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ORIGINAL ARTICLE

Serum Procalcitonin as a Diagnostic and Prognostic Marker for Septic and Aseptic Meningitis

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Key words:
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ABSTRACT

Background: *Meningitis is a life-threatening inflammatory disease of the meninges. If not treated, bacterial meningitis can lead to brain swelling, permanent disability, coma and even death. To reduce the morbidity and mortality related to bacterial meningitis, it is important to differentiate septic meningitis from aseptic meningitis during the acute phase of the disease.* ***Objectives:*** *To evaluate the role of serum procalcitonin (PCT) in the differential diagnosis of septic and aseptic meningitis and to evaluate serum procalcitonin as a prognostic marker for meningitis severity and the success of meningitis treatment plan.* ***Methodology:*** *This study was conducted on total number of 63 subjects that were subdivided into three groups, 25 patients with septic meningitis (**groupI**), 20 patients with aseptic meningitis (**group II**) and 18 age and sex matched subjects without CNS diseases as control (**group III**). All subjects were subjected to full history taking, clinical examination and laboratory investigations. Serum PCT was measured for all the study subjects using ELISA method.* ***Results:*** *Serum PCT at cut off level >0.180 ng/dL clearly distinguished patients with meningitis from control group (P-Value <0.001) while at cut off level >0.492 ng/dL differentiate patients with septic meningitis from those with aseptic meningitis with 100% sensitivity and specificity (P-Value <0.001). All cases that had bad outcome had higher level of PCT than cured cases even after treatment. The most frequently detected organisms in septic meningitis group were St. pneumoniae (28%), Staph. aureus (16%), K.pneuominae (16%), E. coli (12%) and N. meningitides (8%). About 85% of isolated Enterobacteriaceae species were potential ESβLs-producers. 25% of K. pneumoniae isolates were MβLs-producing, E.coli was 100% sensitive to Carbapenems group and Amikacin while K.pneumoniae showed only 75% sensitivity to Carbapenems group and 100% of S. aureus isolates were MRSA. Sensitivity to the new therapeutic drugs was 100% for linezolid and teicoplanin for S. aureus and St. pneumonia. The most frequently detected organisms in aseptic meningitis were Cryptococcus neoformans (5%) and Herpes simplex 1/2 viruses (10%).*
Conclusion: *Serum PCT level can be used as a diagnostic and prognostic marker in patients with meningitis. It can also differentiate between septic and aseptic meningitis*

INTRODUCTION

Meningitis is defined as inflammation of the meninges that covering the brain and spinal cord, and is characterized by an abnormal number of white blood cells (WBCs) in the cerebrospinal fluid (CSF). The meningitis may be caused by a variety of infectious agents, as well as non-infectious diseases and other etiologies[1]. Meningitis has been divided into septic meningitis and aseptic meningitis. Septic or pyogenic meningitis is an acute meningeal inflammation secondary to bacterial infection that generally evokes a polymorph nuclear (PMN) response in the CSF. Aseptic meningitis refers to a meningeal inflammation without evidence of pyogenic bacterial infection on Gram's stain or culture [2]. PCT is a 116 amino acid precursor of calcitonin which under normal circumstances is produced by the thyroid C-cells. Serum concentrations of PCT are normally <0.05 ng/mL but in circumstances of systemic inflammation, particularly bacterial infection, PCT is produced in large quantities by many body tissues. It is detectable within 2- 4 hours and peaks within 6- 24 hours as opposed to C reactive protein (CRP) which begins to rise after 12-24 hours and peaks at 48 hours [3].

This study was performed to evaluate the role of serum PCT as a diagnostic and prognostic marker for septic and aseptic meningitis and investigate the efficacy of PCT than CRP in differentiation between septic and aseptic meningitis.

METHODOLOGY

The study was conducted from December 2016 to November 2017 at Menofia University Hospitals (Egypt) after approval of the Ethical Committee of Faculty of Medicine, Menofia University. Informed consent was obtained from every patient and control subjects. The study involved 45 meningitic patients and 18 age and sex-matched healthy individuals as a control group.

