The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 6387- 6394

# Vitamin D-Binding Protein as a Diagnostic Biomarker for Acute Meningitis

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## ABSTRACT

**Background** Meningitis is an acute inflammation of the pia, arachnoids, and the fluid in the subarachnoid space of the brain. Because there is no diagnostic biomarker, it is difficult to diagnose. **Objective:** The aim of the current study was to evaluate the validity of using cerebrospinal fluid (CSF) Vitamin-D Binding Protein (VDBP) as a new potential marker for diagnosing meningitis. **Patients and methods:** A cross-section study was conducted on 48 patients with manifestations suggesting an acute meningitis, 28 patients with an acute meningitis who were divided into bacterial group containing 10 patients and viral group containing 18 patients confirmed by laboratory investigations and 20 patients who were clinically suspected as an acute meningitis, but excluded by laboratory investigations, the study was conducted within the period from May 2022 to December 2022. CSF and blood samples were obtained in pairs. CSF and serum VDBP were measured in the 3 groups. CSF VDBP concentrations were compared versus serum VDBP concentrations according to disease (viral meningitis vs. bacterial meningitis vs non-meningitis). Receiver operating characteristic (ROC) analysis for diagnosing meningitis using CSF VDBP concentration was performed. **Results:** There was a statistical significant difference as regard the CSF VDBP ($P<0.01$) was found between viral, bacterial and control groups (2.49±.65, 2.43±.55 and 1.74±.25µg/mL, respectively). There was a statistical significant difference ($P<0.05$) in serum VDBP between the viral, bacterial and control groups (214.5±36.5, 197.4±54.8 and 174.3±40.4 µg/mL, respectively). ROC curve analysis showed that the optimum cut-off level of CSF VDBP for diagnosing meningitis was 1.94 µg/mL with a sensitivity of 82.1% and specificity of 85%. AUC of CSF VDBP was 0.865 (95% CI: 0.761–0.969). **Conclusion:** The cerebrospinal fluid (CSF) Vitamin-D Binding Protein (VDBP) level demonstrated an excellent diagnostic performance. It could serve as a potential marker for diagnosing acute meningitis.

**Keywords:** Cerebrospinal fluid, Vitamin D-binding protein, Meningitis Biomarker.

## INTRODUCTION

Meningitis is an acute inflammation of the pia, arachnoids, and the fluid in the subarachnoid space of the brain [1]. There are two main types of meningitis: septic and aseptic [2], with aseptic meningitis being the commonest type. Most cases of meningitis are because of viral, bacterial, fungal, and parasitic infections, Meningitis can also be related to various noninfectious causes [3].

The global incidence of meningitis is 20 cases per 100,000 people; that is, about 1.2 million; the incidence and etiology vary across geographic regions. Aseptic meningitis differs from bacterial meningitis if there is meningeal inflammation with no bacterial growth signs by CSF culture [4].

Acute bacterial meningitis (ABM) is a medical emergency with an estimated incidence of 1.38 cases per 100,000 populations and a mortality rate of 14.3% in western countries [5]. In ABM, 10% of patients die if there is a delay in diagnosis or treatment [6].

Furthermore, survivors of ABM are at an increased risk of cognitive dysfunction or other neurological deficits. Due to the poor utility of clinical indicators in diagnosing meningitis, any patient who presents with meningitis's symptoms must have a lumbar puncture (LP) performed as soon as possible to evaluate the CSF to confirm the diagnosis. Aseptic meningitis CSF findings include low and predominantly lymphocytic pleocytosis, normal glucose levels and normal to slight increase in protein levels [7].

ABM is characterized by a high and predominantly neutrophilic pleocytosis, decreased glucose levels, and an elevated protein level [8]. However, this is not the case in every patient. It varies in elderly subjects and those with partially treated meningitis or immunosuppression. The examiner's skill level can also affect the differential cell count of CSF. As a result, more novel markers are required for more reliable detection of meningitis [9].

Vitamin-D Binding Protein (VDBP) is a 58-kDa multifunctional protein synthesized in the liver and circulates in the bloodstream. It is an acute phase reactant. As a result, VDBP level can fluctuate according to the condition [10-13]. VDBP was originally known as group-specific component globulin, it is recognized to have an important role in vitamin D metabolic transport, in recent years, other functions of VDBP have been discovered, such as actin sequestration and immune response regulation [14].

