Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages 14411-14418
Received 05 March 2021; Accepted 01 April 2021.

# DIAGNOSTIC VALUE OF PROCALCITONIN LEVEL IN PATIENTS WITH BACTERIAL MENINGITIS

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## ABSTRACT

Background: Meningitis is a medical emergency condition and a life-threatening infectious disease of the central nervous system.

Aim: This study aims to assess the laboratory tests that are performed for septic meningitis and to ascertain the diagnostic value of measuring procalcitonin in CSF and serum of patients with bacterial meningitis in Erbil City.

Method: 43 Clinically related specimens of CSF and blood samples through the period extending from June 2019 to October 2020 from different hospitals in Erbil-Kurdistan region. Negative Control; collected from Nanakaly hospital for hematological disorders-Erbil. Consisted of 20 CSF and blood specimens taken from known cases of blood cancer patients after confirmed negative to all parameters of meningitis and have no history of clinical evidence of acute meningitis.

Result: The mean age of the patients was 21.9 years, 27(62.7%) were male and 16 (32.7%) were female. Among the total patient, 12 (28%) presented with bacterial meningitis, 12 (28%) had non-bacterial meningitis and 19(44 %) patients diagnosed with non-meningitis. There was a highest concentration level of all bacterial meningitis biomarkers ( Crp, Pct, Cell count, Neutrophils) were recorded in bacterial meningitis group. The comparison of PCT level between CSF and blood samples in both patients and controls, Data are shown as mean ± SE, a highly significant difference was observed between CSF and blood samples in both patients and controls subjects ($p<0.01$).

Conclusion: PCT is a highly efficient laboratory parameter involving a simple and rapid beside test for diagnosis and prognosis in bacterial meningitis patients.

## INTRODUCTION

Meningitis is a medical emergency condition and a life-threatening infectious disease of the central nervous system (CNS) that affects meninges layers that covers he brain and spinal cord which are the pia mater, the arachnoid, and the subarachnoid space. Meningitis is a significant cause of morbidity and death worldwide (Barichello, 2017). The main causes of meningitis are bacteria and viruses that invade the cerebral spinal fluid (CSF). Bacterial meningitis (BM), an important and acute infection in the CNS, that cause a serious infectious disease; it is linked to a high rate of mortality and morbidity all over the world (Azimi et al., 2020). Parasites and fungi can also be responsible for a small fraction of cases. Meningitis can occur in all age groups nonetheless, bacterial and viral agents could be different in certain age groups than the others (Shih and Koeller, 2015). BM remains a globally concern disease, which may lead to permanent neurological sequelae in survivors or can end with death even with development in management, health care and availability of effective antibiotics (Herold et al., 2019).

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Procalcitonin is an inflammatory biomarker that produced by the c-cells in the thyroid and its concentration in the serum of healthy individuals is very low. During microbial infection, there is an increase of CALC-I gene expression which causes a release of PCT from all parenchymal tissues and differentiated cell types throughout the body, including the liver and peripheral blood mononuclear cells (Bréchot et al., 2015).

CRP is non-specific biomarker which is rapidly increase in any inflammation or disorder but has proved to be helpful in establishing the etiology of some infections. A high CRP level (>100 mg/L) can be indicator to a severe bacterial infection (Butler et al., 2019)

Laboratory examination of CSF is crucial in meningitis with CSF culture considered to be "gold standard" in bacterial meningitis. Moreover, in vitro susceptibility test is required to rationalize the treatment for causative microorganism (Brouwer et al., 2010). High levels of PCT, considering the severity and guide therapy durations, have a high sensitivity and specificity for diagnosing infections (Schuetz et al., 2012).

However microbiological culturing requires at least 24-48 hours and negative cultures do not exclude the presence of infection (Kim et al., 2011), thus a rapid and reliable test to rule out bacterial infection would be helpful in decision making. Procalcitonin (PCT) has recently emerged as a powerful biomarker for an early and accurate diagnosis of bacterial infection and decisive initial antimicrobial therapy (Bele et al., 2011; Matwiyoff et al., 2012; Uzun et al., 2007)

Because of finding higher levels of PCT in severe bacterial infections than in viral infections as well as nonspecific inflammatory diseases, it has emerged as a promising marker for the diagnosis of bacterial infections (Karlsson et al., 2010).

The aim of this study is to assess Inflammatory Biomarkers that are performed for meningitis and to ascertain the diagnostic value of procalistonin level in blood and CSF of suspected meningitis patients in Erbil city.

## PATIENTS AND METHODS

The study conducted on 43 suspected meningitis patients were infants, children and adults aged from 1 month to 75 years referred to Raparin, Hawler, Rzgari Teaching hospital, PAR, Zhin and other private hospitals through the period extending from June 2019 to October 2020 in Erbil-Kurdistan region.

