# The relationship between serum procalcitonin and CURB-65 criteria in hospitalized patients with community acquired pneumonia (CAP)

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**Abstract:** Acute pneumonia is one of the most important and common disease with considerable mortality and morbidity. there are diagnostic scale such as inflammatory markers that one of them is procalcitonin increasing in bacterial infections that is helpful in addition to chest-x ray in diagnosing the pneumonia, hence; in CAP (community acquired pneumonia) is considered as the first marker along with infection. In a descriptive-analytical-cross sectional study, 70 of patients with definite diagnosis of CAP that they were with required conditions to study were assessed. In all patients procalcitonin level was measured before admission and its relation with CURB_65 criteria was assessed. In the last stage, all patients' data was analysed by SPSS software version 16. Totally, 43 (61.4%) of patients were male and 27(38.6%) were female. The mean age of patients was $65.9 \pm 14.8$ that was in the range of 16-88 years old. The mean level of procalcitonin in patients was $4.7 + 1$ ng /ml. In this study, there was no significant relation between CURB-65 criteria and procalcitonin level statistically. 11 of patients died in this assessment unfortunately. The relation of procalcitonin and disease outcomes was not significant. In our study each of CURB-65 parameters in CAP didn't have any significant relation with procalcitonin level statistically, but doing more multicentral studies for confirming or declining the biomarkers roles in CAP seems essential.

## 1. Introduction

Acute pneumonia is one the most common disease with high mortality rate, presence of pneumonia was suspected with clinical findings derived from disease history (fever, cough, sputum, dyspnea) and physical examination (tachycardia, tachypnea, fever and crackle) that would be confirmed after chest x-ray and observation of infiltration. rapid diagnosing and determining of severity and suitable selection of antibiotics therapy, hospitalization and respiratory-vascular protection are essential in order to improve the prognosis of this disease (Donowitz et al., 2010). In the cases with no presence of CURB-65 criteria or presence of one positive parameter, there is indication for outpatient treatment, and in the cases that there is 2 positive parameters, 3 positive parameters or more, there would be indication of inpatient treatment and ICU (intensive care unit) admission, respectively (Lim, 2003). Diagnostic tests including sputum studies and the other respiratory samples, blood cultures, serologic studies, PCR (polymerase chain reaction) and urine studies (detection of Ag) are used in addition to chest x-ray In order to diagnose of pneumonia. Releasing of different cytokines followed by infection is helpful for diagnosing and determining of infection. The markers along with pneumonia include procalcitonin (PCT), CRP(C-reactive protein), STREP-1(soluble triggering receptor expressed on myeloid cells). Procalcitonin, a glycoprotein with 116 aminoacids is secreted by C cells of thyroid gland in response to hypercalcemia (Simona and Gouvin, 2004). The PCT level increases in bacterial infections slightly, but it rarely reaches to higher than 1ng/ml,while in severe bacterial infections increases about 20-200 ng/ml(Christ and Miller, 2007). The procalcitonin levels is a helpful diagnostic marker for determining of pneumonia prognosis due to these main changes in procalcitonin level. Some scientists believed that PCT is produced by liver and (mononuclear cells) MNCs in the blood and is regulated by lipopolysaccharides and cytokines related with sepsis. PCT is produced 4 hours after stimulation, then it reached to peak level after 8 hours, and it is removed as the disease is controlled (Miiler and Harbarth, 2007). The elevated level of PCT in human beings is associated with presence and results of sepsis. Although PCT as a marker is not acceptable and precise, but the PCT level is reliable for controlling of this disease, and it leads to decreased use of antibiotics in lower respiratory infections.PCT increases in bacterial infections

rapidly, so in CAP is the first marker along with infection and elevated level about 0.25-0.5 ng/ml indicate to start of antibiotics therapy. Moreover, decreased level of PCT is helpful to determine duration of antibiotic therapy, and it is helpful in prediction of the rate of mortality (Fmoulin et al., 2001). We decided to assess and study the relationship of PCT level with CURB-65 criteria in the patients with CAP due to the significance of early diagnosing and treating of the CAP.

The functional aim of study is diagnosis of pneumonia by determining the PCT level in CAP and by comparing it with each of parameters, CURB-65 parameters and probably the presence of relation with serum PCT level could be criteria in diagnosing and deciding about hospitalization cases.

## 2. Material and methods

In a cross sectional-analytical-descriptive study, 70 of patients were assessed with definite diagnosis of CAP that they had suitable conditions for this study. All patients were selected by easy sampling method.

