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# Evaluation of IL-6, PCT and CRP levels in sera of Patients with Pneumonia

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**Abstract**
C-reactive protein (CRP) and Procalcitonin (PCT) are biomarkers used in clinical practice for monitoring pneumonia management. Interleukin-6 (IL-6) is an important multi-functional pro-inflammatory cytokine and is implicated in acute inflammatory conditions. This study aimed at evaluating Interleukin 6, Procalcitonin, and C-reactive protein levels in patients with pneumonia. Our study included 50 sputum and blood samples from outpatients who suffered from pneumonia and patients attending The Tuberculosis Center- Baghdad Medical City from the 1st of June to the 12th of December 2020. Sputum specimens were cultured on different media, Gram stained, and were examined using biochemical tests, including oxidase, catalase, IMVIC test, as well as Kligler Iron agar. Optochin, bacitracin sensitivity tests, and confirmative tests by Vitek-2 compact system were also performed. In addition, serum IL-6, PCT, and CRP levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA). Our study showed a high increase in IL-6 levels in Gram-negative bacterial pneumonia compared with Gram-positive pneumonia. Whereas, levels of CRP and PCT were high in mixed bacterial pneumonia. Taken together, those findings suggest that bacteria could modify the response to Gram-positive bacterial components, and different cytokine profiles triggered by Gram-positive and Gram-negative bacteria might bacterial clearance depending on t differences in the cell wall structure.

**Keywords:** Interleukin-6, C-reactive protein, Procalcitonin, Pneumonia, Gram positive, Gram-negative

## Introduction
Pneumonia is the leading cause of morbidity and mortality among children aged less than five years in low and middle-income countries [1]. Pneumonia is typically classified as either community-acquired (CAP) or hospital-acquired (HAP), as the two conditions tend to differ in terms of clinical presentation, pathogenesis, and treatment. CAP is typically caused by antibiotic-sensitive strains of Streptococcus pneumoniae, Klebsiella pneumoniae [2]. However, HAP is more commonly caused by multi-drug resistant strains of Staphylococcus aureus and Pseudomonas aeruginosa [3]. The disease is caused by bacterial and viral infections and to a lesser extent by parasites and fungi [4]. The patient's age and comorbidities play an important role in determining the risk and disease severity of pneumonia. Therefore, patients with other diseases, such as diabetes, cancer, chronic heart failure, chronic obstructive pulmonary disease (COPD), and coronary artery disease have a higher incidence of pneumonia. Lungs contain the airway epithelial cells, tissue-resident alveolar macrophages, and monocytes circulating in the bloodstream. The ability of alveolar macrophages to produce cytokines is believed to be a key factor for the initiation of immune responses in the lungs [5]. Biomarkers are used to diagnose the disease quickly and reduce the length of antibiotic exposure. As a result, biomarkers can aid in the selection of antibiotics as well as the measurement of therapeutic response [6]. For the differential diagnosis of mixed bacterial pneumonia, PCT had a high sensitivity (84%) and a low specificity (64%) for the detection of secondary bacterial infections [7]. CRP is an acute-phase reactant protein that is largely produced during the early phase of the inflammatory response by an IL-6 mediated mechanism that increases CRP transcription. CRP could behave as anti-inflammatory and pro-inflammatory immune mediator [8]. It activates the classic complement pathway and stimulates phagocytic cells via Fc receptors to expedite the removal of cellular debris, damaged cells, and foreign pathogens.
When stimulated with bacterial endotoxin, PCT levels increase approximately 4h after exposure, thereby reacting faster than CRP and slower than IL-6. CRP. shows significant changes 10 to 12h following the onset of infection. Consequently, as an early diagnostic marker, IL-6 is more sensitive than CRP and PCT [9].

## Materials and Methods
### Sample collection and identification
The study included collecting 50 samples of sputum and blood from outpatients who suffered from pneumonia and patients were attending The Tuberculosis Center/Baghdad Medical City during the period from the 1st of June to the 12th of December 2020. Samples were collected under the supervision of a qualified physician with an informed consent of patients. A detailed history of the medical condition and the clinical presentation of each patient were collected as well.

### Sputum Samples
Early morning specimens were preferred for the sputum collection. Samples were grown on different media such as blood agar, MacConkey agar, Chocolate agar, mannitol salt agar, and were incubated at 37°C for 24 hours. The colonies were identified by morphology, lactose fermentation on the MacConkey agar, Gram stain, and biochemical tests, involving oxidase, catalase, indole, methyl red, Voges-Proskauer, citrate utilization [10]. Kligler iron agar, Optochin, bacitracin sensitivity, and Vitek-2 confirmative tests were also used.

