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Validation of the Online Collaborative Ocular Tuberculosis Study Calculator for Tubercular Uveitis

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IMPORTANCE This was the first study, to the authors' knowledge, to statistically evaluate the predictive accuracy of Collaborative Ocular Tuberculosis Study (COTS) calculator in guiding initiation of antitubercular therapy (ATT) in patients with clinically suspicious tubercular uveitis (TBU) in an international cohort.

OBJECTIVE To evaluate the accuracy of a score of 4 or greater on the online COTS calculator in recommending ATT initiation.

DESIGN, SETTING, AND PARTICIPANTS This study was an evaluation of a diagnostic test or technology. Data input required for the COTS calculator were extracted from the COTS-1 study dataset, which comprised retrospective, observational records of patients with TBU who were monitored for 12 months after treatment. Patients were recruited from international ophthalmic centers. In the absence of a traditional criterion standard, the 12-month treatment response to ATT was used to classify patients as disease positive or negative. The accuracy of clinicians at the ATT decision-making stage in the COTS-1 study was set against COTS calculator scores of 4 or greater. Diagnostic accuracy metrics, including sensitivity, specificity, positive predictive value (PPV), precision, recall, and F1 score, were computed. Data collected from January 2004 to December 2014 were analyzed.

EXPOSURES COTS calculator to guide initiation of ATT in patients with TBU.

MAIN OUTCOMES AND MEASURES Comparison of accuracy between clinician judgment and the COTS calculator, analyzed at varying scores and further stratified by tuberculosis endemicity.

RESULTS Of the 492 participants (mean [SD] age, 42.3 [19.0] years; 233 male [47.3%]), application of the COTS calculator identified 225 (45.7%) with high or very high probability to start ATT (score = 4 or 5) and 111 (22.5%) with very high probability alone (score = 5). COTS-5 exhibited the highest specificity (88.7%; 95% CI, 81.4%-93.8%) compared with clinician judgment (29.6%; 95% CI, 21.4%-38.8%), and clinician judgment led in sensitivity (95.5%; 95% CI, 92.9%-97.4%) compared with COTS-5 (26%; 95% CI, 21.6%-30.7%). COTS-4 and COTS-5 balanced specificity (64.3%; 95% CI, 54.9%-73.1%) and sensitivity (48.8%; 95% CI, 43.7%-54%). PPV and sensitivity were consistently higher in the endemic group for all 3 tests.

CONCLUSIONS AND RELEVANCE Results of this diagnostic study suggest that the COTS calculator (score ≥4) was more specific than clinician judgment for ATT initiation. Although clinician judgment is a good first step to identify all potential true positives (with high sensitivity), a second consultation with COTS-5 (with high PPV) may lead to less false positives. This tool, apt for high-prevalence, low-resource settings, recommends ATT more selectively for genuine TBU cases. Large prospective studies are essential to explore potential improvements in the calculator's sensitivity.

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Supplemental content

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Tuberculosis is an airborne disease caused by *Mycobacterium tuberculosis* with a global mortality of 1.6 million people in 2021.[1] Tubercular uveitis (TBU) refers to *M tuberculosis* infection of the eye or *M tuberculosis* infection elsewhere that incites a remote, sterile inflammation in the eye, most commonly presenting as choroidal involvement and retinal vasculitis.[2] Although tuberculosis represents less than 0.5% of uveitis cases in some regions,[3,4] it is estimated to be a leading cause of 22.9% to 48.0% of infectious uveitis cases in endemic countries such as India and Indonesia.[5,6] Globally, it accounts for 4% of all uveitis cases.[7] However, the paucibacillary nature of *M tuberculosis* results in low sensitivities of the acid-fast smear and polymerase chain reaction test, as the low replication rate and few bacteria present in ocular fluid often makes it difficult to establish conclusive presence of *M tuberculosis* in aqueous humor and vitreous humor samples.[8-10] Moreover, collection of ocular fluids are also invasive and not frequently performed.[11] In addition, Lowenstein-Jensen cultures require 6 weeks to process, delaying treatment decisions and leading to negative repercussions. Hence, epidemiological data on the true prevalence of TBU in various parts of the world remain ambiguous as the diagnosis of TBU remains mostly presumptive.[12,13]

The bacillus can infect any ocular tissue, resulting in a myriad of phenotypes, including anterior uveitis with iris nodules, serpiginouslike tubercular choroiditis, choroidal nodule (tuberculoma), occlusive retinal vasculitis, and multifocal choroiditis.[14] Together with a histologically or microbiologically confirmed infection, or a positive interferon gamma release assay (IGRA), or a positive tuberculin skin test (TST), a presumptive diagnosis of TBU can be achieved.[14] Due to the numerous ocular phenotypes, invasive histopathological diagnosis, and limited sensitivity (37.7%-73.3%) of polymerase chain reaction tests, presumptive diagnosis of TBU leads to treatment delays that can result in sight-threatening complications, such as glaucoma, cataract, and cystoid macular edema.[10,15] The treatment process of TBU is often arduous, involving a 4-drug antitubercular therapy (ATT) regimen for a minimum of 6 months, sometimes with no discernible improvement in visual acuity possibly due to a recurrent autoimmune inflammatory response even when *M tuberculosis* is undetectable in the eye.[16]

The Collaborative Ocular Tuberculosis Study (COTS) group developed a novel, online open access and cost-effective tool designed to guide less experienced clinicians in the decision to initiate ATT in patients suspected of having TBU. It is not designed to guide physicians to withhold ATT. The COTS calculator was developed using data from 486 clinical scenario-based questions. These questions were evaluated by 81 uveitis experts, and their assessments were then consolidated through a systematic 2-step Delphi method. This process led to the development of an algorithm, which serves as the foundation of the COTS calculator.[17] This study aims to statistically evaluate the predictive ability, and thus potential clinical applicability, of COTS calculator recommendations to initiate ATT based on the score of 4 and 5 in an international cohort.