Study setting was Imam Reza and Sina hospitals of Tabriz University of medical sciences, From May 2011-september 2012.

Diagnostic criteria for acute pneumonia were respiratory acute symptoms (fever, cough, sputum, dyspnea) along with radiologic signs in chest x-ray. The patients data filled out when referral, According to prepared questionnaire.

Inclusion criteria were: Respiratory symptoms (fever, cough, sputum, dyspnea), Physical findings (dulled sound on percussion, the evidences of canalization, crackle), The radiologic findings (infiltration).

Exclusion criteria were: Cardiac heart failure, Pulmonary thromboembolism, Pulmonary edema, Chronic pneumonia or TB (tuberculosis), Pulmonary occupational diseases, History of recent hospitalization, Hospital-acquired pneumonia, Immunodeficiency. (Consumption of immunosuppressive, transplanted patients, AIDS), Insufficient and incomplete data about patients. Assessed parameters including demographic criteria, behavioural, clinical and para clinical findings. When patients admitted, 2 ml of venus blood was taken from each patient, and the procalcitonin level of that was measured. Measurement of the procalcitonin level was by kits produced by Diasorin Company in Italy (REF 318101) by quantitative determination of PCT method that is a chemiluminescence immune assay sandwich.

The PCT level by this method would be measured 0.1-500 ng/ml.

The results obtained were expressed in the form of mean $\pm$Standard deviation (Mean$\pm$SD) and also percentage and frequency, and then the data was assessed in SPSS version 16

For comparing the quantitative parameters, Student T test and Pearson's correlation coefficient or spearman's were applied and for qualified parameters Chi-square was evaluating test.

In all cases, the results with $P<0.05$ illustrated the significant relation statistically.

## 3. Results

Data related to 70 of patients were analysed statistically that is as follows:

Totally, 43 of patients was male (61.4 %) and 27 were female (38.6%) chart 1. The mean of age of assessed patients was 65.9$\pm$14.8 (Mean $\pm$SD) that they were in the range of 16-88 years old. Patients were subdivided into 4 age groups: There were 3 persons (4.3%), in the age group of below 40-year,7 persons (10%),in 41-50 years old group, 17 persons (24.3%) in 51-60 years old,and 43 persons (61.4%) above 60, 2 cases of patients (2.9%) had the history of alcoholism, 21 cases (30%) the history of smoking and 7 cases (10%) the history of opiates consumption.

Most of patients in this study had the composition of mentioned symptoms that in the following there is description and the frequency comparison in the chart 1 separately. In all of patients PH, PO2, systolic and diastolic blood pressure, the heart rate, the respiratory rate, urea level were measured that all these information and their description is in the chart 2. Blood culture in all patients was done that Just one sample was reported Staphylococcus epidermidis.

According to the chest x-ray, in 27 persons (38.6%) there was involvement in the right lung, in 19 cases (27.1%) in the left lung and in 24 cases both of lungs were involved. The involvement pattern in these patients was the combination of diffused patterns or definite consalidation in CXR (chest X-ray). Serum mean of PCT in the assessed patients was 4.7 $\pm$1.03 ng/ml that was in the range of 0.03-62.12 ng/ml. Among the assessed patients, 16 cases (22.9%) needed to ventilator during clinical process, due to deterioration of disease. The hospital stay was 12.9$\pm$9 days that was in the range of 3-72 days. Among 70 of patients, 59 persons (84.3%) were improved but unfortunately 11 persons (15.7%) despite complete treatment and medical care were died during hospitalization. Description of each of CURB-65 criteria is in the chart 2 with details. In our study 54 of cases (77.1%) had PCT higher than 0.5 ng/ml. In 13 cases (81.2%) of patients with confusion, the PCT level was reported more than 0.5

