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## C-Reactive Protein and Procalcitonin in Predicting Treatment Failure in Community Acquired Pneumonia

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# C-Reactive Protein and Procalcitonin in Predicting Treatment Failure in Community Acquired Pneumonia

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## Abstract

**Introduction:** There has been rising attention in the evaluation of procalcitonin, and C-reactive protein serum levels for predicting treatment efficacy of patients who hospitalized for community acquired pneumonia.

**Methods:** Taken of blood samples for measurement of (CRP) and (PCT), on the day of admittance (PCT-D1; and CRP-D1), within (48–72) hours after the admittance (PCT-D3; and CRP-D3), also in 144–192 h next to admission. CURB 65 in adding to the (Pneumonia Severity Index) were evaluated on the day of admittance.

**Results:** 112 hospitalized patients with CAP were involved in the work. Failure of treatment was recognized in 30 individuals (26.7%). Patients experienced early treatment failure displayed highly significant results of; PCT D1, D3, and CRP D3, PCT D3/D1 ratio, and CRP D3/D1 ratio than in those whose treatment was successful. CRP D1 values were similar in both groups. Patients experienced late treatment failure displayed highly significant elevated values of PCT3, PCT D3/D1, PCT D7, PCT D7/D1, CRP D3, CRP D3/D1, CRP D7, and CRP D7/D1 than in patients who had treatment success. The PCT D1 values augmented with elevating severity of pneumonia. Nevertheless, the results of (CRP-D1) were not.

**Conclusions:** (PCT) should be defined sequentially not on admittance alone to expect the therapy outcome in hospitalized community acquired pneumonia patients.

**Keywords:** C reactive protein, Pneumonia, Procalcitonin, Treatment

## 1. Introduction

Diagnosis of pneumonia is commonly interesting and challenging. Symptoms and signs with huge heterogeneity, for instance dyspnea may be atypical or non-diagnostic, plain X ray of the chest outcomes may be indeterminate, furthermore drawback of pneumonia may be confusing issues.<sup>24</sup>

Medical reports have shown that high mortality rate from (CAP) ensues predominantly in patients suffering from treatment failure.<sup>2</sup> Calculation and evaluation of the disease severity to predict the consequence are fundamentals for optimal distribution of healthcare resources, in addition management preferences in the treatment of CAP. CURB 65 and Pneumonia Severity Index, the scores

have been appropriate for the expectation of patient's mortality and also their application for prediction of other CAP related adverse effect and results still not established. Both scoring methods have limited use in scientific and clinical application, together with shortage of clinical feasibility and merely moderate percentage of sensitivity as well as specificity.<sup>7</sup> In order to overwhelm these application limits, there is upward awareness and clinical researches in the possible practicality and application of biomarkers as per C-reactive protein and also procalcitonin in the management of (CAP).<sup>10</sup>

The usefulness of PCT detection and measurement for evaluating and prediction the outcomes and prospects of patients with CAP still debatable. Majority of the researches concerning the

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effectiveness of measurement of PCT in CAP have concentrated on evaluation and prediction of mortality, and limited researches have explored and assessed anti-microbial usefulness in the short term.<sup>33</sup>

CRP is a well-identified biomarker in various studies and medical backgrounds, however has been believed inadequate as a perfect and beneficial indicator in the treatment and management of CAP patients. In detail, all types of infections, inflammation, stress responses, tumor disease, and autoimmunity can participate, to the elevation of CRP levels in the serum. PCT; is a (116 amino acid) long precursor of calcitonin, which is made by the thyroid gland., Hepatic monocytic cells and macrophages are involved in the (PCT) synthesis in sepsis.<sup>31</sup> The grade of introduction of PCT associates with the organ dysfunction presence and systemic infection severity. Owing to many influences, some researches have stated debatable results and conclusions on the effectiveness of (PCT) and (CRP) in identification of pneumonia in several patients.<sup>16,24</sup> The current work aim was to estimate and evaluate the practicality of consecutive (PCT) and (CRP) measurement during follow up in providing information about the clinical outcome and predicting initial and late failure of treatment to correct treatment in patients hospitalized and presented by community acquired pneumonia.

