



# Evaluation of Biochemical and Hematological Markers of Cerebrospinal Fluid in Patients Suspected with Meningitis

Hadadi Al<sup>1</sup>, Masuadi E<sup>1</sup>, Alouffi S<sup>2\*</sup>, Al Johani SM<sup>3,4</sup>, Al Mugairi A<sup>3</sup>, Al-Sughair A<sup>3</sup>, Alhamad A<sup>3</sup>, Al Saedi R<sup>3</sup>, Al-Shebani M<sup>3</sup>, Bahis A<sup>3</sup>, Mahmoud S<sup>3</sup>, Almutairi AF<sup>3</sup>, Al-Yaesh R<sup>3</sup>, Alhassan I<sup>3</sup>, Alenzi FQ<sup>5</sup>, Tamimi W<sup>1,3\*</sup>

<sup>1</sup>College of Medicine and College of Medical Applied Sciences, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

<sup>2</sup>Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, University of Hail, Hail, Saudi Arabia.

<sup>3</sup>Department of Pathology & Laboratory Medicine, King Abdulaziz Medical City, King Abdulla International Medical Research Center, Riyadh, Saudi Arabia

<sup>4</sup>College of Science and Health Profession, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

<sup>5</sup>College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

## Abstract

**Background:** Cerebrospinal fluid (CSF) and blood cultures are gold standard tests for establishing the diagnosis of meningitis; however, they are labor-intensive and require longer turnaround time before the results are available to the physician. This study was conducted to evaluate the levels of laboratory markers in CSF samples.

**Design and Methods:** A total of 248 CSF samples were received from 137 patients suspected with meningitis. The samples were collected by our physicians and sent to the laboratory for immediate analysis. White blood cell (WBC) count and levels of glucose and total protein (TP) were analyzed. CSF culture was done for all samples in the microbiology laboratory. Diagnostic sensitivity and specificity were calculated.

**Results:** The majority of samples were received from neonates (61 patients [44.5%], aged <1 year), children (36 patients [24.3%], aged <18 years), and adults (40 patients [29.2%], aged >18 years). There were 47 (34.3%) females. Culture results revealed 15 samples (7.7%) positive for bacterial meningitis. Sensitivities for WBC count and TP and glucose levels were 73.3%, 86.7%, and 60%, respectively, and the respective specificities were 75.4%, 36.1%, and 30.7%. Positive predictive values were 20%, 10.2%, and 6.7%, respectively, and negative predictive values were 97.1%, 97%, and 90.2%, respectively. The overall accuracy rates were 75.3%, 40%, and 33%, respectively.

**Conclusion:** CSF and blood cultures demonstrated good sensitivity but low specificity, with the exception of WBC count. These tests were sufficient to rule out meningitis.

Keywords: Cerebrospinal Fluid, Meningitis, CSF

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\*Corresponding author(s): Sultan Alouffi, Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, University of Hail, Hail, Saudi Arabia.

Waleed Tamimi, College of Medicine and College of Medical Applied Sciences, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. Department of Pathology & Laboratory Medicine, King Abdulaziz Medical City, King Abdulla International Medical Research Center, Riyadh, Saudi Arabia

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## Abbreviations

AFB: Acid-fast bacillus; CSF: Cerebrospinal fluid; NPV: Negative predictive value; PPV: Positive predictive value; RBC: Red blood cell; ROC Receiver operating characteristic; TP: Total protein; WBC: White blood cell

## Introduction

Due to the severity and high morbidity and mortality rates of bacterial meningitis, there is an urgent need for a rapid and accurate diagnostic test for bacterial meningitis [1]. However, the majority of meningitis cases (82%–94%) are nonbacterial, which makes the clinical differentiation from bacterial meningitis quite challenging [2].

Neonates are more commonly affected by bacterial meningitis than any other age group. In addition, the clinical presentation of neonatal meningitis is nonspecific despite the significant mortality and morbidity, which presents decision-making



challenges among clinicians regarding whether to perform lumbar puncture on all patients who receive sepsis workup [3-5].

As nonbacterial meningitis accounts for the majority of meningitis cases, these patients are vulnerable to unnecessary investigations, hospitalization, and use of antibiotics unless an accurate and rapid diagnosis is established [6-8].

