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ORIGINAL ARTICLE

Diagnostic Accuracy of CSF and Blood Glucose Ratio in Diagnosis of Bacterial Meningitis in Children Using CSF Culture as Gold Standard

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ABSTRACT

Aim: To find the diagnostic accuracy of CSF and blood glucose ratio in diagnosis of bacterial meningitis in children using CSF culture as gold standard.
Study design: Cross sectional study
Setting and duration: The study was conducted in the department of Pediatric Emergency Medicine, The Children's Hospital and the Institute of Child Health, Lahore, from 15 May 2021 to 15 February 2022.
Methods: A total of 140 children aged 1 month up to 14 years with clinical features suggestive of meningitis was selected. The patients underwent a lumbar puncture after getting consent from parents. The emergency laboratory examinations performed for their predictive value for bacterial meningitis as follows: CSF total cell count, CSF mononuclear cell count, CSF polymorphonuclear cell count, CSF polymorphonuclear/total cell ratio, CSF glucose, CSF/blood glucose ratio. The treatment was then readily started as per protocol for the presumptive diagnosis.
Results: Amongst 145 cases, 51.72%(n=75) were upto 6 years of age while 48.28%(n=70) were between 7-14 years of age, mean+sd was calculated as 6.58+3.15 years, 60% were male and 40%(n=58) were females, mean CSF/Blood glucose ratio was calculated as 0.31+0.08. The diagnostic accuracy of CSF and blood glucose ratio in diagnosis of bacterial meningitis in children using CSF culture as gold standard was recorded as 90.32%, 90.36%, 87.5%, 92.59% and 90.34% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate.
Conclusion: Through the findings of this study, we concluded that the diagnostic accuracy of CSF and blood glucose ratio in diagnosis of bacterial meningitis in children using CSF culture as gold standard is higher but needs its validation through some other local trials in absence of previous data.
Keywords: Bacterial meningitis, CSF culture, CSF/blood glucose ratio, Diagnostic accuracy

INTRODUCTION

Meningitis is serious public health problem demanding early diagnosis, effective treatment, prevention and control[1]**,** Accurate and timely diagnosis of acute bacterial meningitis is essential because outcomes of this disease depends on prompt initiation of appropriate antibiotic therapy[1]**.** Bacterial meningitis (BM) should be treated readily with antibiotics, whereas acute aseptic meningitis (AM) is usually self-limiting.

However, it may be challenging and difficult to differentiate bacterial meningitis from aseptic meningitis because the symptoms and laboratory assays are often similar and overlapping. In addition, classical clinical manifestations of bacterial meningitis in infants and children are usually difficult to recognize because of the absence of signs of meningeal irritation and because of delayed elevation of intracranial pressure. Combination of present CSF variables (proteins, glucose, leucocytes count and ratio of CSF/serum glucose) has been suggested effective in differentiating acute viral meningitis from bacterial meningitis[1].

However, there are serious limitations of the above variables in diagnosing and differentiating bacterial and viral meningitis. Moreover, various lab parameters examined in cerebrospinal fluid (CSF) are less descriptive in children than in adults: in enterovirus meningitis, CSF parameters can be practically identical to those of bacterial meningitis. For example, acute meningitis with predominance of neutrophils in CSF suggests BM; however, herpes simplex-1 infected meningitis presents with >90% neutrophils in CSF[1-2]**.**

Further more, other assays, such as Gram stain, latex agglutination, and polymerase chain reaction-based assays, lack sensitivity[2-7]**.** CSF culture is the gold standard for diagnosing bacterial meningitis[8]**.**

In a recent study conducted in Peshawar, the incidence of CSF culture-proven bacterial meningitis was found to be 49.2% in patients presenting with signs and symptoms suggestive of meningitis[9]**.**