All subjects were submitted to full clinical history taking, physical examination and laboratory tests including:

CSF studies

Under complete aseptic technique, approximately (6-8ml) of CSF were withdrawn in two sterile tubes.First for microbiological studies and the second CSF for physical, cytological and chemical examination. These two tubes were immediately delivered to the laboratory.

Bacteriological studies:

Centrifugation of the CSF was done at 1800 rpm for 10 min. The supernatant was discarded and about 0.5 ml was left behind to suspend the sediment. The swabs taken from the sediment were cultivated on different suitable culture media then stained by Gram stain.

The sediments were cultivated on nutrient agar, human blood agar, macconkey's agar and mannitol salt agar then incubated at 37ºC for 24 hours under aerobic and also cultivated on chocolate agar at 37ºC for 24-72 hours in 5% Co2 atmosphere.

Colonies detected were identified by the standard bacteriological methods.

Antimicrobial susceptibility:

This was determined by disk diffusion method and interpreted according to the methods of the Clinical and Laboratory Standards Institute *(CLSI, 2017).* ESβLs detection by screening disk diffusion and combined disk diffusion confirmatory test. Metallo β-lactamase (MβL) detection methods by screening disk diffusion and confirmatory method by imipenem-EDTA combined disk test.

Viral examination:

For *Herpes simplex* 1/2 *viruses, Cytomegalo virus* and *Epstein-Barr virus* IgM were measured by ELISA according to the manufacture's instruction using HSV1/2, CMV and VCA IgM ELISA Kits (IBL INTERNATIONAL GMBH, a Tecan Group Company)

These testes were based on qualitative immunoenzymatic determination of IgM–class antibodies against virus. Each antigen of HSV1/2, CMV and VCA had been precoated on to well plates to bind corresponding antibodies of the specimen. Only substrate blank is added to A1well, negative control was added to B1well, cut off control was added toC1 and D1 wells and diluted samples were added to the remaining wells test and incubation was done for one hour then washed. Anti IgM conjugate was added to all wells except A1, then incubation and washing again. After addition of chromogen solution the color of the liquid will be changed to blue. By the effect of acid, the color finally becomes yellow.

The optical density (OD) was measured under 450 nm wave lengths carried out within 10 minutes after adding the stop solution.

Fungal examination:

Centrifugation of the CSF was done at 1800 rpm for 10 minutes. The supernatant was discarded and about 0.5 ml was left to suspend the sediment. The swabs taken from the sediment were cultivated on Sabourauds dextrose agar then stained by Gram and india ink stain.

The second CSF sample was examined for physical cytological and chemical characteristics.

Blood samples studies

10 ml of venous blood were taken under complete aseptic conditions for the following investigation:

***Complete blood count*:** by XT-1800I /SYSMEX, Japan.

CRP: by Latex agglutination method.

***Serum PCT*:**

IT was measured for all groups at admission and after treatment in septic meningitis group by ELISA method according to the manufacture's instruction using human PCT ELISA Kits (PELOBIOTECH GmbH) 201-12-0978 CN England.

Human PCT ELISA kits were based on standard sandwich enzyme-linked immune-sorbent assay technology. Monoclonal antibody enzyme had been precoated on to 96-well plates.

Standards (Streptavidin-HRP) and test samples were added to the wells except blank well.

Procalcitonin (PCT) antibodies labeled with biotin was added, and combined with streptavidin-HRP to form immune complex; then incubation and washing were done then chromogen Solution A, B were added, the color of the liquid changes into the blue, and at the effect of acid, the color finally becomes yellow. According to standards' concentration and the corresponding OD values, the standard curve linear regression equation was calculated. The OD values of the sample were added to the regression equation to calculate the corresponding sample's concentration.

Data management:

Data were collected, tabulated, statistically analyzed using an IBM personal computer with statistical package of social science (SPSS) version 20 and Epi Info 2000 programs, the results were expressed as mean, ± SD. The $\chi 2$ -test, the Mann–Whitney test, the t-test, ANOVA (f) test, the Kruskal–Wallis test, Receiver-operating characteristic (ROC) curve and were used for analysis.

P.values less than 0.05 were considered significant. Spearman's correlation was used.

