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Procalcitonin as a Predictor for Severity and Etiology of Community Acquired Pneumonia (CAP)

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim of the Work: To study the role of procalcitonin as a predictor for severity and etiology of community acquired pneumonia (CAP).
Subjects and Methods: This study was carried out on 60 hospitalized adult patients with CAP classified into; group I included 30 mild and moderate (15 atypical and 15 typical CAP) and group II included 30 patients with severe CAP (15 atypical and 15 with typical CAP). All subjects were submitted to full history, full clinical examination, chest X-ray (postero-anterior and lateral views) and CT chest in some cases, routine laboratory investigations (complete blood count, liver function tests, kidney function tests and fasting blood sugar), arterial blood gases, microbiological workup, H1N1 and Corona viruses were performed for all patients according to policy of ministry of health, Kingdom of Saudi Arabia. Procalcitonin (PCT) measured within 24 hours of admission.
Results: The study revealed significant higher level of PCT levels in patients with severe CAP-regardless atypical or atypical-with no significant difference between severe atypical and typical CAP. Significant higher PCT levels in patients with severe CAP than patients with mild and

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moderate CAP. Significant higher level of PCT levels in patients with mild and moderate typical CAP than mild and moderate atypical CAP. The X-Ray and CT findings in relation to typical and atypical CAP revealed that the highest PCT level was recorded in consolidation pattern CAP followed by peri-bronchial pattern then ground glass pattern while the lowest level was recorded in random nodular pattern. Positive correlation between Severity of pneumonia according to pneumonia severity index and PCT level.

Conclusions: PCT measurement may provide an important predictor for severity of CAP, while play a little role as a predictor of etiology.

Keywords: Community-acquired pneumonia; procalcitonin (PCT); pneumonia severity index.

1. INTRODUCTION

Community-acquired pneumonia (CAP) is the most common potentially fatal infectious disease throughout western industrialized countries [1]. In CAP clinical chemistry parameters are used in routine diagnostics every day for the diagnosis of infection and follow-up of the disease [2]. Since CAP is an infectious disease, commonly-used laboratory values include the white blood cell count (WBC) and C-reactive protein (CRP), and in some hospitals may be also procalcitonin (PCT). In recent years biomarkers have been intensively studied in CAP, not only for the correct diagnosis of CAP but also with respect to diagnose its microbiological etiology, severity of disease, prognosis and treatment decisions [3]. Procalcitonin (PCT) is a Calcitonin precursor peptide and is produced during inflammation mainly by parenchymal cells [4]. Ever since PCT was reported to be a sensitive marker of severe bacterial infection, its use for evaluating the severity of respiratory tract infections has gradually increased. Christ-Crain et al. [5] showed that PCT measurements may be used as a guide to substantially reduce the use of antibiotics in patients with lower respiratory tract infections and community-acquired pneumonia (CAP) [6].

1.1 Aim of the Work

To study the role of procalcitonin as an indicator for severity of CAP and as a predictor for the etiology.

2. SUBJECTS AND METHODS

This study was carried out between January 2014 and December 2015 at Madina National Hospital, Kingdom Saudi Arabia on 60 hospitalized adult patients with CAP according to local hospital Ethics Committee and written consent after explaining the aim of this study. classified into; group I included 30 mild and moderate (15 cases with typical CAP and 15 cases with atypical CAP) and group II included 30 patients with severe CAP (15 cases with typical CAP and 15 cases with atypical CAP).All subjects were submitted to, full history and clinical examination, chest X-ray (postero-anterior and lateral views) and CT chest in some cases, routine laboratory investigations (complete blood count, liver function tests, kidney function tests and fasting blood sugar), arterial blood gases, microbiological workup included Gram staining with culture and sensitivity for sputum and tracheal aspirate in mechanically ventilated patients, blood cultures and sensitivity and serological tests for atypical pathogens, *Chlamydia pneumoniae*, *Legionella* species, *Coxiella burnetii* and *Mycoplasma pneumoniae* a fourfold or greater antibody rise by complement fixation test for definition of atypical pneumonia were performed . In addition H1N1 and Corona viruses were performed for all patients according to policy of ministry of health, Kingdom Saudi Arabia. Procalcitonin (PCT) measured within 24 hours of admission, two milliliters of venous blood were collected from each patient under complete aseptic conditions using sterile vacutainers containing Li heparin. Samples were centrifuged, aliquoted & frozen at – 20°C until analyzed. The PCT was measured using an electrochemiluminescence immunoassay "ECLIA" technology on cobas e 411 immunoassay analyzer with measuring range of 0.02-100 ng/mL (Elecsys BRAHMS PCT reagent kit, Roche Diagnostics, Germany).

