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Evaluating the Latent Tuberculosis Diagnostic Tests Using Fuzzy PROMETHEE: A Multi-Criteria Decision Approach

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Abstract

BACKGROUND/AIMS: Latent tuberculosis infection (LTBI) remains a critical challenge in global tuberculosis (TB) control efforts, necessitating effective diagnostic techniques. This study provides a comprehensive analysis of 7 diagnostic methods for LTBI, including QuantiFERON-TB and T-SPOT.TB.

MATERIALS AND METHODS: Seven different diagnostic techniques were evaluated against criteria such as specificity to *Mycobacterium tuberculosis*, sensitivity, cost-effectiveness, accessibility, limitations, turnaround time, etc. using multi-criteria decision-making methods (MCDMs). Weightings for each criterion were applied to account for their relative importance in clinical decision-making. To validate the results obtained using the fuzzy preference ranking organization method for enrichment evaluations we applied two additional MCDMs: the weighted sum method and the technique for order of preference by similarity to ideal solution using the same criteria, alternatives, and weightings.

RESULTS: Indicate that QuantiFERON-TB with a NetFlow of 0.0577 ranks highest in overall performance. T-SPOT.TB and Diaskintest followed closely, with minor variations in their rankings between the methods, while traditional methods such as Tuberculin Skin tests ranked lower due to their limitations in specificity and cross-reactivity. Sensitivity analysis further validated these rankings, suggesting that modern blood-based assays offer superior diagnostic accuracy and operational efficiency.

CONCLUSION: This study highlights the potential of fuzzy-based MCDM for selecting diagnostic tools for LTBI, contributing to more informed clinical practices and effective TB control strategies.

Keywords: Latent tuberculosis infection, diagnosis, comparison, multi-criteria decision-making methods

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INTRODUCTION

Tuberculosis (TB) is a transmissible disease caused by *Mycobacterium tuberculosis,* a bacteria which predominantly affects the lungs.[1] TB is transmitted via airborne particles when individuals infected with pulmonary TB cough, sneeze, or expectorate. Inhalation of a few pathogens is sufficient to contract an infection.[2] Upon acquiring the pathogen, individuals can be classified as having either active tuberculosis (aTB), characterized by clinical symptoms that may spread to multiple organs, or latent tuberculosis infection (LTBI), an asymptomatic state in which 5-10% of individuals may develop aTB in the following months or years.[3,4] Although latent TB is not contagious, there is a significant risk of developing aTB later unless it is not diagnosed and treated, which presents a major obstacle to preventing TB.[4] Therefore, diagnosing and treating LTBI play a crucial role in eliminating the disease. Diagnosing LTBI is challenging, despite the availability of a variety tests.[5] No single test is sufficient, and evaluating the illness requires thorough clinical and radiographic assessment, as well as interpretation of immunological testing. Hence, there is still no gold standard test available for diagnosing LTBI. The available diagnostic procedures can be grouped to include: immune-based responses such as Tuberculin Skin test, Diaskintest, Combination Tuberculosis Skin test, T-SPOT.TB, QuantiFERON-TB Gold and Conventional Tuberculin Skin test, and Enzyme-Linked Immunoassay for Cytokines test. The use of multiple criteria decision-making methods (MCDM) has been widely recognized for its effectiveness in evaluating diverse strategies and alternatives across various domains.[6] An example of MCDM-Preference Ranking Organization METHod for Enrichment Evaluations (PROMETHEE) with fuzzy logic, focuses on enhancing decision quality through rigorous analyses and could be employed in assessing the LTBI treatment strategies. Therefore, this study aims to use one of the successfully applied MCDM approaches, fuzzy preference ranking organization method for enrichment evaluations (F-PROMETHEE), for assessing the effectiveness of the 7 available LTBI diagnostic strategies.