Polymorphism is common in the gene that encodes VDBP (GC). The frequency of its genotype varies according to ethnic population. Furthermore, variations in VDBP affinity for 25(OH)D have been found based on genotype. Two single-nucleotide polymorphisms (SNPs), rs7041 and rs4588, cause 3



Received: 26/02/2023
Accepted: 26/04/2023

main VDBP polymorphic variants (GC1F, GC1S, and GC2). The prevalence of these variants varies according to ethnic group. The GC1F variant has the highest vitamin D affinity, followed by GC1S and GC2 [15-16].

VDBP has been detected in blood, urinary samples, breast milk, CSF, saliva, seminal fluid, ascitic fluid and the surfaces of lymphocytes, neutrophils, and monocytes. VDBP mRNA expression differs in the brain, heart, lung, kidney, placenta, spleen, testis, and uterus [14-15]. As compared to blood VDBP concentrations (which are the highest), lower concentrations were identified in other bodily fluids [16]. VDBP has been discovered in the CSF; however, it is unknown whether it is produced in the CNS. In an animal experiment, it was recently found that supraoptic and paraventricular nuclei exhibited VDBP immunoreactivity [17].

Previous research has correlated alterations in VDBP concentrations to the pathophysiology of a variety of disorders, including multiple sclerosis [13,17,18]. Furthermore, it was found that intrathecal VDBP production was enhanced in severe neurodegeneration, as in Alzheimer's disease, implying that upregulated VDBP might operate as an actin scavenger [19].

Recently CSF VDBP level was reported that it could act as a new diagnostic marker for acute meningitis [20]. The aim of the current study was to evaluate the validity of using CSF VDBP as a new potential marker for diagnosing meningitis.

## PATIENTS AND METHODS

**Study design:** A cross-section study included 48 patients with suspected an acute meningitis who underwent LP to confirm or rule out acute meningitis. within the period from May 2022 to December 2022.

**Study subjects:** This study was conducted on 48 patients with manifestations suggesting an acute meningitis, 28 patients with acute meningitis who were divided into bacterial group containing 10 patients and viral group containing 18 patients confirmed by laboratory investigations, and 20 patients who were clinically suspected as acute meningitis but excluded by laboratory investigations. Patients aged more 18 years old, from both sexes who were presented with clinical pictures of acute meningitis (fever, vomiting, neck stiffness, headache and convulsion) were enrolled in this study. Patients with other causes of increased intra cranial tension or other neurological disease e.g., multiple sclerosis (MS), other causes of fever, coma and chronic infection. Patients with clinical pictures suggestive of cerebro-vascular diseases, patients of chronic kidney diseases (CKD), patients with acute and moderate to severe chronic liver diseases (CLD) and pregnancy, were excluded from this study.

Complete history taking and thorough clinical examination were done including manifestations suggesting an acute meningitis (fever, headache, convulsion, neck rigidity, positive kerning's and Brudzinsky signs and coma).

**Investigations**: CSF and blood samples were obtained. Serum and leukocytes were separated and kept at –80$^{o}$C. CSF analysis including CSF color, aspect, pressure, chemical analysis including protein, glucose, and cellular CSF analysis including total leucocytic count, cellular differential count, gram stain, and culture were done for each patients' CSF sample.

**VDBP Assay:** CSF and serum VDBP concentrations were measured utilizing an enzyme-linked immunosorbent assay (ELISA) kit (Solarbio, China) in accordance to the manufac-turer's guidelines.

**Other laboratory investigations included:** CBC, CRP, RBS, PT. PTT, INR, Liver function tests and kidney function tests.
**Imaging included:** Brain CT and/or Brain MRI.

**Ethical approval:**
**This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Benha University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.**

***Statistical analysis***

Statistical analyses were carried out by IBM SPSS Statistics software, v 25.0. Numbers and percents (%) are calculated for categorical variables while medians and ranges are pre-sented for continuous variables. The significance of normally distributed variables was determined using one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. The correlation between VDBP levels in the CSF and in the serum was examined using simple correlation analysis. ROC curve and AUC were utilized to examine the performance of CSF VDBP. Reference interval was calculated in accordance to guidelines of the Clinical and Laboratory Standards Institute. After ruling out outliers using Tukey method, data set was shown using nonparametric analysis (2.5–97.5th percentile interval). P value $\leq$0.05 was set as statistically significant.

