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Diagnostic accuracy of point-of-care cerebrospinal fluid leucocyte esterase dipstick test for bacterial meningitis in the Emergency Department

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ABSTRACT:

— ***Objective:*** The primary objective was to evaluate the sensitivity and specificity of cerebrospinal fluid (CSF) leucocyte esterase dipstick test for rapid diagnosis of bacterial meningitis. The secondary objective was to determine the diagnostic accuracy of the combination of CSF leukocyte esterase, elevated protein, and low glucose by a semi-quantitative dipstick test for the diagnosis of bacterial meningitis.

— ***Patients and methods:*** This prospective diagnostic accuracy study was conducted from January 2021 to December 2021 at the Medical Emergency Department of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. Patients aged 13 years or older with suspected meningitis based on presenting symptoms were eligible for inclusion. CSF leucocyte esterase strip test was the primary index test, and the combination of CSF leukocyte esterase, protein, and glucose using the Combur-10 strip was the secondary index test. We used a composite reference standard comprising neuro-imaging, CSF cell counts/glucose/protein obtained from the laboratory, and CSF gram stain/culture.

— ***Results:*** 87 patients were included, of which 49 (56.32%) had a final diagnosis of bacterial meningitis based on the results of the composite reference standard. CSF leucocyte esterase had sensitivity of 85.71% (95% CI:72.76-94.06), specificity 42.11% (95% CI:26.31-59.18), positive likelihood ratio (LR+) 1.48 (95% CI:1.10-1.99) and negative likelihood ratio (LR-) 0.34 (95% CI:0.16-0.74) for the diagnosis of bacterial meningitis. The combination of CSF leucocyte esterase, elevated CSF protein and low CSF glucose using dipstick test had sensitivity of 87.76% (95% CI:75.23-95.37), specificity 60.53% (95% CI: 43.39-75.96), LR+ 2.22 (95% CI:1.48-3.34) and LR- 0.20 (95% CI:0.09-0.45).

— ***Conclusions:*** Point-of-care CSF dipstick test combining leucocyte esterase, protein, and glucose has good sensitivity for triaging patients with suspected bacterial meningitis in the Emergency Department.

— ***Keywords:*** Cerebrospinal fluid, Bacterial meningitis, Leucocyte esterase, Point-of-care test, Combur-10, Dipstick test.

INTRODUCTION

Bacterial meningitis is a life-threatening condition that requires prompt recognition and treatment. More than 1.2 million cases of bacterial meningitis occur throughout the world each year. Without treatment, the case-fatality rate can be more than 70%, and one in five survivors of bacterial meningitis may develop permanent *sequelae*, including hearing loss and neurologic disability[1]. Clinical features include fever, headache, neck stiffness, nausea, vomiting, altered sensorium, and seizures. A meta-analysis[2] of diagnostic accuracy studies of classical signs and symptoms of bacterial meningitis revealed sensitivities of 51% for neck stiffness, 53% for Kernig sign, and 66% for

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Brudzinski sign for the diagnosis of bacterial meningitis, indicating that clinical characteristics alone cannot be used to rule out bacterial meningitis[2].

The diagnosis of bacterial meningitis rests on cerebrospinal fluid (CSF) examination performed after a lumbar puncture. In untreated bacterial meningitis, the WBC count is elevated, usually in the range of 1000-5000 cells/mm, with neutrophil predominance in CSF; low CSF glucose concentration in 50%-60% of patients; with CSF protein concentration being elevated in almost all patients with bacterial meningitis. Cultures may take up to 48 hours for the identification of organism[3]. Laboratory results for CSF examination, cultures, and neuro-imaging are often unavailable or delayed in resource-limited settings. Therefore, validated rapid diagnostic tests, which can deliver results timely and economically, are required for the diagnosis of meningitis, particularly for triaging patients with suspected meningitis to rule out the disease. This would reduce delay in starting appropriate treatment and referral for obtaining confirmatory tests.