Key Points

Question What is the predictive accuracy of Collaborative Ocular Tuberculosis Study (COTS) calculator score 4 (COTS-4) and 5 (COTS-5) in guiding initiation of antitubercular therapy in patients with clinically suspicious tubercular uveitis?

Findings In this diagnostic accuracy study including 492 participants, COTS-5 exhibited the highest specificity compared with clinician judgment, and clinician judgment led in sensitivity compared with COTS-5. COTS-4 and COTS-5 had balanced specificity and sensitivity.

Meaning Results suggest that although clinician judgment is a good first step to identify all potential true positives (with high sensitivity), a second consultation with COTS-5 (with high positive predictive value) may lead to fewer false positives.

Methods

Study Design

This study was approved by the ethics committee of the Postgraduate Institute of Medical Education and Research and was conducted in accordance with the principles outlined in the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study. This study followed the Standards for Reporting of Diagnostic Accuracy (STARD) reporting guidelines.

Setting and Participants

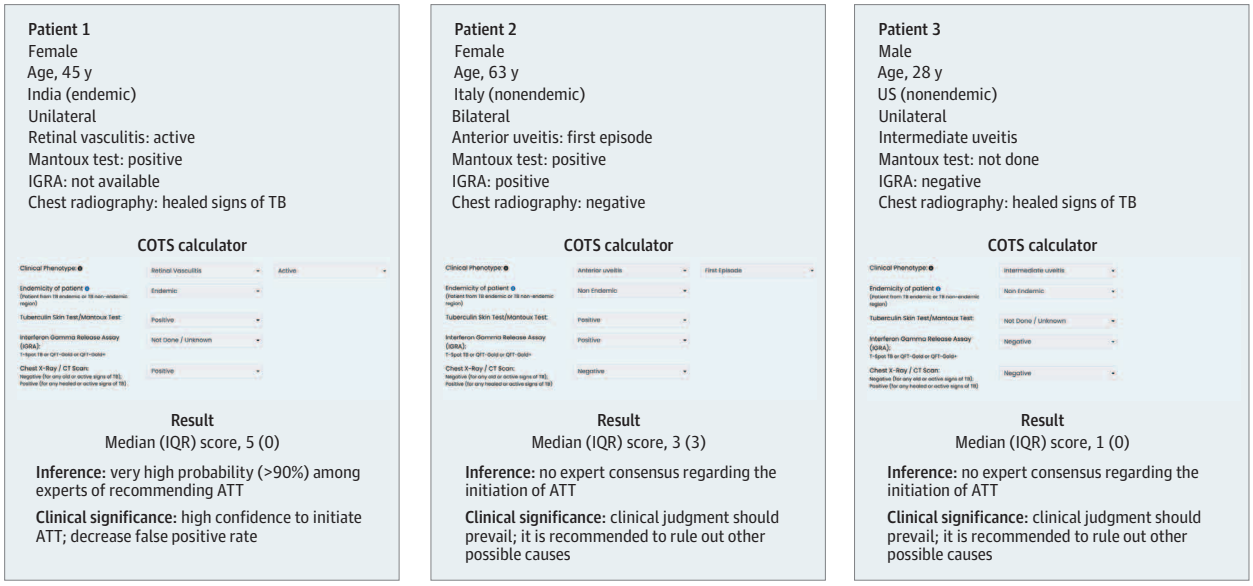
Of the 962 patients with suspected TBU included in COTS-1 from 25 international ophthalmology centers from January 2004 to December 2014, those who had follow-up data at 12 months and the critical information required for defining the patient's disease status (ie, whether ATT was completed or not) and for the COTS calculator input (eye involved, endemicity, disease phenotype, recurrence of uveitis, Mantoux test, IGRA and chest radiography [CXR] results) were included.[2,18,19] For patients with bilateral uveitis, only the clinical phenotype of the right eye was included. Additional demographic factors, such as gender and race, and clinical factors, such as laterality of disease and treatment outcomes, also were extracted.

Patients self-identified with the following races and ethnicities: African, Asian, European or White, Hispanic, Middle Eastern, Oceania, and unknown. Race and ethnicity data were included in the analysis to provide a comprehensive demographic profile of the cohort. Given the international nature of the cohort, reporting these data allows for a clearer understanding of the population's distribution, even though no specific analyses were performed based on these variables.

