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Original Article

Predictive Value of Serum Procalcitonin Levels in Children with Bacterial Meningitis at Tishreen University Hospital

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Abstract *- Bacterial meningitis in children is associated with high morbidity and mortality worldwide, and one in five survivors may have permanent sequelae. For these reasons, a rapid diagnostic evaluation with near 100% sensitivity is essential for optimizing outcomes in children with suspected bacterial meningitis. This study aimed to evaluate the efficiency of procalcitonin (PCT) in predicting bacterial meningitis in children. Methods: This prospective cohort study included (50) patients aged between 30 days and 12 years, presented with clinical features consistent with meningitis, and a lumbar puncture was performed for all children for whom there is no contraindication, and its parameters were studied. Based on CSF culture and direct cytological examination, there were (20) with bacterial meningitis, including (5) who had been previously treated with antibiotics for less than 3 days, there were also (25) with nonbacterial meningitis, and (5) Lumbar puncture was not performed. Serum procalcitonin and C-reactive protein were measured for all children on admission and then repeated 3 days after initiation of intravenous antibiotic therapy. Results: The mean serum PCT was high in the bacterial meningitis group, even in the presence of prior partial treatment, compared to its mean in the nonbacterial meningitis group (9.23 + 6.12 vs 0.10 + 0.14, p = 0.0001), and decreased significantly after 3 days of treatment in the bacterial meningitis group (0.54 + 0.22, p = 0.0001), PCT on admission was also shown to be more sensitive and specific than CRP in diagnosing bacterial meningitis in children. Conclusion: Procalcitonin is considered one of the most important parameters in the early diagnosis of bacterial meningitis in children.*

Keywords *- PCT, Bacterial meningitis, CRP, CSF, Nonbacterial meningitis.*

1. Introduction

Bacterial meningitis is an emergency medical condition classified as a serious central nervous system infection (CNS) infection associated with a significant morbidity and mortality rate [1]. It also leaves permanent neurological sequelae, especially in children requiring immediate diagnosis and treatment [2].

Meningitis in children is often aseptic and does not require any specific treatment. But in about 5% of cases, meningitis is of bacterial origin [3]. The distinction between bacterial and nonbacterial (aseptic) meningitis in the emergency department is difficult sometimes due to their similar clinical features. Therefore, it is recommended to begin treatment directly with antibiotics in children with clinical evidence of acute meningitis or who have cerebrospinal fluid poleocytosis until the results of CSF cultures appear within 48-72 hours. Treatment will be re-evaluated [3,4]. This results from the admission of children with nonbacterial meningitis to the hospital and unnecessary injection of antibiotics, with the presence of a disease environment and accompanying consequences [5]. Thus, distinguishing between aseptic and bacterial meningitis limits unnecessary antibiotic application and hospital admissions [6].

Parameters studied in the cerebrospinal fluid, such as protein level, glucose and leukocytes, in addition to the routine biological parameters in blood like C-reactive protein and white blood cells (WBC), do not give high sensitivity or specificity for distinguishing between bacterial and aseptic meningitis [8 ‹7]. Also, there are cases in which performing a lumbar puncture is contraindicated [9]. Through searching for new parameters, it was found that procalcitonin (PCT) levels in serum could be useful in the early diagnosis of bacterial meningitis in children [10]. This study aimed to evaluate the role of serum procalcitonin in diagnosing bacterial meningitis in children, even in the presence of partial antibiotic treatment and a contraindication for lumbar puncture, and its efficiency in follow-up and evaluation of response to treatment compared to other inflammatory parameters.

2. Procalcitonin

Procalcitonin is a protein with 116 amino acids, a precursor of the hormone calcitonin; the gene (CALC-1) encodes it on chromosome 11, and in healthy individuals, it is synthesized in C cells of the thyroid gland. But, in the context of infection, expression of the CALC-1 gene is induced in neuroendocrine cells of the liver, lung, adipocytes and macrophages.

