Accuracy of clinical scoring systems for the diagnosis of tuberculosis meningitis in a case mix of meningitides a retrospective cohort study

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ABSTRACT
Background: Tuberculosis meningitis (TBM) is elusive to diagnosis. Two widely used clinical scores are the Thwaites diagnostic score (TDS) and The Lancet Consensus score (LCS). We aim to evaluate the accuracy of these scores in a retrospective cohort of meningitis patients.

Methods: A retrospective review of all meningitis cases admitted to a tertiary center in a 7-year period. The primary outcome was the sensitivity and the specificity of a preset cutoff on the TDS and the LCS and finding the best cutoff value with optimum sensitivity and specificity using Receiver operating characteristic (ROC) curve analysis.

Results: We included 156 cases of meningitis; 80 TBM and 76 controls (other meningitides). Seventy-eight (97.5%) of TB cases were suggestive of TBM compared to 45 (59.2%) of controls (p< .001) using the TDS. Sensitivity was 97.5% and specificity was 40.8%. The PPV was 63.4% and the NPV was 93.9%. The area under the ROC curve (AUC) was 0.80 (0.73–0.87 at 95% CI).

When calculated for bacterial meningitis vs TBM a cutoff of 4 showed excellent sensitivity (93%) and specificity (96%). AUC = 0.96 (0.89–1.00 at 95% CI). While for the LCS, 67 (83.3%) were suggestive of TBM vs. 11 controls (14.5%) (p< .001). Sensitivity was 83.8%, specificity was 85.5%, and PPV and NPV were 85.9% and 83.3% respectfully. The AUC was 0.93 (95% CI 0.89–0.97).

Conclusion: The TDS performs best in differentiating bacterial meningitis from TBM and has a good negative predictive value. The LCS has good sensitivity and specificity in differentiating TBM from other forms of meningitides.

1. Introduction

Despite advancements in micro-therapeutic agents, tuberculosis (TB) remains the leading infection leading to death worldwide surpassing HIV [1]. While it mainly affects the lungs, there is increased interest in the extrapulmonary form which is showing relative resurgence and comprises around 15% of TB cases [2,3]. Tuberculous meningitis (TBM) is the severest form of extrapulmonary TB and is the most common form of central nervous (CNS) TB infection. Morbidity and mortality depend on early diagnosis and treatment [4]. Treatment once diagnosed, is relatively straightforward and rely on antituberculous drugs in addition to steroids. There is also emerging advancement in synthesis of newer drugs [5,6] with a possible role of newer synthetic anti-inflammatory drugs [7] [8]. However, the diagnosis often remains elusive.

The clinical presentation includes headache, fever and meningismus; symptoms that are common to all meningitides but nonspecific and diagnostically unreliable [9,10]. While CSF TB culture remains the gold standard for the diagnosis, its sensitivity remains low [11]; in a previous report, cultures were only positive in 45% of probable TB meningitis cases [10] while other reports have reported sensitivities that vary from 17 to 81% [12]. Furthermore, it takes weeks to get the results which is diagnostically inconvenient. Smear microscopy offers pathognomonic diagnosis, but it has very low yield in terms of sensitivity [12]. Additionally, TB Polymerase chain reaction (PCR) and nucleic acid amplification testing of the CSF, while increasingly utilized, have variable sensitivities that are not sufficiently high enough to exclude the diagnosis [10]. Newer tests in this category might have a...
future impact but are yet to be validated in large adult cohorts. One such test is the “real-time quantitative PCR and ELISA to detect a panel of M. tuberculosis antigens (GlcB, HspX, MPT51, Ag85B and PstS1)” [13] with a reported sensitivity and specificity approaching 98% in possible and probable TBM cases in children.

