

Mathematical model for predicting the effectiveness of pulmonary tuberculosis treatment based on the HOMA index and the atherogenicity index

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ABSTRACT

Carbohydrate metabolism disorders increase the risk of developing active tuberculosis and are associated with worse outcomes of tuberculosis treatment. 15% of tuberculosis cases worldwide are estimated to be related to diabetes mellitus. Altered lipid metabolism may influence susceptibility to tuberculosis. Studies have been published on the association between total cholesterol, low-density lipoprotein, and high-density lipoprotein levels and the risk of tuberculosis. Patients with tuberculosis have an increased incidence of cardiovascular and cerebrovascular diseases. Cardiovascular complications of tuberculosis are among the most common extrapulmonary manifestations of the disease.

Keywords: atherogenic index, dyslipidemia, glucose metabolism, human health, hyperglycemia, immune response, insulin resistance, lipid metabolism, macrophages, tuberculosis

1. INTRODUCTION

Carbohydrate metabolism disorders increase the risk of developing active tuberculosis and are associated with worse outcomes of tuberculosis treatment¹. 15% of tuberculosis cases worldwide are estimated to be related to diabetes mellitus². The International Diabetes Federation predicts that the number of people with diabetes worldwide will increase by 55% over the next 20 years³.

Goldhaber-Fiebert et al. have shown that the risk of tuberculosis is increased even at levels of hyperglycemia below the current diagnostic threshold for diabetes⁴. On the other hand, induced hyperglycemia or impaired glucose tolerance is observed in the early stages of tuberculosis⁵. Widespread tuberculosis lesions, altered immune response in people with carbohydrate metabolism disorders, or decreased concentrations of anti-tuberculosis drugs, especially against the background of hyperglycemia, reduce the effectiveness of tuberculosis treatment in patients with carbohydrate metabolism disorders⁶. Optimal glycemic control can improve TB treatment outcomes and prevent many complications. However, TB often results in decreased appetite, weight loss, and decreased physical activity (patients may be fatigued and therefore less active), which can affect glucose homeostasis. TB treatment can have the opposite but unpredictable effects of reducing inflammation and increasing appetite, weight, and physical activity. Some patients may experience paradoxical increased inflammation or appetite loss as side effects of anti-TB drugs. Inflammation associated with active TB can cause insulin resistance, which usually resolves after TB treatment.

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Pulmonary tuberculosis involves various pathological mechanisms, including lipid peroxidation and antioxidant depletion⁷. Mycobacteria contain various types of nonstructural and structural lipids, which serve as the main source of energy and play a crucial role in the pathogenicity, virulence and persistence of mycobacteria⁸. Wilburn et al. argue that lipids play a key role not only in the development of cardiovascular diseases but also in the development of tuberculosis. Cholesterol constitutes approximately one-third of the lipid content of the cell membrane and plays an important role in several metabolic pathways, such as anaplerotic assimilation via the methylcitrate cycle, anaplerotic assimilation via the methylmalonyl pathway and biosynthetic incorporation into methyl-branched polyketide lipids⁹. Altered lipid metabolism may influence susceptibility to tuberculosis. Studies have been published on the association between total cholesterol, low-density lipoprotein, and high-density lipoprotein levels and the risk of tuberculosis¹⁰. Patients with tuberculosis have an increased incidence of cardiovascular and cerebrovascular diseases¹¹. Cardiovascular complications of tuberculosis are among the most common extrapulmonary manifestations of the disease¹².

There are specific biomarkers that reflect cardiovascular disease risk, such as the atherogenic index (AI), the Castelli risk index I and II (CRI-I and II), and the atherogenic coefficient¹³. AI is derived from the logarithmic transformation of the triglyceride to high-density lipoprotein ratio and is considered a meaningful indicator of cardiometabolic health¹⁴. Javardi et al. argue that it is an optimal indicator of dyslipidemia and related disorders¹⁵.

2. MATERIALS AND METHODS

The purpose of the study was to establish the relationship between the HOMA (Homeostasis Model Assessment) index, the atherogenic index and the effectiveness of pulmonary tuberculosis treatment and to build a mathematical model for predicting the effectiveness of pulmonary tuberculosis treatment using these indicators.