## 2. Material and methods

This study was a prospective observational type. Patients hospitalized with pneumonia at Al Sahel Teaching Hospital (excluding hospital acquired pneumonia) with a radiological confirmation was recruited from November 2017 to February 2020.

Only CAP patients were evaluated and analyzed in this work. CAP was diagnosed as specified via the (Infectious Diseases Society of America; and American Thoracic Society rules),<sup>4</sup> such as the radiologically occurrence of a novel chest infiltrates, with a minimum presence of one medical symptom like fever, dyspnea, cough, production of sputum, and pleuritic type of chest pain, and a minimum presence of either coarse rales upon auscultation or raised inflammatory markers, encompassing CRP in addition to white blood cell count. Rejection items were age less than fifteen years, hospital acquired pneumonia and acquired immune deficiency syndrome. The clinical characteristics of the investigated patients involved (age, sex, associated comorbidities, vital signs, routine laboratory investigations, and radiological extent of chest infiltration) were determined. The pneumonia intensity

and severity was evaluated by the PSI, and (CURB-65) comprising of confusion, level of urea more than 7 mmol/L, respiratory rate equal, or more than thirty breaths/minute, systolic blood pressure < (90 mmHg), or diastolic blood pressure  $\leq$  than (60 mmHg), and age equal or more than 65 years.<sup>1</sup>

Sputum and blood were taken on admittance for cultures to identify the causative bacterial organism of CAP. A bacterial etiology was recognized according to items of a preceding article.<sup>27</sup>

PCT and CRP levels in serum were detected on hospital days; (1, 3, and 7), and were defined as (PCT3, CRP7 and PCT7), and (CRP1 and PCT1, CRP3) respectively. CRP and PCT were estimated by using Roche cobas E411 automatic bio-chemistry analyzer. (CRP) concentrations were measured using an immune-turbidimetric method. The analytical and diagnostic cut-off value of (CRP) was established by producer at; 5 mg/L levels of (PCTng/mL) were detected using electrochemiluminescence technology.

Failure of treatment was defined as either perseverance or recurrence of fever more than (37.8 °C) and radiological advance, a 50% or more rise in the degree of chest infiltrates, as well as worsening of the clinical condition, pleural effusion and or empyema, which would require a changing in the antibiotic therapy or death. Success of treatment was described as partial or complete resolve of the symptoms and also clinical and radiological signs of pneumonia from ten to fifteen days without the reappearance of novel symptoms and or signs and without requisite to adjust or change the treatment with antibiotic. Comparing were then completed among patients who had (TS) and (TF). The written informed and learned consents were got from all patients. The research was accepted and approved via the confined ethics commission of General Organization of Teaching Hospital and Institutes (GOTHI).

### 2.1. Statistical analysis

Data and information were gathered, checked out, coded, and recorded into (IBM SPSS) version 23. The quantitative information was given like (mean, and standard deviations); when parametric, and median using range of inter quartile when non-parametric. Similarly, qualitative variables were offered as digit and fractions. The comparing among two collections with qualitative information was completed by Chi-square test. The comparing among two groups with quantitative information and parametric spreading or scattering were completed through (independent t test), whereas

Table 1. Patients with treatment success and treatment failure baseline characteristics.

