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RESEARCH ARTICLE

A STUDY TO COMPARE PROGNOSTIC UTILITY OF PROCALCITONIN WITH EXISTING BIOMARKERS (CRP AND TLC) AND CLINICAL RISK SCORES (PSI AND CURB 65) IN COMMUNITY ACQUIRED PNEUMONIA

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Pneumonia; Community-Acquired Pneumonia; Procalcitonin; Biomarkers; Clinical Risk Scores

Background: Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality. Biomarkers are increasingly being used to distinguish bacterial pneumonia from other causes, to help reduce the duration of antibiotic therapy, and to assess the prognosis of CAP and thereby aiming to complement Pneumonia Severity Index (PSI) and other scores.
Aims & Objective: To compare prognostic utility of procalcitonin (PCT) with existing biomarkers [C-reactive protein (CRP) and total leukocyte count (TLC)] and clinical risk scores (PSI and CURB-65).
Materials and Methods: Fifty patients diagnosed with CAP were included in this study. Baseline serum PCT was measured, which was then stratified according to four predetermined tiers (tier I: <0.1; tier II: 0.1 to <0.25; tier III: 0.25 to <0.5; tier IV: ≥0.5 µg/L). To calculate the severity of pneumonia, patients were classified according to PCT tier, PSI, and CURB-65 scores. Follow-up PCT and reclassification of PSI and CURB-65 were carried out on days 4 and 30.
Results: PCT was more significantly associated with positive bacterial culture than CRP and TLC. Initial PCT level was significantly correlated with TLC ($p = 0.044$), CRP ($p < 0.001$), PSI ($p < 0.001$), and CURB-65 ($p = 0.028$).
Conclusion: Findings in our study showed that the management of severe CAP would be greatly improved if it were possible to identify, early in the course of disease, those patients who are most likely to develop complications and are at the risk of mortality.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common disease and a leading cause of morbidity and mortality across all age groups worldwide. The mortality rate in patients with severe CAP is up to 50% worldwide.[1–3] Like any other disease, having significant morbidity and mortality, CAP also requires assessment of disease severity and prediction of outcome and thereby evaluation of prognosis.[4–8] This information is of utmost importance because it helps in decision-making regarding necessity of inpatient care and duration of antibiotic therapy, which further adds to the overall management and proper allocation and optimization of scarce health care resources in a developing country like India. Currently, the Pneumonia Severity Index (PSI) and CURB-65 scores are the clinical scoring systems used to stratify patients with CAP and to identify seriously ill patients.[4] However, the PSI is complicated to use and requires a computation program to score 20 variables. Biomarkers are increasingly being used to distinguish bacterial pneumonia from other causes, to help reduce the duration of antibiotic therapy, and to assess the prognosis of CAP, and thereby aiming to complement PSI and other scores.[6,9–14] In contrast, few studies found no or poor association between PCT levels and PSI scores.[15,16] Currently, there is no consensus on the relationship between PCT levels, pneumonia severity, and prognosis. Therefore, in the light of above-mentioned conflicting results we conducted this prospective study.

Objectives: The aim of this prospective study was to compare prognostic utility of procalcitonin (PCT) with existing biomarkers [C-reactive protein (CRP) and total leukocyte count (TLC)] and clinical risk scores (PSI and CURB-65).

MATERIALS AND METHODS

This prospective cohort study was conducted at Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India, in the Department of TB and Respiratory Diseases from October 2011 to October 2013. Fifty patients diagnosed with CAP participated in this study. Adult patients of any gender (age > 18 years) with CAP diagnosis confirmed by clinical and radiological findings per Fine et al.[17] were included in the study. Patients were excluded if they were less than 18 years of age; had health care–acquired pneumonia, pneumonia associated with bronchial obstruction, bronchiectasis or known pulmonary tuberculosis, lung cancer, or severe immune suppression [severe neutropenia (<500/cc), long-term use of corticosteroids, transplantation of solid organ/bone marrow, use of immunosuppressant, hypogammaglobulinemia, asplenia]; were pregnant; or experienced polytrauma. Every patient was subjected to detailed history and clinical examination, and thorough routine investigations were performed**.** Arterial blood gas analysis was carried out. For microbiological analysis, blood, sputum, urine, and pleural fluid (whenever required) culture and gram staining were sent. A blood sample was collected at the time of diagnosis to measure baseline serum PCT, which was then stratified according to four predetermined tiers (tier I: <0.1; tier II: 0.1 to <0.25; tier III: 0.25 to <0.5; tier IV: ≥0.5 μg/L). To calculate the severity of pneumonia, patients were classified according to PCT tier, PSI, and CURB-65 scores. We defined low risk as tier I, Classes I–III for PSI, and Group 1 for CURB-65, based on previous criteria.[12,17] All patients were followed up to 30 days or until death, whichever was earlier. Follow-up of PCT and reclassification of PSI and CURB-65 were carried out on days 4 and 30 after admission. Repeat chest radiograph and blood samples were obtained to evaluate the progress of the patient.