Tool Implementation and Interpretation

The COTS calculator uses 5 clinical parameters to generate a score from 1 to 5. The first parameter is the clinical phenotype (anterior, intermediate, panuveitis, retinal vasculitis or choroiditis), including indication of active or inactive disease. The second parameter is country (ie, tuberculosis

Figure 1. Practical Application of the Collaborative Ocular Tuberculosis Study (COTS) Calculator Across 3 Different Scenarios



ATT indicates antitubercular therapy; CT, computed tomography; IGRA, interferon gamma release assay; TB, tuberculosis.

endemic or nonendemic in the region). The next 2 parameters are the patient's results on the TST and/or IGRA. The final parameter is the presence or absence of active or healed tuberculosis infection from a CXR or a chest computed tomography scan.[20] A score of 5 indicates an 81% to 100% probability at which greater than 50% of experts would initiate ATT, and a score of 1 suggests a 0% to 20% probability at which greater than 50% of experts would initiate ATT (**Figure 1**). The COTS calculator aims to assist less experienced clinicians regarding when to begin ATT in patients who are likely to have TBU (eAppendix in Supplement 1). The detailed history and methodology for obtaining consensus among global uveitis experts for the COTS Consensus has been described previously.[20,21]

Key Definitions

All patients who completed ATT were treated with a rifampicin, isoniazid, pyrazinamide, and ethambutol (RIPE) regimen for 6 months. Those who did not complete ATT either did not initiate the 4-drug regimen at all or prematurely terminated the regimen before 6 months. Treatment failure was defined as a persistence or recurrence of inflammation within 6 months of completing ATT (or other treatment), the inability to taper oral corticosteroids to less than 10 mg per day or topical corticosteroid eye drops to less than 2 drops daily, and/or recalcitrant inflammation necessitating corticosteroid-sparing immunosuppressive therapy.[22]

Reference or Comparator Definition

Because there is no criterion standard, we used the treatment response to ATT (success or failure) at 12-month follow-up to determine if the participant was positive or negative for tuberculosis disease. This information is further explained in **Table 1**.

Statistical Analysis

Three diagnostic tests were considered for comparison. Test 1 was the clinician judgment at the time of treatment decision in the COTS-1 study. Test 2 was the use of a COTS calculator score of 4 and 5 (COTS-4 and COTS-5) regardless of the IQR to guide ATT initiation, and test 3 was score 5 (COTS-5) alone as the threshold to recommend ATT treatment. Later on, a 2 × 2 table was constructed to show the potential outcomes of each diagnostic test compared with the best available reference or criterion standard revealing outcome status (disease positive or disease negative). The table will always show 1 predictor variable (diagnostic test result) and an outcome (presence of absence of disease).[23] Sensitivity, specificity, positive predictive value (PPV), precision, recall, and F1 score were computed for each test. In addition, a subgroup analysis comparing the diagnostic accuracy of the 3 tests in nonendemic and endemic groups was performed. Statistical analyses were done using R, version 4.2.3 (R Project for Statistical Computing). Data collected from January 2004 to December 2014 were analyzed.

Results

Of the 962 patients included in the COTS-1 study, 492 (mean [SD] age, 42.3 [19.0] years; 227 female [46.1%]; 233 male [47.3%]; 32 patients [6.5%] were missing information on gender) fulfilled the inclusion criteria. Patients self-identified with the following races and ethnicities: 28 African (5.7%), 323 Asian (65.7%), 75 European or White (15.2%), 3 Hispanic (0.6%), 40 Middle Eastern (8.1%), 1 Oceania (0.2%), and 22 unknown (4.5%). Of 492 patients, 51 (10.4%) did not receive ATT (**Table 2**). Retrospective application of the COTS calculator identified 225 patients (45.7%)

Table 1. Reference or Criterion Standard Defining Presence or Absence of the Outcome for 4 Types of Patients in this Study[a]

Patient	Was ATT completed?	Is there treatment failure?	Disease status	Patients, No.	Implication
A	Yes	Yes	Negative	81	Patient has experienced ATT treatment failure. We can confidently say he/she does not have TBU.
B	Yes	No	Positive	360	Patient has improved after ATT treatment. We can confidently say he has TBU.
C	No	Yes	Positive	17	ATT was not completed, and patient has worsened. Perhaps the patient would have benefitted from ATT. He/she is assumed to be conditionally positive because he/she may have benefitted from an earlier or full course of ATT.
D	No	No	Negative	34	ATT was not completed, and patient has improved (assuming that treatment for other disease is given instead). He/she is assumed to be conditionally negative.

Abbreviations: ATT, antitubercular therapy; TBU, tubercular uveitis.

[a] Table 1 demonstrates the 4 types of patients and how they have been allocated to be disease-positive or disease-negative status. Disease-positive status refers to patients who benefit from ATT, whereas disease-negative status refers to those who do not benefit from the treatment. Patients were considered disease negative either if the patient was suspected to have TBU, received ATT for minimally 6 months and experienced treatment failure from ATT, or if the patient was not suspected to have TBU in the first place, ATT was withheld while treatment for other ocular inflammatory diseases were given instead, and there is improvement of ocular inflammation suggesting there is no treatment failure from the lack of ATT. Moreover, patients with suspected TBU and those who received ATT without treatment failure from ATT were defined as disease positive, including those who were not initially given ATT because the clinical suspicion of TBU was low, yet the ocular inflammation worsened according to the definition of treatment failure.

with high or very high probability to start ATT (score = 4 or 5) and 111 (22.5%) with very high probability alone (score = 5).

