Journal of the Neurological Sciences 370 (2016) 112–118

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Validation of Thwaites Index for diagnosing tuberculous meningitis in a Colombian population

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ARTICLE INFO

Article history:
Received 1 May 2016
Received in revised form 21 August 2016
Accepted 6 September 2016
Available online 9 September 2016

Keywords:
Meningeal tuberculosis
Bacterial meningitis
Diagnosis
Sensitivity
Specificity
ROC curve

ABSTRACT

Objective.: To determine the diagnostic accuracy of Thwaites Index (TI) in a Colombian population to distinguish meningeal tuberculosis (MTB) from bacterial meningitis (BM) and from non-tuberculous meningitis. Exploratory analyses were conducted to assess the TI's validity for patients with human immunodeficiency virus (HIV) and children above six-years-old.
Methods: The study included 527 patients, the TI was calculated and results compared with those of a reference standard established by expert neurologists. Sensitivity, specificity, area under the curve of receiver-operator characteristics (AUC-ROC) and likelihood ratios were calculated.
Results: The AUC-ROC to distinguish MTB from non-tuberculous meningitis was 0.72 (95% CI: 0.67–0.77) for HIV negative adults. AUC-ROC was 0.62 (95% CI: 0.50–0.74) for HIV positive adults and 0.83 (95% CI: 0.68–0.97) for children. For distinguishing MTB from BM the AUC-ROC was 0.78 (95% CI: 0.73–0.83); furthermore, the AUC-ROC was 0.57 (95% CI: 0.31–0.83) for HIV positive adults and 0.86 (95% CI: 0.73–0.99) for children.
Conclusion: The TI was sensitive but not specific when used to distinguish MTB from BM in HIV negative adults. In HIV positive adults the index had low diagnostic accuracy. Moreover, the TI showed discrimination capability for children over 6 years; however, research with larger samples is required in these.

1. Introduction

Tuberculosis (TB) is one of those infectious diseases caused by a single pathogen that cause the highest mortality rates in the world [1]. It is estimated that in 2014 a million and a half people died from TB and, between 2000 and 2014, 43 million deaths were avoided through effective diagnosis and treatment [2]. Meningeal tuberculosis (MTB) amounts to 1% of all forms of tuberculosis and is the most severe form of this disease [3].

At the moment, there is neither a good reference standard nor a test for confirming an MTB diagnosis quickly. Ziehl-Neelsen stain of cerebrospinal fluid (CSF) has low sensitivity (maximum 58%) and culture results take too long to be made available, rendering those useless for making therapeutic decisions [4]. In practice, diagnosis is carried out by gathering clinical and epidemiological evidence as well as laboratory and neuroimaging test results [5,6]. One of the biggest challenges is distinguishing bacterial meningitis (BM) from MTB [7]. To address this, indexes or Clinical Prediction Rules (CPR) have been developed. One of the best known CPR is Thwaites Index (TI), which was developed in Vietnam for a population with high prevalence of TB and low HIV prevalence. This CPR uses five variables including clinical features and basic laboratory tests (see Box 1), with a score less than or equal to 4 being indicative of MTB [8].

The TI has been validated mainly for populations with a high incidence of TB and scarce resources [9–12]. However, at present we are not aware of any validation studies conducted in Latin America, a region

Abbreviations: TB, tuberculosis; MTB, meningeal tuberculosis; CSF, cerebrospinal fluid; BM, bacterial meningitis; CPR, Clinical Prediction Rules; TI, Thwaites Index; HIV, human immunodeficiency virus; AUC-ROC, area under the curve of the receiver-operator characteristics; LR, likelihood ratios; MDOC, meningitis due to other causes.

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http://dx.doi.org/10.1016/j.jns.2016.09.007
0022-510X/

Box 1
Thwaites Index and score for each variable.

Variable	Score
Age in years	
≥ 36	+ 2
<36	0
White blood cell count in blood/ml	
≥ 15,000	+ 4
<15,000	0
Duration of the disease in days	
≥ 6	− 5
<6	0
White blood cell count in cerebrospinal fluid/ml	
≥ 900	+ 3
<900	0
Percentage of neutrophils in cerebrospinal fluid	
≥ 75	+ 4
<75	0

where tuberculosis is endemic and most countries, including Colombia, have intermediate risks of the disease [13].

In common clinical practice, the diagnostic dilemma arises when trying to distinguish MTB from non-tuberculous meningitis regardless of its specific aetiology [7]. Thus, it is important to establish the validity of the index in order to make this differential diagnosis. There are some studies in which relatively low specificities were observed when including patients with BM and cryptococcal meningitis [9,10], but the TI has usually been validated for distinguishing MTB from BM [14,15].