RESULTS

Hemoglobin concentration and WBC count were significantly higher in patients than controls (P<0.001) and there was no statistically significant difference as regard platelet count between them (P>0.05). WBC count was significantly higher in patients with septic meningitis than those with aseptic meningitis (P<0.001).There was non-significant difference between patient with aseptic meningitis and control regarding WBC count. (Table 1)

Table 1: Difference between the studied groups regarding CBC results (no=63).

Items	Septic (No=25)	Aseptic (No=20)	control (No=18)	Test of sig. & p-value
Hemoglobin				
- Mean ± SD	11.4±1.4	10.3±0.89	12.4±1.7	**F = 11.7** **P=0.00**(<0.001)** **P1=0.012*** **P2=0.013*** **P3=0.00****
White blood cells				
- Mean ± SD(/in thousand)	12.1±3.2	7.9±3.01	8.4±9.5	**Kruskal WallisH = 23.1** **P =0.00**(<0.001)** **P1=0.00**** **P2=0.00**** **P3=0.15**
Platelets				
- Mean ± SD(/in thousand)	300.8±90.5	315.5±104.5	280.6±95.5	**Kruskal WallisH = 1.3** **P =0.51(>0.05)** **P1=0.65** **P2=0.68** **P3=0.28**

*Significant. ** Highly significant, SD: standard deviation. No= number.
P1: septic to aseptic P2: septic to control P3: aseptic to controls

C reactive protein and serum PCT level were significantly higher in patients than controls (P<0.001).There was a highly significant increase in CRP and serum PCT level in patients with septic meningitis than those with aseptic meningitis (P<0.001). There was asignificant increase in serum PCT level in patients with aseptic meningitis than controls while there was non-significant difference between patients with aseptic meningitis and control groups regarding CRP concentration (Table 2)

Table (2): CRP and serum PCT in different groups (no=63).

	Septic (No=25)	Aseptic (No=20)	Control (No=18)	Test of significant and P value
PCT				
Mean ±SD	0.705±0.126	0.344±0.78	0.199±0.181	Kruskal Wallis H=45.2 P= 0.00**(<0.001) Mann Whitney 1=5.7, P1=0.00** Mann Whitney 2=5.1, P2=0.00** Mann Whitney 3=3.5, P3=0.00**
CRP				
Mean ± SD	30.8±30.2	2.4±4.5	2.0±4.1	**Kruskal WallisH =25.5** **P= 0.00**(<0.001)** **P1=0.00**** **P2=0.00**** **P3=0.81**

- KWH = Kruskal Wallis H
- Mann Whitney 1, P1 septic to aseptic
- Mann Whitney 2, P2 septic to control
- Mann Whitney 3, P3 aseptic to controls

There was a statistically significant positive correlation between serum PCT level and physical CSF properties (P<0.001). High tension, greyish color and turbidity were more frequent with high PCT. (Table 3) There was a highly statistically significant positive correlation between serum PCT level and (CSF leucocytic count and protein), while there was a highly statistically significant negative correlation between the level of PCT level and CSF glucose (P<0.001) (Table 4)

Table 3: Correlation between CSF physical properties and serum PCT level in the two meningitis groups (no=45).

Items	Serum procalcitonin	Test of significant and p-value
Physical		
Tension		
- High tension (25) **- Normal (20)**	**0.676 ±0.177** **0.380±0.107**	**t = 6.9** **P =0.00** (<0.001)**
Color		
-Greyish (22) **- Colorless(23)**	**0.722±123** **0.375±0.109**	**t= 9.9** **P =0.00** (<0.001)**
Aspect		
-Turbid(16) **- Hazy(12)** **- Clear(17)**	**0.742±0.125** **0.563±0.173** **0.345. ±0.68**	**F= 42.5** **P =0.00** (<0.001)**

Table 4: Correlation between cytological and chemical CSF properties and serum PCT level in the two meningitis groups (no=45).

parameter	Serum PCT	
	r	P value
Cells		
Neutrophils	**0.83**	**0.00****
Lymphocytes	**0.62**	**0.003***
Chemical factors of CSF		
Protein	**0.70**	**0.00****
Glucose	**-0.60**	**0.00****

There was a highly statistically significant positive correlation between serum PCT level and complications before and after treatment. Patients who had complication had high serum PCT level even after treatment and bad prognosis. (Table 5)

Table 5: Relation between complications in septic meningitis patients and serum PCT level before and after treatment (no=25).