## RESULTS

Forty-eight subjects were included with a median age of 23 years. Percentage of females was 45.83%. Among these 48 patients.10 patients were in bacterial meningitis group (20.83%), 18 patients were in viral meningitis group (37.5%) and 20 patients were in control group (41.66%). A significant difference existed between groups as regards convulsion (P<0.01), also regarding neck stiffness (Table 1).

**Table (1): Socio-demographic characteristics and clinical findings among the studied groups:**

| Variables | | Bacterial infection group (N=10) | | Viral infection group (N=18) | | Control (N=20) | | Kruskal-Wallis H | Sig. |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Mean | SD | | |
| Age | | 26.50 | 22.38 | 20.27 | 16.41 | 26.35 | 16.32 | 1.658 | 0.437 |
| N | | | % | N | % | N | % | $X^2$ | Sig. |
| Gender | Male | 4 | 40.0% | 11 | 61.1% | 11 | 55% | 1.164 | 0.559 |
| | Female | 6 | 60.0% | 7 | 38.9% | 9 | 45% | | |
| Residence: | | 100% urban | | | | | | | |
| Clinical findings | | | | | | | | P-value | Sig. |
| Fever | | 7 (70%) | | 12 (66.7%) | | 12 (60%) | | 0.859 | 0.390 |
| Headache | | 7 (70%) | | 10 (55.6%) | | 5 (25%) | | 0.34 | 2.16 |
| Vomiting | | 6 (60%) | | 9 (50%) | | 6 (30%) | | 0.41 | 1.79 |
| Convulsion | | 5 (50%) | | 2 (11.1%) | | 0 (0%) | | **0.039*** | 6.49 |
| Neck stiffness | | 10 (100%) | | 12 (66.7%) | | 2 (10%) | | **0.002*** | 23.04 |
| Kering's sign | | 9 (90%) | | 10 (55.6%) | | 0 (0%) | | **0.003*** | 18.84 |
| Brudzinski's sign | | 10 (100%) | | 9 (50%) | | 0 (0%) | | **0.005*** | 15 |
| Pulse Mean ±SD | | 84.5±8.2 | | 78.8±7.8 | | 84.68±5.6 | | 0.052 | 5.898 |
| Temperature Mean ±SD | | 37.8±1.2 | | 37.4±0.6 | | 37.6±0.9 | | 0.737 | 0.611 |
| Systolic PB Mean ±SD | | 125±10 | | 124±12 | | 120±5 | | 0.411 | 1.781 |
| Diastolic PB Mean ±SD | | 83±6 | | 82±7 | | 80±2 | | 0.570 | 1.125 |

A statistical significant difference was found between groups regarding CRP (P<0.01). However, there were no statistical significant differences (P-value >0.05) regarding Hb, WBCs, Platelets, RBS, ALT, AST, Albumin, PT, PTT, INR, Creatinine, Urea (Table 2).

**Table (2): Laboratory Findings among the studied groups:**

| Groups / Variables | Bacterial infection group (n= 10) | Viral infection group (n=18) | Control group (n= 20) | Test of significance Kruskal-Wallis Test | P-value |
|---|---|---|---|---|---|
| HB(g/d), Mean ±SD | 12.3±1.5 | 13±1.2 | 12.7±1.0 | 0.902 | 0.637 |
| WBCs(/L), Mean ±SD | 12.8±2.9 | 12.2±2.4 | 10.8±2.4 | 3.483 | 0.175 |
| Platelet (/µL), Mean ±SD | 270.5±62.6 | 282.3±35.1 | 278.0±43.1 | 0.500 | 0.779 |
| CRP (mg/dL), Mean ±SD | 62.8±15.3 | 50.9±12.6 | 24.9±5.1 | 18.406 | **<0.010**** |
| RBS (mg/dL), Mean ±SD | 101.0±24.3 | 105.0±25.1 | 107.0±26.3 | 1.216 | 0.545 |
| ALT(u/L), Mean ±SD | 22.1±5.4 | 22.5±5.5 | 21.4±5.2 | 0.306 | 0.858 |
| AST(u/L), Mean ±SD | 36.7±8.8 | 40.1±9.8 | 33.8±8.3 | 0.285 | 0.867 |
| Albumin (gm/dl) Mean ±SD | 4.3±0.43 | 3.9±0.27 | 4.0±0.39 | 4.743 | 0.093 |
| PT (Seconds) Mean ±SD | 16.5±3.0 | 18.0±4.3 | 16.5±3.9 | 1.190 | 0.552 |
| PTT (Seconds) Mean ±SD | 28.0±2.9 | 28.3±2.0 | 28.8±2.2 | 2.204 | 0.332 |
| INR, Mean ±SD | 1.27±0.30 | 1.35±0.32 | 1.22±0.30 | 0.666 | 0.717 |
| Creatinine (mg/dL) Mean ±SD | 0.9±0.1 | 1.0±0.2 | 0.98±0.23 | 1.209 | 0.546 |
| Urea (mg/dL) Mean ±SD | 22.3±5.4 | 30.3±7.4 | 27.3±6.7 | 4.073 | 0.130 |