With the exception of one study [10], all TI validations have excluded patients infected with the human immunodeficiency virus (HIV) [9,12,14,15]. Because of the close relationship between TB and HIV, it is important to know how accurate the TI is for populations infected with this virus. In addition, the TI has not been validated for individuals under 15 years of age because it has been considered that its characteristics may be different in this group [8]. In fact, it has been reported that the behaviour of MTB in individuals less than six-year-old is different than the one in older children and adults. What distinguishes the younger age group are: higher disease incidence, an atypical clinical presentation and worse prognosis [15,16]. Therefore, it is reasonable to believe that the TI might be useful for children over six.

As a result of the challenge posed by MTB diagnosis, particularly in countries where TB is endemic, our goal was to evaluate how accurate the TI is for distinguishing MTB from BM and non-tuberculous meningitis among adults in Medellin, Colombia. Furthermore, exploratory objectives included: assessing the validity of the TI for HIV-infected patients and children over the age of six.

2. Methods

2.1. Participants

A cross-sectional study was conducted with patients who received care between 2000 and 2014 in four tertiary care institutions in Medellín, Colombia. Those institutions were: Hospital Universitario San Vicente Fundación, Instituto Neurológico de Colombia Hospital Pablo Tobón Uribe and IPS Universitaria - Sede Clínica "León XIII". This study was approved by the ethical review boards of the stated institutions before beginning the project.

Potential participants were identified through a search of all meningitis related codes described in the tenth version of the International Classification of Diseases [17]. Inclusion criteria were: being more than six years old and having been diagnosed with meningitis of any aetiology during the hospitalization period. Patients whose data was insufficient for TI calculation were excluded.

2.2. Reference standard

The reference standard was a combination of clinical criteria used in previous TI validation studies (see Box 2) [8,10,18].

2.3. Data collection procedures

Two forms were designed: one for data collection and one for diagnosis. The first form included variables required to calculate the TI (age, white blood cell count in blood, disease duration, CSF's white blood cell count and percentage of neutrophils) as well as other information required for diagnosis. The second form contained the criteria necessary for experts to establish a diagnosis.

An operations manual was created, and training sessions for doctors in charge of data collection were done by reviewing clinical records (SU, JSS, ICV). Subsequently, inter-rater reliability was assessed for a sample of 36 patients and Cohen's kappa (κ) was calculated. [19]. When results obtained by the three doctors who collected data were compared, a high level of agreement was found for the variables age (κ = 0.99; 95% CI 0.99–1.0), percentage of neutrophils in CSF (κ = 0.96; 95% CI 0.93–0.98), and white blood cell count in blood (κ = 0.935; 95% CI 0.88–0.97) and in CSF (κ = 0.92; 95% CI 0.85–0.96). For symptom evolution time, agreement was lower (κ = 0.54; 95% CI 0.29–0.75).

Diagnosis for the reference standard was made using an adaptation of the Best Estimate Diagnosis methodology described by Leckman et al. [20]. For this methodology, two expert neurologists (MET, CSU)

Box 2
Diagnostic criteria for meningeal tuberculosis and meningitis due to other causes.

MTB

1) *M. tuberculosis* isolated from the CSF,or

2) Clinical meningitis plus negative Gram and India ink stains along with negative for bacterial and fungal cultures and one or more of the following:

a) Brain tomography consistent with MTB (hydrocephalus, edema, basal meningeal enhancement).
b) Chest radiograph consistent with active pulmonary TB.
c) History of close contact (living together) with an individual with a confirmed diagnosis of TB.
d) Isolation of the bacillum from body fluids other than CSF.

Bacterial meningitis

1) Pathogenic bacteria isolated from the CSF,or

2) Clinical meningitis with ALL of the following items:

a) Lymphocytes and neutrophils in CSF.
b) Low glucose concentration in CSF (<50% of the blood).
c) Total recovery three months after admission and without any therapy against tuberculosis.

Cryptococcal meningitis

1) India ink stains, negative for fungal culture or positive for cryptococcal antigen in CSF.

Viral meningitis

1) CSF pleocytosis of at least 7 leucocytes/mm^3.
2) A CSF culture that is negative for bacteria
3) Dismissing all possible etiologies except viral.

TB: tuberculosis; MTB: meningeal tuberculosis; CSF: cerebrospinal fluid.

blindly and separately reviewed all patient information. A definitive diagnosis was assigned to a patient when there was agreement between experts; otherwise, a third neurologist evaluated the form and diagnosis was decided by majority. When there was no agreement at all, the diagnosis was labelled meningitis due to unknown cause. Additionally, this diagnostic category could be assigned by experts from the very beginning if aetiology was not clear.