Comparing COTS-4 and COTS-5 (Test 2) With Clinician Judgment (Test 1)

COTS-4 and COTS-5 (test 2) performed with better specificity (64.3%; 95% CI, 54.9%-73.1%) than clinician judgment (test 1; specificity = 29.6%; 95% CI, 21.4%-38.8%). Similarly, COTS-4 and COTS-5 (test 2) performed with poorer sensitivity (48.8%; 95% CI, 43.7%-54.0%) than clinician judgment (test 1; sensitivity = 95.5%; 95% CI, 92.9%-97.4%). In terms of PPV, COTS-4 and COTS-5 (test 2) and clinician judgment (test 1) had similar results (**Table 3**).

Comparing COTS-5 (Test 3) With COTS-4 and COTS-5 (Test 2) and Clinician Judgment (Test 1)

COTS-5 (Test 3) performed with better specificity (88.7%; 95% CI, 81.4%-93.8%) than clinician judgment (test 1; specificity = 29.6%; 95% CI, 21.4%-38.8%). Similarly, COTS-5 (test 3) performed with poorer sensitivity (26%; 95% CI, 21.6%-30.7%) than clinician judgment (test 1; sensitivity = 95.5%; 95% CI, 92.9%-97.4%). In terms of PPV, COTS-5 (test 3) had slightly higher results than clinician judgment (test 1). Moreover, COTS-5 (test 3) performed with better specificity (88.7%; 95% CI, 81.4%-93.8%) than COTS-4 and COTS-5 (test 2; specificity = 64.3%; 95% CI, 54.9%-73.1%). However, COTS-5 (test 3) performed with poorer sensitivity (26%) than COTS-4 and COTS-5 (test 2; sensitivity = 48.8%; 95% CI, 43.7%-54%). In terms of PPV, COTS-5 (test 3) outperformed COTS-4 and COTS-5 (test 2) by 6.5%, which is a meaningful difference as shown by the CI. Therefore, COTS-5 (test 3) had the highest specificity whereas clinician judgment (test 1) had the highest sensitivity. COTS-4 and COTS-5 (test 2) provided a balance between specificity that was better than test 1 and sensitivity that was better than test 3. PPV was best with COTS-5 (Table 3).

Comparative Performance of Diagnostic Tests: Precision, Recall, and F1 Score Analysis

Clinician judgment (test 1) exhibited a precision of 0.82, a recall of 0.95, and an F1 score of 0.88, indicating a balance between precision and recall. The COTS-4 and COTS-5 (test 2) achieved the same precision of 0.82 but had a lower recall of 0.49, resulting in an F1 score of 0.61, suggesting a reduction in overall performance due to the lower recall. The COTS-5 (test 3) showed the highest precision at 0.88; however, it had a significantly lower recall of 0.26, leading to an F1 score of 0.40. These results highlight differences in the tests' abilities to correctly identify positive cases. Despite its lower recall, COTS-5 could be particularly useful in scenarios where minimizing false positives is crucial due to its high precision. **Figure 2** shows the confusion matrix for each test.

Subgroup Analysis: Endemic Group Compared With Nonendemic Group

Sensitivity and PPV were consistently higher in the endemic group compared with the nonendemic group across all 3 tests. A higher PPV is expected in endemic populations as per the nature of statistics. For test 2, specificity of the nonendemic group (79.4%) was higher than that of the endemic group (specificity 58.0%). For test 1 and 3, specificity of the endemic was higher than that in the nonendemic group. Regardless of endemicity, the PPV was highest with COTS-5, and lowest with clinician judgment (Table 3).

Discussion

In this diagnostic study, COTS-5 had the highest specificity, whereas clinician judgment had the highest sensitivity. Combined COTS-4 and COTS-5 provided a potentially optimal trade-off as it picked up fewer false negatives than COTS-5 alone (with better sensitivity) and fewer false positives than clini-

Table 2. Demographic Details of Patients Included

Demography	No. (%)
Gender[a]	
Male	233 (47.3)
Female	227 (46.1)
Unknown	32 (6.6)
Ethnicity	
African	28 (5.7)
Asian	323 (65.7)
European or White	75 (15.2)
Hispanic	3 (0.6)
Middle Eastern	40 (8.1)
Oceania	1 (0.2)
Unknown	22 (4.5)
Eye involved	
Bilateral	347 (70.5)
Left eye	140 (28.5)
Right eye	5 (1.0)
Disease phenotype	
Anterior uveitis, recurrent episode	80 (16.3)
Choroiditis, multifocal	77 (15.7)
Choroiditis, serpiginoid	69 (14.0)
Choroiditis, tuberculoma	18 (3.7)
Intermediate	68 (13.8)
Panuveitis	73 (14.8)
Retinal vasculitis, active	107 (21.7)
Mantoux	
Positive	310 (63.0)
Not done/unknown	139 (28.3)
Negative	43 (8.7)
IGRA	
Positive	37 (7.5)
Not done/unknown	450 (91.5)
Negative	5 (1.0)
CXR	
Positive	90 (18.3)
Not done/unknown	110 (22.4)
Negative	292 (59.3)
Endemicity	
Endemic	375 (76.2)
Nonendemic	117 (23.8)
Was ATT completed?	
Yes	441 (89.6)
No	51 (10.4)
Was there treatment failure?	
Yes	98 (19.9)
No	394 (80.1)
Status	
Disease positive	377 (76.6)
Disease negative	115 (23.4)
COTS calculator	
Score 5	111 (22.6)
Score 4	114 (23.2)
Score 3	143 (29.1)
Score 2	69 (14.0)
Score 1	55 (11.2)

Abbreviations: ATT, antitubercular treatment; CXR, chest radiography; IGRA, interferon gamma release assay.