There are 96 patients with pulmonary tuberculosis were included in the study. At the beginning of treatment, fasting insulin ($\mu\text{U}/\text{mL}$) and glucose (mmol/L) levels were measured in the patients and the HOMA index was calculated from these data as follows:

$$HOMA = \frac{\text{insulin} \times \text{glucose}}{22,5} \quad (1)$$

Total cholesterol (TC; mmol/L) and high-density lipoprotein (HDL; mmol/L) levels were measured, and the atherogenic index (AI) was calculated based on these data:

$$AI = \frac{TC - HDL}{HDL} \quad (2)$$

After completion of treatment, patients were retrospectively divided into 2 groups: Group 1 ($n = 73$) included patients who effectively completed anti-tuberculosis treatment and Group 2 ($n = 23$) included patients in whom anti-tuberculosis treatment was not effective.

The HOMA and AI indices were compared between groups using the Mann-Whitney test. These indices were used to build a mathematical model for predicting the effectiveness of anti-tuberculosis therapy using the discriminant functional analysis method¹⁶. The results were considered significant at $p < 0,05$. For analysis X-ray data used methods of digital image processing and segmentation methods¹⁷⁻²¹.

3. RESEARCH RESULTS AND DISCUSSION

A significant ($p < 0,05$) difference in the HOMA index was found in patients with effective ($1,92 \pm 0,07$ (median – 1,76)) and ineffective ($2,67 \pm 0,24$ (median – 2,56)) anti-tuberculosis treatment (Fig. 1).

A significant ($p < 0,05$) difference in the atherogenic index was also found in patients with effective (3.55 ± 0.12 (median – 3.35)) and ineffective (4.20 ± 0.26 (median – 4.09)) anti-tuberculosis treatment (Fig. 2).

These indicators were later used to build a mathematical model. For patients with pulmonary tuberculosis, a study was provided to examine the influence of the HOMA index and the atherogenic index on the effectiveness of anti-tuberculosis therapy. Discriminant functional analysis allowed us to establish the reliability of the influence of the HOMA index and the atherogenicity index on the effectiveness of anti-tuberculosis treatment (Table 1).

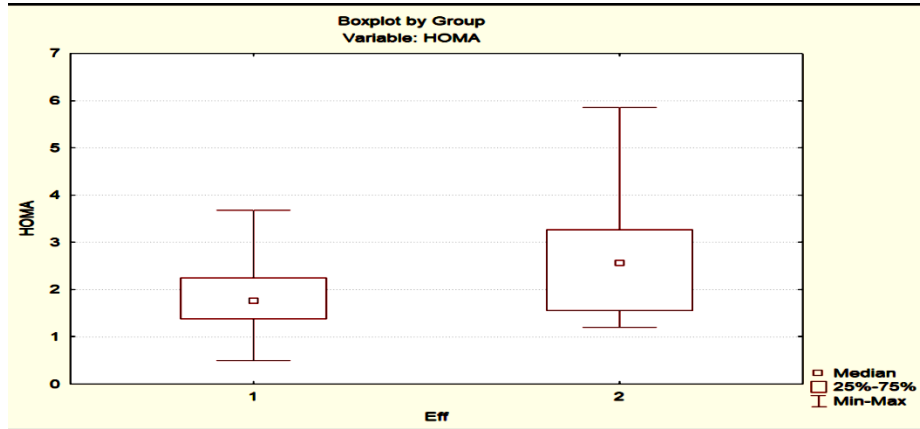


Figure 1. Comparison of the HOMA index in patients with effective (Group 1) and ineffective (Group 2) anti-tuberculosis treatment

Table 1. Summary table of discriminant analysis results for *HOMA* index and atherogenic index in patients with pulmonary tuberculosis

N=96	Discriminant function analysis summary					
	No. of vars in model: 2; grouping: Eff (2 grps) Wilks' lambda: 0,85007 approx. F (2,93)=8,2012 p<0,0005					
	Wilks' Lambda	Partial Lambda	F-remove (1,93)	p-level	Toler.	1-Toler. (R-Sqr.)
<i>HOMA</i>	0.939738	0.904585	9.809614	0.002321	0.996209	0.003791
<i>AL</i>	0.890878	0.954197	4.464198	0.037291	0.996209	0.003791

