

# Thwaites' Diagnostic Scoring and the Prediction of Tuberculous Meningitis

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## Key Words

Thwaites' diagnostic score · Tuberculous meningitis · Viral meningitis

## Abstract

**Objective:** This study was conducted to investigate the applicability of Thwaites' diagnostic criteria in order to differentiate tuberculous from bacterial meningitis. **Material and Methods:** The study was done retrospectively in HIV-negative patients (n = 126) with meningitis. Of the 126 patients, 103 had bacterial meningitis and 23 patients had tuberculous meningitis. The diagnosis was confirmed microbiologically in 59 and 12 patients with bacterial and tuberculous meningitis, respectively. The prediction of tuberculous meningitis was determined by Thwaites' diagnostic scoring using parameters such as age, history of illness, white blood cell count, total cerebrospinal fluid (CSF) white cell count and the percent of neutrophils in CSF. The diagnostic value of the model was assessed by calculating the area under the receiver operating characteristic (ROC) curves. **Results:** The sensitivity and the specificity of Thwaites' diagnostic scoring were 95.6% (22/23) and 70.8% (73/103), respectively. In microbiologically proven cases the sensitivity and the specificity were 91.7% (11/12), 79.7% (57/59), respectively. The area under the ROC curve value for the diagnos-

tic scoring was 0.92. **Conclusions:** Thwaites' diagnostic score was found to be helpful in differential diagnosis of tuberculous meningitis, however, the usefulness of diagnostic scoring should be validated in large series especially in patients with viral meningitis and low CSF glucose levels.

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## Introduction

Although antibiotics were invented more than 50 years ago, meningitis still continues to be a significant cause of morbidity and mortality [1]. Therefore a rapid and accurate clinical evaluation is needed for the determination of risks due to meningitis [2]. Examination of cerebrospinal fluid (CSF) is an important diagnostic tool. Isolation of a microorganism from a CSF culture is essential in the diagnosis, however, practically, this is impossible for each case [3]. Mortality rates are approximately 25–30% in acquired bacterial meningitis despite appropriate antibiotic therapy [4]. Recent studies indicate that delay in the diagnosis and treatment is a main factor associated with higher mortality rates [5]. This study was conducted to evaluate the applicability of the diagnostic criteria of Thwaites et al. [5] in order to differentiate tuberculous from bacterial meningitis.

**Table 1.** Diagnostic criteria for tuberculous and bacterial meningitis

Tuberculous meningitis	Bacterial meningitis
<p><i>M. tuberculosis</i> isolated from CSF or Clinical meningitis with negative Gram and India ink stains, plus sterile bacterial and fungal culture, plus one or more of the following:</p> <ul style="list-style-type: none"> <li>Cranial CT scan consistent with tuberculous meningitis (hydrocephalus, edema, basal meningeal enhancement)</li> <li>Chest radiograph consistent with active pulmonary tuberculosis</li> <li>Good response to antituberculosis chemotherapy</li> </ul>	<p>Pathogenic bacteria isolated from CSF or Clinical meningitis with all of the following:</p> <ul style="list-style-type: none"> <li>Lymphocytes and neutrophils in CSF</li> <li>Low concentration of glucose in CSF (&lt;50% of that in blood)</li> <li>Sterile blood and CSF</li> <li>Full recovery (without antituberculosis chemotherapy) 3 months after admission</li> </ul>

**Table 2.** Weighted DI scores for dichotomized clinical variables used for diagnostic rule in admission

Parameters	DI
Age, years	
≥ 35	2
< 35	0
Blood WBC, 10 <sup>3</sup> /ml	
≥ 15,000	4
< 15,000	0
History of illness, days	
≥ 6	-5
< 6	0
CSF total WBC, 10 <sup>3</sup> /ml	
≥ 900	3
< 900	0
CSF % neutrophils	
≥ 75	4
< 75	0