Similarly, the successor of the WHO recommended Xpert MTB/RIF test (currently in clinical use in middle to high income countries) [13], the “Xpert MTB/RIF Ultra” appears very promising [14]. In addition, some CSF protein bio-signatures (such as VEGF, IL-13, LL-37, IFN-γ and MPO) using a multiplex platform are reported to be of diagnostic potential [15].

The laboratory diagnosis of TBM remains an area of active research looking into the development of more accurate tests with many new methods emerging, however, these remain restricted to the experimental research domain and are unlikely to be available for routine clinical practice in the immediate future, particularly in less privileged regions of the world [13].

Starting empirical treatment on suspicion is an option [16] but the prolonged nature of the treatment with drugs that are sometimes associated with severe adverse reactions epitomizes the need for an accurate TBM diagnosis.

Different clinical scoring systems [17–19] were developed to improve the accuracy of the diagnosis. In 2002, Thwaites et al. [18] published a simple scoring system based on clinical and CSF features that differentiates bacterial meningitis from TBM (Table 1). This score has been validated in several cohorts [20–22]. The Thwaites diagnostic score’s (TDS) sensitivity in differentiating TBM from bacterial meningitis was reported to be 98.2% with a specificity of 43.6% [23]. Similar to this, different clinical scores have attempted to differentiate subgroups of patient with meningitis such as viral [23] or viral and cryptococcal [24] from TBM with varying accuracy and limited success particularly in HIV infected individuals. TDS remains one of the more popular scores, however, its utility in clinical practice which comprises a mixture of causes and in patients with lymphocytic predominance meningitis such as viral and those with low CSF glucose [22] is unclear.

In 2009, an expert consensus meeting took place to unify the diagnostic criteria of TBM for use in clinical research [17] (Table 1). This score was named the Lancet Consensus score (LCS) [20]. This score was subsequently utilized in several studies [20,25]. We aim to study the accuracy of these two diagnostic scores in diagnosing TBM in a cohort of patients with different meningitides.

2. Methods

This is a retrospective exploratory cohort study to evaluate if predetermined cutoff points of the TDS and the LCS are valid in our cohort of meningitides. A retrospective review was conducted on the medical records of all adult patients diagnosed with meningitis in a 7-year period admitted at the Hamad General Hospital, Doha, Qatar. Data extraction was by (YI and HA) and analysis occurred in 2014. Fig. 1 shows the selection process.

Hamad General Hospital is the only tertiary referral governmental hospital in Qatar that admits patients with meningitis. It is accredited by the Joint Commission international, which recognizes high quality healthcare organizations [26]. It caters for a population of around 2.8 million, with a large expatriate community originating mostly from other parts of the Middle East, South Asia, Far East Asia and Africa [10].

2.1. TBM cases classification criteria

Patient were classified as having TBM if they fulfill these criteria (These criteria were previously published [10], and briefly include:

1. Clinical criteria: cases suffering from fever, headache, meningism, altered sensorium or focal deficits on physical examination.
2. CSF criteria: including any of: lymphocytic pleocytosis (> 20 cells/μL, > 50% lymphocytes), decreased glucose (less than 50% of blood glucose) and increased protein levels in the CSF (> 0.5 g/L).

In addition, subjects should have any of the following:

(i) detection of acid-fast bacilli in CSF, or other sterile body fluids, or tissue under direct microscopy with Ziehl-Neelsen stain, or growth of such bacteria in culture,
(ii) detection of M. tuberculosis DNA in CSF or in other sterile body fluids or in tissue with PCR,
(iii) a history of close contact with an active pulmonary TB case
(iv) prior TB infection or family history of TB
(v) Characteristic findings suggestive of TB on brain imaging (basal meningitis, tuberculoma, etc.),
(vi) presence of pulmonary TB findings such as active infiltration, miliary pattern, or cavitation in pulmonary imaging, and
(vii) a favorable response to antituberculous therapy,
(viii) no alternative diagnosis is available.

