



The Roles of Thwaites' and Marais' Diagnostic Scoring Indexes and a Clinical Prediction Model in the Diagnosis of Tuberculous Meningitis

Tüberküloz Menenjit Tanısında Thwaites ve Marais'in Tanı Skor İndeksleri ve Klinik Bir Tahmin Modelinin Rolü

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ABSTRACT

Objective: Tuberculous meningitis (TBM) is the most severe form of extra pulmonary tuberculosis. Bacteriological confirmative tests based on mycobacterial cultures or polymerase chain reaction tests are time-consuming process may not help diagnose every TBM patient. Therefore, practical and easily applicable scoring systems may be helpful in the early diagnosis of TBM and should be applied in the clinical follow-up process.

Methods: The features of 20 patients with TBM were retrospectively evaluated according to the Thwaites' diagnostic scoring indexes (TDSI) and Marais' diagnostic scoring indexes (MDSI) beside a clinical prediction model (CPM) in this study. MDSI, CPM, viral, brucellar, and fungal etiologies were excluded by microscopic, serological, and molecular examinations of cerebrospinal fluid (CSF) and blood in all patients.

Results: All patients were assessed for TBM according to TDSI (100%). Of these, 5 (25%) were considered probable TBM, and 15 (75%) were possible TBM, according to MDSI. The scores were greater than or equal to 6 in all the cases with TBM by CPM, 13 of which were scored as 9 points (65%).

Conclusion: According to the outcomes of our study, the TDSI, MDSI, and CPM assessment methods are easily applicable and helpful techniques for rapid and accurate TBM diagnosis.

Keywords: Tuberculosis, tuberculous meningitis, Thwaites, Marais, clinical prediction model

ÖZ

Amaç: Tüberküloz menenjit (TBM), ekstrapulmoner tüberkülozun en ciddi formudur. Mikobakteriyel kültür ve polimeraz zincir reaksiyonu testlerine dayanan bakteriyolojik doğrulama testleri hem zaman alıcı testlerdir hem de TBM'li her hastanın tanısında yardımcı olmayabilir. Bu yüzden, pratik ve uygulaması kolay diagnostik skorlama indeksleri TBM'nin erken tanısında faydalı olabilir ve klinik takipte kullanılmalıdır.

Gereç ve Yöntem: Bu çalışmada 20 TBM hastasının özellikleri, klinik tahmin modelinin yanı sıra Thwaites ve Marais'in diagnostik skorlama indekslerine (TDSI ve MDSI) göre retrospektif olarak değerlendirildi. Tüm hastalarda BOS ve kanın mikroskopik, serolojik ve moleküler incelemeleri ile viral, brusellar ve fungal etiyolojiler dışlandı.

Tartışma: Tüm hastalar TDSI'ya göre (%100) TBM olarak değerlendirilirken, sırasıyla 5'i (%25) ve kalan 15'i (%75) MDSI'ye göre olası TBM ve olası TBM olarak değerlendirildi. CPM ile TBM olan tüm olgularda puanlar 6'dan büyük veya eşit olup, 13'ü 9 puan (%65) olarak puanlanmıştır.

Sonuç: Çalışmamızın sonuçlarına göre TDSI, MDSI ve CPM değerlendirme yöntemleri TBM'nin hızlı ve doğru teşhisi için uygulanması kolay ve kullanışlı tekniklerdir.

Anahtar Kelimeler: Tüberküloz, tüberküloz menenjit, Thwaites, Marais, klinik tahmin modeli

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INTRODUCTION

Tuberculous meningitis (TBM) is the most severe form of tuberculosis (TB), as its exact incidence and prevalence rates are unknown. However, its incidence is expected to be relatively high, especially in children, human immunodeficiency viruses-infected individuals, and people living in countries with a high burden of pulmonary TB (1). According to the 2019 World Health Organization (WHO) Global TB report, approximately 10 million people were diagnosed with TB in 2018. They lived mainly in Southeast Asia (44%) and Africa (24%). Extra pulmonary TB (EPTB) constitutes 15% of all cases. Nevertheless, the patients from high-incidence countries may manifest a higher prevalence rate. Turkey is among the countries with a prevalence rate of EPTB higher than 30% (2). In Turkey, the total case rate is 15.6 per hundred thousand in 2016, according to the 2018 report of TB (3). Globally, about 1.5 million TB-related deaths occurred worldwide. Without the prompt diagnosis and early treatment of TBM, mortality and morbidity rates are exceptionally high. Also, delayed diagnosis and subsequent therapy significantly contribute to the current high mortality rate (1,4-6).