**In samples showing PCT values < 0.5 ng/mL represent a low risk of severe sepsis and/or septic shock. Samples > 2.0 ng/mL represent a high risk of severe sepsis and/or septic shock. Dilution: Samples with PCT concentrations above the measuring range can be diluted manually with PCT negative human serum or plasma. The recommended dilution is 1:4. The concentration of the diluted sample must be ≥ 20 ng/mL. After manual dilution, multiply the result by the dilution factor [7].

2.1 Inclusion Criteria

1- Adult patients with CAP was defined as an acute illness associated with at least one of the following symptoms as fever, new cough with or without sputum production, pleuritic chest pain, dyspnea, or change in the color of sputum in patients with chronic cough or signs as altered breath sound, rales, plus chest X ray showing an opacity compatible with acute pneumonia [1,2].

2- CAP was diagnosed if the patient fulfilled the criteria for pneumonia and the pneumonia had occurred at home or within 48 hours of admission to hospital without residence in a long-term care facility.

2.2 Criteria of Severe CAP

2.2.1 Major criteria (one)

(1) Invasive mechanical ventilation.

(2) Septic shock with the need for vasopressor.

(3) Progressive lung infiltrates (>50% within 48 hours).

2.2.2 Minor criteria (least three)

(1) Confusion/disorientation.
(2) Respiratory rate >30 breaths/min.
(3) Heart rate >120 beat/min.
(4) Hypotension requiring aggressive fluid resuscitation.
(5) Hypothermia (core temperature, <36°C).
(6) Multilobar infiltrates.
(7) Leucopenia (WBC count <4000 cells/mm³).
(8) Uremia (BUN level, >20 mg/dL).
(9) Severe hypoxemia; PaO2/FiO2 ratio <250.
(10) Thrombocytopenia (platelet count, <100,000 cells/mm3) [8].

Table 1. PSI pneumonia severity index score

Clinical parameter		Scoring
Age		Men = age Women= age -10
Nursing home resident		+ 10
Neoplastic disease		+ 30
Liver disease		+ 20
Congestive heart failure		+ 10
Cerebrovascular disease		+ 10
Kidney disease		+ 10
Altered mental status		+ 20
RR > 30 bpm		+ 20
SBP < 90 mmHg		+ 20
Axillary temperature < 35 or > 40°C		+ 15
HR > 125bpm		+ 10
Arterial pH < 7.35		+ 30
Urea > 78 mg/dL		+ 20
Sodium < 130 mEq/L		+ 20
Glucose > 250 mg/dL		+ 10
Hematocrit < 30%		+ 10
PaO2 < 60 mmHg		+ 10
Pleural effusion		+ 10
Classification	**Mortality %**	**Recommendation**
I - No points	0.1-0.4	Outpatient treatment
II - < 70	0.6-0.7	Outpatient treatment
III - 70-90	0.9-2.8	Observation
IV - 90-130	8.5-9.3	Hospitalization
V - > 130	27.0-31.0	Hospitalization

To calculate the severity of pneumonia we used the PORT predictive PSI scoring system, which classifies patients according to outcome in five risk classes (class I includes patients with the most favorable prognosis, and class V includes those with the poorest prognosis). The score of classes I and II is ≤ 70 points; class III, 71 to 90 points; class IV, 91 to 130 points, and class V, >130 points [9]

2.3 Exclusion Criteria

1- Patients with suspected bacterial or viral infection but in whom no pathogen could be identified were excluded from the study.
2- Patients with an inflammatory process other than pneumonia.
3- Patients with positive Corona and/or H1N1 viruses infection.
4- Patients with a prior hospitalization within 2 weeks of current diagnosis of pneumonia.
5- Patients with long-term care facility.
6- Antibiotic use in the prior 14 days.
7- Immunosuppressed patients including those receiving prolonged corticosteroid treatment.

All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Window.

3. RESULTS

These results revealed highly significant higher level of PCT levels in patients with severe CAP than in patients with mild and moderate CAP.

These result revealed significant higher level of PCT levels in patients with severe CAP-regardless atypical or atypical-with no significant difference between severe atypical and typical CAP.

Table 2. Demographic data of studied groups

		Group I	Group II
Age/year	Range	41-60	47-73
	Mean±SD	49.53±6.55	57.53±9.59
Sex(no.)	Male	17	16
	Female	13	14

M= Mean, SD= Standard Deviations, R= Range

These result revealed significant higher level of PCT levels in patients with mild and moderate typical CAP than mild and moderate atypical CAP.