The TI was calculated using the values assigned to each variable originally by Thwaites (see Box 1 [8]). Experts had no knowledge of this result when establishing diagnosis for the reference standard.

2.4. Statistical methods

All analyses were conducted using Epidat 3.1 software. Subjects participating in the study were described using measures of central tendency and dispersion for quantitative variables and percentages for qualitative ones.

For TI validation, a sample size of 186 subjects with MTB and 372 without it, was estimated using Epidat 3.1 diagnostic testing module. The following values were taken: sensitivity and specificity values - which, based on Thwaites's study - were 86% and 79% respectively [8], a disease free/with disease ratio of 2, a 95% confidence level and 5% precision.

The analyses conducted to validate the TI were divided in two groups: ability to distinguish MTB from BM and ability to distinguish MTB from non-tuberculous meningitis. The area under the curve of the receiver-operator characteristics (AUC-ROC) was estimated for each analysis. Similarly, sensitivity, specificity as well as positive and negative likelihood ratios (LR+ and LR−) were calculated for each possible cut-off score along with their respective confidence intervals of 95% (95% CI). Separate analyses were performed for children (aged between 7 and 14 years) and adults with and without HIV. Furthermore, since having partially treated meningitis may modify the diagnostic features of the TI for distinguishing MTB from BM, a sensitivity analysis was conducted for patients with and without a history of this.

3. Results

The experts reviewed a total of 578 clinical records. Of these, 29 were excluded due to insufficient information for calculating the TI and 22 because no mention of meningitis was found (see Fig. 1). Of the 527 patients included in the study, 317 (60.1%) were males with ages ranging from 7 to 91 and a median of 36 years (interquartile range: 22–53) while 55 (10.4%) were children. Based on the diagnosis made by experts, 157 patients had MTB, 243 BM, 120 meningitis due to other causes (MDOC) and 7 had meningitis due to unknown causes. Table 1 shows the demographic and clinical features of subjects sorted by diagnosis.

For those with MDOC, aetiologies were: viral in 81 individuals (67.5%), cryptococcal in 26 (21.6%), toxoplasma in 5 (4.1%), autoimmune or carcinomatous in 4 (3.3%), neurosyphilis in 3 (2.5%) and chemical in 1 (0.8%).

The diagnosis was confirmed microbiologically for 55 (35.0%) patients with MTB, 100 (41.1%) patients with BM and 33 (27.5%) with MDOC. For BM, the germs identified were: *S. pneumoniae* in 46, *N. meningitidis* in 11, *S. epidermidis* in 6, *L. monocytogenes* in 4, *H. influenzae* in 4, *E. coli* in 3, *S. agalactiae* in 3, *K. pneumoniae* in 2, *S. hominis* in 2 and other microbes in 23.

3.1. Characteristics of TI in adults with and without HIV

Of 472 adults with meningitis, 81 (17.5%) were HIV positive, of those 39 (48.1%) had MTB, 8 (9.9%) had BM, 32 (39.5%) MDOC and 2 (2.5%) meningitis due to unknown causes. Among HIV negative patients, the diagnosis was MTB for 109 (27.9%) of them, BM for 199 (50.9%), MDOC for 78 (19.9%) and meningitis due to unknown causes for 5 (1.3%).

For the ability to distinguish MTB from non-tuberculous meningitis, the AUC-ROC for HIV positive patients was 0.62 (95% CI: 0.50–0.74), and 0.72 (95% CI: 0.67–0.77) for HIV negative patients (see Fig. 2a). For HIV positive patients, the discriminatory ability was low for all cut-off scores and there was a high probability of false positives for MTB as indicated by the low values for specificities and positive likelihood ratios (see Table 2). Using the 3 cut-off, specificity was 11.9% with 16.7% of the 36 TI false positives having BM while the remaining 83.3% had MDOC: 11 cryptococcal, 11 viral, 3 neurosyphilis, 3 toxoplasmosis and 3 indeterminate. In HIV negative patients, the AUC-ROC showed that the cut-off with which the TI had highest sensitivity and specificity was 3, with 90.83% (95% CI: 84.95–96.70) and 42.91% (95% CI: 36.95–48.86) respectively.