Items	Complication (No=4)	No complication (No=21)	Test of significant and p-value
Serum PCT pre			
- Mean ± SD	0.850±0.40	0.677±0.118	**t= 5.2** **P =0.00** (<0.001)**
Serum PCT post			
- Mean ± SD	0.567±0.156	0.384±0.114	**t= 2.8** **P =0.010* (<0.05)**

Culture results in septic meningitis group were negative in 20% and positive for 80%of patients. The most common pathogen was *St. pneuominae* 28% followed by *K. pneuominae* and *S. aureus* 16% followed by *E.coli* 12% and *N. meningitides* 8% (Figure 1-a).

About 85% of Enterobacteriaceae species isolated in this study were potential ESβLs-producers by disk diffusion test. 25% of *K. pneumoniae* isolates were

MβLs-producing. *E.coli* was 100% sensitive to Carbapenems group and Amikacin and 100% resistant to Colistin and Co-trimexazole. *K. pneumoniae* showed only 75% sensitivity to Carbapenems group and 100% resistant to Cephalosporins, Monobactams and Co-trimexazole.100% of *S. aureus* isolates were MRSA. 25%.of *S. aureus* was resistant to vancomycin. Sensitivity to the new therapeutic drugs was 100% for linezolid and teicoplanin for *S. aureus* and *St. pneumoniae*.

Viral examination for *Herpes simplex* 1/2 viruses, *Cytomegalo virus and Epstein-Barr virus* IgM was negative in 90% of patients and positive for 10%. Only two samples were *Herpes simplex positive*.

Culture results in aseptic meningitis group showed *Cryptococcus neoformans* 5% (Figure 1-b).

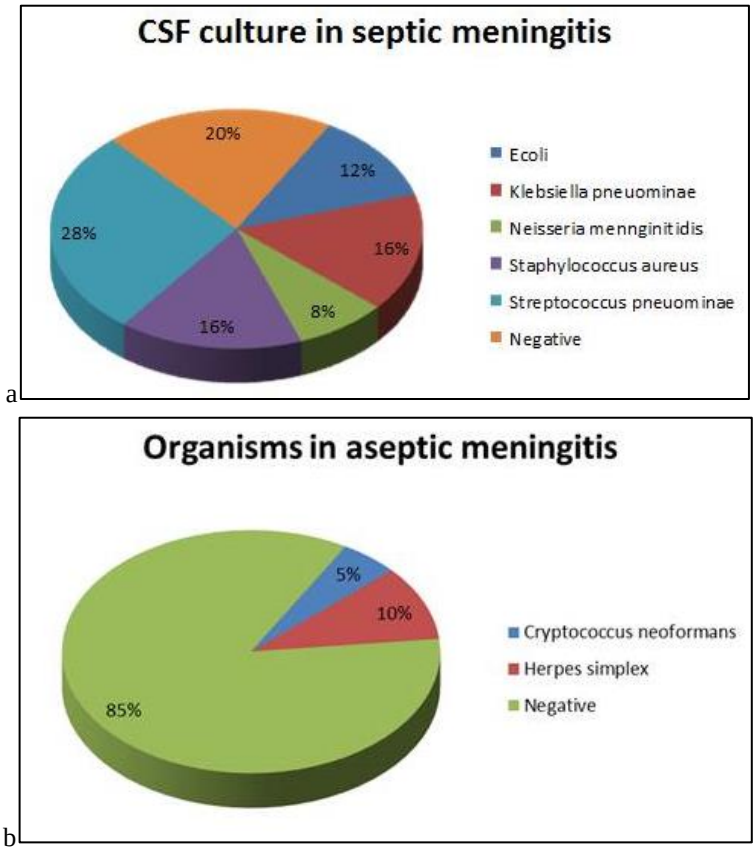


Fig. 1: a) CSF culture in septic meningitis; b) Organism in aspectic meningitis

Serum PCT level at a cut off value more than 0.180 ng/ml had a sensitivity of (100%), and specificity of (77.8%) in diagnosis of meningitis, with a positive predictive value 91.8% and a negative predictive value 100% **.** (Figure 2-a)