Combur-10 (Roche Diagnostics GmbH, Mannheim, Germany) is a ready-for-use patch test strip that can be used for semi-quantitative determination of leukocyte esterase, which is present in granulocytic leukocytes and catalyzes the hydrolysis of an indoxyl-carbonic acid ester to indoxyl[4]. The indoxyl formed reacts with a diazonium salt to produce a purple color. The test for protein is based on the principle of the protein error of a pH indicator tetrachlorophenol-tetrabromosulfophthalein. Glucose determination is based on the glucose oxidase/peroxidase reaction method. The test strips are briefly dipped for about 1 s into the CSF sample, ensuring that all test areas are moistened. The test is to be read visually after 60 s by comparing the reaction colors of the test areas with color blocks on the label.

The primary objective was to determine the sensitivity and specificity of cerebrospinal fluid leucocyte esterase semi-quantitative dipstick test (Combur-10) for rapid diagnosis of bacterial meningitis compared with a composite reference standard comprising laboratory examination of cerebrospinal fluid, microbiological tests, and neuro-imaging. The secondary objective was to determine the sensitivity and specificity of a combination of cerebrospinal fluid leukocyte esterase, elevated CSF protein (>100 mg/dL), and low CSF glucose (<50 mg/dL) by dipstick test for the diagnosis of bacterial meningitis.

PATIENTS AND METHODS

This was a prospective diagnostic accuracy study conducted from January 2021 to December 2021 at the Medical Emergency Department of the Postgraduate Institute of Medical Education and Research, Chandigarh – a tertiary hospital and teaching institute in north India. The protocol was approved by the Ethics Committee of the Postgraduate Institute of Medical Education and Research, Chandigarh (Reference Number – NK/6835/MD/784). Patients presenting to the Medical Emergency Department were eligible for inclusion if they were 13 years or older with suspected meningitis based on the presence of at least one of the following symptoms – fever, headache, neck stiffness, altered sensorium, or seizures. Patients were excluded if they had contraindications to lumbar puncture such as signs of raised intracranial pressure, obstructive hydrocephalus, cerebral edema, space-occupying lesions on neuro-imaging, or infection at the local site, coagulopathy or ongoing anticoagulation therapy. Patients were also excluded if they had a history of spinal surgery, spinal deformity, suspected spinal or epidural abscess, were pregnant women or had contraindications to contrast administration (e.g., acute kidney injury). Patients were enrolled by convenience sampling when one of the investigators (AS) was present in the Emergency Department and after obtaining written informed consent. The treatment of these patients was not altered by enrollment in the study and was decided by the treating physician as per standard treatment protocol followed in the hospital.

Index Test for the Primary Objective

All patients underwent lumbar puncture, following which CSF examination using Combur-10 rapid dipstick for leucocyte esterase was performed at the bedside as the primary index test. The index test results were interpreted by one of the investigators (AS), who was blinded to the results of the reference standard. Combur-10 test strips were briefly dipped for about 1 s into the CSF sample. The color change for leukocyte esterase detection was read visually after 60 s by comparing the reaction color of the test area with the color blocks on the label. It was considered positive if the color change in the dipstick corresponded to ≥10 leucocytes/μL (1+/2+/3+) and considered negative if there was no color change (<10 leucocytes/μL). (Table 1)

Index Test for the Secondary Objective

Color change on Combur-10 dipstick was noted for the combination of CSF leukocyte esterase, protein, and glucose. For leukocyte esterase, it was considered positive if the color change in the dipstick corresponded to 1+/2+/3+ (≥10 leucocytes/μL) and negative if there was no color change (<10 leucocytes/μL). CSF protein was interpreted as positive if the color change in dipstick corresponded to protein >100 mg/dL (2+/3+) and negative if the color change on dipstick corresponded to protein <100 mg/dL (No color change or 1+). CSF glucose was interpreted as positive if there was no color change on the dipstick (i.e., corresponding to glucose <50 mg/dL) and negative if the color change corresponded to glucose ≥50 mg/dL (1+/2+/3+/4+). The index test for the secondary objective was finally interpreted as positive if two or more of the three individual parameters (CSF leukocyte esterase, protein, and glucose) were positive, and as negative if less than 2 of 3 individual parameters were positive.