**Significant at 0.01.

A significant difference in CSF TLC was found among the bacterial, viral and control groups (P<0.001). As regards the CSF pressure, a significant difference existed among bacterial, viral and control groups. The mean value of CSF pressure was significant in the bacterial group and higher than the CSF pressure mean of the control group and the mean of the viral group**.** As regards the CSF Protein, a significant difference was reported between bacterial, viral and control groups. The mean value of CSF Protein was significant in the bacterial group and higher than the in CSF protein mean of the viral group and the mean of the control group (Table 3).

**Table (3): CSF analysis among the studied groups:**

| Groups / Variables | Bacterial infection Group (n= 10) | Viral Infection group (n=18) | Control group (n= 20) | Test of significance Kruskal-Wallis Test | P-value |
|---|---|---|---|---|---|
| CSF TLC (/uL) Mean ±SD | 8981.11±244.1 | 87.78±20.81 | 0.000 | 38.36 | <0.001 ** |
| CSF pressure ($cmH_2O$) Mean ±SD | 3.8±0.63 | 2.8±0.4 | 3.1±0.74 | 4.93 | 0.012* |
| CSF protein (mg/dL) Mean ±SD | 290.9±64.8 | 94.44±23.3 | 48.1±11.8 | 18.8 | <0.001** |
| CSF glucose (mg/dL) Mean ±SD | 43.7±10.61 | 78±17.4 | 84.6±20.42 | 5.29 | 0.07 |

*Significant at 0.05 Level. **Significant at 0.01.

A significant difference in CSF color was found among the bacterial, viral and control groups. The color was clear in 20% in bacterial, 72.2% in viral and 100% in control. As regards the CSF aspect, a significant difference was found between bacterial, viral and control groups. The aspect was clear in 30% in bacterial, 72.2% in viral and 100% in control (Table 4).

**Table (4): CSF Color and aspect analysis among the studied groups:**

| Variables | Bacterial (10) | Viral (18) | Control (20) | Test of significance ($X^2$) | P-value |
|---|---|---|---|---|---|
| **CSF color** | | | | | |
| Clear | 2(20%) | 13(72.2%) | 20(100%) | 17.6 | **<0.001**** |
| White | 2(20%) | 0(0%) | 0(0%) | | |
| Yellow | 4(40%) | 1(5.6%) | 0(0%) | | |
| Red | 2(20%) | 4(22.2%) | 0(0%) | | |
| **CSF aspect** | | | | | **<0.001**** |
| Clear | 3(30%) | 13(72.2%) | 20(100%) | 23.6 | |
| Turbid | 7(70%) | 5(27.8%) | 0(0%) | | |
| **Bacterial infection** | | | | | |
| S.aureus | 2(20%) | | | | |
| Strept/pneumonia | 6(60%) | - | - | - | - |
| E. Coli | 2(20%) | | | | |

**Significant at 0.01.

As regards the CSF VDBP, a significant difference was detected among bacterial, viral and control groups. There was a statistically significant difference in Serum VDBP between bacterial, viral and control groups (Table 5).