**Blood Samples**

Venous blood samples (5 ml) were drawn from pneumonia patients and healthy controls and serum was collected by centrifugation at 3000 rpm for 10 minutes. Then, separated sera were stored in sterilized plain tubes at -20°C for further downstream analyses. Using a fully automated chemistry analyzer, Serum levels of IL-6, CRP, and PCT were quantified by ELISA.

**Result and Discussion**

**Distribution of bacterial isolates according to conventional methods**

The studied group was classified into three subgroups according to Gram stain, cultural characteristics, and biochemical tests. In this study, Staphylococcus aureus positive cultures were the highest among bacterial isolates (35.29%), followed by streptococcus pyogenes (19.11 %), Streptococcus Viridans (8.82 %), and Streptococcus Pneumoniae (5.88 %) Regarding Gram-negative bacteria, (8.82%) of isolates were Klebsiella Pneumonia, (8.82%) Enterobacter Cloacae, (5.88%) Escherichia Coli and Pseudomonas aeruginosa, and (1.74%) Haemophilus influenza (Table 1).

**Table 1**

| Isolate | Type of infection | No. | % |
|---|---|---|---|
| S. aureus | Single | 9 | 26.47 |
| S. Pneumonia | | 2 | 5.88 |
| S. viridans | | 3 | 8.82 |
| S. Pyogens | | 3 | 8.82 |
| H. influenza | | 1 | 2.94 |
| K. pneumonia | | 6 | 17.64 |
| E.coli | | 1 | 2.94 |
| E. cloacae | | 6 | 17.64 |
| Ps.aeruginosa | | 1 | 2.94 |
| Total | | 34 | 100% |
| S. Pyogens+S. aureus | Mixed | 10 | 55.55 |
| S. viridans +S. aureus | | 3 | 16.67 |
| S. aureus +S.Pneumonia | | 2 | 11.11 |
| E. coli+Ps. Aeruginosa | | 3 | 16.67 |
| Total | | 18 | 100% |

Biochemical tests were used to differentiate between Gram-negative and Gram-positive bacteria. Catalase, oxidase, and the optochin test were used to distinguish between species of the optochin-sensitive *Streptococcus pneumoniae* and optochin-resistant alpha-streptococci, and results were reported depending on the presence or absence of distinct inhibition zones. Bacitracin sensitivity test was used for differentiating between species of Streptococcus pyogenes and other beta-hemolytic streptococci. The lung induces robust immune responses to invading pathogenic bacteria. The first layer of defense against infection is barrier function; mucus and cilia work together to clear the airway of debris and pathogens, and surfactant proteins bind bacteria to improve clearance [11]. Mucus contains collectins and defensins which are regulated by the transcription factors nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and specificity protein 1 (Sp-1) [12]. Activation of NF-κB following signaling from the sentinel toll-like receptors (TLRs) stimulates epithelial cells to increase the production of these compounds as well as pro-inflammatory cytokines, which in turn induce increased production of mucin [13]. Alveolar macrophages patrol alveoli, eliminating extracellular bacteria and displaying antigen to T cells. When pathogenic bacteria enter the lung, recognition by pattern recognition receptors occurs in cells at barrier sites. Epithelial cells produce antimicrobial peptides, which can directly lyse bacteria. Alveolar macrophages make interferons (IFNs) and inflammatory cytokines, resulting in neutrophil and monocyte activation and homing to the lung. Bacteria induce variable chemokine responses, but overall cytokine responses are often conserved. The influx of cells into the lung brings fluids, leading to acute respiratory distress syndrome (ARDS) and significant mortality if unresolved [14]. Host defense in the human lungs relies heavily on innate immune mechanisms that prevent the invasion of pathogens. Pneumonia may be caused by Gram-positive bacteria such as *Staphylococcus aureus* and the innate immune recognition of this bacteria is largely achieved through TLR2-dependent distinguishing of lipoteichoic acids (LTA), lipoproteins, and peptidoglycan from the cell surface and endosomes of antigen-presenting cells and type II epithelial cells [15]. When Gram-negative pneumonia such as K. pneumonia enters the lung, bacterium-specific TLRs are activated, secreting cytokines and chemokines that attract and activate neutrophils. These neutrophils kill all bacteria after ingestion. TLR4 plays a crucial role in the recognition of K. pneumoniae by sensing lipopolysaccharides (LPS) present in the outer membrane of this Gram-negative pathogen [16].

**Estimation of levels of biomarkers among patients and controls groups.**

Serum concentrations of IL-6, PCT and CRP were higher among patients as compared with the controls (0.2032±0.0877, 0.1208±0.0243 pg/ml, $p \leq 0.01$), (1.2060±0.6480, 0.0094±0.0198 mg/L, $p \leq 0.01$) and (32.65± 9.46, 5.83±1.55, $p \leq 0.01$), respectively., as shown in (Table 2).