2.2. Control cohort classification criteria

1) Patients were diagnosed as having bacterial, viral or fungal if pathogenic bacteria, viral or fungal pathogens were isolated from the CSF.
2) Partially treated meningitis was diagnosed if:

i) Clinical meningitis is diagnosed.
ii) And all the following:

a) Excess neutrophils or lymphocytes in the CSF, (> 5 cells/μL).
b) A low concentration of glucose in the CSF (< 50% of that in blood).
c) Antibiotic administration prior to CSF drainage.
d) Full recovery without anti-tuberculosis drugs.

3) Aseptic meningitis is diagnosed when CSF shows pleocytosis (> 5cell/μL), no pathogen is detected and no prior antibiotic history and a normal CSF glucose.

2.3. Exclusion criteria

All cases of chemical and iatrogenic meningitis due to intraventricular hemorrhage or post neurosurgical procedures were excluded.

All laboratory investigations were undertaken in HGH standardized labs which are now accredited by the College of American Pathologists (CAP) [20]. All imaging data were reported by qualified radiologist and neuroradiologist as appropriate.

The TBM and non TBM (Control) cohort’s clinical characteristics including age, sex, duration of symptoms, presenting features, serum WBC (count/mm3), CSF WBC (count/mm3), CSF neutrophil
Diagnostic criteria for classification of definite, probable, possible, and not tuberculous meningitis.

| Clinical criteria | Diagnostic score |
|-------------------|------------------|
| Symptom duration of more than 5 days | (Maximum category score = 6) |
| Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks | 4 |
| History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children < 10 years of age) | 2 |
| Focal neurological deficit (excluding cranial nerve palsies) Cranial nerve palsy | 2 |
| Altered consciousness | 1 |
| Symptom duration of more than 5 days | 1 |

| CSF criteria | Diagnostic score |
|--------------|------------------|
| Clear appearance Cells: 10–500 per µl | (Maximum category score = 4) |
| Lymphocytic predominance (> 50%) Protein concentration greater than 1 g/L. | 1 |
| CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2.2 mmol/L. | 1 |
| Clear appearance Cells: 10–500 per µl | 1 |
| Lymphocytic predominance (> 50%) Protein concentration greater than 1 g/L. | 1 |

| Cerebrospinal imaging criteria | Diagnostic score |
|-------------------------------|------------------|
| Hydrocephalus | (Maximum category score = 6) |
| Basal meningeal enhancement Tuberculoma | 1 |
| Infarct | 2 |
| Pre-contrast basal hyperdensity | 1 |
| Hydrocephalus | 2 |

| Evidence of tuberculosis elsewhere | Diagnostic score |
|-----------------------------------|------------------|
| Chest radiograph suggestive of active tuberculosis: signs of tuberculosis = 2; Miliary tuberculosis = 4 | (Maximum category score = 4) |
| CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS | 2 |
| AFB identified or Mycobacterium tuberculosis cultured from another source—in, sputum, lymph node, gastric washing, urine, blood culture | 4 |
| Positive commercial M tuberculosis NAAT from extra-neural specimen | 4 |

Exclusion of alternative diagnoses

An alternative diagnosis must be confirmed microbiologically (by stain, culture, or NAAT when appropriate), serologically (e.g., syphilis), or histopathologically (e.g., lymphoma). The list of alternative diagnoses that should be considered, dependent upon age, immune status, and geographical region, include: pyogenic bacterial meningitis, cryptococcal meningitis, syphilitic meningitis, viral meningo-encephalitis, cerebral malaria, parasitic or eosinophilic meningitis (Angiostrongylus cantonesis, Gnathostoma spinigerum, toxocariasis, cysticercosis), cerebral toxoplasmosis and bacterial brain abscess (space-occupying lesion on cerebral imaging)and malignancy (e.g., lymphoma). The individual points for each criterion (one, two, or four points) were determined by consensus and by considering their quantified diagnostic value as defined in studies.