These tissues lack the ability to cleave procalcitonin into its mature form, calcitonin, which leads to a rapid doubling of its levels in serum [11].

Procalcitonin synthesis in non-thyroid tissues is increased by bacterial lipopolysaccharide (endotoxin), In addition to inflammatory cytokines such as IL-6, IL-1, and TNF-α [12]. Otherwise, its synthesis is inhibited by (IFN-γ) which is secreted mainly in response to viral infections [13].

In bacterial infections, PCT begins to rise rapidly, usually within 2-4 hours, with a half-life of approximately 22-26 hours, and should begin to decline approximately 50% over 24 hours after the systemic infection is controlled [14].

PCT levels do not vary according to age in healthy people, except in newborns; it rises significantly on the third day of birth compared to the first day and decreases on the seventh day of birth; this may be due to the reaction to birth with non-specific activation of the immune system [15].

Current clinical practice has a variety of cut-offs for PCT to determine the initiation and discontinuation of antibiotic therapy, and the clinical scenario plays an essential role in determining which cut-off value to use[16]. However, most studies showed that PCT levels appear clinically significant in the (0.1 to 0.5) ng/mL range. Bacterial infection is considered unlikely when PCT is (0.1 - 0.25), and becomes likely when PCT is higher than 0.25, and more likely when it is higher than 0.5 ng/m [17].

2.1. Procalcitonin in Bacterial Meningitis

Serum PCT is a biomarker with high sensitivity and specificity in identifying patients with sepsis and can be useful for diagnosing bacterial infections. Several studies have evaluated the role of PCT in serum in assessing patients with central nervous system infections. Published data suggests that, compared to other acute phase biomarkers, Serum PCT is superior as a biomarker in acute meningitis and can help differentiate bacterial from viral meningitis.

Furthermore, studies have investigated the role of PCT in monitoring disease severity and evaluating treatment, as patients with higher levels of PCT in the blood have more severe clinical symptoms and a higher mortality rate, and patients in whom no clinical improvement was observed after starting treatment, Their PCT levels were remained higher than normal [18].

Some limitations in the clinical use of PCT in meningitis should be mentioned [19]. One limitation is that serum PCT is not specific for bacterial meningitis and can be elevated in various bacterial infections, including pneumonia, acute otitis media, and sepsis.

In addition, PCT has limited ability to differentiate between acute bacterial infections of the central nervous system, such as meningitis and brain abscesses. Thus, clinicians must consider the full clinical situation when formulating their diagnosis [20].

3. Materials and Methods

This is an Analytic Cohort Study (Prospective) of a group of children admitted to the pediatric Department at Tishreen University Hospital in Lattakia-Syria, whose ages ranged from 30 days to 12 years, and who were suspected of having meningitis, during the period between January 2021 and December 2022.

The medical history was evaluated, and a clinical examination was performed. Laboratory tests were conducted on admission for all children in the study, including PCT, CRP, and other tests. Then, the presence of contraindications for lumbar puncture was assessed. Lumbar puncture was performed in the absence of contraindications, and the cerebrospinal fluid was studied with a cytological and Chemical study, and bacterial culture was performed. The CRP and PCT were re-calibrated 3 days after the child received intravenous antibiotics.

Based on the results of fluid parameters (leukocyte count, neutrophil and lymphocyte counts, and bacterial cultures), the study population consisted of 25 children with nonbacterial meningitis after negative results of culture and direct cytological examination and 15 with previously untreated bacterial meningitis after positive results of culture and cytological examination, 5 patients with bacterial meningitis previously treated with antibiotics for a period not exceeding 72 hours, and 5 cases a lumbar puncture was not performed. Meningitis was possible due to the presence of contraindications for performing the puncture or because the child's parents did not agree to perform it.

After excluding the group that did not have a lumbar puncture, the study consisted of two groups: bacterial meningitis and nonbacterial meningitis.