The gold standard of TBM diagnosis is the identification of *Mycobacterium tuberculosis* bacilli in the cerebrospinal fluid (CSF). Novel culture methods based on liquid media, such as mycobacteria growth indicator tube, have higher positivity rates than the classical Löwenstein-Jensen method. However, the sensitivity and positivity rates of the current laboratory confirmation methods based on mycobacterial culture or polymerase chain reaction (PCR) tests do not exceed 60% (7). These methods require a long-lasting process and a well-trained authorized staff capable of using specific equipment for a positive result (8). Therefore, scoring indexes or clinical prediction models based on clinical, laboratory, radiological, and CSF findings have been developed by researchers (9-11). This study aims to evaluate 20 patients with TBM according to the Thwaites' scoring indexes (TDSI) and Marais' scoring indexes (MDSI) and a clinical prediction model (CPM) and to assess these practical diagnostic approaches to diagnose TBM.

METHODS

This retrospective study included patients with TBM over 18 years of age followed in our hospital between 2015 and 2019. TBM was diagnosed based on clinical, CSF, radiological, and laboratory findings in the cases that presented the clinical picture of meningitis (12) (Table 1). Viral, brucellar, and fungal etiologies were excluded by microscopic, serological, and molecular examinations of

Table 1. Diagnostic criteria for TBM and ABM (12)

TBM	ABM
<i>Mycobacterium tuberculosis</i> isolation from CSF or clinical signs of meningitis	Isolation of bacterial agent from CSF or clinical signs of meningitis
With negative Gram or Indian ink stain and negative culture for bacterial or fungal agents, in the presence of at least one of the following features:	In the presence of all of the following features:
Cranial imaging findings compatible with TB	Pleocytosis in CSF
The signs of accompanying pulmonary TB	CSF/plasma glucose ratio <50%
Positive family history for TB	Negative CSF and blood cultures
Close contact with an active TB case	-
Clinical response to antituberculous therapy	Clinical response to non-specific therapy

TBM: Tuberculous meningitis, ABM: Acute bacterial meningitis, CSF: Cerebrospinal fluid, TB: Tuberculosis

CSF and blood. Ethics Committee approval was obtained from University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (2018/470; 2018-23-18). Since the study was retrospective, patient consent forms were not obtained.

The TDSI, MDSI, and a clinical prediction method supported the diagnosis (Tables 2,3). TDSI included five clinical and laboratory variables. The cases with scores ≤ 4 were considered as having TBM, whereas patients with scores > 4 were classified as bacterial meningitis, according to TDSI. MDSI included criteria for clinical and biochemical analysis of CSF, cerebral imaging, and evidence of extra-neural tuberculosis. Patients with scores of ≥ 12 were considered probable, whereas those with scores of 6-11 were evaluated as possible TBM, according to MDSI criteria. The cases with culture or PCR positivity were assessed as "definite TBM." The following four rules were accepted in the CPM for TBM (11): 1) Duration of symptoms before admission ≥ 5 days; 2) neurological stage II and III; 3) CSF/blood glucose ratio ≤ 0.5 ; 4) CSF protein level ≥ 100 mg/dL. This model accurately predicts 89.1% of cases with TBM, according to Hristea et al. (11). TBM staging was performed according to the British Medical Research Council criteria: Patients with mild and non-specific symptoms were considered as stage I, those with mild alteration of consciousness or with cranial nerve palsies were considered as stage II, and those with major neurological deficits or coma were considered as Stage III (13). All cases were treated with classical four-drug antituberculous therapy for 12 months and with additional