Currently, cerebrospinal fluid (CSF) culture is the gold standard for the diagnosis of bacterial meningitis, and when prior antibiotics are not administered, this is diagnostic in 70%–85% of the cases. However in the acute setting, CSF culture is not useful because the routine culture takes approximately 2–5 days before the results are acquired. Although nucleic acid amplification tests have been clinically used for the diagnosis of a variety of common causes of meningitis during the past decade, they are not readily available in the initial evaluation of suspected meningitis due to the technical expertise required for performing these tests [9-20].

Preliminary CSF culture results and the clinical symptoms are useful parameters that can be used to determine whether to commence antibiotics in pediatric patients, and in fact these parameters are clinically used to differentiate between viral meningitis and bacterial meningitis [21].

The components of CSF proteins include albumin, transferrin, and immunoglobulin in addition to globulin and other enzymes [22]. Furthermore, CSF protein level is a useful clinical marker of endothelial cell permeability in neurological disorders based on the fact that CSF protein levels are increased due to increased

endothelial cell permeability [23]. Therefore, in the present study, we evaluated the levels of laboratory markers in CSF samples.

## Materials and Methods

### Study area

This study was performed in King Abdulaziz Medical City, a tertiary care hospital in Riyadh, Saudi Arabia.

### Study population

Adult and pediatric patients with a clinical suspicion of meningitis were routinely referred to undergo a lumbar puncture.

### Study design

This was a retrospective electronic record review of CSF samples collected over a 1-year period in 2014 using the QuadraMed Electronic Medical Record System. All samples were processed at the Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City. A clinical suspicion of meningitis was defined as having any combination of the following symptoms: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurologic deficit, and altered consciousness or lethargy, with no other general medical condition explaining them. Patients already receiving specific treatment were excluded. All included patients underwent a lumbar puncture using standard procedures. CSF samples were sent within 1 h of collection to the laboratory for microbiological analysis (acid-fast bacillus staining), culture for mycobacteria in Ogawa medium, Gram's stain, culture for common bacteria, cytological analysis (total white blood cell [WBC] count and determination