3.1. Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included Means, Standard Deviations (SD), Frequency and Percentages. Inferential Statistical based on statistics: Paired T student test for the difference between the means of two related groups, One Way ANOVA test to study the differences in means between more than two groups, Pearson Correlation Coefficient to study the correlation between quantitative variables, Independent T student test for the difference between the means of two related groups. The Receiver Operating characteristics (ROC) curve was constructed, and the area under the curve (AUC) was established to assess PCT and CRP to predict bacterial meningitis in children. P-value < 0.05 was considered statistically significant.

4. Results

The study included (50) children with suspectable meningitis. The ages of the children participating in the study ranged from 30 days to 12 years, and the mean age was 3.8 ± 6.08 years. Table (1) shows the distribution of the population of 50 children according to age groups admitted to the Department of Paediatrics at Tishreen University Hospital in Latakia 2021-2022.

Table 1. Distribution of study population according to age groups

Age groups(years)	Number	Percentage(%)
<1	6	12%
1-4	13	26%
5-9	18	36%
10-12	13	26%
Total	50	100%

The mean age of the children participating in the study was 3.8 + 6.08 years

Table 2. Distribution of study population according to gender

Gender	Number	Percentage(%)
Male	32	64%
Female	18	36%
Total	50	100%

Table 3. Distribution of study population according to final diagnosis

Final (most likely) diagnosis	Percentage(%)	Number
Nonbacterial meningitis	25	50 %
Bacterial meningitis	15	30 %
Possible unclassified meningitis*	5	10 %
Partially treated bacterial meningitis	5	10 %

*: Meningitis was considered probable and not classified when a lumbar puncture was not performed because there was a contraindication or the child's parents did not consent to its procedure

Table 4. PCT and CRP on admission for study groups

Population groups (N=50)	Mean ± SD(CRP)	Mean ± SD(PCT)
Bacterial meningitis (N=15)	100.2 ± 40.5	10.1 ± 3.5
Possible meningitis N=5)(	7.75 ± 4.11	1.47 ± 0.51
Partially treated bacterial meningitis (N=5)	23.5 ± 11.9	0.48 ± 0.20
Nonbacterial meningitis (N=25)	49.4 ± 24.4	0.10 ± 0.06
P-value	0.008	0.001

*P-value is significant at < 0.05 level

Based on the traditional criteria for parameters of CSF and the results of bacterial cultures, It was noted in Table (3) that 50% of the study population was finally diagnosed with nonbacterial meningitis, followed by 30% bacterial meningitis, 10% each for probable meningitis and partially treated bacterial meningitis.

Table 5. Distribution of duration of hospitalization in study groups

Population groups (N=50)	Duration of hospitalization Mean ± SD	P-value
Bacterial meningitis (N=15)	11.86 ± 5.7	**0.02**
Possible meningitis (N=5)	7 ± 5.1	
Partially treated bacterial meningitis (N=5)	6.80 ± 3.8	
Nonbacterial meningitis (N=25)	6.96 ± 3.9	

*P-value is significant at < 0.05 level

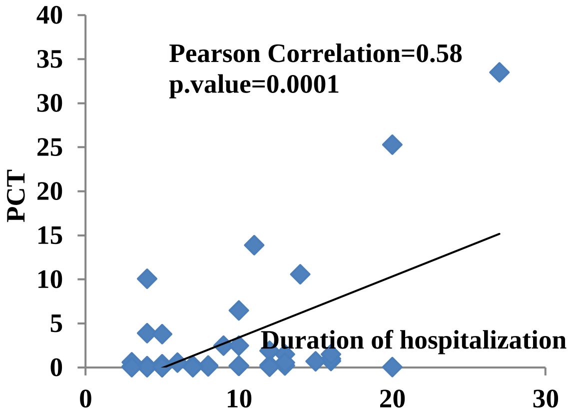

Fig. 1 Pearson Correlation between admission PCT values and hospitalization duration

The non-specific meningitis group, which includes 5 cases and constitutes 10% of the population, was excluded in the following distribution, and the participating children who underwent lumbar puncture were redistributed according to two groups.