Quantitative data between two independent groups were analyzed using the unpaired t-test and Mann Whitney U test as appropriate. Associations between two or more categorical variables were assessed using Chi-square (χ²) test and Fisher Exact test as appropriate. A two-sided P value < .05 was considered to be statistically significant. All statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc., Chicago, Ill., USA). Sample size calculation was not done as this was a retrospective, exploratory all-inclusive study.

The primary outcome was to calculate and evaluate the validity and accuracy of the TDS and the LCS in our cohort of meningitis patients. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of a preset cutoff on the Thwaites diagnostic score (TDS) and the Lancet consensus score (LCS) for diagnosing TBM as well as determining the suitable cutoff value with optimum sensitivity, specificity, PPV and NPV using the ROC curve analysis. The TDS and the LCS were calculated for all cases. The TDS were dichotomized to either suggestive of TBM (score of 4 or less) or not suggestive of TBM (> 4) as was reported by Thwaites et al. [18], whereas, the LCS was dichotomized to either suggestive of possible or probable TBM (score of 6 or more) or not suggestive of possible or probable TBM (< 6) as was reported by Marais et al. [17]. Additional comparisons utilizing these cutoffs were made between the TBM cohort and controls as well as other subsets of each cohort such as definite (culture positive TBM) versus bacterial and non-bacterial and so forth.

2.5. Ethical consideration

This study was approved by the Hamad Medical Corporation Medical Research Center, research protocol #13006/13.

3. Results

The cohort consisted of 156 cases of meningitis: 80 cases of TBM (35 culture proven and 45 cases of probable/possible TBM) and 76 controls (18 aseptic, 23 viral, 28 bacterial, three partially treated bacterial and four fungal).

3.1. Demographics and clinical features

Males were 127, comprising (81.4%) of the cohort. The mean age of the cohort was (33.4 + 12) years, range (18–80). The cohort ethnicities' and clinical characteristics of TBM and non-TBM (controls) are summarized in Table 3. The entire cohort was HIV negative. In these 2 cohorts there was no difference in terms of fever, or meningismus (the most common meningitis presenting features), however, TBM statistically showed more neurological deficits, psychiatric manifestation and systematic features such as weight loss and fever (Table 3).
3.2. CSF findings

TBM had significantly lower CRP, peripheral WBCs, CSF WBCs and CSF neutrophilia values ($p < .05$), while there was no significant difference in CSF protein between the two cohorts.

3.3. TDS and LCS scores

The mean TDS was $1 + 5.1$ (range $-5 - 13$ IQR $= 7$). The distribution of TDS among the cohort is illustrated in supplement 1. Using the TDS and a cutoff of 4; 78 (97.5%) of the TB cases were suggestive of TBM, compared to 45 (59.2%) of the controls ($p < .001$). Sensitivity was 97.5% and specificity was 40.8%. The area under the ROC curve (AUC) (supplement 2) was 0.80 (0.73–0.87 at 95% CI). The PPV was 63.4% and the NPV was 93.9%. When calculated for culture positive TBM vs bacterial cases; the sensitivity was 100% and the specificity was 80.7% with a PPV of 85.4% and an NPV value of 100%. Other subgroup analysis can be found in Table 4. A lower cutoff of 2 was associated with a sensitivity of (94%) and a specificity of (50%) when calculated for the entire cohort. Whereas a cutoff of 4 was the best when calculated for bacterial meningitis vs TBM; with a sensitivity of (93%) and a specificity of (96%); AUC $= 0.96$ (0.89–1.00 at 95% CI).