**Table (5): CSF, Serum Vitamin D binding protein analysis among the studied groups:**

| Groups / Variables | Bacterial infection group (n= 10) | Viral infection group (n=18) | Control group (n= 20) | Test of significance Kruskal-Wallis Test | P-value |
|---|---|---|---|---|---|
| CSF VDBP (µg/mL) Mean ±SD | 2.43± 0.55 | 2.49± 0.61 | 1.74± 0.25 | 18.301 | ** **0.01** |
| Serum VDBP (µg/mL) Mean ±SD | 197.4±48.7 | 214.5±6.5 | 174.3±40.4 | 7.623 | * **0.05** |

*Significant at 0.05 Level. **Significant at 0.01.

At a cut off value 1.94 mg/dl of the marker (VDBP), the area AUC was 0.865 meaning that it has a strong diagnostic performance with sensitivity, specificity, PPV, NPV, accuracy, 95% CI, P (82.1%, 85%, 88.5, 77.3, 83.3, 0.761-0.969, < 0.001 respectively) (Table 6). ROC curve analysis was used to calculate the optimum cut-off level or CSF VDBP in order to diagnose meningitis. The optimum cut-off of CSF VDBP was 1.94 μg/mL with a sensitivity of 82.1% and specificity of 85%. AUC of CSF VDBP was 0.865 (95% CI: 0.761–0.969) (Figure 3).

**Table (6): Diagnostic performance of CSF VDBP:**

| Variable | AUC | Cutoff | Sensitivity | Specificity | PPV | NPV | Accuracy | 95% CI | P-value |
|---|---|---|---|---|---|---|---|---|---|
| **CSF VDBP level** | 0.865 | 1.94 mg/mL | 82.1% | 85% | 88.5 | 77.3 | 83.3 | 0.761–0.969 | 0.001 |

Plot graphs for CSF VDBP levels **(Figure 1)** and for serum VDBP levels were obtained in the three groups **(Figure 2).**