Table 3. PCT level in sever CAP versus mild and moderate CAP

	Severe CAP	Mild and moderate CAP	t. test	P- value
Number	30	30		
Range	6.36-15.7 (ng/ml)	0.34-3.15 (ng/ml)	9.21	<0.001
Mean ± SD	10.32±4.4	1.96±1.56		

PCT = Procalcitonin, CAP = Community Acquired Pneumonia

Table 4. PCT level in severe typical and atypical CAP

	Atypical	Typical	t. test	P- value
Number	15	15		
Range	6.36-16.8 (ng/ml)	8.04-17.7 (ng/ml)	1.82	> 0.50
Mean ± SD	9.9±7.4	11.9±6.56		

Table 5. PCT level in mild and moderate CAP

	Atypical	Typical	t. test	*P*- value
Number	15	15		
Range	0.11-0.45(ng/ml)	2.3-4.7(ng/ml)	4.56	< 0.05
Mean ± SD	0.13±0.29	2.9±1.84		

Table 6. X-ray and CT findings in relation to typical and atypical CAP

X-ray and CT findings	Atypical	Typical	t. test	P- value
Consolidation predominant pattern (Alveolar/lobar Pneumonia)	2	13	8.95	<0.001
Peri-bronchial nodules predominant pattern (Broncho-pneumonia)	15	15	0.001	>0.05
Ground glass opacity predominant pattern	11	2	7.42	<0.001
Random nodules predominant pattern	2	0	2.13	>0.05

Fig. 1 revealed that, the highest PCL level was recorded in consolidation pattern followed by peri-bronchial pattern then ground glass pattern while the lowest level was recorded in random nodule pattern.

Fig. 2 revealed, positive Correlation between Severity of pneumonia according to pneumonia severity index and PCT level.