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In clinical practice, mostly before definitive CSF bacterial cultures are available, majority of patients with acute meningitis are treated with broad-spectrum antibiotics targeting bacterial meningitis. Even though in general, this does not seriously harm the aseptic meningitis patients; however, it may enhance the local frequency of antibiotic resistance and cause antibiotic side effects, nosocomial infections and increased medical costs[1-6]**.**

Thus, it is not only important to recognize bacterial meningitis patients who promptly need antimicrobial therapy but also aseptic meningitis patients who do not need antibiotics and/or hospital stays. To address these issues, it has been proposed recently that CSF lactate may be a good marker that can differentiate bacterial meningitis (>6mmol/l), from partially treated meningitis (4 to 6mmol/l) and aseptic meningitis (<2mmol/l)[2]**.**

However, the other investigations are of the opinion that the elevated CSF lactate level is a non-specific finding and occurs in number of diseases such as meningitis, hypoxic cerebral injury, subarachnoid haemorrhage and head injury[2,5,7]**.**

In addition, the CSF lactate level is likely to be affected by the administration of antimicrobials[2] and measuring CSF lactate is not routinely performed. In a similar study conducted previously in Japan the sensitivity and specificity of CSF/Blood glucose ratio were found to be 92.9% & 92.9% respectively. Given the burden of meningitis and the mortality associated with it, it is thus necessary to identify a marker which can help the treating physician to offer the best possible treatment to patients in a timely manner under resources constraints.

There is no study previously done in Pakistan on the utility of CSF/blood glucose ratio for the diagnosis of bacterial meningitis. It is thus of paramount importance to study the utility of readily available marker.

PATIENTS AND METHODS

It was a Cross sectional study held at the department of Pediatrics Emergency Medicine, The Children's Hospital and the Institute of Child Health, Lahore from 15 May 2021 to 15 February 2022.The criteria of inclusion was children aged between one month to 14 years of both genders with signs and symptoms suggestive of

meningitis for less than 72 hours. Children having tuberculous or fungal meningitis assessed from lab results, children with bacterial meningitis who received antibiotics before lumbar puncture and patients with trauma and post surgery were excluded. Sample size of 145 cases is calculated with 95% confidence, 5% margin of error for 92.9%[2] sensitivity, 5% margin of error for specificity 92.9%[2] of CSF/blood glucose ratio by taking expected percentage of bacterial meningitis i.e. 42.2%[9] in the diagnosis of bacterial meningitis by taking CSF culture as gold standard. Non Probability consecutive sampling technique was used. A total of 145 children was selected. The patients underwent a lumbar puncture after getting consent from parents. The emergency laboratory examinations performed for their predictive value for bacterial meningitis as follows: CSF total cell count, CSF mononuclear cell count, CSF polymorphonuclear cell count, CSF polymorphonuclear/total cell ratio, CSF glucose, CSF/blood glucose ratio. The treatment was then readily started as per protocol for the presumptive diagnosis. After the receipt of culture results from the laboratory, final diagnosis was made and values for determining the accuracy of CSF/blood glucose ratio was calculated. Statistical analysis was done using SPSS version 20. Qualitative data like gender, bacterial meningitis on CSF culture and CSF/Blood glucose ratio was presented as frequencies and percentages. Quantitative data, age and CSF/Blood glucose ratio was presented as mean and standard deviation. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy was calculated using 2X2 tables for CSF/Blood glucose ratio in the diagnosis of bacterial meningitis by taking CSF culture as gold standard. Data was stratified for age, gender to deal with effect modifiers. Post stratification chi-square test was applied taking p value <0.05 as significant.

Operational Definitions: Meningitis: Patients with signs and symptoms suggesting meningitis such as fever (>98^{0}F), fits, vomiting, neck stiffness, headache, lethargy, bulging anterior fontanel (any of these) and a total cells count in the CSF of more than 5 cells/µL was considered to have meningitis.

Bacterial Meningitis: Bacterial meningitis was defined as the growth of a pathogen from CSF culture.