Table 2. Thwaites' diagnostic scoring index (9)

Parameters	DI
Age ≥36	2
Age <36	0
Blood WBC ≥15000	4
Blood WBC <15000	0
History of illness ≥6 days	(-5)
History of illness <6 days	0
CSF WBC ≥900 ise	3
CSF WBC <900 ise	0
CSF % neutrophils ≥75	4
CSF % neutrophils <75	0
Total score ≤4	TBM

CSF: Cerebrospinal fluid, DI: Diagnostic index, TBM: Tuberculous meningitis, WBC: White blood cell

dexamethasone therapy for 8 weeks in the presence of severe neurological deficits.

RESULTS

Patients over 18 years of age who presented the clinical picture of meningitis between 2015 and 2019 were assessed. TBM diagnosis was established based on clinical, CSF, radiological, and laboratory features. Viral, brucellar, and fungal etiologies were excluded by microscopic, serological, and molecular examinations of CSF and blood in all patients. Of the patients with TBM, 16 (80%) were male, whereas the ages of patients ranged between 18 and 72 years (range, 39.05±15.52 years). The most common symptoms were headache (90%), altered consciousness (75%), and neck rigidity (70%). Convulsion (25%), paresis/plegia (25%), and cranial nerve palsy (20%) were the other neurological findings detected in the TBM cases. Twelve (60%), five (25%), and three (15%) patients were assessed as stage II, stage III, and stage I, respectively. According to CSF analysis, 76% of patients had a CSF/blood glucose ratio below 0.3 and had a protein concentration above 100 mg/dL, whereas pleocytosis (>20/mm³) was detected in 90% of patients. PCR and culture positivity rates were 45% separately, whereas five patients showed both culture and PCR positivity, four patients had only PCR, and four patients had only culture positivity. The rate of concomitant pulmonary TB was 25%. Four (20%) patients died despite antituberculous therapy. All patients were assessed as TBM according to TDSI (100%), whereas five (25%) and the remaining 15 (75%) were considered as probable TBM and possible TBM according to MDSI. The scores were greater

Table 3. Marais' diagnostic scoring index (10)

Parameters	
Clinical criteria	Max score =6
Symptom duration more than 5 days	4
Systemic symptoms suggestive of TB (one or more of the following):	2
Weight loss, night sweats, persistent cough >2 weeks	
History of recent close contact with an individual with pulmonary TB or positive TST or IGRA	2
Focal neurological deficit (excluding cranial nerve palsies)	1
Cranial nerve palsy	1
Altered consciousness	1
CSF criteria	Max score =4
Clear appearance	1
Cells: 10-500 per µL	1
Lymphocytic predominance	1
CSF to plasma glucose ratio less than 50% or absolute CSF glucose less than 2.2 mmol/L	1
Cranial imaging criteria	Max score =6
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarction	1
Pre-contrast basal hyperdensity	2
Evidence of TB elsewhere	Max score =4
Chest radiograph suggestive of active TB: Signs of TB = 2; miliary TB = 4	2/4
CT/MRI/USG evidence for TB outside of CNS	2
AFB identified or <i>Mycobacterium tuberculosis</i> cultured from another source- i.e., sputum, lymph node, gastric washing, urine, blood culture	4
Positive commercial <i>M. tuberculosis</i> NAAT from extra-neural specimen	4
Patients with no cranial imaging	
Total score 6-9	Possible
Total score ≥ 10	Probable
Patients with cranial CT/MRI	
Total score 6-11	Possible
Total score ≥12	Probable

TB: Tuberculosis, CSF: Cerebrospinal fluid, CT/MRI/USG: Computed tomography/Magnetic resonance imaging/Ultrasonografi

than or equal to 6 in all the cases with TBM by CPM, 13 of which were scored as 9 points (65%).

Table 4 summarizes the cases with TBM and their outcomes according to TDSI, MDSI, and CPM criteria with additional findings supporting TBM.