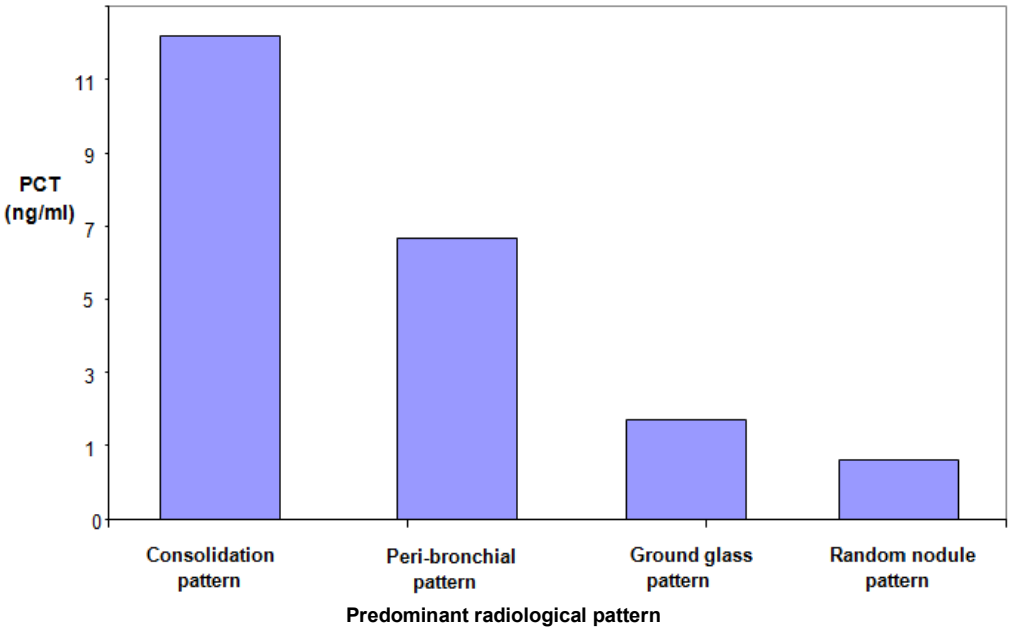

Fig. 1. Procalcitonin level in relation to predominant radiological pattern

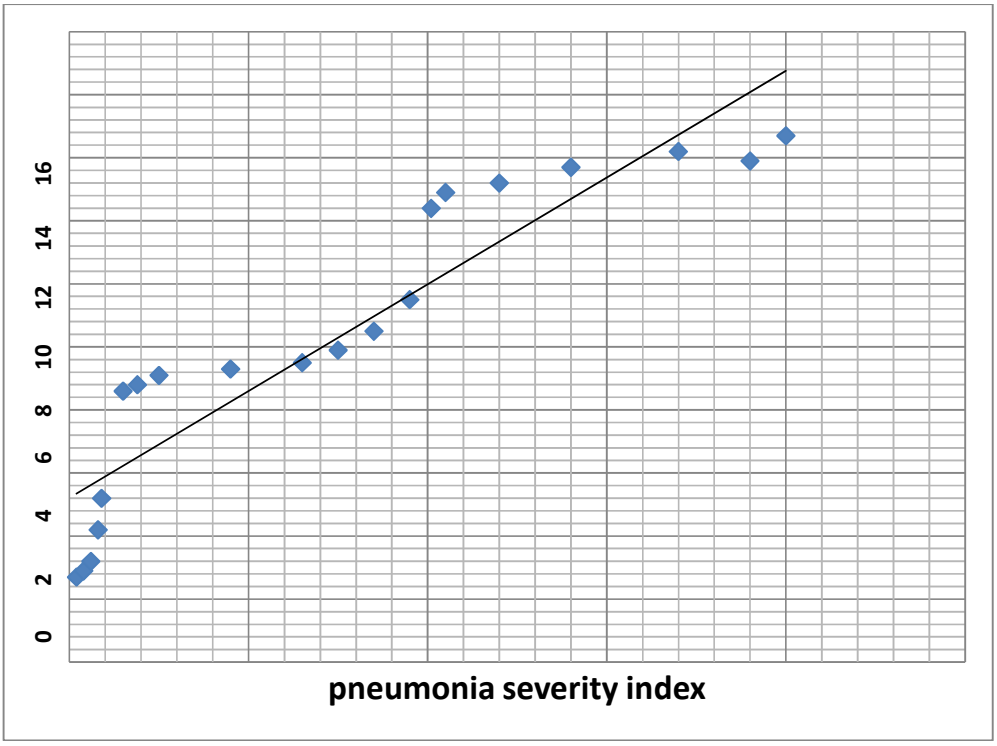

Fig. 2. Correlation between PCT level and severity of pneumonia

There was significant difference in consolidation predominant pattern (Alveolar/lobar Pneumonia) and ground glass opacity predominant pattern between typical and atypical CAP, while there was no significant difference in peri-bronchial nodules predominant pattern (Broncho-pneumonia) and random nodules predominant pattern between typical and atypical CAP.

4. DISCUSSION

The present study was done to assess the role of procalcitonin as an indicator for severity of CAP. The demographic data of the studied subjects included in this study are illustrated in Table 2. Group I included 30 patient (17: male and 13: female) group II also included 30 patient (16: male and 14: female).The mean age of group I was 49.53± 6.55 years while the mean age of group II was 57.53± 9.59 years. In our study, PCT levels (ng/ml) in patients with severe CAP were (R:6.36-15.7, mean ±SD 10.32±4.4) while in mild and moderate CAP were (R: 0.34-3.15, mean ±SD 1.96±1.56) these results revealed highly significant elevation of PCT levels in patients with severe CAP than in patients with mild and moderate CAP Table 3. This in agreement with the results of Peter Berg & Bjarne Ørskov Lindhardt [10]. This result can be explained by, PCT increases markedly during severe infection as many tissues express PCT throughout the body in response to sepsis [11]. These tissues include C cells of the thyroid, pulmonary and pancreatic tissues [12]. In this study, PCT levels (ng/ml) in patients with severe atypical CAP were (R:6.36-16.8, mean ±SD 9.9±7.4) while in severe typical CAP were (R:8.04-17.7 , mean ±SD 11.9±6.56) these result revealed significant higher level of PCT levels in patients with severe CAP- regardless typical or atypical-with no significant difference between severe atypical and typical CAP (Table 4). This result in agreement with study done by Mar Masia et al. [13] they concluded that in CAP patients with a high PSI score, procalcitonin levels were elevated independently of the microorganism implicated, and there were no significant differences in procalcitonin values between main etiologic groups. Procalcitonin levels are raised in severe systemic inflammatory syndrome and sepsis and also in noninfectious marked systemic inflammation, such as inhalation burn injury [14] or chemical pneumonitis [15]. Our study showed, PCT levels in patients with mild and moderate atypical CAP were (R: 0.11-0.45, mean ±SD 0.13±0.29) while in mid and moderate typical CAP were (R:, 2.3-4.7 mean ±SD 2.9±1.84) these results revealed significant higher PCT levels in patients with mild and moderate typical CAP than mild and moderate atypical CAP (Table 5). These results in agreement with the results of study done by Hedlund & Hansson [16] who found that PCT was significantly lower in patients with atypical (Mycoplasma, Chlamydophila, Legionella) than typical bacterial etiology of CAP ($p = 0.03$) – a correlation also reported by Krüger et al. [17] with an AUC of 0.69 (0.66-0.71) at a cut-off value of 0.1 ng/ml and an odds ratio (OR) of 8.3 (95% CI 4.8-14.5). With a cut-off value of 0.25, the OR was 3.2 (2.1-5.0).The same results obtained by Schuetz et al. [6] as they found that, the median PCT was significantly higher in patients with typical than in patients with atypical CAP: 7.64 ng/ml (range 0.26-63.16) versus 0.80 (0.13-34.90) $p = 0.031$. However, the AUC was 0.745 with a wide 95% CI (0.555-0.935). Toikka et al. [18] who reported a significant rise in PCT levels in children with bacterial than viral pneumonia and it was in the case pertaining to the extreme value in the CAP group, the clinical condition of the patient was found to deteriorate progressively. As a result, in later stages, the criterion of sepsis was evident, explaining the high level of PCT [19]. Castelli et al. [20] reported that patient deteriorating progressively with evident criteria of sepsis, had a high PCT level, with a positive correlation between serum PCT concentration and the severity of infection, clinical course, and mortality.