MATERIALS AND METHODS

Fuzzy PROMETHEE Approach

F-PROMETHEE is an MCDM approach that employs fuzzy set theory to address uncertainty and imprecision in alternative evaluations, and was implemented in this study. Multiple criteria are suggested for ranking the alternatives (LBTI diagnostics). The parameters most frequently considered in the literature when determining the most effective diagnostic alternatives for LTBI include specificity, sensitivity, effectiveness, accessibility, limitations, ability to discriminate between latent and aTB, cost-effectiveness, cross-reactivity, turnaround time, and Food and Drug Administration (FDA) approval. Criteria serve as a benchmark for evaluating different alternatives. The relative importance of each criterion was assessed to determine its weight. Consequently, experts were consulted to assign relative importance levels to the selected criteria analyzed. Table 1 presents the decision matrix of the TB diagnostic strategies, which are evaluated using a linguistic scale shown in Table 2. The Yager index is used for defuzzification, and the Gaussian preference function is applied in the PROMETHEE analysis.

Table 1. The decision matrix of the selected TB strategies

Weightings	**M**	**M**	**VH**	**M**	**M**	**M**	**L**	**H**	**M**	**H**	
Alternatives/ criteria	**Specificity**	**Sensitivity**	**Effectiveness**	**Accessibility**	**Limitation**	**ADLATB**	**CE**	**CR**	**Avg. TT**	**FDA approved**	**References**
Tuberculin Skin test	L	M	H	H	Requires two visits, FP, FN, skilled personnel, induration [H]	Yes	VL	Yes	4 days	Yes	1,7,8
Diaskintest	VH	H	VH	H	Induration [L]	No	H	Yes	3 days	Yes	2,9
Combination Tuberculosis Skin test	M	M	M	M	FN, impaired immune response [L]	Yes	L	Yes	1 day	Yes	2,10
T-SPOT.TB	H	H	H	M	Specific time for sample collection assay, induration [M]	No	L	Yes	1 day	Yes	2,11,12
QuantiFERON	VH	VH	VH	M	Inability to distinguish LTBI and aTB, FP/ FN, accessibility, requires skilled personnel [M]	No	H	No	1 day	Yes	2,13,14
ELISA	VH	VH	H	M	Cross reactivity, inability to different A and LTBI, needs skilled personnel [H]	No	M	Yes	2 days	No	2
Conventional Tuberculin Skin test	VH	H	VL	H	Positive predictive value, skin reactivity [L]	No	M	No	4 days	No	15,16

LTBI: Latent tuberculosis infection, aTB: Active tuberculosis, FP: False positive, FN: False negative, ADLATB: Ability to discriminate between latent and active TB, Avg.: Average, TT: Turnaround time, CR: Cross-reactivity, CE: Cost effect, VH: Very high, H: High, M: Moderate, L: Low, VL: Very low.

Statistical Analysis

Sensitivity Analysis

In this section, a sensitivity analysis was conducted to evaluate the robustness of the prior results. This study examines the impact of altering the weights of the evaluation criteria on the final ranking of the alternatives. The objective was to assess how changes in the relative significance of the selected criteria could influence the reliability of the conclusive outcome. In the sensitivity analysis, the weight of only two criteria was adjusted while keeping all other criteria constant. In the current study, significance weights were established for each criterion using a linguistic scale (Table 2). The weight of two essential criteria was adjusted: "Effectiveness," formerly rated as "very high", was decreased to "moderate", while "sensitivity," previously rated as "moderate", was elevated to "high". These modifications led to QuantiFERON-TB retaining its premier status, with a slightly decreased NetFlow (0.0475) (Table 3). This implies that altering the relative weights of individual criteria does not substantially impact the final ranking order. The single minor alteration is observed between the Conventional Tuberculin Skin Test and the Tuberculin Skin Test, characterized by a modest variance in NetFlow rankings. The initially integrated comprehensive ranking remained unchanged, despite variations in the outranking net flow values.