The study was conducted on 43 suspected meningitis patients who were infants, children and adults aged from 1 month to 75 years old at different hospitals in Erbil-Kurdistan region including Raparin, Hawler, Rzgari Teaching hospital, PAR, Zhin and other private hospitals through the period extending from June 2019 to October 2020 in Erbil city.

Negative Control; collected from Nanakaly hospital for hematological disorders-Erbil. Consisted of 20 CSF and blood specimens taken from known cases of blood cancer patients after confirmation of all clinically related samples as negative to all paramiters of meningitis and have no history of clinical evidence of acute meningitis.

Blood and CSF samples were collected from each individual of study groups. Immunomicrobiologic investigations were done to estimate level of different immunological biomarkers in the serum and CSF of study groups by quantitative determination of procalcitonin (USCN), by enzyme linked immune sorbent assay (ELISA) and finally, hs-CRP in blood (roche Diagnostics) by the cobas e 411 analyzer which is a fully automated analyzer that uses ElectroChemiLuminescence (ECL) technology for immunoassay analysis.

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All conventional diagnostic methods were done for all CSF specimens including gram stain, differential cell count, biochemical and microbiological tests Isolation and identification of the causative agents in the CSF samples were also done by culturing on MacConkey, Blood, and Chocolate agar and in Brain heart infusion broth (BD BBL, USA) under aseptic conditions. They cultured according to the standard microbiological procedure. Bacterial growth was observed after overnight incubation of the agar plates at 37°C in 5% CO2 atmosphere. The bacterial isolates were identified by conventional methods and the type of isolated bacteria and antibiotic susceptibility profiles were determined by the Vitek system (Biomeurex). Statistical analysis was performed by SPSS (Statistical Package for Social Sciences) version 26. The study was undertaken after gaining approve of the ethics committee of the college of Medicine/ Hawler medical university.

## RESULT

The study was designed to investigate some immunological Inflammatory biomarkers (PCT, CRP, IL8,IL-10 ) in suspected acute meningitis patients and control group The microbiological profile was also done on patient groups; and the association between concentration levels of these biomarkers in each group and the microbial isolates were investigated. The age of the patients, ranged from 1 month to 79 years with a mean age of 21.9 years, in which 27(62.7%) patients were male and 16 (32.7%) patients were female. Among the total patient population, 12 (28%) presented with bacterial meningitis . Also 12 (28%) patients had non-bacterial meningitis and 19 (44 %) patients diagnosed with non-meningitis that Showed in Table.1

**Table.1 Demographic characteristics of suspected meningitis patients.**

| **Patient Characteristics** | **Value** |
|---|---|
| Age (Years): Mean+ SE | 21.93+ 4.09 |
| **Gender:** | |
| Male/Female**No. (%)** | 16 (37.3)/ 27(62.7) |
| **Result of Study group** | |
| Bacterial meningitis: No. (%) | 12 (28) |
| Non-bacterial meningitis: No. (%) | 12 (28) |
| Non-meningitis: No. (%) | 19 (44) |

All 43 suspected meningitis patient were differentiated to 3 groups tht1 shown in Fig.1. which are Bacterial Meningitis Group (B.M) were 12 (28) patients, Aseptic Meningitis Group (A.M) were 12 (28%) patients and Non-Meningitis Group (N.M) were 19 (44%) patients according of the immunological inflammatory biomarkers (CRP, PCT) and microbiological parameters (differential cell count, glucose, protein, gram stain, culture)

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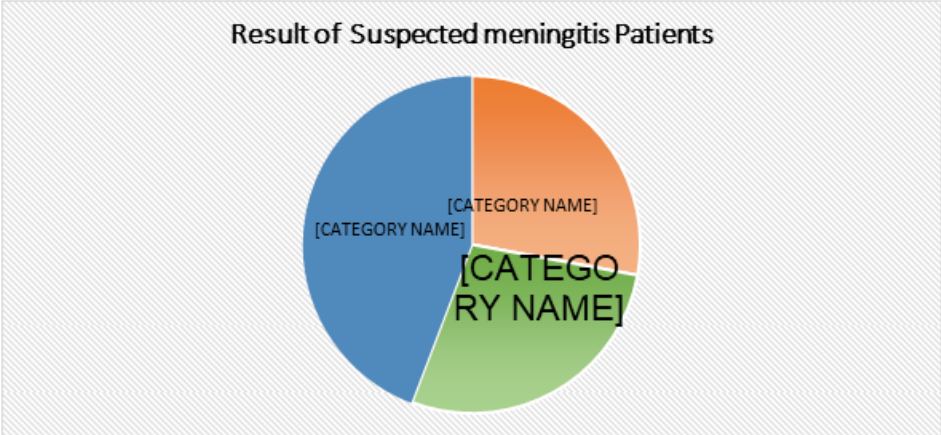
**Fig.1 : Result of all suspected meninges cases according meningitis diagnostic parameters .**




The concentration level of inflammatory biomarkers in isolated microorganisms in table.1 shows that there was a highest concentration level of all bacterial meningitis biomarkers ( Crp, Pct, Cell count, Neutrophils) were recorded in bacterial meningitis group.