Table 6. Distribution of the population into two groups

Population groups	**Number**	**Percentage (%)**
Bacterial meningitis	20	44.5 %
Nonbacterial meningitis	25	55.5 %
Total	45	100 %

Table 7. PCT and CRP on admission in population two groups

Population groups(N=45)	**Mean ± SD (PCT)**	**Mean ± SD (CRP)**
Bacterial meningitis(N=20)	9.23 ± 4.12	74.3 ± 38.7
Nonbacterial meningitis(N=25)	0.10 ± 0.06	49.4 ± 24.4
P-value	0.0001	0.03

*P-value is significant at < 0.05 level

Table 8. PCT on admission and after treatment in two population groups

Population group (N=45)	**Mean ± SD PCT admission**	**Mean ± SD PCT after treatment**	**P-value**
Bacterial meningitis (N=20)	9.23 ± 4.12	0.54 ± 0.22	**0.0001**
Nonbacterial meningitis (N=25)	0.10 ± 0.06	0.07 ± 0.05	**0.04**

*P-value is significant at < 0.05 level

Table 9. CRP on admission and after treatment in two population groups

Population groups (N=45)	**Mean ± SD CRP admission**	**Mean ± SD CRP after treatment**	**P-value**
Bacterial meningitis (N=20)	74.3 ± 38.7	26.2 ± 14.4	**0.009**
Nonbacterial meningitis (N=25)	49.4 ± 24.4	12.8 ± 9.6	**0.01**

*P-value is significant at < 0.05 level

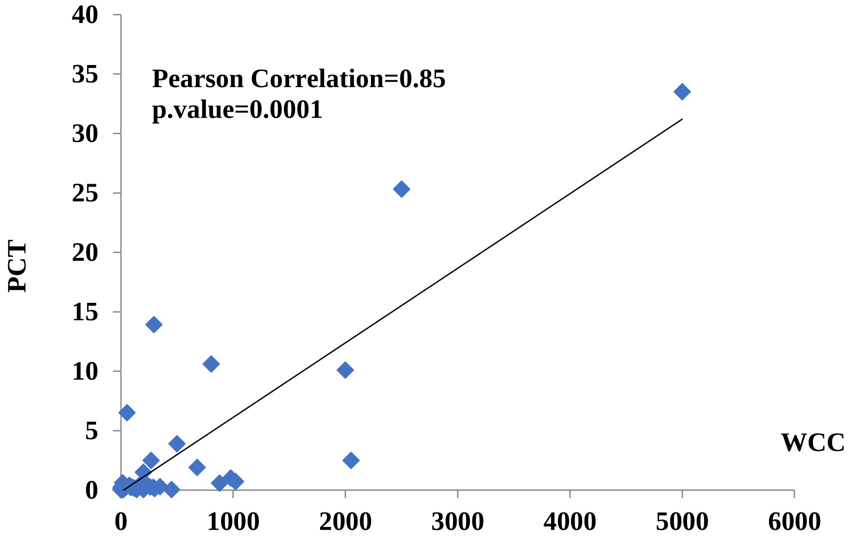

Fig. 2 Pearson Correlation between admission PCT values and white cell count in CSF