		Total	Treatment Failure Group	Treatment Success Group	Test-Value	P Value	Sig
		No. = 112	No = 30	No. = 82			
Age (yrs.)	Mean ± SD	57.28 ± 7.39	56.57 ± 5.81	57.99 ± 8.97	-0.807 <sup>b</sup>	0.421	NS
Sex	Females	41 (36.6%)	9 (30.0%)	32 (39.0%)	0.771 <sup>a</sup>	0.380	NS
	Males	71 (63.4%)	21 (70.0%)	50 (61.0%)			
Curb	Mean ± SD	1.77 ± 1.105	2.00 ± 1.23	1.54 ± 0.98	-1.780 <sup>b</sup>	0.075	NS
Types of co-morbidities	COPD	4 (3.6%)	1 (3.3%)	3 (3.7%)	0.007 <sup>a</sup>	0.935	NS
	Renal	12 (10.7%)	2 (6.7%)	10 (12.2%)	0.702 <sup>a</sup>	0.402	NS
	Ch. Ht. Dis.	29 (25.9%)	8 (26.7%)	21 (25.6%)	0.013 <sup>a</sup>	0.910	NS
	DM	10 (8.9%)	4 (13.3%)	6 (7.3%)	0.978 <sup>a</sup>	0.323	NS
	Malig	10 (8.9%)	4 (13.3%)	6 (7.3%)	0.978 <sup>a</sup>	0.323	NS
PSI	Liver	7 (6.3%)	2 (6.7%)	5 (6.1%)	0.012 <sup>a</sup>	0.912	NS
	Mean ± SD	105.385 ± 23.09	120.03 ± 18.73	90.74 ± 27.45	5.395 <sup>b</sup>	<0.001	HS

Non-Significant: P > 0.05, Significant: P < 0.05, Highly Significant: P < 0.01.

<sup>a</sup> Chi Square Test.

<sup>b</sup> Independent T-Test.

with non-parametric spreading and distribution were completed by usage of (Mann Whitney test). To evaluate the relationship among two quantitative factors or parameters in the same cluster done by usage of Spearman correlation coefficients. To evaluate the greatest cut-off point in addition to its sensitivity; specificity; positive predictive value; negative predictive value; and area under curve (Receiver operating characteristic curve) was used. The confidence break or interval was established to 95% and the border and margin of fault or error established and recognized was adjusted to 5%. Consequently, the P-value was considered significant at level less than 0.05.

### 3. Result

An entirely 112 hospitalized (CAP) patients (71 were males and 41 were females) mean age were 57.28 ± 7.39 years; were involved in the current work. Failure of treatment was recognized in 30 patients (26.7%). The initial and early (CURB-65) and (PSI) scores were 1.77 ± 1.1 and 105.385 ± 23.09, correspondingly. There were no important changes in age, sex, co-morbidities, or (CURB-65 score) at the presentation and initial stage among the TS, and TF individuals. PSI score, on the other hand, were considerably raised in the TF patients (Table 1). Patients had associated co-morbidities comprising chronic cardiac disease; (n = 29), chronic renal disease; (n = 12), chronic liver disease; (n = 7), COPD, (n = 4), malignant disease (n = 10), and diabetes (n = 10). Dyspnea (n = 81, 72.3%) and cough (n = 88, 78.5%) were the most common symptoms. No major changes of co-morbidities and symptoms were found among treatment success group and treatment failure group (Table 1).

Patients submitted to (PCT-D1; D3; and D7) determination, correspondingly. The initial and late failure of treatment rates were 16% (18/112) and 5.3% (6/112), correspondingly, and the mortality rate in thirty days of admittance was 5.3% (6/112). The utmost common causal micro-organism was Streptococcus pneumonia (27.6%).

When comparing treatment success patients and initial treatment failure patients, patients who had initial treatment failure displayed highly significant raised PCTD1; D3; and CRPD3, but similar CRPD1 values. As concerning the D3/D1 ratio, both (CRP and PCT) were highly significant raised in initial treatment failure patients than in patients who had treatment success (Table 2). This specified that successive determination of these serum biomarker values were beneficial in expecting whether the original (CAP) management would be effective and successful. Patients had late treatment failure presented with highly significant raised values of PCT3, PCT D3/D1, PCT D7, PCTD7/D1, CRPD3, CRP D3/D1, CRP D7, and CRPD7/D1 than in patients with treatment success (Table 3).

The (PCTD1) values elevated with raised pneumonia severity according to (PSI score) (Figure 1). Nevertheless, the values of (CRPD1) were not.