[a] Gender was extracted from clinical records.

cian judgment (with better specificity). Clinician judgment tended to pick up all the positive cases, given a high sensitivity of 95.5%. However, clinician judgment had lower PPV than COTS-5, which meant that clinician judgment had more false positives (Figure 2).

Previous COTS Consensus guidelines defined consensus to initiate ATT at a median score of 5, which represents more than half of all included experts choosing to initiate ATT 81% to 100% of the time in that particular clinical scenario. A median score of 4 indicates lower confidence in initiating ATT, which represents more than half of all experts choosing to initiate ATT 61% to 80% of the time, and therefore, clinical scenarios with a median score 4 were shortlisted for further detailed discussion in the COTS Consensus meetings to clarify reasons for differences in opinion. Based on current literature, it is also stated that median scores of 4, 3, 2, and 1 are not part of the COTS Consensus guidelines and do not imply that ATT should not be initiated.[20] The idea of a threshold to initiate ATT confidently based on COTS median score 5 in the current literature is mainly consensus derived. Consensus, although backed by experience and evidence, underwent statistical validation through this retrospective diagnostic accuracy study.

Here, we evaluated the crucial clinical question as to what extent a positive or negative diagnostic test indicated a person with the disease in question: TBU.[24] Sensitivity and specificity are indices for evaluating the validity of a binary diagnostic test with a known reference or criterion standard. In the case of TBU, an existing criterion-standard diagnostic method with close to 100% specificity and 100% sensitivity that is readily available under reasonable conditions is not plausible.[20,25] What is the trade-off with a high-sensitivity yet low-specificity test? There is both a high true-positive and false-positive rate. ATT, the first-line 4-drug treatment regimen (RIPE) given over a minimum of 6 months for tuberculosis, has well-established adverse effects.[26,27] The incidence of ATT-induced hepatotoxicity, which includes potentially fatal adverse reactions, ranges between 2% and 28%.[28] Mortality rate among patients with ATT-associated acute liver failure is high at 67.1%, and only 32.9% recovered with medical treatment. In a single-center analysis[29] reviewing 1223 patients, 5.7% of cases of acute liver failure were ATT associated, with a significant proportion of patients treated empirically with ATT. Risk factors include preexisting liver disease, advanced-age malnutrition, HIV positivity, female sex, and slow acetylator status.[28,29] Moreover, a meta-analysis[30] showed that treatment interruption was a significant risk factor for development of multidrug resistant (MDR) tuberculosis. Patients who had previously treated tuberculosis or who experience adverse drug reactions are more likely to encounter tuberculosis treatment interruption.[31] Therefore, patients presenting ambiguously for TBU should be carefully selected to complete a full course of first-line tuberculosis treatment, as noncompliance with the tuberculosis treatment regimen can predispose the patient to developing MDR tuberculosis. MDR tuberculosis poses a public health risk and second-line tuberculosis treatment targeted at MDR tuberculosis has even more adverse effects.[32,33] With these risks in mind, clinicians should

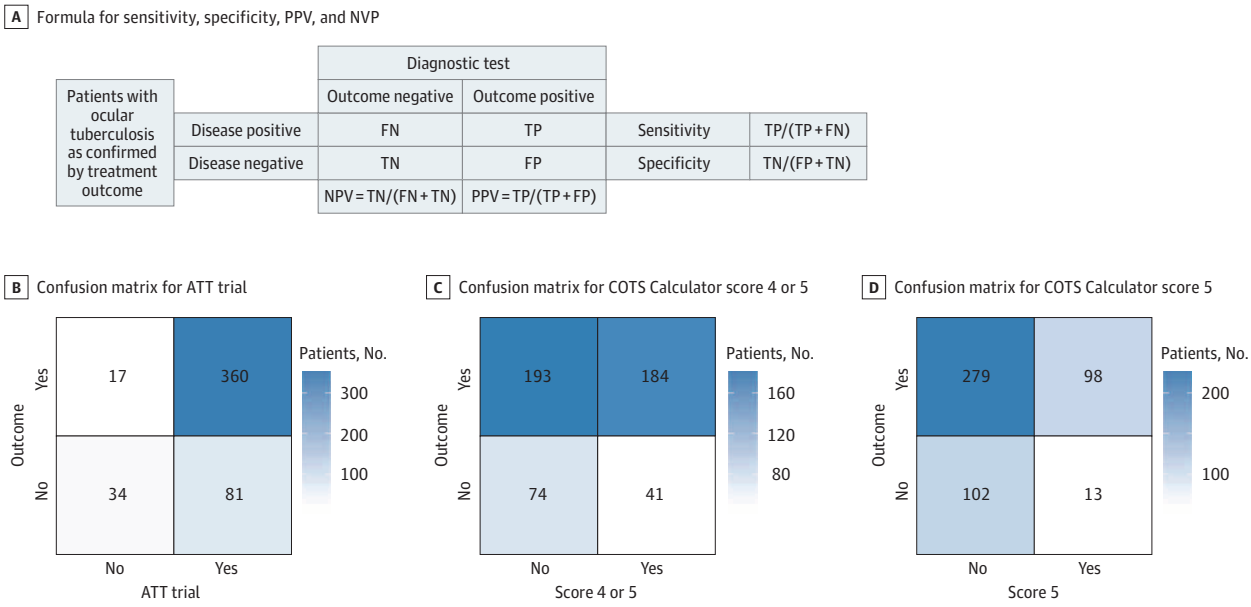
Table 3. Predictive Values of Test 1, 2, and 3 Stratified by Endemic and Nonendemic Subgroups[a]