Table 1. Pre-specified criteria for interpretation of Primary and Secondary Index Tests.

	Index Tests	
Interpretation	**Primary Index Test**	**Secondary Index Test**
Positive	Color change on Combur-10 dipstick test for CSF leucocyte esterase corresponding to >10 leucocytes/μL (1+/2+/3+)	Any 2 or more of the following 3 criteria met by Combur-10 dipstick test for CSF: 1. Positive CSF leucocyte esterase (1+/2+/3+) 2. CSF protein >100 mg/dL (2+/3+) 3. CSF glucose <50 mg/dL (No color change)
Negative	No color change on Combur-10 dipstick test for CSF leucocyte esterase (corresponding to <10 leucocytes/μL)	Less than 2 of the 3 criteria mentioned above present

We used a composite reference standard comprising: (1) Neuro-imaging [Contrast Enhanced Magnetic Resonance Imaging (CEMRI)]; (2) CSF cell counts (total and differential) and biochemistry (glucose/ protein) obtained in the laboratory; and (3) microbiological investigations including CSF gram stain and culture. The assessors of the components of the reference standard were blinded to the results of the index test. The patient was classified as meningitis if any one of three criteria (neuro-imaging, CSF biochemistry and cell counts, microbiological investigations) were positive and as not meningitis, if all the three were negative. Contrast Enhanced Magnetic Resonance Imaging (CEMRI) of the brain was reviewed by a neuro-radiologist blinded to the index test results and classified as likely to be meningitis or not meningitis based on meningeal enhancement, parenchymal involvement, extra-axial collections, and meningo-vasculitis. For CSF biochemistry and cell counts obtained from the laboratory, it was interpreted as positive if any 3 out of the following 4 criteria were positive: (i) CSF total cell count >5 cells/μL, (ii) differential cell count >70% neutrophils, (iii) CSF protein >100 mg/dl (iv) CSF Glucose <40 mg/dl. CSF gram stain and culture were considered positive if they showed the presence or growth of bacteria.

Missing Data

If one out of three components of the composite reference standard could not be completed, the patients were included in the analysis based on the other two available components of the composite reference standard, with the missing component being categorized as negative, and the final diagnosis was based on the other two components of the composite reference standard. For instance, if CEMRI could not be obtained, it was considered negative, and the patient was still included in the study, provided the other two investigations, i.e., microbiological (CSF gram stain/ culture), and CSF cell counts/biochemical investigations, were available. If two or more components of the composite reference standard were missing, the patients were excluded from the analysis.

Statistical Analysis

Index test results for the primary objective were compared to the composite reference standard results. Meningitis detected by both the index test and the reference standard were classified as true positive, whereas those detected by neither were classified as true negative. Meningitis positive by the index test but negative by the reference standard were classified as false positive. In contrast, meningitis negative by the index test but positive by the reference standard were classified as false negative. Index test results for the secondary objective were analyzed in the same manner. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were calculated with 95% confidence intervals for the index test results compared to the reference standard using MedCalc (Software Version 20.027).

RESULTS

From January 2021 to December 2021, 100 patients presenting to the Emergency Department of the Postgraduate Institute of Medical Education and Research, Chandigarh, with suspected meningitis were assessed for eligibility and invited to participate. Figure 1 shows the flow of patients through the study for the primary index test of CSF leucocyte esterase by rapid dipstick. Seven patients were excluded due to contra-indications for lumbar puncture, and six denied consent for participation in the study. 87 patients were finally included, 50 participants (57.47%) were male, and 37 (42.5%) were female. The median age of participants was 33 years (range 13-84). The predominant presenting symptoms were altered sensorium (97.7%), fever (96.6%), and headache (82.8%), whereas seizures (33.3%) and neck rigidity (31%) were less frequent.