DISCUSSION

Despite its decreased incidence in recent years, TB, particularly TBM, remains a leading cause of infection-related deaths worldwide. TBM is a severe and fatal disease that presents diagnostic and treatment difficulties. Antituberculous therapy prevents mortality and disability in less than half of the cases (14). A significant rate of morbidity and mortality related to TM results from the dysregulated immune response and delayed diagnosis and treatment (15,16). Therefore, early and accurate TBM

diagnosis remains of critical importance regarding disease eradication. Definitive diagnosis of TBM is based on isolation of Mycobacterium tuberculosis from CSF by staining and/or culture or PCR techniques. However, the identification of the agent by culture or PCR techniques is not possible in every patient.

In this study, PCR or culture positivity was determined in only 45% of patients with TBM. Heemskerck et al. (17) have compared sensitivity levels of MDSI and other laboratory methods, including conventional Ziehl-Neelsen (ZN) staining, modified ZN staining, culture test, and Xpert PCR analysis for TBM diagnosis. Compared with MDSI, the sensitivity levels of the techniques mentioned above were 33.9%, 34.5%, 31.8%, and 25.1%, respectively. In another study conducted by Feng et al. (18), the sensitivity levels of the conventional and modified ZN procedures were compared with TB culture. They were determined to be 3.3%

Table 4. The features of TBM cases according to three diagnostic indexes

Patients	TDSI					MDSI					CPM					
	Age ≥ 36	WBC ≥ 15.000	DSBA ≥ 6 days	Pleocytosis ≥900	CSF PNL ≥ 75%	Score	Clinical criteria	CSF criteria	Imaging criteria	EMTB	Score	DSBA ≥5 days	Stage II/III	CSF Glucose < 0.5	CSF protein >100 mg/dL	Score
1	0	0	-5	0	0	-5	5	4	0	0	9	3	0	3	1	7
2	0	0	-5	0	0	-5	5	4	0	0	9	3	2	3	0	8
3	0	0	-5	3	0	-2	5	4	0	0	9	3	2	3	1	9
-4	0	0	-5	0	0	-5	4	4	1	0	9	3	0	3	1	7
5	0	0	-5	0	0	-5	5	3	0	0	8	3	2	0	1	6
6	0	4	-5	0	0	-1	1	3	0	2	6	3	2	3	1	9
7	0	0	-5	0	0	-5	5	4	2	2	13	3	2	3	1	9
8	2	0	-5	0	0	-3	5	4	1	0	10	3	2	3	1	9
9	2	0	-5	0	0	-3	6	3	0	4	13	3	2	3	1	9
10	2	0	-5	0	0	-3	6	4	2	0	12	3	2	3	1	9
11	2	0	-5	0	0	-3	5	4	3	2	14	3	2	3	1	9
12	2	0	-5	0	0	-3	5	3	1	0	9	3	2	3	1	9
13	0	0	-5	0	0	-5	4	4	1	2	11	3	0	3	0	6
14	0	4	0	0	0	4	1	4	1	1	7	0	2	3	1	6
15	0	0	-5	0	0	-5	6	3	2	0	11	3	2	3	1	9
16	2	0	-5	0	0	-3	4	2	1	0	7	3	2	0	1	6
17	2	4	-5	0	0	1	5	4	2	0	11	3	2	3	1	9
18	0		-5	0	0	-5	6	4	2	2	14	3	2	3	1	9
19	2	0	-5	0	0	-3	5	4	1	0	10	3	2	3	1	9
20	2	0	-5	0	0	-3	2	4	0	0	6	3	2	3	1	9

TDSI: Thwaites' diagnostic scoring indexes, TBM: Tuberculous meningitis, WBC: White blood cell

and 82.9% versus 15.4%, respectively. Hooker et al. (19) have determined that the rates of culture positivity assessed by the Löwenstein-Jensen and BACTEC methods were 20.7% and 35.7% in patients with TBM, respectively. Hence, ZN staining and culture methods are known as the cornerstone and gold standards for diagnosing TBM. However, their positivity rates do not exceed 60%, even in the best-trained hands or best-equipped laboratories (18). According to a review by WHO in 2014, the nucleic acid test sensitivity rate was higher than that of culture methods for diagnosing TBM (80.5% versus 62.8%, respectively) (20). As a consequence, highly sensitive diagnostic tests for TBM remain elusive and impractical. Therefore, we need to improve affordable diagnostic methods or develop novel practical diagnostic approaches to achieve better TBM outcomes (21).