**Table 2:** Mean concentrations of IL-6, CRP, and PCT among studied groups.

| Biomarkers | Patients (50) | Controls (25) | P value |
|---|---|---|---|
| | mean±SD | mean±SD | |
| IL-6 | 0.2032 ± 0.0877 | 0.1208 ± 0.0243 | 0.0003 |
| CRP | 32.65 ± 9.46 | 5.83± 1.55 | 0.0005 |
| PCT | 1.2060±0.6480 | 0.0094 ± 0.0198 | 0.0006 |

The current study showed the level of IL-6 in the serum of patients with pneumonia caused by Gram-negative bacteria (0.2308±0.0952 pg/ml) is higher than its level in Gram-positive bacteria (0.1855±0.03905 pg/ml) and mixed bacterial infection due to Gram-positive and Gram-negative bacteria (0.2226±0.1740 pg/ml) with no significant statistical differences (Table 3).

**Table 3:** Estimation of IL-6 levels among patients exposed to Gram-negative, Gram-positive, and mixed bacterial infections.

| Groups | No. | IL-6 (pg/ml) | p-value |
|---|---|---|---|
| | | mean± SD | |
| Gram negative infection | 13 | 0.2308a±0.0952 | 0.242 |
| Gram Positive infection | 29 | 0.1855a±0.03905 | |
| Mixed bacterial infections | 8 | 0.2226a ±0.1704 | |

The findings of this study show that the level of serum IL-6 in Gram-negative bacteria is higher than in Gram-positive bacteria and mixed bacterial infection. It agrees with the study of [17], which indicates that IL-6 levels are

Significantly higher in patients with pneumococcal pneumonia than in The bacteria thus seem to modify the response to Gram-positive bacterial components. The different cytokine profiles stimulated by Gram-positive and Gram-negative bacteria might optimize the clearance of bacteria that differ in the cell wall structure[18]. A host may respond differently to LPS of Gram-negative bacteria and LTA of Gram-positive bacteria. Gram-positive and Gram-negative bacteria have different effects on microcirculation [18]. This finding agrees with another study which shows that higher IL-6 concentrations determined in LPS-containing Gram-negative bacteria) as compared with that from Gram-positive bacteria, and can probably be attributed to the activation of different primary TLRs. TLR4 has been identified as the main receptor for enteric LPS, while TLR2 has been linked to Gram-positive cell wall components [19].

**Estimation of PCT levels among Gram-negative, Gram-positive, and mixed bacterial infection**

PCT levels in mixed bacterial infection (Gve+ and Gve – infection) are higher than Gram-negative and Gram-positive infections (Table 4).

**Table 4:** levels of PCT among the three studied groups (Gram-negative, Gram-positive, and mixed bacterial infection).

| Groups | NO. | PCT (mg/L) mean±SD | (p-value) |
|---|---|---|---|
| Gram-negative infection | 13 | 1.232 a± 0.619 | 0.239 |
| Gram-positive infection | 29 | 1.102 a± 0.677 | |
| Mixed bacterial infection | 8 | 1.540 a ±0.522 | |

Our findings are in agreement with a previous study that indicates higher levels of PCT are found in pneumonia patients compared with the healthy control group [20]. Furthermore, Cabral *et al*., 2019 reported that levels of PCT in patients infected by Gram-negative bacteria are higher than in Gram-positive infected individuals. Although the mechanism driving PCT synthesis in response to various bacterial infections is unknown, it could be explained by the distinct interactions of Gram-positive and Gram-negative bacteria with host cells. The mechanism may involve LTA and LPS, in addition to different pathogen-associated molecular patterns (PAMPs) interacting with several TLRs present on human cells [21].

**Table 5:** Levels of serum CRP among Gram-negative, Gram-positive and mixed bacterial infection).

| Groups | NO. | CRP (mg/ml) mean± SD | p-value |
|---|---|---|---|
| Gram-negative infection (Gve-) | 13 | 131.6 a ± 15.8 | 0.048 |
| Gram-positive infection (Gve+) | 29 | 64.9 b 10.9 | |
| Mixed bacterial infection (Gve-& Gve+) | 8 | 172.0 a ± 19.3 | |
| *Means with different letters in the same column show statistical significance (P≤0.05). ANOVA | | | |

These results coincide with Nerhing *et al*., 2017 who found that the level of CRP in patients with (Gve -) infection is higher than in (Gve+) infection but disagree with Deirmengian *et al*., 2016 who identified that the Gram staining of bacteria is not correlated with CRP levels.