All 87 patients completed the primary and secondary index tests. No significant adverse events occurred as a result of lumbar puncture. All patients also had CSF cell counts and biochemistry results performed in the routine laboratory as part of the composite reference standard, of which 34 (39%) were interpreted as positive for bacterial meningitis and 53 (61%) as negative for bacterial meningitis based on the pre-specified crite-

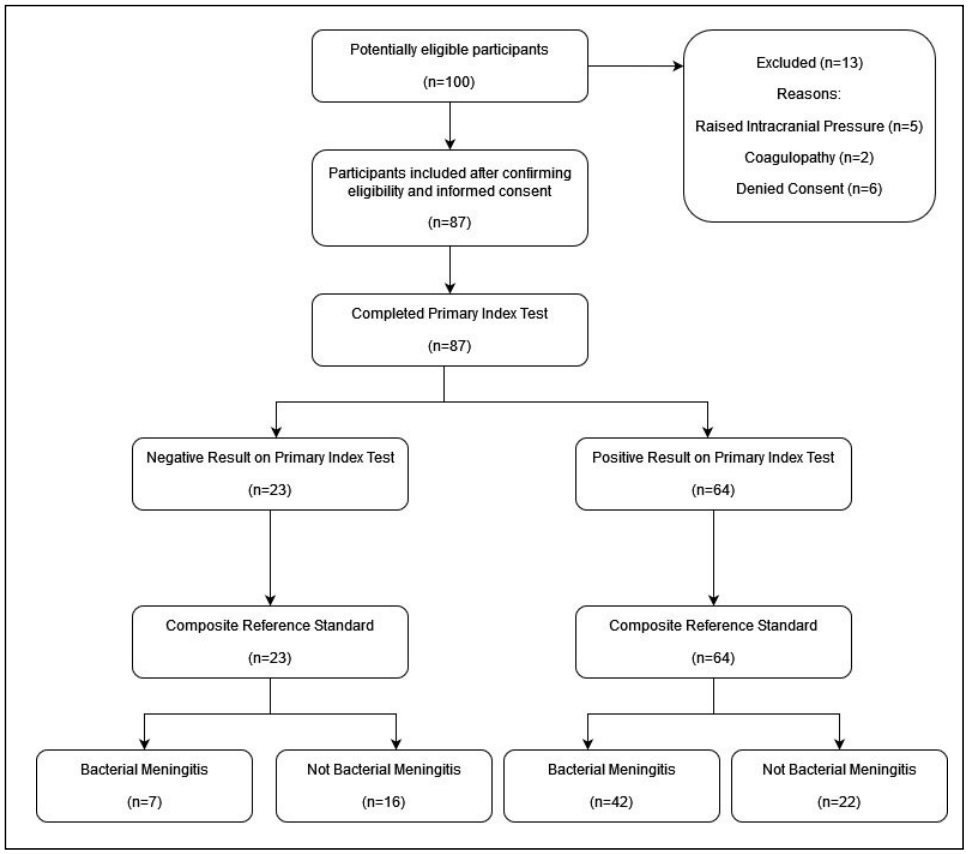

Figure 1. Flow diagram of participants through the study.

ria. 78 patients underwent neuro-imaging, of which 36 (46.15%) were interpreted as positive for bacterial meningitis by a neuro-radiologist. The mean time delay between index test and neuro-imaging was 3 days. Out of the 87 patients, neuro-imaging could not be performed in 9 patients, but for all these 9 patients, the other two components of the reference standard were completed, i.e., CSF cell counts/biochemistry and microbiological tests (Gram stain and culture) results were available. 80 patients had results of CSF microbiological tests (Gram stain and culture) available, of which only 7 showed growth/ presence of bacteria (*Streptococcus pneumoniae* – 2, *Pseudomonas aeruginosa* – 2, *Staphylococcus haemolyticus* – 1, *Klebsiella oxytoca* – 1, *Leclercia spp.* – 1), possibly due to initiation of antibiotic therapy before the performance of lumbar puncture; while 2 showed the presence of *Cryptococcus spp.* None of the patients had two or more components of the reference standard missing; all 87 patients completed the composite reference standard. 49 (56.32%) patients had a final diagnosis of bacterial meningitis, and 38 (43.66%) did not have meningitis based on the results of the composite reference standard.