Study End Points: Our primary end point was 30-day mortality. Secondary end point included length of stay, disease-specific complications, and ICU admission.

Statistical Tools: All data were analyzed using Statistical Program for the Social Sciences, version 16.0 (SPSS, Chicago, IL). All calculations were also carried out using the same software. Discrete data were analyzed by cross tabulation using descriptive method. Continuous data were analyzed using univariate analysis. Means of both group patients (survivor group and nonsurvivor group) were analyzed using independent Student *t*-test. Multiple variables were analyzed using multivariate analysis. For prognostic utility of PCT, Kaplan–Meier survival curves were plotted. Results were expressed as mean ± SD and as medians (ranges). Differences with *p*-value less than 0.05 were considered to be statistically significant.

RESULTS

Demographic profile and patient characteristics are described in Table 1.

Table 1: Study cohort, demographic, and patient characteristics

Characteristics			Survivor (n = 44)	Nonsurvivor (n = 6)	*p*-Value
Age (mean ± SD), years			50.11 ± 14.90	68.83 ± 3.97	**<0.001**
Sex	Male (52%)		22 (50.0)	4 (66.7)	0.443
	Female (48%)		22 (50.0)	2 (33.3)	
Smoking			12 (27.3)	2 (33.3)	0.756
Alcohol			6 (13.6)	1 (16.7)	0.841
Comorbidity	No		36 (81.8)	2 (33.3)	**0.001**
	Yes	COPD	6 (16.6)	1 (16.7)	
		Renal	2 (4.5)	1 (16.7)	
		Diabetes	0	2 (33.3)	
		Total	8	4	
Respiratory rate (≥30/min)			18 (40.9)	5 (83.3)	0.050
Pulse rate (≥125/min)			18 (40.9)	6 (100)	**0.008**
Na (<130 mEq/L)			13 (29.5)	3 (50.0)	0.314
Blood pressure (<90 mm Hg)			10 (22.7)	5 (83.3)	**0.002**
Blood urea nitrogen (>20)			11 (25.0)	3 (50.0)	0.201
Confusion			9 (50.5)	5 (83.3)	**0.001**
PaO_2 (<60 mm Hg)			5 (11.4)	4 (66.7)	**0.001**
Platelet count (<1 lac/cc)			8 (18.2)	5 (83.3)	**0.001**
Multilobe/bilateral			11 (25.0)	5 (83.3)	**0.004**
Pleural effusion			3 (6.8)	4 (66.7)	**<0.001**
TLC (mean)			10100.0 ± 2065.16	13200.0 ± 3679.51	**0.049**
PCT	Median		0.195	2.96	**0.005**
	IQR		0.070–0.537	0.41–7.77	
CRP	Median		7.50	16.0	**0.010**
	IQR		5.0–12.75	8.75–28.75	
LOS (mean)			8.30 ± 2.99	8.83 ± 4.57	**0.701**
PSI	I		4 (9.1)	0	**0.016**
	II		16 (36.4)	0	
	III		16 (36.4)	1 (16.7)	
	IV		7 (15.9)	4 (66.7)	
	V		1 (2.3)	1 (16.7)	
	Low risk		33 (75.0)	1 (16.7)	**0.004**
	High risk		11 (25.0)	5 (83.3)	
CURB-65	1		27 (61.4)	1 (16.7)	**0.046**
	2		13 (29.5)	3 (50.0)	
	3		4 (9.1)	2 (33.3)	
	Low risk		29 (65.9)	1 (16.7)	**0.021**
	High risk		15 (34.1)	5 (83.3)	
ICU admission	No		41 (93.2)	2 (33.3)	**<0.001**
	Yes		3 (6.8)	4 (66.7)	
Adverse events	No		39 (88.6)	1 (16.7)	**<0.001**
	Yes		5 (11.4)	5 (83.3)	
Positive bacterial culture	No		39 (88.6)	0	**<0.01**
	Yes		5 (11.4)	6 (100)	

Nonsurvivors had significantly increased median PCT levels at the time of admission compared to survivors [2.96, IQR (0.41–7.77)] versus [0.195, IQR (0.070–

0.537)], p = 0.005. Nonsurvivors also had significantly increased median CRP levels at the time of admission compared to survivors [16, IQR (8.75–28.75)] versus [7.50, IQR (5.0–12.75)], p = 0.01 (Table 2).