While for the Lancet Consensus Score (LCS) the mean score was $7.4 + 4.5$ (range $0–18$ IQR $= 8$), the distribution of the LCS score is shown in supplement 1. Sixty-seven (83.3%) of the TB cohort had a cutoff of 6 and were suggestive of TBM vs. 11 (14.5%) controls ($p < .001$). Sensitivity was 83.8%, specificity was 85.5%, PPV was 84.9% and NPV was 83.3%. The area under the ROC curve was 0.93 (95% CI 0.89–0.97) (supplement 2). The cutoff of 6 was found to have the greatest sensitivity and specificity. A cutoff of more than 12 had a 100% specificity but a poor sensitivity of only 33.8%. Other subgroup analysis can be found in Table 4.

4. Discussion

The used TBM criteria are entry criteria that was used to diagnose the TBM and are broad and are based on clinician judgment. On the other hand, the case definition criteria (LCS) is a research tool that is not used routinely in clinical practice. The premise of the paper is to see if the LCS and TDS are helpful in differentiating TBM from other meningitides in a real-world case mix of meningitides.

The whole cohort is male predominant. This is explained by the fact that the population of Qatar is male skewed with young male laborers from the Indian subcontinent featuring prominently. These laborers come to Qatar to work in the construction of stadia and other necessary infrastructure in preparation for the hosting of the football World cup in 2022 [27]. While the whole cohort is young, the TBM cases were significantly younger than the controls thus, vindicating why age is part of the TDS with 2 points added to the score when the age is > 36 years.

Ethnicity-wise South Asians feature prominently in both TBM and non-TBM cohorts, this probably reflects the demographics of the region where young South Asians constitute most of the population with local Qataris constituting only about a tenth of the population in Qatar [10]. There seems to be paucity of TBM cases in the Qatari population [10]; this could be due the impact of the universal newborn BCG vaccination in Qatar [28], healthcare availability and access, low prevalence of HIV [10], environmental [29] or even genetic factors [30].

Additionally, it is noteworthy that the whole cohort is HIV negative. This could be explained by the states policy of testing all expatriates (the majority of the cohort) before issuing residency permits coupled
with the low HIV prevalence in Qatar [10].

Thwaites et al. have highlighted the diagnostic uncertainty when attempting to diagnose TBM [9]. The TDS is a clinical tool aimed at helping clinicians. It is clinically attractive as it is simple and utilizes clinical and laboratory means that are widely available. The TDS performs well in differentiating bacterial meningitis from TBM [18]. In this study, the TDS performed well vs bacterial meningitis in ruling out TBM (sensitivities of 100%), in agreement with Sunbul et al. [22].

This sensitivity was maintained across all subgroup analysis (Table 4), thus making it a good test to rule out TBM when scores are more than 4 (SnNOUT) [31].

On the other hand, the LCS, showed overall good sensitivity and specificity at a cutoff of 6. However, it was marginally worse in comparison to the TDS in ruling out the TBM (97.5% vs 83.8%) but offered much higher specificity (Table 4). This superior specificity was maintained across all subgroups (81.3%–92.2%) which would be good in

Table 3
Ethnicities and clinical characteristics of the cohort.