The AUC-ROC for the ability to distinguish MTB from BM was 0.57 (95% CI: 0.31–0.83) for HIV positive patients (see Fig. 2b). This group had an extremely high probability of false positives even though sensitivity was 97.44% (95% CI: 91.19–100.00) with a cut-off score of 2 or 3 (see Table 3). For HIV negative patients, the AUC-ROC was 0.78 (95% CI: 0.73 to 0.83) and the best cut-off was 3, with a sensitivity of

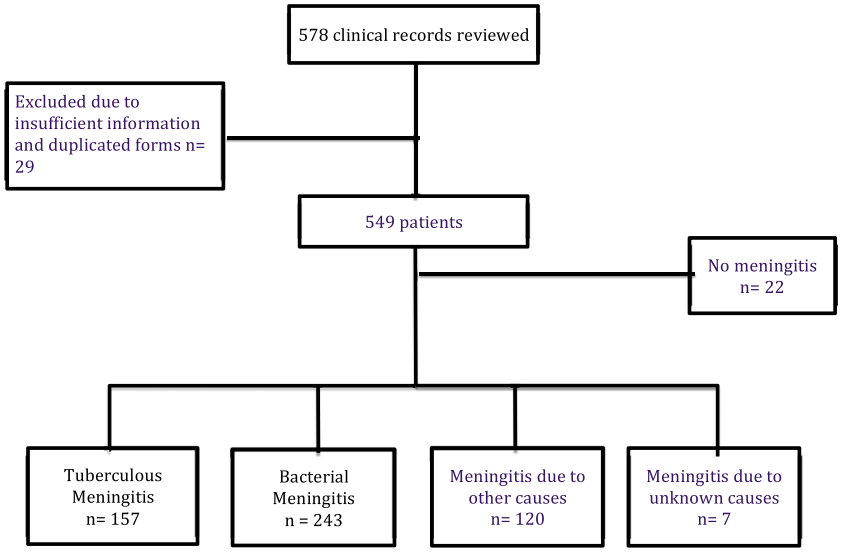

Fig. 1. Flowchart.

Table 1
Clinical, sociodemographic and laboratory features of patients with MTB, BM and meningitis due to other causes upon admission.

Feature	Meningeal tuberculosis (n = 157)	Bacterial meningitis (n = 243)	Meningitis due to other causes (n = 120)	Meningitis of undetermined aetiology (n = 7)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Age in years	38 (26–54)	35 (20–54)	36 (22–52)	28 (22–47)
Glasgow coma scale upon entrance	14 (11–15)	14 (11–15)	15 (14–15)	13 (9–15)
Evolution time	15 (8–30)	4 (2–7)	6 (3–14)	2 (1−20)
White blood cell count in blood	9400 (6660–13,100)	13,100 (8800–18,800)	8400 (6600–11,375)	11,400 (5600–14,400)
White blood cell count in the CSF	82 (18–202)	263 (65–1045)	36 (10–90)	32 (20–54)
Percentage of neutrophils in the CSF	33 (10–66)	78 (36–90)	17 (1–53)	39 (2–75)
Feature	Meningeal tuberculosis (n = 157)	Bacterial meningitis (n = 243)	Meningitis due to other causes (n = 120)	Meningitis of undetermined aetiology (n = 7)
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Male	102 (65,0)	138 (56,8)	71 (59,2)	6 (85,7)
Children (7 to 14 years)	9 (5,7)	36 (14,8)	10 (8,3)	0 (0,0)
Previous exposure to antibiotics	69 (43,9)	82 (33,7)	31 (25,8)	1 (16,7)
Presence of cephalalgia	122 (77,7)	198 (81,5)	108 (90,0)	5 (71,4)
Presence of vomit	65 (41,4)	130 (53,5)	61 (50,8)	2 (28,6)
Altered state of consciousness	90 (57,3)	134 (55,1)	33 (27,5)	4 (57,1)
Presence of meningeal signs	80 (51,0)	150 (61,7)	52 (43,3)	3 (42,9)
HIV positive patients	40 (25,5)	8 (3,3)	33 (27,5)	2 (28,6)
Death	27 (17,2)	40 (16,5)	13 (10,8)	0 (0,0)

CSF: cerebrospinal fluid, HIV: human immunodeficiency virus, IQR: interquartile range.

90.83% (95% CI: 84.95–96.70) and a specificity of 56.28% (95% CI: 49.14–63.42). With a cut-off score of 4, which is the value set by the index's authors, sensitivity remained unchanged but specificity was 46.23% (95% CI: 39.05–53.41).

When conducting the analyses for distinguishing MTB from BM for the 138 patients with partially treated meningitis, corresponding to 35.3% of HIV negative adults, the AUC-ROC was 0.74 (95% CI: 0.65–0.83). For patients who did not have a history of partially treated meningitis, this value was 0.81 (95% CI: 0.75 to 0.88). With a cut-off score of 3, the sensitivity for patients with partially treated meningitis was 92.31% (95% CI: 84.10 to 100.00), specificity was 49.25% (95% CI: 36.64–61.97), the LR+ 1.82 (95% CI: 1.42–2.33) and the LR− 0.16 (95% CI: 0.06–0.41); Similarly, sensitivity for patients without meningitis was 90.20% (95% CI: 81.05–99.34), specificity was 61.42% (IC95%: 52.56–70.28), the LR+ was 2.34 (95% CI: 1.84 to 2.96) and the LR− 0.16 (95% CI: 0.07–0.37).