Test	Endemicity	Sensitivity, %	Overall sensitivity, % (95% CI)	Specificity, %	Overall specificity, % (95% CI)	PPV, %	Overall PPV, % (95% CI)	Precision	Recall	F1 score
Clinician judgment (test 1)	Endemic	95.9	95.5 (92.9-97.4)	30.9	29.6 (21.4-38.8)	83.4	81.6 (79.8-83.4)	0.82	0.95	0.88
	Nonendemic	94.0		26.5		75.7				
COTS-4 and COTS-5 (test 2)	Endemic	54.4	48.8 (43.7-54.0)	58.0	64.3 (54.9-73.1)	82.5	81.8 (77.5-85.4)	0.82	0.49	0.61
	Nonendemic	28.9		79.4		77.4				
COTS-5 (test 3)	Endemic	26.5	26.0 (21.6-30.7)	90.1	88.7 (81.4-93.8)	90.7	88.3 (81.5-92.8)	0.88	0.26	0.40
	Nonendemic	24.1		85.3		80.0				

Abbreviation: PPV, positive predictive value.

[a] Overall sensitivity and specificity represent the values obtained when combining both groups (endemic and nonendemic).

Figure 2. Potential Outcomes of a Diagnostic Test and Confusion Matrix for Each Test



A, Formula for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). B, Confusion matrix for the antitubercular therapy (ATT) trial. C, Confusion matrix for Collaborative Ocular Tuberculosis Study (COTS) calculator score 4 or 5. D, Confusion matrix for COTS calculator score 5. FN indicates false negative; FP, false positive; NVP, negative predictive value; TN, true negative; TP, true positive.

be careful to empirically treat every patient who has suspected TBU with ATT, especially those with risk factors. Clinician judgment was shown to have high sensitivity yet low specificity, posing a risk of unnecessary ATT use in patients with false-positive disease.

PPV was highest with COTS-5 and lowest with clinician judgment, with both sensitivity and PPV consistently higher in endemic groups across all tests. There was no clear correlation between endemicity and specificity. PPV indicates the likelihood that a positive test result confirms the disease, based on Bayes theorem, which relates to the accuracy of the test and disease prevalence.[34] The higher PPV in endemic populations aligns with higher tuberculosis prevalence. The COTS calculator should not be used for unlikely TBU cases, as PPV depends on pretest probability. The high PPV with COTS-5 in both endemic and nonendemic settings demonstrated its efficacy in recommending ATT for clinically suspected TBU cases, guiding clinicians to make confident treatment decisions.

Different thresholds generated varying levels of sensitivity and specificity according to the endemicity setting (Table 3). In regions with a high tuberculosis burden, the pretest probability of a positive result is higher, and there is a greater need for the test to prioritize specificity. This is crucial to prevent the overburdening of health care systems with false positives, which can lead to unnecessary treatments, potential drug resistance, and increased health care costs—issues that are especially problematic in high-prevalence, resource-constrained settings where misdiagnosis may lead to inappropriate use of ATT.[35-37] Conversely, in countries where the tuberculosis prevalence is low, the test could be calibrated to be more sensitive, enhancing its ability to detect true cases of tuberculosis and thereby preventing missed diagnoses in patients with less obvious symptoms to avoid visual morbidity. Therefore, use of the COTS calculator might need to be adapted according to the local tuberculosis prevalence to optimize its use and

ensure that it meets the public health needs specific to the region.

Despite its utility to make informed decisions even in the absence of extensive diagnostic resources, the calculator should not be used in isolation. Although this approach increases specificity, it also involves a trade-off with reduced sensitivity. A score below 4 on the COTS calculator does not unequivocally rule out the need for ATT, due to the absence of a consensus on handling such cases,[20] as some cases may still require treatment due to various factors such as local practice variations, the initiation of immunosuppression, systemic status, and local guidelines. Special situations, including diagnostic dilemmas and the risk of infection with resistant organisms, also necessitate a more nuanced approach beyond the calculator's scope. Therefore, although the calculator aids in decision-making by reducing unnecessary ATT administration, the final judgment should accommodate individual patient circumstances and not rely solely on the calculator. Clinician judgment should serve as a vital initial step to identify potential true positives with high sensitivity, and consulting the COTS calculator subsequently could lead to fewer false positives and a more judicious use of ATT.