Table 2: Median PCT and CRP in survivors and nonsurvivors

	Survivor (n = 44)	Nonsurvivor (n = 6)	*p*-Value
Median PCT	0.195	2.96	**0.005**
Median CRP	7.50	16.0	**0.010**

Table 3: Relationship between median PCT level and PSI class

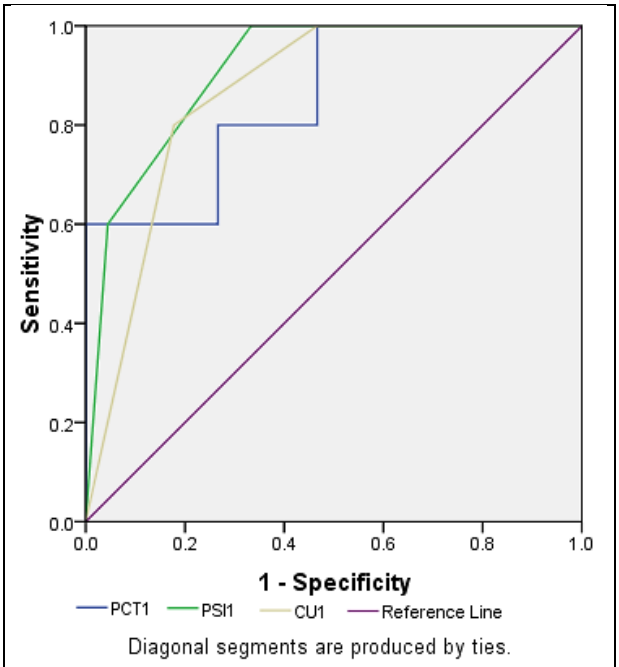
PSI class	PCT (µg/L)		*p*-Value
	Median	IQR	
Class I (n = 4)	0.030	0.030–0.030	**0.004**
Class II (n = 16)	0.160	0.052–0.455	
Class III (n = 17)	0.350	0.195–1.525	
Class IV (n = 11)	0.480	0.090–3.440	
Class V (n = 2)	4.265	0.090–8.440	

Table 4: Relationship between median PCT level and CURB-65 groups

CURB-65 groups	PCT (µg/L)		*p*-Value
	Median	IQR	
Group 1 (n = 28)	0.175	0.050–0.490	**0.043**
Group 2 (n = 16)	0.400	0.202–3.405	
Group 3 (n = 6)	0.485	4.077–5.945	

Table 5: Logistic regression results for predicting severe pneumonia and mortality

PCT tier	PSI class ≥ 4		CURB-65 group ≥ 2		Mortality	
	OR	95% CI	OR	95% CI	OR	95% CI
I	1.0	–	1.0	–	Undefined	Undefined
II	1	0.1776–5.632	1.1	0.2222–5.445	1.0	–
III	1.2	0.1637–8.798	1.65	0.264–10.31	1.4	0.3194–60.6
IV	2.625	0.5744–12	2.514	0.581–10.88	2.75	0.2479–30.51



Biomarkers	AUC
PCT	0.839
PSI	0.911
CURB-65	0.864

Figure 1: ROC curves of PCT, PSI, and CURB-65 for prediction of mortality

Median PCT level was 0.030 (minimum) for PSI class I and 4.265 (maximum) for PSI class V. Higher median PCT level was significantly associated with the higher PSI class (Table 3). Median PCT level was 0.175 (minimum) for CURB-65 group 1 and 0.485 (maximum) for group 3. Higher median PCT level was significantly associated with the higher CURB-65 group (Table 4). Among 16 PSI high-risk patients, 25%, 18.7%, 12.5%, and 43.8% were, respectively, in PCT tier I, tier II, tier III, and tier IV. Among 20 CURB-65 high-risk patients, 25%, 20%, 15%, and 40.0% were, respectively, in PCT tier I, tier II, tier III, and tier IV. TLC, CRP, and PCT were significantly associated with positive bacterial culture; PCT was more significantly associated than CRP and TLC. Initial PCT level was significantly correlated with TLC (p = 0.044), CRP (p < 0.001), PSI (p < 0.001), and CURB-65 (p = 0.028). CRP level was correlated with PSI (p < 0.001) and CURB-65 (p = 0.043). PSI was correlated with CURB-65 (p < 0.001). Logistic regression analysis showed odds ratio for predicting severe pneumonia for PSI and CURB-65 remained same/slightly increased at PCT tier II, increased at PCT tier III, and showed more than twofold increase for PSI and CURB-65 at PCT tier IV. Odds ratio for predicting mortality remained same at PCT tier II and showed more than twofold increase at PCT tier IV (Table 5). Receiver operating characteristic (ROC) curves of baseline PCT, PSI, and CURB-65 for predicting mortality in pneumonia showed that area under the curve (AUC) for PSI and CURB-65 was more than that for PCT. So PCT appears to be an inferior predictor of mortality in pneumonia than PSI and CURB-65 (Figure 1).