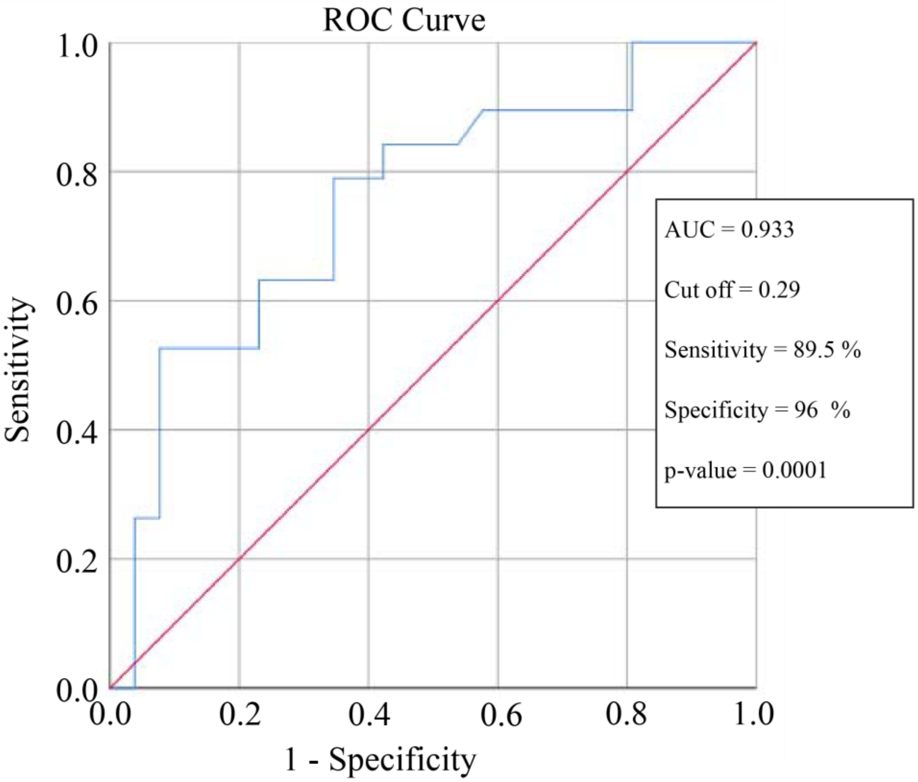

Fig. 3 ROC diagram showing the sensitivity and specificity of PCT in bacterial meningitis

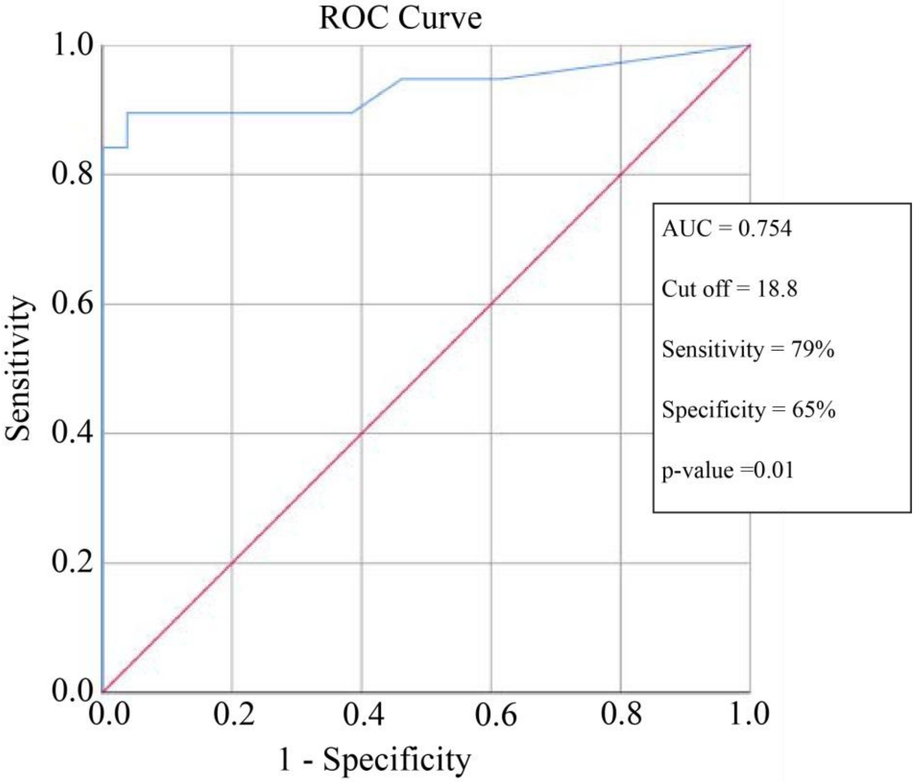

Fig. 4 ROC diagram showing the sensitivity and specificity of CRP in bacterial meningitis