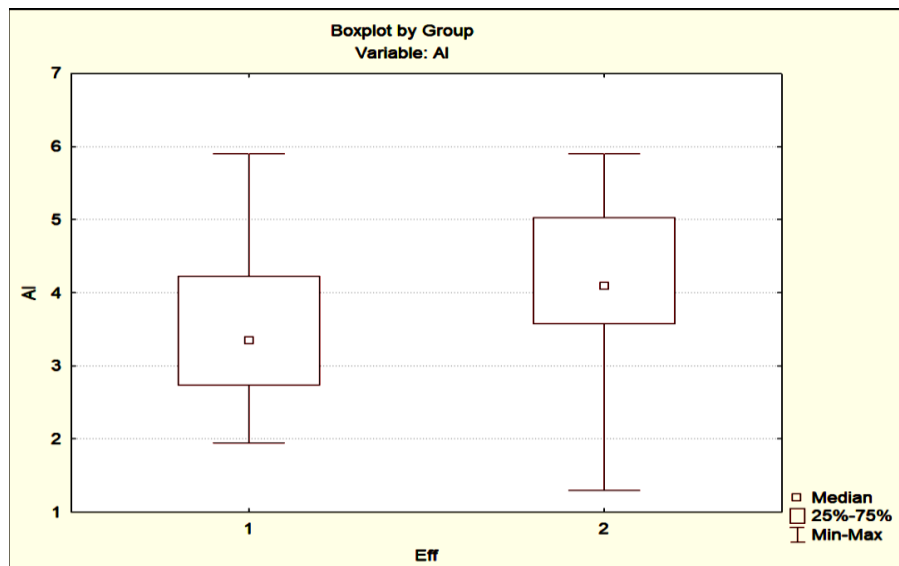


Figure 2. Comparison of the atherogenic index in patients with effective (Group 1) and ineffective (Group 2) anti-tuberculosis treatment

The classification matrix (Table 2) displays information about the number and percentage of classified observations in each group in reverse order and indicates high (81.25%) sensitivity and specificity.

Table 2. Discriminant analysis protocol classification table

Group	Classification matrix Rows: observed classifications Columns: predicted classifications		
	Percent correct	G_1:1 p=0,77083	G_2:2 p=0,22917
G_1:1	98,64865	73	1
G_2:2	22,72727	17	5
Total	81,25000	90	6

The factor structure coefficients (Table 3) obtained from factor analysis are correlations between the variables in the model and the discriminant function. These correlations can be viewed as the factor loadings of the variables on each discriminant function.

Table 3. Classification functions of the discriminant analysis protocol for the influence of the HOMA index and the atherogenic index on the effectiveness of anti-tuberculosis therapy in patients with pulmonary tuberculosis

Variable	Classification functions; grouping: Eff	
	G_1:1 p=0,77083	G_2:2 p=0,22917
<i>HOMA</i>	2,87870	3,8639
<i>AL</i>	2,84677	3,3482
<i>Constant</i>	-8,20002	-13,6579

By presenting the discriminant analysis equation, in which group “1” corresponds to effective treatment and group “2” to ineffective treatment, in linear form and substituting the values of constants and coefficients, we can obtain 2 quantities:

$$A = 2,8787 \cdot HOMA + 2,84677 \cdot AI - 8,20002;$$

$$B = 3,8639 \cdot HOMA + 3,3482 \cdot AI - 13,6579.$$

where *HOMA* is the *HOMA* index, *AI* is the atherogenicity index.

The evaluation of the obtained data is performed as follows:

- If $A > B$, then the effectiveness forecast is favorable;
- If $A < B$, then the effectiveness forecast is unfavorable.

Clinical example:

A 52-years-old woman; effective completion of anti-tuberculosis treatment. At the beginning of treatment, a disseminated form of pulmonary tuberculosis, massive bacterial excretion, and pronounced symptoms of tuberculosis intoxication were observed (Fig. 3).

HOMA index – 2,51, atherogenicity index – 2,9.

Calculation of the prognosis for the effectiveness of treatment for the patient:

$$A = 2,8787 \cdot 2,51 + 2,84677 \cdot 2,9 - 8,20002 = 7,28115$$

$$B = 3,8639 \cdot 2,51 + 3,3482 \cdot 2,9 - 13,6579 = 5,750269$$

$A > B$, therefore the prognosis for the effectiveness of treatment is favorable, which is confirmed by clinical data.

At the end of the course of anti-tuberculosis treatment, the patient had sputum conversion, disappearance of local and general intoxication symptoms, and positive X-ray dynamics (Fig. 4).