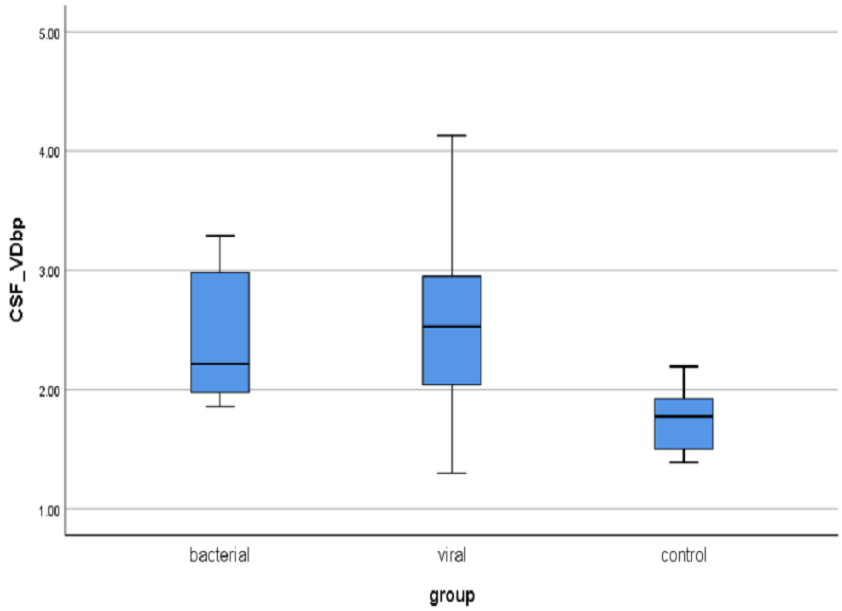


**Figure (1): CSF VDBP findings in bacterial, viral, and control groups.**

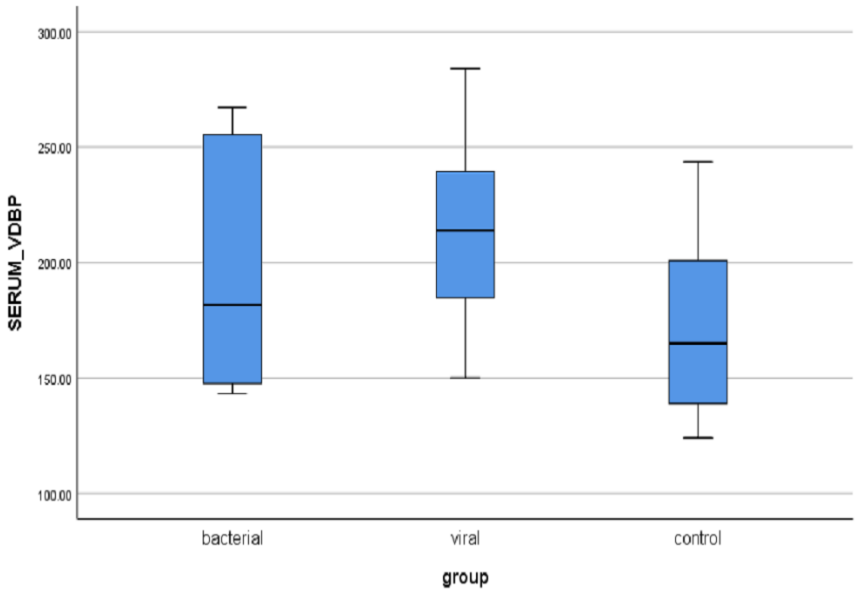


**Figure (2): Serum VDBP findings in bacterial, viral, and control groups.**

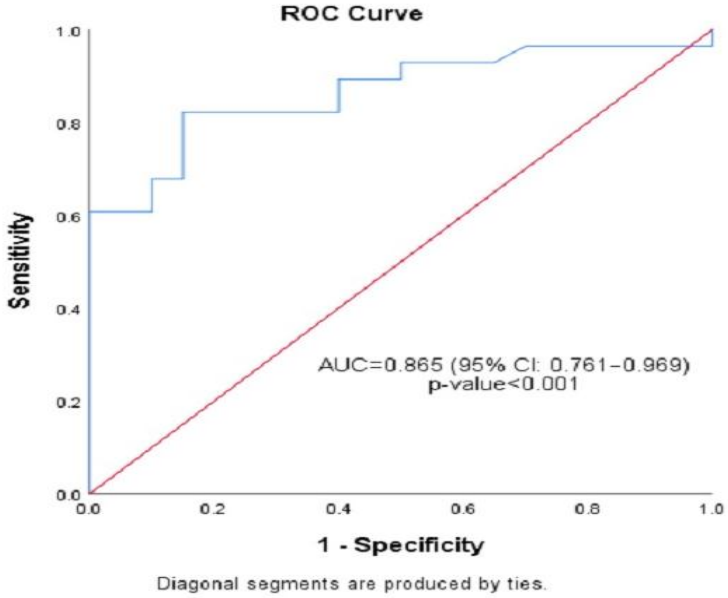


**Figure (3):** Receiver operating characteristics (ROC) curve analysis of VDBP level in CSF for diagnosis of acute meningitis**.**

## DISCUSSION

Meningitis is an infection of the meninges, caused by infection with bacteria, viruses, or fungi. It can cause severe complications, such as brain damage and death [1]**.** Clinical signs and CSF findings are not reliable enough to rule out meningitis, Therefore, new biomarkers are needed to improve the accuracy of meningitis diagnosis [21].

VDBP is formed in the liver and circulates in the bloodstream. It is an acute phase reactant. As a result, its level can fluctuate depending upon the condition and can be used as diagnostic biomarker [10,11].

There was a significant statistical difference as regard convulsions (p-value < 0.05) among bacterial, viral and control groups, it was present in 50% in bacterial meningitis**,** 11.1% in viral meningitis and 0% in control group. This results was in partial agreement with **Brouwer *et al.*** [22] who found that convulsions occur in approximately 20% to 40% of adults with bacterial meningitis.

In term of meningeal irritation signs such as neck rigidity, positive kerning's and Brudzinsky signs, a significant statistical difference (P-value <0.05) existed among bacterial and viral groups compared with control group, they were present in 100%, 90% and 100% of cases of bacterial meningitis and in 66.7%, 55.6 % and 50% of viral meningitis and 10%, 0%, 0% in control group , respectively. Our findings were in accordant with **Ndreu *et al.*** [23] study which reported neck rigidity, positive kerning's and Brudzinsky signs in 73.1%, 55.2% and 56.7% of patients with meningitis respectively

A significant statistical difference (P-value <0.01) existed amongst groups regarding CRP. The mean of CRP in the bacterial group (62.8±24) was higher compared with the viral group (50.9±22.5), and the control group (24.9±9.4). These results were agreed with those of **Streharova *et al.*** [24] who found that CRP occurs in 19.4% of bacterial meningitis and 3.6% of viral meningitis.