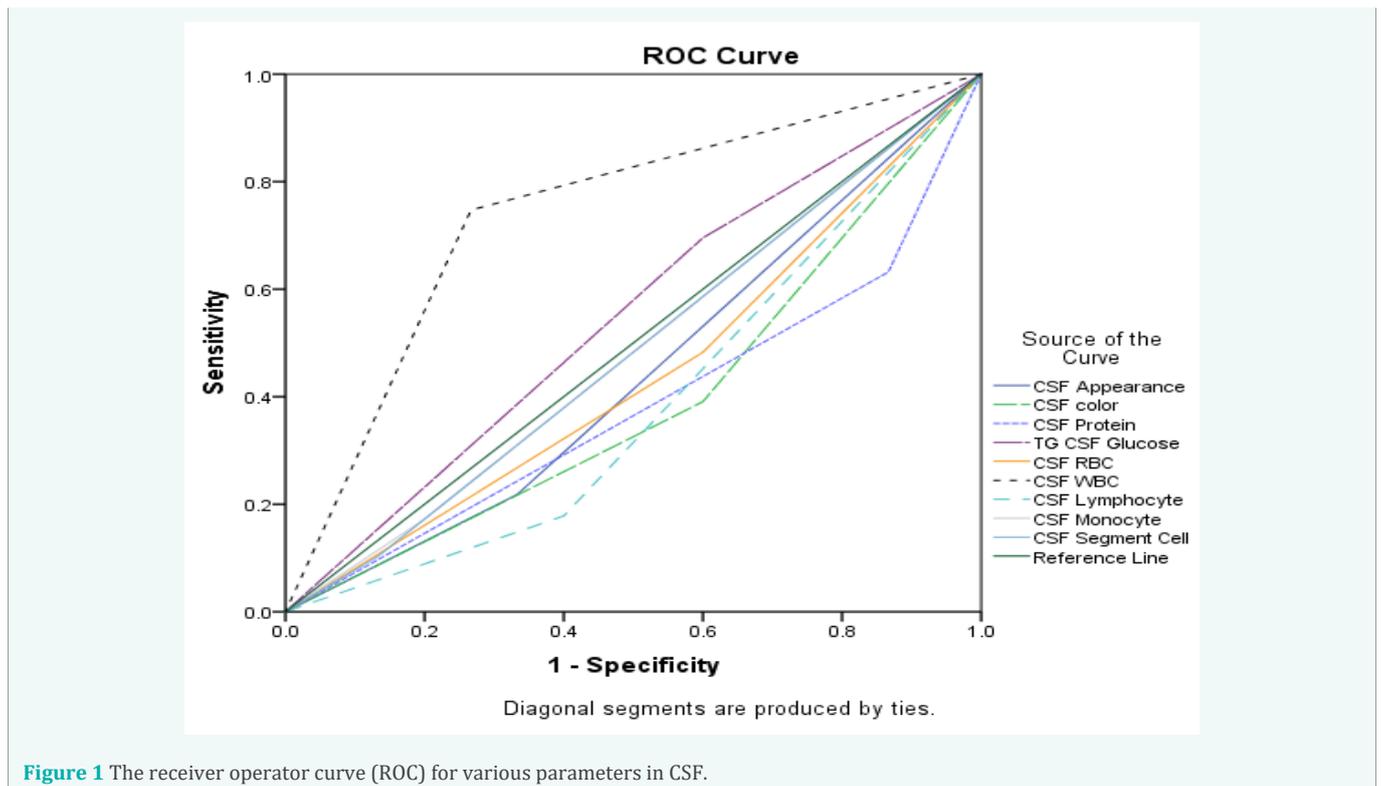


Figure 1 The receiver operator curve (ROC) for various parameters in CSF.



of the percentage of lymphocytes), and biochemical (glucose and protein) analyses. Based on the clinical findings, the physicians requested for further tests/procedures (biopsy or culture of other body fluids and/or lymph node aspiration).

### Laboratory examination

All CSF samples were processed at the Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, during 2014. Only results obtained from samples collected by lumbar puncture that had documented microbiological, culture, and biochemical results were analyzed in this study. Patients who did not have complete results or documents were excluded from analysis, leaving a total of 248 samples from 137 patients. All CSF specimens were processed according to standard protocols, which included a cell count, differential count, Gram's stain, and CSF protein (mg/L) and glucose (mmol/L) estimation. Hematological and biochemical markers were evaluated in these samples, including differential leukocyte or WBC count, red blood cell (RBC) count, and levels of glucose and total protein (TP). The fluids were also visually checked for appearance, color, and turbidity. The analyzers used in this study were Advia 2120 from Siemens Company for measuring hematological markers and Architect from Abbott Company for measuring biochemical markers.

**Parameter cutoff values and statistical analysis:** The diagnostic parameters in CSF considered in this study were evaluated at their respective cutoff values as follows: TP >400 mg/L and glucose levels 60–80 mg/dL (for patients aged <12 years) and 40–70 mg/dL (for patients aged >12 years). The cutoff values for WBC and RBC counts were as follows: for adults aged >12 years, 5 WBCs/ $\mu$ L or  $\times 10^6$ /L and 10 RBCs/ $\mu$ L or  $\times 10^6$ /L; for infants aged <1 year, 30 WBCs/ $\mu$ L or  $\times 10^6$ /L; for those aged <4 years, 20 WBCs/ $\mu$ L or  $\times 10^6$ /L; and for those aged <12 years, 10 WBCs/ $\mu$ L or  $\times 10^6$ /L. The cutoff values for other cells were as follows: for adults, lymphocytes 40%–80% and neutrophils 0%–6%, and for neonates, lymphocytes 5%–35% and neutrophils 0%–8%. Data were analyzed using SPSS version 20. Baseline characteristics were presented as frequencies and percentages. Chi-square test was used to assess the association between CSF culture results and other CSF properties. Sensitivity analysis and receiver operating characteristic (ROC) curves were used to evaluate the accuracy of CSF properties with the CSF culture results. A test was considered to be statistically significant when the P value was <0.05.

### Results

A total of 248 CSF samples were collected from 137 patients. There were 47 (34.3%) female and 90 (65.7%) male patients enrolled in this study. The majority of patients (61 [44.5%]) were neonates aged <1 year. There were 36 (26.3%) children aged <18 years. The remaining 40 (29.2%) adult patients were aged <18 years. The results of CSF culture revealed 180 (92.3%) negative and 15 (7.7%) positive cases of bacterial meningitis. The positive results disclosed *Actinobacter baumannii* in two cases, *Enterobacter cloacae* in one case, coagulase-negative *Staphylococci* in four cases, *Pseudomonas aeruginosa* in six cases,

and *Streptococcus agalactiae* (Group B streptococci) in two cases.