ng/ml there was no significant relation between confusion and PCT level in statistical analysis (P=0.47). 48 cases of patients with Urea$\geq$ 20 mg/ml (80%), the PCT level was higher than 0.5 ng/ml ; in statistical analysis there was no significant relation between Urea$\geq$20 mg/ml and PCT level statistically (P=0.16). 48 cases of patients with Respiratory Rate $\geq$ 30, PCT level was higher than 0.5 ng/ml ; There was no significant relation between RR$\geq$30 and PCT level statistically (P=0.17). According to this assessment, there was not any significant relation between systolic and dioastolic blood pressures of CURB-65 with serum PCT level (P=0.45,P=0.22 respectively). 27 cases of patients (71%) with age$\geq$65, serum PCT level was more than 0.5 ng/ml; so there was no significant relation between Age$\geq$ 65 and serum PCT level (P=0.15).
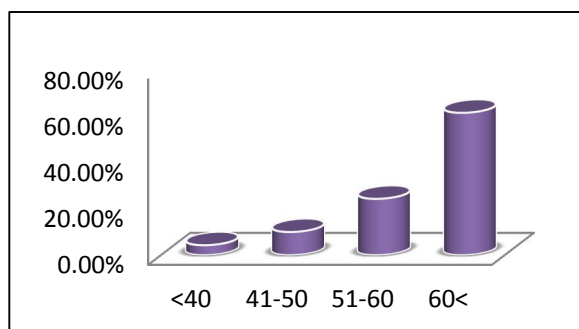
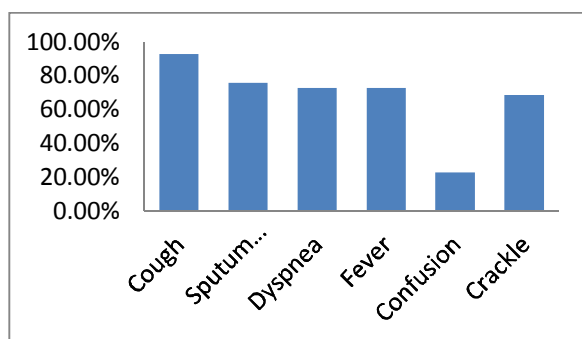

CHART 1: Frequency chart of different age groups



CHART 2: Frequency chart of clinical finding in patients

TABLE 1: Description of paraclinical parameters in the patients

| Variable | Mean±SD | Range |
|---|---|---|
| SBP | 121.6±21.2 | (90-180) |
| DBP | 73.3±9.16 | (48-90) |
| PH | 7.36±0.09 | (7.12-7.67) |
| PO$_2$ | 60.5±16.8 | (27-108) |
| Pulse Rate | 100±17 | (40-143) |
| Respiratory Rate | 32±11 | (18-40) |
| Urea | 40.5±18.6 | (16-97) |

TABLE 2: Description of CURB-65 criteria in patients

| CURB-65 | | N (%) |
|---|---|---|
| C | Confusion | 16 (22.9%) |
| U | Urea $\geq$20 $^{mg}$/$_{dl}$ | 60 (85.7%) |
| R | Respiratory Rate $\geq$30 | 44 (62.9%) |
| B | Systolic BP $\leq$90 mmHg | 3 (4.3%) |
| | Diastolic BP $\leq$60 mmHg | 11 (15.7%) |
| 65 | Age $\geq$65 | 38 (54.3%) |

## 4. Discussion

Pneumonia in pathological definition means infection of alveoli, distal respiratory ducts, and interstitial tissue of lungs shown by increasing in lung weight, substitution of spongy tissue by dense tissue and accumulating of blood cells and macrophages in the alveoli (Tan et al., 1998). In clinical definition, pneumonia is a set of symptoms and signs including fever, shaking chills, cough, pleuretic chest pain, sputum production, hyperthermia, hypothermia, increasing in respiratory rate, dulled sound on Percussion over the affected lung, respiratory bronchial sounds, egophony, crackle, pleural friction rub that they are along with a blurry image of chest in radiography. CAP is a pneumonia that occurs in non-hospitalized patients (Olaechea et al., 2003).CAP is the most common type of respiratory infection that leads to illness in 1% of community people (6 million of American people) yearly that about one fifth of these people would need to be hospitalised and treated. Pneumonia causes disease in 8-15 persons in 1000 people yearly that the most percentage of patients are children and the elderly people. The incidence of this disease in cold seasons is more and it is more common in male than female (ParsaYekta et al., 2001). Pneumonia is made by invasion of variant factors such as viruses, chlamydia, bacteria, mycoplasma, rickettsia, fungi, and parasites that most common of them is bacteria (Rello et al., 2001) Elderly people in comparison to young people show non-respiratory symptoms rather more; for example, it is less common the presence of fever and leucocytosis in this group. Cough is common in 80% of CAP cases that is along with sputum usually, but sputum may not be seen in elderly people or people that they are not able to cough. CAP may be manifested without any respiratory symptoms, but these symptoms may be prominent that indicate the definite diagnosis. These symptoms also include stomach ache, confusion, and headache that confusion is more common in elderly people (Leone et al., 2002). According to the studies, at least 82% of CAP cases were along with a main factor that the most common of them had included heart diseases specially cardiac heart failure (CHF) involving 14% of disease cases and 19% of disease cases were with the other diseases . The other