**Table:2. Inflammatory Biomarkers Related to Isolated Microorganisms**

| Isolated Microorganisms | CRP g/dL | PCT - blood ng/mL | PCT-CSF ng/mL | Differential cell count | | |
|---|---|---|---|---|---|---|
| | | | | Cells (NO./ uL) | Neut.% | LYM % |
| Staphylococcus aureus | 35.6 | 1.78801 | 828.724 | 170 | %35 | %65 |
| Staphylococcus lentus | 25.4 | 1.72484 | 762.602 | 410 | %75 | %25 |
| Pseudomonas aeroginosa | 39.1 | 1.58266 | 538.989 | 317 | %45 | %55 |
| Pseudomonas aeroginosa | 5.2 | 1.56421 | 510.211 | 2820 | %95 | %5 |
| Staphylococcus haemolyticus | 18.44 | 1.56347 | 507.445 | 115 | %100 | |
| Klebsiella Pneumoniae | 19.8 | 1.28409 | 405.865 | 10320 | %98 | %2 |
| Klebsiella Pneumoniae | 39 | 1.24850 | 397.232 | 577 | %90 | %10 |
| Acinetobacter baumannii | 39.1 | 1.15188 | 374.252 | 317 | %45 | %55 |
| Acinetobacter baumannii | 6.3 | 1.13578 | 351.357 | 5720 | %100 | |
| Acinetobacter baumannii | 11.87 | 1.14348 | 335.352 | 665 | %95 | %5 |
| Enterococcus faecalis | 24.6 | 1.12322 | 312.569 | 102 | %70 | %30 |
| Streptococcus pluranimalium | 2.8 | 1.10859 | 290.564 | 456 | %55 | |

Comparison of inflammatory biomarkers between study groups witch are patients with Bacterial meningitis, aseptic meningitis, non-meningitis and control groups were detailed in Table 2. There was Highly significant difference between the Bacterial meningitis group with other groups ($P > 0.05$). the mean concentration of CRP-Blood,PCT-Blood and PCT-CSF in B.M

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Group were 22.26 ±3.98 , 1.306± 0.67, and0.467 ±0.0 respectively. While the the mean concentration of Blood CRp-Blood,PCT-Blood and PCT-CSF in Control Group were 3.08 ±0.52, 0.125 ±0.07, 0.018 ±0.02 respectively.

**Table 3: The descriptive statistics for the mean concentration of Inflammatory Biomarkers among Study Groups.**

| Inflammatory Biomarkers | Aseptic meningitis Mean ± S.E | Bacterial meningitis Mean ± S.E | Non-meningitis Mean ± S.E | Control Patients Mean ± S.E | P. Value ANOVA |
|---|---|---|---|---|---|
| CRP | 3.85 ±2.12 | 22.26 ±3.98 | 3.96 ±1.09 | 3.08 ±0.52 | 0.001 |
| PCT - Blood | 0.859 ±0.23 | 1.306 ±0.67 | 0.566 ±0.31 | 0.125 ±0.07 | 0.001 |
| PCT - CSF | 0.160 ±0.060 | 0.467 ±0.049 | 0.035 ±0.018 | 0.018 ±0.02 | 0.001 |

## DISCUSSION

Meningitis is an emergency medical condition that requires rapid diagnosis, which gives an important clue for immediate initiation of empiric antibiotic treatment and minimize the probability of serious complications.(Kim et al., 2021).

Procalcitonin is an inflammatory biomarker that produced by the c-cells in the thyroid. (Bréchot et al., 2015). The source of CSF procalcitonin in the central nervous system are the neurons, astrocytes, and microglia in the parenchyma and meningeal cells. Normal concentration level of serum PCT is <0.05 ng/mL, with a half-life of 25–30 hors . Procalcitonin has been used as a tool for the assessment of disease severity. In addition to bacterial infections, increased PCT levels have been identified in other clinical conditions, including severe fungal infections, trauma, burns, major surgery, and medical therapy that stimulates cytokine production(Velissaris et al., 2018)

CRP is non-specific biomarker which is rapidly increase in any inflammation or disorder but has proved to be helpful in establishing the etiology of some infections. A high CRP level (>100 mg/L) can be indicator to a severe bacterial infection (Butler et al., 2019)

Recently, several studies were designed for rapid diagnosis of bacterial meningitis and analyzing inflammatory biomarkers level for reaching therapeutic decisions.