Table 1 describes the appearance and color of all CSF samples received in our laboratory. The majority of samples were clear 192 (81%) and had no turbidities. Other samples appeared slightly cloudy (16 [6.8%]), heavily cloudy (18 [7.6%]), or bloody (11 [4.6%]). Regarding the color of CSF samples, the majority were colorless (158 [66.7%]). On the other hand, 60 (25.3%) samples were xanthochroid and 20 (8.4%) samples had other colors.

Table 2 shows the number and percentage of normal and abnormal results for different markers in the CSF samples. Not all tests were done on every sample, and the maximum (248 results) tests were performed for TP and the lowest (122 results) for neutrophils. The percentage of normal results for all markers ranged from the lowest (16.4%) for neutrophils to the highest (76.8%) for WBCs. On the other hand, the abnormally high results ranged from 6.1% for lymphocytes to 64.8% for neutrophils, and the abnormally low results ranged from 15.5% for TP to 41.5% for monocytes. Other results for rare, few, or occasional findings were 29.9% for lymphocytes and 22.0% for monocytes.

Table 3 presents the values for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and the p value for different CSF markers. The results indicated that the highest sensitivity of 86.7% was found for both TP and neutrophils, whereas the lowest sensitivity of 33.3% was found for the appearance of CSF samples. The specificity ranged from the lowest of 10.2% for neutrophils to the highest of 75.4% for WBC count. The PPVs were found to be low for all parameters, ranging from 7.6% to 20%. In contrast, the NPVs were better for all parameters, ranging from 83.8% for lymphocytes to 97% for TP. Among all parameters, the p values were found to be significant only for WBCs (<0.00001) and lymphocytes (0.032). Fig. 1 illustrates the ROC curve for the various CSF parameters.

### Discussion

In this study, we evaluated some biochemical and hematological parameters in the CSF collected from patients with suspected meningitis in Saudi Arabia. This issue was raised to identify rapid and more sensitive and specific markers to aid in the diagnosis of meningitis, which was because the CSF culture, although being the gold standard test, requires long time to provide the information to clinicians.

**Table 1:** Description of the appearance, conditions and color of all CSF samples. The number and percentage are shown are included.

Parameter	Condition of CSF	N (%)
CSF Appear	Clear	192 (81%)
	Slightly Cloud	16 (6.8%)
	Heavy Cloud	18 (7.6%)
	Bloody	11 (4.6%)
Color	colorless	158 (66.7%)
	Xanthochroid	60 (25.3%)
	other color	20 (8.4%)



**Table 2:** Number and percentage of normal and abnormal results for different biochemical and hematological CSF markers. NA means “not applicable”.

CSF Parameter	Normal n(%)	Low n(%)	High n(%)	Rare, Few, occasional n(%)
Total Protein	102 (42.9%)	37 (15.5%)	109 (41.6%)	NA
Glucose	75 (31.6%)	54 (22.8%)	108 (46.5%)	NA
Red Cells	129 (54.4%)	NA	108 (45.6%)	NA
White Cells	182 (76.8%)	NA	55 (23.2%)	NA
Lymphocytes	40 (27.2%)	54 (36.7%)	9 (6.1%)	44 (29.9%)
Monocytes	35 (28.5%)	51 (41.5%)	10 (8.1%)	27 (22.0%)
Neutrophils Segs	20 (16.4%)	NA	79 (64.8%)	23 (18.9%)

**Table 3:** The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), AUC = area under the curve and the p-value for different CSF markers.

CSF Parameter	Sensitivity %	Specificity %	PPV %	NPV %	AUC	P-value
Total Protein	86.7	36.1	10.2	97	0.614	0.074
Glucose	60	30.7	6.7	90.2	0.564	0.457
Red Cells	40	48.6	6.1	90.6	0.443	0.396
White Cells	73.3	75.4	20	97.1	0.741	<0.00001
Lymphocytes	40	17.3	5.7	83.8	0.389	0.032
Monocytes	80	16.95	7.6	90.9	0.486	0.764
Neutrophils Segs	86.7	10.2	7.6	90	0.485	0.700
Appearance	33.3	78.3	11.4	93.4	0.442	0.299
Color	40	60	11.4	94.8	0.394	0.11