As shown in Table (1), the most frequent age group present in the study was the group (5-9) years with a rate of 36%, followed by the group (1-4) and (10-12) with a rate of 26%, and the least frequent age group was (less than one year) and its percentage reached 12% of the studied population. It was noticed from Table (2) that 64% of the study population were males and 36% were females, with a Sex Ratio (M: F) = 1.8: 1. And it was noted from Table (3) that 50% of the study population were diagnosed of nonbacterial meningitis, followed by 30% of bacterial meningitis, and 10% for each of probable meningitis and partially treated bacterial meningitis.

As shown in Table (4) a significant difference was found between the four groups regarding the mean values of CRP on admission (p: 0.008), which were the highest in the bacterial meningitis group (100.2 ± 40.5), lower than that in the nonbacterial meningitis group (49.4 ± 24.4), and slightly lower than that in the group of partially treated bacterial meningitis(23.5 ± 11.9), while in probable meningitis group, it was the lowest (7.75 ± 4.11). As well as the PCT on admission, we noted that there is a statistically significant difference between the groups (p: 0.001); the mean of PCT was higher in the bacterial meningitis group (10.1 ± 3.5) and was lower in the group of probable meningitis (1.47 ± 0.51), followed by the mean in the partially treated bacterial meningitis group (0.48 ± 0.20). The lowest mean was in the nonbacterial meningitis group (0.10 ± 0.06).

It was noticed from Table (5) that there was a statistically significant difference (p; 0.02) regarding the mean values of the duration of hospitalization between the study groups. The highest mean duration of hospitalization was in the untreated bacterial meningitis group (11.86 ± 5.7) days, and the lowest mean duration of hospitalization was in the partially treated meningitis group (6.80 ± 3.8) days.

It is observed from Figure (1) that the Pearson correlation = 0.58, which suggests the existence of a positive correlation between the two variables; as the PCT values on admission increase, the duration of hospitalization increases, with statistically significant differences (p: 0.0001). After excluding the meningitis group, It was noticed from Table (6) that the percentage of nonbacterial meningitis in the population was higher than bacterial meningitis (55.5% vs. 45.5%).

Table (7) shows a statistically significant difference between the two groups (bacterial and nonbacterial meningitis) regarding the mean values of both PCT and CRP on admission. The mean PCT was significantly high in the bacterial meningitis group and low in the nonbacterial meningitis group (9.23 ± 4.12 vs 0.10 ± 0.06, p = 0.0001). The mean of CRP showed an increase in both groups but to a lesser extent in the nonbacterial meningitis group (74.3 ± 38.7 vs 49.4 ± 24.4, p = 0.03).

It was noticed from Table (8) that there was a statistically significant difference(p: 0.0001) between the two groups with regard to the mean values of PCT at admission and after treatment, where the mean PCT at admission was (9.23 ± 4.12) in the bacterial meningitis group, and decreased after treatment to (0.54 ± 0.22), and the mean PCT at admission was (0.10 ± 0.06) and became(0.07 ± 0.05) after treatment in the nonbacterial meningitis group with a statistically significant difference (p: 0.04).

As shown in Table (9), there was a statistically significant difference between the two groups (p: 0.009) regarding the mean values of CRP at admission and after treatment, where the mean CRP on admission was (74.3 ± 38.7) in the bacterial meningitis group, and decreased after treatment to (26.2 ± 14.4). Also, there was a significant difference between the two groups regarding the CRP mean, which decreased after treatment to (12.8 ± 9.6, p = 0.01) in the nonbacterial meningitis group.