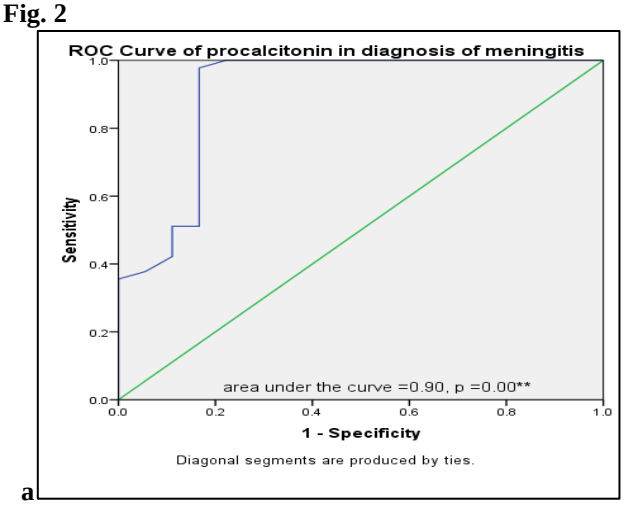
Serum PCT level at a cut off value more than 0.492ng/ml had a sensitivity of 100%, and specificity of 100% in differentiation between septic meningitis and aseptic meningitis, with a positive predictive value 100% and a negative predictive value 100%.(Figure 2-b)

Serum PCT level at a cut off value more than 0.342pg/ml have a sensitivity of 100%, and specificity of 83.3% in differentiation between septic meningitis and control, with a positive predictive value (89.3%) and a negative predictive value 100%.(Figure 2-c)

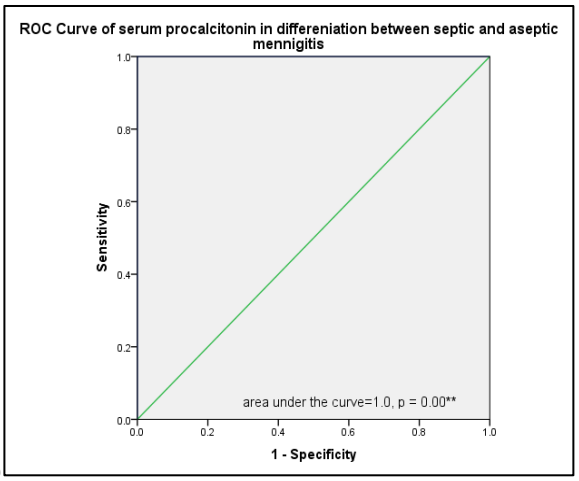
Serum PCT levels at a cut off value more than0. 180ng/ml has a sensitivity of 100% and specificity of77.8%in differentiation between aseptic meningitis and control, with a positive predictive value (83.3%) and a negative predictive value 100 %.(Figure 2-d)

Serum PCT was more sensitive than CRP in differentiation between septic and aseptic meningitis (Figure 2-e)