## Subjects and Methods

This study was done retrospectively in adult patients admitted to the Department of Clinical Microbiology and Infectious Diseases, Ondokuz Mayıs University School of Medicine, Samsun, Turkey. A total of 126 HIV-negative patients were included. Of these, 103 were diagnosed with acute bacterial meningitis, and 23 with tuberculous meningitis. A lumbar puncture was performed routinely if not contraindicated. Characteristics like appearance, pressure, cell count per milliliter, protein and glucose levels were evaluated in CSF samples. CSF samples were stained with Gram, Ehrlich-Ziehl-Neelsen (EZN) and India ink stains. Samples were cultured on blood and chocolate agars and Löwenstein-Jensen medium. The diagnosis was confirmed microbiologically in 59 and 12 patients with bacterial and tuberculous meningitis, respectively. Differential diagnosis of tuberculous and bacterial meningitis was performed according to published criteria [5] (table 1).

The prediction of tuberculous meningitis was determined by Thwaites' diagnostic scoring using parameters such as age, history of illness, white blood cell count (WBC), total CSF white cell count and the percent of neutrophils in CSF. The diagnostic index for each of the five variables is shown in table 2 [5].

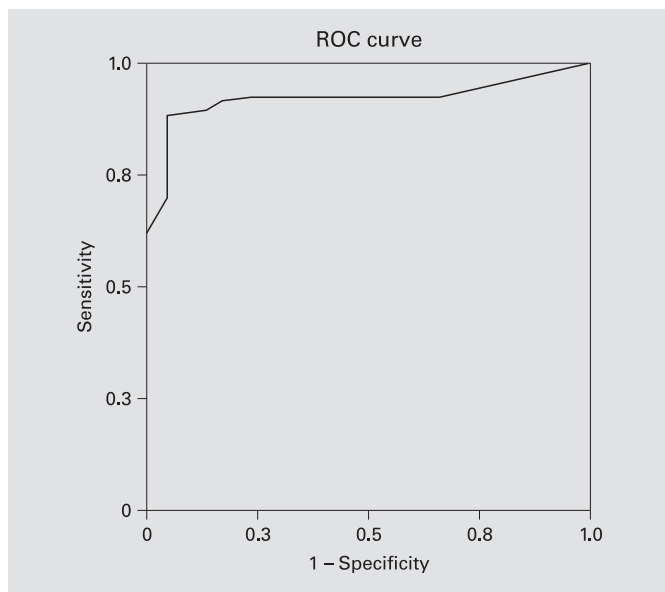
The total diagnostic index (DI) was calculated for each patient according to the formula: DI (age) + DI (blood WBC) + DI (history of illness) + DI (CSF white cell count) + DI (CSF % neutrophils). As Thwaites et al. [5] stated the three points close to the top left-hand corner of the curve correspond to cutoffs of 4, 3, or 2. Patients with DI scores ≤ 4 are classified as having tuberculous meningitis while those with DI scores > 4 are classified as having a version of bacterial meningitis.

Data were analyzed in SPSS for Windows version 10.0. The diagnostic value of the model was assessed by calculating the area under the receiver operating characteristic (ROC) curves.

## Results

The clinical and laboratory findings in the 126 patients at first admissions are shown in table 3. The sensitivity and the specificity of the Thwaites' diagnostic scoring for prediction of tuberculous meningitis in patients with clinical meningitis were 95.8% (23/24) and 71.6% (73/102), respectively. In microbiologically proven cases the sensitivity and the specificity were 91.7% (11/12), 79.7% (57/59), respectively.

*Mycobacterium tuberculosis* was isolated in 12 of 23 patients with tuberculous meningitis (52.1%) on Löwenstein-Jensen or Bactec media. In 103 patients with acute bacterial meningitis, responsible pathogens were identified in 43 (41.7%) (*Streptococcus pneumoniae* in 25, *Staphylococcus aureus* in 7, other *Streptococcus* spp in 5, *Neisseria meningitidis* in 4 and Gram-negative bacillus in 3). The optimum cutoff for the total DI was found with the use of an ROC curve. The area under the ROC curve value for the diagnostic scoring was 0.92 (fig. 1).