Positive culture: A specimen of CSF showing growth of a pathogen >1HPF on CSF culture was taken as positive culture.

Negative culture: a specimen of CSF showing no growth of pathogen on CSF culture shall be taken as a negative culture

Optimal cut-off for CSF/Blood glucose ratio: The optimal cut-off for CSF/Blood glucose ratio was 0.36. This cut off is consistent with that used in previous studies.[2]

CSF/Blood glucose ratio less than or equal to 0.36 was taken as suggestive of bacterial meningitis.

CSF/Blood glucose ratio more than 0.36 was non-suggestive of bacterial meningitis.

Accuracy: Accuracy was calculated as the proportion of patients accurately diagnosed by CSF to blood glucose ratio and in means of sensitivity, specificity, positive predictive value, and negative predictive value.

Diagnostic Accuracy: True positive case+True negative case/Total number of patients in the studyX100

Sensitivity: True positive/True positive + False negative X100

Specificity: True negative/True negative + False positiveX100

PPV: True positive/True positive + False positiveX100

NPV: True Negative/True Negative + False Negative X 100

True Positives: Patients whose CSF/Blood glucose ratio is less than or equal to 0.36 and CSF cultures show growth of a pathogen

True Negative: Patients whose CSF/Blood glucose ratio is more than 0.36 and CSF cultures don't show growth of a pathogen.

False positive: Patients whose CSF/Blood glucose ratio is less than or equal to 0.36 but the CSF cultures don't show growth of a pathogen.

False Negatives: Patients whose CSF/Blood glucose ratio is more than 0.36 but the CSF cultures show growth of a pathogen.

RESULTS

A total of 145 cases fulfilling the inclusion/exclusion criteria were enrolled to find the diagnostic accuracy of CSF and blood glucose ratio in diagnosis of bacterial meningitis in children using CSF culture as gold standard. Age distribution shows that 75(51.72%) were upto 6 years of age while 70(48.28%) were between 7-14 years of age, mean+sd was calculated as 6.58+3.15 years.(FIG: 1).Gender distribution of the patients shows that 60% were male and 58(40%) were females. Mean CSF/Blood glucose ratio was calculated as 0.31+0.08. Bacterial meningitis on CSF culture was recorded in 63(43.45%) whereas 82(56.55%) had no findings of it (Fig. 2). The diagnostic accuracy of CSF and blood glucose ratio in diagnosis of bacterial meningitis in children using CSF culture as gold standard was recorded as 90.32%, 90.36%, 87.5%, 92.59% and 90.34% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate. (Table:1) The data was stratified for age, gender to deal with effect modifiers. Post stratification chi-square test was applied taking p value <0.05 as significant (Fig. 3&4).

Figure 1: Age distribution (n=145)

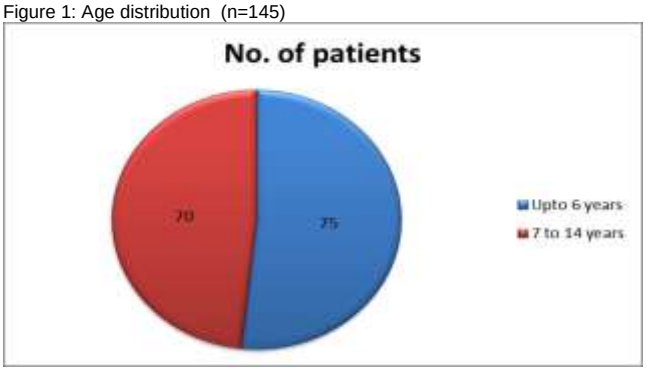


Figure 2. Bacterial Meningitis on CSF Culture (n=145)