DISCUSSION

We studied the role of serum PCT as a predictor of prognosis in CAP in relation to other inflammatory biomarkers, such as CRP and TLC, as well as already existing predictive clinical scores, such as PSI and CURB-65. PCT levels were broadly spread across tiers I, II, III, and IV. When stratifying patients according to initial PCT levels, 32%, 24%, 14%, and 30% were, respectively, in PCT tier I, tier II, tier III, and tier IV. Number of patients varied in different studies depending on the sample size. Huang et al.[18] found 32.8% patients in tier I whereas Schuetz et al.[16] found only 12.7% patients in tier I. The risk of ICU admission, disease-specific complications, adverse events, mortality, extent of lung involvement, and bacterial culture positivity significantly increased with higher PCT tiers. Schuetz et al.[16] also found that risk of ICU admission and adverse events increased with increased PCT. In our study, 25% patients each in PSI and

CURB-65 high-risk groups were in PCT tier I (<0.1 μg/L) and were not associated with mortality. This finding was similar to that in a study by Huang et al.[18] in which 23.1% PSI high-risk and 21.9% CURB-65 high-risk patients belong to tier I. Of six deaths in our study, one patient (16.7%) was in PSI low-risk and PCT tier II (<0.25 μg/L). When Kaplan–Meier curves were plotted according to different PCT tiers, we found that in overall patients, PCT tiers did not significantly separate patients for mortality (p = 0.182), whereas in PSI high-risk patients, PCT tiers significantly separated patients with mortality (p = 0.037). Patients with PCT < 0.25 μg/L had no risk of mortality in PSI high-risk group. In CURB-65 high-risk patients, PCT tiers did not significantly separate patients for mortality (p = 0.101). In low-risk group, there was only one death so plot could not be drawn. We can conclude that overall, patients with PCT < 0.25 μg/L had low risk of 30-day mortality and in PSI high-risk group, patients with PCT < 0.25 μg/L had no risk of 30-day mortality. In contrast to our findings, Huang et al.[18] showed that in PSI and CURB-65 high-risk patients, PCT < 0.1 μg/L had low 30-day mortality. We can conclude that PCT is a better predictor of mortality than PSI and CURB-65 in high-risk patients. In overall patients, PCT tiers did not significantly separate patients for adverse events (p = 0.634). PCT (p = 0.001) was more significantly associated with positive bacterial culture than CRP (p = 0.003) and TLC (p = 0.011). In contrast, study by Park et al.[19] showed significant correlation between bacterial culture positivity and PCT as well as CRP but not with TLC. Correlation study between inflammatory biomarkers and prediction scores showed that initial PCT level was significantly correlated with PSI (p < 0.001) and CURB-65 (p = 0.028). CRP level was correlated with PSI (p < 0.001) and CURB-65 (p = 0.043). Similar findings were found in the study by Park et al.[19] Logistic regression analysis was carried out to determine the correlation between PCT levels and severity and morality risk in patients with CAP. Odds ratio for predicting severe pneumonia for PSI and CURB-65 remained same/slightly increased at PCT tier II, increased at PCT tier III, and showed more than twofold increase for PSI and CURB-65 at PCT tier IV. Odds ratio for predicting mortality remained same at PCT tier II and showed more than twofold increase in PCT tier IV. Similar study with different PCT cutoff range was performed by Kim et al.[20] in all age groups and odds ratio increased across different PCT cutoff range for predicting severe pneumonia and mortality.

Our study showed that PCT performed better than CRP and TLC. A study by Kim et al.[20] also showed that PCT performed better than CRP and TLC for prediction of severity in CAP in elderly patients. We concluded that PCT is a better predictor of mortality in PSI high-risk patients. This finding correlates with the findings in a study by Huang et al.[18] Like any other study, our study also had limitations. First, an objective and gold standard prognostic test for CAP is missing to compare with the performance of PCT. Then, high cost of PCT discouraged more frequent serial monitoring. In our study, only two follow-up PCT values could be obtained. Knowledge of assay characteristics, particularly functional assay sensitivity, strengths, pitfalls, and optimal cutoff ranges are the prerequisites for its optimal use. Also, sample size in this study was limited. Finally, outpatients with CAP were not included in our study; therefore, our results cannot be extrapolated to this population.

CONCLUSION

In the light of these findings in our study it appears that the management of severe CAP would be greatly improved if it were possible to identify, early in the course of disease, those patients who are most likely to develop complications and are at the risk of mortality. Although the full potential of PCT must still be established, it appears that it may be a helpful marker as a predictor of prognosis in high-risk patients.

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