RESULTS

In this study, one of the decision-making tools known as F-PROMETHEE was proposed to rank 7 diagnostic methods for identifying LTBI based on selected parameters. This included sensitivity, specificity for *Mycobacterium tuberculosis,* cost, limitations, effectiveness, accessibility, cross-reactivity, FDA approval, and the time it takes to generate the result (Table 1). Among all the investigated methods, QuantiFERON-TB Gold proved to be the most efficient diagnostic tool with a NetFlow of 0.0557, indicating superior performance in specificity, sensitivity, and cost-efficiency. After QuantiFERON-TB, Diaskintest achieved the second-highest NetFlow (0.0296), indicating its high sensitivity and accessibility, especially for immunocompromised individuals. Conventional diagnostic methods, including the Tuberculin Skin tests, had a relatively lower NetFlow of -0.0407 and -0.0732, a consequence of low specificity and cross-reactivity, particularly in subjects vaccinated with Bacillus Calmette-Guérin. Results are summarized in Table 4.

Validation of Results with Weighted Sum and TOPSIS MCDM Methods

To validate the results obtained using the F-PROMETHEE approach, two more MCDM methods were applied: The weighted sum method (WSM) and the Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS). The same criteria, alternatives, and weightings from

Table 4. Ranking of the latent tuberculosis infection tests using F-PROMETHEE

Rank	Alternatives	NetFlow (Phi)	Positive outranking flow (Phi+)	Negative outranking flow (Phi-)
1	QuantiFERON	0.0557	0.0687	0.0130
2	Diaskintest	0.0296	0.0514	0.0218
3	T-SPOT.TB	0.0236	0.0404	0.0168
4	ELISA	0.0070	0.0373	0.0302
5	Combination Tuberculin Skin test	-0.0021	0.0390	0.0411
6	Tuberculin Skin test	-0.0407	0.0311	0.0718
7	Conventional Tuberculin Skin test	-0.0732	0.0285	0.1016

F-PROMETHEE: Fuzzy Preference Ranking Organization METHod for Enrichment Evaluations

Table 2. Linguistic scale and the weights assigned to criteria

Ranking Linguistic scale	Fuzzification scale	Criteria
VH	(0.75, 1, 1)	Effectiveness
H	(0.50, 0.75, 1)	Cross-reactivity, FDA-approved
M	(0.25, 0.50, 0.75)	Average turnaround time, ability to discriminate between latent and active TB, limitation, accessibility, sensitivity, specificity
L	(0, 0.25, 0.50)	Cost effectiveness
VL	(0, 0, 0.25)	

FDA: Food and Drug Administration, VH: Very high, H: High, M: Moderate, L: Low, VL: Very low.

Table 3. Sensitivity analysis results

Rank	Alternatives	NetFlow (Phi)	Positive outranking flow (Phi+)	Negative outranking flow (Phi-)
1	QuantiFERON	0.0475	0.0615	0.0140
2	Diaskintest	0.0209	0.0377	0.0167
3	T-SPOT.TB	0.0193	0.0428	0.0235
4	ELISA	0.0031	0.0343	0.0312
5	Combination Tuberculin Skin test	0.0026	0.0395	0.0369
6	Conventional Tuberculin Skin test	-0.0449	0.0307	0.0757
7	Tuberculin Skin test	-0.0485	0.0277	0.0762

Table 5. Comparison between fuzzy PROEMTHEE, weighted sum method and TOPSIS methods

Alternatives	PROMETHEE net flow	Rank (PROMETHEE)	WSM score	Rank (WSM)	TOPSIS score	Rank (TOPSIS)
QuantiFERON	0.0557	1	0.8785	1	0.9201	1
T-SPOT.TB	0.0236	3	0.8602	2	0.8932	2
Diaskintest	0.0296	2	0.8157	3	0.8450	3
ELISA	0.0070	4	0.7820	4	0.8104	4
Combination Tuberculin Skin test	-0.0021	5	0.7455	5	0.7793	5
Tuberculin Skin test	-0.0407	6	0.6924	6	0.7245	6
Conventional Tuberculin Skin test	-0.0732	7	0.6712	7	0.7004	7

PROMETHEE: Preference Ranking Organization METHod for Enrichment Evaluations, WSM: Weighted sum method, TOPSIS: Technique for Order of Preference by Similarity to Ideal Solution

the F-PROMETHEE analysis were applied to ensure consistency and comparability. The rankings obtained using F-PROMETHEE, WSM, and TOPSIS methods are presented in Table 5.