When areas under the ROC curves for the parameters and items were tested, the factors and parameters that best anticipated failure of treatment were the levels of (PSI score) and PCT on admittance, and (PCT) and (CRP) levels on D3 (Figure 2). (Table - 4). Baseline level of PCT >1.1 ng/mL; had a 66.67% sensitivity and a 73.17% specificity, in suspecting treatment failure (Figure 2) (Table 4).

AUC of ROC analysis for PCT D3/D1 and (PSI) for expecting the accurateness of evaluating treatment failure are presented in (Figure 3) (Table 5). (PCT

Table 2. Comparison between early treatment failure and treatment success as regard PCT and CRP levels.

		Early Treatment failure Median (IQR)	Treatment Success Median (IQR)	Test Value	P Value	sig.
PCT1 ng/mL	Median (IQR)	1.5 (1.2–3.1)	1 (0.6–2.3)	–3.489	0.000	HS
PCT3 ng/mL	Median (IQR)	1.9 (1.1–3.2)	0.6 (0.4–1.2)	–4.246	0.000	HS
PCT D3/D1	Median (IQR)	1.19 (0.9–1.38)	0.45 (0.4–1.02)	–4.546	0.000	HS
PCT7 ng/mL	Median (IQR)	0.28 (0.23–0.3)	0.21 (0.11–0.37)	–1.179	0.238	NS
PCT D7/1	Median (IQR)	0.13 (0.08–0.2)	0.16 (0.11–0.2)	–1.537	0.083	NS
CRP1 mg/L	Median (IQR)	75 (64–84)	73 (61–86)	–0.131	0.896	NS
CRP3 mg/L	Median (IQR)	76 (70–94)	46 (39–72)	–3.851	0.000	HS
CRP (D3/D1)	Median (IQR)	1.2 (0.9–1.26)	0.58 (0.58–1.11)	–4.039	0.000	HS
CRP7 mg/L	Median (IQR)	24 (22–27)	22 (19–29)	–0.608	0.543	NS
CRP7 (D7/D1)	Median (IQR)	0.35 (0.26–0.39)	0.31 (0.25–0.38)	–0.501	0.616	NS

Non-Significant:  $P > 0.05$ , Significant:  $P < 0.05$ , Highly Significant:  $P < 0.01$ .

D3/D1), when added to (PSI), had significantly improved predictive ability for treatment failure.

#### 4. Discussion

This work aimed and directed to define whether levels of (PCT) and (CRP) on admittance to hospital and through follow up predict the response and reaction to therapy in hospitalized patients who had community acquired pneumonia.

The included patient's medical characteristics in this work had frequent co-morbidity of pulmonary disorders, congestive heart failure, diabetes mellitus, and cancer. This is in accordance with previous research.<sup>32</sup> Consequently, most previous studies concentrate on the serum biomarkers analytical performance, particularly PCT and CRP on the detection and diagnosis of pneumonia.<sup>7,19,21,22,26,27</sup> Only very limited researches analyzed the predictive values of these biomarkers levels in the serum in the consequences and outcome of pneumonia.<sup>15,18,28,29</sup> A dynamic measurement of biomarkers could capture and detect the disease progress and might be more perfect and efficient in assessing the prospects and prognosis of pneumonia.

In the current study, the most perfect and effective parameters that predict treatment failure were (PCT1, PCT3, and CRP3). Previous study found that (PSI score) and the level of (PCT) were the most helpful parameters that predict treatment failure, and treatment failure were developed in about (15%) of (CAP) patients admitted to hospital, and nearly (6%) present rapidly progressive pneumonia.<sup>25</sup> In a previous research observing the prognosis and outcome of pneumonia in fifty-three sequential patients had CAP; the temperature of the body and WBC on admission and day 3 displayed no changes among the group of survivors and nonsurvivors group.<sup>3</sup> Alternatively, originally elevated and constant increased levels of the patient's biomarkers have been revealed to clarify and recognize the patients who at risk of develop failure of treatment, and these investigated biomarkers can benefit clinicians to well manage their patients.<sup>14</sup>

Ramirez et al. investigated the inflammatory biomarkers role in the identification of CAP patients with severe pneumonia who required admission to ICU. They stated that CAP patients who had severe pneumonia but decreased levels of serum (PCT) could be carefully admitted to the hospital regular

Table 3. Comparing among late treatment failure group and treatment success group as regard PCT and CRP levels.