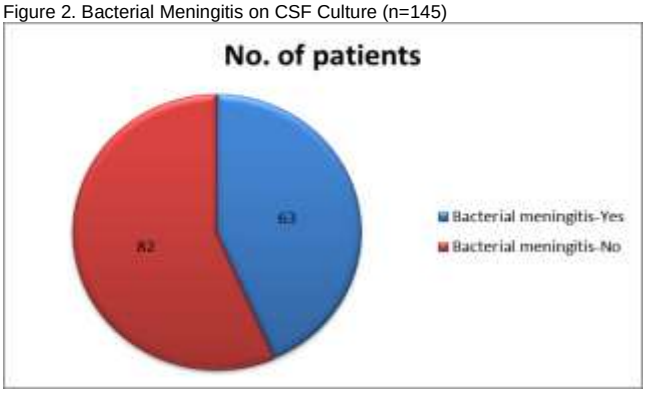
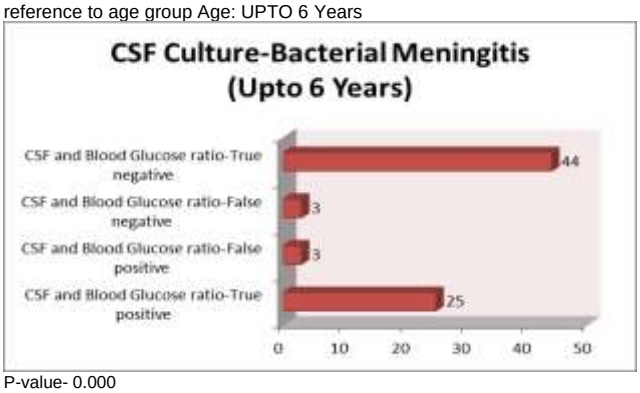


Table 1: Diagnostic Accuracy of CSF and Blood Glucose Ratio in Diagnosis of Bacterial Meningitis in Children Using CSF Culture as Gold Standard (n=145)

CSF and Blood Glucose ratio	CSF Culture		Total
	Bacterial Meningitis (Positive)	Bacterial Meningitis (Negative)	
Positive	True positive(a) 56	False positive (b) 8	a + b 64
Negative	False negative(c) 6	True negative (d) 75	c + d 81
Total	a + c 62	b + d 83	145

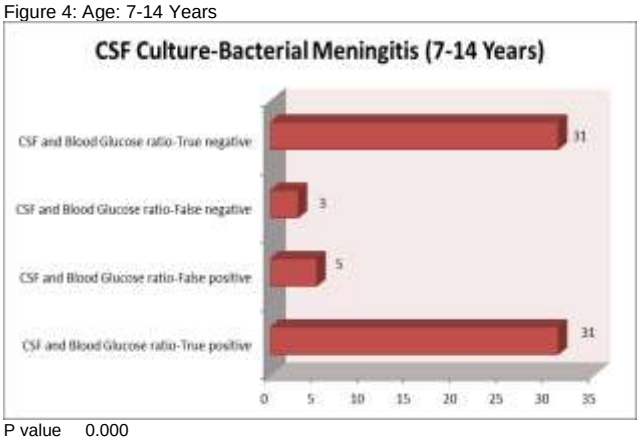
Sensitivity = a / (a + c) x 100 =90.32%
Specificity = d / (d + b) x 100 = 90.36%
Positive predictive value = a / (a + b) x 100 = 87.5%
Negative predictive value = d / (d + c) x 100 = 92.59%
Accuracy rate = a + d / (a + d + b + c) x 100 = 90.34%

Figure 3: Relationship of CSF/ Blood Glucose ratio & CSF Culture with reference to age group Age: UPTO 6 Years