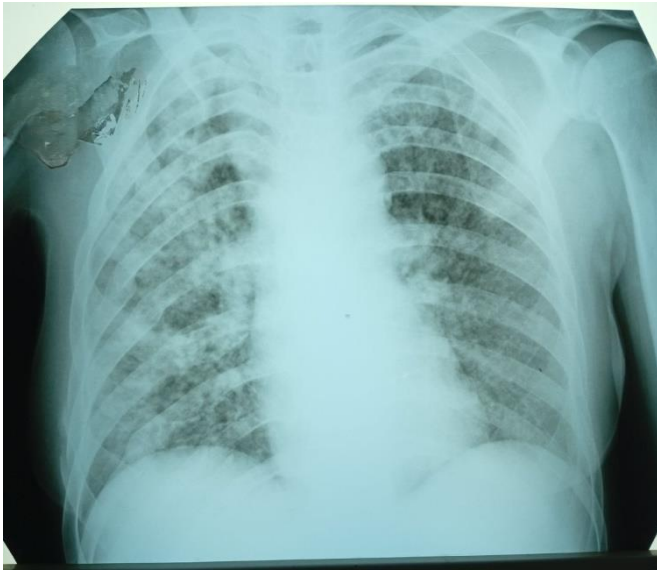


Figure 3. A 52-years-old woman, chest X-ray at the beginning of anti-tuberculosis treatment

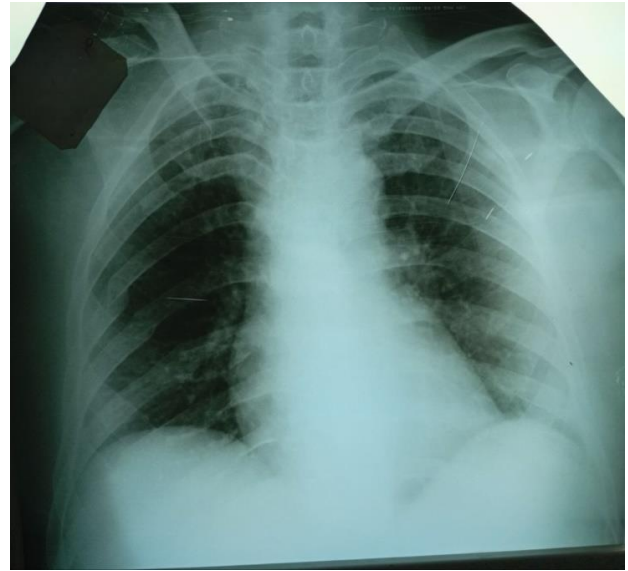


Figure 4. A 52-years-old woman, chest X-ray shows positive X-ray dynamics at the end of the course of anti-tuberculosis treatment

A 60-years-old woman, ineffective anti-tuberculosis treatment. At the beginning of treatment, miliary pulmonary tuberculosis was diagnosed. The patient had cachexia, pronounced symptoms of intoxication, and severe cough (Fig. 5).

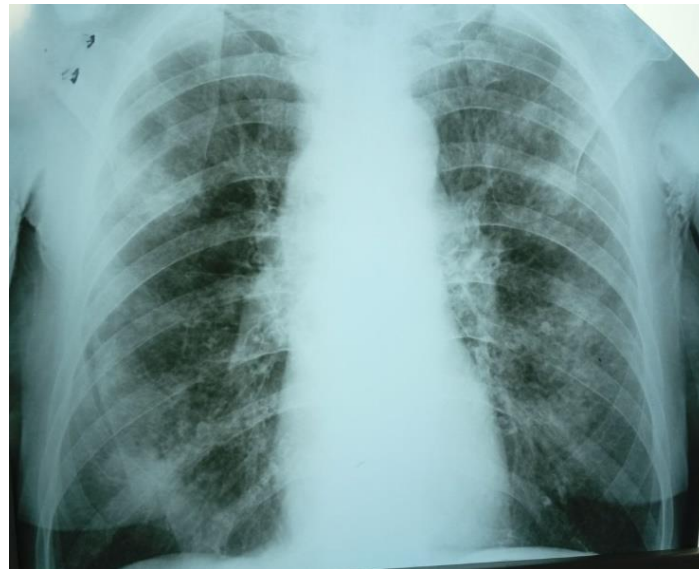


Figure 5. A 60-years-old woman, chest X-ray before start of anti-tuberculosis treatment

The *HOMA* index is 4.11, the atherogenicity index is 5.03.