		Late treatment failure	Treatment Success	Test Value	P-Value	Sig.
PCT1 ng/mL	Median (IQR)	2.1 (1.6–2.1)	1 (0.6–2.3)	–1.408	0.159	NS
PCT3 ng/mL	Median (IQR)	2.6 (2.5–2.7)	0.6 (0.4–1.2)	–3.110	0.002	HS
PCT D3/D1	Median (IQR)	1.24 (1.19–1.28)	0.45 (0.4–1.02)	–3.460	0.001	HS
PCT7 ng/mL	Median (IQR)	2.85 (2.7–3)	0.21 (0.11–0.37)	–3.529	0.00	HS
PCT D7/1	Median (IQR)	1.35 (1.31–1.47)	0.17 (0.15–0.2)	–3.508	0.00	HS
CRP1 mg/L	Median (IQR)	73 (59–90)	73 (61–86)	–0.263	0.792	NS
CRP3 mg/L	Median (IQR)	105 (97–108)	46 (39–72)	–3.482	0.00	HS
CRP (D3/D1)	Median (IQR)	1.4 (1.2–1.48)	0.58 (0.58–1.11)	–3.780	0.00	HS
CRP7 mg/L	Median (IQR)	76 (63–78)	22 (19–29)	–3.569	0.00	HS
CRP7 (D7/D1)	Median (IQR)	1.03 (0.86–1.06)	0.31 (0.25–0.38)	–3.654	0.00	HS

Non-Significant:  $P > 0.05$ , Significant:  $P < 0.05$ , Highly Significant:  $P < 0.01$ .



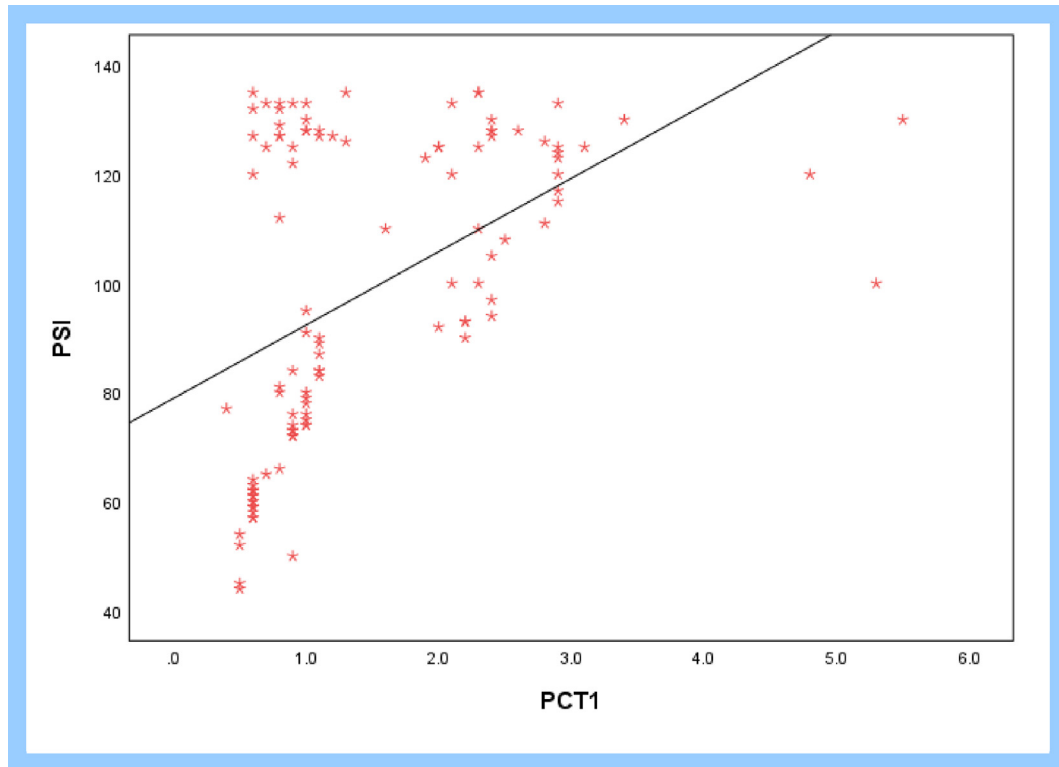


Figure 1. Correlation between procalcitonin level on hospital admission day 1 and pneumonia severity index (PSI).