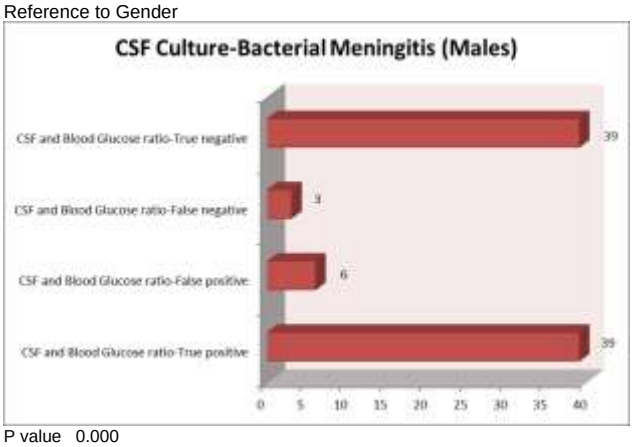
P-value- 0.000
Sensitivity = a / (a + c) x 100 =89.29%
Specificity = d / (d + b) x 100 = 93.62%
Positive predictive value = a / (a + b) x 100 =89.29%
Negative predictive value = d / (d + c) x 100 = 93.62%
Accuracy rate = a + d / (a + d + b + c) x 100 = 92%

Figure 4: Age: 7-14 Years



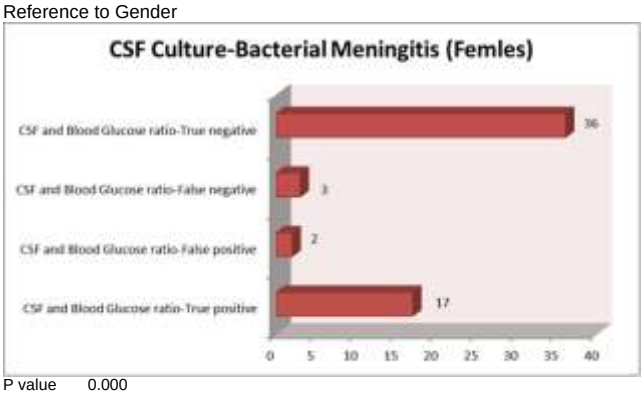
P value 0.000
Sensitivity = a / (a + c) x 100 =91.18%
Specificity = d / (d + b) x 100 = 86.11%
Positive predictive value = a / (a + b) x 100 = 86.11%
Negative predictive value = d / (d + c) x 100 = 91.18%
Accuracy rate = a + d / (a + d + b + c) x 100 = 88.57%

Figure 5: Relationship of CSF/Blood Glucose ratio and CSF Culture with Reference to Gender



P value 0.000
Sensitivity = a / (a + c) x 100 =92.86%
Specificity = d / (d + b) x 100 = 86.66%
Positive predictive value = a / (a + b) x 100 =86.67%
Negative predictive value = d / (d + c) x 100 = 92.86%
Accuracy rate = a + d / (a + d + b + c) x 100 = 89.66%

Fig. 6: Relationship of CSF/Blood Glucose ratio and CSF Culture with Reference to Gender



P value 0.000
Sensitivity = a / (a + c) x 100 =85%
Specificity = d / (d + b) x 100 = 94.74%
Positive predictive value = a / (a + b) x 100 = 89.47%
Negative predictive value = d / (d + c) x 100 = 92.31%
Accuracy rate = a + d / (a + d + b + c) x 100 = 91.38%

DISCUSSION

Bacterial meningitis, an inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that happens in response to bacteria and bacterial products, continues to be an important cause of mortality and morbidity in neonates and children[10,11].

However, mortality and morbidity vary by age and geographical location of the patient and the causative organism. Patients at risk for high mortality and morbidity include newborns, those living in low-income countries, and those infected with Gram-negative bacilli and Streptococcus pneumoniae[10,11]. Severity of illness on presentation (e.g., low score on Glasgow coma scale), infection with antimicrobial resistant organisms, and incomplete knowledge of the pathogenesis of meningitis are additional factors contributing to mortality and morbidity associated with bacterial meningitis[10-12].

The mortality of untreated bacterial meningitis approaches 100% and, even with optimum treatment, mortality and morbidity might happen. Neurological sequelae are relatively common in survivors of meningitis, particularly after pneumococcal meningitis[10-12].