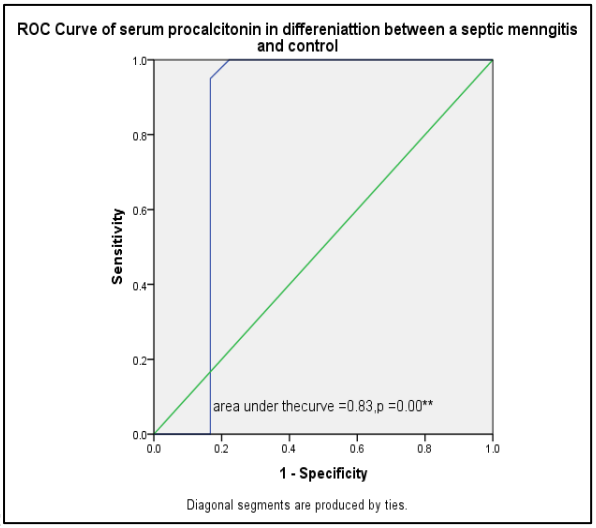
Fig. 2



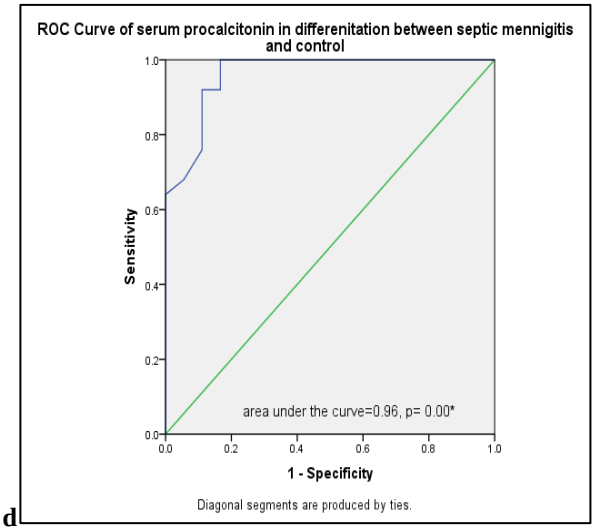
a



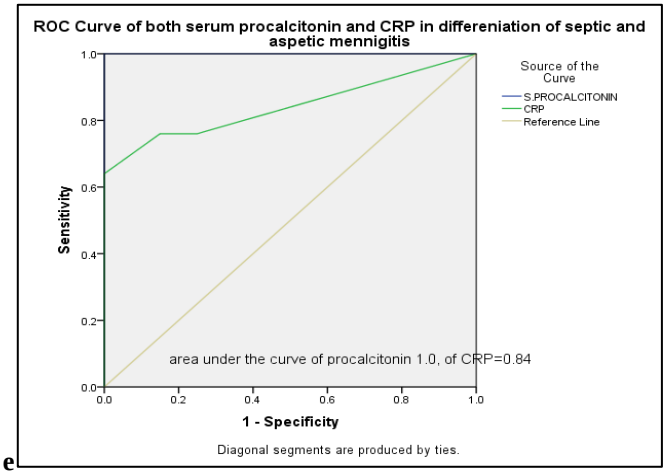
b



c



d



e

a- ROC curve of value of serum PCT level in diagnosis of meningitis
b- ROC curve of serum PCT in differentiation between septic and aseptic meningitis.
c- ROC curve of serum PCT in differentiation between septic meningitis and control.
d- ROC curve of serum PCT in differentiation between aseptic meningitis and control
e-ROC curve of both serums PCT and CRP in differentiation of septic and aseptic meningitis. This figure shows that the area below PCT 100% is greater than the area below CRP 84%.

DISCUSSION

Meningitis is a dreadful inflammation in the meninges and CSF of human central nervous system [4].Distinguishing septic from aseptic meningitis is difficult due to considerable overlap in clinical symptoms and laboratory findings [5].

A quick, sensitive, and specific diagnostic method is essential to initiate early treatment against the meningococcal meningitis patients during an outbreak. Traditional methods of diagnosis involve culture, latex agglutination (LA) and biochemical tests, which are either non confirmatory or have some limitations [6]

Our study showed that, there was a high statistically significant difference between group I and group II of patients regarding peripheral leucocytic count with mean value (12.1 ± 3.2^3) in group I versus (7.9 ± 3.01^3) in group II ($p < 0.001$).This results was in agreement with *Makoo et al.,* [7] and *Alkholi et al.,* [8] who found that the mean PMN count was significantly higher in patients with bacterial meningitis than in those with viral meningitis. Furthermore a significantly higher CSF leukocyte count with marked increase in the PMN count was recorded in septic meningitis group compared to the aseptic meningitis group ($p<0.001$).Also, we noted highly significant differences in the CSF WBCs and CSF polymorph % ($P < 0.001$), with higher values in the bacterial meningitis patients. These results are similar to those of *El-Kapany* [9]*and Viallon et al* [10].The present study revealed a highly significant increase in the frequency of positive CRP in group I patients when compared to group II ($p <0.001$). These results were in agreement with *Yetkin et al.,* [11] who stated that, there were high statistically significant differences in CRP ($p <0.001$) between patients with septic meningitis and those with aseptic meningitis.