Calculation of the prognosis for the effectiveness of treatment:

$$A = 2,8787 \times 4,11 + 2,84677 \times 5,03 - 8,20002 = 17,9506901;$$

$$B = 3,8639 \times 4,11 + 3,3482 \times 5,03 - 13,6579 = 19,064175.$$

$A < B$, therefore, the prognosis for treatment effectiveness is unfavorable, which is confirmed by clinical data.

Despite the intensive phase of anti-TB therapy, the patient died 14 days after the start of anti-TB treatment. The cause of death was recognized as tuberculosis.

Impaired glucose metabolism and insulin resistance in particular lead to dysfunction of macrophages, which play a key role in anti-TB immunity and granuloma formation. High glucose levels induce M2 polarization of macrophages instead of the classical M1 polarization²². M2 macrophages have impaired phagocytic capacity and also support the growth of MTB by expressing high levels of pro-inflammatory cytokines such as IL-4 and IL-10. Hyperglycemia also reduces neutrophil migration to the site of infection due to glycated collagen, which is a result of glycation end product receptor on neutrophils. There is also a general decrease in chemotaxis, defective phagocytosis and reduced bactericidal capacity. The number of dendritic cells is also reduced; this reduces phagocytosis as well as stimulation of CD4 cells, thus resulting in an overall decrease in the adaptive response to MTB infection. Hyperglycemia also leads to inhibition of IFN- γ and TNF- α secretion, which reduces the bactericidal effect on MTB²³.

Foamy cell macrophages filled with lipid droplets are feature of developing tuberculous granuloma²⁴. They differ from those observed in systemic lipid disorders such as obesity and atherosclerosis both quantitatively (number of lipid droplets per cell and foam cells per granuloma) and qualitatively (lipid composition)²⁵. While atherosclerotic foam cells are cholesterol-dominated, tuberculous granulomas are rich with triglycerides²⁶. Mycobacterial ligand, which signals through macrophage receptors, alters the triglyceride content of the cells²⁷. This indicates a dynamic remobilization of intracellular lipids in macrophages infected with MTB, which may promote bacterial growth²⁸. A study by Vrieling et al. demonstrated that macrophages loaded with low-density lipoproteins have a greater mycobacterial burden²⁹. It should also be noted that lipids themselves are a key feature of the tuberculous granuloma, with areas of extracellular lipid deposition³⁰. This is thought to occur through the death of infected cells and extraneous foamy macrophages, suggesting that over time the metabolic stresses caused by depleted glycolysis, intense fatty acid oxidation, and mitochondrial reprofiling may eventually become too much for the cells, burdened with pathogen growth, ultimately leading to cell death. Dysregulated macrophage necrosis (indicative of dysfunctional) releases the metabolic contents of the cell along with extracellular MTB and ultimately leads to granuloma disintegration and spread³¹.

Mathematical modeling allows us to predict the effectiveness of anti-tuberculosis therapy at the initial stages of treatment and take measures to increase it in advance. In previous studies, we built a model for predicting the effectiveness of anti-tuberculosis therapy based on the levels of inflammatory markers, namely Human-beta-defensin-1, ferritin, and interleukin-6³². However, these markers require additional special studies, while indicators of carbohydrate and lipid metabolism are more often determined in routine practice, so their use for prognostic purposes is more economically justified.

4. CONCLUSIONS

In our study, significantly lower levels of the *HOMA* index and the atherogenic index were found in patients whose anti-tuberculosis treatment subsequently proved to be effective. On the one hand, this proves the importance of normal glucose and lipid metabolism for the formation of an adequate anti-tuberculosis immune response and the healing of tuberculous lesions. On the other hand, this suggested the possibility of using these indices as predictors of the effectiveness of anti-tuberculosis therapy. Based on the data obtained, a mathematical model was built basing on the *HOMA* index and the atherogenic index before the start of anti-tuberculosis treatment. This model allows predicting the effectiveness of anti-tuberculosis therapy.

Elevated levels of the *HOMA* index and the atherogenic index at the beginning of treatment are associated with a higher risk of ineffectiveness of anti-tuberculosis therapy. Based on the data obtained, we built a mathematical model for predicting the effectiveness of anti-tuberculosis treatment.

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