Our results showed that TP, neutrophils, monocytes, and glucose have better sensitivity in detecting bacterial meningitis; however, these parameters showed poor specificity and therefore can be used only for ruling out bacterial meningitis. On the other hand, parameters such as RBCs, lymphocytes, and color demonstrated poor sensitivity and specificity. Although the lowest sensitivity of 33.3% was found for the appearance of CSF samples, it showed good specificity. Hence, this test can be considered as one of the methods for including the diagnosis of bacterial meningitis. Finally, the WBC count showed good combination of sensitivity and specificity and can be used as the first choice to either rule in or rule out bacterial meningitis. This finding is in agreement with that reported by White et al who found that WBC count was the most useful parameter for discriminating bacterial meningitis from other causes [24]. In addition, they detected better sensitivity and specificity for TP than our results, which may be because they used a higher (600 mg/L) cutoff value for discriminating bacterial from nonbacterial meningitis, whereas we used 400 mg/L that may have resulted in comparable sensitivity but lower specificity compared with those reported by White et al. Another reason could be the differences in the analyzer and technology used for measuring the TP levels in their study and our study. They used Beckman Coulter Synchron Clinical Systems (Beckman Coulter, Brea, CA, USA), whereas we used the Architect C16000 analyzer (Abbott, Springfield, IL, USA). The low sample size in our study may also be another contributor to these differences.

In the study of Manning L et al, in which they prospectively

collected and examined CSF samples from 1192 children who participated in their study, the CSF was clear in 77.5% and cloudy in 4.5% of the children [25]. These data are consistent with our findings, where we found that the CSF samples were clear in 81%, slightly cloudy in 6.8%, and heavily cloudy in 7.6% of the patients. We detected a low diagnostic value using these visual parameters. Unfortunately, no diagnostic accuracy of these visual parameters was reported in the study of Manning L et al to enable comparison with our study results. Nevertheless, this comparison would not add much value due to the fact that the utilization of these visual parameters is not accurate in the evaluation of patients with suspected meningitis and other laboratory analyses, including the gold standard CSF culture, will remain the best and the first choice to order. Manning L et al also reported that 58 (4.9%) children had positive cultures [25]. Similarly but slightly higher, we reported that 7.7% of suspected cases for meningitis had positive cultures.

At a cutoff of 330 mg/L for TP, Manning L et al calculated the sensitivity and specificity as 99.5% and 25.2%, respectively for TP and 99.6% and 98.7%, respectively, for WBCs (leukocytes), as they used 20 cells/mm<sup>3</sup> as a cutoff value [25]. Similarly, when they increased the cutoff value for TP to 1000 mg/L and retained the same WBC cutoff value, the sensitivity of TP decreased slightly to 96.3, but the specificity dramatically increased to 83.8% [25].

Manning L et al found that the total CSF leukocyte count had good diagnostic precision with an AUC ROC of >97.5% and an optimal cutoff value of  $\geq 20$  cells/mm<sup>3</sup> [25]. They reported that the diagnostic precision of CSF protein was lower than that of



CSF leukocyte count. They used a semiquantitative method to measure glucose and protein levels, which was performed using dipsticks (Acon Laboratories, San Diego, USA) [25].

Another study conducted by Liu YJ et al investigated the CSF samples collected from 123 Chinese patients of whom 80 had bacterial meningitis and 43 had nonbacterial meningitis [26]. They found a lower sensitivity of 88.75% for CSF leukocytes but a better specificity of 90.7% at a cutoff of  $116 \times 10^6/L$ . However, a very low sensitivity of 43.75% for TP but a better specificity of 86.05% were observed at a cutoff of 1140 mg/L [26]. These findings may support our abovementioned explanation that the sample size could have contributed to the calculation of diagnostic accuracy. Liu YJ et al also reported a CSF glucose sensitivity of 65% and a specificity of 67.4%.

## Conclusion

Our study demonstrated that some laboratory parameters in CSF samples showed good sensitivity but low specificity, with the exception of leukocytes. These tests were sufficient to rule out meningitis. However, CSF culture will remain the gold standard test to accurately diagnose bacterial meningitis. The limitations of this study were the low sample size and the retrospective design, and therefore, further studies are required to reach a solid conclusion.

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