In our study, CSF culture was positive in 20 patients of group I 80 % while it was negative in 5 patients of the same group 20%. The most frequently detected organisms were *St. pneumoniae* 28%, *S. aureus* 16%, *K. pneuominae* 16%, *E. coli* in 12% and *N. meningitides*8%. This result agreed with *Shaban and Siam.* [12] who stated that Pneumococcal meningitis is currently the leading cause of meningitis in Egypt. *Alam et al* [13], found that *St. pneumoniae* was the most common isolated organism 47.4% followed by *N. meningitides* 33.9 %%, *H. influenzae* 10.2% and other Gram negative bacteria 8.5% among Egyptian populations. These differences could be attributed to differences in the study population and age of the patients.

In the current study, *Herpes simplex* viruses were the causative organisms in two samples representing 10%of aseptic group. This result agreed with *Logan and McMahon,* [14] who stated that Enterovirus infections, such as coxsackie and echoviruses, comprise more than 80% of all episodes of aseptic meningitis and are the most commonly identified causes of CNS viral infections and other viruses that can cause meningitis include *herpes simplex* virus 2 (and less commonly type 1), *LCMV* (*lymphocytic choriomeningitis*) virus represents the remain.

Procalcitonin (PCT) is a 116-amino-acid protein that is produced primarily by the C cells of the thyroid gland and secreted from leukocytes in the peripheral blood [15]In healthy individuals, PCT is secreted at levels that are below the detectable limit. However, serum PCT levels increase markedly in patients suffering from bacterial infections [16]

In our study, the PCT levels were highly significantly elevated in the septic meningitis group in comparison to aseptic meningitis and the controls. Our findings were as expected by *Li et al.,* [17], since PCT is a well-recognized marker for bacterial infection [10,18,19,20]

In our study, serum PCT levels were significantly higher in septic meningitis group than the aseptic meningitis group with a mean of (0.705 ± 0.126) versus (0.344 ± 0.78) and both were significantly higher than that of the control group (0.199 ± 0.181).Using a cut off value of (0.492 ng/ml) serum PCT could distinguish patients with septic meningitis from those with aseptic meningitis with a sensitivity and specificity of (100%) respectively. When this cut off point decreases to (0.180 ng/ml) it can also differentiate between meningitis and control group with a sensitivity and a specificity of (100%) and (77.8%) respectively.

Also these results agree with Prasad et al., [21]who reported that, the mean level of serum PCT in patients with septic meningitis and control group was (22,669.21 ± 7,656.45 pg/ml) and (3,943.8±632.27 pg/ml) respectively and showed a highly significant difference among both groups ($p<0.001$).

Similar results were reported by *Konstantinidis et al.,* [22] who showed in their study arelatively high diagnostic value of serum PCT test in patients with septic meningitis. Its sensitivity was 100%, specificity was 96.43%, PPV 95%, and NPV 100%. In group with VM, sensitivity was 27.27%, Specificity 96.43%, PPV 75%, and NPV 77.14%.

In the present study, serum PCT is more sensitive than CRP in differentiation between septic and aseptic meningitis, the sensitivity of PCT was 100% while CRP was 84%. These results agree with *Ibrahim et al.,* [23] who reported that, Serum PCT is more accurate than the currently available markers for differentiating between viral and bacterial meningitis Conversely there is a large overlap of usually determined parameters like glucose, protein and cells of the CSF and to a lesser extent, the CRP concentration. The PCT values were highly discriminant in all cases

We found also that all cases that had bad outcome complication had higher level of PCT than cured cases.

There was a highly statistically significant positive correlation between serum PCT level and complications.

CONCLUSION

Serum PCT can be used as a diagnostic and prognostic marker in patients with meningitis. It can also differentiate between septic and aseptic meningitis. All cases that had bad outcome had higher level of PCT than cured cases.

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