It is observed from Figure (2) that Pearson's correlation = 0.85, which suggests the existence of a positive correlation between the two variables, whereas the PCT values increase on admission, the white blood cell count values in CSF increase, with statistically significant difference (p = 0.0001). Applying the Receiver Operating Characteristics Curve (ROC-Curve) test to differentiate between bacterial and nonbacterial meningitis in children. It was observed from Figure (3) that the area under the curve (AUC) was (0.933) for PCT on admission, and the cut-off value was greater than or equal to 0.29, achieving a sensitivity of 89.5% and a specificity of 96% for diagnosing bacterial meningitis and for CRP, the area under the curve for CRP at admission was (0.754). The cut-off value for serum CRP at admission was greater than or equal to 18.8, achieving a sensitivity of 79% and a specificity of 65% for diagnosing bacterial meningitis in children of our study.

5. Discussion

When dealing with meningitis children, early diagnosis of the type of infection (bacterial or viral) is the vital element with the greatest impact on the clinical course, treatment, and improved prognosis and survival of the patient [21]. In this context, interest is increasing in laboratory parameters that can quickly differentiate between bacterial and viral meningitis in children [22].

The ideal biomarker for bacterial infection and, specifically, bacterial meningitis should allow early diagnosis, inform the prognosis of the disease, and facilitate therapeutic decisions. Procalcitonin levels cover these features better compared to other commonly used biomarkers [21], as it can be used as a diagnostic and prognostic parameter and has shown promising results for deciding whether to stop or continue antibiotic therapy, thus reducing unnecessary exposure to these antibiotics and improving clinical outcomes for children. For this purpose, this study was conducted.

The majority of studies around the world reported that meningitis most commonly occurs in the age group immediately following birth (less than a month) due to the incomplete maturation of the child's immune system. However, our study excluded this age group from its population because there is a close association between high PCT and The first days of life without the presence of bacterial infection[23]. The mean age of the children participating in the study was 3.8 + 6.08 years. The most common age group in our study was between 5-9 years, at a rate of 36%. This may be due to the low level of awareness for parents of children in this study, especially on using the Haemophilis influenzae vaccine.

Also, studies indicate the predominance of infection in males [24]. This is what our study found, as the Percentage of males was 64% of all children participating, with a ratio of (1.8:1) (males: females).

After laboratory and clinical evaluation, the population was classified into four groups. The highest final diagnosis in the population was nonbacterial meningitis (50%) and lower than bacterial meningitis (15%). Partially treated bacterial meningitis and probable meningitis were equally common in our study, and their percentage was (10%). This distribution is consistent with all studies that have dealt with meningitis in children, especially in countries where the Haemophilus influenzae vaccine is included in their national vaccine program.

By evaluating the duration of hospitalization, it was found that it ranged from 3 to 27 days, with an average of 8 + 5.1 days. Our study also found a statistically significant difference between the population groups. The average duration of hospitalization was higher in the bacterial meningitis group (11.86 ± 5.7) days and less than that in the probable meningitis group, and the two averages were less than that with close values in meningitis partially treated bacterial meningitis and nonbacterial meningitis were. As for the relationship between PCT at admission and the duration of hospitalization, we used Pearson's correlation in our study and found a positive relationship between them. This indicates the importance of the diagnostic value of PCT on admission for bacterial meningitis, as high values of PCT indicate a more severe illness and a longer duration of hospitalization. This is consistent with the prognosis of bacterial meningitis.

To evaluate the diagnostic value of PCT on admission, our study found a statistically significant difference between the four groups for PCT, and the mean values for PCT were very high in the bacterial meningitis group (10.1 ± 3.5) compared to the nonbacterial meningitis group(0.10 ± 0.06), the mean in partially treated bacterial meningitis was lower than in the absence of treatment (0.48 ± 0.20), but it remained higher than the average in the nonbacterial group. The group in which a lumbar puncture was not performed, and meningitis was likely also showed a high mean PCT (1.47 ± 0.51). In comparison with CRP, our study found that the mean CRP at admission was high (100.2 ± 40.5) in the bacterial meningitis group. To a lesser extent, it was higher than its normal range in both the nonbacterial meningitis group. (49.4±24.4). This suggests the high diagnostic value of PCT in diagnosing bacterial meningitis in children as early as possible and shows the superiority of PCT over CRP in distinguishing between bacterial and nonbacterial meningitis from the beginning of the disease prognosis.