Gram-positive and Gram-negative bacteria-driven pneumonia exhibit different mechanisms of inducing acute lung injury or inflammation. Pulmonary epithelial cells (PECs), alveolar macrophages (AMs), innate lymphoid cells (ILCs), and different pattern-recognition receptors (PRRs), including TLRs and inflammasome proteins are involved in neutrophil infiltration and All induction during pneumonia-dependent ALI. Resolving of inflammation is frequently observed during ALI associated with pneumonia. Differences in the immune response to pneumonia-induced ALI caused by Gram-positive or Gram-negative bacteria should be considered to design specific immune-based therapeutics. The innate immune system serves as the first line of defense against foreign pathogens via recognizing their PAMPs or microbe-associated molecular patterns (MAMPs). Also, innate immune cells recognize the damage or danger-associated molecular patterns (DAMPs) generated during the pro-inflammatory conditions disturbing immune homeostasis. The recognition of PAMPs, MAMPs, and DAMPs involves several PRRs, including TLRs [22]

**Correlation between the studied parameters in pneumonia patients**

Results in table (6) elucidated the association between IL-6 with PCT which show a negative association (r = -0.188, p>0.01). Whereas there is a positive correlation between IL-6 and CRP (r= 0.271, p>0.01).

**Table 6:** Correlation between the studied Parameters in Pneumonia patients

| Parameter | | PCT | CRP |
|---|---|---|---|
| IL-6 | Pearson correlation | -0.188 | 0.271 |
| | p-value | 0.192 | 0.057 |

**Correlation is significant at the 0.01 level (2-tailed), * correlation is significant at the 0.05 level (2-tailed)

**Correlation between the PCT and CRP among the three groups of study**

Results in table (7) identified the correlation between IL-6 and PCT in the studied groups (Gram-positive, Gram-negative and mixed bacterial infection). We found a negative association between the examined parameters (r= -0.280, p>0.01), (r= -0.251, p<0.01) and (r= -0.407, p<0.01, respectively).

While there was a negative correlation between IL-6 and CRP in Gram-negative pneumonia (r=-0.109, p<0.01), a positive correlation between those immune mediators was detected in Gram-positive and mixed bacterial infection (r= 0.722, p<0.01), (r= 0.518, p<0.01).

**Table 7:** Correlation between PCT and CRP among studied groups

| Group of Study | Parameter | | PCT | CRP |
|---|---|---|---|---|
| Gram-negative | IL-6 | Pearson correlation | -0.280 | -0.109 |
| | | p-value | 0.354 | 0.722 |
| Gram-positive | | Pearson correlation | -0.251 | 0.230 |
| | | p-value | 0.189 | 0.230 |
| Mixed bacterial infections (Gve-, Gve +) | | Pearson correlation | -0.407 | 0.518 |
| | | p-value | 0.317 | 0.189 |
| **Correlation is significant at the 0.01 level (2-tailed), * correlation is significant at the 0.05 level (2-tailed). | | | | |

The result agrees with another study which refers that the serum PCT and CRP concentrations are strongly correlated [23]. CRP protects against bacterial infection by promoting the pneumococcal C-polysaccharide attachment and opsonizing bacteria for phagocytosis and death [24]. Excessive bacterial inflammation may stimulate the expression of IL-6 and other pro-inflammatory factors such as IL-1 and tumor necrosis factor (TNF- α) during the acute phase, and those events may be associated with the enhancement of CRP expression [25].

## Conclusion

This study aimed to evaluate levels of serum quantitative C -reactive protein or nterleukin- 6 and Procalcitonin in pneumonia patients comparing with healthy individual and revealing the correlation between the studied parameters. sera levels of IL-6 in Gve- bacterial pneumonia in studied group showed high percentage comparing to Gve+ and mix bacterial pneumonia group. The inflammatory index CRP and PCT showed high increase in mixed bacterial pneumonia group as compared to Gve - and Gve+ in studied group and as compared to healthy control group in all.

There were negative correlations between PCT, IL-6 and CRP in Gram-negative pneumonia and a positive correlation between IL-6 and CRP was detected in Gram-positive and mixed bacterial infection.

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## Author Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- This research is taken from masters thesis
- The current study was conducted at medical city and Al-Kadhimiya Teaching Hospital in Baghdad during the period from the 1st June to December 2020. This study included sputum collection from **75** pneumonia patients of both gender at different age groups and collecting Peripheral blood specimens from patients and from 25 healthy control group.
- Ethical Clearance: The project was approved by the local ethical committee in University of Tikrit –college of science

## Author's Contribution Statement

Hafsa Abdul-Redha Abass, Suha Maher Abed and Mayada Noori Iqbal contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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