3.2. Characteristics of TI in children

Of the 55 children, two were HIV positive. One had MTB and the other cryptococcal meningitis. Due to this low frequency, we limited the analysis to HIV negative children. Thus, of the HIV negative children, 8 (15.1%) were diagnosed with MTB, 36 (67.9%) with BM and 9 (17.0%) with MDOC.

The AUC-ROC was 0.83 (95% CI: 0.68 to 0.97) for the ability to distinguish MTB from non-tuberculous meningitis, (see Fig. 3a). With a cut-off score of 4, the value for sensitivity was 100%, but specificity was low. For cut-off scores from 0 to 3, sensitivity was 87.50% and specificity ranged from 55.56% to 60% (see Table 2).

For the ability to distinguish MTB from BM, the AUC-ROC was 0.86 (95% CI: 0.73 to 0.99) (see Fig. 3b). With a cut-off of 4, specificity was very low despite sensitivity being high. Conversely, cut-off scores between 0 and 3 improve specificity, as the values range from 66.66% to 72.22%, but decrease sensitivity to 87.5% (see Table 3).

4. Discussion

This study showed that TI when applied to a Colombian population of HIV negative adults with meningitis, has high sensitivity, both for distinguishing MTB from BM and MTB from non-tuberculous meningitis, although specificity for the latter distinction is lower. Conversely, the TI showed very low diagnostic accuracy in HIV positive patients. Furthermore, our results suggest that TI has similar properties in adults and children over 6 years.

When using the cut-off score proposed by the authors who designed the TI [8], sensitivity was excellent but specificity was unacceptably low. Exploring other cut-offs, we found 3 to be the cut-off associated with the best sensitivity and specificity values in HIV negative adults. Thus our discussion from here on focuses on the TI using the new cut-off.

The high sensitivity found for distinguishing MTB from BM in adults without HIV is similar to findings of other studies [9–12,14,15], but the low specificity contrasts with most others which have reported values between 70.8% and 87.9% [8,9,12,14]. A study from China which reported 43.6% specificity explained it as a result of antibiotic use before hospital admission and authors referred to this condition as partially treated meningitis [15]. They observed that, after removing those patients from the sample, specificity increased to 82.9%. In our hands, an equivalent analysis resulted in 49.2% specificity for patients with a history of partially treated meningitis and 61.4% in individuals without such precedent. We observed that antibiotic use also had some influence, but specificity was still lower than the value reported by the study from China. Another possible explanation for the low specificity found is that Colombia is a country with intermediate risk of TB and its epidemiological characteristics are different from those of most settings where the TI has been validated [9,10,15]. This points to the need to create a new index for countries with intermediate TB burdens such as is the case for most of Latin America. In fact, new CPRs with good diagnostic accuracy have already been created in several countries [14,21,22]. For example, in India a new index was created including variables such as living in rural areas, disease duration, low percentage of neutrophils in the CSF, diplopia, hemiparesis and a clear CSF [14]. An alternative to the creation of a new CPR is to use the TI as a part of a work up process that includes several diagnostic tools. Marais et al. published a proposal for the definition of MTB cases for clinical research which included clinical and CSF criteria in addition to neuroimaging and evidence of TB in other locations [23].

The TI has also been used to differentiate MTB from non-tuberculous meningitis but its specificity has been lower than the value found for distinguishing MTB from BM with values between 43% and 68% [9,10]. This low specificity is consistent with our findings and is expected as it indicates an increased probability of false positives when making a differential diagnosis of meningitis cases whose aetiologies are associated with clinical and laboratory features resembling those of MTB.