**Fig. 1.** ROC curve for prognostic index.

## Discussion

The detection of microorganisms in CSF samples by either microscopy or culture and the prediction of antibiotic susceptibility is very important in the management of meningitis. However, these studies are not accomplished routinely. Besides, culture applications are time-consuming in tuberculous meningitis and early diagnosis is hard to establish. Therefore, epidemiological data, pathogenesis and clinical findings must be assessed cautiously in the earlier course of the disease in patients with meningitis [6].

Our study revealed that neck stiffness is a common finding in meningitis, but it does not differentiate bacterial from tuberculous meningitis. On the other hand, tuberculous meningitis must be kept in mind particularly, if the disease course is longer than usual and the cranial nerve paralysis exists. Leukocytosis and an increase in neutrophil count in CSF indicate bacterial meningitis.

**Table 3.** Clinical and laboratory findings in patients with acute bacterial and tuberculous meningitis

Parameters	Tuberculous meningitis (n = 23)	Bacterial meningitis (n = 103)	p value
Age, years	42.9	41.0	0.5
Range	18–76	16–99	
Male/female	6/17	67/36	
Fever, °C	37.2 ± 0.2	37.4 ± 0.1	0.5
Headache	21 (91.3%)	84 (81.5%)	0.25
Duration of illness	15.04 ± 1.9	3.85 ± 0.3	p < 0.001
Neck stiffness	22 (95.6%)	93 (90.2%)	0.7
Consciousness			
Conscious	1 (4.3%)	28 (27.2%)	–
Sleepy	5 (17.5%)	17 (16.5%)	–
Somnolence	9 (39.1%)	43 (41.7%)	–
Coma	8 (34.8%)	15 (14.6%)	–
Hemiplegia	3 (13.0%)	12 (11.7%)	1.0
Cranial nerve palsies	9 (39.1%)	9 (8.7%)	0.001
WBC count, × 10 <sup>3</sup> /ml	10,572 ± 907.6	17,176 ± 896.8	p < 0.001
% neutrophils	78.3 ± 4.0	82.2 ± 1.0	0.5
Sedimentation rate, h	35.2 ± 5.0	61.1 ± 3.3	p < 0.001
Appearance of CSF			
Clear	15 (62.8%)	15 (14.7%)	–
Purulent	–	73 (71.6%)	–
Xanthochromic	8 (37.2%)	12 (11.8%)	–
CSF total WBC, × 10 <sup>3</sup> /ml	286 ± 44.2	5,449 ± 1,300	0.05
CSF % neutrophils	30.9 ± 5.9	81.9 ± 2.5	p < 0.001
CSF/blood glucose	0.24%	0.24%	0.5
CSF protein, g/dl	291 ± 45.6	373 ± 29.9	0.1
EZN/Gram stain positivity	3 (13.0%)	65 (65.7%)	–
Culture positivity	12 (52.1%)	43 (41.7%)	–

Mean ± standard error of the mean (SEM).

Laboratory parameters like total WBC in CSF, CSF/blood glucose ratio and protein level in CSF were found to show no significant differences in tuberculous and bacterial meningitis.

When the diagnostic score of Thwaites et al. [5] was applied to our patients with clinical meningitis, the sensitivity and specificity for prediction of tuberculous meningitis were 95.8 and 71.6%, respectively, but for patients with positive bacterial result confirmed by microscopy and/or culture evidence of bacteria in CSF the predictive values for sensitivity and specificity were 91.7 and 79.7%, respectively, thereby making Thwaites's diagnostic scor-

ing a useful technique for differential diagnosis of tuberculous meningitis, but we suggest that the usefulness of the diagnostic scoring should be validated in large series especially in patients with viral meningitis and low CSF glucose levels.

### Conclusion

The results show that the Thwaites' diagnostic score is helpful in differentiating tuberculous from bacterial meningitis.

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