Levels of glucose in the cerebrospinal fluid (CSF) are used to discriminate bacterial meningitis from viral meningitis. Children with bacterial meningitis typically have low levels of CSF glucose because of glycolysis by both white cells and the pathogen and impaired CSF glucose transport. The level of CSF glucose is typically interpreted in relation to that of serum glucose, since glucose passes across the blood–brain barrier. Given the burden of meningitis and the mortality associated with it, it is thus necessary to identify a marker which can help the treating physician to offer the best possible treatment to patients in a timely manner under resources constraints. There is no study previously done in Pakistan on the utility of CSF/blood glucose ratio for the diagnosis of bacterial meningitis.

It is thus of paramount importance to study the utility of readily available marker. In our study, out of 145 cases, 75(51.72%) were upto 6 years of age while 70(8.28%) were between 7-14 years of age, mean+sd was calculated as 6.58+3.15 years, 60% were male and 58(40%) were females, mean CSF/Blood glucose ratio was calculated as 0.31+0.08. The diagnostic accuracy of CSF and blood glucose ratio in diagnosis of bacterial meningitis in children using CSF culture as gold standard was recorded as 90.32%, 90.36%, 87.5%, 92.59% and 90.34% for sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate.

The findings of our study are in agreement with a previous study conducted previously in Japan[2] where the sensitivity and specificity of CSF/Blood glucose ratio were found to be 92.9% &

92.9% respectively. Jiao FY and others[13] are of the view that the diagnosis of bacterial meningitis can be difficult nowadays when antibiotics are freely used in infants and children with fever due to infection, so that a positive smear or culture may be difficult to achieve. In areas where sophisticated methods of diagnosis may be hard to come by, the simple procedure of simultaneously estimating the blood and cerebrospinal fluid (CSF) glucose levels may be helpful in distinguishing bacterial meningitis from viral meningitis. Classical signs of meningitis such as nuchal rigidity, bulging fontanelle, photophobia, and a positive Kernig's or Brudzinski's sign (more common in children older than 12 to 18 months) may also be present[14].

A recent systematic review found that the presence of meningeal signs increased the likelihood of the diagnosis of meningitis, and conversely their absence decreased the likelihood,[15] however, other studies have shown that no classical symptoms and signs of meningitis are able to distinguish accurately between children with or without meningitis[16] and so these signs should be interpreted with caution.

Seventy four proven cases of bacterial meningitis and aseptic meningitis were investigated prior to treatment. There were 36 cases of bacterial meningitis and 38 cases of aseptic meningitis. The CSF glucose/plasma glucose ratio was calculated for each patient. The cases were divided into two groups; Group A with CSF glucose/plasma glucose ratio of (0.38-2.0) and Group B with CSF glucose/plasma glucose ratio of (0.1-0.35).

In Group A, two out of 59 cases died while in Group B, nine out of 15 died ($p < 0.01$). 44 out of 59 in Group A recovered fully while only two out of 15 in Group B were cured ($p < 0.01$). It was also found that 54.2% in Group A were admitted in deep coma compared with 86.7% in Group B ($p < 0.05$) and 25.4% in Group A were admitted with seizures while 66.7% in Group B had convulsion ($p < 0.01$).

Hence, a low CSF glucose/plasma glucose ratio was associated with a poor outcome. The mechanisms responsible for these findings are discussed especially with reference to the blood-brain barrier (BBB).In absence of previous studies conducted locally, our data is primary and needs its validation through some-other local studies, so that this readily available marker may be used for the diagnosis bacterial meningitis in children.

CONCLUSION

Through the findings of this study, we concluded that the diagnostic accuracy of CSF and blood glucose ratio in diagnosis of bacterial meningitis in children using CSF culture as gold standard is higher but needs its validation through some other local trials in absence of previous data.

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