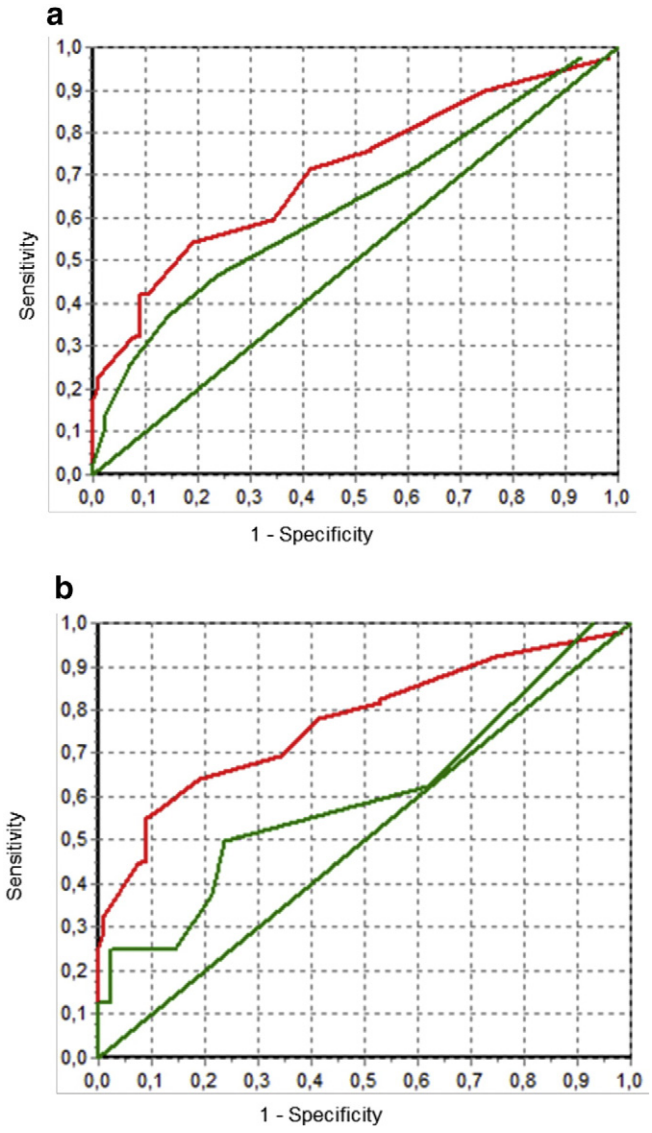

Fig. 2. Receiver-operator characteristics curves of Thwaites Index for patients with and without HIV.

Although it was part of an exploratory objective and the subsample was small, we found that for HIV positive patients the diagnostic accuracy was low with a null discriminatory ability. This, together with findings of other studies where HIV prevalence is high [10], suggests that the TI is not useful as a diagnostic tool for MTB in individuals with HIV. This poor diagnostic performance may be due to the greater frequency of meningitis with aetiologies whose clinical and laboratory features resemble those of MTB; such as *Cryptococcus*. In addition, alterations in the immune response of patients with HIV could also be responsible for it [24]. For this reason, other projects have sought to create new CPRs specific for populations with a high HIV prevalence [25,26]. This need persists in countries with a low prevalence of HIV such as Colombia [27] because TB/HIV coinfection is common in all settings.

Interestingly, performance of the TI in children aged 7 to 14 was similar to that of HIV negative adults. The AUC-ROC was slightly higher regarding the ability to distinguish MTB from BM and from non-tuberculous meningitis. This suggests that the TI could be applicable to children within this age group; however, the optimal cut-off score was difficult to establish since results were similar, with scores between 0 and 3. This difficulty is probably due to the small sample size; hence, further research in children is needed.

The limitations of this study include: 1) The retrospective design makes it necessary to collect data from clinical records, which can lead to biases due to inaccuracy of recorded information and the absence of standardized clinical and para-clinical evaluations for all patients. 2) The reference standard for the final diagnosis was imperfect as tests available for MTB are not sufficiently sensitive and specific. For this reason, we decided to rely on the independent diagnoses of expert neurologists. Although they were not aware of the results of the TI, it is unlikely that they were not familiar with parameters used to calculate it when making their diagnosis. Thus, independence of the test from the reference standard could not be guaranteed. 3) When selecting the sample, patients with history of traumatic brain injury, ventricle-peritoneal shunt and nosocomial meningitis were not excluded or quantified. This could have influenced the results. 4) Cases of immunosuppression different from HIV were not recorded and these can be frequent in high-complexity hospitals such as those involved in our study; this may have affected the accuracy of the TI.

5. Conclusions

Given its sensitivity, the TI is useful as a screening test to define the empiric start of treatment for BM. However, TI results suggesting MTB

Table 2
Characteristics of the Thwaites Index to distinguish a diagnosis of meningeal tuberculosis (MTB) from one of non-tuberculous meningitis in children and adults.