causative agents including dysfunction of gag reflex, decreasing in mucociliary function, immunodeficiency diseases, decreasing in fever response to infection, inefficient function of cardiovascular system and problems in central nervous system (Shamszade Amiri, 2006). Aspiration is probably the main factor in the infective cases by anaerobic microbes.In the young and elderly people different statistics have been reported (Seguin et al., 2006). Procalcitonin is the progenitor of calcitonin hormone that is secreted by C cells of thyroid gland exclusively in response to hormonal stimulation while different cells in the other organs also can produce procalcitonin in response to pro-inflammatory stimulators especially acterial factors. Procalcitonin is the most reliable parameter for diagnosing and differentiating between the bacterial infections and the viral infections in patients that are hospitalized due to acute agents Such as burns, inflammations, surgeries, respiratory problems, and neonatal infections in early hours in emergency centres and hospitals (Aleva and Boersma, 2005). If the procalcitonin level in serum or plasma was more than 0.5 ng/ml in early 2-24 hours, it might be a sign of a bacterial infection; in the cases that this level increases after 6 hours, it is a appropriate marker that indicates sepsis shock in this patients, and it is necessary to start of antibiotics therapy (Oriano Sanchez et al., 2003). The plasma level of PCT is lesser than 0.5 ng/ml in healthy people, while it might increase to 1000 ng/ml in the patients with sepsis, severe sepsis, and sepsis shock (Esposito, 2005).Releasing of procalcitonin in the blood causes to activate the INF (interferon) receptor that lead to inhibiting of the IL-1 (interleukin-1) beta receptor and this feature is a helpful tool for differentiation bacterial infections from viral infections. PCT in comparison to CRP (C -reactive protein) has higher sensitivity and specificity (Kaplan et al., 2002). The main biologic role of PCT remains unclear mainly; however, recent studies probably showed the pathological role of PCT in sepsis. PCT protein could absorb the leukocytes, and it can also modulate the nitric oxide production by endothelial cells.PCT is a stable protein in the plasma and blood samples, in normal temperature (25ºC), more than 80% of early protein has stability after 24 hours and this level in conditions kept in the refrigerator would be more than 90 % (Marrie et al., 2009).The level of PCT independent on infectious processes increases after different traumas, main surgeries, severe burns or in neonates. The declining level of PCT to basic amounts is rapid in these patients, and further increasing in PCT could indicate sepsis attack viral infections, bacterial colonization,local infections, allergic diseases,autoimmune diseases and transplant rejection that usually don't lead to considerable increasing in PCT level. Nowadays, measurement of procalcitonin level is postulated to differentiate acute bacterial meningitis from aseptic meningitis, but it is already to dubious applying this method clinically (Lamping et al., 2010). a study done by Femolin et al in 2001showed the rapid increasing in PCT level in bacterial infections, so it is resulted that CAP procalcitonin is the first marker along with infection and the elevated level about 0.25-0.5 ng/ml needs to antibiotic therapy; Moreover, the decreasing level of that is effective for deciding about duration of antibiotic therapy, and it also is helpful in prediction of mortality rate (Fmoulin et al., 2001). Masia et al in a study found out that the serum PCT level dependent on disease severity was different to assess CAP cases; according to this study PCT not only is a discriminant of microbial etiology, but also is a prognostic marker in high risk patients in the severity of disease (Masia and Gatierrcz, 2010).The other study by Holm et al demonstrated that the PCT level more than 0.06 ng/ml and also CRP more than 20ng/ml are probably followed by radiological evidences of pneumonia, bacterial infection and next hospitalization; in this study, the value of PCT as an inflammatory prognostic marker was reported low (Holm, 2007). According to presence of challenges in diagnosing and treating of CAP and the importance of this issue, in this study we assessed the relation between PCT level and CURB-65 criteria in patients with CAP.in statistical centre of Iran, no study was done in this issue and just some limited studies in this field were found that we used them in order to compare the results in this portion. As it was mentioned, PCT increases rapidly in bacterial infections, so in CAP is the first marker along with infection and the elevated level about 0.25-0.5ng/ml is the indication for starting the antibiotics therapy; moreover, the decreased level is useful in deciding about the duration of treatment and it is also useful in prediction of mortality rate (Fmoulin et al., 2001).