ward.<sup>12</sup> Additional previous researches<sup>5,8</sup> also studied the significance of monitoring and follow up serum levels of (CRP) and or (PCT) revealed that delayed improvement in these biomarkers could predict an unfavorable consequence.

Detection of patients who had (CAP) and more vulnerable to develop failure of treatment is very significant as this condition is accompanying by

raised mortality rates.<sup>25</sup> The current work has found that in patients suffering from failure of treatment, (PCT) serum levels on admittance to hospital were considerably elevated and continued raised throughout the first three days of therapy.

Schuetz and his associates reported that when examining and studying relative alterations in the concentrations of (PCT) among admittance and day

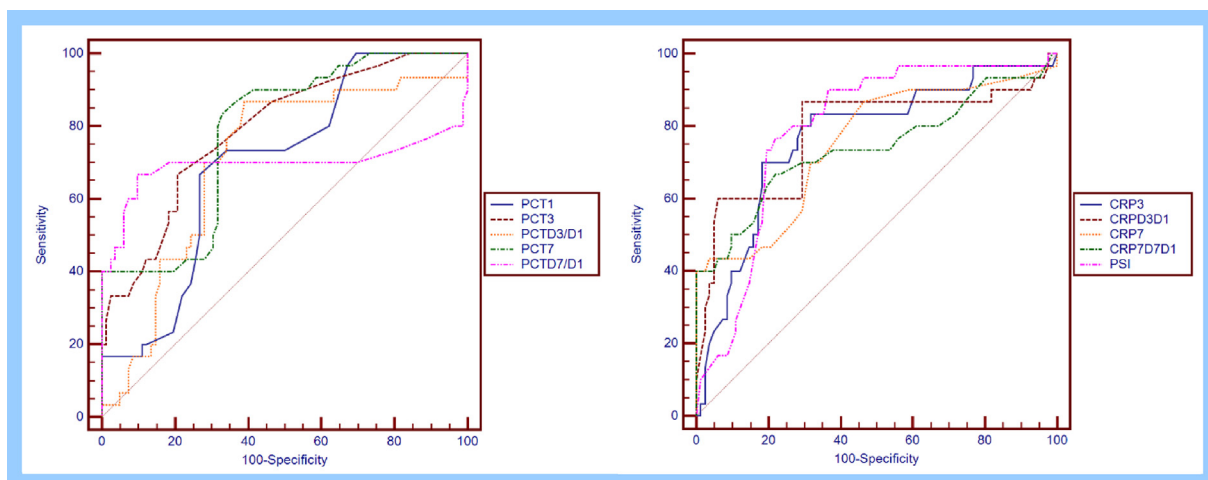


Figure 2. Receiver Operating Characteristic curve between treatment failure and treatment success.

Table 4. Values of sensitivity and specificity for PCT1, PCT3 CRP3, and PSI for predicting treatment failure.

	Cut-off Point	AUC	Sensitivity	Specificity	+ PV	- PV
PSI	>122	0.793	76.67	78.05	56.1	90.1
PCT1	>1.1	0.696	66.67	73.17	47.6	85.7
PCT3	>0.7	0.790	66.67	79.27	54.1	86.7
CRP3	>72	0.768	70.00	81.71	58.3	88.2