In the present study, we assessed the predictive value of two biomarkers, such as CRP in blood and Procalcitonin in blood and CSF of 43 suspected meningitis patients, according ti the result of inflammatory biomarkers and culture result, 28% of patients were diagnosed with bacterial meningitis. Also, 28% of patients had aseptic meningitis, and 44% were diagnosed with non-meningitis. Significantly increased value of biomarkers concentration level was found in bacterial meningitis patients as compared to other groups.

According to our study on suspected meningitis patients, 68.7% of patients were males, 32.7% of patients were females, the ratio of male to female was 1.6:1. This result corresponds with studies carried out in Sulaimani city of Iraq that showed 68% of cases were males, and 32% of cases were females, with the sex ratio of male to female 2:1 (Saeed and Al, 2017). Also, in other studies within meningitis patients in Iran and India, the sex ratio were 2:1 and 1.27:1.(Mosavi-

Jarrahi et al., 2009; Yadhav Ml, 2014). Factors underlying these sex differences are poorly understood, but a hypothetical model developed which assumes increased susceptibility to infectious disease such as relative immune deficiency in a proportion of males. There are two hypotheses for why boys have weaker immune systems than females.

The first is Y-chromosome in boys increases their vulnerability because X chromosomes contain a higher number of immune-related genes. Males and females are differentiated by chromosomes biologically. Normally, males have one X and one Y chromosome (XY), and females have two X chromosomes (XX). That means, since females have two X chromosomes, they have a better immune response than males. Another reason for weaker immune systems in males may be due to Sex hormones. Testosterone hormone in males has much higher than in females, which seems to inhibit B and T-lymphocytes of the immune system – (Ritchie and Roser, 2019).

There was Highly significant difference between the Bacterial meningitis group with other groups ($P > 0.05$). the mean concentration of CRP-Blood,PCT-Blood and PCT-CSF in B.M Group were 22.26 ±3.98 , 1.306± 0.67, and0.467 ±0.0 respectively. While the the mean concentration of CRP-Blood,PCT-Blood and PCT-CSF in Control Group were 3.08 ±0.52, 0.125 ±0.07, 0.018 ±0.02 respectively.

In our study, erum PCT with diagnostic cut-off point > 0.5 ng/ml, significantly higher in patients with bacterial meningitis than aseptic meningitis. The mean PCT level in bacterial meningitis was 1.306± 0.67 ng/ml while in aseptic meningits was 0.859 ±0.23 ng/ml ($p < 0.001$). This result is similar to that obtained by Chaudhary at al., 2018. where PCT concenration increased in bacterial meningitis but not in aseptic meningitis

This increase in serum PCT level in bacterial meningitis can be explained by the increase of calcitonin gene (CALC-I gene) expression and release of PCT from all parenchymal tissues and differentiated cell types throughout the body in presence of bacterial lipopolysaccharides and cytokines associated with severe bacterial infections .(Ibrahim et al., 2011)

the mean concentration level of serum PCT in non-meningitis and control group were 0.566 ±0.0.31 ng/ml, and 0.125 ±0.23 ng/ml respectively in our study that corresponds with other studies. Circulating levels of PCT in normal cases are very low, usually below 0.01 ng/ml and in viral infection and inflammation, the concentrations increase slightly but rarely above 1.0 ng/ml.(Mills et al., 2006)

It has been known for along time that differential cell count differentiate bacterial and non-bacterial infection including meningitis (Scheld et al., 2002).Similarly CSF cytochemistry is used in ruling out meningitis cases(Meisner, 2014). In our study, cell count was significantly higher in bacterial meningitis. WBC count in CSF rises as a result of inflammatory cytokines released during meningitis. The CSF WBC count was significantly higher in bacterial meningitis (mean = 3587 cell/mL), compared with viral meningitis (mean = 159 cell/mL) ($P < .001$)

This result is in agreement with other studies where leukocytosis was valuable in differentiation between bacterial and non-bacterial infections but not an independent marker of serious bacterial infection like PCT (Sanaei Dashti et al., 2017).

## CONCLUSION AND RECOMMENDATIONS:

The maximum PCT level has prognostic value in meningitis patients. PCT can recommend being used as a diagnostic tool in patients with infectious complications with or without bacteremia .

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