In the study of Stolz et al, the sensitivity and specify of bacterial infection symptoms and signs was low in deciding to start antibiotic therapy in lower respiratory tract infection, while in chest x-ray infiltration along with the PCT level higher than 50 mg/l or higher than 0.1 ng/ml was very helpful to decide to start treating by antibiotics (Stolz and Chris, 2006).

In other studies, PCT was more useful than the other markers as diagnostic marker in determination of the disease severity and the risk of death, and it is mainly a Guide criterion in order to determine the necessity of antibiotic therapy; according to studies determination of PCT lead to decreasing of misused antibiotic therapy (Nakeeb and Clermont, 2005).

In other study done by Holm et al in 2007, the results indicated that PCT level was higher than 0.06 ng/ml and CRP level higher than 20ng/ml were associated with radiological evidences of pneumonia, bacterial infection and following hospitalization, While the positive predictive value was low for both inflammatory markers as clinical and functional criteria (Holm, 2007).

A prospective cohort study indicated that physicians considered the risk of death in the patients with CAP more than the real rate and this leads to non-essential admission in hospitals; the scoring systems were designed for categorization of the patients based on mortality risk and in order to help for deciding about admission in hospitals. There are significant differences between the scoring system of disease severity in Europe (CURB-65) and USA (pneumonia severity index).The thorax society of UK protect from CURB-65 scoring system designed to diagnose the patients with pneumonia while the index of pneumonia severity diagnose the lower risk patients (Durington and Summers, 2008). In all of assessments no similar study was done in the assessment of a relationship between higher PCT level and CURB-65 criteria In the study of Masia et al, the results indicated that serum PCT level was different in assessment of CAP dependent on the severity of disease. According to this study PCT not only is significant to diagnose the microbial etiology, but also is a prognostic marker in the patients with high risk of disease severity (Masia and Gatierrcz, 2010).

In our study the relation between PCT level and CURB-65 was assessed .In 54 cases (77.1%) the PCT level was higher than 0.5 ng/ml ; in this study there was no significant relation between the PCT level and CURB-65 criteria; For example, in 13 cases (81.2%) of 16 patients with confusion, the PCT level was higher than 0.5 ng/ml, so in analytical study the relation between confusion and PCT level was not significant statistically (P=0.47) this non-significant relation was due to the PCT level higher than 0.5 ng/ml in the patients without confusion. According to this point the relationship between serum PCT level and confusion and the other CURB-65 criteria is datable and doubtful. The mean duration of hospitalization was 12.9$\pm$9 days in the range of 3-72 days. Among assessed 70 of patients, 59 persons (84.3%) improved but unfortunately 11 persons (15.7%) died despite complete medical care and treatment. In a research done by Muller et al in 2007, the results indicated the significance of the PCT level along with the other symptoms and signs of pneumonia including chest-x ray and clinical symptoms (Miiler and Harbarth, 2007). In this study also similar to Muller's study the clinical symptoms

and chest-x ray findings were assessed, chest-x ray showed the involvement of right lung in 27 of cases (38.6%), the involvement of left lung in 19 cases (27.1%), and in 24 of cases (34.3%) both lungs were involved. The pattern of involvement in CXR was combination of diffused patterns and consolidation.

In contrast to our study, in Muller's study the relation between PCT level and CURB-65 criteria was not assessed. Mirjam et al in a similar study in looking for the role of PCT as a sole diagnostic and therapeutic marker found that PCT is not useful to diagnose the CAP and need to interpret along with the other symptoms and findings (Mirjam and Steven, 2010). As it was expressed the results of Mirjam's study was similar to Muller's. With considering the results obtained in different studies about PCT criteria and its relation to CURB-65 criteria in diagnosing of CAP, it can be resulted that CURB-65 criteria is a helpful method for diagnostic decision and treatment management in CAP. In our study 54 of patients (77.1%) had the PCT level higher than 0.5 ng/ml; furthermore, in the statistical analysis there was no significant association between disease outcome and serum PCT level statistically. (P=0.51)In contrast to our study in none of the assessed studies in this field, the relation between serum PCT level and clinical disease outcome was assessed. However, the diagnostic role of procalcitonin and decision based on its serum level is datable and more studies appear to be needed in a larger sample and also comparing Procalcitonin with other diagnostic biomarkers in CAP assessment of PCT level in hospital-acquired pneumonia

## 5. Conclusion

Our study showed no significant association between serum PCT level and CURB-65 parameters in CAP. Further studies to confirm or decline the present biomarkers in CAP, is recommended.

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