In the present study the X-Ray and CT findings in relation to typical and atypical CAP patients revealed that, there was significant difference in consolidation predominant pattern (Alveolar/lobar Pneumonia) 2 patients with atypical CAP and 13 with typical CAP, also significant difference in ground glass opacity predominant pattern 11 patients with atypical CAP and 2 with typical CAP, while no significant difference in peri-bronchial nodular predominant pattern (Broncho-pneumonia) 15 patients with atypical CAP and 15 with typical CAP, no significant difference in random nodular predominant pattern 2 patients with atypical CAP and no one with typical CAP (Table 6) and Fig. 1. Thus, in cases of severe pneumonia where the role of PCT is limited in differentiation between atypical CAP and typical CAP, we can use X ray and CT findings as a guide for the etiology specially if consolidation predominant pattern and ground glass opacity predominant pattern are found. Also our study revealed positive correlation between severity of pneumonia according to pneumonia severity

index and PCT level Fig. 2. This in agreement with El-dib et al. [21], their study was conducted over 50 patients with clinical and radiological findings compatible with CAP they found that, there was a statistically significant rise of PCT in severe CAP as its mean levels were 4.7± 0.5 and 11.9 ± 27 ng/ml in mild and severe CAP groups respectively. Also in agreement with Vandack Nobre and Isabela Borges [22] and Li Chen et al. [23] they concluded that serum PCT levels are significantly related with detection of CAP pathogen and severity of CAP cases. These results can be explained by microbial toxins and pro-inflammatory mediators (IL-1β, TNF-α, IL-6) induce a significant increase of PCT release from parenchymal organs. Increased PCT concentrations are detectable within 2 h of an infectious bacterial stimulus, which is a more prompt increase compared with CRP, but slower when compared with cytokines, for example IL-6. PCT levels are not elevated in viral infections, because in contrast to bacterial infections a viral infection does not lead to a ubiquitous increase of CALC-1 gene expression and a constitutive release of PCT from all parenchymal tissues and differentiated cell types throughout the body. In a meta-analysis of hospitalized patients, PCT was found to be more sensitive and specific compared with CRP in the differential diagnosis of bacterial infections from noninfectious causes of inflammation. PCT also shows a higher sensitivity to differentiate between viral and bacterial infections [24]. In contrast to systemic infections, localized infections may not lead to systemic elevation in both PCT and CRP serum levels. PCT is very stable even at room temperature and has a half-life of approximately 24 h [7]. As a result of a bacterial stimulus, PCT serum concentrations can increase more than 100,000-fold compared with the base value. PCT is very stable *in vitro*, thus no special pre-analytic procedures are mandatory. Unlike other inflammatory biomarkers including CRP, there are studies showing that PCT production is not significantly suppressed by corticosteroid pretreatment [25].

5. CONCLUSIONS

Procalcitonin can be used as an indicator for severity of CAP. Also, in mild to moderate cases, Procalcitonin and radiological imaging can help in prediction of etiology of pneumonia and subsequently to select empiric antimicrobial therapy. However, further studies among larger number of patients are recommended to corroborate these observations.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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