels in patients with CAP (30). However, another study that included both out-patient and in-patient settings reported a comparable accuracy for PCT and CRB-65, based on AUC [0.80 (0.75-0.84) versus 0.79 (0.74-0.84)] (31). Berg and Lindhardt conducted a systematic review on the role of PCT in adult patients with CAP and suggested that although complications during admission, severity of disease measured with various scales (mostly PSI, CRB-65 and CURB-65) and death within a month all tend to correlate with higher PCT, no definite cut-off was found, and PCT should always be interpreted carefully (25). Based on the results of our study, in comparison with the defined severity scores, PCT level alone is a week predictor of pneumonia severity.

In the second arm of the study, we added the PCT level factor to each scoring system as a risk factor for IHM and IVRS requirement and calculated the AUC for each new model. Previously, Huang et al, in 2008 demonstrated that adding PCT levels to the assessment of high clinical risk patients significantly improved the possibility to rule out the likelihood of death. They also demonstrated that simply adding PCT test results to the PSI and CURB-65 in all subjects led to only minimal improvement in test performance. In their study, the AUC of PSI score increased from 0.83 to 0.85 (21). We also demonstrated that adding the PCT levels to the defined scoring systems resulted in improvement of the AUC for each score. Menéndez et al also calculated the AUCs of the different logistic regression models with combinations of markers and cytokines added to the prognostic scales. They found that CRP significantly improved the diagnostic value of both PSI and the CURB65/CRB65 scales. The best AUC (0.88) in their study was achieved with the PSI together with CURB65 and CRP; whereas the AUC of prognostic scales in prediction of 30-day mortality after adding PCT level to PSI, CRB-65 and CURB-65 was 0.83 (0.77-0.89), 0.83 (0.76-0.89), and 0.84 (0.77-0.90), respectively (30). In our study, the best accuracy for prediction of IHM was

obtained for PSI plus PCT and IDSA/ATS 2007 plus PCT with AUC of 0.869 and 0.868, respectively. The best accuracy for predicting IVRS requirement was obtained for SMART-COP plus PCT with AUC of 0.881.

Schuetz et al. assessed the need for recalibration of well-established pneumonia severity prediction scores in a special population. Accordingly, because management strategies of patients with CAP depend on cut-off values of absolute predicted mortalities and the observation of discordance between the reported mortality rates of patients with CAP and original studies, it is essential that predicted risks agree with observed risks in the studied population. They referred to it as calibration. Miscalibration may lead to risk underestimation or overestimation (32). We recalculated the best threshold of predicting IHM and IVRS requirement for each validated scoring system alone and after addition of PCT levels. The analysis resulted in only slightly different values compared with original studies.

CONCLUSION

Our study is one of the first to prospectively analyze the power of different scoring systems and PCT level alone and in combination for prediction of both IHM and IVRS requirement. Upon calculating the power of PCT levels in predicting the outcome of pneumonia, we found that PCT level alone was a week predictor of pneumonia severity. Therefore, we do not suggest using PCT level alone as a predictor for mortality and IVRS requirement in patients who present with CAP. We suggest PSI plus PCT and IDSA/ATS 2007 plus PCT as accurate predictors for IHM and SMART-COP plus PCT for IVRS requirement in hospitalized CAP patients (Figure 2). We also suggest using CRB-65 plus PCT instead of CURB-65 for predicting IHM and IVRS requirement with better accuracy (0.882 and 0.865 compared with 0.712 and 0.806, respectively). However, the present study has also some limitations, such as the limited number of patients, single-center design, assessment of hospitalized patients only and semi-quantitative technique for measuring PCT levels. In addition, because of the limited number of ICU beds, the number of patients admitted to the ICU was far less than the actual number of patients who needed intensive care. The difference in the efficacy and quality of intensive care among patients with severe illness could be a potential confounder in our study. Further large-scale, randomized controlled trials are recommended.

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Conflict of Interests

None.

Author Contributions

HamidReza Naderi: study conception and design, drafting article, critical revision of article, and final approval of article; Fereshte Sheybani: study conception and design, data acquisition, data analysis and interpretation, drafting article, critical revision of article, and final approval of article; MohammadReza Sarvghad: study conception and design, drafting article, critical revision of article, and final approval of article; Mehdi Jabbari Nooghabi: study conception and design, data analysis and interpretation, statistics, drafting article, critical revision of article, and final approval of article.

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