Table 2 shows the results of CSF leucocyte esterase by Combur-10 dipstick test (primary index test) in relation to the final diagnosis of bacterial meningitis by the composite reference standard. CSF leucocyte esterase by dipstick had a sensitivity of 85.71% (95% CI: 72.76-94.06) and specificity of 42.11% (95% CI: 26.31-59.18) for the diagnosis of bacterial meningitis, with a positive likelihood ratio of 1.48 (95% CI: 1.10-1.99) and a negative likelihood ratio of 0.34 (95% CI: 0.16-0.74). Table 3 shows the results for the combination of CSF leucocyte esterase, elevated CSF protein (>100 mg/dL), and low CSF glucose (<50 mg/dL) by Combur-10 dipstick test (secondary index test) in relation to the final diagnosis of bacterial meningitis. The combination of CSF leucocyte esterase, elevated CSF protein and low CSF glucose using the rapid dipstick test had a sensitivity of 87.76% (95% CI: 75.23-95.37) and specificity of 60.53% (95% CI: 43.39-75.96), with a positive likelihood ratio of 2.22 (95% CI: 1.48-3.34) and a negative likelihood ratio of 0.20 (95% CI: 0.09-0.45).

Table 2. Contingency table for CSF leucocyte esterase by Combur-10 dipstick test (primary index test) in relation to the final diagnosis of bacterial meningitis.

Primary Index Test	Composite Reference Standard		Total
	Meningitis	Not Meningitis	
Positive	42	22	64
Negative	7	16	23
Total	49	38	87

Table 3. Contingency table for combination of CSF leucocyte esterase, elevated CSF protein (>100 mg/dL) and low CSF glucose (<50 mg/dL) by Combur-10 dipstick test (secondary index test) in relation to the final diagnosis of bacterial meningitis.

Secondary Index Test	Composite Reference Standard		Total
	Meningitis	Not Meningitis	
Positive	43	15	58
Negative	6	23	29
Total	49	38	87

DISCUSSION

Acute bacterial meningitis can lead to a severe life-threatening illness in all age groups if not promptly diagnosed and treated with appropriate antibiotics that cross the blood-brain barrier[5]. The classical clinical presentation of meningitis is observed in less than half of the patients, and the usual signs and symptoms do not provide optimal sensitivity and specificity for the diagnosis of bacterial meningitis, which can lead to a delay in starting appropriate antimicrobial therapy[6]. When meningitis is suspected based on the clinical presentation, the key to diagnosis is the examination of cerebrospinal fluid. CSF culture is considered the gold standard for diagnosis of bacterial meningitis; however, it is positive only in 70-85% of patients with bacterial meningitis who have not received antimicrobials before lumbar puncture, and the yield decreases significantly when antibiotics are administered before CSF collection. Culture results are often unavailable for the first 48 hours. Gram stain has good specificity, but sensitivity is low (10-93% depending on the organism and administration of antibiotics before lumbar puncture)[7]. In low-resource healthcare settings, CSF cytology, biochemistry, and reliable microbiologic laboratory tests and neuro-imaging are often unavailable. Physicians in these settings often empirically treat patients with fever, headache, and/or altered sensorium for bacterial meningitis without the support of laboratory data and rely solely on clinical examination and subjective assessments, which have poor diagnostic accuracy[8,9]. Latex agglutination tests for bacterial antigens are available for various common organisms. However, their increase in sensitivity over Gram stain and culture is modest, and these require cold chain and lab infrastructure; hence, they are not used widely in resource-limited settings[10]. Cost remains a significant barrier to adopting nucleic acid amplification tests and new molecular diagnostics in routine use. Hence, there is a need for rapid, accurate, and affordable point-of-care (POC) tests to aid in the triage and diagnosis of patients with suspected bacterial meningitis. Combur-10 strips, designed for urine analysis, can be used to test CSF for several components, including leucocyte esterase, protein, and glucose, that are potentially useful for the diagnosis of bacterial meningitis[11].