3, day 5, and day 7, survivors had a significant lowering of PCT concentration from admission to day3.<sup>13</sup> In another research, (CRP) follow up was a better predictor of the patient's clinical result than leukocyte counts and body temperature.<sup>3</sup> This current study extended and confirmed these results as it exhibited that in CAP patients who had success of treatment the levels of serum (PCT) and (CRP) were lower on the first day of admittance and continued to decrease to minor levels on day3, in distinction to the treatment failure patients in whom these both two markers, on day3, seemed to be the best predictors of treatment failure. Also Tasbakan et al., in 2016 found similar results.<sup>25</sup>

In the current work there was no statistically important changes of the serum levels of serum (CRP1) between the group of treatment success and the group of treatment failure, however (CRP3) were statistically significant higher in treatment failure group. This results specified that the original serum levels of (CRP) could not offer valuable or beneficial data to assist in treatment failure expectation in

hospitalized patients who had CAP, these results were in accordance with the data and results from preceding study.<sup>32</sup> Former researches had reported that only (CRP) initial levels determining did not increase the clinical scores of mortality, however follow the (PCT) kinetics did so.<sup>13,20</sup> The (CRP) levels only on day three but not on admittance (D0) were the potent predictors of the late treatment failure.<sup>6</sup> However, ITO et al., institute that the PCT and CRP original levels were raised in nonsurvivors more than in survivors.<sup>23</sup> The difference in basic features and characteristic of the study groups in these study was the chief etiology for the dissimilar results as regard (CRP). The common age in the current work was younger than of study of ITO's (57.28 vs 73.2), which was above 65 years old, denoting the more severe CAP disease or more complicate comorbidities.

(PCT) serum level has been indicated as a useful marker for starting or even dismissing antibiotic treatment in multiple clinical and medical situations in the former researches.<sup>9,11,20</sup> In the current work we definite the usefulness and prognostic role of (PCT) and (CRP) in (CAP) patient's treatment outcome. Successive serum levels of (PCT3, PCT7, CRP3, and CRP7) were statistically significant lower in group of treatment success CAP than the group of treatment failure. In brief, the current study observed and detected that treatment failure group of patients developed an additional noticeable

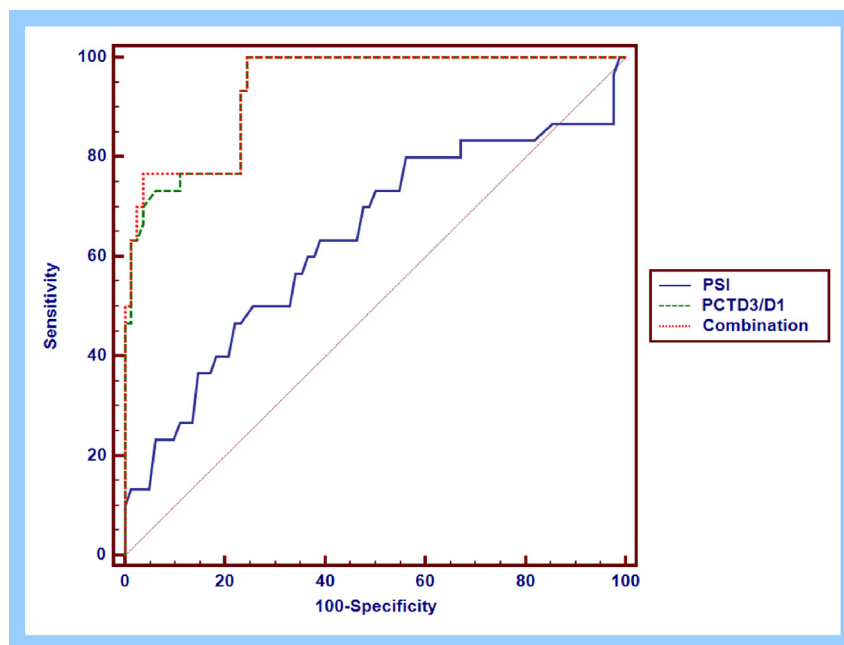


Figure 3. Receiver Operating Characteristic Curve Study demonstrates That PCT D3/D1, in Adding to PSI, had Significantly Better Prognostic Ability for Treatment Failure.