Regarding the physical CSF characters, significant differences were detected between cases with bacterial meningitis and cases with viral meningitis regarding tension, color and aspect of CSF:

Regarding the CSF color, a significant difference existed among bacterial, viral and control groups (Chi-square Test=17.6, P<0.01). Change in CSF color was found in 80% in bacterial, 27.8% in viral and 0% in control. These results were in agreement with **Lebel *et al.*** [25] who found that CSF color was significantly different between subjects with bacterial meningitis and subjects with viral meningitis. In the bacterial meningitis group, CSF color was more likely to be cloudy or purulent, while in the viral meningitis group, CSF color was more likely to be clear or slightly cloudy.

As regards the CSF aspect, a significant statistical difference was found among bacterial, viral and control groups (Chi-square Test=23.6, P<0.01). Turbidity was found in 70% in bacterial, 27.8% in viral and 0% in control groups. Such results were similar to **Wang *et al.*** [26] who found that CSF turbidity was significantly higher in bacterial meningitis than in viral meningitis.

A there was a statistical significant difference among the bacterial, viral and control groups as regards the CSF pressure (Kruskal-Wallis Test=4.93, P<0.05). The mean pressure was significant in the bacterial group (μ = 3.8±0.63) and higher than the CSF pressure mean of the control group (μ = 3.1±0.74) and the mean of the viral group (μ = 2.8±0.78).

The TLC was higher in the bacterial group (μ = 8981.11±31539.10) than that of the viral group (μ =

87.78±97.51), and control groups (Kruskal-Wallis Test=38.36, P<0.001) and this was statisticaly significant, this was in agreement with **Jyoti *et al.*** [27] who found a significant difference in CSF TLC between the bacterial, viral, and control groups. The mean CSF TLC was highest among the bacterial meningitis cases (258 cells/mm3), followed by the viral meningitis cases (85 cells/mm3), and controls (2 cells/mm3).

As regards CSF protein, a significant difference existed among the three study groups (Kruskal-Wallis Test=18.8, P<0.01). The mean values of in CSF protein were in bacterial, viral and control groups (μ = 290.9±64.8, 94.44±108.44, and 48.1±24.8, respectively). Such findings were similar to **Brouwer *et al.*** [28] who disclosed in their study that a significant difference in the mean CSF protein level between the bacterial meningitis group (2.99 g/L) and control group (0.28 g/L).

Our study demonstrated that, culture results in bacterial meningitis cases were positive in 10 cases (100%). The most commonly isolated microorganisms were St. pneumoniae in 6 cases (60%), Staph aureus in 2 cases (20%) and E Coli in 2 cases (20%). This was similar with **Brouwer *et al.*** [29] who found that CSF culture was positive in 70-85% of cases with bacterial meningitis.

In the current study, CSF VDBP was statistically significantly higher in meningitis groups than control group (P<0.01) and this was in accordant with **Lee *et al.*** [20] who found that CSF VDBP was higher in acute meningitis cases than control.

In the present study ROC curve analysis revealed that CSF VDBP concentrations in meningitis cases had a high predictive value. CSF VDBP has a sensitivity of 82.1% and a specificity of 85 % at a cut-off level of 1.94 μg/mL for diagnosing meningitis and this was in agreement with **Lee *et al.*** [20] who found that at a cut off level of 1.96 μg/mL, the CSF VDBP has an excellent diagnostic performance, with sensitivity of 82.4% and specificity of 85.9%.

This suggests that CSF VDBP levels could serve as a valuable novel biomarker for diagnosing meningitis.

## CONCLUSION

The CSF VDBP cut-off level of 1.94 μg/mL has an excellent diagnostic performance, with 82.1% sensitivity, 85% specificity, and an AUC of 0.865. As a result, CSF VDBP could be a possible marker for diagnosing acute meningitis.

There are some limitations to this study. First and foremost, it was a cross-sectional study, so other studies are required to evaluate the mentioned marker in prognosis. Second, despite the fact that the disease group encompassed a variety of diseases, the number of patients in each category was very modest. More researches with a larger number of patients in each group are thus required. Third, this preliminary data shows that CSF VDBP can be used to differentiate between different etiologies of meningitis according to CSF VDBP levels. Hence further studies might elaborate on this perspective.

**Sponsoring financially:** Nil.
**Competing interests:** Nil.

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