Joshi et al[12] conducted a study to determine if the Combur-10 urinary reagent strip was useful for making a semi-quantitative assessment of protein, glucose, and the presence of leukocyte esterase in CSF; and suggested that there is good agreement between the urinary reagent strip test performed on CSF and laboratory methods of determining CSF protein, glucose, and neutrophils. They found that leukocyte esterase positivity by test strip had a sensitivity of 85.2% and a specificity of 89.6% for detecting CSF granulocytes of more than 10/mm^3. In the present study, we evaluated the diagnostic accuracy of CSF leucocyte esterase by strip test, individually and in combination with elevated CSF protein and low CSF glucose, in patients with suspected meningitis, in relation to the final diagnosis established based on a combination of neuro-imaging, laboratory parameters, and microbiological tests. When used alone, CSF leucocyte esterase had high sensitivity but poor specificity for the diagnosis of bacterial meningitis. Shokouhi et al[13] studied the diagnostic accuracy of CSF leukocyte esterase test using Medi-Test Combi (Medi-Test, France) and found a sensitivity of 84.6% and a specificity of 94.5%. While the sensitivity correlates well with the sensitivity of Combur-10 test strips in our study, the higher specificity may be explained by the exclusion of patients with non-infectious etiologies (brain tumors and stroke) and those with a traumatic lumbar puncture with CSF contaminated by blood. However, Krishnamurthy et al[14] found that even when CSF is contaminated with blood due to a traumatic lumbar puncture, the specificity of the leucocyte esterase strip remains high for the diagnosis of bacterial meningitis.

Chikkannaiah et al[15] studied the diagnostic accuracy of various cut-offs on Combur-10 strips for proteins, glucose, and leukocyte esterase compared to routine lab CSF cytology and biochemistry. They found that the strip test demonstrated a high sensitivity (96.6%) and specificity (94.5%) for leukocytes ≥10 cells/mm^3; sensitivity of 96%, and specificity of 87.1% for proteins at a cut-off ≥100 mg/dl, while the strip was less specific (45.8%) at a cut-off of ≥30 mg/dl. With respect to glucose, the strip was highly specific (100%) but had poor sensitivity (28.5%). To the best of our knowledge, our study is the first to explore the combination criteria of CSF leucocyte esterase, elevated protein, and low glucose by rapid dipstick test for the diagnosis of meningitis. The results of this study support the use of the Combur-10 strip combining CSF leucocyte esterase, protein, and glucose for triaging patients with suspected pyogenic meningitis with high sensitivity. The combined dipstick test may be used as a point-of-care aid to decision-making in primary care settings in combination with clinical information before referral for confirmatory cytological, biochemical, and microbiological analysis of CSF.

This study had some limitations. Neuro-imaging could not be performed in 9 patients, and microbiological test results were unavailable for 7 patients. The average time delay between the index test and neuro-imaging was 3 days, during which the disease condition might have evolved either due to the natural course or clinical interventions (for instance, steroids and antibiotics may reduce the severity of meningeal inflammation), modifying the radiological findings.

CONCLUSIONS

Cerebrospinal fluid leucocyte esterase by strip test had high sensitivity but poor specificity for the diagnosis of bacterial meningitis. The results of this study support the use of cerebrospinal fluid rapid dipstick test combining leucocyte esterase, protein, and glucose as a point-of-care aid to decision making for triaging patients with suspected pyogenic meningitis with high sensitivity, before referral for confirmatory cytological, biochemical and microbiological analysis of CSF.

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Authors' Contribution:
SCS conceptualized the study. SCS and AS drafted the study protocol. AS and CKA contributed to data collection. SCS and AS contributed to the statistical analysis and drafted the manuscript. CKA and MSB contributed to its revision. All authors agree to take responsibility for the paper as a whole.

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