| Ethnicities     | TBM = 80 | Controls = 76 | P value |
|-----------------|----------|---------------|---------|
| Qatari          | 2(2.5%)  | 11(14.5%)     | NA      |
| South Asiansb  | 61(76.3%)| 35(46.1%)     |         |
| Africans        | 8(10%)   | 9(11.8%)      |         |
| Filipinos       | 67(85%)  | 8(10.5%)      |         |
| Othersc         | 3(3.8%)  | 13(17.1%)     |         |
| Gender M        | 65(81.3%)| 62(81.6%)     | 0.96    |
| Gender F        | 15(18.8%)| 14(18.4%)     |         |
| Age(years) mean| 30.3 ± 8.9| 36.6 ± 14.0  | 0.001   |
| Duration of symptoms| 35(43.8%)| 67(88.2%)     | < 0.001 |
| Fever           | 63(78.8%)| 55(72.4%)     | 0.35    |
| Headache        | 57(73.3%)| 56(73.3%)     | 0.73    |
| Meningismus     | 45(55.3%)| 35(45.6%)     | 0.20    |
| Nausea & vomiting | 38(47.5%)| 43(56.6%)     | 0.26    |
| Altered sensorium| 37(46.3%)| 23(30.3%)     | 0.04    |
| Cranial nerve palsy | 18(22.0%)| 3(3.9%)       | 0.001   |
| Limb weakness   | 17(21.3%)| 3(3.9%)       | 0.001   |
| Night sweats    | 12(15.0%)| 2(2.6%)       | 0.01    |
| Weight loss     | 10(12.5%)| 2(2.6%)       | 0.02    |
| Change in personality | 9(11.3%) | 2(2.6%)       | 0.04    |
| Seizures        | 9(11.3%)  | 8(10.5%)      | 0.89    |
| Papilledema     | 5(6.3%)   | 2(2.6%)       | 0.28    |
| Fatigue         | 4(5.0%)   | 2(2.6%)       | 0.44    |
| WBC (mean)      | 9.2 ± 3.6 | 13.4 ± 10.2   | 0.001   |
| CRP (mean)      | 14.1 ± 23.9 | 59.3 ± 79.6  | 0.001   |
| Chest x-ray*    | Normal   | 55(68.8%)    | 59(84.3%)| 0.04    |
| Abnormal        | 23(28.8%)| 11(15.7%)     |         |
| CSF WBC count/mm³(mean) | 320.6 ± 292.5 | 930,225.8 ± 8,035,064 | 0.026 |
| Median (Range)  | 246(0-1485) | 340(70,055,555) |         |
| CSF differential(mean) | Neutrophils% | 20.8 ± 25.8 | 44.5 ± 40.1 | < 0.001 |
| Lymphocytes%    | 70.7 ± 31.2 | 54.1 ± 39.4  | 0.04    |
| CSF Protein(gm/dL) | 2.9 ± 5.5   | 2.5 ± 2.7    | 0.50    |
| Outcome         | Death     | 4(5.0%)      | 5(6.6%)  | 0.67    |
| Discharge with disability | 14(17.5%) | 3(3.9%)       | < 0.01  |
| Recovery without disability | 62(77.5%) | 64(84.2%)     | 0.3     |
| Recurrence      | 0(0%)     | 4(5.3%)      | 0.11    |

a Missing Data, Normal values: CRP (0-5 mg/l), WBC = (4-10 × 10³/mm3, CSF WBC(0–5),CSF protein(0–0.5 g/l).
b South Asians were formed of (Indian, Pakistani, Bangladeshi, SriLankan and Nepali) patients.
c Others include (Far East Asians, Caucasians and non-Qatari Middle Easterner).

This sensitivity was maintained across all subgroup analysis (Table 4), thus making it a good test to rule out TBM when scores are more than 4 (SnNOUT) [31].

On the other hand, the LCS, showed overall good sensitivity and specificity at a cutoff of 6. However, it was marginally worse in comparison to the TDS in ruling out the TBM (97.5% vs 83.8%) but offered much higher specificity (Table 4). This superior specificity was maintained across all subgroups (81.3%–92.2%) which would be good in

Table 4
Sensitives, specificities, positive predictive value (PPV) and negative predictive value (NPV) positive & negative likelihood ratios (LR+, LR-) for the Thwaites diagnostic score (TDS) and Lancet consensus score (LCS).