	Cut-off score	Sensitivity (CI 95%)	Specificity (CI 95%)	Positive likelihood ratio (CI 95%)	Negative likelihood ratio (CI 95%)
HIV negative children (n = 53, 8 with MTB)	4	100,00 (93,75–100,00)	33,33 (18,45–48,22)	1,50 (1,22–1,84)	–
	3	87,50 (58,33–100,00)	55,56 (39,93–71,18)	1,97 (1,30–2,99)	0,23 (0,04–1,43)
	2	87,50 (58,33–100,00)	57,78 (42,24–73,32)	2,07 (1,35–3,19)	0,22 (0,03–1,38)
	1	87,50 (58,33–100,00)	60,00 (44,58–75,42)	2,19 (1,40–3,41)	0,21 (0,03–1,32)
	0	87,50 (58,33–100,00)	60,00 (44,58–75,42)	2,19 (1,40–3,41)	0,21 (0,03–1,32)
	−1	75,00 (38,74–100,00)	71,11 (56,76–85,46)	2,60 (1,41–4,77)	0,35 (0,10–1,18)
HIV negative adults (n = 391, 109 with MTB)	4	90,83 (84,95–96,70)	33,33 (27,65–39,01)	1,36 (1,23–1,51)	0,28 (0,15–0,51)
	3	90,83 (84,95–96,70)	42,91 (36,95–48,86)	1,59 (1,41–1,79)	0,21 (0,12–0,39)
	2	88,99 (82,66–95,33)	43,62 (37,65–49,58)	1,58 (1,40–1,78)	0,25 (0,15–0,44)
	1	80,73 (72,87–88,60)	55,67 (49,70–61,65)	1,82 (1,55–2,14)	0,35 (0,23–0,52)
	0	65,14 (55,73–74,54)	60,99 (55,12–66,86)	1,67 (1,37–2,04)	0,57 (0,44–0,75)
	−1	57,80 (48,07–67,53)	73,40 (68,07–78,74)	2,17 (1,69–2,80)	0,57 (0,46–0,72)
HIV positive (n = 81, 39 with MTB)	4	100,00 (98,72–100,00)	2,38 (0,00–8,18)	1,02 (0,98–1,07)	–
	3	97,44 (91,19–100,00)	11,90 (0,92–22,89)	1,11 (0,98–1,25)	0,22 (0,03–1,76)
	2	97,44 (91,19–100,00)	14,29 (2,51–26,06)	1,14 (0,99–1,30)	0,18 (0,02–1,42)
	1	92,31 (82,66–100,00)	26,19 (11,70–40,68)	1,25 (1,02–1,53)	0,29 (0,09–0,98)
	0	84,62 (72,01–97,22)	38,10 (22,22–53,97)	1,37 (1,04–1,79)	0,40 (0,18–0,93)
	−1	76,92 (62,42–91,43)	45,24 (28,99–61,48)	1,40 (1,02–1,94)	0,51 (0,26–0,99)

HIV: human immunodeficiency virus.

Table 3
Characteristics of the Thwaites Index to distinguish a diagnosis of meningeal tuberculosis (MTB) from one of bacterial meningitis in children and adults.

	Cut-off score	Sensitivity (CI 95%)	Specificity (CI 95%)	Positive likelihood ratio (CI 95%)	Negative likelihood ratio (CI 95%)
HIV negative children (n = 44, 8 with MTB)	4	100,00 (93,75–100,00)	38,69 (21,58–56,20)	1,64 (1,26–2,12)	–
	3	87,50 (58,33–100,00)	66,67 (49,88–83,45)	2,63 (1,54–4,46)	0,19 (0,03–1,19)
	2	87,50 (58,33–100,00)	69,44 (53,01–85,88)	2,86 (1,64–5,00)	0,18 (0,03–1,14)
	1	87,50 (58,33–100,00)	72,22 (56,20–88,24)	3,15 (1,75–5,67)	0,17 (0,03–1,09)
	0	87,50 (58,33–100,00)	72,22 (56,20–88,24)	3,15 (1,75–5,67)	0,17 (0,03–1,09)
	−1	75,00 (38,74–100,00)	75,00 (59,47–90,53)	3,00 (1,50–6,00)	0,33 (0,10–1,12)
HIV negative adults (n = 308, 109 with MTB)	4	90,83 (84,95–96,70)	46,23 (39,05–53,41)	1,69 (1,47–1,95)	0,20 (0,11–0,36)
	3	90,83 (84,95–96,70)	56,28 (49,14–63,42)	2,08 (1,76–2,46)	0,16 (0,09–0,30)
	2	88,99 (82,66–95,33)	57,29 (50,16–64,41)	2,08 (1,75–2,48)	0,19 (0,11–0,33)
	1	80,73 (72,87–88,60)	65,33 (58,46–72,19)	2,33 (1,88–2,88)	0,29 (0,20–0,44)
	0	65,14 (55,73–74,54)	70,85 (64,29–77,42)	2,23 (1,73–2,89)	0,49 (0,37–0,65)
	−1	57,80 (48,07–67,53)	79,40 (73,53–85,27)	2,81 (2,04–3,85)	0,53 (0,42–0,67)
HIV positive (n = 47, 39 with MTB)	4	100,00 (98,72–100,00)	12,50 (0,00–41,67)	1,14 (0,88–1,49)	–
	3	97,44 (91,19–100,00)	12,50 (0,00–41,67)	1,11 (0,85–1,45)	0,21 (0,01–2,95)
	2	97,44 (91,19–100,00)	25,00 (0,00–61,26)	1,30 (0,87–1,94)	0,10 (0,01–1,00)
	1	92,31 (82,66–100,00)	25,00 (0,00–61,26)	1,23 (0,82–1,85)	0,31 (0,06–1,55)
	0	84,62 (72,01–97,22)	25,00 (0,00–61,26)	1,13 (0,74–1,72)	0,62 (0,15–2,52)
	−1	76,92 (62,42–91,43)	37,50 (0,00–77,30)	1,23 (0,70–2,16)	0,62 (0,21–1,78)