This is consistent with the study conducted by Mintegi S. et al. in 2020 [25], which included 1,009 children aged between 29 days and 14 years in 25 hospitals in Spain between 2011 and 2018 and found 917 cases of aseptic meningitis and 92 cases of bacterial meningitis. It found that PCT and protein in CSF could be used reliably to accurately differentiate between bacterial and aseptic meningitis in children.

Our current study also found a positive correlation between PCT on admission and the white blood cell count in CSF, which suggests that the importance of lumbar puncture for diagnosis is reduced and provides an alternative method for diagnosis when there are contraindications for it and increases the early diagnostic value of PCT even before performing a lumbar puncture.

Also, in our current study, the cut-off of PCT on admission for diagnosing bacterial meningitis was (0.29) using the ROC-Curve test to differentiate between bacterial meningitis and nonbacterial meningitis. The area under the curve was high (AUC=0.933), and the cut-off achieved a sensitivity of 89.5% and a specificity of 96% for diagnosing bacterial meningitis. According to CRP analysis, the area under the curve was less (AUC = 0.754), and the cut-off value for serum CRP on admission (18.8) achieved a sensitivity of 79% and a specificity of 65% for diagnosing bacterial meningitis. This confirms the findings that PCT is better than CRP for differentiating between bacterial and aseptic meningitis in children.

This is consistent with a meta-analysis study by Kim H et al. in 2021 in Korea [20]; it included 18 studies with 1462 children, intending to evaluate the accuracy of PCT as a diagnostic value for bacterial meningitis in children, sensitivity, specificity, and diagnostic value (DOR) of the combined PCT were 87%, 85%, and 35.85, respectively, and the area under the curve for serum PCT was (0.921). All included studies also showed that serum PCT has a higher diagnostic accuracy for detecting bacterial meningitis than other conventional biomarkers, including serum C-reactive protein and leukocyte count, leukocyte and neutrophil counts in CSF, and protein and glucose levels in CSF.

Considering the average PCT at admission and 3 days after treatment, and after excluding the group that did not undergo a lumbar puncture, our study found a statistically significant difference between the two study groups with regard to the mean values of PCT on admission and 3 days after treatment, as the mean PCT at admission was higher than it after treatment (9.23 ± 4.12 vs 0.54 ± 0.22). However, despite its decrease after treatment, it remained higher than the mean PCT values for the nonbacterial meningitis group on admission, which were (0.10 ± 0.06) and decreased after treatment to (0.07 ± 0.05), with a difference Statistically significant. This suggests the prognostic importance of PCT in both bacterial and aseptic meningitis in children and its role in monitoring treatment and follow-up. It emphasizes the necessity of repeating the assay for cases that did not find clinical improvement after starting treatment with antibiotics.

In a prospective study published in 2017 in China, conducted by Zhang X.F et al. [26]. Serum PCT and CSF PCT were measured in three groups of patients: 24 patients with bacterial meningitis, 20 patients with viral meningitis, and 22 patients with tuberculous meningitis. Serum PCT values were significantly higher in the bacterial meningitis group but significantly decreased in this group after 72 hours of treatment.

In addition, admission CSF PCT levels were significantly lower in viral meningitis compared with tuberculous and bacterial meningitis patients, but CSF PCT values did not change significantly with treatment. The researchers concluded that serum PCT changes over time could be useful in assessing disease progression and response to treatment in patients with bacterial meningitis.

6. Conclusion

Performing PCT assay early, before starting treatment, when meningitis is suspected in children, is used to distinguish the bacterial origin from the nonbacterial one accurately.

When there is a contraindication for performing a lumbar puncture, it can be used as a reliable alternative diagnostic method. Also, its measurement after treatment gives a general picture of the prognosis of the disease. Finally, PCT has a higher sensitivity and specificity than CRP in diagnosing bacterial meningitis in children.

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