Limitations

The retrospective nature of the study led to some limitations. Determining the true disease/outcome status in TBU was challenging due to the lack of a criterion standard test and the complex nature of TBU, which involves both infectious and inflammatory processes. Indirect autoimmune reactions either induced by tuberculosis and its antigens, or stemming from other systemic causes, added to the complexity of the disease state.[9] Some patients could experience paradoxical worsening of inflammation on initiation of ATT, and corticosteroids were often used, complicating retrospective outcome status assessment. Moreover, among the 492 patients, 51 did not receive ATT: 17 in group C and 34 in group D. Group C patients, who showed no clinical improvement without ATT, had varied IGRA results, complicating their conditional-positive status. Recording their ocular outcomes, anti-inflammatory therapy use, subsequent ATT, or tuberculosis strain (including if MDR was present) would have enhanced the study. Group D patients, who improved without ATT, were likely condition negative (Table 1). As for group A and B patients who did receive ATT, treatment failure in group A could be possibly secondary to poor compliance or poor tolerance to ATT regimen, or due to an MDR strain. Group B patients whose outcomes improve with ATT may be confounded by presence of concurrent anti-inflammatory therapy use (Table 1).

Additionally, this study included patients from both endemic and nonendemic regions, highlighting the need for multinational collaboration. However, variations in follow-up and treatment practices (use of corticosteroids and immunosuppressive agents) across centers could have added bias. Another limitation might be that of case selection bias. The COTS-1 database comprises patients with an already high index of suspicion of having TBU, which could lead the calculator to favor a higher score supporting initiation of ATT. Future prospective studies should focus on the predictive accuracy of the COTS calculator across larger, more heterogenous databases across different regions. This approach could increase sample sizes, reduce type I errors,[38] and ensure genomic or microbiological confirmation for all patients.

Conclusions

This diagnostic study found that using a COTS calculator score cutoff of 4 or greater was associated with improved specificity for recommending the initiation of ATT compared with relying on clinician judgment alone. This tool, suitable for low-resource settings, could provide guidance to recommend initiation of ATT more selectively than clinician judgment to patients who have TBU . The ideal use of this tool occurs when clinician judgment serves as a crucial initial step to identify potential true positives with high sensitivity, followed by subsequent consultation with the COTS calculator, which can lead to fewer false positives and a more judicious use of ATT.

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Invited Commentary

Tuberculosis Uveitis—Consumed by Uncertainty

Nicholas A. V. Beare, MB ChB, MD; Geraint Davies, BM, PhD

Uveitis caused by *Mycobacteria tuberculosis* remains difficult to diagnose and difficult to treat.[1] Even the recognized tuberculosis uveitis (TBU) phenotypes (choroidal granuloma, retinal vasculitis, serpiginous chorioretinopathy, and granulomatous chronic anterior uveitis) are diverse and not specific to tuberculosis, but tuberculosis can present with almost any uveitic phenotype. The tuberculin skin test (TST) and interferon-γ reactivity assay (IGRA) tests for tuberculosis infection only indicate exposure to tuberculosis and currently provide no information on whether the tuberculosis is active or the cause of the uveitis. If active tuberculosis is known or discovered in the lungs or another site that is amenable to biopsy or culture, this is extremely helpful but is often not present.

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Part of the reason for these complexities is that, in addition to causing a direct infection in the eye, tuberculosis can also cause an immune-mediated uveitis by inciting inflammation through nonviable components in the eye or even from a remote infection elsewhere in the body.[2] Experimental animal uveitis requires the use of subcutaneously injected adjuvants, the most common of which is heat-killed *M tuberculosis*. Evidence for this phenomenon in humans includes the presence of autoreactive T cells in the vitreous of patients with TBU.[3] This accounts for why polymerase chain reaction testing for tuberculosis DNA in aqueous and vitreous samples has low sensitivity.[2] The sensitivity of polymerase chain reaction testing rises in phenotypes involving mycobacteremia and direct ocular infection.[4]

Getting the correct diagnosis is important because treatment for tuberculosis, including TBU, is prolonged and potentially toxic, including toxic effects that can affect vision. Even a full course of antituberculosis treatment (ATT) may not give TBU a prolonged remission, again, probably because of perpetuation of an immune-mediated uveitis. The autoreactive T cells in TBU are resistant to activation-induced cell death.[3]

The prevalence of tuberculosis and TBU varies widely across regions and communities. This affects the predictive value of a positive TST or IGRA test result. In communities of high prevalence (tuberculosis endemic), such as in South Asia or Africa, the positive predictive value of the IGRA test is higher than in low-prevalence settings (nonendemic). However, one must remember that the IGRA tests only inform about exposure to tuberculosis; therefore, there is also a greater chance that a positive IGRA test result is incidental to a uveitis episode. In lower-prevalence settings, the positive predictive value is less, but the likelihood of a positive exposure test being relevant to the uveitis is higher.