HIV: human immunodeficiency virus.

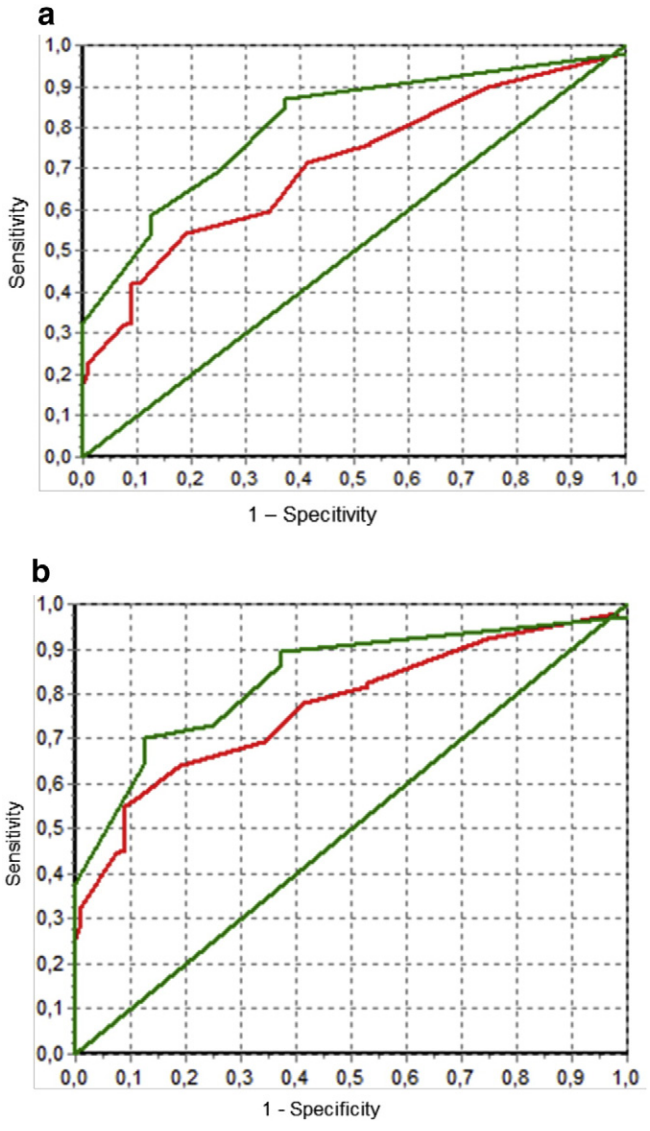

Fig. 3. Receiver-operator characteristics curves of Thwaites Index in HIV negative adults and children.

have a high probability of being false positives. Thus, other laboratory tests, neuroimaging and prospective evaluation of response to treatment would be required in those situations. In the case of other aetiologies which could be mistaken for MTB such as cryptococcal meningitis, there are quick and easy ways of establishing these diagnoses, which compensates for the TI's low specificity. For other diseases such as viral meningitis, there is often no definitive diagnosis. However, their course is usually benign and they improve without specific treatment.

The TI does not have diagnostic accuracy for HIV positive patients. Therefore, other alternatives for etiological classification of meningitis should be considered for this population. For children over 6 years, the diagnostic accuracy of the TI seems to be similar to that of adults, but further research with larger sample sizes is required to accurately establish the operating characteristics and the appropriate cut-off point.

A future assessment of the usefulness of including other variables to improve the specificity of the MTB diagnosis is necessary. Such variables could be: neuroimaging findings and results of nucleic acid amplification tests.

Acknowledgements

We would like to thank the San Vicente Foundation University Hospital, the Colombian Neurological Institute, Pablo Tobón Uribe Hospital and the IPS Universitaria Clinica Leon XIII. This study was sponsored by the 2013–2014 sustainability funding given to the Clinical Epidemiology Academic Group (GRAEPIC). The funding source was not involved in study design nor data collection, analysis or selection for publication.

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