Table 5. PCT D3/D1, in Adding to PSI, had Significant Better Prognostic Ability for Treatment Failure.

	Cut-off Point	AUC	Sensitivity	Specificity	+ PV	- PV
PSI	>122	0.793	76.67	78.05	56.1	90.1
PCT3/1	>0.5	0.704	86.67	60.98	44.8	92.6
Combination	–	0.939	100.00	75.61	60.0	100.0

inflammatory reaction at presentation, and this pro-inflammatory state failed to recover or even show improvement within three days of treatment.

This current work presented that sequential (PCT) measurements and detection were beneficial for expecting the efficacy of treatment of patients with (CAP) and (PCT) level on admission was greater in group of treatment failure patients than in the group of treatment success. Some previous studies have revealed that successive (PCT) measurement and detection was beneficial for expecting the prognosis of CAP patients.<sup>13,17,20</sup> The current study revealed that addition of serial (PCT) measurements on the admittance day and after three days (D3) to the (PSI) was beneficial for predicting treatment failure of hospitalized patients with (CAP). Consequently, sequential measurements and detection of PCT are valuable not simply for expecting prognosis, outcomes and efficacy of treatment, but moreover for improving and rising the prognostic capacity of the (PSI). In the evaluation and assessment of the pneumonia severity, levels of (PCT) on admittance correlated and linked perfectly to the pneumonia severity index PSI, nonetheless the levels of (CRP) on admittance did not, this observation was in agreement with preceding study.<sup>33</sup>

The current work, showed that measurement and detection of (PCT) were perfect in expecting the treatment efficacy and prognosis, alongside in assessment of pneumonia severity consequently, there is a consideration that PCT is more beneficial than CRP as a marker in management of CAP patient. Nevertheless, the elevated price of detection of (PCT) must be taken into consideration, though the effectiveness and value of sequential measurement and detection of (PCT) was established. The price of antibiotics treatment may be decreased as antibiotics therapy might be altered or even introduced initially without use and continuance of ineffectual antibiotics.<sup>33</sup>

Also PCT directed antibiotic treatment has been described to decrease not simply the intake of antibiotic but similarly decrease the antibiotics adverse effects and mortality in patients who had lower respiratory tract infections.<sup>30</sup> Consequently, sequential measurements and determinations of (PCT) are perfect and valuable for expecting

treatment efficacy and mortality, and for antimicrobial stewardship.<sup>33</sup>

In clinical and medical practice, clinicians caring for CAP patients would favor usage a cut off value for (PCT) and (CRP) that would determine the high risk patients group. In the previous research directed by Schuetz et al.,<sup>13</sup> a baseline (PCT) level of more than 1 ng/mL in CAP patients predicted the development of adverse outcome. Similarly, Tasbakan and his associates<sup>25</sup> found a baseline level of (PCT) more than 1 ng/mL had a 56.5% sensitivity and a 78.6% specificity to expect treatment failure in patients who had (CAP). Together with the results of this current work, there seems to be an agreement about cut-off value of (1.1 ng/mL) for PCT in predicting treatment failure.

## 5. Conclusion

For evaluation the treatment efficacy in hospitalized community acquired pneumonia patients, serial procalcitonin and C reactive protein levels measurement is indicated. When the values of these two parameters rise after admittance to the third day, the treatment with antibiotics may require to be altered, and patients who have worsened may need near observation and impeccable monitoring.

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## Authors contributions

T.S.G.: concept, acquisition of data, writing, reviewing, and publishing. M.W.E.: acquisition of data and reviewing. The authors have read, reviewed, and approved the final manuscript.

## Conflict of interest

There are no conflicts of interest.

## Abbreviations

AUC	areas below the (ROC) curves
CAP	community acquired pneumonia
COPD	chronic obstructive pulmonary disease
CRP	C reactive protein
D1, D3, D7	day 1, day 3, day 7
ICU	intensive care unit
PCT	Procalcitonin
PSI	pneumonia severity index
ROC	Receiver Operating Characteristic
TF	treatment failure
TS	treatment success
WBC	white blood count



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