The results indicate strong agreement among the three methods, with minor variations in rankings for certain alternatives. QuantiFERON-TB Gold consistently emerged as the top-ranking diagnostic method. The Conventional Tuberculin Skin Test ranked lower across all methods due to its limitations in specificity, sensitivity, and turnaround time.

DISCUSSION

This study highlights the effectiveness of modern blood-based diagnostic tools like QuantiFERON-TB and T-SPOT.TB for detecting LTBI. Consistent with findings in the literature,[2,12] our results demonstrate that traditional methods such as the Tuberculin Skin test are being surpassed due to their limitations, including cross-reactivity, false positives, and prolonged turnaround times, particularly in Bacillus Calmette-Guérin-vaccinated populations. QuantiFERON-TB emerged as the most reliable diagnostic tool, achieving the highest ranking across all methods (PROMETHEE, WSM, and TOPSIS). Its superior performance is attributed to high sensitivity, high specificity, minimal cross-reactivity, and a quick turnaround time of 24 hours. T-SPOT.TB and Diaskintest followed closely, with minor variations in their rankings between the methods. Notably, T-SPOT.TB exhibited strong performance regarding sensitivity, while Diaskintest demonstrated slightly better specificity and reliability in certain evaluations. The lower rankings of traditional methods, such as Tuberculin Skin test and the Conventional Tuberculin Skin test, further underscore their limitations in diagnostic accuracy and operational efficiency due to their prolonged turnaround time and operational complexity. The close agreement between the F-PROMETHEE, WSM, and TOPSIS results validates the robustness and reliability of findings, similar to the approach.[17] This study represents the first application of F-PROMETHEE for a comprehensive comparison of 7 LTBI diagnostic tests, making it challenging to conduct a comparative analysis with previous studies in the field.

Study of Limitations

The evaluation of the study was simplified to seven LTBI diagnostic tests and ten criteria. Incorporating more diagnostic tests, such as biomarkers, and diagnostic criteria would change the rankings and potentially improve the study.

CONCLUSION

The results emphasize the role of improved diagnostics like QuantiFERON-TB, Diaskintest, and T-SPOT.TB for the diagnosis and management of LTBI. The sensitivity analysis further validates these findings, showing that even when the weights applied to the evaluation measures are different, the modern blood-based assays are still the most accurate diagnostic tools for LTBI. These findings will provide knowledge to clinicians and policymakers in the enhancement of TB control, especially where the identification of LTBI cases remains paramount.

MAIN POINTS

- QuantiFERON-TB is the most favorable latent tuberculosis infection (LTBI) diagnosis amongst the 7 compered LTBI tests, considering selected criteria.
- Following QuantiFERON-TB, the next best ranks are T-SPOT.TB and Diaskintest for LBTI diagnosis.
- Validation of Fuzzy Preference Ranking Organization METHod for Enrichment Evaluations results using Technique for Order of Preference by Similarity to Ideal Solution and weighted sum method confirms QuantiFERON-TB as the top-rank

ETHICS

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Concept: D.E., N.S., E.P.O., B.U., D.U.O., T.Ş., Design: D.E., N.S., E.P.O., B.U., D.U.O., T.Ş., Data Collection and/or Processing: D.E., N.S., E.P.O., B.U., D.U.O., T.Ş., Analysis and/or Interpretation: D.E., N.S., E.P.O., B.U., D.U.O., T.Ş., Literature Search: D.E., N.S., E.P.O., B.U., D.U.O., T.Ş., Writing: D.E., N.S., E.P.O., B.U., D.U.O., T.Ş.

DISCLOSURES

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