The Collaborative Ocular Tuberculosis Study (COTS) aims to unravel some of these complexities of TBU and help clinicians in their decision-making. COTS has collected retrospective data on patients with TBU from 25 participating centers across the world and led consensus-building exercises in diagnosis and treatment. COTS has used a 2-stage modified Delphi process to establish a consensus on initiation of treatment in different clinical scenarios and used this to develop an algorithm (COTS calculator).[5] The algorithm uses patient data (uveitis phenotype, activity, tuberculosis endemicity, TST, IGRA, and chest radiography) to produce a score from 1, very low probability (<20%) that experts will initiate ATT, to 5, very high probability (81%-100%) that experts would initiate ATT. In addition, the algorithm uses an IQR expressing the level of consensus for the score.

The COTS has now tested this algorithm against a reference standard of disease-positive or disease-negative status at 12 months.[6] Patients with disease-negative status either had no ATT and improved or had no response to ATT, defined as persistence or recurrence of inflammation within 6 months of completing ATT (or other treatment) and the inability to taper oral prednisolone to less than 10 mg per day or topical corticosteroid eye drops to less than 2 eye drops daily, and/or recalcitrant inflammation necessitating corticosteroid-sparing immunosuppressive therapy. Patients with disease-positive status were contrary to the latter description.

Clearly, this standard is imperfect in being a surrogate criterion standard and itself prone to misclassification. Patients with TBU may not respond to a full course of ATT; multidrug-resistant tuberculosis may cause treatment failure, and non-tuberculosis uveitis may improve despite ATT, particularly if concurrently treated with systemic or intravitreal corticosteroid. Yet given all the difficulties in establishing a definitive diagnosis of TBU, this is a reasonable standard to use.

In the COTS database of suspected TBU cases, the treating clinician did not initiate ATT in 10% of cases, and yet the COTS calculator found a low, or very low, probability of starting ATT in 25%. This suggests that perhaps contributing clinicians are overtreating those with uveitis as having suspected TBU. This is reflected in the low specificity of their diagnosis against a disease-positive status of 31% in endemic areas and 27% in nonendemic areas.

A new diagnostic method for TBU such as the COTS calculator, which uses results from other tests, needs to have a high specificity in order to avoid subjecting individuals with

Supplementary Online Content

Zhang L, Rojas-Carabali W, Choo SS, et al; Collaborative Ocular Tuberculosis Study (COTS) Group. Validation of the online collaborative ocular tuberculosis study calculator for tubercular uveitis. *JAMA Ophthalmol*. Published online October 31, 2024. doi:10.1001/jamaophthalmol.2024.4567

eAppendix. COTS Calculator Implementation and Interpretation

eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. COTS Calculator Implementation and Interpretation

The COTS-calculator incorporates the results from five different parameters. First, the clinical phenotype (anterior, intermediate, panuveitis, retinal vasculitis or choroiditis), including indication of active or inactive disease. Second, country (TB endemic or TB non-endemic region). The next two parameters are the patient's results for the TST and/or IGRA. Lastly, presence or absence of active or healed TB infection from a CXR.[1]

Each expert was asked to rank 486 scenarios on a scale of 1 to 5, 1 being unlikely to start ATT and 5 being most likely to start ATT, based on the findings in these five important parameters. 81 experts' responses were synthesized to give a score and an interquartile range (IQR) which will determine whether ATT should be initiated confidently in a patient with ocular tuberculosis.

The median score ranges from 1 to 5, 5 indicating a 81-100% probability at which >50% of experts would initiate ATT and 1 suggesting a 0-20% probability of >50% experts initiating ATT. Upon analysis of all 81 experts' response, COTS recommends based on consensus to start ATT if a median score of 5 is obtained. The IQR from 0 to 3 indicates the degree of consensus between experts. An IQR of 0 represents absolute consensus, in which more than 90% of experts are in agreement about starting ATT.

An IQR of 0 or 1 shows strong consensus, while an IQR of 2 or 3 suggests poor consensus among experts.[1,2] The COTS-calculator aims to recommend less experienced clinicians to start ATT promptly in patients who are likely to have TBU. (see credit roster, Supplementary Material 1). Median scores of 1, 2, 3 and 4 are not part of the consensus guidelines and do not imply that ATT should not be initiated. However, the COTS consensus group further discussed on cases which generated Median score 4 to deliberate on whether the 61-80% probability of >50% experts initiating ATT can be used to guide clinicians to start ATT also. Further information on how the COTS-calculator was built is available in *Agrawal et al.*[1]

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2. Agarwal A, Agrawal R, Gunasekaran DV, et al. The Collaborative Ocular Tuberculosis Study (COTS)-1 Report 3: Polymerase Chain Reaction in the Diagnosis and Management of Tubercular Uveitis: Global Trends. *Ocul Immunol Inflamm*. 2019;27(3):465-473. doi:10.1080/09273948.2017.1406529

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Data Sharing Statement

Zhang. Validation of the Online Collaborative Ocular Tuberculosis Study Calculator for Tubercular Uveitis. *JAMA Ophthalmol*. Published October 31, 2024. doi:10.1001/jamaophthalmol.2024.4567

Data
Data available: No

Additional Information
Explanation for why data not available: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.