| Test                          | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | LR+ (95% CI) | LR- (95% CI) |
|-------------------------------|----------------------|----------------------|--------------|--------------|--------------|--------------|
| **TDS cutoff=4**              |                      |                      |              |              |              |              |
| Culture Positive TBMVs Bacterial | 100% (90.1–100)       | 80.7% (63.7–90.8)    | 85.4% (71.6–93.1) | 100% (86.7–100) | 5.2 (3.7–7.2) | 0.0          |
| Culture Positive TBM Vs Nonbacterial | 100% (90.1–100)       | 12.5% (5.86–24.7)    | 45.5% (34.8–56.5) | 100% (61–100)  | 1.14 (1.09–1.2) | 0.0          |
| Culture Positive TBM Vs Controls | 100% (90.1–100)       | 40.8% (30.4–52)      | 43.8(33.4–54.7) | 100% (89-00)  | 1.69 (1.6–1.8) | 0.0          |
| All suspected TBM Vs controls | 97.5% (91.3–99.3)     | 40.8% (30.4–52)      | 63.4% (54.6–71.4) | 93.9% (80.4–98.3) | 1.65 (1.6–1.7) | 0.06 (0.02–0.18) |
| **LCS cutoff=6**              |                      |                      |              |              |              |              |
| Culture Positive TBM Vs Bacterial | 85.7% (70.6–93.4)     | 92.9% (77.4–98.3)    | 93.8% (79.9–98.3) | 83.9% (67.4–92.9) | 12(4.5–32.3)  | 0.15(0.11–0.23) |
| Culture Positive TBM Vs Nonbacterial | 85.7% (70.2–93.7)     | 81.3% (68.1–89.8)    | 76.9% (61.7–87.4) | 88.6% (76.9–91.3) | 4.6(3.6–5.8)  | 0.2(0.1–0.3)  |
| Culture Positive TBM Vs controls | 85.7% (70.6–93.7)     | 85.5% (75.9–91.7)    | 73.2% (58.1–84.3) | 92.9% (84.3–96.9) | 5.9(4.9–7.2)  | 0.2(0.1–0.3)  |
| All suspected TBM Vs controls | 83.8% (74.2–90.3)     | 85.5% (75.9–91.7)    | 85.9% (76.5–91.9) | 83.3% (73.5–90)  | 5.8 (4.8–7)  | 0.19 (0.16–0.22) |

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ruling in the disease (SpPIN) [31].

Real world cases are a mixture of bacterial, viral, fungal and mycobacterial and differentiating these clinical diverse conditions may be difficult based on a single diagnostic score. The diagnosis of bacterial meningitis is usually straightforward, but the diagnostic challenge is with aseptic and lymphocytic meningitis where no organism is isolated.

While the TDS and the LCS intersect at certain components such as duration of illness and CSF WBC, there is only moderate agreement in diagnosing TBM between these two tests (kappa 0.53) [20]. However, they can be complimentary making use of the higher sensitivity of the TDS and its simplicity to rule out the disease in a good number of cases then applying the more labor and expense extensive LCS to utilize its good specificity particularly where clinical suspicion is high. However, it is noteworthy that the LCS has been developed as a case definition research tool to improve standardization and aids comparisons between studies and enhance generalizability. It is more detailed and less clinically attractive as it requires more extensive clinical and radiological data gathering and access to imaging facilities. It should be used cautiously in clinical practice as it may be challenging.

5. Strength & limitation

The strength of this study lies in the multiethnic nature of the population cohort in a comprehensive center with extensive use of neuroimaging allowing for good implementation of the LCS criteria and emulating the real-world situation by studying a case mix of meningitides.

The limitation includes the retrospective nature of the analysis and the potential presence of selection bias as clinicians tend to lean towards the diagnosis of TBM if there is any historical exposure to TB such as a history of close contact with an active pulmonary TB case, a family history of TB, prior TB infection, or if no alternative diagnosis is available. Additionally, a major drawback would be presence of small unequal number of patients in each category as well as the absence of a statistically calculated sample size. The absence of HIV positive cases is another drawback.

6. Conclusion

In conclusion, TDS can reliably differentiate TBM from bacterial meningitis with good accuracy, however it cannot be used as diagnostic method to reliably differentiate TBM from others due to its low specificity. The higher specificity of the LCS is best utilized for confirming meningitis with good accuracy, however it cannot be used as diagnostic tool for ruling in the disease (SpPIN) [31].

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