Clinical-based diagnostic approaches, such as TDSI, MDSI, and CPM, have been developed to eliminate these disadvantages, proven efficacy (11,22-26). Sunbul et al. (23) have applied this method in 126 patients with TBM and reported it as practical, sensitive, and specific. In contrast, Sulaiman et al. (25) evaluated the TDSI method in 391 patients with TBM and detected it in 99% of cases. They reported that the TDSI method showed weak positivity in differentiating TBM from subacute meningitis and chronic meningitis. They also reported high specificity (99.1%) despite having low sensitivity (1.2%), whereas 50% of the 162 cases diagnosed with TBM were evaluated as either possible TBM or probable TBM, according to the MDSI method. The same study determined that MDSI was statistically significant in discriminating TBM from fungal and viral meningitis leading to chronic meningitis, except in undiagnosed subacute meningitis cases. A study conducted in our country found that all the TBM cases were scored according to TDSI, and 70% of patients had maximum scores (26). Likewise, in another study from our country, Erdem et al. (24) have analyzed both TDSI and MDSI methods and demonstrated that the TDSI method was effective in the cases with brucellar and tuberculous meningitis. The cases with TBM had statistically higher scores than those with brucellar meningitis assessed by MDSI. They found that the number of the cases classified as "probable" among the cases with TBM and "possible" among the cases with brucellar meningitis were higher when assessed by MDSI. Considering these results, they have noted that some cases with brucellar meningitis may be incorrectly diagnosed as TBM, according to both scoring indexes. Therefore, it is recommended to consider neurobrucellosis regarding etiology, particularly in chronic meningitis cases diagnosed with TBM in endemic regions, according to TDSI and MDSI. In addition, all the cases in our study had scores of ≤ 4 by TDSI, whereas 75% and 25% of the 20 cases were classified

in the possible and probable TBM categories by MDSI, respectively. However, in all our study patients categorized as possible TBM by MDSI, neurobrucellosis was excluded by serological and cultural methods.

A CPM developed by another study conducted in Romania presented a rapid clinical diagnostic model with good sensitivity and specificity to differentiate TBM from viral meningitis (11). This CPM model was evaluated in another study. This is a rapid clinical scoring method with a sensitivity of 96.7% and specificity of 81.1% in differentiating cases with TBM from those with viral meningitis by scores of ≥ 6 (27). Similarly, the scores were greater than or equal to 6 in all TBM cases in our study by CPM, 13 of which scored 9 points (65%). According to the outcomes of our study, the TDSI, MDSI, and CPM assessment methods are easily applicable and useful techniques for rapid and accurate TBM diagnosis.

CONCLUSION

Considering that available microbiological diagnostic methods used for TBM are impractical, time-consuming, and have low sensitivity, clinicians should use rapid diagnostic methods, such as TDSI, MDSI, or CPM to avoid complications due to delayed TBM diagnosis. An evaluation of the role of these valuable methods in the rapid and accurate TBM diagnosis by comprehensive studies involving larger sample sizes is needed.

ETHICS

Ethics Committee Approval: Ethics Committee approval was obtained from University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (2018/470; 2018-23-18).

Informed Consent: Patient consent forms were not obtained.

Authorship Contributions

Concept: K.K.Y., Design: Ş.N.K., Data Collection or Processing: Ş.N.K., G.Ü., S.Ş., E.C.Ü., R.K., Analysis or Interpretation: Ş.N.K., Literature Search: Ş.N.K., Writing: Ş.N.K., G.Ü., S.Ş.

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